Dissertation

High-density lipoprotein (HDL) in Allergy and Skin Diseases: Elucidating the effects on HDL composition, metabolism and function

submitted by

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STATUTORY DECLARATION

I hereby declare that this thesis is my original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Athina Trakaki
Graz, March 2021

DISCLOSURES

This cumulative dissertation is based on the following original papers:

- *Trakaki A[1], Sturm G J[2], Pregartner G[3], Scharnagl H[4], Eichmann T O[5], Trieb M[1], Knuplez E[1], Holzer M[1], Stadler J T[1], Heinemann A[1,6], Sturm E M[1], Marsche G[1,6]* **Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function.** Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 2019; 1864(10): 1280-1292.
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- *Trakaki A[1] and Marsche G[1,6]* **High-Density Lipoprotein (HDL) in Allergy and Skin Diseases: Focus on Immunomodulating Functions.** Biomedicines 2020; 8(12): 558.
- *Trakaki A[1] and Marsche G[1,6]* **Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins.** Biomedicines 2021; 9(6): 587.

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ABBREVIATIONS

ABC	ATP-binding cassette transporter
ABCA1	adenosine triphosphate-binding cassette subfamily A member 1
ABCG1	ATP-binding cassette subfamily G member 1
apo	apolipoprotein
ATP	adenosine triphosphate
CETP	cholesteryl ester transfer protein
HDL	high-density lipoprotein
ICAM-1	intracellular adhesion molecule 1
IgE	immunoglobulin E
IL	interleukin
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
Lp-PLA2	lipoprotein-associated phospholipase A2
LPS	lipopolysaccharide
NF-κB	nuclear factor-κB
PAF	platelet-activating factor
PAF-AH	platelet-activating factor-acetyl hydrolase
PLTP	phospholipid transfer protein
PON1	paraoxonase 1
PON2	paraoxonase 2
PON3	paraoxonase 3
S1P	sphingosine-1-phosphate
SAA	serum amyloid A
SPHK	sphingosine kinase
SR-BI	scavenger receptor class B type 1
Th1	T helper 1
Th2	T helper 2
Th17	T helper 17
TNF-α	tumor necrosis factor alpha
VCAM-1	vascular cell adhesion molecule 1

VLDL very-low-density lipoprotein

ZUSAMMENFASSUNG

In den letzten Jahrzehnten hat die Prävalenz von allergischen und entzündlichen Hauterkrankungen dramatisch zugenommen, was mit Veränderungen der Umweltbelastung und der Lebensgewohnheiten zusammenhängt. High-Density-Lipoproteine (HDL) sind die am stärksten angereicherten Lipoproteine und sind hinsichtlich ihrer Struktur, Zusammensetzung und biologischen Funktionen am heterogensten. Trotz starker Hinweise auf eine wichtige Rolle von HDL bei der Modulation der Aktivität diverser Immunzellen, ist die Funktion von HDL bei allergischen und entzündlichen Hauterkrankungen noch kaum verstanden.

Im ersten Teil meiner Dissertation habe ich die Zusammensetzung, Partikelverteilung und die funktionellen Eigenschaften von HDL bei Patienten mit allergischer Rhinitis untersucht. Wir konnten zeigen, dass eine allergische Rhinitis zu deutlichen Veränderungen der HDL-Zusammensetzung führt. Insbesondere beobachteten wir erhöhte Spiegel von HDL-assoziiertem Apolipoprotein (Apo) A-II, Triglyceriden und Lyso-Phosphatidylcholinen, während HDL-assoziiertes ApoA-I und Phosphatidylcholin bei Patienten mit allergischer Rhinitis verringert waren. Weiters zeigte eine Analyse der HDL-Subfraktionen eine Abnahme der kleineren und dichten HDL3-Partikel. Darüber hinaus haben wir eine umfassende funktionelle Charakterisierung der HDL Partikel gemacht. So konnten wir zeigen, dass HDL von Patienten mit allergischer Rhinitis eine beeinträchtigte anti-oxidative Kapazität aufweist und eine beeinträchtigte Fähigkeit zur Unterdrückung der Expression des pro-inflammatorischen Transkriptionsfaktor NF-κB bei Monozyten zeigte. Dies war mit einer HDL induzierten Sekretion von pro-inflammatorischen Zytokinen verbunden, wie Tumornekrosefaktor alpha, Interleukin (IL) 1 beta, IL-4, IL-6 und IL-8. Wir konnten bei Seren von Patienten mit allergischer Rhinitis im Vergleich zu Kontroll Seren eine beeinträchtigte Cholesterin-Ester-Transferprotein- und Paraoxonase-Aktivität feststellen, aber eine erhöhte Lipoprotein-assoziierte Phospholipase A2-Aktivität. Zu unserer Überraschung zeigte HDL von Patienten mit allergischer Rhinitis eine erhöhte Fähigkeit zur Hemmung eosinophiler Effektoraktivitäten nach Eotaxin-2/CCL24-Stimulation. Die Veränderungen in der HDL-Zusammensetzung und -Struktur bei allergischer Rhinitis beeinflussen somit direkt die HDL-Funktionalität.

Im zweiten Teil meiner Dissertation untersuchte ich, ob eine Antipsoriatika-Therapie mit Biologika einen Einfluss auf die HDL-Zusammensetzung, Partikelverteilung und Funktionalität hat. Wir konnten zeigen, dass Psoriasis-Patienten zu Studienbeginn im Vergleich zu gesunden Kontrollen eine signifikant beeinträchtigte Cholesterin-Efflux-Kapazität von apoB-depletiertem Serum aufweisen. Weiters waren auch die Aktivitäten der Lecithin-Cholesterin-Acyltransferase und Paraoxonase reduziert und die Größenverteilung der HDL Partikel verändert. Überraschenderweise stellten wir fest, dass eine kurze- (3 bis 6 Monate) und insbesondere eine mittelfristige- (1 bis 2 Jahre) anti-psoriatische Therapie die Cholesterin-Effluxkapazität wie auch die anti-inflammatorische Aktivität von HDL deutlich beeinträchtigen. Auf der anderen Seite, erhöhte die anti-psoriatische Therapie jedoch die Aktivität der Lecithin-Cholesterin-Acyltransferase- und Paraoxonase. Die anti-psoriatische Therapie führte zu Veränderungen in der HDL-Zusammensetzung, insbesondere zu einer Erhöhung der HDL-assoziierten ApoA-II und Phosphatidylcholinwerte, aber zu einer Verringerung der HDL-assoziierten freien Cholesterinspiegel. Wir konnten zeigen, dass alle biologischen Wirkstoffe ähnliche Veränderungen der HDL-Zusammensetzung, der Subklassenverteilung und der Cholesterin-Efflux Kapazität verursachten. Dies deutet darauf hin, dass die beobachteten Veränderungen nicht auf die direkte Wirkung eines bestimmten biologischen Wirkstoffs zurückzuführen sind, also möglicherweise indirekt verursacht wurden. Um dies im Detail zu verstehen und sichere Schlüsse zu ziehen, sind allerdings weitere Studien notwendig.

Schließlich habe ich im Rahmen meiner Dissertation die vorhandene Literatur zu den neu identifizierten immunmodulatorischen Effekten von HDL in zwei Übersichtsarbeiten zusammengefasst.

Zusammenfassend konnte ich während meiner Dissertation erste Hinweise liefern, dass allergische Rhinitis mit Veränderungen des HDL-Stoffwechsels verbunden ist. Dies beeinflusst die HDL-Zusammensetzung und die funktionellen Eigenschaften, was auf einen neuen Konnex zwischen HDL-Stoffwechsel und Allergie hindeutet. Darüber hinaus konnte ich zeigen, dass wirksame biologische anti-psoriatische Therapien komplexe Veränderungen in der HDL-Struktur, -Zusammensetzung und -Metabolismus induzieren, die die Funktionalität von HDL-Partikeln tiefgreifend beeinflussen. Dies deutet darauf hin, dass eine biologische anti-psoriatische Therapie möglicherweise das kardiovaskuläre Risiko erhöhen könnte.

ABSTRACT

In recent decades, the prevalence of allergy and inflammatory skin diseases has increased dramatically, a fact that is associated to changes in environmental exposures and lifestyle practices. High-density lipoprotein (HDL) particles comprise the most abundant lipoproteins and the most heterogeneous in terms of their structure, composition and biological functions. Despite strong evidence on the role of HDL in modulating immune cell activity, the function of HDL in allergic and inflammatory skin diseases is yet poorly understood.

In the first part of my thesis, I investigated the HDL composition, particle distribution as well as functional properties in subjects suffering from allergic rhinitis. We were able to demonstrate that allergic rhinitis is associated with marked alterations in HDL composition, specifically with increased levels of HDL-associated apolipoprotein (apo) A-II, triglycerides and lyso-phosphatidylcholine. On the other side, allergic rhinitis was associated with decreased levels of HDL-associated apoA-I and phosphatidylcholine. Analysis of HDL subfractions revealed a decrease in the HDL3 subclass in allergic rhinitis patients in comparison to controls. Moreover, when performing a thorough functional characterization of allergic rhinitis-derived HDL, we could demonstrate that HDL of allergic rhinitis patients showed an impaired anti-oxidative capacity and an impaired ability to suppress monocyte nuclear factor-κB expression. This was linked to secretion of pro-inflammatory cytokines including tumor necrosis factor alpha, interleukin (IL) 1 beta, IL-4, IL-6 and IL-8. In addition, we observed impaired cholesteryl-ester transfer protein and paraoxonase activities, but improved lipoprotein-associated phospholipase A2 activity in sera from allergic rhinitis patients in comparison to controls. To our surprise, apoB-depleted serum as well as HDL derived from allergic rhinitis patients showed an increased ability to suppress eosinophil effector responses due to eotaxin-2/CCL24 stimulation in comparison to controls. We observed multiple and complex associations of the composition/structure of allergic rhinitis-HDL with metrics of HDL function suggesting a link between HDL functionality and allergic rhinitis.

In the second part of my thesis, I investigated the HDL composition, particle distribution and functionality in psoriasis subjects under biologic anti-psoriatic therapy. We demonstrated that in comparison to healthy controls, serum samples of psoriasis patients at baseline showed significantly impaired cholesterol efflux capacity, lecithin-cholesterol acyltransferase and

paraoxonase activities and increased levels of the intermediate HDL subclass. Importantly, short- (3 to 6 months) and especially intermediate-term (1 to 2 years) biologic anti-psoriatic therapy markedly impaired HDL-cholesterol efflux capacity and rendered HDL pro-inflammatory; however, it increased lecithin-cholesterol acyltransferase and paraoxonase activities. In addition, intermediate-term biologic anti-psoriatic therapy impaired the adenosine triphosphate-binding cassette subfamily A member 1-mediated cholesterol efflux capacity and the anti-oxidative capacity of apoB-depleted serum and decreased the large HDL subclass. Alterations were also observed in the composition of HDL at intermediate-term therapy, specifically increased apoA-II and phosphatidylcholine but decreased free cholesterol levels were observed in comparison to baseline. We observed that all biologic agents caused similar changes in HDL composition, subclass distribution and cholesterol efflux capacity, indicating that the observed effects are not due to the effect of a particular biological active agent.

Finally, as part of my thesis I reviewed and evaluated the existing literature regarding the newly identified changes in the composition, metabolism and function of HDL in allergic and inflammatory skin diseases, as well as the immune cell modulatory activities of HDL and HDL-associated components. I summarized this literature in two review articles.

In summary, during my thesis I was able to provide first evidence that allergic rhinitis is associated with alterations in HDL metabolism, which affect thereby HDL composition and functional properties, suggesting a novel link between HDL metabolism and allergy. Moreover, I demonstrated that effective biologic anti-psoriatic therapies are associated with complex changes in HDL structure, composition and metabolism that profoundly affect the functionality of HDL particles, suggesting that biologic anti-psoriatic therapy might increase the cardiovascular risk.

1. INTRODUCTION

1.1. High-density lipoprotein (HDL)

From an evolutionary point of view, lipoproteins are not only considered as lipid transporters, but they also bear important functions in many aspects of immunity. Of all lipoproteins, HDL possesses the highest affinity not only for binding, but also for neutralizing pathogen-associated lipids including lipopolysaccharide (LPS) and lipoteichoic acid [1, 2]. Pathogen-associated lipids are responsible for promoting excessive immune activation during bacterial infections [2–4] and importantly an inverse association of HDL-cholesterol with sepsis severity and morbidity [2] and death from infection [5] was demonstrated. HDL particles are considered as cholesterol transporters, since they mediate the reverse cholesterol transport pathway, in which cholesterol from extrahepatic peripheral tissues is transferred back to the liver [6].

1.1.1. Metabolism of HDL

HDL particles are the most abundant lipoproteins and the most heterogeneous in terms of their structure, composition and biological functions. Specifically, plasma HDL comprises a heterogeneous group of small discoid as well as spherical particles, which differ in density, size/diameter and electrophoretic mobility [7]. This heterogeneity is a result of differences in the relative apolipoprotein (apo) and lipid content of HDL [6].

The biogenesis of HDL begins in the liver and intestine, which secrete lipid-free apoA-I [8]. Secreted apoA-I interacts thereafter physically and extracellularly with the membrane lipid transporter adenosine triphosphate (ATP)-binding cassette subfamily A member 1 (ABCA1), leading to the initial and rapid recruitment of cellular cholesterol and phospholipids to lipid-poor apoA-I particles. Lipidated apoA-I acquires additional free cholesterol and phospholipids from extrahepatic peripheral tissues such as the arterial wall macrophages via interaction with ABCA1, thus leading to the formation of discoid, nascent HDL particles consisting of apolipoproteins (mainly apoA-I) and small amounts of lipids (mainly free cholesterol and phospholipids) [9]. Via the action of lecithin-cholesterol acyltransferase (LCAT), an enzyme responsible for the conversion of cholesterol to cholesteryl esters, discoidal HDL particles are converted into the spherical, large, mature HDL particles, which are predominantly present in normal human plasma [2, 6]. HDL particles are on a constant

remodelling process as they transport cholesterol between cells and other lipoproteins. Mature HDL particles can undergo further remodelling either via particle fusion or via surface remnant transfer mediated by phospholipid transfer protein (PLTP) [10]. Based on their density, mature HDL particles can be separated into the lipid-rich, light, large HDL2 particles and the protein-rich, more-dense, smaller HDL3 particles [7]. Conversion of large HDL2 into small HDL3 particles is promoted by cholesteryl ester transfer protein (CETP), which mediates the transfer of cholesteryl ester from HDL to apoB-containing lipoproteins, or by scavenger receptor class B type 1 (SR-BI), which mediates the selective uptake of HDL-associated cholesteryl ester by the liver and steroidogenic organs. Moreover, endothelial lipase-mediated hydrolysis of phospholipids and hepatic lipase-mediated hydrolysis of core triglycerides also contribute to the conversion of HDL2 into HDL3 particles [11]. Specifically, the CETP-mediated transfer of cholesteryl ester between HDL and triglyceride-rich lipoproteins leads to the generation of triglyceride-rich HDLs, which can be further hydrolysed to smaller particles via the action of hepatic lipase [12, 13]. Moreover, the combined activity of hepatic lipase and CETP promotes the reduction in HDL size, the formation of lipid-poor HDL particles, as well as the lipid-free apoA-I shedding from HDL, which can interact with ABCA1 in the next lipidation cycle [14]. ABCA1 and ATP-binding cassette subfamily G member 1 (ABCG1) both play a significant role in the reverse cholesterol transport pathway. Specifically, ABCA1 is responsible for the transfer of cellular cholesterol and phospholipids, while ABCG1 promotes cholesterol efflux to more mature HDL particles [15]. Furthermore, lipids within HDL are primarily catabolized in the liver, either as holoparticles, via uptake by SR-BI or through low-density lipoprotein (LDL) receptor for apoE-containing HDL, or separately from HDL via transfer to very-low-density lipoprotein (VLDL) and LDL through the action of CETP [6, 16] (Figure 1).

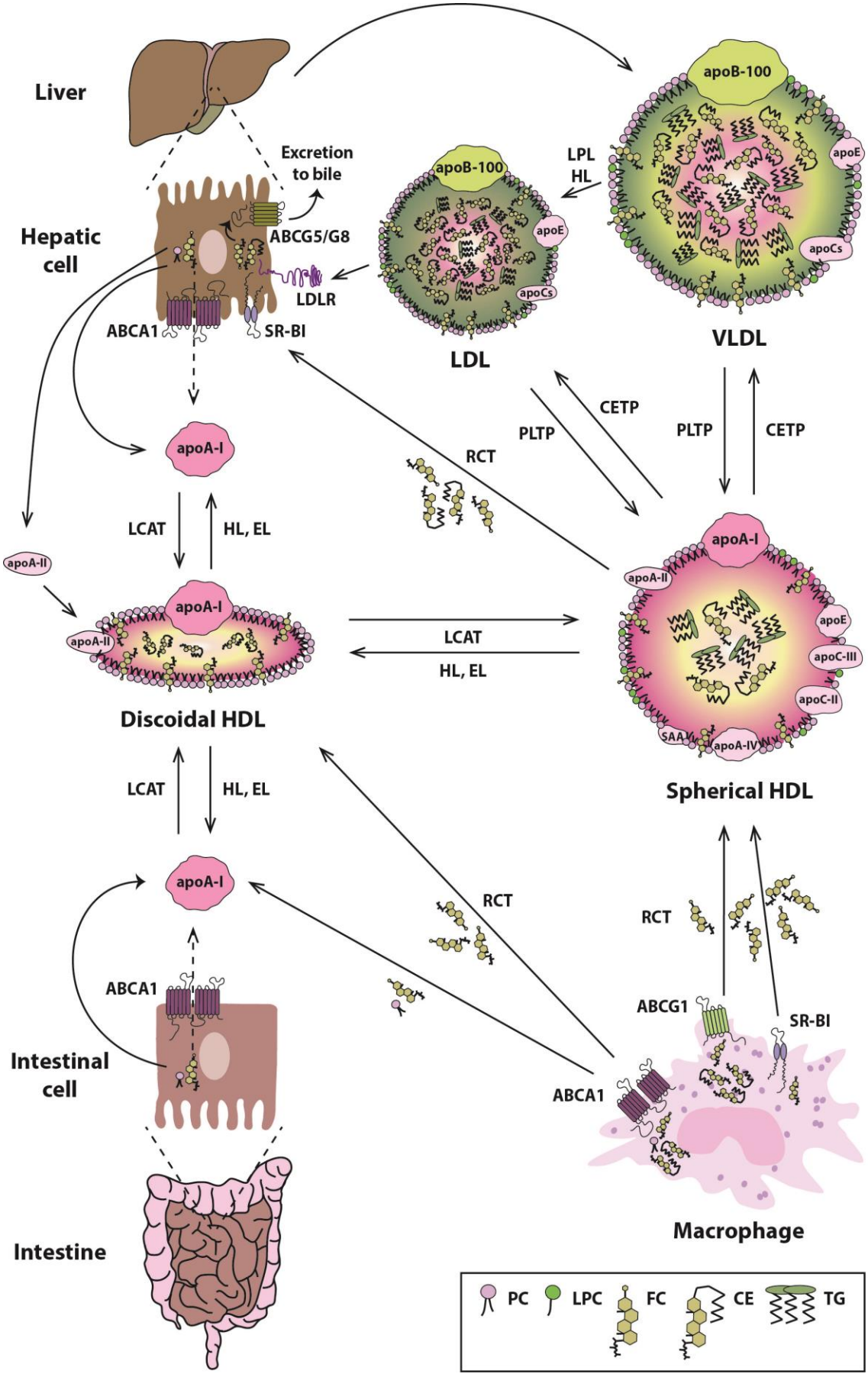
Liver
Excretion to bile
Hepatic cell
ABCG5/G8
LDLR
ABCA1
SR-BI
apoB-100
apoE
apoCs
LDL
LPL
HL
apoB-100
apoE
apoCs
VLDL
CETP
PLTP
PLTP
CETP
RCT
apoA-I
LCAT
HL, EL
apoA-II
apoA-I
apoA-II
Discoidal HDL
LCAT
HL, EL
apoA-I
apoA-II
apoE
apoC-III
apoC-II
SAA
apoA-IV
Spherical HDL
LCAT
HL, EL
apoA-I
RCT
RCT
ABCA1
Intestinal cell
ABCG1
SR-BI
ABCA1
Macrophage
Intestine
PC
LPC
FC
CE
TG

Figure 1: Metabolism of HDL. *The metabolism of HDL is a multistep process that involves: (i) the secretion of lipid-free apolipoproteins by the liver or intestine, (ii) the acquisition of phospholipids and cholesterol via ABCA1, ABCG1, and SR-BI, (iii) the maturation by LCAT-mediated cholesterol esterification and (iv) the final uptake of lipids by the liver. Cholesterol uptake is either mediated directly via SR-BI, or indirectly via CETP-mediated transfer of cholesteryl ester to VLDL and LDL and uptake of VLDL/LDL by the LDL-Receptor. Subsequently, the liver excretes cholesterol into the bile, either directly via the action of ATP-binding cassette (ABC) transporters G5/G8, or indirectly following oxidation to bile acid and secretion via ABCB11 [69,70]. Abbreviations represent: ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; ABCG5, ATP-binding cassette subfamily G member 5; ABCG8, ATP-binding cassette subfamily G member 8; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoA-IV, apolipoprotein A-IV; apoB-100, apolipoprotein B-100; apoC, apolipoprotein C; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; EL, endothelial lipase; FC, free cholesterol; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPC, lyso-phosphatidylcholine; LPL, lipoprotein lipase; PC, phosphatidylcholine; PLTP, phospholipid transfer protein; RCT, reverse cholesterol transport; SAA, serum amyloid A; SR-BI, scavenger receptor class B type I; TG, triglyceride; VLDL, very low-density lipoprotein.*

1.1.2. HDL-associated proteins

Along with apoA-I and apoA-II, which comprise the main protein constituent of HDL, other less abundant proteins are also present such as apoA-IV, apoC-II, apoC-III, apoE, serum amyloid A (SAA) and others [17]. However, not all protein species are present on every single HDL particle, since most proteins are only associated with a small fraction of the HDL particles [17]. Although some studies reported that more than 100 different proteins are associated with HDL [18], recent evidence suggested that the HDL proteome of mature HDL2 and HDL3 subclasses may be less complex, containing less than 20 proteins identified as a result of extensive purification [19].

ApoA-I comprises the main structural and functional protein component of HDL. ApoA-I is a 28 kDa protein of amphipathic structure, which is responsible for lipid binding and accounts for approximately 70 % of the total protein content of HDL [20–22]. ApoA-I plays an important role in the biogenesis and function of HDL [6]; it is involved in the interaction with

cellular receptors, activation of LCAT, while it is responsible for HDL's multiple anti-atherogenic activities [23].

ApoA-II is the second most abundant protein component of HDL and accounts for approximately 15 - 20 % of the total HDL protein, while almost half of the HDL particles may contain apoA-II [24]. ApoA-II is predominantly synthesized in the liver and intestine [25], while being more hydrophobic compared to apoA-I, it circulates as a homodimer, which is comprised of two identical polypeptide chains connected by a disulfide bridge [26–28].

ApoCs comprise a family of small exchangeable apolipoproteins, which are primarily synthesised by the liver. ApoC-I is the smallest apolipoprotein of this family and associates both with HDL and VLDL, while it is involved in the activation of LCAT and the inhibition of CETP and hepatic lipase. ApoC-II is also associated both with HDL and VLDL and is able to activate several triacylglycerol lipases. ApoC-III is present within the HDL and VLDL particles, while it has the ability to inhibit hepatic lipase and lipoprotein lipase [23].

ApoE comprises a key functional and structural HDL glycoprotein component, although its content in HDL is much lower in comparison to apoA-I [29]. It is synthesised in multiple cell types and tissues such as macrophages, endocrine tissues, the liver and the central nervous system [23]. ApoE contains eight amphipathic alpha-helical repeats and displays detergent-like properties towards phospholipids [30].

SAA exists in two different forms, SAA1 and SAA2, resembling approximately 93 % sequence homology [23]. SAA comprises a highly conserved, acute phase protein, predominantly synthesised by the liver. Concentrations of SAA in serum can increase up to 1000-fold of the basal levels during acute inflammation [31–33]. Under these conditions SAA displaces apoA-I in HDL, thus becoming a major apolipoprotein component of circulating HDL [32, 34, 35].

CETP is primarily expressed by the liver and adipose tissue, while in the circulation it shuttles between HDL and apoB-containing lipoproteins. CETP is responsible for the bidirectional transfer of cholesteryl esters and triglycerides between HDL and apoB-containing lipoproteins including VLDL and LDL [36].

Other less abundant HDL-associated proteins are apoC-IV, apoD, apoF, apoJ (clusterin), apoL-I, apoM and others [19].

1.1.3. HDL-associated lipids

Besides apoliproteins, more than 200 different lipid species have been identified in HDL particles [37, 38]. Both the structure and the dynamic properties of lipids are significantly dependent on their location in the HDL particle (core, intermediate region, or surface) [39]. Specifically, phospholipids (mainly glycerophospholipids), lyso-phospholipids [40, 41] such as lyso-phosphatidylcholines [42], sphingolipids such as sphingolmyelin and sphingosine-1-phosphate (S1P) [43–45], and free cholesterol are found on the surface of HDL particles, while the hydrophobic core consists of triglycerides and cholesteryl esters [40].

Phospholipids account for approximately 37 - 49 mol % of total lipids in the HDL particle [23]. Phosphatidylcholine, lyso-phosphatidylcholines, sphingolipids and plasmalogens are the most abundant phospholipids in HDL particles, while other less frequent phospholipids are phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine and others [23]. Specifically, phosphatidylcholine is the principal plasma phospholipid (32 - 35 mol % of total HDL lipids), and its distribution is even across all HDL subpopulations [37]. Lyso-phosphatidylcholine is another important phospholipid accounting for 1.4 - 8.1 mol % of total HDL lipids. It is generated as a result of the regulated degradation of phosphatidylcholine by phospholipases, or as a result of the LCAT activity, which is consistent with the preferential association of LCAT with HDL particles [46]. Specifically, LCAT has been reported to associate particularly with the smaller, more-dense HDL particles. The latter HDL particles are enriched with lyso-phosphatidylcholine by two fold approximately, as compared to larger, more-light HDL particles [47]. Circulating lyso-phosphatidylcholines are intensively studied in the context of inflammation, carried mainly by albumin and to a lesser extent by HDL. Lyso-phosphatidylcholine concentration can increase dramatically in inflammatory states [48, 49]. Specifically, the hydrolytic action of lipoprotein-associated phospholipase A2 (Lp-PLA2) on oxidized phosphatidylcholine or secreted phospholipases A2 during inflammation leads to the formation of lyso-phosphatidylcholine, which comprises a biomarker of inflammation. Consequently, lyso-phosphatidylcholines are widely regarded as potent pro-inflammatory and harmful mediators; however increasing evidence of more recent studies shows anti-inflammatory properties under various pathological conditions [49–51].

Sphingolipids account for approximately 5 - 7 mol % of total lipids in circulating HDL particles [23]. The most abundant of the sphingolipid family is sphingomyelin (5.6 - 6.6 mol

% of total HDL lipids) [37, 47, 52], a structural lipid originating from triacylglyceride-rich lipoproteins and only to a minor extent from nascent HDL [53], which enhances surface lipid rigidity [54, 55]. S1P is a potent bioactive lyso-sphingolipid that is generated by sphingosine phosphorylation via the the sphingosine kinase (SPHK) [56]. In plasma, approximately 65 - 80 % of S1P is associated with HDL and is mainly bound to apoM. Specifically, S1P associates preferentially with smaller, more-dense HDL particles compared to larger, more-light HDLs [46]. HDL-associated S1P is less susceptible to degradation than S1P bound to albumin or free S1P, which suggests an important role of HDL in the uptake, systemic function as well as cellular degradation of S1P. Importantly, S1P was shown to have a central protective role in the pathogenesis of a many of inflammatory disorders, such as rheumatoid arthritis, asthma and atherosclerosis, via macrophage function [57] and endothelial barrier function [58–61] modulation. S1P is also associated with signals for immune cell activation and differentiation including cytoskeletal reorganization, chemotaxis and mobilization of calcium [62].

Free (unesterified) sterols, dominated by cholesterol, are located on the surface of the HDL lipid monolayer (8 - 13 mol % of total lipids) and are responsible for fluidity regulation [23]. Specifically, free cholesterol present in HDL particles reflects the key role of these particles in cholesterol transport throughout the body. Other less abundant sterols present in lipoproteins are oxysterols, estrogens, lathosterol, phytosterols and ergosterol [63].

Cholesteryl esters contribute up to approximately 36 mol % of total HDL lipid content, which along with triglycerides are located in the hydrophobic core of HDL particles. Cholesteryl esters are mainly formed in plasma HDL as a result of the LCAT activity, which catalyses the transesterification of phospholipids and free cholesterol [37, 47, 52].

HDL-associated triglycerides represent approximately 3 mol % of total HDL lipids [37, 46, 47, 52, 64]. The most dominant triglyceride species in HDL are the ones containing linoleic, oleic and palmitic acid moieties [23], while triglyceride species profile is conserved between the HDL2 and HDL3 particles [64].

1.1.4. HDL-associated enzymes

The main HDL-associated enzymes include paraoxonases, LCAT and platelet-activating factor acetyl hydrolase (PAF-AH).

Human paraoxonase 1 (PON1), paraoxonase 2 (PON2) and paraoxonase 3 (PON3) comprise the paraoxonase family of enzymes, which are calcium-dependent lactonases [65]. Among these, PON1 and PON3 are mainly associated with HDL, exhibiting paraoxonase, esterase and lactonase activities [66]. PON1 is largely synthesized in the liver, as well as in the colon and kidney [67] and it protects both HDL and LDL against oxidation. Moreover, PON1 enhances the reverse cholesterol transport by facilitating the binding of HDL particles to macrophages, while it is responsible for the reduction of aortic and macrophage oxidative status associated with decreased syperoxide anion production [68–71]. PON3 is predominantly expressed in the liver and possesses properties similar to PON1, displaying potent lactonase activity, however limited arylesterase and no paraoxonase activities [23].

LCAT is an HDL-associated enzyme responsible for the esterification of free cholesterol to cholesteryl esters [72]. LCAT is primarily expressed in the liver, while in plasma approximately 75 % of the enzyme is associated with HDL [23].

PLTP is synthesised in the liver, kidney, pancreas, placenta, heart, lung, brain and skeletal muscle, while in the circulation it is primarily associated with HDL [23]. PLTP plays a role in extracellular phospholipid transport and can bind lipopolysaccharide, while it is responsible for the conversion of HDL into larger and smaller particles [10, 11], mediating the phospholipid transfer among lipoproteins [73]. Moreover, PLTP has been reported to contribute to the anti-oxidative capacity of HDL [17].

PAF-AH, also known as Lp-PLA2, is an HDL-associated enzyme that is responsible for the cleavage of platelet-activating factor (PAF) via hydrolysis of the sn-2 ester bond, yielding biologically inactive lyso-PAF [74]. PAF-AH cleaves phospholipid substrates bearing a short residue at the sn-2 position and is therefore able to hydrolyse pro-inflammatory oxidized short-chain phospholipids [75, 76]. The majority of plasma PAF-AH in the circulation is bound to LDL, specifically to small, dense LDL and to lipoprotein (a) [77], however approximately 30 % is also associated with HDL [78].

1.2. HDL function

HDL possesses several functions mainly attributing to its anti-atherogenic activities including anti-oxidative, anti-inflammatory, anti-thrombotic, anti-infectious and vasodilatory activities, as well as the ability to mediate cholesterol efflux from cells [79, 80].

1.2.1. Cholesterol efflux capacity of HDL

Foam cells are formed as a result of lipid accumulation within macrophages, which comprises a main feature of atherogenesis [81]. In order to counteract this process, cells have developed strategies such as the release of excess cholesterol to extracellular lipid acceptors. Specifically, cholesterol efflux from arterial wall macrophages and peripheral cells to plasma HDLs comprises an important anti-atherosclerotic mechanism and is the first step of the reverse cholesterol transport [82]. The process of efflux involves cholesterol localized on the cellular plasma membrane, which may derive from intracellular sites including the Golgi apparatus and the late endosomal/lysosomal compartment. Specifically, cholesterol in endosomes and lysosomes derives from lipoprotein uptake and undergoes hydrolysation by acid hydrolase; while cholesterol localized in the endoplasmic reticulum originates from endogenous synthesis and can be delivered to intracellular organelles via a non-vesicular pathway that involves protein carriers [83]. The lipoprotein-derived cholesterol is rapidly released into the cytoplasm and delivered throughout the cells [84]. Under physiological conditions, the intracellular cholesterol content is rather low (about 20 %), since most of it is transferred to the plasma membrane. There, it establishes a dynamic equilibrium with the endoplasmic reticulum and the Golgi system pools [85]. The plasma membrane bilayer contains distinct lipid environments of steady state equilibrium. Lipid rafts are characterized by a liquid-ordered state, which is tightly packed. In lipid rafts cholesterol associates with caveolin and sphingolipids, a fact that plays a crucial role in cell signalling, while a few studies utilizing macrophages demonstrated that the major mechanisms of cholesterol efflux are independent of lipid rafts [86]. The non-raft membrane microdomains are the principal source of cholesterol available for interaction/efflux with extracellular acceptors including the ABCA1 transporter [87, 88]. Moreover, the reverse cholesterol transport pathway can also be triggered from extracellular matrix-associated cholesterol microdomains, the formation of which is mediated by the ABCG1 transporter [89].

Several mechanisms are responsible for cholesterol efflux including passive diffusion according to cholesterol gradient concentration, as well as active pathways including a unidirectional ATP-dependent pathway mediated by the ABCG1 transporter, a unidirectional ATP-dependent pathway mediated by the ABCA1 transporter and a bidirectional pathway involving SR-BI [80, 90]. The efficacy of different HDL subpopulations in promoting

cholesterol efflux via the aforementioned receptor-mediated pathways is dependent on the specific receptors involved. Specifically, lipid-free and/or poorly lipidated apoA-I potently and dose-dependently induces the efflux of cholesterol via interaction with the ABCA1 transporter. In addition to lipid-free/lipid-poor apoA-I, small discoid reconstituted HDL particles of 7.8 nm diameter resembling plasma pre-β1 HDL can efficiently efflux cellular cholesterol via the ABCA1 transporter [91]. Importantly, small HDL particles play a major role in cellular cholesterol efflux, along with the ability of ABCA1 to account for the greater part of macrophage cholesterol efflux in comparison to other HDL receptors [90, 92]. This profound capacity of small HDL particles to affect cellular cholesterol efflux can be accounted for by distinctly high surface lipid fluidity and relative low lipid content. This can induce conformational changes in apoA-I relative to light, large HDL, resulting in increased capacity to acquire large phospholipid amounts, enhanced exposure to the aqueous phase, as well as enhancement of the activity of LCAT [93, 94]. Along with the major role of small HDL and ABCA1 in mediating cellular cholesterol efflux, SR-BI and ABCG1 mediated cholesterol efflux to large HDL particles contributes significantly to the net cholesterol efflux. Specifically, large, lipid-rich HDL particles comprise a more efficient ligand for the SR-BI mediated cholesteryl ester cellular uptake in comparison to small, lipid-poor HDL, which is consistent with the role of these particles in reverse cholesterol transport [95]. SR-BI-mediated cholesterol efflux to large HDL2 particles is greater compared to that to small HDL3 particles. This can be attributed to the higher phospholipid content of larger HDL particles, which results in greater lipid surface [95]. Moreover, ABCG1 efficiently transports sterols, such as 7-ketocholesterol and cholesterol, to mature α-HDL particles [95]. In a similar manner, large, lipid-rich HDLs of a diameter of 9.6 mm or greater potently promote the ABCG1-mediated cholesterol efflux [91]. Different HDL subclasses comprise similarly effective acceptors via the receptor-dependent pathway of passive diffusion [95]. To summarize, on the basis of particle number, large, lipid-rich HDL particles are more effective in promoting cholesterol efflux, whereas on the basis of phospholipid content, small, dense HDL particles are more potent in promoting cholesterol efflux [96, 97].

1.2.2. Anti-oxidative capacity of HDL

HDL can potently protect LDL and other lipoproteins from oxidative stress induced by one-electron and two-electron species. Specifically, HDL particles are able to protect both protein

and lipid moieties of LDL from free radical-induced oxidation, via inhibition of the accumulation of primary and secondary oxidation products [98]. A non-uniform distribution of lipids, apolipoproteins as well as enzymes across the HDL particle seems to underlie this observation. Small, protein-rich, dense HDL particles are potent protectors of LDL oxidation by inactivation of lipid hydroperoxides, which comprise primary products of LDL lipid peroxidation [93]. Consequently, accumulation of products of secondary lipid peroxidation including short-chain oxidised phospholipids and aldehydes is potently inhibited by small, dense HDL3 particles [93]. Since aldehydes are able to interact with amino acid residues of apoB to form protein adducts, covalent LDL protein moiety oxidation is also potently hindered by HDL3 [93]. In addition to this, another study indicated that small, dense HDL3 particles are more resistant to oxidative modification in comparison to large, light HDL2 particles [99]. Via a two-step mechanism involving the initial transfer of phospholipid hydroperoxides from LDL to HDL, HDL is able to protect LDL from one-electron oxidants causing oxidative damage. This process is governed by the HDL surface monolayer rigidity and subsequently by the reduction of phospholipid hydroperoxide by redox-active apoA-I methionine residues, leading to the formation of redox-inactive phospholipid hydroxides [98, 100], a process that is more efficient in HDL3 compared to HDL2 particles [100]. Specifically, the diminished content of free cholesterol and sphingomyelin present in small, dense HDL particles [46] results in increased surface lipid monolayer fluidity, thus facilitating the incorporation of oxidised lipids including those derived from LDL oxidation [98]. Moreover, small, dense HDL3 particles are relatively enriched in apoA-I [46].

In addition, enzymatic components that potentially contribute to the anti-oxidative HDL properties via hydrolysis of oxidised phospholipids include PAF-AH, LCAT and PON1 [79], although they are weakly reactive towards lipid hydroperoxides [101–103]. Hydrolysis of short-chain oxidised phospholipids by HDL-associated hydrolytic enzymes appears to be enhanced in small, dense HDL3 particles and enrichment of enzymatic activities of PAF-AH, LCAT and PON1 in HDL3 could account for this effect [6]. The major activity of HDL-associated PON1 is that of a calcium-dependent lactonase, rather than a peroxidase [104], since its affinity for lactones is much higher compared to that for lipid hydroperoxides [105]. On the other hand, LCAT and PAF-AH show potent activity in hydrolysing phospholipid hydroperoxides generated during lipoprotein oxidation [101, 102]. Irrespective of the enzyme

involved, hydrolysis of phospholipid hydroperoxides leads to the release of lyso-phosphatidylcholine and a free fatty acid hydroperoxide [105].

1.2.3. Anti-inflammatory potential of HDL

HDL particles display potent anti-inflammatory properties. Specifically, HDLs are able to inhibit monocyte and neutrophil activation and subsequent pro-inflammatory chemokine and cytokine production and infiltration in the arterial wall. Additionally, HDL particles potently inhibit the adhesion of monocytes to the endothelium as well as the expression of cytokine-induced adhesion molecules in endothelial cells [106, 107]. Specifically, HDL inhibits endothelial cell adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin, which are responsible for the binding of monocytes at sites of developing atherosclerosis [108]. The pathway of ABCA1-mediated and ABCG1-mediated cellular lipid efflux appears to be involved in the inhibitory actions of HDL towards monocytes and endothelial cells [106]. Other anti-inflammatory HDL properties may involve the hydrolysis of pro-inflammatory oxidised lipids by the HDL-associated enzymes PON1 and PAF-AH, which is mechanistically similar to the roles of these enzymes in the anti-oxidative activities of HDL [93, 98]. ApoA-I appears to mediate many anti-inflammatory HDL activities, while phospholipids including sphingosylphosphorylcholine, saturated lyso-phosphatidylcholines and S1P also show potent anti-inflammatory activities [51, 109]. HDL particle heterogeneity appears also to affect the anti-inflammatory potential of HDL. Specifically, small, dense, protein-rich HDL3 particles have been reported to be superior in comparison to large, light, lipid-rich HDL2 particles in inhibiting VCAM-1 expression in endothelial cells [110], which is consistent with the potent anti-oxidant activity of small, dense HDL3 particles [98]. These distinct anti-inflammatory properties of HDL3 and HDL2 particles can be related to differences in their phospholipid composition, rather than differences in their proteome [6, 110].

1.3. HDL in allergy and inflammatory skin diseases

The skin, one of the largest immunologic organs in our bodies, often comprises a target for immunologic and allergic responses [111]. Specifically, atopic dermatitis, contact dermatitis, psoriasis, angioedema, urticaria and others comprise immune-mediated skin diseases that are very common nowadays [111]. Genetic as well as environmental factors are responsible for

these diseases, the majority of which is of inflammatory and chronic nature [111]. A lot of skin disorders are known over the years to be associated with dyslipidemia, while some of the dermatological therapies applied are also known to predispose to abnormalities in lipid levels [112]. In recent decades, the prevalence of allergic diseases has increased dramatically, a fact that is associated to changes in lifestyle practices and environmental exposures [113]. Although strong evidence suggests that HDL particles potently influence the activity of a plethora of immune cells, such as neutrophils, eosinophils, monocytes and macrophages [40, 114], the exact role of HDL in allergic diseases is only poorly understood [115]. In most species, HDL is quantitatively the most important lipoprotein, while mechanistic evidence points towards a role of HDL particles in physiological immune response [116]. Importantly, low levels of HDL-cholesterol have been associated with increased risk of autoimmune disease in the general population [117]. Taking these into consideration, the potential role of HDL in other diseases, such as allergic diseases and infections, has gained much attention over the recent decades.

1.3.1. Psoriasis and HDL

Psoriasis is a common, chronic, inflammatory skin disease that is equally prevalent in both sexes [118] and affects approximately 2-3 % of the population in westernized countries [119]. A few studies so far have demonstrated that HDL derived from psoriasis patients shows compositional alterations associated with impaired HDL-cholesterol efflux capacity [120, 121]; however the effects of biologic agents on HDL function remain poorly investigated. Characteristics of psoriasis include the appearance of red scaly plaques, which are predominately present on the scalp, the umbilical region, the perianal and over the elbows and knees; however they may affect any part of the body [119]. The pathogenesis of the disease is complex and involves the activation of plasmacytoid dendritic cells by epidermal antigens as a result of skin trauma [122], followed by myeloid dendritic cell maturation, which promote thereafter T cell differentiation into T helper 1 (Th1) and T helper 17 (Th17) cells via interleukin (IL) 6, IL-12 and IL-23 secretion [123]. Moreover, activated keratinocytes produce a plethora of pro-inflammatory chemokines and cytokines, which are responsible for the recruitment of inflammatory cells from the circulation, ultimately leading to a “vicious cycle” of excessive immune response [124]. Importantly, psoriasis has been associated with

systemic metabolic disorders including cardiovascular disease, obesity as well as an increased diabetes prevalence [125] and dyslipidemia [126, 127].

Current treatment options for psoriasis include topicals, such as agents including vitamin A, synthetic vitamin D3 and anthralin, and corticosteroids; phototherapy including broad and narrowband-ultraviolet B, laser ultraviolet B and psoralen and ultraviolet A; systemics including cyclosporine, methotrexate and acitretin; and finally biologic therapeutics which target IL-17, IL-23p40 or tumor necrosis factor alpha (TNF-α) [128].

1.3.2. HDL in allergic rhinitis

Allergic rhinitis is an immunoglobulin E (IgE) mediated disease affecting both children and adults [129]. It is characterized by nasal congestion, rhinorrhea (nasal discharge), nasal itching and sneezing [130] and affects approximately one in every four individuals in westernized countries [129]. Allergic rhinitis comprises a global health problem that leads to major burden and disability worldwide; it contributes to unproductive or missed time at work and sleep problems [131], while in children it leads to decreased involvement in outdoor activities [132]. Allergic rhinitis comprises a disorder affecting the nose that is predominantly caused by environmental allergen exposure in genetically predisposed individuals [129, 133]. Common allergens are mainly proteins and glycoproteins found in airborne particles, such as grass pollinosis, ragweed and dust mite, while allergens vary greatly in different parts of the world.

The pathophysiology of allergic rhinitis is complex, comprising an early- and a late-phase allergic response [134]. The process is triggered by exposure to several common aeroallergens, such as pollen, mites and/or animal dander, that are recognised by antigen-specific IgE receptors on basophils and mast cells of pre-sensitised individuals [134]. The early-phase allergic response is characterized by degranulation of mast cells and is associated with the onset of acute nasal and ocular symptoms, including itching, sneezing, nasal blockage and rhinorrhea, within minutes [134–136]. Histamine release by mast cells in the nasal mucosa is responsible for these symptoms, while the effects of other pro-inflammatory mediators including leukotrienes, prostaglandins and kinins also increase vascular permeability leading to the formation of edema [134–136]. The late-phase allergic response is dependent on allergen dose and patient susceptibility, falling in peak after a period of hours, and is characterized predominantly by nasal blockage and to a lesser extent by watery

discharge [129]. During the late-phase response neutrophils, basophils, monocytes, eosinophils and T-cells are recruited, while multiple mediators are being released, such as cytokines, leukotrienes and prostaglandins [137–140]. This late-phase inflammatory reaction is associated with further tissue edema, tissue remodeling and the development and perpetuation of nasal congestion [141, 142]. These late-phase reactions and modifications in tissue responsiveness contribute to bronchial hyper-responsiveness [134].

Importantly, recent studies suggested that allergic rhinitis is associated not only with alterations in HDL-cholesterol levels, but also with alterations in the composition of HDL. Specifically, an increase in both of the major HDL apolipoproteins, apoA-I and apoA-II, in the mucus proteome of allergic rhinitis patients was reported [143–145], while apoA-I levels were also increased in the nasal lavage fluids of subjects with persulfate-associated rhinitis following challenge with potassium persulfate [146]. In addition to this, specific IgE levels of house dust mite were reported to be associated with reduced HDL-cholesterol [147] and reduced myocardial infarction odds [148]. However, the potential role of HDL particles in allergic rhinitis remains poorly investigated and no evidence is available on the HDL particle functionality in allergic rhinitis patients.

2. RESULTS

The results section is a short summary of the following scientific publications:

1. Trakaki A, Sturm G J, Pregartner G, Scharnagl H, Eichmann T O, Trieb M, Knuplez E, Holzer M, Stadler J T, Heinemann A, Sturm E M, Marsche G **Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function.** Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 2019 Oct; 1864(10): 1280-1292.
2. Trakaki A, Wolf P, Weger W, Eichmann T O, Scharnagl H, Stadler J T, Salmhofer W, Knuplez E, Holzer M, Marsche G **Biological anti-psoriatic therapy profoundly affects high-density lipoprotein function.** Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 2021 Jul; 1866(7): 158943.
3. Trakaki A and Marsche G **High-Density Lipoprotein (HDL) in Allergy and Skin Diseases: Focus on Immunomodulating Functions.** Biomedicines. 2020 Dec 1; 8(12): 558.
4. Trakaki A and Marsche G **Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins.** Biomedicines. 2021 May 21; 9(6): 587.

Ad 1.) The aim of my first project was to assess whether HDL derived from allergic rhinitis patients displays altered protein and lipid composition, associated with altered HDL functional properties. We used biochemical analyses, mass spectrometry and various cell-based assays in order to assess alterations in HDL composition, particle distribution and function, utilizing both apoB-depleted serum and isolated HDL from 43 allergic rhinitis patients and 20 healthy controls. Importantly, we observed decreased anti-inflammatory and anti-oxidative properties of apoB-depleted serum and HDL derived from allergic rhinitis patients, but an improved ability of suppressing eosinophil effector responses, upon eotaxin-2/CCL24 stimulation, including shape change and chemotaxis. The impaired anti-inflammatory potential of allergic rhinitis-derived HDL was accompanied with an impaired ability of suppressing pro-inflammatory cytokine secretion including IL-1β, IL-4, IL-6, IL-8 and TNF-α. Moreover, the HDL composition in terms of HDL-associated proteins and lipids, as well as the HDL particle distribution, were markedly altered in allergic rhinitis patients in comparison to controls. Specifically, HDL derived from allergic rhinitis patients had

significantly decreased content of apoA-I and phosphatidylcholine, but increased content of apoA-II, triglyceride and lyso-phosphatidylcholine in comparison to controls. Analysis of HDL subfractions revealed a decrease in HDL3 particles in allergic rhinitis patients in comparison to controls, but no change in HDL2 and small HDL3 particles. Through performing an in depth correlation analysis, we observed multiple and complex associations of allergic rhinitis-HDL composition and structure with allergic rhinitis-HDL function [149].

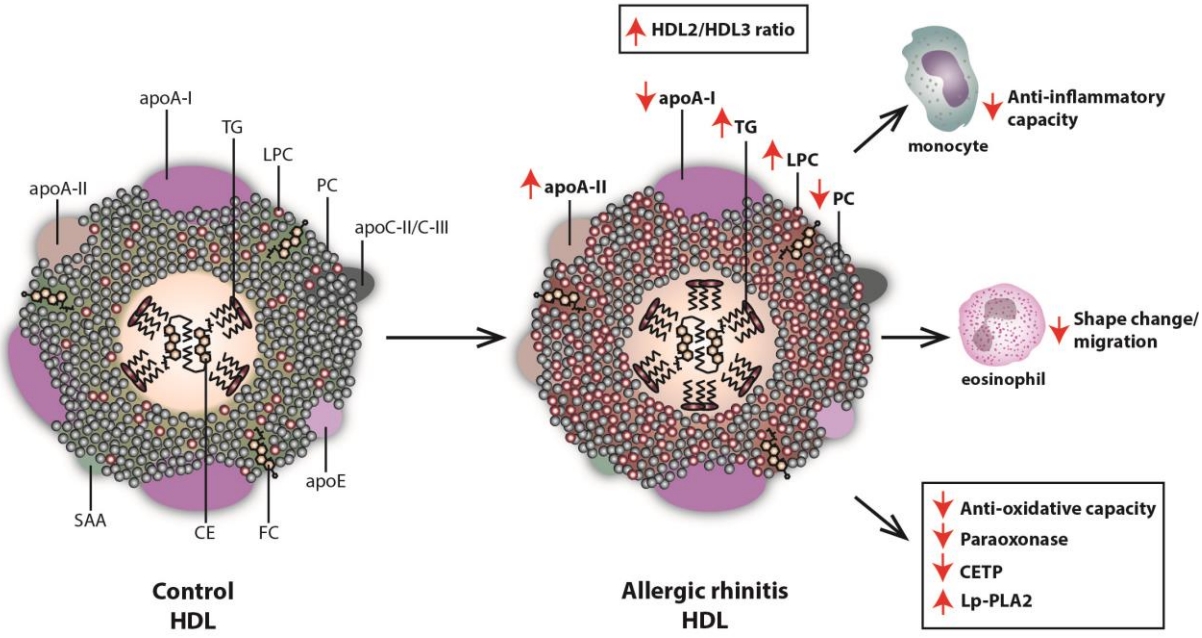

Figure 2: Graphical Abstract. Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function. *Abbreviations represent: apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FC, free cholesterol; HDL, high-density lipoprotein; LPC, lyso-phosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase A2; PC, phosphatidylcholine; SAA, serum amyloid A; TG, triglyceride. Image reproduced from Trakaki et al.* [149] *under creative commons licence CC-BY-NC-ND 4.0.*

Ad 2.) The aim of my second project was to assess whether short- and intermediate-term biologic anti-psoriatic therapy affects the composition and functional properties of HDL. Blood samples were taken from 27 real-world psoriasis patients at baseline (no therapy with biologics) and after short-term (3 to 6 months) and intermediate-term (1 to 2 years) biologic anti-psoriatic therapy and from 17 healthy volunteers. Biologic agents included anti-IL-12/23p40 (ustekinumab), anti-IL17A (secukinumab) or anti-TNF-α (etanercept or adalimumab) antibodies. We were able to demonstrate that metrics of HDL function including

cholesterol efflux capacity of apoB-depleted serum, paraoxonase and LCAT activities were impaired in psoriasis patients at baseline in comparison to healthy volunteers, while an increase in the intermediate HDL subclass was also observed. Surprisingly, we observed that short- and especially intermediate-term biologic anti-psoriatic therapy rendered HDL pro-inflammatory and significantly reduced the HDL-cholesterol efflux capacity, but on the other hand increased the LCAT and paraoxonase activities. Moreover, intermediate-term biologic anti-psoriatic therapy led to significantly impaired ABCA1-mediated cholesterol efflux capacity and anti-oxidative capacity of apoB-depleted serum, while a decrease of the large HDL subclass was also observed. Additionally, we observed alterations in the composition of HDL particles at intermediate-term therapy with biologics, including significantly increased HDL-associated apoA-II and phosphatidylcholine levels, but decreased free cholesterol levels, in comparison to baseline. All biologics caused similar changes in HDL composition, subclass distribution and cholesterol efflux capacity, suggesting that the observed effects are not attributed to the action of a specific drug [150].

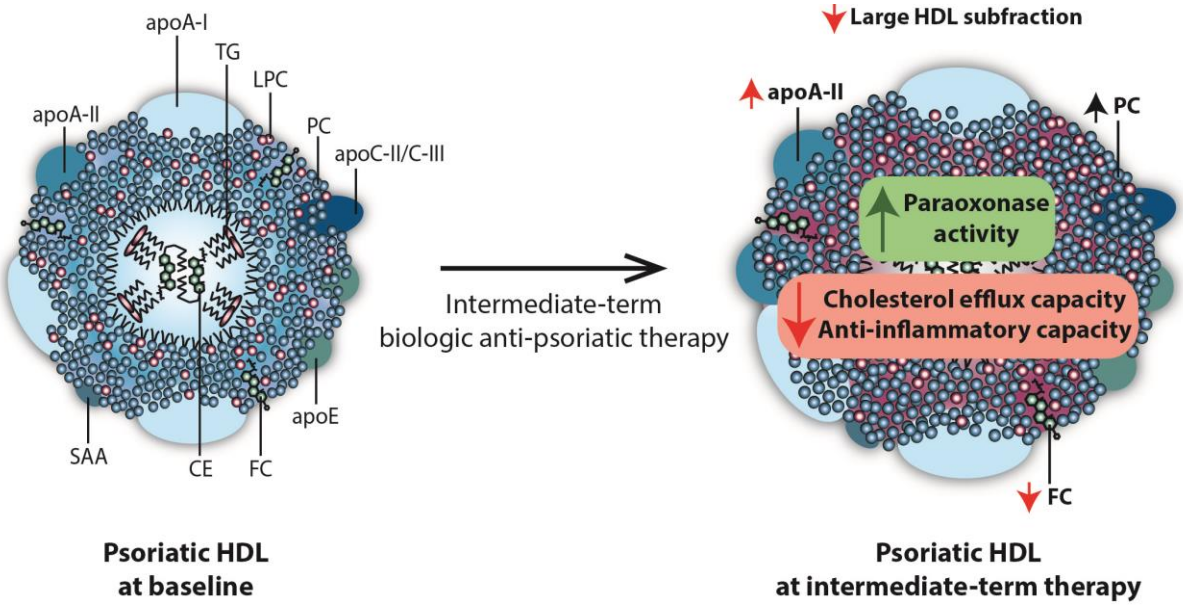

Figure 3: Graphical Abstract. Biological anti-psoriatic therapy profoundly affects high-density lipoprotein function. *Symbols represent: green rectangle/arrow, improved HDL functional property; red rectangle/arrow, impaired HDL functional properties; short black arrow, alteration in HDL particle composition; short red arrows, alterations in HDL particle composition/distribution linked with impaired HDL functionality. Abbreviations represent: apo, apolipoprotein; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; LPC, lyso-phosphatidylcholine; PC,*

phosphatidylcholine; SAA, serum amyloid A; TG, triglyceride. Image reproduced from Trakaki et al. [150] *under creative commons licence CC-BY 4.0.*

Ad 3.) As part of my thesis, I reviewed and evaluated literature regarding the newly identified changes in the composition, metabolism and function of HDL in allergic and inflammatory skin diseases including allergic asthma, allergic rhinitis, atopic dermatitis, psoriasis, urticaria and angioedema [151]. Recent studies provide evidence that allergies and skin diseases significantly affect the composition, metabolism and function of HDL, which in turn could have a significant impact on disease progression, but may also affect the risk for cardiovascular disease and infections. Interestingly, not only a loss in function, but also, sometimes, a gain in function of certain HDL properties is observed due to a specific pathological background [151]. Therefore, changes in the HDL functionality are at least partially explained by disease specific changes in the composition of HDL [151].

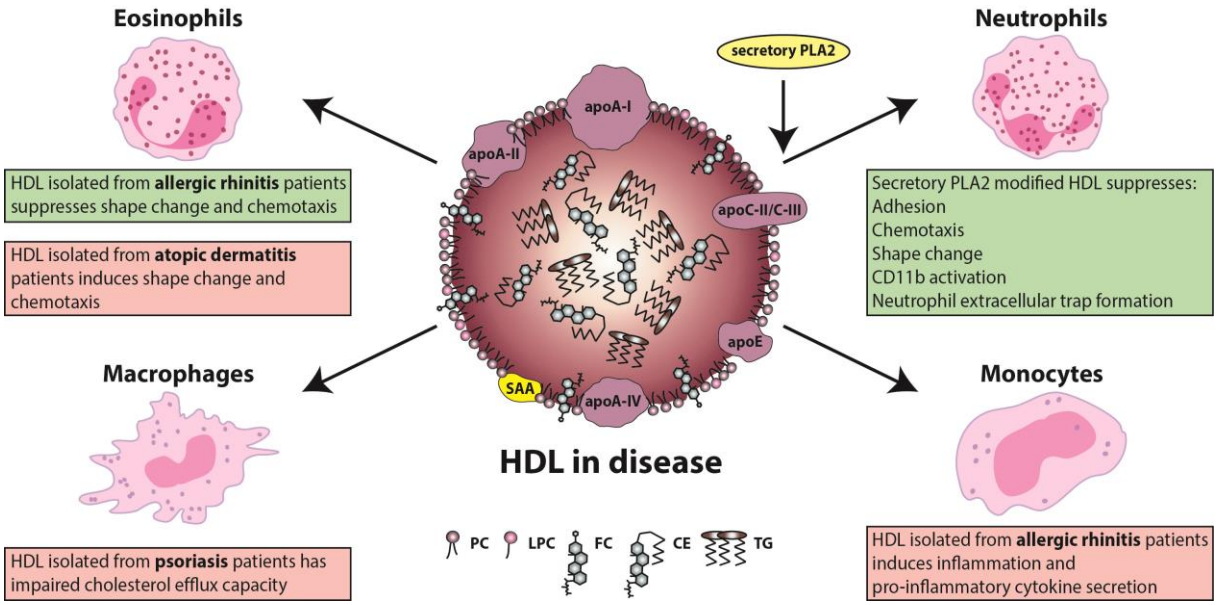

Figure 4: High-Density Lipoprotein (HDL) in Allergy and Skin Diseases: Focus on Immunomodulating Functions. *Abbreviations represent: apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoA-IV, apolipoprotein A-IV; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; CD, cluster of differentiation; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; LPC, lyso-phosphatidylcholine; PC, phosphatidylcholine; PLA2, phospholipase A2; SAA, serum amyloid A; TG, triglyceride. Rectangle shadings represent: green, beneficial effect of HDL; red, detrimental effect of HDL. Image reproduced from Trakaki et al.* [151] *under creative commons licence CC-BY 4.0.*

Ad 4.) Finally, I reviewed and evaluated the immune cell modulatory activities of HDL and HDL-associated components, including HDL-associated proteins, lipids and enzymes, as well as HDL mimetic peptides [152]. HDL composition, function as well as plasma levels have been associated with altered immune responses and accumulating evidence suggests an important modulatory ability of HDL particles and purified HDL-associated proteins and lipids in the activation state and function of immune cells [152]. Along with the long known anti-inflammatory role of HDL in inflammation and infections, HDL was recently proposed to have a role in allergy and atopic skin diseases. Specifically, alterations in the ability of HDL to modulate immune cell activation, apoptosis, chemotaxis, cell surface markers' expression and pro-inflammatory cytokine secretion have been observed. Such alterations could have a major impact on disease progression, affecting the risk for cardiovascular disease and infections. Several groups over the years have demonstrated important effects of HDL components on neutrophil, eosinophil, dendritic cell, monocyte and macrophage activation and function [152]. HDL mimetic peptides were also shown to have an effect in the activation status of several immune cells [152], and reconstituted forms of HDL have already been applied in clinical use to reduce cardiovascular risk or are being exploited to reduce inflammation in diseases such as type 2 diabetes and rheumatoid arthritis [153, 154]. HDL and its associated components appear to have a major impact on the modulation of the activation status of immune cells and various aspects of their function and comprise a promising tool for future therapeutic interventions [152].

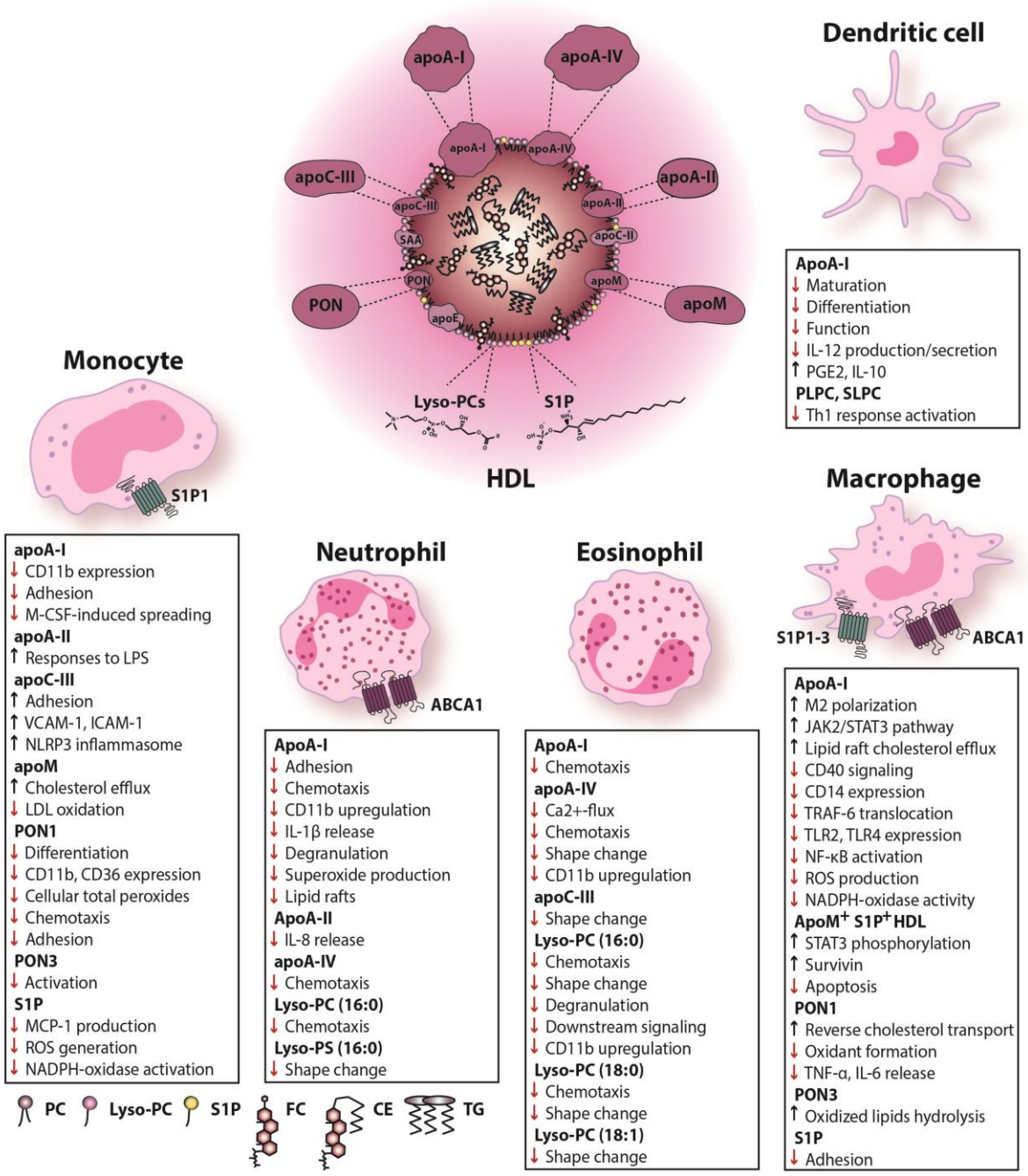

Figure 5: Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins. *Abbreviations represent: ABCA1, ATP-binding cassette subfamily A member 1; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoA-IV, apolipoprotein A-IV; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; apoM, apolipoprotein M; CD, cluster of differentiation; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; JAK2, Janus kinase 2; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; NADPH, nicotinamide adenine dinucleotide phosphate;*

NLRP3, nod-like receptor family pyrin domain-containing 3; PC, phosphatidylcholine; PGE2, prostaglandin E2; PLPC, 1-palmitoyl-2-linoleoyl-phosphatidylcholine; PON, paraoxonase; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; S1P1, sphingosine-1-phosphate receptor 1; S1P2, sphingosine-1-phosphate receptor 2; S1P3, sphingosine-1-phosphate receptor 3; SAA, serum amyloid A; SLPC, 1-stearoyl-2-linoleoyl-phosphatidylcholine; STAT3, signal transducer and activator of transcription 3; TG, triglyceride; Th1, T helper type 1; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α; TRAF-6, TNF receptor-associated factor 6; VCAM-1, vascular cell adhesion molecule 1. Image reproduced from Trakaki et al. [152] *under creative commons licence CC-BY 4.0.*

3. DISCUSSION

During my PhD, I examined how allergy and skin diseases, specifically allergic rhinitis and psoriasis, affect the composition and functional properties of HDL. I could demonstrate that allergic rhinitis is associated with marked changes in HDL subclass distribution and HDL-associated components, including apolipoproteins, lipids and enzymes, leading to marked changes in the functionality of HDL particles. Furthermore, I observed that psoriasis treatment with biologic therapeutics led to alterations in the HDL composition, subclass distribution and metabolism, associated with alterations in the functional properties of HDL. By reviewing current literature on HDL in allergic and skin diseases, along with the immune cell modulatory properties of HDL, I contributed two concise studies discussing the role of HDL and its immunomodulatory properties in allergies and inflammatory skin diseases. In summary, this dissertation elucidates the role of HDL in allergy and skin diseases and advances our understanding of the role of HDL in diseases, other than cardiovascular disease.

3.1. Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function (Biochim Biophys Acta - Mol Cell Biol Lipids. 2019 Oct; 1864(10): 1280-1292).

Allergic rhinitis is an IgE mediated disease that affects approximately one in every five individuals in the general population and is strongly linked to asthma and conjunctivitis [129, 155]. Despite the strong evidence that HDL particles modulate immune responses, the role of HDL in allergic rhinitis remains poorly investigated. The aim of this study was to assess whether allergic rhinitis has an effect on the composition and function of HDL [149].

In the beginning, the clinical characteristics of the study subjects were evaluated. We observed that allergic rhinitis patients had unaltered serum levels of triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and C-reactive protein in comparison to healthy controls. As expected, total IgE levels of allergic rhinitis patients were above the normal range for each subject, which was dependent on their age, whereas normal total IgE levels were observed in the control group [149]. Similarly, studies from different groups also reported unchanged triglyceride [156–158], total cholesterol [157] and LDL-cholesterol [157] levels in allergic rhinitis patients in comparison to controls, whereas other studies reported increased triglyceride [159], total cholesterol [156, 158, 159] and LDL-cholesterol [156, 158,

159] levels in allergic rhinitis patients. Regarding HDL-cholesterol levels, results coming from an earlier study reported increased levels in allergic rhinitis children [160], while more recent studies reported decreased [156] or unchanged [157–159] levels. In 2016, Vinding *et al.* reported that increased levels of HDL-cholesterol in children with allergic rhinitis or asthma were associated with a decreased risk of sensitization against aeroallergens [161]. Importantly, a recent study emphasized the prevalence of dyslipidemia in allergic rhinitis patients, reporting a relationship between dyslipidemia presence and sensitization to certain allergens [162]. Interestingly, we observed that allergic rhinitis-HDL-associated apoE was significantly associated with specific IgE levels of grass pollen, while weaker associations with allergic rhinitis-HDL-associated SAA, subclass distribution and metrics of allergic rhinitis-HDL function, including paraoxonase, Lp-PLA2 and cholesterol efflux activities, were also observed [149]. Associations of specific IgE levels of certain allergens with metrics of HDL composition were also observed in other studies; specifically, specific IgE levels of house dust mite were reported to be associated with reduced HDL-cholesterol [147] and reduced myocardial infarction odds [148].

It is known that alterations of lipid metabolism, inflammation, or activation of the innate immune system can modulate the composition of HDL [163]. However, there is little work addressing the possible consequences of allergy on HDL metabolism and HDL functionality. We hypothesized that HDL from subjects suffering from allergic rhinitis displays an altered protein and lipid composition associated with altered functional properties. We used mass spectrometry, biochemical analyses and various cell-based assays to assess alterations in the function of apoB-depleted serum and isolated HDL from allergic rhinitis patients. We observed that HDL derived from allergic rhinitis patients had significantly increased levels of apoA-II, but decreased levels of apoA-I, while no change was observed in HDL-associated apoC-II, apoC-III, apoE and SAA [149]. Other studies reported an increase in apoA-I and apoA-II in the mucus proteome of allergic rhinitis patients suggesting a direct modulation of the immune response by HDL-associated apolipoproteins [143–145]. Moreover, apoA-I levels were also increased in the nasal lavage fluids of subjects with persulfate-associated rhinitis following challenge with potassium persulfate [146]. In addition, although we did not evaluate HDL-associated apoA-IV in the present study, a recent study by Roula *et al.* reported decreased apoA-IV levels in allergic rhinitis patients in comparison to controls [164]. ApoA-IV comprises an endogenous anti-inflammatory protein that potently suppresses effector

functions of eosinophils [164]. Another study by Makino *et al.* showed that serum levels of apoA-IV were significantly increased in sublingual immunotherapy treated in comparison to placebo treated seasonal allergic rhinitis patients and that apoA-IV was negatively associated with the clinical symptom-medication and quality of life scores [165]. Therefore, apoA-IV could be a potential target molecule for the treatment of seasonal allergic rhinitis [165]. Moreover, in 2020 Chung *et al.* reported that apoE was up-regulated in nasal secretomes obtained from chronic rhinosinusitis patients [166], a condition frequently associated with allergic rhinitis [167], concluding that apoE could be a potential biomarker of nasal mucosal inflammation [166].

We next assessed potential alterations in HDL-associated lipids. We observed that patients'-derived HDL had significantly increased levels of triglycerides and lyso-phosphatidylcholine (species 16:0, 18:0, 18:1), but decreased levels of phosphatidylcholine, while no change was observed in HDL-associated free cholesterol, cholesteryl ester and sphingomyelin [149]. Interestingly, the triglyceride HDL content was strongly associated with HDL-associated apoC-III levels in allergic rhinitis patients [149], which is consistent with the fact that apoC-III delays the catabolism of triglyceride-rich particles [168]. Owing to these marked changes in the composition of HDL derived from allergic rhinitis patients, we were subsequently interested in evaluating whether HDL subclass distribution and functional properties were affected owing to the disease background.

A number of studies suggest that oxidative stress is an important mediator in the pathogenesis of allergic respiratory diseases including allergic rhinitis and asthma [169–171]. Specifically, although under physiological conditions a balance is maintained between reactive oxygen species and anti-oxidants, in allergic inflammation conditions production of reactive oxygen species from damaged cells or inflammatory reactions leads to an imbalance, which is characterized by more oxidative stress [172]. Elevated levels of reactive oxygen species induce a variety of pathological changes, highly relevant in airway and nasal mucosas, including increased airway reactivity, lipid peroxidation, increased nasal mucosal sensitivity and secretions, increased vascular permeability and production of chemoattractant molecules [173]. Therefore, we assessed whether allergic rhinitis affects the anti-oxidative capacity of apoB-depleted serum, via evaluating the ability of apoB-depleted serum to inhibit free radical-induced oxidation of the fluorescent dye dihydrorhodamine [174]. Interestingly, we observed that apoB-depleted sera of allergic rhinitis patients were less potent in inhibiting the

oxidation of dihydrorhodamine in comparison to sera from healthy controls [149]. In subsequent experiments, we evaluated whether allergic rhinitis affects the anti-inflammatory potential of apoB-depleted serum. For that purpose, we assessed the ability of apoB-depleted serum to modulate LPS-induced activation of the pro-inflammatory transcription factor nuclear factor-κB (NF-κB) in monocytes [174, 175]. We observed that the majority of apoB-depleted sera of controls potently inhibited NF-κB expression, while a significantly impaired inhibitory activity, which even exhibited a pro-inflammatory phenotype, was observed in sera of allergic rhinitis patients [149].

To demonstrate that the aforementioned effects in apoB depleted serum were directly caused by an altered HDL functionality, HDL was isolated from sera of controls and allergic rhinitis patients. Similar to apoB-depleted sera, HDL isolated from allergic rhinitis patients was less potent in inhibiting the oxidation of dihydrorhodamine and showed an impaired ability to suppress the expression of NF-κB in monocytes [149]. A significant association was observed between apoB-depleted sera and isolated HDL in terms of their ability to inhibit dihydrorhodamine oxidation and to suppress NF-κB expression [149]. Importantly, HDL derived from allergic rhinitis patients was less potent in suppressing monocyte cytokine secretion including TNF-α, IL-1β, IL-4, IL-6, IL-8 and IL-12p70 in comparison to HDL derived from healthy volunteers [149]. This loss of anti-inflammatory activity of HDL derived from allergic rhinitis patients may play a role in disease severity and progression during the late-phase response, as most of the aforementioned cytokines are involved in allergic inflammation. Specifically, IL-1β is implicated in different allergic disorders via inflammasome-dependent activation [176] and has been recently proposed as a potential biomarker for allergic rhinitis [177]. IL-4 is released by T helper 2 (Th2) cells and leads to eosinophil recruitment, activation and mucosal flux during the late-phase response [129], while it is the strongest regulatory factor mediating the production of IgE [178]. IL-6 is also a Th2-type cytokine and is involved in the proliferation and maturation of mast cells, as well as in the induction of IgE synthesis [179]. IL-8 induces the migration of leukocytes, a process involved in the late-phase allergic response [179]. Finally, TNF-α is a principal mediator of the acute inflammatory response including allergic rhinitis [180] and is released both from macrophages and mast cells through IgE-dependent mechanisms [181]. TNF-α is responsible for the activation of signaling pathways that regulate the cell surface expression adhesion molecules such as ICAM-1 of eosinophils and the release of eotaxin [182].

HDL particles carry important biologically active enzymes, such as paraoxonase, LCAT and Lp-PLA2 [72], which may be affected in allergic conditions. Therefore, we next wanted to assess, whether allergic rhinitis has an effect on HDL-associated enzymes. We observed that the activity of HDL-associated paraoxonase was significantly impaired in apoB-depleted sera of allergic rhinitis patients in comparison to controls [149]. Our results are in line with a previous study in allergic rhinitis children, where serum levels of paraoxonase were significantly decreased [183]. HDL-associated paraoxonase in an esterase with vascular protective activities [184], which can exert a protective effect against oxidative damage of circulating cells and lipoproteins [185], having endothelial protective [186] and anti-inflammatory activities [187]. Reactive oxygen species production by cells infiltrating the nasal mucosa is one of the main characteristics of the late-phase response in allergic rhinitis [183], therefore a defective anti-oxidative capacity of HDL in allergic rhinitis patients may lead to an impaired ability to counteract reactive oxygen species production in the nasal mucosa of patients.

Interestingly, we observed that the activity of HDL-associated Lp-PLA2 in PAF hydrolysis was increased in apoB-depleted sera derived from allergic rhinitis patients in comparison to controls [149]. Lp-PLA2 is responsible for the hydrolysis of short- and medium-chain phospholipids [188] and is thought to play a role in allergic rhinitis owing to its ability to hydrolyze PAF. PAF is a factor assumed to be involved in mucus secretion, since its levels were increased in nasal lavage of allergic rhinitis patients upon pollen nasal challenge [189] and is considered the strongest inducer of vascular permeability; therefore it plays a key role in nasal congestion and rhinorrhea [190, 191]. In addition, PAF may be responsible for airway hyperactivity or persisting airway inflammation [192] including activation of neutrophils and eosinophils to generate superoxide anions and to release granule constituents [193, 194]. However, a recent study reported a negative association between Lp-PLA2 activity and asthma severity score, specifically decreased enzyme activity was observed in severe asthmatics in comparison to non-severe asthmatics [195]. Therefore, our results suggest that decreased PAF levels owing to an improved Lp-PLA2 activity in allergic rhinitis patients might contribute to decrease allergic inflammation, although the effects might be dependent on the specific allergic disease background. This is in agreement with a recent review summarizing the beneficial effects of PAF blockage in allergic rhinitis symptoms [196]. In addition, Lp-PLA2 produces lyso-phosphatidylcholine via phospholipid hydrolysis [188],

therefore the increased activity of this enzyme could potentially contribute to lyso-phosphatidylcholine formation in HDL from allergic rhinitis patients.

Moreover, we assessed the LCAT and the CETP activities in sera of allergic rhinitis patients and controls. Although we observed no difference in the activity of LCAT, we were able to demonstrate a significantly impaired CETP activity in sera of allergic rhinitis patients in comparison to controls [149]. LCAT is secreted from the liver and catalyzes the transfer of fatty acids at position sn-2 of phosphatidylcholine to free cholesterol in plasma, which results in the formation of lyso-phosphatidylcholine and cholesteryl esters on the surface of LDL and HDL [197, 198], converting discoidal HDL into spherical HDL [199]. In addition, LCAT increases the size of HDL through conversion of HDL3 to HDL2, an important step during reverse cholesterol transport [199]. Surprisingly, the LCAT activity was negatively correlated with the lyso-phosphatidylcholine content of HDL derived from allergic rhinitis patients [149], although its established role in the formation of HDL-associated lyso-phosphatidylcholine. One possible explanation for this contra-intuitive finding could be that the LCAT activity can be inhibited by lyso-phosphatidylcholine [200]. CETP circulates in the plasma and is mainly bound to HDL [201], while it mediates the bidirectional transfer of cholesteryl esters and triglycerides between plasma lipoproteins [36]. An association between CETP activity and allergic rhinitis HDL content of triglyceride and lyso-phosphatidylcholine was observed, however no association was observed with HDL-cholesterol levels [149]. We currently have no clear explanation for this, and further studies are warranted to understand the underlying mechanisms.

We next evaluated the ability of apoB-depleted serum to remove cholesterol from cells, which comprises an important anti-atherogenic property of HDL [15]. No difference was observed in the cholesterol efflux capacity of apoB-depleted serum between allergic rhinitis patients and controls [149]; although a few studies have reported that the presence of allergic rhinitis is associated with decreased cardiovascular risk [202, 203].

Eosinophil-rich inflammation has long been associated with allergic inflammation and asthma. Eosinophils release lipid mediators, such as cysteinyl leukotrienes, which cause airflow obstruction and bronchial epithelial damage, and basic proteins that are cytotoxic [204]. Tissue accumulation of eosinophil granulocytes is a characteristic feature of allergic diseases [205, 206], and eosinophil infiltration plays a role in the induction and maintenance

of on-going allergic inflammation [207]. For that purpose, we next investigated whether apoB-depleted sera or isolated HDL of controls or allergic rhinitis patients could potentially have an effect on eosinophil activation and chemotaxis. Surprisingly, both apoB-depleted sera and isolated HDL of allergic rhinitis patients showed an improved ability to suppress eotaxin-2/CCL24-induced eosinophil activation, as was evaluated by the change in shape and chemotaxis in comparison to controls [149]. In addition, the abilities of apoB-depleted sera and isolated HDL to inhibit agonist-induced eosinophil effector responses were significantly correlated [149]. Moreover, the improved ability of allergic rhinitis-HDL in suppressing eosinophil activation was associated with apoA-II, apoC-III, phosphatidylcholine, lyso-phosphatidylcholine and triglyceride content of allergic rhinitis-HDL [149], supporting the notion that allergic rhinitis is associated with complex alterations in HDL composition and function, linked to gain or loss of functional properties. Recently, it was shown that HDL enriched in unsaturated lyso-phosphatidylcholine 16:0 effectively suppressed eosinophil effector responses [208]. HDL derived from allergic rhinitis patients is significantly enriched in lyso-phosphatidylcholine 16:0, therefore our data suggest that the specific lyso-phosphatidylcholine species contributes to the improved ability of allergic rhinitis-derived HDL to suppress eosinophil effector responses [149]. However, HDL isolated from atopic dermatitis patients showed impaired ability to suppress eosinophil effector responses [208], therefore compositional alterations in HDL particles due to a specific pathological background might be responsible for the observed effects.

Finally, we assessed whether allergic rhinitis affects HDL subclass distribution. We observed a decrease in the medium sized HDL3 subclass, while large HDL2 and small HDL3 subclasses were not altered [149]. By performing an in-depth correlation analysis, we observed that changes in the HDL3 subclass were associated with the impaired ability of allergic rhinitis-HDL to suppress monocyte cytokine secretion [149], which is consistent with the fact that HDL3 particles are superior to larger HDL2 particles in suppressing inflammatory responses [6]. Moreover, small, dense HDL3 particles are superior to large, light HDL2 particles in removing oxidized lipids from cell membranes and other lipoproteins [6], therefore our data suggest that a reduction in the HDL3 subclass could potentially contribute to the low anti-oxidative capacity observed in HDL of allergic rhinitis patients.

To summarize, we provide first evidence that allergic rhinitis influences HDL metabolism, affecting thereby HDL composition and functional properties, suggesting a novel link between allergy and HDL metabolism.

3.2. Biological anti-psoriatic therapy profoundly affects high-density lipoprotein function (Biochim Biophys Acta - Mol Cell Biol Lipids. 2021 Jul; 1866(7): 158943).

Psoriasis comprises a common chronic inflammatory skin disease associated with increased cardiovascular risk [118, 209]. One of the main treatment options to reduce systemic inflammation include biologic agents against diverse inflammatory cytokines such as targeting IL-17A [210], IL-12/23p40 [211] and TNF-α [212, 213]; however it has been demonstrated that biologics show both beneficial and adverse effects on the cardiovascular system [214]. A few studies so far have demonstrated that HDL derived from psoriasis patients shows compositional alterations associated with impaired HDL-cholesterol efflux capacity [120, 121]; however the effects of biologic agents on HDL function remain poorly investigated. Therefore, in the present study we aimed to elucidate whether short- and intermediate-term biologic anti-psoriatic therapy affects the composition and function of HDL [150].

In the beginning, we evaluated the clinical characteristics of the study cohort. We observed that in comparison to healthy controls, psoriasis patients at baseline had significantly decreased HDL-cholesterol levels and increased serum triglyceride levels, while no change was observed in total cholesterol and LDL-cholesterol between the two groups [150], although most studies reported increased LDL-cholesterol levels [215–217]. Other studies have also demonstrated decreased HDL-cholesterol levels in psoriasis patients in comparison to controls [120, 121, 126, 216, 218–241], while increased [127, 242–244] or unaltered [215, 217, 245–260] levels have also been reported. In agreement with our results, other groups have also reported increased serum triglyceride levels in psoriasis patients in comparison to healthy volunteers [127, 216, 217]. Moreover, patients at short- and intermediate-term biologic anti-psoriatic therapy showed unchanged serum levels of C-reactive protein, triglycerides, total cholesterol and HDL-cholesterol in comparison to baseline, while LDL-cholesterol was slightly decreased at intermediate-term therapy in comparison to baseline [150]. Our results are in line with previous studies in psoriasis patients under etanercept [261], ixekizumab [262], secukinumab [263] or other biologic treatments [264] reporting also no

treatment-associated effects on HDL-cholesterol levels. However, other studies in psoriasis patients under topical, systemic or biologic therapeutics reported an association of the specific psoriasis therapeutic intervention with an increase [265–271] or a decrease [227, 272, 273] in the levels of HDL-cholesterol. These contradictory results regarding the levels of HDL-cholesterol in psoriasis patients under therapy might not only be dependent on the duration of the treatment but also on the specific pharmacological agent.

The composition of HDL has been shown to be altered in psoriasis patients. Specifically, in psoriasis patients under topical and/or systemic treatment, it was demonstrated that the HDL content of apoA-I, total cholesterol, free cholesterol, cholesteryl esters, sphingomyelin and phosphatidylcholine was significantly decreased, while levels of apoA-II and acute-phase proteins, including α-1-antitrypsin and SAA, were significantly increased in comparison to controls [120]. In addition, other studies reported increased [242, 243], decreased [126, 224, 227], or unchanged [217, 232, 239, 246, 249, 253] apoA-I levels in psoriasis patients in comparison to healthy controls. Therefore, in subsequent steps we were interested whether biologic anti-psoriatic therapy alters the composition of HDL in terms of HDL-associated proteins and lipids. Interestingly, we observed complex alterations in the HDL composition. Specifically, although no change in HDL's main protein component, apoA-I, was observed, HDL-associated apoA-II was significantly increased at intermediate-term therapy [150]. Moreover, HDL-associated apoC-III was increased, while HDL-associated apoE was decreased at short-term therapy in comparison to baseline. Regarding the lipid content of HDL, we observed an increase in HDL-associated phosphatidylcholine and a decrease in HDL-associated free cholesterol at intermediate-term therapy in comparison to baseline [150]. Levels of apoC-II, SAA, total phospholipids, cholesteryl esters, triglycerides, lyso-phosphatidylcholine and sphingomyelin did not change during biologic anti-psoriatic therapy [150]. Importantly, we observed that the aforementioned alterations in HDL composition were not driven by the action of a specific biologic agent, since all biologics induced similar effects [150].

After observing alterations in the composition of HDL, it was reasonable to investigate whether the HDL subclass distribution was also affected, since the composition along with the subclass distribution of HDL particles strongly determines its functional properties, including the anti-atherogenic properties [23]. In comparison to healthy controls, psoriasis patients at baseline showed significantly increased intermediate HDL subclass, although no change was

observed in the large and the small HDL subclasses [150]. However, Tom *et al.* reported a decrease in the large HDL subclass in pediatric psoriasis patients in comparison to controls, yet no change in the small or medium HDL subclasses was observed [253], while Yu *et al.* demonstrated an increase in the small HDL subclass in psoriasis patients associated with aortic inflammation [237]. Importantly, we observed that intermediate-term biologic anti-psoriatic therapy led to a significant reduction in the large HDL subclass in comparison to baseline, while only a trend towards an increase in the small HDL subclass was observed [150]. No change was observed in the intermediate HDL subclass during therapy [150]. However, a previous study in psoriasis patients under topical and/or systemic therapeutics reported opposing results; specifically the large HDL subclass of psoriasis patients under treatment was significantly increased in comparison to baseline [236]. Moreover, another study reported an increase in the HDL-particle number after phototherapy treatment of psoriasis patients in comparison to baseline levels, as well as a significant reduction of the HDL-particle number in psoriasis patients treated with adalimumab (anti-TNF-α antibody) [274]. Along with this, another study in psoriasis patients under tofacitinib (an oral janus kinase inhibitor) treatment reported a striking increase in total HDL particles accompanied with an increase in the small HDL subclass in comparison to baseline measurements [265].

The marked changes observed in the HDL proteome and lipidome as well as in HDL particle distribution after biologic anti-psoriatic therapy led us to investigate further whether major functional properties of HDL were also affected during therapy. HDL-mediated protection against atherosclerosis is assumed to be of pleiotropic nature and the ability of HDL to promote reverse cholesterol transport is thought to play a key role. Cholesterol efflux capacity of HDL is inversely associated with cardiovascular mortality independently of HDL-cholesterol levels and other risk factors [275–277] and is a remarkably stable biomarker in the general population [278]. We observed that cholesterol efflux capacity of apoB-depleted sera of psoriasis patients at baseline was significantly impaired in comparison to healthy controls [150]. This is in line with previous studies [120, 121, 236, 253], suggesting that the development of coronary atherosclerosis in psoriatic patients may be related, at least in part, to an impaired cholesterol efflux capacity of HDL [120, 279]. To our surprise, we observed that cholesterol efflux capacity of apoB-depleted sera of psoriasis patients at short- and intermediate-term biologic anti-psoriatic therapy was significantly impaired in comparison to baseline (no therapy) [150]. Interestingly, all biologics induced similar effects in the

cholesterol efflux capacity of apoB-depleted sera [150]. A recent study in psoriasis patients under adalimumab treatment also showed a reduced cholesterol efflux capacity [274], while combination of adalimumab with methotrexate induced similar effects [280]. However, when HDL-cholesterol efflux capacity was assessed utilizing THP-1 instead of J774.2 cells, no effect of adalimumab was observed [281]. Moreover, tofacitinib [265], and secukinumab (anti-IL-17A antibody) [263], had no effect on cholesterol efflux capacity, while in another study systemic and/or topical treatment appeared to even recover cholesterol efflux capacity [236]. Many factors, including HDL composition and particle size, can influence the functionality of HDL particles [163]. ApoB-depleted serum contains various HDL subpopulations along with preβ-1 HDL and lipid-poor apoA-I, which are acceptors of cholesterol efflux mediated by ABCA1 [92, 282] in addition to the small- and intermediate-sized HDL particles including the 3b and 3c subfractions [6, 283]. Interestingly, we demonstrated a decrease in the ABCA1-mediated-cholesterol efflux of apoB-depleted sera at intermediate-term therapy in comparison to baseline, although the small- and intermediate-sized HDL subclasses were not altered during therapy [150]. Therefore, we assume that a reduction of preβ-1 HDL and/or lipid-poor apoA-I or an impaired functionality of these particles due to compositional changes may be responsible for the decrease in ABCA1-mediated cholesterol efflux observed.

In order to determine directly the functionality of HDL particles in terms of their ability to promote cholesterol efflux, HDL was isolated and used in similar cholesterol efflux experiments. Cholesterol efflux mediated by isolated HDL, including large HDL subclasses, is mainly mediated by ABCG1, SR-BI and passive diffusion [95], while ABCA1 has only a minor contribution, since a large fraction of lipid-poor apoA-I is lost during the ultracentrifugation process [19, 236]. Interestingly, we observed that the cholesterol efflux capacity of HDL was markedly decreased both at short- and at intermediate-term biologic anti-psoriatic therapy in comparison to baseline, which is in agreement with the markedly decreased levels of the large HDL subclass at intermediate-term therapy [150]. Importantly, the large HDL subclass was positively associated with the cholesterol efflux capacity [150]. Therefore, the overall anti-psoriatic therapy-associated reduction in the cholesterol efflux capacity could be attributed to a reduction of preβ-1 HDL and/or lipid-poor apoA-I, as well as to the decrease in the large HDL subclass. In addition to this, alterations in the composition of HDL particles could also potentially attribute to the effects observed. Specifically, the content

of HDL-associated apoA-II was negatively associated with the cholesterol efflux capacity of apoB-depleted serum [150], while it has been reported that apoA-II decreases HDL-cholesterol efflux capacity [284]. Therefore, the increase of apoA-II at intermediate-term therapy could also contribute to the changes in cholesterol efflux capacity.

So far, a study reported that the anti-inflammatory potential of HDL was markedly impaired in psoriasis patients in comparison to controls [232]. Therefore, we were interested to investigate whether the anti-inflammatory properties of HDL were affected by biologic anti-psoriatic therapy. We observed that intermediate-term biologic anti-psoriatic therapy led to a significant decrease of the anti-inflammatory HDL potential in comparison to baseline [150]. A few studies reported that apoA-II overexpression turns HDL from an anti-inflammatory/anti-oxidant to a pro-inflammatory/pro-oxidant lipoprotein [285, 286], therefore the observed increase of HDL-associated apoA-II at intermediate-term therapy could be responsible for the decrease in the anti-inflammatory HDL potential observed.

In the following experiments, we were interested in evaluating whether other important functional properties of HDL were affected by biologic anti-psoriatic therapy. For that purpose, we next assessed the HDL-associated paraoxonase activity. We observed a markedly impaired paraoxonase activity of apoB-depleted sera of patients in comparison to healthy controls [150]. Our results are in agreement with the majority of the studies [232, 233, 236, 252, 287–289], while a few studies reported improved [249, 250] or unchanged [120] enzyme activity in psoriasis patients in comparison to controls. Surprisingly intermediate-term biologic anti-psoriatic therapy recovered the impaired paraoxonase activity [150]. Similar to apoB-depleted sera, patients'-derived isolated HDL also showed an increased paraoxonase activity at intermediate-term therapy [150]. In good agreement with our results, also topical and/or systemic treatment of psoriasis tended to recover HDL-associated paraoxonase activity [236].

The total anti-oxidative potential of HDL has been reported to be impaired [216] or unaltered [120, 236] in psoriasis patients in comparison to controls. Therefore, we were also interested in determining whether biologic anti-psoriatic therapy could have an effect in the anti-oxidative capacity. To determine the anti-oxidative capacity of apoB-depleted sera and isolated HDL of psoriasis patients at baseline and during biologic anti-psoriatic therapy, we evaluated their ability to inhibit free radical-induced oxidation of the fluorescent dye

dihydrorhodamine. We observed that the anti-oxidative potential of apoB-depleted sera at intermediate-term therapy was significantly impaired in comparison to baseline, however this effect was not reflected when using isolated HDL [150], suggesting that factors other than HDL affect the anti-oxidative capacity of apoB-depleted serum. This is in line with the fact that HDL particles are only minor contributors to the anti-oxidative potential of serum irrespective of the oxidation mechanism in addition to HDL [290, 291], given that other serum components such as alpha-tocopherol and albumin also possess anti-oxidant properties [292, 293]. Our results are in agreement with another study including psoriasis patients under topical and/or systemic treatment, in which also no change was observed in the anti-oxidative potential of HDL [236]. The decrease in the anti-oxidative potential of apoB-depleted sera could be attributed to the increased apoA-II levels observed in HDL at intermediate-term biologic anti-psoriatic therapy, since it has been reported that overexpression of apoA-II turns HDL from an anti-oxidant to a pro-oxidant lipoprotein [285, 286].

Finally, we were interested in evaluating whether the LCAT and CETP activities were affected due to biologic anti-psoriatic therapy. LCAT is an important enzyme facilitating the esterification of free cholesterol to cholesteryl esters, leading to the formation of more spherical HDL particles [6]. In comparison to controls, we observed a significantly impaired LCAT activity in sera derived from psoriasis patients at baseline, which was recovered after intermediate-term biologic anti-psoriatic therapy [150]. This is in line with previous studies, in which topical and/or systemic treatment improved the LCAT activity in comparison to baseline [236, 265]. Importantly, the LCAT activity was negatively associated with the free cholesterol HDL content, which is in line with the well-established role of LCAT in the formation of cholesteryl esters [294]. No significant change was observed in the activity of CETP during biologic anti-psoriatic therapy [150], which is in line with reports that topical and/or system psoriasis treatment did not affect CETP activity [236].

To summarize, through this study we provide the novel evidence that biologic anti-psoriatic therapy markedly impairs the cholesterol efflux capacity of apoB-depleted serum and isolated HDL, as well as the anti-inflammatory potential of HDL. However, it increases the LCAT and paraoxonase activities. In addition, treatment with biologic agents alters the HDL composition and subclass distribution, however all biologics caused similar changes in HDL composition, particle distribution and cholesterol efflux capacity. This suggests that the observed effects are not directly attributed to the action of a specific drug. It has to be noted that a further

impairment of HDL-cholesterol efflux capacity due to biologic anti-psoriatic therapy might further increase the risk of psoriasis patients for cardiovascular diseases.

3.3. High-Density Lipoprotein (HDL) in Allergy and Skin Diseases: Focus on Immunomodulating Functions (Biomedicines. 2020 Dec 1; 8(12): 558). Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins (Biomedicines. 2021 May 21; 9(6): 587).

Prompted by the marked changes observed in HDL proteome, lipidome and functional properties in patients with allergic rhinitis and psoriasis in our previous studies, we were interested to further review the existing literature on HDL in allergy and skin diseases [151], as well as on the immunomodulatory activities of HDL [152].

The prevalence of allergy and inflammatory skin diseases has dramatically increased in the latest decades, a fact that is linked to alterations in lifestyle practices and environmental exposures [113, 295]. Despite strong evidence that HDL potently influences the activity of several immune cells [40, 114], the exact role of HDL particles in allergic and skin diseases is not clearly understood [112, 115], while recently the potential role of HDL in diseases other than cardiovascular disease has gained much attention. A few groups so far have investigated the relation of allergic or atopic asthma, a chronic inflammatory airway disease [296], with serum dyslipidemia and HDL-cholesterol levels; however the results regarding a potential association are conflicting [157, 160, 297–313], not allowing a firm conclusion regarding a direct association or effect [151]. It is of importance though that accumulating evidence points towards an association of pulmonary disorders and pulmonary function with HDL-cholesterol [115]. In addition, results from studies in atopic dermatitis patients reporting among others the HDL-cholesterol levels are also of contradictory nature [208, 306, 314]. However, recently atopic dermatitis was associated with complex alterations in HDL composition and function, which led to the formation of dysfunctional HDL particles [151, 208]. Moreover, although literature regarding a potential role of HDL in urticaria and angioedema, two inflammatory skin diseases, is limited, a few studies reported an association of urticaria with HDL-cholesterol levels [315, 316], while angioedema patients were recently demonstrated to be at higher cardiovascular risk [317].

Lipoproteins interact with a plethora of immune cells, key players of the innate and adaptive immune system and accumulating evidence points towards an important modulatory ability of

HDL particles, purified HDL-associated proteins and lipids, as well as HDL-associated enzymes in the activation state and functional properties of immune cells [152]. Alterations in the ability of HDL to modulate immune cell activation, apoptosis, chemotaxis and expression of cell surface markers along with pro-inflammatory cytokine secretion have been observed [152]. Over the years, several groups have attempted to demonstrate both in *in vitro* and *in vivo* experiments, which HDL components are primarily responsible for the observed effects including anti-allergic and anti-inflammatory effects [152]. Interestingly, purified apoA-I, apoA-IV and lyso-phosphatidylcholine could efficiently suppress the activation, adhesion and chemotaxis of neutrophils [50, 164, 318–320]. Moreover, the activation and function of eosinophils were efficiently inhibited by apoA-I, apoA-IV, apoC-III and lyso-phosphatidylcholine [51, 164, 208, 321]. ApoA-I was also shown to promote macrophage M2 polarization and cholesterol efflux [87, 322–324]. However, apoA-I suppressed reactive oxygen species production, toll-like receptor expression and activation of inflammatory response in macrophages [325–327], as well as dendritic cell maturation, differentiation and function [328–330]. Furthermore, apoC-III effectively suppressed eosinophil shape change [208], although it induced monocyte adhesion and inflammasome activation and increased expression of vascular adhesion molecules of endothelial cells [331–333]. HDL-associated paraoxonase has also been shown to affect monocyte and macrophage adhesion, chemotaxis, inflammatory cytokine release as well as expression of cell surface markers [334–336]. In addition, apoA-I and apoE mimetic peptides have also gained attention regarding their abilities to modulate immune cell responses [152] and reconstituted forms of HDL have already been applied in clinical use [153, 154].

To summarize, currently available literature points towards a role of HDL in allergic and skin diseases. Several groups have demonstrated alterations in HDL composition and particle distribution in such diseases, which affect the functional properties of HDL particles including their immunomodulating abilities [151]. Of particular interest, not only a loss in function but also a gain in function concerning the HDL properties is observed, which is linked to the specific pathological background [151]. However, future studies are needed in order to demonstrate a potential causality of altered HDL functional properties in disease progression. In addition, HDL and its associated components appear to have a major impact on the modulation of immune cell activation status and various aspects of immune cell function and comprise a promising tool for future therapeutic interventions [152].

4. CONCLUSION

Although HDL particles have strongly been associated with reduced cardiovascular risk, HDL-cholesterol raising therapies failed to improve the cardiovascular outcome and recent studies challenged the causal role of low HDL-cholesterol in cardiovascular diseases. At the same time, research into the composition, distribution and functionality of HDL particles in diseases other than cardiovascular disease, such as allergies and inflammatory skin diseases, has begun to attract attention.

The data from this thesis reveal that allergic and skin diseases are associated with marked changes in the HDL proteome, lipidome and subclass distribution, leading to alterations in the functionality of HDL particles. Not only a loss in function, but also a gain in function concerning the HDL functionality was observed, which is dependent on the specific pathologic background. Over the years, several groups have demonstrated alterations in the ability of HDL and HDL-associated components to modulate immune cell activation, chemotaxis and pro-inflammatory cytokine secretion. Our data suggest a novel link between allergy and HDL metabolism. Importantly, we also provide the novel evidence that anti-psoriatic therapy with biological therapeutics, including anti-IL-17A, anti-IL-12/23p40 and anti-TNF-α agents, is associated with complex changes in HDL structure, composition and function that might further increase the risk of psoriasis patients for cardiovascular diseases. This is of importance given the already increased cardiovascular risk of psoriasis patients. Therefore, the functional impairment of HDL's ability to promote cholesterol efflux in psoriasis patients might further contribute to excessive mortality from cardiovascular disease.

HDL and its associated components, including proteins, lipids and enzymes, appear to have a major impact on the modulation of immune cell activation status and various aspects of immune cell function; therefore, they comprise a promising tool for future therapeutic interventions.

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Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function

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ABSTRACT

Despite strong evidence that high-density lipoproteins (HDLs) modulate the immune response, the role of HDL in allergies is still poorly understood. Many patients with allergic rhinitis (AR) develop a late-phase response, characterized by infiltration of monocytes and eosinophils into the nasal submucosa. Functional impairment of HDL in AR-patients may insufficiently suppress inflammation and cell infiltration, but the effect of AR on the composition and function of HDL is not understood. We used apolipoprotein (apo) B-depleted serum as well as isolated HDL from AR-patients (n = 43) and non-allergic healthy controls (n = 20) for detailed compositional and functional characterization of HDL. Both AR-HDL and apoB-depleted serum of AR-patients showed decreased anti-oxidative capacity and impaired ability to suppress monocyte nuclear factor-κB expression and pro-inflammatory cytokine secretion, such as interleukin (IL)-4, IL-6, IL-8, tumor necrosis factor alpha and IL-1 beta. Sera of AR-patients showed decreased paraoxonase and cholesteryl-ester transfer protein activities, increased lipoprotein-associated phospholipase A2 activity, while lecithin-cholesterol acyltransferase activity and cholesterol efflux capacity were not altered. Surprisingly, apoB-depleted serum and HDL from AR-patients showed an increased ability to suppress eosinophil effector responses upon eotaxin-2/CCL24 stimulation. Mass spectrometry and biochemical analyses showed reduced levels of apoA-I and phosphatidylcholine, but increased levels of apoA-II, triglycerides and lyso-phosphatidylcholine in AR-HDL. The changes in AR-HDL composition were associated with altered functional properties. In conclusion, AR alters HDL composition linked to decreased anti-oxidative and anti-inflammatory properties but improves the ability of HDL to suppress eosinophil effector responses.

1. Introduction

High-density lipoproteins (HDLs) are conserved and present in most species, suggesting an important biological role from an evolutionary standpoint. HDL particles are structurally and metabolically heterogeneous, due to the persistent remodeling by lipolytic enzymes and

Abbreviations: apo, apolipoprotein; AR, allergic rhinitis; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; IgE, immunoglobulin E; IL, interleukin; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LPC, lyso-phosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase A2; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; PAF, platelet-activating factor; PC, phosphatidylcholine; PON, paraoxonase; sIgE, specific immunoglobulin E; TNF, tumor necrosis factor

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apolipoprotein (apo) exchange with other circulating lipoproteins and tissues [1]. HDL contains several apolipoproteins, the two major proteins being apoA-I and apoA-II, and a large number of less abundant proteins including apoCs, apoE, serum amyloid A (SAA) and some enzymes such as lecithin-cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), paraoxonase (PON) and lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor (PAF) acetylhydrolase [2–6] HDL particles are involved in a number of physiological processes. The most studied and, conceivably, best understood function of HDL is its ability to promote the transport of excess cholesterol from peripheral tissues to the liver for excretion, a mechanism thought to confer protection against atherosclerotic cardiovascular disease [7]. In addition, HDL-associated apolipoproteins, lipids and enzymes modulate endothelial function [8] and have potent anti-inflammatory [9] and anti-oxidative properties [1,10] Besides its well-known anti-atherogenic properties, HDL takes part in regulating proliferation of hematopoietic stem cells in the bone marrow [11]. HDL is involved in protection against certain parasitic infections, as certain apolipoproteins found in HDL confer human resistance towards infection with *Trypanosoma brucei brucei* [12]. Furthermore, HDL-associated apolipoproteins and lipids as well as HDL-associated enzymes are thought to regulate immune responses, given that HDL suppresses immune cell activation [13], including chemotaxis and shape change of eosinophils [14]. Biological activities of HDL may change and new evidence suggests that in some pathological conditions, such as coronary artery disease [15], psoriasis [16], chronic kidney disease [17], rheumatoid arthritis [18] and atopic dermatitis [14], HDL may lose its protective properties [19].

AR is an immunoglobulin E (IgE) mediated disease that affects approximately one in every four individuals in westernized countries and is characterized by nasal itching, sneezing, watery discharge and congestion [20]. Upon the initial sensitization process, several common aeroallergens cleave tight junctions in the airway epithelium and activate epithelial cells. Dendritic cells process the antigen and present it to T cells, which along with a plethora of cytokines and chemokines lead to activation of B cells for the production of specific IgE (sIgE) [21]. Upon re-exposure of sensitized individuals, the allergen binds to IgE on mast cells, which release preformed and newly synthesized mediators, such as histamine, platelet activating factor, interleukins, prostaglandins and tumor necrosis factor (TNF) alpha (TNF-α), and proteases, such as tryptase and chymase [22]. This step comprises the early-phase response, which is accompanied by early rhinitis symptoms. Approximately half of the AR-patients develop a late-phase response, which is characterized by stimulation, production, maturation and subsequent infiltration of inflammatory cells, such as monocytes, basophils and eosinophils, towards the nasal submucosa. Release of mediators by inflammatory cells enhances and sustains the inflammation, leading to more persistent symptoms [22–25]. A significant increase in the presence of activated eosinophils has been reported in patients with seasonal AR after allergen challenge [26].

In spite of the strong evidence that HDL modulates immune responses, the role of HDL in allergy remains poorly understood and no evidence is available on HDL function in AR. Functional impairment of HDL may inadequately suppress inflammation and effector responses of immune cells in AR-patients.

In the present study, we hypothesized that HDL from subjects with AR displays an altered protein and lipid composition associated with altered functional properties. We used mass spectrometry, biochemical analyses and various cell-based assays to assess alterations in function of apoB-depleted serum and isolated HDL from AR-patients. We observed decreased anti-oxidative and anti-inflammatory properties of apoB-depleted serum and HDL from AR-patients, but on the other hand an improved ability to suppress eosinophil effector responses. Our findings support our hypothesis and suggest a link between HDL functionality and AR.

2. Materials and methods

2.1. Ethical approvals

The Institutional Review Board of the Medical University of Graz approved the study protocol (27-528 ex 14/15) in accordance with the Declaration of Helsinki. Informed consent was obtained from all study subjects.

2.2. Study subjects

Blood was sampled from 43 patients with seasonal allergic rhinitis (AR-patients) and from 20 non-allergic healthy subjects in serum tubes (Greiner Bio-One, Kremsmünster, Austria). The mean (± standard deviation) age of included subjects was 20.2 ± 6.5 and the age range was 8–36 years. Overweight subjects or subjects suffering from diabetes were excluded from the study. During childhood and adolescence the ratio between weight and height markedly varies with sex and age, so the cut-off values that determine the nutritional status of those aged 0–19 years are gender- and age-specific. Therefore, for participants ≤18 years of age, overweight was defined as a body mass index (BMI) > 90th percentile. Study subjects were not under medication when blood was drawn. All included AR-patients had at least detectable serum sIgE levels in blood and positive skin prick tests to grass pollen. Non-allergic individuals were not sensitized to the most common allergens such as grass pollen, birch pollen or house dust mite and had low total IgE levels.

2.3. Blood sampling

After blood was drawn, serum tubes were incubated for 30 min at room temperature and subsequently centrifuged at 1800 × *g* for 10 min at 4 °C. Serum was collected and stored at −70 °C. Specific and total IgE antibody levels in the AR-patients' sera were measured using the ImmunoCAP 250 (Thermo Fisher Scientific, Waltham, USA) according to the manufacturer's instructions. SIgE values > 0.35 kU/L were considered positive [27]. AR-patients were sensitized to different pollens such as grass, birch, mugwort, ash and ragweed, to house dust mite and to mold.

2.4. Preparation of apoB-depleted serum

ApoB-depleted serum was prepared by addition of 40 µL polyethylene glycol (Sigma-Aldrich, Darmstadt, Germany) (20% in 200 mmol/L Glycine buffer) to 100 µL serum with gentle mixing. Serum was incubated at room temperature for 20 min and after centrifugation (10,000 rpm, 20 min, 4 °C) the supernatant was recovered [28]. Samples were stored at −70 °C until use.

2.5. Isolation of HDL

HDL was isolated from controls (n = 20) and AR-patients (n = 43). Density of serum was adjusted by addition of potassium bromide (Sigma-Aldrich, Darmstadt, Germany) to 1.24 g/mL and a two-step density gradient was generated in centrifuge tubes (16 × 76 mm, Beckman Coulter) by layering the density-adjusted serum (1.24 g/mL) underneath a KBr density solution (1.063 g/mL) [29]. The tubes were sealed and centrifuged at 65,000 rpm for 6 h at 15 °C in a 90Ti fixed angle rotor (Beckman Instruments, Krefeld, Germany). After centrifugation, the visible HDL-containing band (containing HDL2 and HDL3 subfractions) was collected, concentrated using Vivaspin Turbo 4 ultracentrifugation spin columns (Sartorius, Göttingen, Germany), desalted using the PD MiniTrap G-25 columns (GE Healthcare, Vienna, Austria) and stored at −70 °C in the presence of 5% sucrose (Sigma-Aldrich, Darmstadt, Germany) as cryoprotectant, as described [30].

2.6. Biochemical quantification of HDL-associated proteins

ApoA-I, apoA-II, apoC-II and apoE were determined by immunoturbidimetry using reagents from DiaSys (Holzheim, Germany) and standards from Siemens (Marburg, Germany; apoA-I, apoE) and Kamiya Biomedical (Seattle, WA, USA; apoA-II, apoC-II). All lipoprotein analyses were performed on an Olympus AU640 analyzer (Beckman Coulter, Brea, CA), as previously described [31]. ApoC-III was quantified using the Human Apolipoprotein CIII ELISA Kit (Abcam, Cambridge Science Park, Cambridge, UK), a method that has a sensitivity of 0.3 ng/mL. SAA was evaluated using a human SAA ELISA Kit (Invitrogen, Carlsbad, California, USA), which has a sensitivity of 4 ng/mL, according to the manufacturer's instructions.

2.7. Determination of serum and HDL lipid composition

Non-esterified cholesterol, cholesteryl esters, total cholesterol and triglycerides were determined by commercially available kits (Diasys Diagnostic Systems GmbH, Holzheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald equation using HDL cholesterol values measured in apoB-depleted serum.

2.8. Mass spectrometry analysis of HDL lipid composition

Samples containing 100 μg protein (1 μg/μL aqueous solution) were extracted according to Matyash et al. [32] in 700 μL methyl-tert-butyl ether (MTBE)/methanol (3/1, v/v) containing 500 pmol butylated hydroxytoluene, 1% acetic acid, and internal standards [IS; 40 pmol 17:1 lyso-phosphatidylcholine (LPC), 50 pmol d18:1/17:0 sphingomyelin, Avanti Polar Lipids, Alabaster, AL, USA; 250 pmol 17:0/17:0 phosphatidylcholine (PC), Larodan, Solna, Sweden]. Total lipid extraction was performed under constant shaking for 30 min at room temperature. After addition of 40 μL dH_2O (140 μL total aqueous phase) and further incubation for 30 min at room temperature, samples were centrifuged at 1000 ×*g* for 15 min. 500 μL of the upper, organic phase were collected and dried under a stream of nitrogen. Lipids were resolved in 250 μL MTBE/methanol (3/1, v/v) and diluted in 2-propanol/methanol/dH_2O (7/2.5/1, v/v/v) for UHPLC-qTOF analysis. Chromatographic separation was performed on an 1290 Infinity II LC system (Agilent, Santa Clara, CA, USA) equipped with a Luna omega C18 column (2.1 × 50 mm, 1.6 μm; Phenomenex, Torrance, CA, USA) running a 20 min linear gradient from 55% solvent A (H_2O; 10 mM ammonium acetate, 0.1% formic acid, 8 μM phosphoric acid) to 100% solvent B (2-propanol; 10 mM ammonium acetate, 0.1% formic acid, 8 μM phosphoric acid). The column compartment was kept on 50 °C. A 6560 Ion Mobility Q-TOF mass spectrometer (Agilent, Santa Clara, CA, USA) equipped with Dual AJS ESI source was used for detection of lipids in positive Q-TOF mode. Data acquisition was done by MassHunter Data Acquisition software (B.09, Agilent, Santa Clara, CA, USA). Lipids were manually identified and lipid feature extraction was performed using MassHunter Profinder (V.10, Agilent, Santa Clara, CA, USA). Data were normalized for recovery, extraction, and ionization efficacy by calculating analyte/IS ratios (AU) and expressed as AU/μg protein.

2.9. C-reactive protein (CRP) determination

CRP levels were evaluated using the CRP Human ELISA Kit (Thermo Scientific, Rockford, USA), which has a sensitivity of < 10 pg/mL.

2.10. Gradient gel electrophoresis

Isolated HDL (5 μg protein per lane) was separated by gradient gel electrophoresis (4–16% Native Page, Life Technologies, Vienna, Austria) under nonreducing and nondenaturing conditions, as described previously [30]. The HDL2, medium sized HDL3 and small HDL3 particles were estimated using the Image Lab software, Bio-Rad, Austria, as described [33].

2.11. Arylesterase activity of PON

Ca^{2+}-dependent arylesterase activity of PON was determined by a photometric assay using phenylacetate substrate, as described [16]. Activities were calculated from the slopes of the kinetic chart of four independent experiments, measured in duplicates.

2.12. Determination of the anti-oxidative capacity of HDL

The anti-oxidative activity of apoB-depleted serum and isolated HDL was determined as previously described with modifications [34]. Briefly, dihydrorhodamine was suspended in DMSO to a 50 mM stock, which was diluted in HEPES (20 mM HEPES, 150 mM NaCl, pH 7.4) containing 1 mM 2,2′-azobis-2-methyl-propanimidamide-dihydrochloride (Sigma-Aldrich, Darmstadt, Germany) to a 10 μM working reagent. Either 10 μL of apoB-depleted serum (1:10 diluted) or 10 μL of isolated HDL (1 mg/mL) were placed in 384-well plates (Greiner Bio-One, Kremsmünster, Austria) and the volume was adjusted to 100 μL with HEPES buffer containing 10 μM dihydrorhodamine. The increase in fluorescence due to oxidation of dihydrorhodamine was monitored using an xMark plate reader (Biorad, Vienna, Austria) for 90 min at 538 nm. After an initial lag phase of about 20 min, the rate of oxidation was linear. The increase in fluorescence was calculated from the linear range and used for comparison. The increase in fluorescence per minute of dihydrorhodamine in the absence of apoB-depleted serum or isolated HDL was set to 100%, and individual apoB-depleted serum (three independent experiments measured in duplicates) or isolated HDL (three independent experiments measured in duplicates) samples were calculated as percentage of inhibition of dihydrorhodamine oxidation.

2.13. Lp-PLA2 activity assay

Lp-PLA2 activity of apoB-depleted serum was measured using a commercially available photometric assay (Cayman, Europe) using 2-thio PAF as substrate. Activities were calculated from the slopes of the kinetic chart of three independent experiments, measured in duplicates.

2.14. LCAT activity

LCAT activity of serum was measured in duplicates, using a commercially available kit (Merck, Darmstadt, Germany) according to the manufacturer's instructions. Specifically, samples were incubated with LCAT substrate for 4 h at 37 °C. The fluorescent substrate emits fluorescence at 470 nm. When the substrate is hydrolyzed by LCAT, a monomer is released that emits fluorescence at 390 nm. The LCAT activity is assessed over time and expressed in change of 470/390-nm emission intensity [35].

2.15. CETP activity

CETP activity of serum was measured in duplicates, using a commercially available kit (Merck, Darmstadt, Germany) according to the manufacturer's instructions. Specifically, the assay uses a proprietary substrate that enables the detection of CETP-mediated transfer of neutral lipid from the substrate to a physiological acceptor. The transfer activity results in an increase in fluorescence intensity (λ_{ex} = 465/ λ_{em} = 535 nm).

2.16. Determination of nuclear factor-κB (NF-κB) expression and cytokines release evaluation

U937 monocytic cells containing a 5× NF-κB green fluorescence protein (GFP) reporter cassette were cultivated in RPMI 1640 (Life

Technologies, Carlsbad, California, USA) containing 10% fetal bovine serum (FBS) (Life Technologies, Carlsbad, California, USA) and 1% penicillin/streptomycin (Pan-Biotech, Aidenbach, Germany). The cells were pretreated for 90 min with either 7% apoB-depleted serum or isolated HDL (50 μg/mL), in two and three independent experiments, respectively, measured in duplicates. Subsequently, the cells were stimulated for 24 h with lipopolysaccharide (LPS) (50 ng/mL) (Sigma, Darmstadt, Germany), collected by centrifugation at 400 ×*g* for 7 min and fixed with 100 μL fixative solution, which was prepared as previously described [36]. The expression of NF-κB was assessed by flow cytometry and cytokines released by U937 monocytic cells were quantified using a multiplex bead-based immunoassay (Thermo Scientific, Rockford, USA). The assay range was 9.35–38,300 pg/mL for IL-4, 6.74–27,600 pg/mL for IL-6, 2.38–9750 pg/mL for IL-8, 1.56–6400 pg/mL for IL-12p70, 6.42–26,300 pg/mL for TNF-α and 2.39–9800 pg/mL for IL-1 beta.

2.17. HDL-cholesterol efflux capacity

HDL-cholesterol efflux capacity of apoB-depleted serum was assessed, as described [7,28]. Briefly, J774.2 cells (Sigma-Aldrich, Darmstadt, Germany) were maintained in Dulbecco's modified eagle medium (DMEM) (Life Technologies, Carlsbad, California, USA) in the presence of 10% FBS and 1% penicillin/streptomycin. Cells were plated on 48-well plates (Greiner Bio-One, Kremsmünster, Austria) (300,000 cells/well), cultured for 24 h and loaded with 0.5 μCi/mL radiolabeled [^{3}H]-cholesterol (Hartmann Analytic, Braunschweig, Germany) in DMEM supplemented with 2% FBS and 1% penicillin/streptomycin in the presence of 0.3 mM 8-(4-chlorophenylthio)-cyclic AMP (Sigma-Aldrich, Darmstadt, Germany) overnight. After labeling, cells were rinsed with serum-free DMEM containing 1% penicillin/streptomycin and equilibrated with serum-free DMEM containing 1% penicillin/streptomycin and 2 mg/mL bovine serum albumin (Sigma-Aldrich, Darmstadt, Germany) for 2 h. Subsequently [^{3}H]-cholesterol efflux was determined by incubating cells for 3 h with 2.8% apoB-depleted serum. Cholesterol efflux was expressed as radioactivity in the cell culture supernatant relative to total radioactivity (in the cell culture supernatant and cells) of two independent experiments, measured in duplicates. All steps were performed in the presence of 2 μg/mL of the acyl coenzyme A cholesterol acyltransferase inhibitor Sandoz 58-035 (Sigma-Aldrich, Darmstadt, Germany).

2.18. Preparation of human eosinophils

Human peripheral blood eosinophils were isolated, as described [37]. Briefly, blood was drawn from healthy, non-allergic subjects and platelet-rich plasma was separated by centrifugation. Dextran sedimentation was used to remove erythrocytes, while polymorphonuclear leukocytes were obtained by density gradient separation using Histopaque. Eosinophils were further purified using negative magnetic selection through a respective antibody cocktail coupled to magnetic beads (StemCell Technologies, Vancouver, Canada). Purity and viability were > 98% after isolation.

2.19. Shape change assay

Purified eosinophils were pretreated with either 2.5% apoB-depleted serum or isolated HDL (50 μg/mL) for 30 min at room temperature and stimulated afterwards with eotaxin-2/CCL24 (3 nM) (Immunotools, Friesoythe, Germany) for 5 min at 37 °C. Subsequently, the samples were fixed and the change in shape of eosinophils was estimated as increase of forward scatter [38,39]. Responses were expressed as percent of vehicle (eotaxin-2/CCL24 in the absence of apoB-depleted serum or isolated HDL) treated cells of five and three independent experiments, respectively, measured in duplicates with eosinophils from different donors.

2.20. Chemotaxis assay

Eosinophils were pretreated with either 2.5% apoB-depleted serum or isolated HDL (50 μg/mL) for 30 min at room temperature. Then, cells were placed in the upper compartment of Transwell inserts with 5 μm pore size filters (Corning, Acton, MA, USA) and were allowed to migrate towards eotaxin-2/CCL24 (30 nM) in the bottom compartment for 1 h at 37 °C. Afterwards, migrated cells were fixed and enumerated on a flow cytometer, while responses were expressed as percent of vehicle (eotaxin-2/CCL24 in the absence of apoB-depleted serum or isolated HDL) treated cells of three independent experiments, respectively, measured in duplicates with eosinophils from different donors.

2.21. Statistical analysis

Data were tested for normality using the Shapiro-Wilk normality test. Data are presented as means and standard deviations if normally distributed or medians and first and third quartile if not. Differences between the two groups were analyzed using the Student's *t*-test or the Mann-Whitney *U* test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. Gender differences were evaluated using the Fisher's exact test. Correlations between apoB-depleted serum and isolated HDL were determined using Pearson's correlation coefficient *r*, whereas other correlations were assessed using Spearman's correlation coefficient *rho* due to the skewed nature of many of the parameters. The general significance level for the analyses was set to $\alpha = 0.05$. However, because of the large amount of correlation analyses performed for functional properties of HDL with HDL-composition and -distribution, the significance level was reduced to 0.01 for these analyses (presented in heat maps). Statistical analyses were performed using GraphPad Prism (Version 6.01, GraphPad Software), SPSS Statistics (Version 23) and R (Version 3.5.3).

3. Results

3.1. Clinical characteristics of study subjects

Patients with AR showed unchanged serum levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and CRP when compared to controls (Table 1). Total IgE levels of AR-patients were above the normal range for each subject, depending on their age, whereas the control group showed normal total IgE levels. AR-patients

Table 1
Clinical characteristics of study subjects.

	Controls	AR-patients	*p*-Value
n	20	43	
Age (y)	21.1 ± 1.38	19.7 ± 7.82	0.444
Gender Male (%)	7 (35.0)	24 (55.8)	0.177
Total cholesterol (mg/dL)	173.0 (155.2–214.4)	174.2 (146.0–192.3)	0.250
HDL-cholesterol (mg/dL)	57.4 (46.9–76.3)	50.4 (43.4–61.6)	0.097
LDL-cholesterol (mg/dL)	93.4 (80.6–113.0)	101.3 (83.2–114.5)	0.668
Triglyceride (mg/dL)	82.6 (68.5–121.0)	65.8 (51.3–105.3)	0.103
CRP (mg/L)	0.72 (0.46–1.82)	0.56 (0.15–2.26)	0.288
Total IgE (kU/L)	16.0 (5.6–73.2)	117.0 (48.0–206.0)	< 0.001
sIgE grass pollen (kU/L)	sIgE negative	21.5 (6.1–52.2)	

Data are presented as mean ± standard deviation, median with first and third quartiles, or as absolute and relative frequencies. Differences between the two groups were analyzed with Student's *t*-test, with Mann-Whitney *U* test, or with Fisher's exact test, respectively. n, number of subjects; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; IgE, immunoglobulin E; sIgE, specific immunoglobulin E; kU/L, kilounits per liter; AR, allergic rhinitis.

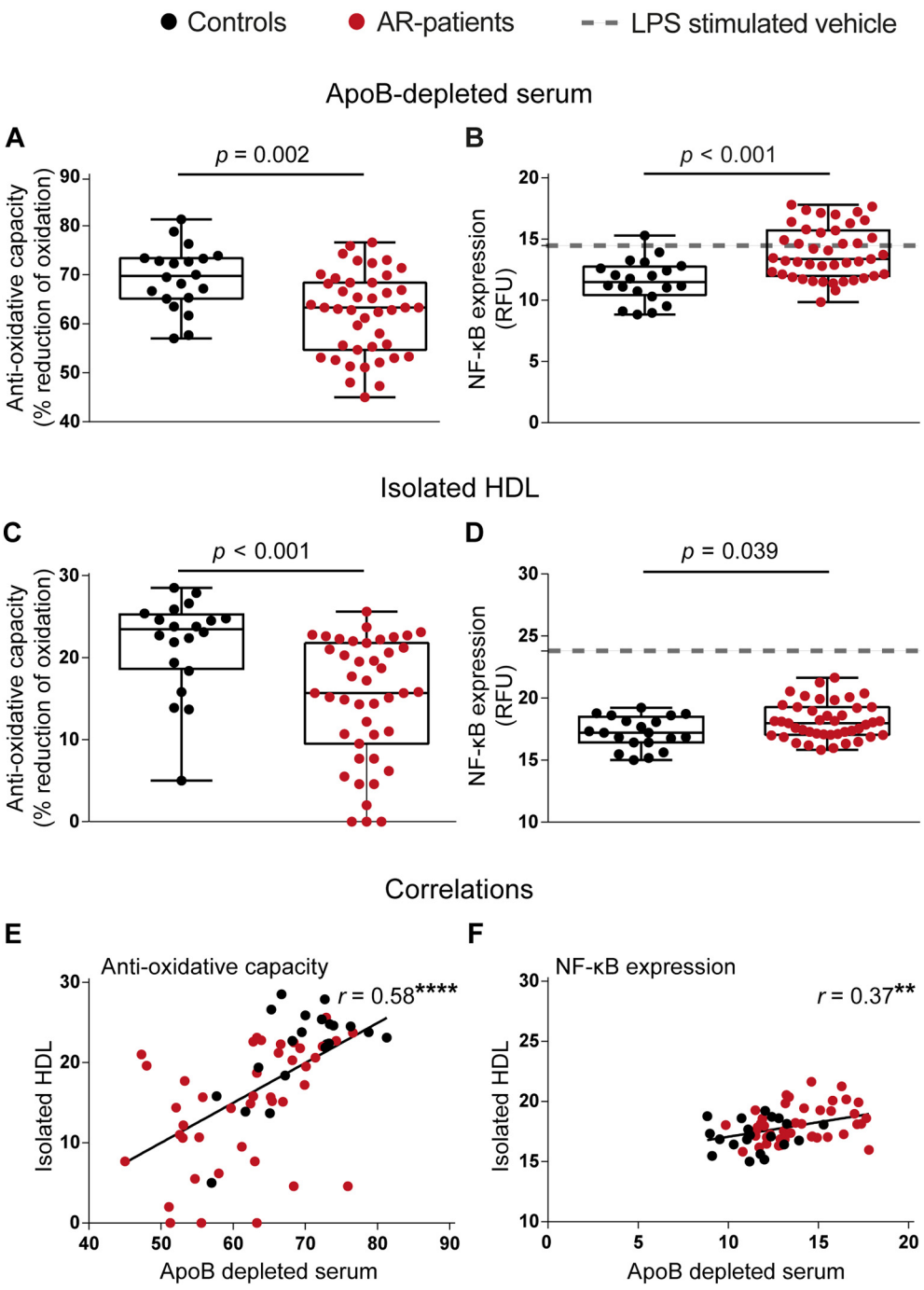

Fig. 1. Allergic rhinitis is associated with impaired anti-oxidative and anti-inflammatory capacity of apoB-depleted serum and isolated HDL.
ApoB-depleted serum or isolated HDL of controls (n = 20) and AR-patients (n = 43) was used in different assays. Inhibition of oxidation was measured by incubating apoB-depleted serum (A) or isolated HDL (C) with dihydrorhodamine in three independent experiments, respectively, measured in duplicates. The anti-inflammatory capacity of apoB-depleted serum (B) or isolated HDL (D) was evaluated using U937 monocytes containing a reporter cassette for NF-κB. Cells were pretreated with 7% apoB-depleted serum or HDL (50 μg/mL) for 90 min and subsequently stimulated with LPS (50 ng/mL) for 24 h. GFP-NF-κB expression was assessed by flow cytometry in two and three independent experiments, respectively, measured in duplicates. The grey dashed line indicates LPS treated cells in the absence of apoB-depleted serum or isolated HDL. Scatter plots of the anti-oxidative capacity (E) and anti-inflammatory potential (F) of apoB-depleted serum and isolated HDL. (A–D) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. (E, F) The Pearson correlation coefficients (*r*) are noted. $^{**}p < 0.01$, $^{****}p < 0.0001$. AR, allergic rhinitis; RFU, relative fluorescence units; HDL, high-density lipoprotein; LPS, lipopolysaccharide; apoB, apolipoprotein B.

had elevated sIgE levels for grass pollen (Table 1, Supplementary Table 1), while all tested sIgE for controls were below the reference values. SIgE for grass pollen, birch pollen and house dust mite were the most frequent and abundant, while ash, mugwort and ragweed pollen as well as mold were less frequent (Supplementary Table 1).

3.2. Altered HDL functionality in AR-patients

In first experiments, we assessed whether AR affects the anti-oxidative and anti-inflammatory activity of apoB-depleted serum (containing all HDL subclasses, but no apoB-containing low-density lipoproteins) from AR-patients and control subjects. For that purpose, we evaluated the ability of apoB-depleted serum to inhibit free radical-induced oxidation of the fluorescent dye dihydrorhodamine [33]. Interestingly, we observed that apoB-depleted sera from AR-patients were less potent in inhibiting dihydrorhodamine oxidation when compared to control sera (Fig. 1A). In subsequent experiments, we tested the anti-inflammatory activity of apoB-depleted serum by assessing its ability to inhibit LPS-induced activation of the pro-inflammatory transcription factor NF-κB in monocytes [33,40]. We observed that almost all apoB-depleted sera of controls inhibited NF-κB expression, whereas sera of AR-patients showed a significantly impaired inhibitory activity (Fig. 1B), and many AR samples even exhibited pro-inflammatory activity.

We isolated HDL from sera of AR-patients and controls to study whether these effects were directly caused by an altered HDL functionality. Similar to apoB-depleted sera, isolated HDL from AR-patients (AR-HDL) was less potent in inhibiting dihydrorhodamine oxidation (Fig. 1C) and showed an impaired ability to suppress NF-κB in monocytes (Fig. 1D). Importantly, we observed a significant correlation

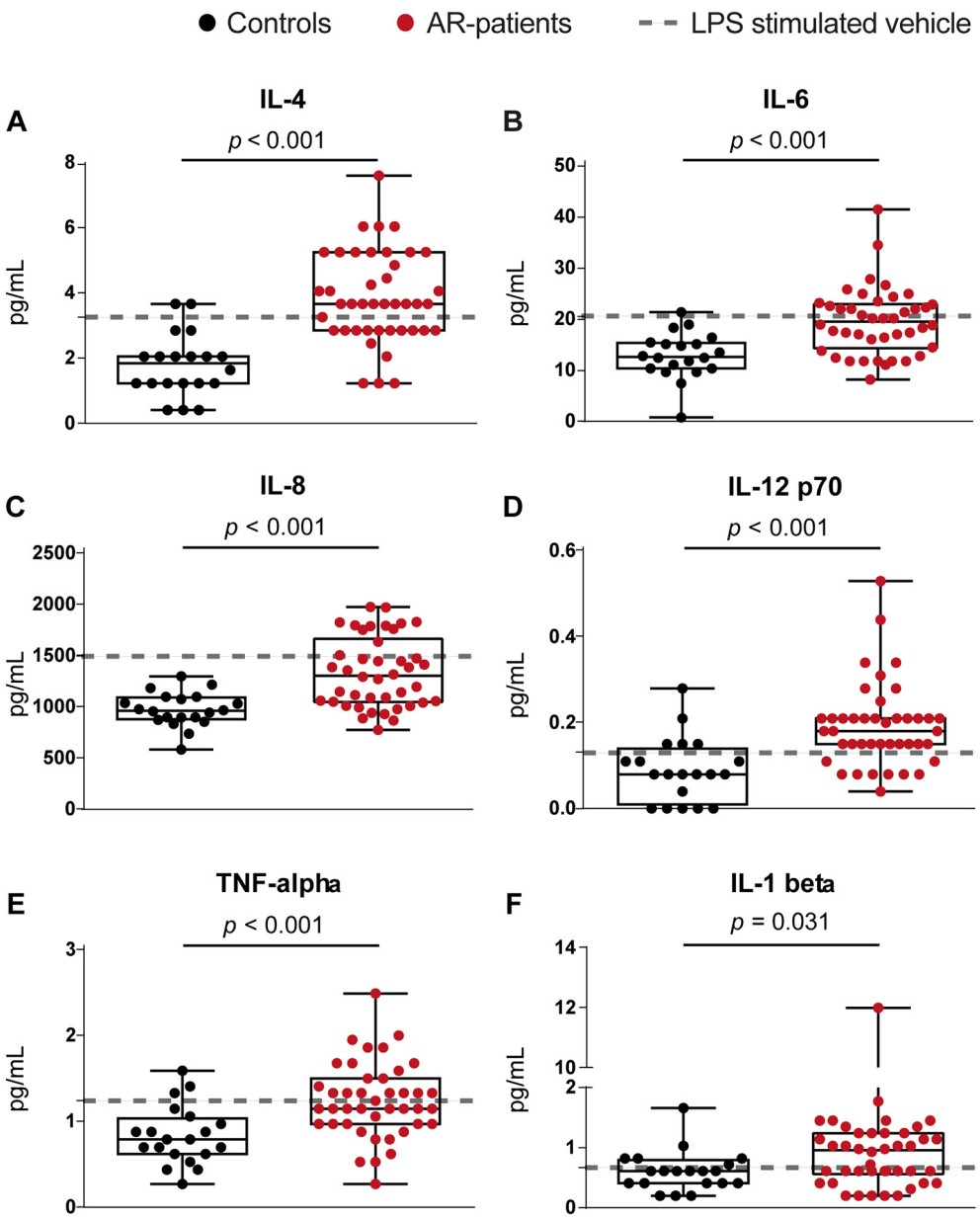

Fig. 2. Impaired ability of AR-HDL to suppress monocyte cytokine secretion.
Monocytes were pretreated with isolated HDL of controls (n = 20) and AR-patients (n = 42) and stimulated with LPS to induce cytokine release. Upon treatment the supernatants were collected and cytokines were assessed using a multiplex bead-based immunoassay. (A) Interleukin (IL-) 4, (B) IL-6, (C) IL-8, (D) IL-12 p70 (E), TNF-α and (F) IL-1 beta. (A–F) Differences between the two groups were analyzed with the Mann-Whitney U test. The grey dashed line indicates LPS treated cells in the absence of isolated HDL. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. AR, allergic rhinitis; IL, interleukin; TNF, tumor necrosis factor; LPS, lipopolysaccharide.

between apoB-depleted sera and isolated HDL in terms of their ability to inhibit dihydrorhodamine oxidation (Fig. 1E) and to suppress NF-κB expression (Fig. 1F). Furthermore, AR-HDL was less potent in suppressing monocyte cytokine secretion (including IL-4, IL-6, IL-8, IL-12 p70, TNF-α and IL-1 beta) when compared to HDL of controls (Fig. 2A-F). The NF-κB inhibitory activity of HDL was significantly correlated with the ability of HDL to modulate cytokine production (Supplementary Table 2).

3.3. Altered HDL-associated enzyme activities in AR-patients

HDL acts as reservoir for a number of biologically active enzymes that may be affected by AR. HDL-associated PON is an esterase with vascular protective activities [41]. Compared to apoB-depleted sera of controls, PON activity was significantly decreased in apoB-depleted serum of AR-patients (Fig. 3A). Another HDL-associated enzyme is Lp-PLA2, that hydrolyzes short- and medium-chain phospholipids [42]. Lp-PLA2 is thought to play a role in AR due to its ability to hydrolyze PAF, which is assumed to be involved in mucus secretion. Increased PAF levels have been found in nasal lavage of AR-patients after nasal challenge with pollen [43]. Interestingly, we found that activity of Lp-PLA2 in hydrolyzing PAF was increased in apoB-depleted serum of AR-patients (Fig. 3B). These data suggest reduced anti-oxidative/anti-inflammatory activity of AR-HDL but an improved capability to decompose platelet-activating factor.

During HDL maturation, free cholesterol is esterified to cholesteryl ester by LCAT [44]. LCAT converts discoidal HDL into spherical HDL and increases the size of HDL through the conversion of HDL3 to HDL2 [45], which is considered to be an important step during reverse cholesterol transport. However, we observed no significant difference in the LCAT activity of sera derived from AR-patients in comparison to controls (Fig. 3C). CETP is responsible for the bidirectional transfer of cholesteryl esters and triglycerides between plasma lipoproteins [46]. We observed significantly decreased CETP activity in sera derived from AR-patients in comparison to control sera (Fig. 3D). Moreover, the ability of HDL to remove membrane cholesterol from cells (cholesterol efflux capacity, an important anti-atherogenic property of HDL) was not altered (Supplementary Fig. 1).

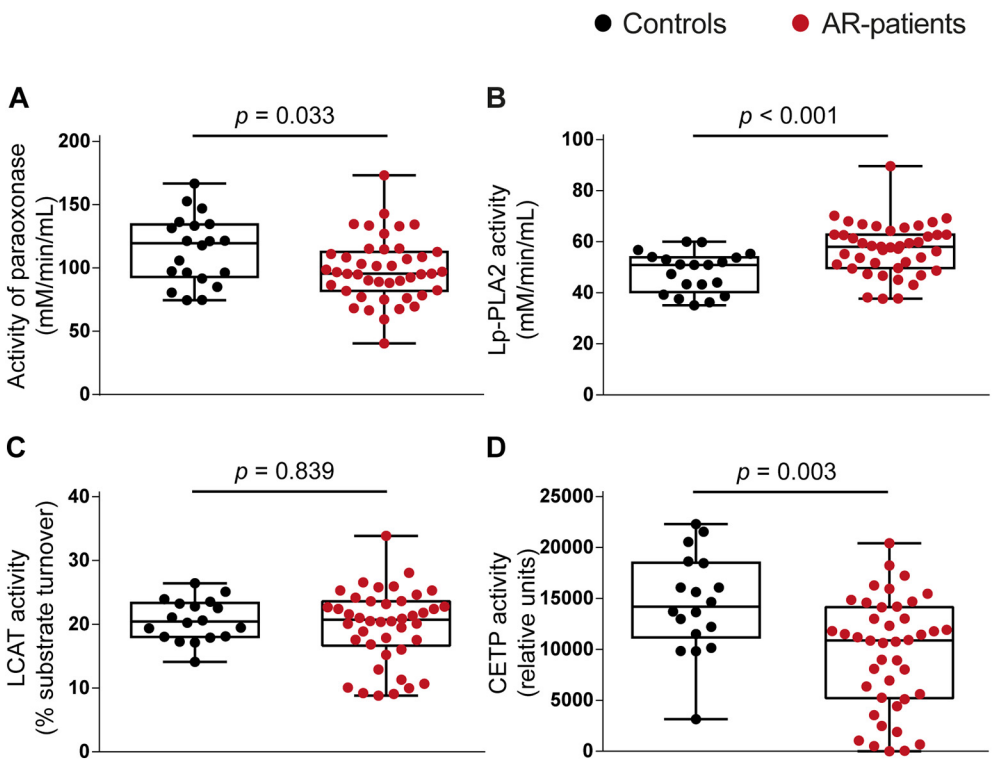

Fig. 3. AR shows altered PON, Lp-PLA2 and CETP activities.
(A, B) ApoB-depleted serum from controls (n = 20) and AR-patients (n = 43) was used in different assays. (A) Arylesterase activity of paraoxonase (PON) was measured using phenylacetate as substrate. Activities were calculated from the slopes of the kinetic chart of four independent experiments, measured in duplicates. (B) Lp-PLA2 activity was measured using 2-thio platelet-activating factor as substrate. Activities were calculated from the slopes of the kinetic chart of three independent experiments, measured in duplicates. (C) The LCAT activity in serum of controls (n = 18) and AR-patients (n = 42) was evaluated. (D) The CETP activity in serum of controls (n = 18) and AR-patients (n = 42) was evaluated. (A–D) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. AR, allergic rhinitis; Lp-PLA2, lipoprotein-associated phospholipase A2; LCAT, lecithin-cholesterol acyltransferase; CETP, cholesteryl ester transfer protein.

3.4. AR-HDL shows an improved ability to suppress eosinophil effector responses

Infiltrated inflammatory cells like eosinophils play a role in inducing and maintaining on-going allergic inflammation [47]. We investigated whether apoB-depleted sera or isolated HDL of AR-patients or controls can affect eosinophil activation (shape change) and chemotaxis. For that purpose, freshly isolated eosinophils from healthy subjects were pretreated with either apoB-depleted sera or isolated HDL, followed by stimulation with eotaxin-2/CCL24. The change in forward scatter was monitored by flow cytometry [48]. Surprisingly, apoB-depleted sera as well as isolated HDL of AR-patients showed an improved ability to suppress eotaxin-2/CCL24-induced eosinophil shape change when compared to controls (Fig. 4A, C).

To study the effects of AR on eosinophil chemotaxis, eosinophils were pretreated with either apoB-depleted sera or isolated HDL and allowed to migrate towards eotaxin-2/CCL24 in Transwell inserts. Similar to shape change experiments, apoB-depleted sera as well as isolated HDL of AR-patients showed an improved ability to suppress eotaxin-2/CCL24-induced eosinophil chemotaxis, when compared to controls (Fig. 4B, D). Moreover, the abilities of apoB-depleted sera and isolated HDL to inhibit agonist-induced eosinophil effector responses were significantly correlated (Fig. 4E, F).

3.5. Composition of AR-HDL is markedly altered

It is known that alterations of lipid metabolism, activation of the innate immune system, or inflammation, can modulate the content of apolipoproteins in HDL [19]. Owing to the marked changes observed in AR-HDL functionality, we were interested in assessing HDL composition. AR-patients showed decreased levels of apoA-I (Fig. 5A) and increased levels of apoA-II (Fig. 5B) compared to controls. No difference was observed in the apoC-II content (Fig. 5C), while a trend towards increased apoC-III ($p = 0.063$) content (Fig. 5D) was observed in AR-HDL. ApoE (Fig. 5E) and SAA (Fig. 5F) levels were not altered in HDL from AR-patients. When assessing the lipid composition of AR-HDL, we observed no change in free cholesterol (Fig. 6A) and cholesteryl ester (Fig. 6B) content of AR-HDL, but markedly increased levels of triglycerides (Fig. 6C). AR-HDL-associated PC content was decreased (Fig. 6D), whereas LPC content was strikingly increased (Fig. 6E). Sphingomyelin content was not altered in AR-HDL (Fig. 6F). A more detailed analysis of the different PC, LPC and sphingomyelin species is given in Supplementary Fig. 2.

HDL particles are diverse in structure and composition representing the basis for their functional heterogeneity. HDL particles can be subdivided into large, cholesterol-rich spherical HDLs and more dense, protein-rich HDLs that appear to display the most potent atheroprotective properties [44]. When performing gradient gel electrophoresis to separate HDL subfractions, we observed a decrease in the medium sized HDL3 subclass in AR-patients (Fig. 7A), whereas other HDL subfractions, such as small HDL3 and large HDL2 particles were not altered (Fig. 7B, C). A representative gradient gel electrophoresis of HDL subfractions is shown in Fig. 7D.

3.6. Metrics of AR-HDL function are associated with AR-HDL composition and structure

Owing to the marked alterations in AR-HDL composition and function, we performed an in depth correlation analysis to determine which proteins and lipids in AR-HDL are associated with an altered function. We observed multiple and complex associations (Supplementary Fig. 3), suggesting that alterations in the composition and structure of AR-HDL affect distinct functional properties. The highest number of associations was seen with AR-HDL triglyceride and LPC content as well as with the PC/LPC and HDL2/HDL3 ratios. All these factors were associated with multiple functional properties of AR-HDL, such as anti-oxidative and anti-inflammatory activities, cholesterol efflux capacity, and inhibition of eosinophil shape change, as well as with enzyme activities, such as PON, CETP and LCAT.

We observed weaker associations between AR-HDL apoA-I and apoA-II content and AR-HDL PON activity along with the ability of AR-HDL to suppress eosinophil shape change. ApoC-II content of AR-HDL was associated with LCAT activity and anti-inflammatory potential of HDL, while apoE content was associated with the ability of apoB-

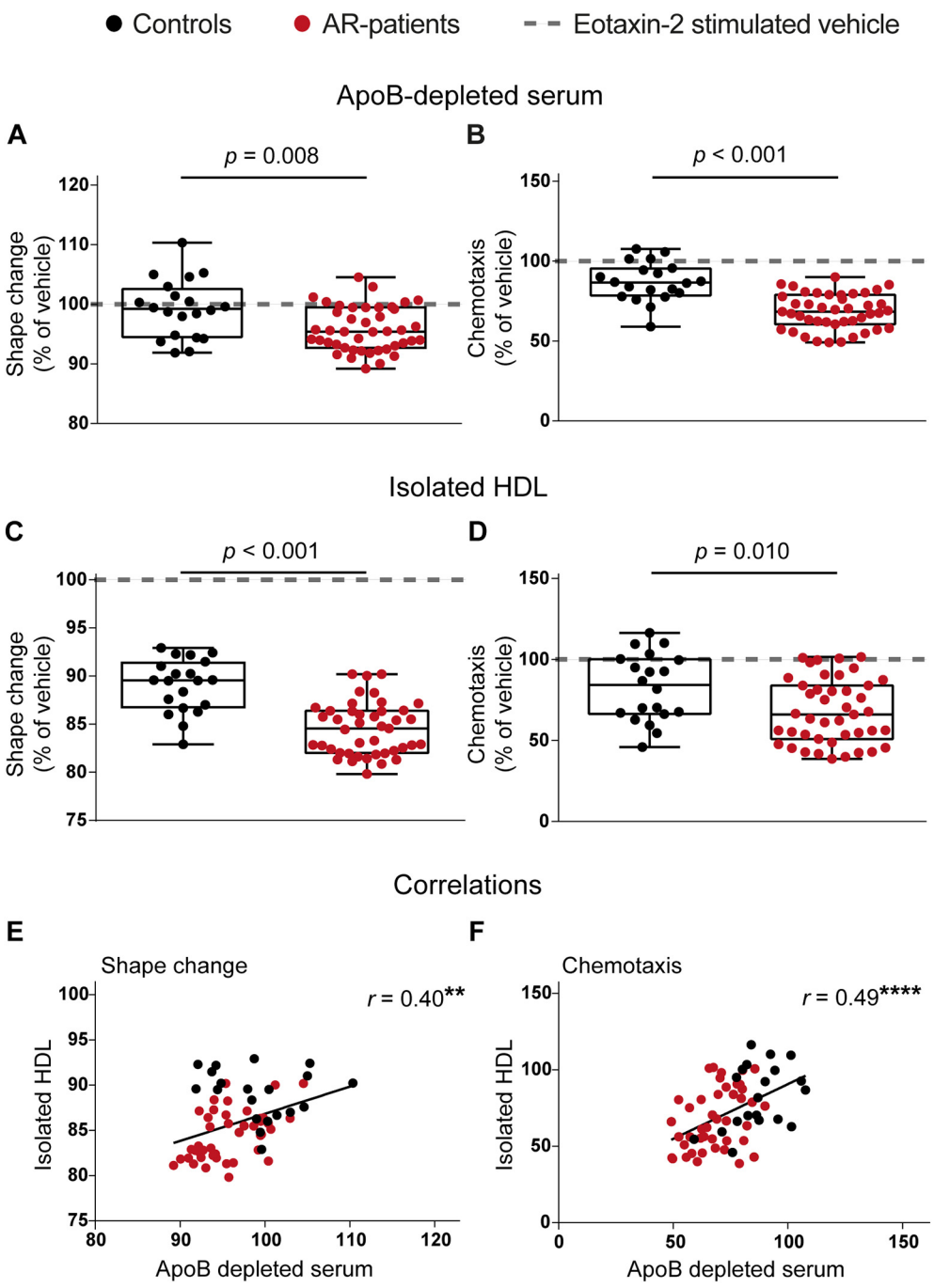

Fig. 4. AR-HDL shows improved ability to suppress eosinophil effector responses. ApoB-depleted serum or isolated HDL of controls (n = 20) and AR-patients (n = 43) was examined for their ability to modulate eosinophil effector responses. Isolated human eosinophils were pretreated with apoB-depleted serum (A) or isolated HDL (C) followed by stimulation with eotaxin-2/CCL24. Shape change was analyzed by flow cytometry. Responses were expressed as percent of vehicle (eotaxin-2/CCL24 in the absence of apoB-depleted serum or isolated HDL) treated cells (indicated by the grey dashed line) of five and three independent experiments, respectively (measured in duplicates with eosinophils from different donors). Eosinophils were pretreated with apoB-depleted serum (B) or isolated HDL (D), placed in Transwell inserts and allowed to migrate towards eotaxin-2/CCL24. Responses were expressed as percent of vehicle (eotaxin-2/CCL24 in the absence of apoB-depleted serum or isolated HDL) treated cells (indicated by the grey dashed line) of three independent experiments, respectively (measured in duplicates with eosinophils from different donors). Scatter plots of apoB-depleted serum and isolated HDL eosinophil shape change (E) and eosinophil chemotaxis (F). (A–D) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. (E, F) The Pearson correlation coefficients (*r*) are noted. $^{**}p < 0.01$, $^{****}p < 0.0001$. AR, allergic rhinitis; HDL, high-density lipoprotein; apoB, apolipoprotein B.

depleted serum of AR-patients to suppress eosinophil chemotaxis (Supplementary Fig. 3). Considerably weaker and sometimes qualitatively different associations, between HDL composition and functional properties, were observed in controls (Supplementary Fig. 4).

3.7. Specific IgE levels are associated with metrics of AR-HDL composition, distribution and function

Prompted by the marked alterations in AR-HDL composition, distribution and functionality, we next assessed potential associations with specific IgE levels of grass pollen, the most abundant allergen in the AR-patients group (Supplementary Table 3). We observed that specific IgE levels of grass pollen were significantly correlated with AR-HDL-associated apoE and weakly correlated with AR-HDL-associated SAA, AR-HDL-distribution, AR-HDL-associated PON and Lp-PLA2 activities as well as the capacity of AR-HDL to modulate cholesterol efflux.

4. Discussion

In the present study, we provide first evidence that AR is associated with alterations in HDL metabolism, thereby affecting HDL composition and functionality (Fig. 8). Both isolated HDL, as well as apoB-depleted serum of AR-patients, showed decreased anti-oxidative and anti-inflammatory activities, but an improved ability to suppress agonist-induced eosinophil effector responses. Interestingly, the activities of apoB-depleted sera and isolated HDL were correlated, suggesting that AR-associated changes in HDL function are reflected in apoB-depleted serum.

An important observation of the present study was that AR-HDL is defective in the suppression of monocyte NF-κB expression and

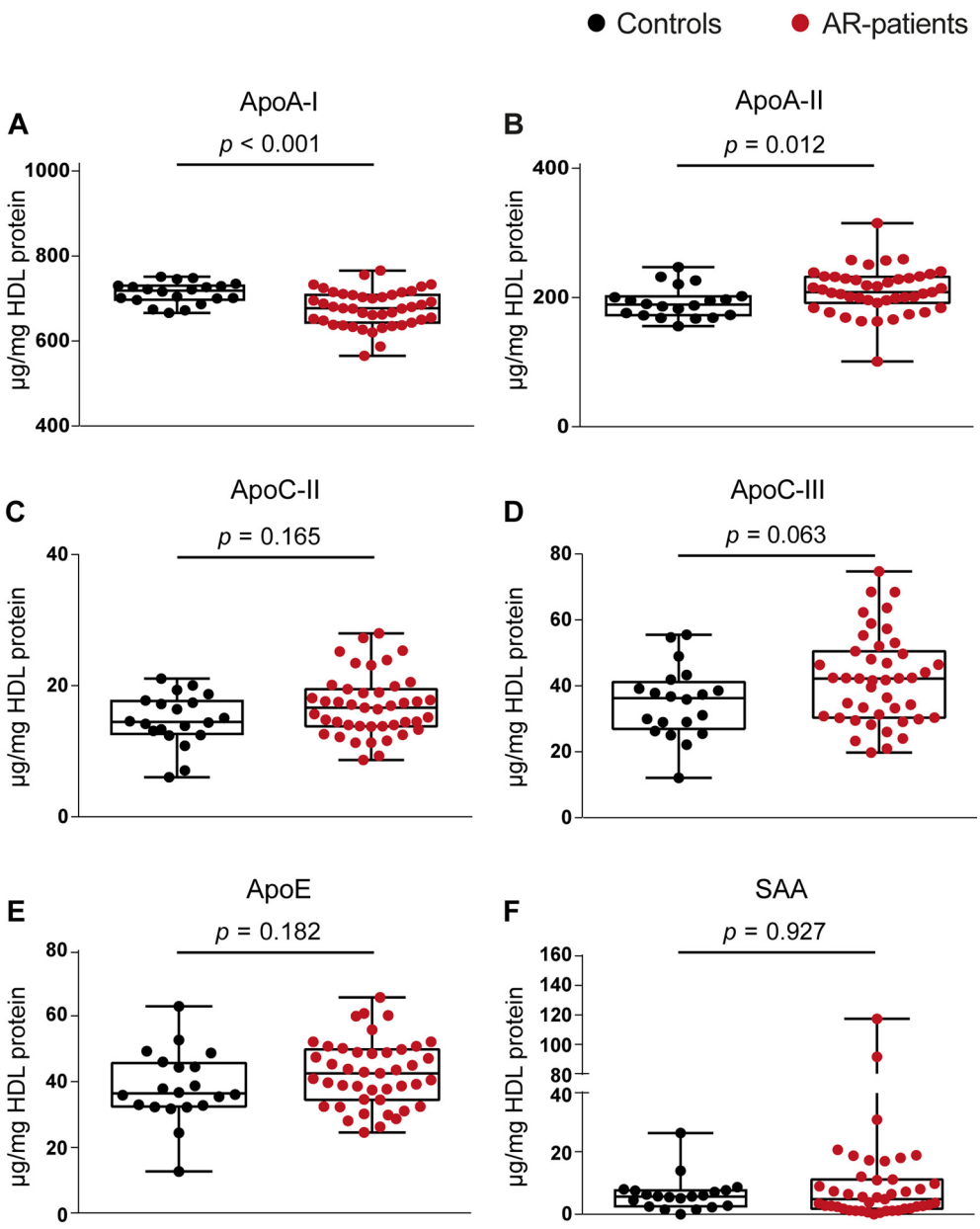

Fig. 5. Protein composition of HDL.
HDL-associated proteins from controls (n = 20) and AR-patients (n = 43), including apoA-I (A), apoA-II (B), apoC-II (C) and apoE (E) were determined by immunoturbidimetry. ApoC-III (D) and serum amyloid A (SAA) (F) were measured by ELISA. (A–F) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. AR, allergic rhinitis; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; SAA, serum amyloid A; HDL, high-density lipoprotein.

subsequent cytokine secretion, including IL-4, IL-6, IL-8, IL-12 p70, TNF-α and IL-1 beta. The loss of anti-inflammatory activity of AR-HDL may contribute to the progression and severity of the disease during the late-phase response of AR, as most of these cytokines are involved in allergic inflammation. For example, TNF-α activates signaling pathways that regulate the release of eotaxin and the cell surface expression of the intercellular adhesion molecule 1 of eosinophils [49]. IL-4 is a cytokine released by Th2 cells and involved in the late-phase reaction of AR, leading to eosinophil recruitment, activation and mucosal influx [20]. In addition, IL-6 is a Th2-type cytokine involved in the induction of IgE synthesis, proliferation and maturation of mast cells, while IL-8 is a chemokine known to induce leukocyte migration, that has been reported to be involved in the late-phase allergic reaction [50]. IL-1 beta plays a role in different allergic disorders via inflammasome-dependent activation [51].

In the late-phase response of AR, cells that infiltrate the nasal mucosa produce a variety of mediators, including reactive oxygen species [52]. Previous studies have shown that the major HDL apolipoproteins, apoA-I and apoA-II, are significantly elevated in the mucus proteome of AR patients, suggesting that HDL-associated apolipoproteins directly modulate the immune response [53–55]. In the present study, we observed that the anti-oxidative capacity and the PON activity of AR-HDL are reduced. PON is a calcium-dependent lactonase [56] with antioxidant [57], anti-inflammatory [58] and endothelial protective activities [59]. Importantly, previous studies reported that serum PON levels in children with AR were significantly lower [52], which is consistent with the reduced PON and anti-oxidative activity of AR-HDL observed in our study. These previous studies, together with our results, suggest a defective anti-oxidant capacity of HDL in AR, which may lead to an impaired ability to counteract the production of reactive oxygen species in the nasal mucosa of AR patients.

Surprisingly, we observed that AR-HDL showed an improved ability to suppress eotaxin-2/CCL24 induced eosinophil shape change and chemotaxis, when compared to HDL from controls. This supports the notion that AR is associated with complex alterations in HDL composition and function, linked to loss, as well as to gain of functional properties. Interestingly in this regard, the improved ability of AR-HDL to suppress eosinophil shape change was associated with apoA-II, apoC-III, LPC, PC and triglyceride content of AR-HDL.

A striking observation of the present study was the increased

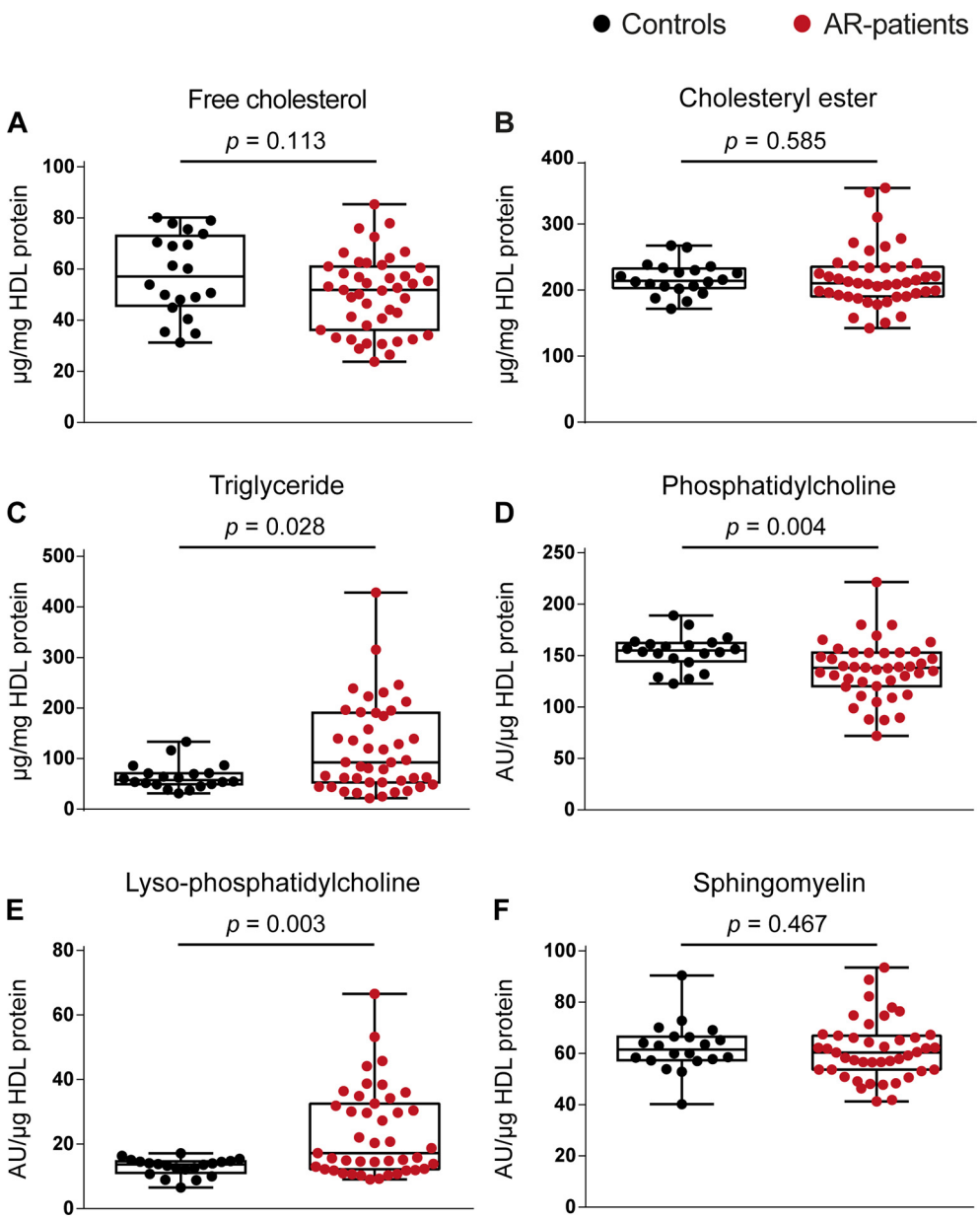

Fig. 6. Lipid composition of HDL.
HDL-associated lipids from controls (n = 20) and AR-patients (n = 43), including free cholesterol (A), cholesteryl ester (B) and triglyceride (C) were determined with commercially available kits. Phosphatidylcholine (D), lyso-phosphatidylcholine (E) and sphingomyelin (F) were determined with mass spectrometry. (A–F) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. AR, allergic rhinitis; AU, analyte/IS ratio; HDL, high-density lipoprotein.

triglyceride and LPC contents of AR-HDL, which were strongly associated with most metrics of AR-HDL function. The question now is why these complex lipid changes occur in AR-HDL. One reason might be that the triglyceride content is strongly associated with the apoC-III levels in AR-HDL ($p < 0.001$), consistent with the fact that apoC-III delays the catabolism of triglyceride-rich particles [60]. Triglyceride-rich HDL is a natural hepatic lipase substrate, that hydrolyses phospholipids and triglycerides from HDL [61]. In addition, we found that the Lp-PLA2 activity of AR-HDL was significantly increased. Lp-PLA2 hydrolyzes short- and medium-chain phospholipids and produces LPC [42]. Thus, hepatic lipase and Lp-PLA2 are likely candidates that induce, or at least contribute, to LPC formation in AR-HDL.

We have recently shown that HDL enriched with unsaturated LPC 16:0 effectively suppresses neutrophil [62] and eosinophil [14] effector responses. Since LPC 16:0 is significantly enriched in AR-HDL, our data suggest that LPC 16:0 in AR-HDL contributes to AR-HDL's improved ability to suppress eosinophilic effector responses. In line with our results, LPC levels in plasma and bronchoalveolar fluid were found to be elevated in rhinitis patients [63]. Despite its established role in the formation of HDL-associated LPCs, we observed that LCAT activity in the AR-sera remained unchanged. Surprisingly, LCAT activity was negatively associated with LPC content in AR-HDL. One possible explanation for this contra-intuitive finding is that LPC can inhibit LCAT activity [64].

In addition to the changes in the lipid composition of AR-HDL, our data show that changes in the HDL3 subfraction are related to the impaired ability of AR-HDL to suppress the secretion of monocyte cytokines. This is consistent with previous reports that HDL3 particles are superior to larger and more lipid-rich HDL2 particles in suppressing inflammatory responses [44]. In addition, it has been reported that

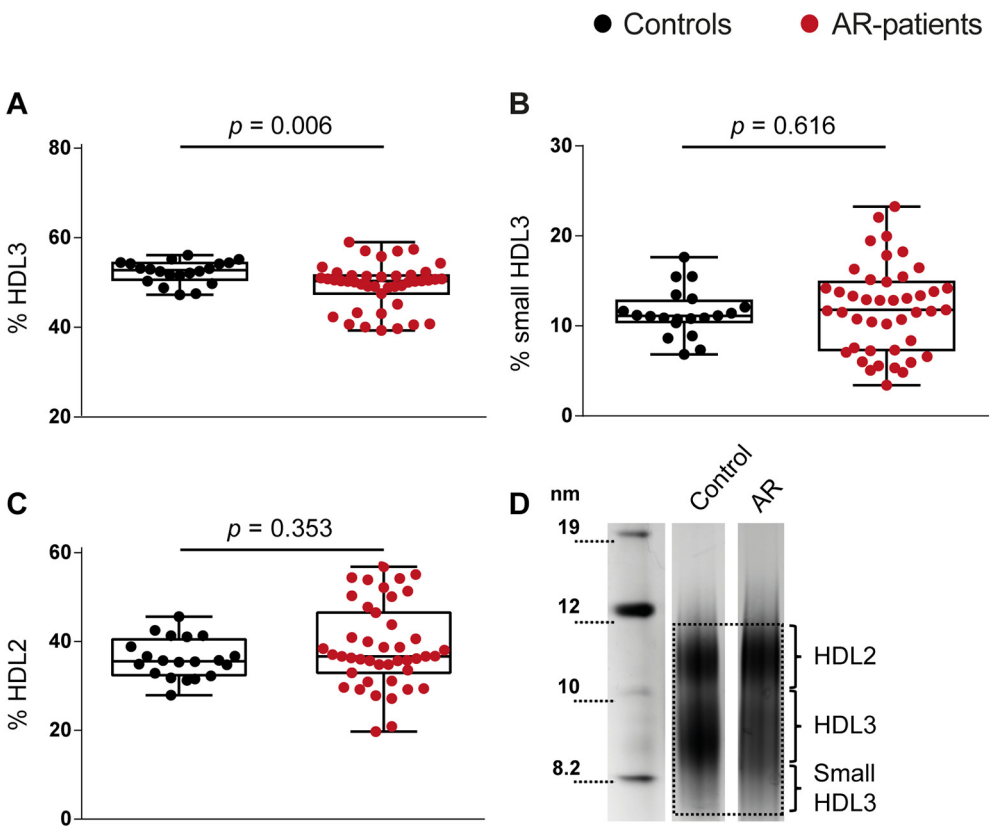

Fig. 7. Analysis of HDL subgroup distribution.
Isolated HDL of controls (n = 20) and AR-patients (n = 43) was separated by non-reducing and nondenaturing gradient gel electrophoresis. HDL-proteins were stained with Coomassie brilliant blue to determine distribution of HDL3 (A), small HDL3 (B) and HDL2 (C) subfractions. A representative gradient gel electrophoresis of HDL of one patient and one control sample is shown (D). (A–C) Differences between the two groups were analyzed with the Mann-Whitney U test. Individual data are depicted on top of boxplots showing median and interquartile range as well as minimum and maximum values. AR, allergic rhinitis; HDL, high-density lipoprotein.

small, dense HDL3 particles are superior to large, light HDL2 particles in removing oxidized lipids from other lipoproteins and cell membranes [44]. Therefore, our data suggest that the reduced content of the HDL3 subfraction contributes to the low anti-oxidant capacity of AR-HDL.

Another interesting observation of the present study was that CETP activity in sera of AR patients was significantly impaired. CETP

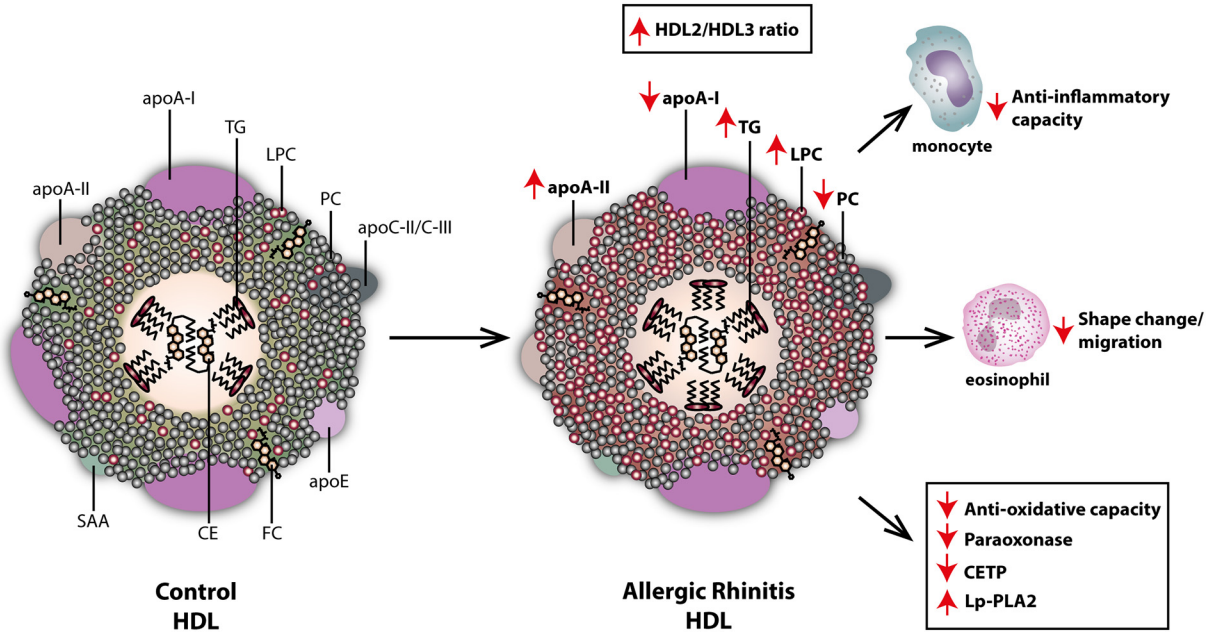

Fig. 8. Schematic illustration of HDL remodeling in AR-patients.
HDL from AR-patients exhibits various alterations in the protein and lipid composition linked to altered functional properties. Profound alterations in AR-HDL-lipid composition are observed, such as an increase in the AR-HDL-triglyceride and -LPC content and a decrease in the HDL-PC content. AR-HDL is significantly enriched in apoA-II, while apoA-I and the medium sized HDL3 are decreased. In AR-patients, the activity of Lp-PLA2 is markedly increased, while activities of paraoxonase and CETP are significantly decreased. AR-HDL shows impaired anti-oxidative and anti-inflammatory capacities, but an improved ability to inhibit eosinophil effector responses. HDL, high-density lipoprotein; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; SAA, serum amyloid A; TG, triglyceride; LPC, lyso-phosphatidylcholine; PC, phosphatidylcholine; CE, cholesteryl ester; FC, free cholesterol; CETP, cholesteryl ester transfer protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

circulates in plasma and is mainly bound to HDL [65], while it distributes cholesterol esters, triglycerides and to a lesser extent phospholipids between plasma lipoproteins [46]. We observed that CETP activity clearly correlated with triglyceride and LPC levels of AR-HDL, but interestingly, not with HDL cholesterol levels. We currently have no explanation for this, and further studies are needed to understand underlying mechanisms. In summary, our results suggest that AR induces complex changes in serum enzyme activities that affect HDL composition and function.

After detecting significant changes in AR-HDL composition, distribution and functionality, we investigated possible associations with the specific IgE values of grass pollen, the most common allergen in the AR patient group. We observed that specific IgE values of grass pollen were significantly correlated with AR-HDL-associated apoE, while we observed weaker correlations with AR-HDL-associated SAA, AR-HDL distribution, AR-HDL-associated PON and Lp-PLA2 activities, and the ability of AR-HDL to modulate cholesterol efflux.

Interestingly, we observed no impact of gender on AR-HDL functional properties (Supplementary Table 4) and we observed no change in cholesterol efflux capacity of AR-HDL when compared to HDL of controls, indicating that this major anti-atherogenic property of HDL [66] is not affected.

We acknowledge limitations to this study. Due to the laborious experiments and analyses, we had to keep the patient number rather small. Moreover, our study is exploratory and due to the design limited to be correlative in nature, not permitting causal inference. Therefore, further studies in larger cohorts are warranted to confirm our results. Strengths of our study are that we measured multiple metrics of HDL functionality, as well as HDL composition, in relatively young individuals, excluding a major contribution of age-associated diseases to alterations in AR-HDL composition and function.

In summary, the results of our study provide new evidence that AR significantly influences HDL composition and functionality, suggesting a novel link between HDL metabolism and allergy.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbalip.2019.06.007.

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Biological anti-psoriatic therapy profoundly affects high-density lipoprotein function

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ABSTRACT

Psoriasis is a common chronic inflammatory skin disease linked to increased cardiovascular risk. Functional impairment of high-density lipoprotein (HDL) may contribute to excessive cardiovascular mortality in psoriasis patients. Anti-cytokine therapies with biologics have been efficiently used for the management of psoriasis, however little data is available on the effects of biologic anti-psoriatic therapies on the composition and functionality of HDL. Blood samples were taken from 17 healthy volunteers and from 27 real-world psoriasis patients at baseline (no therapy with biologics) and after short-term (3 to 6 months) and intermediate-term (1 to 2 years) therapy. The biologics used included anti-interleukin (IL)-12/23p40 (ustekinumab), anti-IL17A (secukinumab) or anti-tumor necrosis factor-α (etanercept or adalimumab) antibodies. We observed that in psoriasis patients at baseline, metrics of HDL function including cholesterol efflux capacity of apolipoprotein B-depleted serum ($p = 0.021$), paraoxonase ($p < 0.001$) and lecithin-cholesterol acyltransferase ($p < 0.001$) activities were impaired, when compared to controls. Unexpectedly, we observed that short- and especially intermediate-term therapy with biologics markedly reduced HDL cholesterol efflux capacity ($p < 0.001$) and rendered HDL pro-inflammatory ($p < 0.001$), but increased paraoxonase ($p = 0.009$) and lecithin-cholesterol acyltransferase ($p = 0.019$) activities. All biologics caused similar changes in HDL composition, subclass distribution and cholesterol efflux capacity. Our results provide evidence that anti-psoriatic therapy with biologic agents is associated with changes in HDL functionality, particle composition and subclass distribution.

1. Introduction

Psoriasis is a common chronic inflammatory skin disease affecting approximately 2–3% of the population in Western countries and is equally prevalent in both sexes [1]. Pro-inflammatory cytokines and chemokines produced by activated keratinocytes recruit a variety of inflammatory cells from the circulation, leading to a "vicious cycle" of excessive immune response [2]. Specifically, increased cardiovascular risk of psoriasis patients has been observed in epidemiological and clinical studies [3]. Increased levels of inflammatory cytokines

Abbreviations: ABCA1, adenosine triphosphate-binding cassette subfamily A member 1; ABCG1, adenosine triphosphate-binding cassette subfamily G member 1; apo, apolipoprotein; cAMP, cyclic adenosine monophosphate; CANTOS, canakinumab anti-inflammatory thrombosis outcome study; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; DMEM, Dulbecco's Modified Eagle's Medium; FC, free cholesterol; HDL, high-density lipoprotein; IL, interleukin; LCAT, lecithin-cholesterol acyltransferase; LPC, lyso-phosphatidylcholine; NF-κB, nuclear factor-κB; PASI, psoriasis area and severity index; PC, phosphatidylcholine; PLTP, phospholipid transfer protein; SAA, serum amyloid A; SR-BI, scavenger receptor class B type I; TG, triglyceride; TNF, tumor necrosis factor.

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interleukin (IL) 6 and IL-1β are associated with an elevated risk of atherosclerotic cardiovascular disease, regardless of lipid levels [4]. Treatment with the anti-IL-1β monoclonal antibody canakinumab in the canakinumab anti-inflammatory thrombosis outcome study (CANTOS) led to a significant reduction in recurrent cardiovascular events [5]. Currently, various biologics against diverse inflammatory cytokines [2], such as targeting tumor necrosis factor (TNF)-α (etanercept [6] and adalimumab [7]), IL-17A (secukinumab [8]) and IL-12/23p40 (ustekinumab [9]) are applied with great efficiency in the therapy of psoriasis [10]. Biological active agents reduce systemic inflammation and are a very effective means of treating the skin manifestations of psoriasis. Biologics show both beneficial and adverse effects on the cardiovascular system [10]. For example, results from studies with TNF-α inhibitors are contradictory regarding the effects on cardiovascular risk [11–13]. In particular, data from a recent study have shown that administration of the anti-IL12/23 active agent ustekinumab can trigger severe cardiovascular events in patients at high cardiovascular risk and may be linked to plaque destabilization [14].

The ability of high-density lipoprotein (HDL)s to promote cholesterol efflux is inversely associated with early, asymptomatic atherosclerotic vascular disease in the general population [15] and with incident of cardiovascular events among the general population [16,17]. HDL cholesterol efflux capacity is a biomarker for subclinical coronary atherosclerosis in psoriasis patients [18]. When compared to healthy subjects, HDL isolated from psoriasis patients shows compositional changes, associated with impaired HDL-cholesterol efflux capacity [19–21]. Some aspects of HDL composition and function [22] as well as post-translational oxidization of HDL [23] were shown to be restored by anti-psoriatic therapy, however effects of biologics on HDL function remain poorly investigated.

In the present study, we investigated whether short- and intermediate-term anti-psoriatic therapy with various biologic agents affects HDL composition and function.

2. Materials and methods

2.1. Materials

Please see the Materials section in the Supplementary Material.

2.2. Ethical approvals

The Institutional Review Board of the Medical University of Graz approved the study protocol (21-523 ex 09/10) in accordance with the Declaration of Helsinki. Informed consent was obtained from all study subjects.

2.3. Characteristics of study subjects and blood collection

Blood specimens were sampled from 17 healthy volunteers (control) (10 males and 7 females) and from 27 patients with moderate to severe chronic psoriasis (16 males and 11 females) at baseline (no therapy with biologics), after 3 to 6 months (short-term) and after one up to two years (intermediate-term) therapy with biologics. Biologic therapeutics included anti-IL-12/23p40 (ustekinumab), anti-IL17A (secukinumab) or anti-TNF-α (etanercept or adalimumab) antagonists. The sample size power was based on our previous study [22]. The blood samples were taken during the year and seasonal effects should therefore not affect the results. The clinical characteristics of study subjects are given in Supplementary Tables 1 and 2. Specifically, 13 patients were treated with ustekinumab, 7 patients with secukinumab, 4 patients with etanercept and 3 patients with adalimumab. The majority of patients did not have any previous treatment with biologics (biologic naive) (Supplementary Table 2). The mean age (±standard deviation) of enrolled psoriasis subjects was 39.9 ± 15.0 and the age range was 18.9–69.3 years at the study entry (Supplementary Tables 1 and 2), while the mean age (±standard deviation) of enrolled healthy volunteers was 38.2 ± 8.9 (Supplementary Table 1). Blood collection, serum isolation, as well as apolipoprotein (apo) B-depleted serum preparation, were performed as previously described [24].

2.4. Isolation of HDL

HDL was isolated from serum of psoriasis patients at baseline (n = 27) and at short-term (n = 27) and intermediate-term (n = 27) therapy with biologic agents. We used an optimized one-step ultracentrifugation procedure to minimize HDL oxidation as previously described [24]. To avoid storage induced effects on HDL composition/structure [25], HDL isolation from stored serum (−70 ° C) of all psoriasis subjects (all time points) was performed at once within one week. To isolate HDL, density of serum was adjusted by addition of potassium bromide to 1.24 g/mL and a density gradient was generated in centrifuge tubes (16 × 76 mm) by layering the density-adjusted serum (1.24 g/mL) underneath a potassium bromide density solution (1.063 g/mL). The tubes were sealed and centrifuged at 65,000 rpm for 6 h at 15 ° C in a 90 Ti fixed angle rotor. After centrifugation, the visible HDL-containing band (containing HDL2 and HDL3 subclasses) was collected, concentrated using Vivaspin Turbo 4 ultracentrifugation spin columns and de-salted using the PD MiniTrap G-25 columns. Isolated HDL samples were stored at −70 ° C in the presence of 5% sucrose as cryoprotectant to avoid storage induced damage of HDL composition/structure, as described [25].

2.5. Biochemical quantification of HDL-associated apolipoproteins (apos)

ApoA-I, apoA-II, apoC-II, apoC-III and apoE were determined by immunoturbidimetry in apoB-depleted serum of psoriasis patients, as previously described [24].

2.6. Determination of serum and HDL lipid composition

Non-esterified cholesterol and total phospholipids were determined in apoB-depleted serum, cholesteryl esters, total cholesterol and triglycerides were determined both in serum and in apoB-depleted serum of healthy controls and psoriasis patients, using commercially available kits, as previously described [24]. Low-density lipoprotein-cholesterol was calculated according to the Friedewald equation using HDL-cholesterol values measured in apoB-depleted serum of healthy controls and psoriasis patients.

2.7. Mass spectrometry analysis of HDL lipid composition

The detailed description of the method can be found in the Supplementary Material.

2.8. C-reactive protein (CRP) and serum amyloid A (SAA) determination

CRP and SAA levels were evaluated in serum of psoriasis patients by enzyme-linked immunosorbent assay, as previously described [24].

2.9. Analysis of HDL subclasses

HDL subclasses were determined in serum of healthy controls and psoriasis patients using the Lipoprint System according to the manufacturer's instructions. The detailed description of the method can be found in the Supplementary Material.

2.10. Arylesterase activity of paraoxonase

Ca^{2+}-dependent arylesterase activity of paraoxonase was determined in apoB-depleted serum or in isolated HDL by a photometric assay using phenylacetate as substrate, as described with modifications [24]. Briefly, apoB-depleted serum (1.5 μL of 1:10 dilution) or isolated HDL (2

μg of protein) was added to 200 μL buffer containing Tris (100 mmol/L), $CaCl_2$ (2 mmol/L, pH 8.0) and phenylacetate (1 mmol/L). The rate of hydrolysis of phenylacetate was monitored by the increase of absorbance at 270 nm, while readings were taken every 15 s at room temperature to generate a kinetic plot. The slope from the kinetic chart was used to determine $\Delta Ab270_{nm}$/min. Enzymatic activity was calculated with the Beer-Lambert Law from the molar extinction coefficient of 1,310 $L \times mol^{-1} \times cm^{-1}$ for phenylacetate, in two independent experiments respectively, measured in duplicates.

2.11. Determination of the anti-oxidative capacity of HDL

The anti-oxidative activity of apoB-depleted serum and of isolated HDL of psoriasis patients was determined using dihydrorhodamine as described [24]. Briefly, dihydrorhodamine was suspended in DMSO to a 50 mM stock, which was diluted in HEPES (20 mM HEPES, 150 mM NaCl, pH 7.4) containing 2,2′-azobis-2-methyl-propanimidamide-dihydrochloride (1 mM) to a 10 μM working reagent. ApoB-depleted serum (10 μL of 1:10 dilution) or isolated HDL (10 μg of protein) was placed in 384-well plates and the volume was adjusted to 100 μL with HEPES buffer containing 10 μM dihydrorhodamine. The increase in fluorescence due to oxidation of dihydrorhodamine was monitored using an xMark plate reader for 90 min at 538 nm. After an initial lag phase of about 20 min, the rate of oxidation was linear. The increase in fluorescence was calculated from the linear range and used for comparison. The increase in fluorescence per minute of dihydrorhodamine in the absence of apoB-depleted serum or isolated HDL was set to 100%, and individual apoB-depleted serum or isolated HDL samples (three independent experiments measured in duplicates, respectively) were calculated as percentage of inhibition of dihydrorhodamine oxidation.

2.12. Lecithin-cholesterol acytransferase (LCAT) and cholesteryl ester transfer protein (CETP) activities

LCAT and CETP activities of serum were measured in duplicates, respectively, using commercially available kits [24].

2.13. Determination of nuclear factor-κB (NF-κB) activation

NF-κB activation was determined using U937 monocytes containing a 5× NF-κB green fluorescence protein reporter cassette [26]. Briefly, cells were cultivated in RPMI 1640 containing 10% fetal bovine serum and 1% penicillin/streptomycin and pretreated for 90 min with isolated HDL (50 μg protein/mL), in three independent experiments, measured in duplicates. Subsequently, cells were stimulated for 24 h with lipopolysaccharide (50 ng/mL), collected by centrifugation at 400 ×*g* for 7 min and fixed with 100 μL fixative solution, which was prepared as previously described [27]. The activation of NF-κB was assessed by flow cytometry.

2.14. HDL cholesterol efflux capacity

HDL cholesterol efflux capacity of apoB-depleted serum (2.8%) of healthy controls and psoriasis patients, and of isolated HDL (50 μg protein/mL) of psoriasis patients, was assessed in J774.2 cells. Briefly, cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) in the presence of 10% fetal bovine serum and 1% penicillin/streptomycin. Cells were plated on 48-well plates (300,000 cells/well), cultured for 24 h and loaded with 0.5 μCi/mL radiolabeled [^{3}H]-cholesterol in DMEM supplemented with 2% fetal bovine serum and 1% penicillin/streptomycin in the presence or absence of 0.3 mM 8-(4-chlorophenylthio)-cyclic adenosine monophosphate (cAMP) overnight, to induce or not respectively the expression of adenosine triphosphate-binding cassette subfamily A member 1 (ABCA1). After labeling, cells were rinsed with serum-free DMEM containing 1% penicillin/streptomycin and equilibrated with serum-free DMEM containing 1% penicillin/streptomycin and 2 mg/mL bovine serum albumin for 2 h. Subsequently [^{3}H]-cholesterol efflux was determined by incubating cells for 3 h with apoB-depleted serum (2.8%) or isolated HDL (50 μg protein/mL). Cholesterol efflux was expressed as radioactivity in the cell culture supernatant relative to total radioactivity (in the cell culture supernatant and cells) of two independent experiments respectively, measured in duplicates. ABCA1-mediated-cholesterol efflux of apoB-depleted serum was calculated by the difference between cAMP-stimulated and cAMP-non-stimulated cholesterol efflux of two independent experiments (measured in duplicates), respectively. All steps were performed in the presence of 2 μg/mL of an acyl coenzyme A cholesterol acyltransferase inhibitor (Sandoz 58-035), as previously described [15,24].

2.15. Statistical analysis

Data were tested for normality using the Shapiro-Wilk normality test. Data are presented as mean and standard deviation, if normally distributed, or as median and first and third quartile, if not (Supplementary Table 1 and Table 1). Differences between healthy controls and psoriasis patients at baseline were analyzed using the Student's *t*-test, two-tailed, if normally distributed, or the Mann-Whitney *U* test, two-tailed, if not normally distributed. Gender differences were evaluated using the Fisher's exact test. Differences between psoriasis patients at baseline and at short-term or intermediate-term therapy were analyzed with Repeated Measures One-way ANOVA using Dunnett's multiple comparisons test, if normally distributed, or with the Friedman test using Dunn's multiple comparisons test, if not normally distributed. Individual data are depicted in scatter dot plots showing median. Correlations between apoB-depleted serum and isolated HDL were determined using Pearson's correlation coefficient *r* (Fig. 1). Other correlations mentioned in the text were determined using Pearson's correlation coefficient *r* or Spearman's correlation coefficient *rho*, due to the skewed nature of some of the parameters. The significance level for the analyses was set to $\alpha = 0.05$. Statistical analyses were performed using GraphPad Prism (Version 8.0.1) and SPSS Statistics (Version 23).

Our study provided >90% power to detect differences in the cholesterol efflux capacity of apoB-depleted serum or isolated HDL, as well as in the ABCA-1-mediated cholesterol efflux, the paraoxonase activity, the anti-oxidant and the anti-inflammatory capacities of HDL, as described in our previous study [22].

3. Results

3.1. Clinical response of study subjects

Clinical characteristics, medical history and individual treatment plans are given in Supplementary Tables 1 and 2. The evaluation of the psoriasis area and severity index (PASI) showed a marked improvement in disease severity over the treatment period (Supplementary Tables 1 and 2). Anti-psoriatic treatment did lead in all but one patient (no. 12) to a highly satisfactory treatment response with reduction of PASI below 3 (Supplementary Table 2). Circulating CRP levels remained unchanged during therapy (Supplementary Table 1). Patients at short-term (3 to 6 months) and intermediate-term (one up to two years) therapy showed unchanged serum levels of total cholesterol, HDL-cholesterol and triglycerides in comparison to baseline (Supplementary Table 1). Low-density lipoprotein-cholesterol was slightly decreased at intermediate-term therapy ($p = 0.049$) in comparison to the corresponding baseline values (Supplementary Table 1). In comparison to healthy controls, psoriasis patients at baseline had significantly increased triglyceride levels ($p = 0.002$) and decreased HDL-cholesterol levels ($p = 0.002$) (Supplementary Table 1).

Table 1
Protein and lipid composition of HDL. HDL-associated proteins including apoA-I, apoA-II, apoC-II, apoC-III and apoE were determined by immunoturbidimetry and SAA by enzyme-linked immunosorbent assay; HDL-associated lipids including free cholesterol, cholesteryl-esters, triglycerides and total phospholipids were determined with commercially available kits. Phosphatidylcholine, lyso-phosphatidylcholine and sphingomyelin were determined using mass spectrometry, for psoriasis patients at baseline (n = 27) and at short-term (n = 27) and intermediate-term (n = 27) therapy with biologic agents. Data are presented as mean ± standard deviation or median with first and third quartile. Differences between baseline and short-term or intermediate-term therapy were analyzed with Repeated Measures One-way ANOVA or with the Friedman test. Data are considered significant at $p < 0.05$. Specifically, $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$. Abbreviations represent: apo, apolipoprotein; HDL, high-density lipoprotein; SAA, serum amyloid A.

	Baseline (no therapy)	Short-term therapy	*p* value	Intermediate-term therapy	*p* value
ApoA-I (% HDL protein)	68.8 ± 5.7	69.4 ± 4.9	0.648	68.8 ± 4.4	0.999
ApoA-II (% HDL protein)	19.8 ± 2.5	20.0 ± 2.8	0.333	20.8 ± 3.0	**0.011**
ApoC-II (% HDL protein)	1.4 (1.2–2.2)	1.6 (1.4–1.9)	0.553	1.5 (1.1–1.7)	>0.999
ApoC-III (% HDL protein)	3.9 (3.5–6.7)	5.2 (4.3–8.3)	**0.002**	4.4 (3.5–6.3)	0.644
ApoE (% HDL protein)	2.2 (1.7–2.7)	1.1 (0.8–1.8)	**<0.001**	2.1 (1.8–2.6)	0.347
SAA (% HDL protein)	1.0 (0.6–2.8)	1.0 (0.5–1.7)	0.347	0.8 (0.5–1.5)	0.392
Free cholesterol (% HDL lipid)	6.1 ± 1.0	6.0 ± 1.9	0.957	5.2 ± 1.7	**0.004**
Cholesteryl ester (% HDL lipid)	20.4 ± 4.3	19.7 ± 4.8	0.810	20.7 ± 3.6	0.882
Triglyceride (% HDL lipid)	11.6 ± 3.0	12.7 ± 3.3	0.155	12.0 ± 4.2	0.773
Total phospholipids (% HDL lipid)	61.8 ± 3.8	61.5 ± 5.3	0.963	62.1 ± 1.8	0.894
Phosphatidylcholine (fmol/μL)	1269.0 ± 169.9	1411.0 ± 277.1	0.061	1527.0 ± 327.8	**<0.001**
Lyso-phosphatidylcholine (% Phosphatidylcholine)	3.1 (2.4–3.6)	3.5 (2.8–4.1)	>0.999	2.2 (1.8–3.6)	0.114
Sphingomyelin (% Phosphatidylcholine)	14.7 (13.2–16.8)	14.9 (12.7–19.4)	>0.999	14.5 (11.3–16.6)	0.828

3.2. Biologic anti-psoriatic therapy decreases cholesterol efflux capacity and the anti-inflammatory capability of HDL

Cholesterol efflux capacity is a biomarker that remains remarkably stable over time in the general population [28]. To determine whether anti-psoriatic therapy with biologics affects HDL cholesterol efflux capacity over time, we used an established assay [15,29] using cAMP stimulated J774.2 macrophages and apoB-depleted serum (or isolated HDL) as cholesterol acceptors. This cholesterol efflux assay is used to test the ability of apoB-depleted serum to promote cholesterol efflux from cells overexpressing ABCA1. In line with results of our previous studies [19,22], psoriasis patients at baseline showed significantly impaired cholesterol efflux capacity when compared to controls ($p = 0.021$) (Fig. 1a). Unexpectedly, cholesterol efflux capacity of apoB-depleted serum was significantly decreased after short- ($p = 0.003$) and intermediate-term ($p < 0.001$) anti-psoriatic therapy in comparison to baseline measurements (Fig. 1b). Notably, the effect of biologics on cholesterol efflux capacity was independent of sex, age, PASI at study entry, presence of psoriatic arthritis and previous treatment history of the patients, irrespective whether they were biologic-naive or not (data not shown). Interestingly, all biologics induced similar effects on cholesterol efflux capacity of apoB-depleted serum (Supplementary Fig. 1). Lipid-poor HDL, as well as preβ-1 HDL, are efficient inducers of ABCA1-mediated cholesterol efflux [30,31]. When calculating the ABCA1-dependent-cholesterol efflux (difference in efflux between cAMP-stimulated and non-stimulated J774.2 macrophages), we observed that after intermediate-term therapy ABCA1 mediated cholesterol efflux capacity of apoB-depleted serum was impaired ($p < 0.001$) (Fig. 1c).

To determine whether biologics affect the functionality of mature HDL, we isolated HDL from sera of psoriasis patients. Cholesterol efflux mediated by isolated (mature) HDL is mainly mediated by adenosine triphosphate-binding cassette subfamily G member 1 (ABCG1), scavenger receptor class B type I (SR-BI) and passive diffusion, with only a minor contribution from ABCA1, given that a large fraction of lipid-poor apoA-I is lost during ultracentrifugation [22,32]. We found a significant negative effect of biologic anti-psoriatic on cholesterol efflux capacity of isolated HDL (Fig. 1d), clearly suggesting that anti-psoriatic therapy affects the functionality of mature HDL. Cholesterol efflux capacities of apoB-depleted sera and isolated HDL correlated significantly ($r = 0.64$) (Fig. 1e).

3.3. Biologic anti-psoriatic therapy affects anti-inflammatory properties of HDL

HDL isolated from healthy subjects shows anti-inflammatory properties [33]. We next tested the ability of HDL to modulate lipopolysaccharide-induced activation of the pro-inflammatory transcription factor NF-κB in monocytes. HDL isolated from psoriasis patients at short-term therapy with biologics did not affect NF-κB activation in monocytes, when compared to baseline values. However, at intermediate-term therapy we observed that isolated HDL increased NF-κB activation ($p < 0.001$) (Fig. 1f).

3.4. Biologic anti-psoriatic therapy improves arylesterase activity of HDL-associated paraoxonase

Next, we investigated whether other important functional properties of HDL are affected during anti-psoriatic therapy. For that purpose, we assessed HDL-associated paraoxonase activity and the anti-oxidative capacity of apoB-depleted serum. In comparison to healthy controls, apoB-depleted serum of psoriasis patients at baseline showed a significantly impaired paraoxonase activity ($p < 0.001$) (Fig. 2a). Interestingly, we observed an increase in the paraoxonase activity of apoB-depleted sera of psoriasis patients at intermediate-term therapy in comparison to baseline ($p = 0.004$), whereas at short-term therapy only a trend towards increased activity was observed ($p = 0.059$) (Fig. 2b). Similar to apoB-depleted sera, isolated HDL from psoriasis patients showed an increased paraoxonase activity at intermediate-term therapy in comparison to baseline ($p = 0.009$) (Fig. 2c).

3.5. Biologic anti-psoriatic therapy does not decrease the anti-oxidative capacity of HDL

The ability of apoB-depleted serum of psoriasis patients to inhibit free radical-induced oxidation of the fluorescent dye dihydrorhodamine was markedly reduced at intermediate-term therapy ($p = 0.012$) (Fig. 3a). However, the anti-oxidative capacity of isolated HDL was not altered (Fig. 3b), suggesting that other factors than HDL affect the anti-oxidative capacity of apoB-depleted serum. This is in line with the fact that HDL particles are minor contributors to the anti-oxidant capacity of plasma, irrespective of the oxidation mechanism in addition to HDL [34].

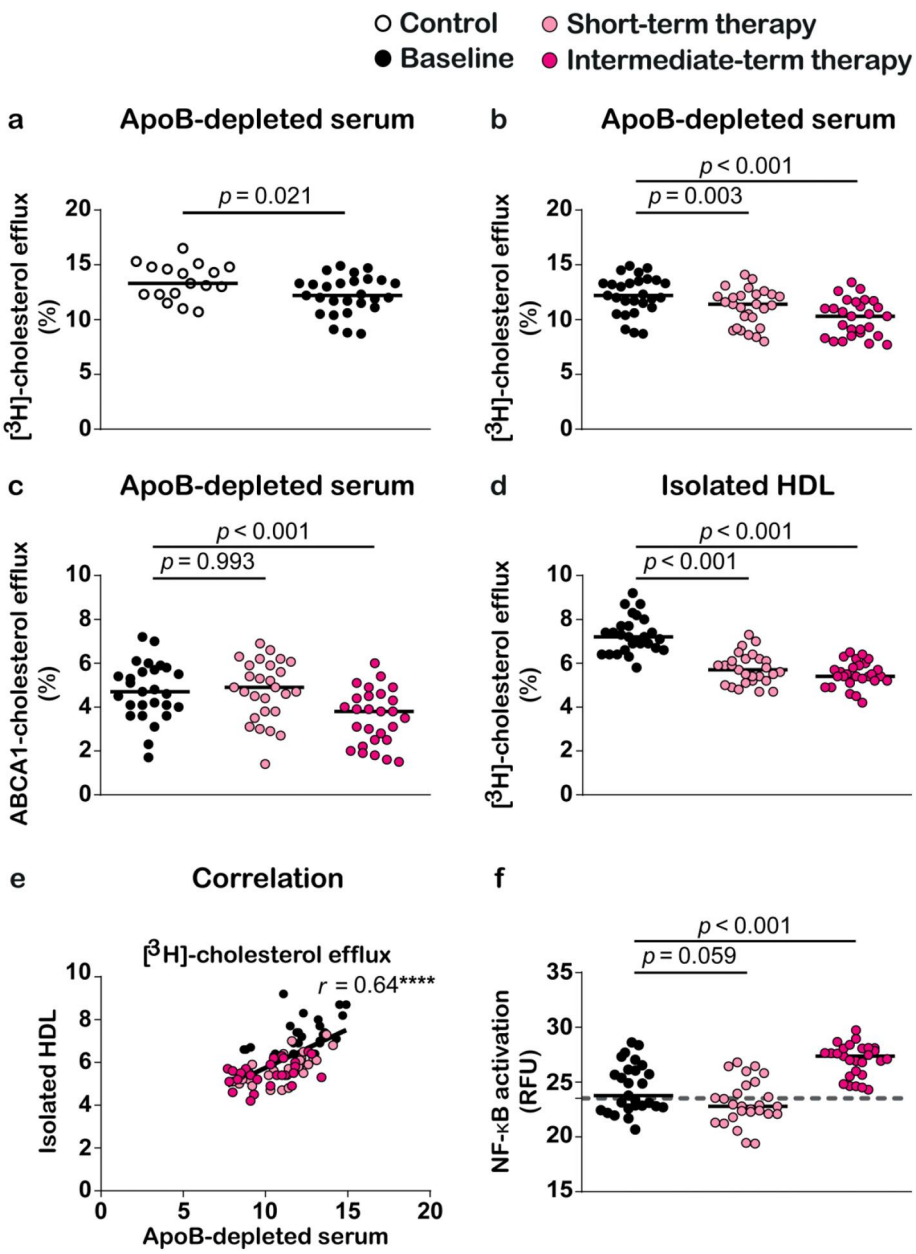

Fig. 1. Biologic anti-psoriatic therapy decreases the HDL-cholesterol efflux capacity and the anti-inflammatory potential of HDL. The cholesterol efflux capacity of apoB-depleted serum (a, b) or isolated HDL (d) of healthy controls (n = 17) and/or of psoriasis patients (n = 27) at baseline and during short- and intermediate-term therapy was investigated in cAMP-stimulated J774.2 macrophages. (c) The cholesterol efflux capacity of apoB-depleted serum of psoriasis patients was additionally investigated in non-cAMP-stimulated J774.2 macrophages to evaluate the ABCA1-mediated-cholesterol efflux. (e) Association of cholesterol efflux capacity of apoB-depleted serum and isolated HDL. Pearson's *r* is noted. (f) HDL's ability to modulate lipopolysaccharide-induced activation of NF-κB in monocytes was evaluated in psoriasis patients at baseline (n = 27), at short-term and at intermediate-term therapy. The grey dashed-line represents lipopolysaccharide treated cells in the absence of HDL. (a) Student's *t*-test, two-tailed, data are depicted in scatter dot plots showing median. (b–d, f) Repeated Measures One-way ANOVA, data are depicted in scatter dot plots showing median. Symbol represents: ****, $p < 0.0001$. Abbreviations represent: ABCA1, adenosine triphosphate-binding cassette subfamily A member 1; apo, apolipoprotein; HDL, high-density lipoprotein; NF-κB, nuclear factor-κB; RFU, relative fluorescence units.

3.6. Biologic anti-psoriatic therapy alters HDL subclass distribution and increases LCAT activity

The composition and subclass distribution of HDL particles strongly determines their anti-atherogenic properties [35]. We analyzed HDL subclass distribution using automated electrophoresis on a Lipoprint system. In comparison to healthy controls, psoriasis patients at baseline showed no significant alterations in the larger HDL subclasses (Fig. 4a), but increased intermediate HDL subclasses ($p < 0.001$) (Fig. 4b) and a non-significant trend towards decreased small HDL subclasses ($p = 0.088$) (Fig. 4c). Importantly, we observed that intermediate-term therapy with biologics further altered HDL subclass distribution. Specifically, at intermediate-term therapy we observed a decrease of the larger HDL subclass ($p = 0.002$) (Fig. 4d), but no significant change in the intermediate HDL subclass (Fig. 4e) and a trend ($p = 0.053$) towards an increase in the small HDL subclass (Fig. 4f). The large HDL subclass was positively correlated with the cholesterol efflux of apoB-depleted serum ($r = 0.448$, $p < 0.001$), while the intermediate HDL subclass showed a negative association ($r = -0.492$, $p < 0.001$) (data not shown). Representative distributions of HDL subclasses assessed by the Lipoprint system are given in Supplementary Fig. 2 and 3. All biologics induced similar effects in the large HDL subclass distribution (Supplementary Fig. 4a–d).

LCAT is essential for the esterification of cholesterol, leading to the formation of more spherical HDL particles [36]. LCAT activity was significantly impaired in psoriasis patients at baseline in comparison to healthy controls ($p < 0.001$) (Fig. 5a). Of note, LCAT activity increased after intermediate-term therapy in comparison to baseline ($p = 0.019$) (Fig. 5b), while the CETP activity was not changed (Supplementary Fig. 5).

3.7. Biologic anti-psoriatic therapy alters HDL composition

Analysis of HDL composition of psoriasis patients indicated no change in HDL's main protein constituent apoA-I, whereas apoA-II content of HDL was increased at intermediate-term therapy ($p = 0.011$) (Table 1). Notably, we observed increased levels of apoC-III ($p = 0.002$) and decreased levels of apoE ($p < 0.001$) at short-term therapy in

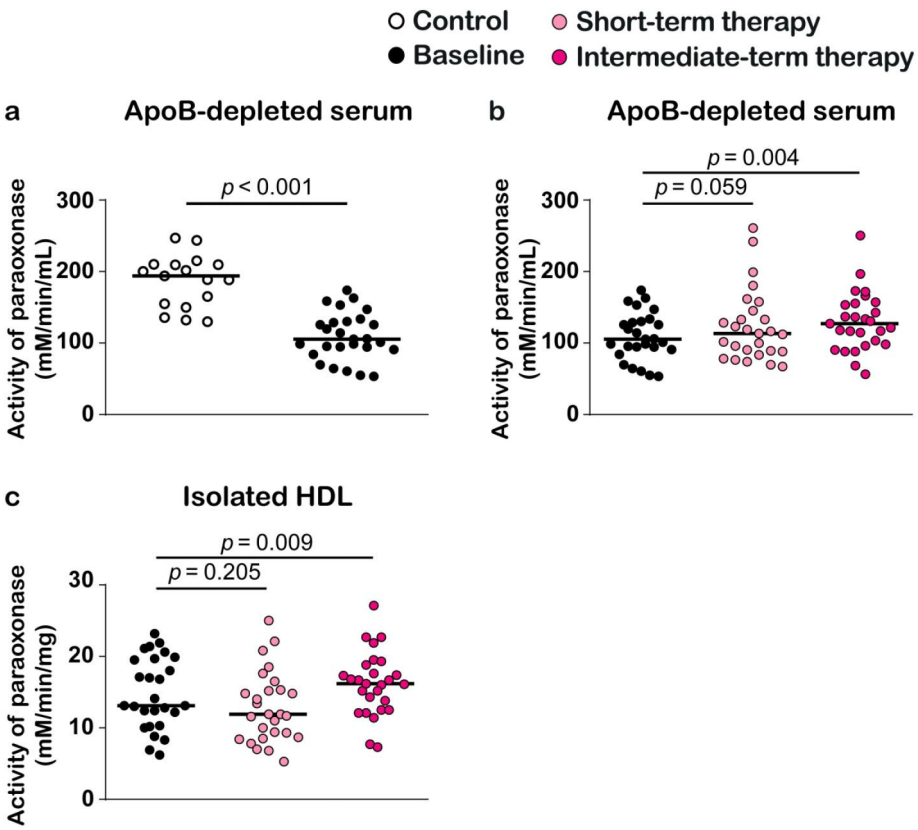

Fig. 2. Biologic anti-psoriatic therapy improves the arylesterase activity of HDL-associated paraoxonase. Arylesterase activity of paraoxonase was evaluated in apoB-depleted serum (a–b) or isolated HDL (c) of healthy controls (n = 17) and/or of psoriasis patients (n = 27) at baseline, and at short-term and intermediate-term therapy. (a) Student's *t*-test, two-tailed, data are depicted in scatter dot plots showing median. (b–c) Repeated Measures One-way ANOVA or Friedman test, data are depicted in scatter dot plots showing median. Abbreviations represent: apo, apolipoprotein; HDL, high-density lipoprotein.

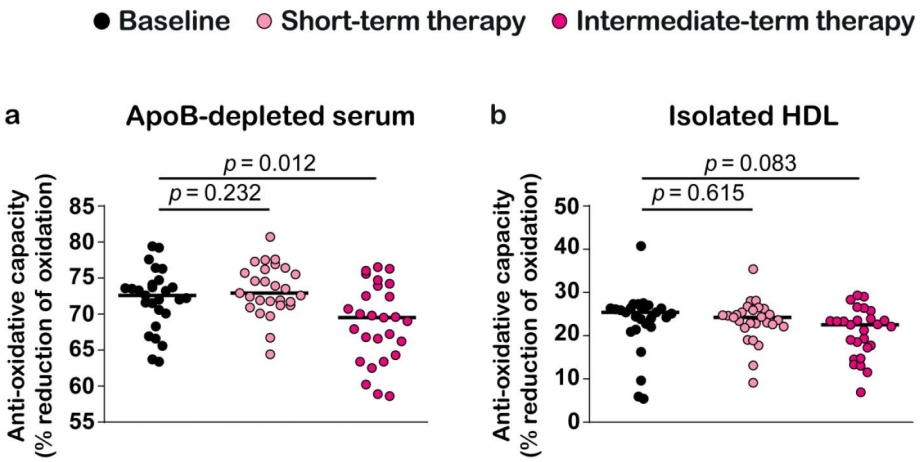

Fig. 3. Biologic anti-psoriatic therapy does not decrease the anti-oxidative capacity of isolated HDL. The anti-oxidative capacity was evaluated in apoB-depleted serum (a) or in isolated HDL (b) of psoriasis patients (n = 27) at baseline, and at short-term and intermediate-term therapy. (a, b) Repeated Measures One-way ANOVA or Friedman test, data are depicted in scatter dot plots showing median. Abbreviations represent: apo, apolipoprotein; HDL, high-density lipoprotein.

comparison to baseline, which normalized at intermediate-term therapy. Levels of apoC-II and SAA remained unchanged during therapy (Table 1).

Regarding the lipid composition of HDL, we observed no change in the cholesteryl ester, triglyceride, total phospholipid, lysophosphatidylcholine and sphingomyelin content of HDL during anti-psoriatic therapy (Table 1). Interestingly, increased HDL phosphatidylcholine content ($p < 0.001$) and decreased HDL free cholesterol content ($p = 0.004$) were observed at intermediate-term anti-psoriatic therapy in comparison to baseline. At short-term biologic anti-psoriatic therapy though, only a trend towards increased HDL phosphatidylcholine content was observed in comparison to baseline ($p = 0.061$), while HDL content of free cholesterol remained unchanged (Table 1). All biologics induced similar effects in HDL-associated lipids (Supplementary Fig. 4e–l).

4. Discussion

In the present study, we demonstrate that effective biologic anti-psoriatic therapies are associated with marked changes in HDL composition and functionality (Fig. 6). We observed that biologic therapy is associated with complex changes in HDL structure, composition and metabolism that profoundly affect HDL function.

Biological active agents are very effective in treating the skin

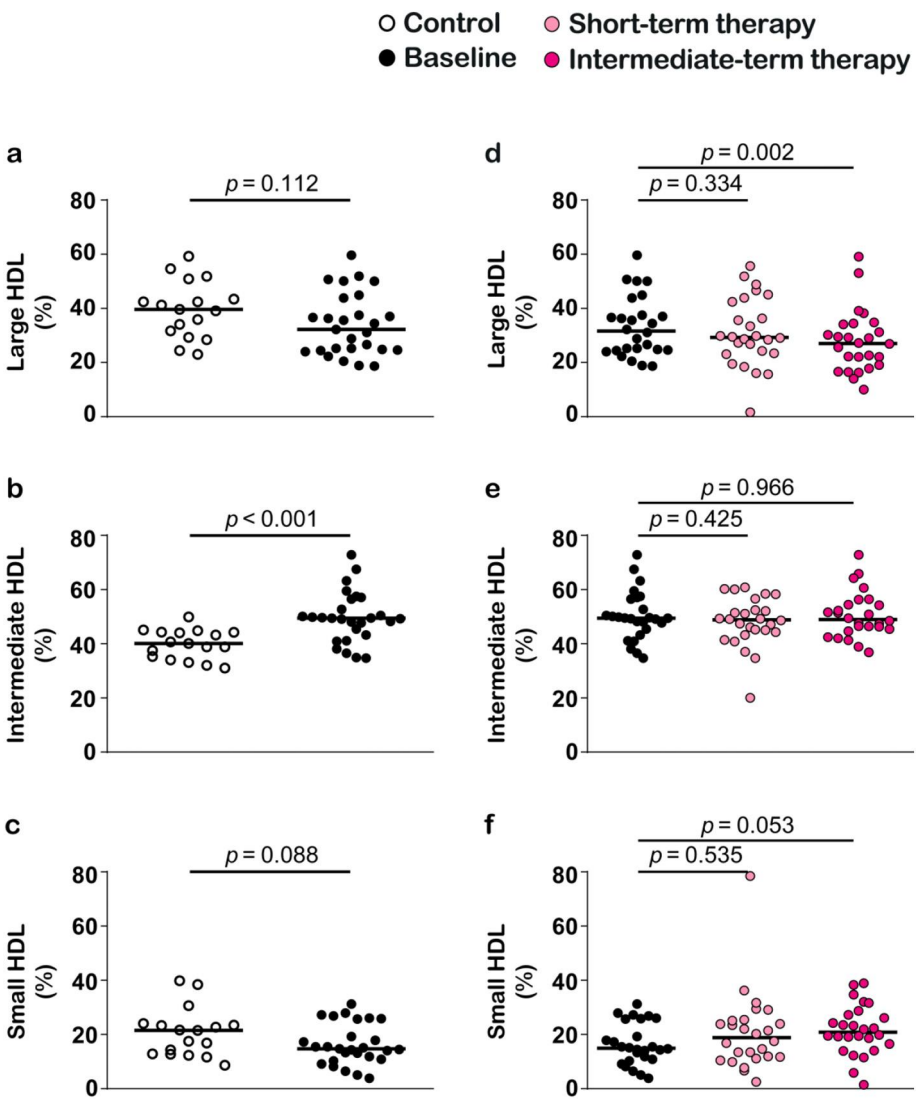

Fig. 4. Biologic anti-psoriatic therapy alters HDL subclass distribution. HDL subgroup distribution was determined in serum of healthy controls (n = 17) and of psoriasis patients (n = 26) at baseline, at short-term and at intermediate-term therapy, by an electrophoretic method on polyacrylamide gels (Lipoprint System). HDL-lipids were stained with a lipophilic dye to determine the distribution of large, intermediate and small HDL particles. Distribution of (a) large HDL, (b) intermediate HDL and (c) small HDL of healthy controls in comparison to psoriasis patients at baseline. (d) Large HDL, (e) intermediate HDL and (f) small HDL distribution of psoriasis patients at baseline, and at short- and intermediate-term therapy. (a–c) Student's *t*-test, two-tailed, data are depicted in scatter dot plots showing median. (d–f) Repeated Measures One-way ANOVA or Friedman test, data are depicted in scatter dot plots showing median. Abbreviation represents: HDL, high-density lipoprotein.

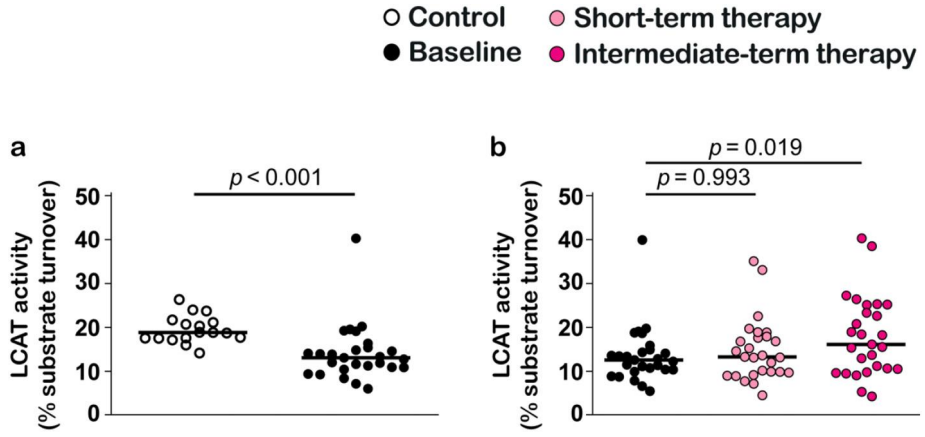

Fig. 5. Biologic anti-psoriatic therapy increases LCAT activity. The LCAT activity was evaluated in serum of healthy controls (n = 17) and of psoriasis patients (n = 27) at baseline, at short-term and at intermediate-term therapy. (a) Mann-Whitney *U* test, two-tailed, data are depicted in scatter dot plots showing median. (b) Friedman test, data are depicted in scatter dot plots showing median. Abbreviation represents: LCAT, lecithin-cholesterol acyltransferase.

manifestations of psoriasis by targeting/reducing pro-inflammatory cytokines and chemokines produced by activated keratinocytes. This appears to effectively block the recruitment of a variety of inflammatory cells from the circulation, which leads to a "vicious cycle" of excessive immune response [2].

Ustekinumab is a human monoclonal antibody neutralizing IL-12

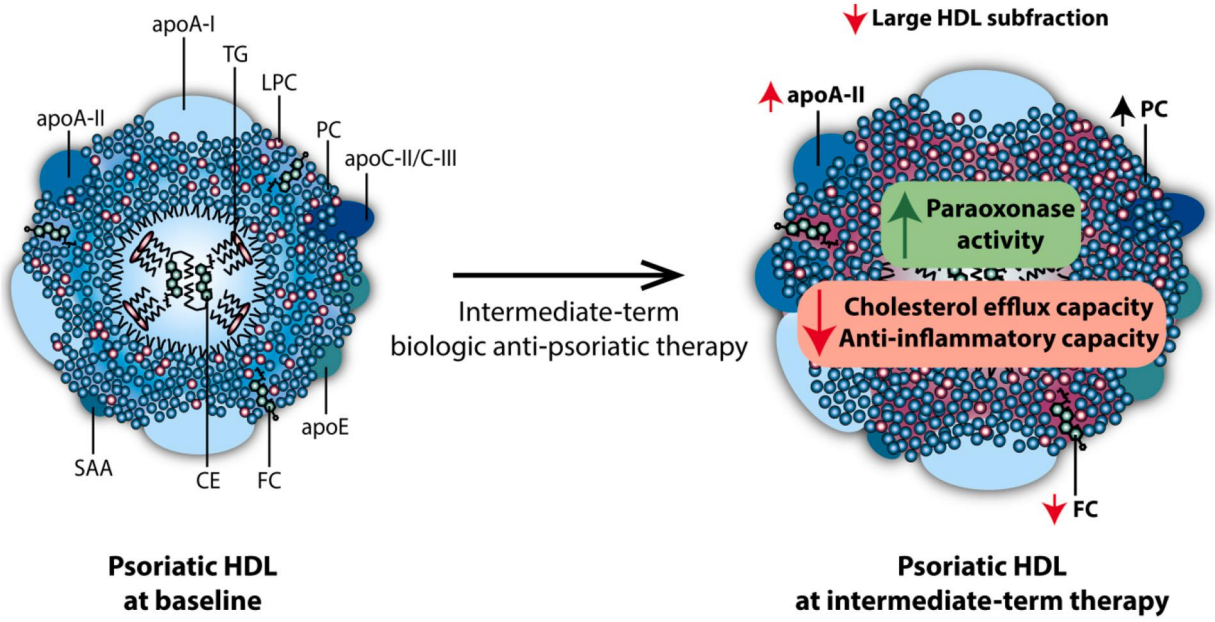

Fig. 6. Schematic illustration of HDL remodelling at intermediate-term biologic anti-psoriatic therapy. HDL from psoriasis patients at intermediate-term biologic anti-psoriatic therapy exhibits alterations in HDL-apolipoprotein and -lipid composition and HDL particle distribution, linked to altered HDL functionality. Symbols represent: green rectangle/arrow, improved HDL functional property; red rectangle/arrow, impaired HDL functional properties; short black arrow, alteration in HDL particle composition; short red arrows, alterations in HDL particle composition/distribution linked with impaired HDL functionality. Abbreviations represent: apo, apolipoprotein; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; LPC, lyso-phosphatidylcholine; PC, phosphatidylcholine; SAA, serum amyloid A; TG, triglyceride.

and IL-23 bioactivity, via blocking their interaction with the IL-12Rβ1 receptor [37], inhibiting both the Th1 and the Th17 signaling pathways that are up-regulated in psoriasis [38]. Specifically, IL-23 promotes the clonal expansion and differentiation of Th22 cells that produce IL-22, which works together with IL-19/IL-36γ to alter the terminal differentiation and proliferation of keratinocytes [38]. IL-12 is produced by activated dendritic cells and promotes the influx of Th1 cells into the lesional psoriatic skin [38]. Secukinumab is a recombinant, high-affinity, fully human immunoglobulin G1κ monoclonal antibody that selectively binds and neutralizes IL-17A via inhibition of its interaction with the IL-17 receptor, resulting in inhibition of pro-inflammatory cytokine and chemokine release [37,39,40]. Specifically, IL-17A acts alone or synergistically with TNF-α and induces the expression of psoriasis-related genes in keratinocytes, leading to epidermal hyperplasia and the production of antimicrobial peptides [38]. Etanercept and adalimumab are TNF-α inhibitors that block the interaction of TNF-α with cell-surface receptors and down-regulate Th17-activated genes, cell products as well as downstream effector molecules, while they may reduce IL-22 and IL-17A serum levels. Specifically, TNF-α, acting as a pro-inflammatory cytokine secreted both by T cells and antigen-presenting cells within the lesional skin, is responsible for stimulating keratinocyte pro-inflammatory mediator production and for facilitating entry of inflammatory cells into the lesional skin, via induction of adhesion molecules on vascular endothelial cells [41,42].

Importantly, the observed changes in HDL particle composition and distribution were similar across the different types of biological anti-psoriatic therapy and did not appear to be due to the effect of any particular biological active agent (Supplementary Fig. 4). This suggests that the effects on HDL functionality induced by biologic anti-psoriatic therapy may be a side effect of the effective reduction in skin manifestations and/or skin inflammation. However, we cannot exclude that an unidentified common downstream event, after blockade of TNF-α, IL-17A or IL12/23, affects HDL metabolism and function. However, further studies are needed to understand the complex underlying mechanisms.

Of note, biological agents may have adverse effects on the cardiovascular system depending on the target and mode of action of the cytokine concerned [10]. Results with TNF-α inhibitors are conflicting [11–13] and the anti-IL12/23 agent ustekinumab may even trigger severe cardiovascular events in patients at high cardiovascular risk [14]. In addition, there was controversy over the risk of major cardiovascular events associated with treatment with the anti-IL-12/23 antibody briakinumab, and the marketing authorization application was withdrawn [43,44]. However, it should be noted that other studies with ustekinumab showed a neutral effect on cardiovascular parameters [45–48]. Few data are available on IL-17A inhibitors, such as secukinumab, mainly concerning the efficacy and safety of the antibody [39,49,50]. A few case reports [51,52] and more extensive studies suggested mixed effects on cardiovascular risk factors [53–55].

It is assumed that HDL-mediated atheroprotective activities are pleiotropic in nature. The ability of HDL to promote reverse cholesterol transport, is thought to play a key role and has been inversely associated with cardiovascular mortality independently of HDL-cholesterol level and other risk factors [16,17,56] The development of coronary atherosclerosis in psoriasis patients may be partially related to impaired cholesterol efflux capacity from macrophages [18,19], which was also observed in our study. We observed that anti-psoriatic therapy with biologics was associated with a severely impaired cholesterol efflux capacity of HDL and apoB-depleted serum. Many factors, including HDL particle size and composition, significantly influence the functionality of HDL [57]. ApoB-depleted serum contains various HDL subpopulations along with lipid-poor apoA-I and the preβ-1 HDL particles, which are acceptors of cholesterol effluxed by ABCA1 [30,31] in addition to the intermediate- and small-sized HDL particles including the 3b and 3c subfractions [36,58]. Interestingly, we observed a reduction of ABCA1-mediated-cholesterol efflux of apoB-depleted serum at intermediate-term therapy, although analysis of the HDL subclass distribution revealed that the intermediate and the small HDL subclasses were not significantly altered. Therefore, one may assume that the decreased ABCA1 mediated cholesterol efflux of apoB-depleted serum is either due to a reduction of lipid-poor apoA-I and/or preβ-1-HDL particles or to an impaired functionality of these particles due to changes in their

composition.

To directly determine the functionality of HDL particles during biologic anti-psoriatic therapy, we isolated HDL and evaluated HDL-mediated cholesterol efflux. It has to be noted, that during the ultracentrifugation procedure a large fraction of lipid-poor apoA-I and a part of the lipid-poor preβ-1 HDL particles are lost [22,32], whereas large and intermediate HDL subclasses are efficiently isolated. Interestingly, we observed that anti-psoriatic therapy significantly reduced the cholesterol efflux capacity of isolated HDL. This is in agreement with the significant reduction seen in the large HDL subclasses after intermediate-term therapy. Large HDLs are very efficient acceptors of cholesterol effluxed by ABCG1, SR-BI and passive diffusion [59].

Therefore, one might assume that the overall anti-psoriatic therapy associated reduction in the cholesterol efflux capacity of apoB-depleted serum could be explained by the decrease in the large HDL subclass and a reduction of lipid-poor apoA-I and/or preβ-1-HDL particles.

Moreover, other factors in addition to changes in HDL subclass distribution might also affect the cholesterol efflux capacity of HDL. We noted that the anti-psoriatic therapy was associated with complex changes in HDL composition; specifically, with altered apoC-III and apoE content of HDL at short-term therapy, but increased apoA-II and phosphatidylcholine and decreased free cholesterol HDL content at intermediate-term therapy. We observed that LCAT activity correlated negatively with the free cholesterol content of HDL ($r = -0.226$, $p = 0.043$), in line with the well-established role of LCAT in the formation cholesteryl-esters via the transfer of fatty acids to free cholesterol [60]. LCAT activity was significantly impaired in comparison to healthy controls but increased during anti-psoriatic therapy. Of note, a strong positive correlation between large HDL particle functionality and free cholesterol concentrations was recently reported [61] suggesting that a reduction of free cholesterol content of HDL at intermediate-term therapy contributes to an impaired HDL cholesterol efflux capacity. Moreover, we observed an increase in the HDL content of apoA-II after intermediate term therapy. Some studies reported that overexpression of apoA-II turns HDL from an anti-oxidant/anti-inflammatory to a pro-oxidant/pro-inflammatory lipoprotein [62,63]. Moreover, apoA-II appears to decrease HDL cholesterol efflux capacity [64]. We observed that the apoA-II-HDL content was negatively associated with the cholesterol efflux capacity of apoB-depleted serum ($r = -0.375$, $p = 0.001$). Therefore, the increased apoA-II content of HDL during intermittent therapy could also be contributing to the changes in HDL functionality.

No difference was observed in the CETP activity after short- or intermediate-term biologic anti-psoriatic therapy, which is in agreement with our previous study, where (mainly) topical psoriasis treatment was applied [22].

It has to be noted that other enzyme activities may also be affected by anti-psoriatic therapy, such as phospholipid transfer protein (PLTP) activity. PLTP promotes the conversion of intermediate HDL3 particles into larger or smaller particles [65,66] and may affect HDL structure and function. We cannot exclude a potential effect of this enzyme in modulating HDL subclass distribution.

In agreement with our results, also some other studies reported that adalimumab reduces HDL cholesterol efflux capacity either after 52 weeks of treatment [67], or after 6 weeks of treatment when adalimumab was combined with methotrexate [68]. However, when HDL cholesterol efflux capacity was assessed using a different assay protocol utilizing THP-1 cells instead of J774.2 cells, no effect of adalimumab was observed [69]. Interestingly, (mainly) topical anti-psoriatic therapy even appeared to improve the cholesterol efflux capacity of isolated HDL after one year of treatment [22]. Somewhat surprisingly, we observed that anti-psoriatic-therapy increased paraoxonase and LCAT activities but did not alter the anti-oxidant capacity of isolated HDL, given that there is evidence that both paraoxonase and LCAT have anti-oxidative properties [70,71]. Similar to results of the present study, also topical treatment of psoriasis patients was associated with increased LCAT and paraoxonase activities and no difference was observed in the anti-oxidative capacity of isolated HDL [22]. Interestingly, somewhat different from the results of the present study, topical anti-psoriatic therapy [22] showed a tendency to improve HDL cholesterol efflux capacity after one year, suggesting that systemic therapy with biologics and the associated dramatic improvement of psoriatic skin lesions have some other effects on HDL composition and function.

Interestingly, we observed that anti-oxidative capacity of apoB-depleted serum was decreased after intermediate therapy, but this was not seen in isolated HDL. This might be explained by the notion that HDL makes only a very small contribution (1–2%) to the overall anti-oxidant capacity of serum, irrespective of oxidation mechanism [34,72], since other serum components such as albumin and alpha-tocopherol have also anti-oxidant properties [73,74].

We acknowledge limitations to this study. Due to the laborious experiments and analyses, we had to keep the patient number rather small. Therefore, the small sample size is a limitation of this study and larger studies are needed to draw firm conclusions. Moreover, since the observed complex effects on HDL composition, metabolism and function cannot be attributed to the effect of a specific drug, we were not able to draw direct mechanistic conclusions. Therefore, the improvement of psoriatic skin lesions themselves (leading to a reduced overall inflammatory state with normalization of skin-derived systemic cytokine and chemokine levels) may be responsible for some of the changes in HDL composition and function.

5. Conclusions

In summary, we provide the novel evidence that biologic anti-psoriatic therapy markedly reduces the cholesterol efflux capacity of apoB-depleted serum and isolated HDL and the anti-inflammatory potential of HDL, but increases paraoxonase and LCAT activities. Treatment with biologics alters HDL composition and subclass distribution. All biologics caused similar changes in HDL composition, subclass distribution and cholesterol efflux capacity, suggesting that the observed effects are not attributed to the action of a specific drug. Since psoriasis is associated with impaired HDL cholesterol efflux capacity, a further reduction through biologic anti-psoriatic therapy might increase the cardiovascular risk. Future studies are needed to investigate not only therapy-related improvements in skin condition, but also possible effects on the frequency of atherothrombotic events.

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CRediT authorship contribution statement

Athina Trakaki: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Peter Wolf:** Project administration, Resources, Writing – review & editing. **Wolfgang Weger:** Resources, Writing – review & editing. **Thomas O. Eichmann:** Investigation, Writing – review & editing. **Hubert Scharnagl:** Investigation, Writing – review & editing. **Julia T. Stadler:** Investigation, Writing – review & editing. **Wolfgang Salmhofer:** Resources, Writing – review & editing. **Eva Knuplez:** Writing – review & editing. **Michael Holzer:** Writing – review & editing. **Gunther Marsche:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbalip.2021.158943.

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Review

High-Density Lipoprotein (HDL) in Allergy and Skin Diseases: Focus on Immunomodulating Functions

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Abstract: From an evolutionary perspective, lipoproteins are not only lipid transporters, but they also have important functions in many aspects of immunity. High-density lipoprotein (HDL) particles are the most abundant lipoproteins and the most heterogeneous in terms of their composition, structure, and biological functions. Despite strong evidence that HDL potently influences the activity of several immune cells, the role of HDL in allergies and skin diseases is poorly understood. Alterations in HDL-cholesterol levels have been observed in allergic asthma, allergic rhinitis, atopic dermatitis (eczema), psoriasis, urticaria, and angioedema. HDL-associated apolipoprotein (apo) A-I, apoA-IV, and apoC-III, and lyso-phosphatidylcholines potently suppress immune cell effector responses. Interestingly, recent studies provided evidence that allergies and skin diseases significantly affect HDL composition, metabolism, and function, which, in turn, could have a significant impact on disease progression, but may also affect the risk of cardiovascular disease and infections. Interestingly, not only a loss in function, but also, sometimes, a gain in function of certain HDL properties is observed. The objective of this review article is to summarize the newly identified changes in the metabolism, composition, and function of HDL in allergies and skin diseases. We aim to highlight the possible pathophysiological consequences with a focus on HDL-mediated immunomodulatory activities.

Keywords: high-density lipoprotein; HDL composition; HDL function; allergy; skin disease; psoriasis; allergic rhinitis; atopic dermatitis; allergic asthma; immunomodulation

1. Introduction

The prevalence of allergic and inflammatory skin diseases has dramatically increased in recent decades, a fact that is linked to changes in environmental exposures and lifestyle practices [1,2]. Despite strong evidence that high-density lipoprotein (HDL) potently influences the activity of several immune cells, including monocytes, macrophages, eosinophils, and neutrophils [3,4], the role of HDL particles in allergies and skin diseases is still poorly understood [5,6]. HDL particles are regarded as cholesterol transporters, mainly mediating the reverse cholesterol transport from extrahepatic peripheral tissues back to the liver. Although their association with reduced cardiovascular risk is well established [7–10], HDL-cholesterol raising therapies failed to improve the cardiovascular outcome [11–13], and recent studies challenged the causal role of low HDL-cholesterol levels in cardiovascular diseases [14].

HDL is quantitatively the most important lipoprotein in most species and mechanistic evidence points towards a role of HDL in physiological immune function [15], while low HDL-cholesterol levels are associated with a high risk of autoimmune disease in individuals from the general population [16].

In this context, the potential role of HDL in other diseases, such as infections and allergies, but also skin diseases, has gained much attention.

Apolipoprotein (apo) A-I is the main structural and functional apoprotein of HDL [17], and it plays a key role in the induction of cholesterol efflux from cells [18]. The interaction of HDL with cells results in cholesterol depletion in specific membrane microdomains enriched in cholesterol and sphingolipids, named lipid rafts, a mechanism that is known to disrupt raft-dependent signaling [19,20]. Their main role is the compartmentalization of molecules to form functional platforms for biological processes, such as toll-like receptors (TLRs) [21]. The lipid composition of rafts determines their function; the modification of lipid raft composition can modulate raft-dependent signaling due to protein delocalization and alter immune cell biological functions [21]. HDL, along with apoA-I, have been shown to disrupt the plasma membrane of lipid rafts in antigen presenting cells, leading to the inhibition of their capacity to stimulate T cell activation [22]. On the other hand, lyso-phosphatidylcholine, which is one of the main phospholipid subtypes carried by HDL particles [23], has been shown to directly activate TLRs 1, 2, and 4 in the absence of classical TLR-ligands; however, in the presence of classical TLR-ligands, it induces an anti-inflammatory phenotype [24]. TLRs are expressed by a plethora of cells in the skin, including Langerhans cells, keratinocytes, and several immune cells [25,26]. Furthermore, TLRs are implicated in the pathogenesis of atopic dermatitis [25,27,28] and psoriasis [25,28].

The composition and particle distribution of HDL are significantly altered in allergic and skin diseases, which ultimately lead to altered HDL functionality and an altered ability of HDL to modulate immune cell effector responses [4,29–36]. Here, we will provide an updated review on the novel identified activities of HDL in allergic diseases, including allergic asthma and allergic rhinitis, and common skin diseases. We will focus on how HDL modulates the immune cell function of certain cell types that are implicated in the pathogenesis of allergic and skin diseases.

2. HDL Metabolism, Composition and Function

HDL particles are heterogeneous in terms of their composition, structure, and biological functions. The biogenesis of HDL is a complex process [37]. The first step in HDL formation is the secretion of apoA-I by the liver and intestine [38]. Secreted apoA-I interacts thereafter with ATP-binding cassette (ABC) transporter A1 (ABCA1), which leads to the rapid recruitment of cellular phospholipids and cholesterol to lipid-poor apoA-I. Afterwards, the lipidated apoA-I is gradually converted into discoidal HDL particles, containing unesterified cholesterol [39]. The acquisition of cholesterol and the esterification of free cholesterol to cholesteryl esters by the enzyme lecithin cholesterol acyltransferase (LCAT) [40] lead to the evolution of more mature, large-sized particles [41]. HDLs are extensively remodeled in the bloodstream via the action of lipid transfer proteins, such as cholesteryl-ester transfer protein (CETP), LCAT, and phospholipid transfer protein (PLTP). CETP is responsible for the bidirectional transfer of cholesteryl esters and triglycerides between plasma lipoproteins [42]. PLTP mediates the phospholipid transfer among lipoproteins [43], which converts HDL into larger and smaller particles [44,45]. In addition, certain lipases, such as endothelial and hepatic lipases, as well as lipid exchange with cellular transporters, such as ABCA1 and ABCG1, and scavenger receptor class B type I (SR-BI), affect HDL maturation and catabolism [46,47]. Plasma endothelial and hepatic lipases have specificity for phospholipids and triglycerides of large HDL and apoB-containing lipoproteins remnants [48,49]. The hydrolysis of triglycerides and phospholipids of HDL leads to the conversion of HDL2 into HDL3 and pre-beta HDL [45]. ABCA1 and ABCG1 both play a crucial role in the reverse cholesterol transport pathway. ABCA1 is responsible for the transfer of cellular phospholipids and cholesterol to lipid poor apoA-I, while ABCG1 promotes cholesterol efflux to more mature HDL particles [45]. SR-BI is primarily expressed by the liver, but it is also found in other tissues [50]. SR-BI absorbs cholesterol and cholesteryl ester of HDL without causing HDL degradation in the liver [51]. SR-BI also promotes cholesterol efflux from macrophages and other cell types to HDL particles, thus acting as a bidirectional cholesterol transporter [52] (Figure 1).

HDL can be divided into the relatively cholesterol-rich, larger, spherical, and less dense HDL2 particles (1.063–1.125 g/mL), and the more protein-rich, smaller, and denser HDL3 particles (1.125–1.21 g/mL) [53]. The latter particles appear to display the most potent atheroprotective properties [54]. In addition to apoA-I and apoA-II, which are the main protein components, HDL particles contain other less abundant proteins, including apoA-IV, apoC-II, apoC-III, apoE, and serum amyloid A (SAA) [55]. Some studies reported that more than 100 different proteins are associated with HDL, which suggests a multiple functionality for the HDL particles [56]. Not all protein species are present on every single HDL particle, and most proteins are only carried by a small fraction of the HDL particles [57]. However, there is recent evidence that the HDL proteome of mature HDL3 and HDL2 subclasses may be less complex than expected and contains less than 20 proteins after extensive purification [58]. This seems to contradict other publications that assume a much more complex HDL proteome [57,59,60]. However, in these publications, not only HDL2 and HDL3 were isolated and investigated, but also pre-beta HDL. Therefore, the different number of identified proteins is due to the other purification strategies of the HDL subclasses. Moreover, more than 200 lipid species have been identified in HDL particles [61,62], including cholesterol (free or esterified), triglycerides, phospholipids, lyso-phospholipids, and sphingolipids [54]. The structure and dynamic properties of lipids significantly depend on their location in the particle (surface, intermediate region, core). Not only hydrophobicity, but also conformational entropy of the molecules, are the driving forces in the formation of the HDL structure [63]. For example, apoA-I has a strong preference for binding to HDL (d = 8–12 nm), as compared to larger, less curved low-density lipoproteins (LDL) (d = 20–24 nm) or very low-density lipoproteins (VLDL) (d = 40–100 nm). The high radius of curvature of HDL as compared to other lipoproteins causes packing defects of phospholipids, and this is the reason why other lipids and amphipathic proteins associate with HDL when compared to other lipoproteins [64]. In addition to the promotion of cellular cholesterol efflux, HDL particles display a number of anti-inflammatory activities, such as cytoprotective, vasodilatory, anti-oxidative, anti-thrombotic, and anti-infectious activities [54]. Among the HDL associated enzymes, paraoxonase (PON) is known to exert a protective effect against oxidative damage of circulating cells and lipoproteins and to modulate the susceptibility of HDL to atherogenic modifications, such as homocysteinylation and glycation, even exerting an anti-inflammatory role [65]. Other HDL-associated enzymes are LCAT, platelet-activating factor-acetyl hydrolase (PAF-AH) (also known as lipoprotein-associated phospholipase A2 (Lp-PLA2)), and PLTP. Among these, LCAT is responsible for the esterification of free cholesterol to cholesteryl esters [40]. PAF-AH is mainly associated with low-density lipoproteins, however about 30% is also associated with HDL [66]. PAF-AH is the major enzyme catabolizing platelet-activating factor (PAF) and PAF-like lipids, which are potent inflammatory mediators [67,68]. PLTP is a lipid transfer protein that is involved in the remodeling of HDL particles [44] and it has been reported to contribute to the anti-oxidative HDL activity [57].

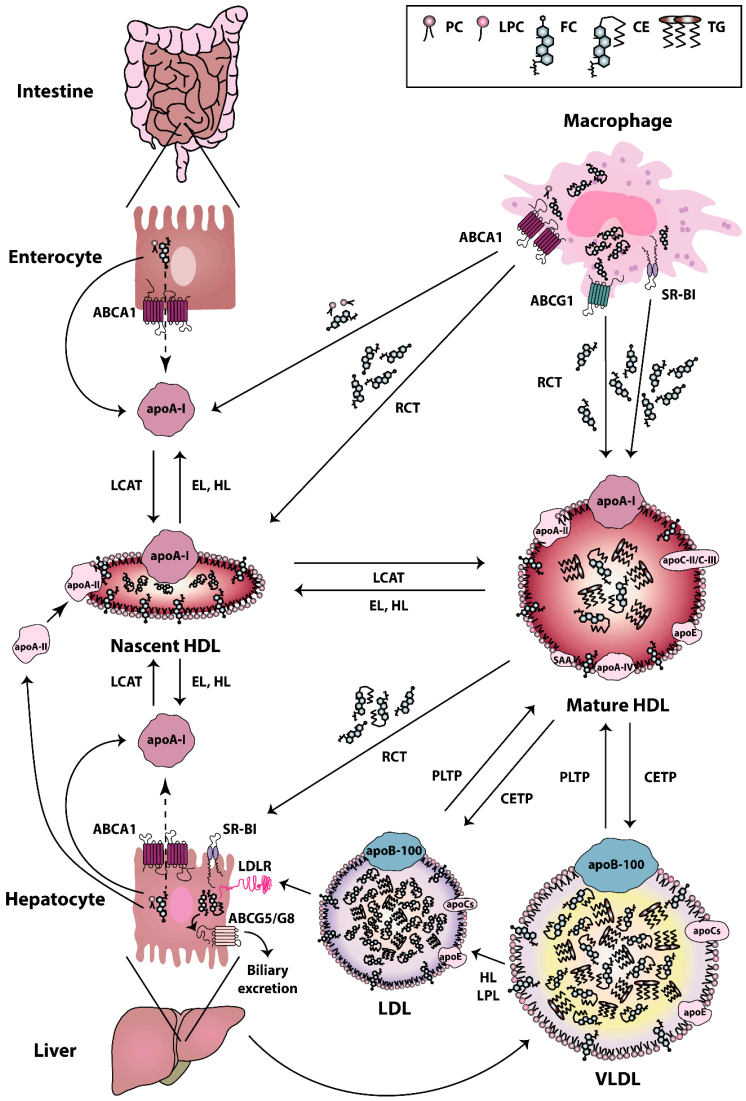

Figure 1. High-density lipoprotein (HDL) metabolism. HDL metabolism is a multistep process involving (i) the secretion of lipid-free apolipoproteins by the liver or intestine, (ii) the acquisition of cholesterol and phospholipids via ATP-binding cassette (ABC) transporter A1 (ABCA1), ABCG1, and scavenger receptor class B type I (SR-BI), (iii) the maturation by lecithin cholesterol acyltransferase (LCAT)-mediated cholesterol esterification and (iv) the final uptake of lipids by the liver. Cholesterol uptake is either mediated directly via SR-BI, or indirectly via cholesteryl-ester transfer protein (CETP)-mediated transfer of cholesteryl ester to very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) and uptake by the LDL-Receptor. The liver excretes then cholesterol into the bile, either directly via the action of ABCG5/G8 transporters, or indirectly following oxidation to bile acid and secretion via ABCB11 [69,70]. Abbreviations represent: ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; ABCG5, ATP-binding cassette subfamily G member 5; ABCG8, ATP-binding cassette subfamily G member 8; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoA-IV, apolipoprotein A-IV; apoB-100, apolipoprotein B-100; apoC, apolipoprotein C; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; EL, endothelial lipase; FC, free cholesterol; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPC, lyso-phosphatidylcholine; LPL, lipoprotein lipase; PC, phosphatidylcholine; PLTP, phospholipid transfer protein; RCT, reverse cholesterol transport; SAA, serum amyloid A; SR-BI, scavenger receptor class B type I; TG, triglyceride; VLDL, very low-density lipoprotein.

3. Potential Role of HDL in Atopic Allergic Diseases

3.1. Relation of HDL with Asthma

Allergic (or atopic) asthma is a chronic airway inflammatory disease and it is the most common form of asthma [71]. It is estimated that more than 330 million individuals worldwide suffer from asthma, with this number potentially increasing by a hundred million more by 2025 [72]. Asthma most commonly onsets in childhood, where it is often associated with seasonal allergic rhinitis and atopic dermatitis; however, one in four individuals may experience recurring or persisting symptoms in adulthood [73]. It is a complex disease, implicating multiple genetic and environmental factors, in which allergen exposure often induces intermittent attacks of coughing, wheezing, breathlessness, and airway hyper-reactivity [73]. Allergic asthma is associated with T helper cell type 2 immune responses, which promote eosinophilic inflammation and immunoglobulin E (IgE) production, through specific cytokine release [74].

Several studies so far have examined the relation of asthma with serum dyslipidemia, reporting positive [75–78], negative [79–82], or no association [83–86]. Accumulating evidence suggests an association of HDL-cholesterol with pulmonary function and pulmonary disorders [5]. Reports on serum HDL-cholesterol levels among asthmatic individuals vary, with some studies demonstrating higher [79,81,87], lower [88–91], or unchanged [76,80,92,93] levels in comparison to controls. A direct correlation between HDL-cholesterol levels and asthma could not yet be shown due to these contradictory data. In 2012 Yiallouros et al. reported that low levels of serum HDL-cholesterol in childhood are associated with an increased risk for asthma in adolescence, which suggests a potential role of HDL in the pathogenesis of pediatric asthma [89]. This is in line with a study by conducted by Cirillo et al., reporting that higher systemic levels of HDL are associated with less severe airflow obstruction in both asthmatics and healthy subjects [94]. These data are in agreement with a recent meta-analysis reporting significantly lower serum HDL-cholesterol in asthmatic in comparison to non-asthmatic children, although, in adults, the aforementioned difference was not significant [95]. Moreover, Barochia et al. reported that the concentration of large HDL particles in serum was positively correlated with the forced expiratory volume (FEV_1) and lung function in atopic asthmatic subjects [96,97]. A few years later, the same group reported that the concentration of HDL particles was negatively correlated with the blood eosinophil number in atopic asthmatics, supporting the concept that serum HDL levels are linked to systemic type 2 inflammation in atopic asthma [98]. In addition to this, Rastogi et al. reported an inverse association between HDL-cholesterol and circulating monocytes, a cell population rapidly recruited to the lung upon inflammation in obese, adolescent asthmatics [99]. Moreover, Ouyang et al. demonstrated a sex association of allergic sensitization and HDL. In particular, the risk of allergic sensitization was four times higher in men when the HDL-cholesterol levels were below 40 mg/dL, while, in women, a less strong association was observed [100]. It has to be noted that other studies reported no association between asthma severity and HDL-cholesterol levels [101,102] and opposite findings were even reported in one study [103]. In this study, higher HDL-cholesterol levels were associated with decreased FEV_1 and forced vital capacity (FVC) among healthy, male adolescents, which was not observed in female adolescents [103].

Besides HDL-cholesterol levels, Cirillo et al. reported a positive correlation of serum apoA-I levels with less severe airflow obstruction in asthmatic individuals [94]. Barochia et al. confirmed this, reporting that serum apoA-I was positively correlated with FEV_1 and lung function in atopic asthmatics, which implied that circulating concentrations of apoA-I may have a protective effect on airflow obstruction in asthma [96]. The ApoA-I levels were decreased in bronchoalveolar lavage fluid of patients with moderate to severe asthma, which suggested an augmentation of disease severity due to lower apoA-I levels in the lung [104]. ApoA-I attenuates lipopolysaccharide (LPS)-mediated neutrophilic inflammation [105], which has been associated with an increased risk for asthma and wheezing [106,107]. In addition, its immunomodulatory and anti-inflammatory properties may be relevant for adaptive immune responses in allergic asthma, since apoA-I can suppress adaptive immunity through the

inhibition of function, differentiation, and maturation of dendritic cells [22,108,109]. The ApoA-I levels are dramatically decreased in patients with chronic obstructive pulmonary disease and correlate with FEV_1/FVC, which suggested a relationship to disease severity [110].

In addition to altered HDL-cholesterol and apoA-I levels, lower plasma paraoxonase and arylesterase activities have been observed in asthmatic patients [90,93]. Lp-PLA2 activity was negatively correlated with asthma severity score and it was lower in asthmatic women [111]. However, it has to be noted that only 20–30% of this enzyme is associated with HDL [66]. PAF, which is the substrate of Lp-PLA2, was detected in higher concentrations in sputum [112,113] and bronchoalveolar lavage fluid [113] of asthmatic subjects in comparison to non-asthmatic. Moreover, increased PAF levels were observed in the human plasma during acute asthma attacks [114–116] and upon allergen challenge [117], while the lung tissues of asthmatic patients have increased mRNA levels of PAF receptor [118].

In summary, due to contradictory data, an association between HDL-cholesterol levels and asthma could not yet be shown. However, most studies reported that a decrease in apoA-I levels is associated with an increased risk of asthma development, while higher apoA-I levels are associated with less severe airflow obstruction in asthmatics.

Interestingly, mice with a genetic deletion of apoA-I display a phenotype of increased lung inflammation and oxidative stress, along with enhanced airway hyperresponsiveness [119]. Studies using murine models of experimental asthma have identified a role for the apoA-I/ABCA1 pathway in mediating neutrophilic airway inflammation [120]; it was demonstrated that endogenous apoA-I negatively regulates ovalbumin-induced neutrophilic airway inflammation [121]. Furthermore, apoA-I mimetic peptides have been extensively studied in murine models of experimental asthma (reviewed in detail [120,122]). ApoA-I mimetic peptides attenuate the development of airway inflammation, remodeling, and hyperresponsiveness [105], and decrease eosinophil counts [123].

3.2. Allergic Rhinitis is Associated with Complex Alterations in HDL Composition and Function

Allergic rhinitis is an IgE-mediated disease, which is strongly linked to asthma and conjunctivitis [124,125]. Allergic rhinitis affects approximately 20% of the population and it is characterized by nasal itching, sneezing, watery discharge, and congestion [124,125]. Although originally considered as a disorder mainly localized to the nose and nasal passages, current evidence proposes that it may represent a component of a systemic airway disease of the entire respiratory tract [125]. Allergic rhinitis is caused by inhaled allergens in genetically predisposed individuals, mainly proteins and glycoproteins that are found in airborne particles, such as grass pollinosis, ragweed, and dust mite [124].

HDL-cholesterol is increased in allergic rhinitis children [79], and there is strong evidence that HDL plays an important role in allergic rhinitis. A study conducted by Vinding et al. reported that high HDL-cholesterol levels in children with asthma or allergic rhinitis were associated with a lower risk of sensitization against aeroallergens [126]. HDL particles are diverse in composition and structure, representing the basis for their functional heterogeneity [54]. Evaluation of allergic rhinitis-derived HDL particle distribution via gradient gel electrophoresis revealed a significant decrease in the HDL3 subclass in comparison to controls, while other HDL subclasses were not altered [29]. The change in HDL3 subclass was associated with an impaired ability of allergic rhinitis HDL to suppress monocyte cytokine secretion [29], which is consistent with reports of the HDL3 subclass being superior to the HDL2 subclass in inflammatory responses' suppression [54]. Moreover, correlations of specific IgE levels of grass pollen were detected with the HDL2/HDL3 ratio and the small HDL3 subclass in allergic rhinitis patients [29].

Interestingly, recent findings suggested that allergic rhinitis has profound effects on the composition of HDL. HDL that is isolated from allergic rhinitis patients has a significantly reduced content of apoA-I and phosphatidylcholine, but an increased content of apoA-II, lyso-phosphatidylcholine, and triglycerides, in comparison to HDL isolated from non-allergic healthy controls [29]. The compositional alterations of HDL are closely linked to alterations of HDL functional

properties [29]. Other studies reported an increase in apoA-I and apoA-II, which are the major HDL apolipoproteins, in the mucus proteome of allergic rhinitis patients, suggesting a direct modulation of the immune response by HDL apolipoproteins [127–129]. Increased apoA-I levels were also detected in nasal lavage fluids of subjects with persulfate-associated rhinitis after challenge with potassium persulfate [130]. Moreover, in allergic rhinitis patients, correlations of specific IgE levels of grass pollen were observed with apoE and SAA content of HDL [29]. It has been reported that specific IgE levels of house dust mite are associated with reduced odds for myocardial infarction [131] and reduced HDL-cholesterol [132]. In another study, allergic rhinitis was associated with metabolic syndrome [133]. A recent study conducted by Roula et al. reported decreased levels of the HDL apolipoprotein apoA-IV in allergic rhinitis patients in comparison to the controls. Importantly, apoA-IV is an endogenous anti-inflammatory protein that potently suppresses effector functions of eosinophils [134]. Moreover, Makino et al. identified the serum levels of apoA-IV to be significantly increased in sublingual immunotherapy treated in comparison to placebo treated seasonal allergic rhinitis patients [135]. ApoA-IV was negatively correlated with the clinical symptom-medication and quality of life scores. The authors concluded that apoA-IV might be a potential target molecule for the treatment of seasonal allergic rhinitis [135]. Moreover, Chung et al. reported that apoE was up-regulated in nasal secretomes that were obtained from chronic rhinosinusitis patients [136], a condition that is frequently associated with rhinitis [137], demonstrating that it can potentially be a biomarker of nasal mucosal inflammation [136], while increased levels of apoA-I were found in sinonasal mucosa obtained from chronic rhinosinusitis patients with nasal polyps [138].

Structural and compositional alterations in HDL affect HDL function in individuals suffering from allergic rhinitis. HDL that was isolated from allergic rhinitis patients showed an impaired anti-oxidative and anti-inflammatory capability, as well as an impaired ability to suppress pro-inflammatory cytokine secretion [29].

Of particular interest, HDL that was derived from allergic rhinitis patients showed an improved ability to suppress eosinophil effector responses upon eotaxin-2/CCL24 stimulation. This gain of anti-allergic activity of isolated HDL was linked to altered apoA-II, apoC-III, lyso-phosphatidylcholine and phosphatidylcholine content of HDL [29]. Moreover, sera from allergic rhinitis patients showed decreased CETP and paraoxonase activities and increased Lp-PLA2 activity [29]. Decreased serum paraoxonase levels were also observed in children with allergic rhinitis [139].

In summary, there is strong evidence that HDL plays an important role in allergic rhinitis. The evaluation of allergic rhinitis-derived HDL particle distribution revealed a significant decrease in the HDL3 subclass and profound effects on the composition of HDL. Alterations in the HDL structure and composition are linked to decreased anti-oxidative and anti-inflammatory properties, but an improved ability of HDL to suppress eosinophil effector responses.

4. HDL in Inflammatory Skin Diseases

The skin is one of the largest immunologic organs, while it is often a target for allergic and immunologic responses [140]. Immune-mediated skin diseases, such as contact dermatitis, atopic dermatitis, psoriasis, urticaria, angioedema, and autoimmune blistering disorders are becoming all the more common nowadays, while most of them are chronic and inflammatory with both environmental and genetic factors contributing [140]. Many skin disorders are known to be associated with dyslipidemia, while some of the dermatological therapies are also known to predispose to lipid abnormalities [6].

4.1. Atopic Dermatitis is Associated with Complex Alterations in HDL Composition and Function

Atopic dermatitis (or eczema) is the most common atopic disease in young children and the most common skin disease in childhood [141]. Atopic dermatitis comprises a common chronic inflammatory skin disease with heterogeneous clinical phenotypes that are determined by both genetic and epigenetic dispositions [142]. In more than half of the patients the disease starts before the age of 6, while a less

frequent onset is observed after the age of 20 [143]. Atopic dermatitis has different onset patterns and disease course is associated with distinct clinical features, food intolerance, risk of concomitant allergic diseases, and impact of psychic factors on symptoms [143]. In the last years, associations of atopic dermatitis with other inflammatory diseases have been reported, including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease [144], and increased cardiovascular risk [145–149].

Although there is evidence that HDL is an important modulator of the immune response, few studies have investigated the role of HDL in human atopic dermatitis. A study conducted by Schäfer et al. reported increased HDL-cholesterol levels in patients in comparison to controls [76]; however, another study by Agón-Banzo et al. on a pediatric population, along with the study by Trieb et al., reported no difference [35,150].

A further study reported that apoA-I was highly expressed in the horny layer of the skin of atopic dermatitis patients in comparison to controls and it was associated with the severity of specific eruptions [151]. In a recent study by Trieb et al., the composition of HDL was evaluated in atopic dermatitis patients and control subjects [35]. Interestingly, the authors identified complex HDL compositional alterations. Specifically, the authors observed a significant enrichment of atopic dermatitis-HDL in apoA-II, the acute-phase protein SAA, and phosphatidylinositol, while a trend towards increased sphingomyelin content of atopic dermatitis-HDL was also observed [35]. Moreover, a significant reduction in atopic dermatitis-HDL content of apoC-III, apoE, cholesteryl ester, free cholesterol, lyso-phosphatidylcholine (especially 16:0 species), and phosphatidylethanolamine was observed when compared to the control subjects [35].

Eosinophils comprise a cell subset inducing tissue damage in the inflammatory infiltrate within the dermis of atopic dermatitis patients [152]. The effector responses of HDL isolated from patients suffering from atopic dermatitis and healthy controls were evaluated in a previous study while using freshly isolated human eosinophils [35]. Eosinophils were stimulated with eotaxin-2/CCL24 in the presence or absence of HDL (isolated from patients suffering from atopic dermatitis and healthy controls) and morphological changes (evaluated by the change in shape via flow cytometry) or chemotaxis was monitored. Of particular interest, the majority of HDL that was isolated from atopic dermatitis patients increased agonist induced eosinophil effector responses when compared to control-HDL. The authors demonstrated that the HDL-associated apoC-III and lyso-phosphatidylcholine species 16:0 and 18:0 effectively suppressed eosinophil shape change and migration [35]. Interestingly, the HDL content of apoC-III and lyso-phosphatidylcholine species 16:0 and 18:0 was much lower in HDL that was isolated from atopic dermatitis patients, and it was linked to an impaired ability of HDL to supress eosinophil effector responses. Moreover, by performing a detailed correlation analysis between function and composition of HDL isolated from atopic dermatitis patients, the authors demonstrated that the HDL-triglyceride content was negatively associated with the HDL activity towards agonist-induced eosinophil shape change and migration. In contrast, the HDL-associated SAA was associated with the ability of HDL to suppress agonist-induced eosinophil shape change [35]. In addition, the HDL-associated paraoxonase activity was decreased in atopic dermatitis-HDL; however, no change was observed in the capacity of atopic dermatitis-HDL to mobilize cholesterol from cells, when compared to the control-HDL [35].

In conclusion, there is increasing evidence that atopic dermatitis is associated with profound alterations in the HDL composition, linked to the formation of dysfunctional HDL. In contrast to the HDL that was isolated from allergic rhinits patients [29], the ability of HDL to suppress eosinophil effector responses is suppressed in atopic dermatitis, which suggests disease specific links between HDL composition, dysfunction, and disease severity.

4.2. HDL in Psoriasis

Epidemiological and clinical studies have shown a consistent association of psoriasis with systemic metabolic disorders, including an increased prevalence of diabetes, obesity, and cardiovascular

disease [153]. Psoriasis is a common chronic inflammatory skin disease, which affects approximately 2–3% of the population in Western countries [154], and it is equally prevalent in both sexes [155]. Psoriasis is characterized by the appearance of red scaly plaques, affecting any part of the body, but predominately appearing over elbows and knees, on the scalp, the perianal, and the umbilical region [154]. The pathogenesis of psoriasis is complex, involving the activation of plasmacytoid dendritic cells by epidermal antigens due to skin trauma as the initial step [156], followed by maturation of myeloid dendritic cells, which promote the differentiation of T cells into Th1 and Th17 cells, via the secretion of interleukin (IL)-6, IL-12, and IL-23 [157]. Pro-inflammatory cytokines and chemokines that are produced by activated keratinocytes are able to recruit a variety of inflammatory cells from the circulation, leading to a "vicious cycle" of excessive immune response [158].

Already in the 90s, studies reported alterations in plasma lipids [159,160] and HDL-apolipoprotein content [159] in psoriatic children. The results from studies evaluating, among others, HDL-cholesterol levels between psoriasis patients and controls, vary greatly, reporting either increased [161–164], decreased [30,31,33,34,165–188] or unchanged [32,189–205] levels. Interestingly, Yu et al. demonstrated an increase in the small HDL subclass in psoriasis patients, which was associated with aortic inflammation [31], while Tom et al. reported a decrease in the large HDL subclass in paediatric psoriasis patients in comparison to controls, but no change in the small or medium HDL subclasses was observed [32].

Anti-inflammatory, anti-psoriatic therapies appear to induce complex changes in the HDL-cholesterol levels. The current treatment options include topicals, such as corticosteroids, as well as agents such as anthralin, synthetic vitamin D3 and vitamin A; phototherapy, including broad and narrowband-ultraviolet B (UVB), laser UVB, and psoralen and ultraviolet A (PUVA); systemics, such as methotrexate, cyclosporine, and retinoid receptor inhibitors (acitretin); and, biological therapeutics targeting tumor necrosis factor (TNF)-alpha, IL-23p40, or IL-17 [206]. Tofacitinib, an oral janus kinase (JAK) inhibitor [207–209], metformin, an anti-inflammatory agent activating adenosine monophosphate-activated protein kinase (AMPK) [210], and adalimumab [211], etanercept [212], or other TNF-alpha blockers [213] appear to increase HDL-cholesterol levels; whereas, topical [178] or systemic treatment with methotrexate [214] or acitretin [215] seem to decrease HDL-cholesterol levels. Etanercept [216], anti-IL17A antibodies, such as ixekizumab [217] and secukinumab [218], or other biologic treatments [219], appear not to affect HDL-cholesterol levels. In 2014, Holzer et al. demonstrated an increase in the large HDL subclass in psoriasis patients upon systemic and/or topical treatment in comparison to baseline [33]. In 2018 Mehta et al. reported an increase in the HDL-particle number at 12 weeks of phototherapy and a trend towards increase after adalimumab treatment, however at 52 weeks of adalimumab treatment a significant reduction of the HDL-particle number was observed in comparison to the baseline [220]; while, treatment with secukinumab induced no change in HDL particle number and size [218]. In 2017, Wolk et al. reported a striking increase in total HDL particles upon different dosages of tofacitinib for four or 16 weeks in comparison to baseline measurements; specifically the authors observed an increase in the small HDL subclass, while medium and large HDL subclasses remained unchanged [207]. Much like the effects of systemic or biological therapeutics on HDL-cholesterol levels, the distribution of HDL particles is also affected, since it appears to be dependent not only on the pharmacological agent, but also on the duration of treatment. In 2012, a study evaluated several aspects of HDL composition in HDL that was isolated by ultracentrifugation in a small cohort of psoriasis patients receiving mainly topical treatment [30]. Among the main HDL-associated proteins and lipids, the authors were able to demonstrate a reduction in the levels of apoA-I, total cholesterol, cholesteryl esters, free cholesterol, phosphatidylcholine and sphingomyelin, and an increase in the levels of apoA-II and acute-phase proteins, such as SAA and α-1-antitrypsin, in HDL that is derived from psoriasis patients in comparison to the controls [30]. However, previous studies reported increased [161,162], decreased [165,176,178], or unchanged [32,167,185,189,199,205] apoA-I levels in psoriasis patients compared to healthy controls.

Due to these contradictory data, no direct and clear correlation between psoriasis and HDL quantity, particle size distribution, or composition has been demonstrated so far. Further studies are necessary in order to understand the observed effects.

However, the effects of anti-psoriatic therapy on some metrics of HDL function are more evident. During the last decade, studies coming from several groups have demonstrated significantly impaired HDL-cholesterol efflux capacity in psoriasis patients in comparison to controls [30,32–34], which appeared to recover upon systemic and/or topical treatment [33]. HDL-mediated cholesterol efflux capacity was negatively associated with psoriasis area severity index score [30,33], being significantly impaired in patients with higher psoriasis area severity index score [32], while it was positively associated with impaired levels of apoA-I, phosphatidylcholine, sphingomyelin [30], and total phospholipid HDL content [33]. A recent study conducted by Mehta et al. indicated reduced cholesterol efflux capacity at 52 weeks of adalimumab treatment [220]. The JAK inhibitor tofacitinib showed no change in cholesterol efflux capacity upon a 16-week treatment, as was recently reported by Wolk et al. [207], while secukinumab treatment for 12 or 52 weeks also induced no change [218].

Furthermore, the anti-inflammatory potential of HDL was markedly impaired in psoriasis patients when compared to controls [185]. Of particular interest, a study identified apoA-I, HDL-cholesterol, and HDL-cholesterol efflux capacity to be predictors of noncalcified coronary burden in psoriasis [221]. Moreover, an improved HDL-associated Lp-PLA2 activity in patients in comparison to controls was observed [30,33], which was positively correlated with the psoriasis area severity index score [30]. Upon systemic and/or topical treatment or biologic treatment, patients showed improved LCAT activity in comparison to the baseline [33,207].

In conclusion, recent studies provided clear evidence that psoriasis affects HDL composition that is linked to a significantly impaired capability to mobilize cholesterol from macrophages, a crucial step in reverse cholesterol transport. HDL quantity and other functionalities assessed in psoriasis patients, including paraoxonase activity and anti-oxidative properties of HDL, are contradictory. Interestingly, as demonstrated by Asefi et al., PON 55 methionine allele is a risk factor for psoriasis [222]. However, in psoriasis patients, unchanged [30], improved [204,205], or impaired [33,185,186,203,223–225] paraoxonase activity was observed in comparison to healthy controls. Rocha-Pereira et al. showed a significantly reduced total anti-oxidant potential in patients in comparison to controls [183], while others observed no difference in the anti-oxidant HDL capacity [30,33].

All of these data only suggest a loss of cholesterol efflux capacity of HDL in patients with psoriasis, corresponding to the increased cardiovascular risk of these patients, while other metrics of HDL quantity and quality are inconclusive. This also suggests that studying the influence of anti-psoriatic agents on HDL-cholesterol efflux capacity may help to identify treatment strategies with beneficial effects on long-term cardiovascular outcome.

4.3. HDL in Urticaria

Urticaria is a common chronic clinical condition that presents with angioedema, wheals (hives), or both [226], occurring in 15–25% of individuals at some point of life [227], and it is one of the 10 most common dermatoses [228]. Urticaria presents a high burden for the patient due to its chronic course and the difficulties in diagnosis and treatment, ultimately reducing performance and quality of life [229]. Urticaria is characterized by a recurrent, pruritic, wheals of pale, central swelling, and surrounding epidermal erythema, with the potential of appearance over any part of the body and with lesions ranging in size from a few millimeters to several centimeters [227]. Mast cells are the primary effector cells in urticaria, and their degranulation leads to a rapid release of a plethora of inflammatory mediators, such as leukotrienes, prostaglandins, and histamine, which, in turn, cause vasodilation and leakage of plasma below and in the skin. A more delayed secretion of inflammatory cytokines follows, including IL-4, IL-5, and TNF-alpha, potentially leading to further inflammatory responses and longer lasting lesions [230]. The pathogenesis, classification, diagnosis, and treatment

options of urticaria have been extensively reviewed elsewhere [226,227,231], and they are not in the focus of the current review.

A study conducted by Amin and Rushdy has recently demonstrated significantly decreased serum levels of HDL-cholesterol in chronic spontaneous urticaria patients in comparison to control subjects, which were negatively associated with TNF-alpha [232]. Similarly, another study also demonstrated a reduction of serum HDL-cholesterol levels in chronic spontaneous urticaria patients in comparison to the controls, with HDL-cholesterol levels being negatively associated with right and left carotid intima media thickness, discussing the likelihood of a potentially increased atherosclerosis risk in those patients [233]. Further studies are warranted in order to confirm a potential link of HDL and urticaria.

4.4. HDL in Angioedema

Angioedema, in the absence of urticaria, is a rare condition that manifests itself by sudden, localized, non-pitting, erythematous, or skin-colored swelling of certain body parts, including the skin, mucous membranes, or both, the upper respiratory and intestinal epithelial linings [234]. Heat and pain comprise additional symptoms of the skin, although they are hardly accompanied by itching, desquamation, or staining of the skin [234]. When present, angioedema should be diagnosed with caution, since alternative diagnoses, including acquired angioedema, hereditary angioedema, or angioedema that is associated with angiotensin-converting enzyme inhibitors, all comprising life-threatening conditions, might also be true [227]. It can be further classified to idiopathic, histaminergic, hereditary type I, hereditary type II, and hereditary with normal C1 inhibitor, acquired and angiotensin-converting enzyme (ACE) inhibitor-induced [227]. Angioedema results from the release of vasoactive mediators, which increase the vascular permeability in the skin and submucosa, leading to plasma vascular leakage and a resulting edema, which can be attributed either to bradykinin- or to histamine-mediated mechanisms [227]. The exact pathophysiology, diagnosis, and treatment options have been described elsewhere [227,234], and they are not in the scope of this review.

Several different studies have determined the serum levels of HDL-cholesterol in angioedema patients, however currently no literature on potential HDL-associated compositional alterations in angioedema is available. A study conducted by Sloane et al. evaluating the potential side effects of long-term stanozolol therapy in hereditary angioedema patients has revealed reduced HDL-cholesterol levels after stanozolol treatment is some of the patients [235]. Other studies, evaluating possible adverse effects of danazol treatment, revealed significantly lower levels of serum HDL-cholesterol [236,237] and apoA-I in danazol treated patients when compared to control groups (either untreated patients or patients without long-term danazol treatment), as well as a higher risk of abnormally low HDL-cholesterol levels in danazol treated patients, indicating that long-term use of this drug is associated with increased early atherosclerosis risk [236]. A similar study by Birjmohun et al., which evaluated the effects of short- and long-term danazol treatment, revealed decreased apoA-I and HDL-cholesterol levels in short-term treated patients in comparison to the baseline measures, while long-term treatment did not adversely affect HDL-cholesterol concentration and apolipoproteins between patients and controls [36]. A more recent study by Nebenführer et al. revealed that danazol treated patients suffering from hereditary angioedema with C1 inhibitor deficiency had higher cardiovascular risk, as evaluated by the high body mass index and LDL/HDL ratio, in comparison to healthy controls [238].

Currently, information on functionality of HDL-associated enzymes in angioedema patients is only available by the study of Birjmohun et al., which evaluated the effects of short- and long-term danazol treatment in hereditary angioedema patients. This study revealed no adverse effects of short- and long-term danazol treatment on PON-1, PLTP, and CETP activities along with CETP mass between patients and controls. However, a trend towards decreased LCAT activity was observed in the long-term, although unaltered in the short-term danazol treated patients [36]. Further studies in larger cohorts are necessary in order to confirm the observed effects and understand the possible pathophysiological role of HDL in angioedema.

5. Conclusions

From an evolutionary point of view, lipoproteins display important functions in many aspects of immunity. Of all lipoproteins, HDL has the highest affinity for binding and neutralizing pathogen-associated lipids (e.g., LPS and lipoteichoic acid) [41,239], which mediate excessive immune activation in bacterial infections [41,240,241]. Research into the composition, distribution, and functionality of HDL particles in allergic and skin diseases has begun to attract attention, with several groups demonstrating changes in the composition and function of HDL. Figure 2 summarizes the functional alterations of HDL on its immunomodulating abilities, due to a pathological background.

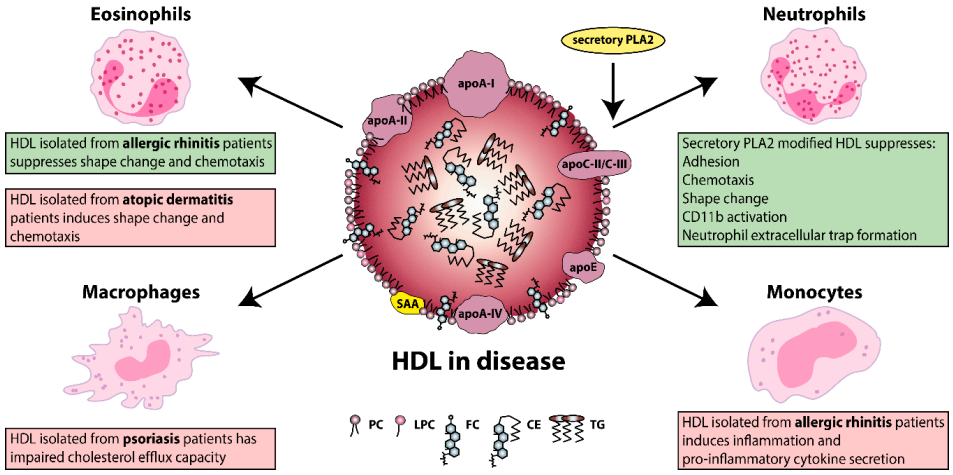

Figure 2. Overview of immunomodulating functions of HDL on different allergic and skin diseases. HDL differently modulates eosinophil effector responses in allergic rhinitis [29] and atopic dermatitis [35]. In psoriasis, HDL showed impaired HDL-cholesterol efflux capacity [30,32–34], while in allergic rhinitis HDL induced nuclear factor-κB (NF-κB) expression and pro-inflammatory cytokine secretion of monocytes [29]. Secretory phospholipase A2 (PLA2)-modified HDL prevented agonist-induced neutrophil activation, including shape change, cluster of differentiation (CD) 11b activation, neutrophil extracellular trap (NET) formation, adhesion under flow and migration of neutrophils [242]. Abbreviations represent: apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoA-IV, apolipoprotein A-IV; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; CD, cluster of differentiation; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; LPC, lyso-phosphatidylcholine; PC, phosphatidylcholine; PLA2, phospholipase A2; SAA, serum amyloid A; TG, triglyceride. Rectangle shadings represent: green, beneficial effect of HDL; red, detrimental effect of HDL.

Of particular interest, not only a loss in function but also a gain in function regarding HDL properties is observed due to a specific pathological background. For instance, eosinophil effector responses are being effectively suppressed by HDL derived from allergic rhinitis patients; however atopic dermatitis-HDL induces rather the opposite effect [29,35]. These changes in the HDL functionality are at least partially explained by disease specific changes in HDL composition. HDL that is isolated from patients with allergic rhinitis contains elevated levels of lyso-phosphatidylcholine and apoC-III, whereas the opposite is seen in HDL from patients with atopic dermatitis.

A major weakness in HDL research is that HDL-cholesterol levels vary widely between different studies of the same disease background, which is possibly due to different study design, disease duration, or the presence of concomitant diseases, making it difficult to draw firm conclusions. However, the results of several studies provide compelling evidence that allergies and skin diseases significantly affect the composition and metabolism of HDL, which, in turn, could have a significant impact on disease progression and the risk of infection and cardiovascular disease.

HDL particles in allergic and inflammatory skin diseases have an altered composition, which results in an altered functionality; however, these changes are not consistent for different pathological backgrounds. Currently, there are no tests available for measuring the composition, function, and inflammatory properties of HDL in clinical practice. It is not clear to what extent inflammatory-HDL alterations are a driving force or only a biomarker of the disease. Future studies are needed in order to demonstrate causality.

ApoA-I, which is the major protein component of HDL particles, but also apoA-IV and certain HDL-associated lyso-phospholipids, are endogenous, anti-inflammatory mediators that potently suppress effector cell functions in eosinophils and neutrophils and show a variety of positive effects. Thus, exogenously applied apolipoproteins may represent a novel pharmacological approach for the treatment of allergic inflammation and inflammatory skin diseases. It remains to be seen whether these concepts can be translated into new therapeutic interventions for allergies and skin diseases.

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Abbreviations

ABC	ATP-binding cassette
ACE	angiotensin-converting enzyme
AMPK	adenosine monophosphate-activated protein kinase
apo	apolipoprotein
CD	cluster of differentiation
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
EL	endothelial lipase
FC	free cholesterol
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
HDL	high-density lipoprotein
HL	hepatic lipase
IgE	immunoglobulin E
IL	interleukin
JAK	janus kinase
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LPC	lyso-phosphatidylcholine
LPL	lipoprotein lipase
Lp-PLA2	lipoprotein-associated phospholipase A2
LPS	lipopolysaccharide
NET	neutrophil extracellular trap
NF-κB	nuclear factor-κB
PAF	platelet-activating factor
PAF-AH	platelet-activating factor-acetylhydrolase
PC	phosphatidylcholine
PLA2	phospholipase A2
PLTP	phospholipid transfer protein
PON	paraoxonase
PUVA	psoralen and ultraviolet A
RCT	reverse cholesterol transport
SAA	serum amyloid A
SR-BI	scavenger receptor class B type I
TG	triglyceride
TLRs	toll-like receptors
TNF	tumor necrosis factor
UVB	ultraviolet B
VLDL	very low-density lipoprotein

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Review

Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins

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Abstract: Lipoproteins interact with immune cells, macrophages and endothelial cells - key players of the innate and adaptive immune system. High-density lipoprotein (HDL) particles seem to have evolved as part of the innate immune system since certain HDL subspecies contain combinations of apolipoproteins with immune regulatory functions. HDL is enriched in anti-inflammatory lipids, such as sphingosine-1-phosphate and certain saturated lysophospholipids. HDL reduces inflammation and protects against infection by modulating immune cell function, vasodilation and endothelial barrier function. HDL suppresses immune cell activation at least in part by modulating the cholesterol content in cholesterol/sphingolipid-rich membrane domains (lipid rafts), which play a critical role in the compartmentalization of signaling pathways. Acute infections, inflammation or autoimmune diseases lower HDL cholesterol levels and significantly alter HDL metabolism, composition and function. Such alterations could have a major impact on disease progression and may affect the risk for infections and cardiovascular disease. This review article aims to provide a comprehensive overview of the immune cell modulatory activities of HDL. We focus on newly discovered activities of HDL-associated apolipoproteins, enzymes, lipids, and HDL mimetic peptides.

Keywords: high-density lipoprotein; HDL function; immunomodulation; neutrophils; monocytes; macrophages; dendritic cells; T cells; eosinophils

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1. Introduction

From an evolutionary point of view, lipoproteins are not only described as lipid transporters, but are also known to display important immunomodulating functions. Specifically, of all lipoproteins, high-density lipoprotein (HDL) particles have the highest affinity for binding and neutralizing pathogen-associated lipids, such as lipoteichoic acid and lipopolysaccharide (LPS) [1,2], which are responsible for mediating excessive immune activation during bacterial infections [1,3,4]. This is thought to be of considerable importance in septic conditions [5], reflected by an inverse association of HDL cholesterol with death from infection [6] along with sepsis severity and morbidity [1]. Moreover, infusion of the apolipoprotein (apo) A-I mimetic peptide 4F decreased mortality and morbidity in experimental sepsis models [7]. In addition, HDL inhibits endothelial cell adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin, which are responsible for the binding of monocytes at sites of developing atherosclerosis [8]. Interestingly, HDL is also reported to have anti-parasitic effects [1].

However, an increasing number of studies have shown that chronic systemic inflammatory disorders significantly affect HDL composition and function. Such disorders include systemic lupus erythematosus and rheumatoid arthritis [9–12], atrial fibrillation [13], psoriasis [14–22], chronic kidney disease [23–26], liver failure [27], as well as allergic and skin diseases, including allergic rhinitis [28–30], asthma [31–33] and atopic dermatitis [34]. In turn, altered HDL function may have a significant impact on the progression of the disease and influence the risk of infections and cardiovascular disease [35].

This review provides a comprehensive overview of immune cell modulatory activities of HDL and its associated proteins, lipids and enzymes. We focus on newly discovered effects of HDL-associated apolipoproteins (and mimetic peptides of apolipoproteins), HDL-associated enzymes, such as paraoxonase (PON), as well as HDL-associated lipids, including sphingosine-1-phosphate (S1P) and lysophospholipids, on the function of immune cells; specifically dendritic cells, monocytes, macrophages, neutrophils, eosinophils and T cells.

2. HDL Composition

2.1. HDL-Associated Apolipoproteins and Lipids

HDL particles consist of an outer amphipathic layer of several apolipoproteins, including apoA-I, apoA-II, apoA-IV, apoCs, apoD, apoJ and apoM and many other proteins enriched in lesser amounts [36]. Besides apolipoproteins, free cholesterol, phospholipids (mainly glycerophospholipids), lysophospholipids [37,38] such as lysophosphatidylcholine (LPC) species [39], and sphingolipids, such as sphingomyelin and S1P [40–42], are found on the surface of HDL particles. At the same time, the hydrophobic core consists of cholesteryl esters and triglycerides [37].

2.2. HDL-Associated Enzymes

HDL particles carry important enzymes, such as paraoxonase, which can exert a protective effect against oxidative damage of circulating lipoproteins and cells [43]. Among the enzymes of the paraoxonase family, paraoxonase 1 (PON1) and paraoxonase 3 (PON3) are mainly associated with HDL and exhibit paraoxonase, lactonase and esterase activities [44]. PON1 protects HDL and low-density lipoprotein (LDL) against oxidation, reduces macrophage and aortic oxidative status associated with decreased superoxide anion production, and enhances the reverse cholesterol transport by facilitating the binding of HDL particles to macrophages [45–48]. Other HDL-associated enzymes are platelet-activating factor acetylhydrolase (PAF-AH), also known as lipoprotein-associated phospholipase A2 (Lp-PLA2), which is the major enzyme catabolizing potent inflammation mediators, such as platelet-activating factor (PAF) and PAF-like lipids [49–51]. Lecithin-cholesterol acyltransferase (LCAT), which is responsible for free cholesterol to cholesteryl ester esterification [52], and phospholipid transfer protein (PLTP), a lipid transfer protein implicated in the remodeling of HDL particles [35,53], are important HDL-associated enzymes.

3. Immunomodulatory Functions of HDL

HDL seems to have evolved as part of the innate immune system since the HDL proteome consists of apolipoproteins involved in lipid metabolism and many immune regulatory proteins [37]. In addition to this, HDL-associated lipids, such as S1P and lysophosphatidylcholine, are potent immune modulators.

3.1. HDL-Associated Lipids Show Potent Immunomodulatory Functions

S1P is a potent bioactive sphingolipid generated by sphingosine phosphorylation via the sphingosine kinase (SPHK) [54]. Approximately 65–80% of S1P in plasma is associated with HDL, mainly bound to apoM. S1P is rapidly degraded by intracellular S1P lyase or dephosphorylated by S1P phosphatases in most cells; however, its levels in the blood and lymph are in the range of nanomolar to micromolar [55]. HDL-associated S1P is less susceptible to degradation than free S1P or S1P bound to albumin, suggesting an important role of HDL in regulating the uptake, systemic function and cellular degradation of S1P. Although the mechanism of S1P efflux from cells to HDL is not clearly established, it involves specific transporters, such as adenosine triphosphate (ATP)-binding cassette family transporters [56–58], including ATP-binding cassette subfamily A member 1 (ABCA1) [59–61]. S1P plays a central protective role in the pathogenesis of many inflammatory disorders, including asthma, rheumatoid arthritis and atherosclerosis, through modulation of endothelial barrier function [62–65] and macrophage function [66]. In addition to this, S1P

is associated with signals for immune cell activation and differentiation, such as calcium mobilization, chemotaxis and cytoskeletal reorganization [67].

Circulating lysophosphatidylcholines are carried by HDL and are intensively studied in the context of inflammation. Their concentration can increase dramatically in inflammatory states [68,69]. Lysophosphatidylcholines are widely regarded as pro-inflammatory and harmful mediators. Still, an increasing number of recent studies demonstrated potent anti-inflammatory and anti-allergic properties [69–72]. Lysophosphatidylcholines should be recognized as important homeostatic mediators involved in all stages of vascular inflammation.

Thus, HDL composition and function both in humans and in animal models are associated with altered immune responses. Activation of various cell types is implicated in cell-mediated immunity. The available literature indicates the ability of HDL to affect functions of dendritic cells, monocytes, macrophages, and lymphocytes. This occurs mainly through the modulation of cholesterol content in lipid rafts, which strongly influences immune cell activation [73].

3.2. HDL and Monocyte Function

3.2.1. Effects of HDL and HDL-Associated Apolipoproteins and Lipids on Monocyte Function

Monocytes are heterogeneous cells that circulate in the blood and play a crucial role in innate immunity. During inflammation, monocytes circulate through the blood and extravasate into inflamed tissues, providing nonspecific protection against foreign pathogens, mainly through mechanisms such as phagocytosis and cytokine production [73].

HDL and apoA-I were shown to suppress the expression of the adhesion molecule cluster of differentiation (CD) 11b of monocytes and monocyte adhesion to endothelial cells [74]. Moreover, HDL reduces monocyte inflammatory response in humans [74], while both HDL and apoA-I inhibit macrophage colony-stimulating factor (M-CSF)-induced monocyte spreading through the decrease of cell division control protein 42 homolog (Cdc42) levels [75]. These data suggested that HDL prevents monocyte cytoskeletal reorganization, a step required for migration towards a chemotactic signal [76]. However, it has been suggested that apoA-II enhances the response of monocytes to LPS by suppressing the inhibitory activity of LPS-binding protein. This suggests a pro-inflammatory function of apoA-II in controlling the host response to bacterial LPS and raises the possibility that apoA-II plays a role in antimicrobial host defense [77].

In addition, apoC-III was recently identified to activate the nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in human monocytes by inducing an alternative NLRP3 inflammasome via caspase-8 and dimerization of toll-like receptor (TLR) 2 and TLR4. This suggests that apoC-III inhibition might comprise a potential therapeutic target for vascular and kidney diseases [78]. ApoC-III increased monocyte adhesion to endothelial cells under static and flow conditions [79] and expression of VCAM-1 and ICAM-1 on endothelial cells, via activation of protein kinase C-β and nuclear factor-κB (NF-κB) [80]. It has been suggested that low HDL cholesterol levels, modified/dysfunctional apoA-I and reduced expression of ABCA1/ATP-binding cassette subfamily G member 1 (ABCG1) in monocytes/macrophages may be sufficient to induce inflammasome activation in humans [81]. Such changes occur commonly in patients with chronic kidney disease, poorly controlled type 2 diabetes and aging [82–88]. Interestingly, HDL isolated from allergic rhinitis patients and psoriasis patients under treatment with biologics also showed significantly impaired capacity to suppress NF-κB and subsequent pro-inflammatory cytokine secretion in a human monocyte cell line [28,89].

Approximately 5% of all HDL particles contain apoM. ApoM-containing HDL was shown to inhibit Cu^{2+}-induced LDL oxidation and to stimulate cholesterol efflux from THP-1 foam cells more efficiently than apoM-lacking HDL [90]. Moreover, apoM-containing HDL or recombinant apoM-bound S1P reduced endothelial cell adhesion to monocytes by reducing the abundance of adhesion molecules VCAM-1 and E-selectin, but not ICAM-1, and maintained endothelial barrier integrity. In contrast, apoM alone and apoM-lacking

HDL induced opposite effects [91]. The activation of the S1P receptor 1 was sufficient and essential to promote this anti-inflammatory effect [91].

HDL inhibited monocyte adhesion and spreading on endothelial cells under shear-flow conditions and suppressed migration in response to the chemokine monocyte chemoattractant protein-1 (MCP-1) [76]. The capacity of HDL from healthy subjects to inhibit MCP-1 production, reactive oxygen species generation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation appeared to be mediated by S1P and sphingosylphosphorylcholine, two lysosphingolipids present on HDL [92].

3.2.2. Effects of HDL-Associated Enzymes on Monocyte Function

Differentiation of monocytes into macrophages and the subsequent process of foam cell formation is the first stage of atherosclerosis development [93]. HDL-associated PON1 was shown to inhibit monocyte-to-macrophage differentiation via inhibition of CD11b and CD36 expression and of total cellular peroxides during phorbol-12-myristate-13-acetate-induced THP-1 monocytes differentiation [94]. The authors of the respective study concluded that this effect could be related to PON1 peroxidase-like activity [94]. PON1 is known to hydrolyze the pro-inflammatory mediator platelet-activating factor, which activates monocytes and leads to their transformation into macrophages [95]. Another study demonstrated that PON1 could reduce monocyte chemotaxis and adhesion to endothelial cells, resulting from the oxidation of palmitoyl, linoleoyl glycerophosphorylcholine [96]. Moreover, in vitro studies showed that HDL-associated paraoxonase and PAF-AH potently inhibit monocyte transmigration in response to oxidized LDL [97]. This ability was reduced in acute inflammatory states due to the accumulation of serum amyloid A (SAA) in HDL particles [98]. PON3 was also shown to inhibit monocyte activation and LDL oxidation [99–101]. An older study showed that HDL isolated from apoA-II transgenic mice stimulated lipid hydroperoxide formation in arterial wall cells and induced transmigration of monocytes, which was linked to decreased levels of paraoxonase [102]. Upon glycation, both HDL and paraoxonase lost their ability to inhibit monocyte adhesion to human aortic endothelial cells in response to oxidized-LDL in vitro. This fact could potentially contribute to the atherosclerosis acceleration observed in type 2 diabetes patients [103].

3.2.3. Effects of Reconstituted HDL, Mimetic Peptides and Overexpression of ApoA-I/HDL on Monocyte Function

Reconstituted HDL infusion in type 2 diabetes mellitus patients resulted in a reduction of CD11b expression [104]. The overexpression of apoA-I/HDL in diabetic mice improved cholesterol efflux from bone marrow progenitors, suppressed their proliferation, monocyte production and the general recruitability of monocytes into plaques and inflammatory sites and promoted plaque macrophage polarization to the M2, atherosclerosis-resolving state [105].

Moreover, the apoE mimetic peptide Ac-hE18A-NH2 reduced monocyte adhesion in human umbilical vein endothelial cells and interleukin (IL)-6 and MCP-1 secretion and inhibited LPS-induced VCAM-1 expression [106].

The effects of apoB-depleted serum, isolated HDL, reconstituted HDL, HDL-associated apolipoproteins, and mimetic peptides on monocyte function, both in human studies and in studies utilizing animal models are summarized in Table 1.

Table 1. Effects of apoB-depleted serum, HDL, reconstituted HDL, HDL-associated apolipoproteins or mimetic peptides on monocyte function in human studies utilizing primary monocytes or a monocyte cell line and in studies utilizing animal models.

ApoB-Depleted Serum, HDL, HDL-Associated Protein, rHDL, Mimetic Peptide	Human Study/Animal Model/Cell Line	Effect on Monocytes	References
Human studies			
apoB-depleted serum, HDL	Allergic rhinitis patients/psoriasis patients under biologic treatment, U937 cell line	Decreased anti-inflammatory potential	[28,89]
HDL	Human monocytes/endothelial cells	Decreased CD11b activation, adhesion, chemotaxis, spreading	[74–76]
rHDL-containing apoA-I and PC	Type 2 diabetes patients monocytes	Decreased CD11b expression	[104]
4F-peptide	Human monocytes, THP-1 cell line	Promoted M2 polarization, attenuated TLR4, CD14 and lipid raft expression	[107]
Ac-hE18A-NH_2-peptide	Human umbilical vein endothelial cells, monocytes	Decreased adhesion, IL-6, MCP-1 secretion, VCAM-1 expression	[106]
Animal studies			
HDL/apoA-I	Diabetic apoA-I-Tg mouse model	Improved cholesterol efflux, suppressed proliferation and monocyte production	[105]

A summary of the effects of the apoB-depleted serum, HDL, reconstituted HDL, HDL-associated apolipoproteins, as well as apoA-I and apoE mimetic peptides on monocyte activation and functional properties is given, as described from human studies or studies utilizing animal models. Abbreviations: apoA-I—apolipoprotein A-I; apoB—apolipoprotein B—CD—cluster of differentiation; HDL—high-density lipoprotein; IL-6—interleukin 6; MCP-1—monocyte chemoattractant protein-1; PC—phosphatidylcholine; rHDL—reconstituted high-density lipoprotein; Tg—transgenic; TLR4—Toll-like receptor 4; VCAM-1—vascular cell adhesion molecule 1.

3.3. HDL and Macrophage Function

Monocytes can differentiate into two different types of macrophages upon different cytokine activation. M1 macrophages are regarded as pro-inflammatory and are induced by T helper type 1 (Th1) cytokines, including interferon γ, tumor necrosis factor (TNF) α (TNF-α), IL-2, and LPS. M2 macrophages are implicated in the resolution of inflammation via suppression of cytokine secretion and promotion of wound healing and tissue remodeling [44,108]. Several humoral factors may modify the balance between M1 and M2 phenotypes. Specifically, HDL increased the expression of M2 macrophage markers in mice, resulting in atherosclerotic plaque regression and in changes both in the content and in characteristics of monocyte-derived macrophages [109]. In humans, apoA-I promoted M2 polarization [107]. At the same time, mature HDL appeared not to influence the alternative differentiation of primary human macrophages towards the M2 phenotype [110].

3.3.1. Effects of HDL and HDL-Associated Apolipoproteins on Macrophage Function

It is known that the interaction of HDL with macrophages leads to many cellular responses important for the control of atherosclerosis, such as cholesterol efflux, suppression of TLR4 signaling, reduction of apoptosis during efferocytosis, and modulation of membrane lipid levels to support macrophage migration [76]. HDL and reconstituted HDL were demonstrated to reduce the inflammatory response mediated by TLRs by activating transcription factor 3 [111]. ApoA-I was shown to inhibit TLR2 receptor expression and to decrease NF-κB activation and pro-inflammatory cytokine production in human monocyte-derived macrophages [112]. Another study examined the effect of HDL on macrophage inflammatory response inhibition to the TLR4 ligand LPS [113]. It was observed that the TIR-domain-containing adapter-inducing interferon-β (TRIF)-related

adaptor molecule (TRAM)/TRIF arm of the TLR4 signaling branch was significantly suppressed by HDL, suggesting that HDL inhibits both the MyD88 and the TRAM/TRIF actions of TLR4 activation [113]. However, a recent study showed overt pro-inflammatory effects of HDL-mediated passive cholesterol depletion and lipid raft disruption in murine and human primary macrophages in vitro [114]. These pro-inflammatory effects were confirmed in vivo in peritoneal macrophages from apoA-I transgenic mice, which have elevated HDL levels [114]. Several other studies have shown that HDL can bind, sequester and neutralize LPS, thus preventing the activation of monocytes and macrophages [115–117]. Specifically, LPS bound to soluble CD14 can be shuttled to HDL and neutralized in a process implicating lipopolysaccharide-binding protein [115,116]. At the same time, HDL can also neutralize LPS by promoting its release from the surface of macrophages and monocytes [117]. Non-insulin-dependent diabetic subjects with cardiovascular disease depicted increased CD14 levels on the surface of CD14++/CD16- monocytes [118]. CD14 is essential for MyD88-independent LPS signaling via TLR4 [119], and it was shown that both HDL and apoA-I can attenuate the monocyte surface expression of CD14 [107,120]. Moreover, HDL and apoA-I inhibited NADPH oxidase activity, p47phox translocation from the cytoplasm to the plasma membrane, and NADPH oxidase 2 expression in human macrophages incubated under high glucose [121]. Furthermore, apoA-I, through ABCA1-dependent cholesterol efflux, suppressed pro-inflammatory signaling of CD40 in macrophages by preventing TNF receptor-associated factor 6 translocation to lipid rafts [122]. Although apoA-II was less effective than apoA-I in cholesterol efflux from macrophages and impaired the effect of apoA-I only when the relative amount of apoA-I to apoA-II was low [123]; interestingly, a recent study demonstrated that the presence of apoA-II in HDL particles enhanced the ABCA1-mediated efflux compared to HDL particles containing apoA-I and no apoA-II [124].

Moreover, apoA-I binding to ABCA1 in macrophages promoted signaling via Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway [125], suppressing LPS-induced pro-inflammatory cytokines release [76]. Specifically, the interaction of apoA-I with ABCA1 increases phosphorylation, thereafter activating JAK2, which, in turn, increases the binding activity of apoA-I and ABCA1 transporter [126–128]. In addition, JAK2 increases the transporter activity of ABCA1 [129,130], an activity known to have an anti-inflammatory effect. Once JAK2 is activated, it then activates STAT3 [125,128], which is independent of the ABCA1 lipid transport activity [131]. ABCA1 contains two potential docking units with STAT3, which are necessary for STAT3 phosphorylation by apoA-I/ABCA1/JAK2 [130]. It has been proposed that the transcription factor STAT3 performs an anti-inflammatory function in macrophages [125,132] and mediates IL-6 signaling pathways [125,128], suggesting that ABCA1 functions as a direct anti-inflammatory receptor owing to JAK2/STAT3 activation [125,131]. However, it has been reported that the JAK2/STAT3 pathway can also exhibit a pro-inflammatory effect [125,128,132–134], highlighting the complexity of parallel processes, which require further investigation. STAT3 regulates several fundamental cellular processes, such as cell migration, proliferation, differentiation and inflammation [135]. At the same time, it also regulates apoptosis via induction of apoptosis inhibitor B-cell lymphoma 2 expression [136,137]. Moreover, mutations in ABCA1 violating the ABCA1/STAT3 complex did not affect the ABCA1-mediated cholesterol efflux. However, they abrogated the ability of ABCA1 to suppress cytokine secretion in response to LPS [138]. It has been demonstrated that macrophage cholesterol load associated with ABCA1 inhibition increases IL-6 production [139]. IL-6 controls inflammatory responses associated with the involvement of innate and adaptive immunity [140]. Specifically, IL-6 was reported to reduce the pro-inflammatory response of human macrophages via induction of IL-4 and IL-10 anti-inflammatory cytokines and reduction of IL-1β pro-inflammatory cytokine secretion [139]. Induction of IL-10 by IL-6 may be involved thereafter in activation support of STAT3 in macrophages with the contribution of the specific receptor IL-10R [139,141]. Moreover, IL-6 was reported to induce the ABCA1 expression and to enhance the transporter-mediated cholesterol efflux

to apoA-I with the participation of the JAK2/STAT3 pathway [139]. Thus IL-6 production by lipid-loaded macrophages promotes ABCA1 gene expression, which leads to increased ABCA1-mediated cholesterol efflux via JAK2/STAT3 activation, thereby reducing foam cell formation and free cholesterol accumulation [142]. Apart from IL-6, other cytokines can also modulate ABCA1 expression, including interferon γ (IFN-γ), platelet-derived growth factor and IL-1β, which have an inhibitory effect, whereas IL-10 and transforming growth factor-beta 1 have an inducing effect [131]. This suggests that JAK2/STAT3 may represent an important signaling pathway to reduce pro-inflammatory response and accumulation of cellular lipids [128,139,143], which correlates with the anti-inflammatory mechanism of ApoA-I/ABCA1 interaction and activation of the JAK2/STAT3 signaling pathway [125,143].

Overexpression of apoA-I in mice had a protective role against atherosclerosis, in line with promoting macrophage-specific reverse cholesterol transport in vivo [144]. Moreover, HDL derived from human apoA-II transgenic rabbits exerted stronger cholesterol efflux capacity and inhibitory effects on the inflammatory cytokine expression by macrophages in vitro than HDL derived from non-transgenic rabbits [145]. Transgenic rabbits had reduced aortic and coronary atherosclerosis and reduced macrophages in atherosclerotic lesions, suggesting that enrichment of apoA-II in HDL particles has atheroprotective effects and that apoA-II may become a target for treating atherosclerosis [145]. In human apoA-II transgenic mice on a chow diet, overexpression of human apoA-II maintained effective reverse cholesterol transport from macrophages to liver and feces, even in a situation of HDL deficiency [146]. Another study in human apoA-II transgenic mice also indicated an increased ability of plasma of these mice to extract cholesterol from macrophages, implying a potential antiatherogenic effect [147]. Both HDL and apoA-I removed cholesterol from lipid rafts via ABCA1, scavenger receptor class B type 1 (SR-BI) and ABCG1, reducing the inflammatory response in macrophages and inhibiting the ability of antigen-presenting cells to stimulate T-lymphocytes [74,148]. In the presence of an acidic pH, a characteristic of inflammatory tissue sites and human atherosclerotic lesions, HDL particles undergo spontaneous remodeling. An acidic pH promoted forming of lipid-poor apoA-I and the fusion of larger HDL particles [149], enhancing the ability to promote cholesterol efflux from cultured human macrophage foam cells [149]. However, it must be noted that the cholesterol efflux capacity of HDL derived from patients suffering from atrial fibrillation, acute coronary syndrome, chronic kidney disease or psoriasis, was significantly impaired compared to control subjects, as was evaluated in J774 and RAW 264.7 macrophages, respectively [13,14,23,89,150–152].

In asymptomatic familial hypercholesterolemia patients, higher macrophage cholesterol efflux capacity, as well as higher S1P and apoM content of HDL, were found, suggesting a potential protective role against premature coronary heart disease [153]. ApoM levels were reported as a potential biomarker for coronary artery disease [154,155]; however, another study did not identify apoM as a predictor of coronary heart events [156]. Reduced circulating apoM is independently associated with adverse outcomes across the spectrum of human heart failure [157]. In human apoM transgenic mice, the ability of HDL to mediate cholesterol efflux from peritoneal mouse macrophages and to protect against LDL oxidation was improved [158]. Hepatocyte-specific apoM transgenic mice had larger plasma HDLs enriched with apoM, cholesteryl ester, LCAT and S1P, however in vivo macrophage reverse cholesterol transport capacity was similar to that of wild-type mice [159]. ApoM-enriched HDL derived from apoM-transgenic mice showed an increased in vitro cholesterol efflux capacity from macrophages compared to HDL derived from wild-type mice [160]. However, apoM had no major effect on the excretion of cholesterol into feces [160]. Moreover, in apoM deficient mice, cholesterol accumulated in large HDL particles and HDL to preβ-HDL conversion was impaired. Cholesterol efflux capacity of apoM-deficient HDL was reduced in vitro, indicating that apoM is important for preβ-HDL formation and cholesterol efflux capacity of HDL [161].

3.3.2. Effects of HDL-Associated Lipids on Macrophage Function

Following endotoxin expression, macrophages express high levels of S1P, which activate in turn S1P receptor 2 and S1P receptor 3, triggering the expression of pro-inflammatory mediators, such as C–C motif chemokine ligand (CCL) 2, IL-1β and IL-18 [162].

In a recent study, a link between anti-apoptotic effects of HDL on macrophages and HDL-S1P content was demonstrated [163]. Specifically, like S1P, HDL induced STAT3 phosphorylation, survivin expression and inhibition of caspase-3 activation. These effects were mimicked by lipids isolated from HDL and by apoM-containing HDL, but not by apoA-I or HDL deprived of S1P and apoM. Pharmacological antagonists of S1P receptors attenuated the anti-apoptotic signaling produced by HDL in macrophages [163]. Another study showed that HDL-S1P and albumin-S1P reduced macrophage adhesion to endothelial cells in vitro [164].

Activation of S1P receptor 1 is involved in macrophage polarization towards an anti-inflammatory phenotype [165]. At the same time, in a thioglycollate peritonitis model, S1P inhibited macrophage migration through S1P receptor 2 ligation [166]. A more recent study demonstrated that HDL stimulated migration of macrophages was dependent on SR-BI and was blocked by S1P receptor antagonists [167]. S1P was recently recognized as an intermediate in liver X receptor (LXR)-stimulated ABCA1-mediated cholesterol efflux. S1P/S1P receptor 3 signaling was identified as a positive feedback regulator of macrophage cholesterol efflux by sphingolipids [168]. In atherosclerosis animal models, S1P receptor 2 deficiency was associated with reduced inflammation and monocyte/macrophage recruitment [162,169]. In contrast, S1P receptor 3 was shown to mediate the chemotactic effect of S1P [170]. S1P binding to the S1P receptor was shown to provoke an anti-inflammatory macrophage phenotype via inhibition of pro-inflammatory cytokine production and NF-κB activation, inhibiting macrophage cell death and increasing cyclic adenosine monophosphate production [66].

3.3.3. Effects of HDL-Associated Enzymes on Macrophage Function

Among the paraoxonase family of enzymes, PON1 and PON3 are mainly associated with HDL [44]. PON1 was shown to directly impact inflammation via attenuation of inflammatory cytokine release of macrophages, such as TNF-α and IL-6 [171]. PON1 treated mice depicted smaller mouse peritoneal macrophages with a lower granulation level than those isolated from control mice [94].

Both PON1 and PON3 are thought to reduce the lipoprotein atherogenicity through hydrolysis of oxidized lipids [172,173], resulting in reduced uptake of atherogenic lipoproteins by macrophages [174]. When macrophages were exposed to HDL in the presence of a PON1 antibody, cholesterol efflux capacity and the ability of HDL to inhibit macrophage-dependent oxidation of LDL were impaired [175]. Similarly, PON1-deficiency in mice resulted in increased oxidative stress both in serum and peritoneal macrophages [176]. Incubation of mouse peritoneal macrophages with HDL derived from PON1 transgenic mice enhanced the cholesterol efflux capacity compared to HDL derived from $PON1^{-/-}$ mice [47]. It has been shown that PON1 interacts with lipid rafts on the plasma membrane [177]. In addition, PON1 was shown to inhibit mouse peritoneal macrophage cholesterol biosynthesis and atherogenesis, potentially through its phospholipase A2-like activity [178]. In addition, the PON1-192R/Q human polymorphism resulted in reduced PON1 stability, lipolactonase activity and macrophage cholesterol efflux, implying a potential role of the polymorphism to atherosclerosis susceptibility [179]. Expression of PON3 in apoE-deficient mice resulted in significantly lower serum levels of lipid hydroperoxides and enhanced macrophage cholesterol efflux potential [180]. Moreover, human paraoxonase gene cluster transgenic overexpression repressed atherogenesis and promoted atherosclerotic plaque stability in apoE-deficient mice [181].

Along with its ability to reduce lipid peroxides in HDL, PON1 was shown to reduce oxidant formation in macrophages [182]. Specifically, PON1 overexpression in an experimental diabetes mouse model was associated with decreased macrophage-associated oxidative

stress, decreased diabetes development and mortality [183]. In addition, overexpression of human PON1 in mice with combined leptin and LDL receptor deficiency resulted in a significant reduction of total plaque volume and the volume of plaque macrophages and of plaque-associated oxidized LDL [184].

3.3.4. Effects of Reconstituted HDL and Mimetic Peptides on Macrophage Function

Reconstituted HDL consisting of apoA-I complexed with phosphatidylcholine inhibited TLR2 receptor expression and decreased NF-κB activation and pro-inflammatory cytokine production in human monocyte-derived macrophages [112]. Moreover, infusion of reconstituted HDL in healthy individuals protected from inflammatory events caused by LPS [120], while in type 2 diabetes mellitus patients it increased the capacity of plasma to receive cholesterol from THP-1 macrophages [104]. Discoidal reconstituted HDL containing phosphatidylcholine complexed with apoA-I inhibited reactive oxygen species production, NADPH oxidase activity, p47phox translocation from the cytoplasm to the plasma membrane and NADPH oxidase 2 expression in human macrophages incubated under high glucose [121]. Reconstituted HDL-containing S1P could induce macrophage cholesterol efflux independently of S1P but had additional S1P-mediated effects on endothelial cell tube formation mediated by Akt/ERK/NO through the S1P receptor 2 and S1P receptor 3 [185]. Reconstituted HDL carrying apoE exhibited properties similar to those of HDL carrying apoA-I, but with a lower capacity to stabilize PON1 and to induce its antiatherogenic functions, including inhibition of LDL oxidation and stimulation of macrophage cholesterol efflux [186].

It has been shown that the apoA-I mimetic peptide 4F promoted the M2 macrophage polarization [107]. In addition, the apoA-I mimetic peptide 4F removed cholesterol from lipid rafts. It downregulated TLR cell surface expression in LPS-treated monocyte-derived macrophages, resulting in downregulation of genes modulated by the TLR pathway [107,187]. Oral administration of the apoA-I mimetic peptide 4F in mice promoted forming of preβ-HDL with increased paraoxonase activity, resulting in improved HDL anti-inflammatory properties and cholesterol efflux capacity both in vitro and in vivo [188,189]. Intranasal administration of full-length human apoA-I to house dust mite-challenged mice lead to a decreased number of bronchoalveolar lavage fluid macrophages, associated with a reduction in airway inflammation [31].

The effects of apoB-depleted serum, isolated HDL, reconstituted HDL, HDL-associated apolipoproteins, lipids and enzymes, as well as mimetic peptides on macrophage function, both in human studies and in studies utilizing animal models are summarized in Table 2.

Table 2. Effects of apoB-depleted serum, HDL, reconstituted HDL, HDL-associated apolipoproteins, lipids and enzymes or mimetic peptides on macrophage function in human studies utilizing monocyte-derived macrophages or cell lines and in studies utilizing animal models.

ApoB-Depleted Serum, HDL, HDL-Associated Protein/ Lipid/Enzyme, rHDL, Mimetic Peptide	Human Study/Animal Model/Cell Line	Effect on Macrophages	References
Human studies			
apoB depleted serum, HDL	Atrial fibrillation, psoriasis, acute coronary syndrome or renal disease patients, J774.2 and RAW 264.7 macrophages	Impaired cholesterol efflux capacity	[13,14,23,89,150,151]
LpA-I/A-II HDL particles	RAW 264.7 macrophages	ApoA-II presence in HDL particles enhanced ABCA1-mediated cholesterol efflux compared to LpA-I particles	[124]

Table 2. *Cont.*

ApoB-Depleted Serum, HDL, HDL-Associated Protein/ Lipid/Enzyme, rHDL, Mimetic Peptide	Human Study/Animal Model/Cell Line	Effect on Macrophages	References
HDL, rHDL or commercially obtained HDL	Human bone-marrow-derived macrophages	Increased gene and protein expression of pro-inflammatory IL-12 and TNF-α and decreased anti-inflammatory IL-10 via a mechanism involving lipid raft disruption and PKC	[114]
HDL, rHDL-containing apoA-I and PC	Human monocyte-derived macrophages	Inhibited ROS production, NADPH oxidase activity, Nox2 expression	[121]
rHDL-containing apoA-I and PC	Human monocyte-derived macrophages	Inhibited TLR2 expression, decreased NF-κB activation and pro-inflammatory cytokine production	[112]
rHDL-containing apoA-I and PC	Type 2 diabetes patients, THP-1 macrophage-derived foam cells	Improved plasma cholesterol efflux capacity	[104]
4F-peptide	Human monocyte-derived macrophages	Promoted M2 polarization, attenuated TLR4, CD14 and lipid raft expression	[107]
4F-peptide	Human monocyte-derived macrophages, THP-1 macrophage-derived foam cells	Depleted cholesterol from lipid rafts, downregulated TLR cell surface expression and signaling pathway	[107,187]
Animal studies			
HDL	Atherosclerosis regression mouse model	Increased M2 macrophage markers	[109]
HDL	Mouse peritoneal macrophages	Suppressed TRAM/TRIF arm of TLR4 signaling	[113]
HDL	Bone-marrow-derived macrophages/peritoneal macrophages derived from apoA-I Tg mice	Enhanced TLR1/2, TLR3, TLR4, TLR7/8 and TLR9 responses	[114]
HDL	Human apoA-II-Tg Japanese white rabbit model	Stronger cholesterol efflux capacity and inhibitory effects on inflammatory cytokine secretion by macrophages	[145]
HDL	Human apoA-II-Tg mice	Human apoA-II maintained effective reverse cholesterol transport from macrophages to feces despite an HDL deficiency. Increased mice plasma ability to extract cholesterol from macrophages	[146,147]
apoA-I	House dust-mite mouse model	Decreased airway inflammation and number of bronchoalveolar lavage fluid macrophages	[31]
HDL, apoM-enriched HDL	apoM-Tg mouse model	Improved cholesterol efflux capacity and protection against LDL oxidation	[158,160]

Table 2. *Cont.*

ApoB-Depleted Serum, HDL, HDL-Associated Protein/ Lipid/Enzyme, rHDL, Mimetic Peptide	Human Study/Animal Model/Cell Line	Effect on Macrophages	References
apoM-deficient HDL	apoM-deficiency mouse model	Impaired cholesterol efflux capacity	[161]
D-4F-peptide	apoE-deficiency mouse model	Improved HDL-mediated cholesterol efflux	[189]
PON1-Tg mouse model-derived HDL	Mouse peritoneal macrophages	Improved cholesterol efflux capacity	[47]
PON1	PON1-deficiency mouse model-derived macrophages	Decreased cellular peroxide content, superoxide anion release and oxidation of LDL	[176]
PON1	PON1-deficiency mouse model-derived peritoneal macrophages	Inhibited cholesterol biosynthesis and atherogenesis	[178]
PON1	PON1-Tg diabetes mouse model	Decreased diabetes-induced macrophage oxidative stress	[183]
PON3	apoE-deficiency mouse model	Decreased lipid hydroperoxides, improved macrophage cholesterol efflux capacity	[180]
HDL-S1P	Myocardial ischemia/reperfusion mouse model	Decreased adhesion to endothelial cells	[164]
rHDL-containing apoA-I, PC and S1P	RAW264 macrophages	Induced cholesterol efflux	[185]

A summary of the effects of apoB-depleted serum, HDL, reconstituted HDL, HDL-associated apolipoproteins, lipids and enzymes, as well as apoA-I mimetic peptides on macrophage activation and functional properties is given, as described from human studies utilizing monocyte-derived macrophages or studies utilizing animal models. Abbreviations: apoA-I—apolipoprotein A-I; apoB—apolipoprotein B—apoE—apolipoprotein E; apoM—apolipoprotein M; CD—cluster of differentiation; HDL—high-density lipoprotein; LDL—low-density lipoprotein; NADPH—nicotinamide adenine dinucleotide phosphate; NF-κB—nuclear factor-κB; Nox2—nicotinamide adenine dinucleotide phosphate oxidase 2; PC—phosphatidylcholine; PKC—protein kinase C; PON1—paraoxonase 1; PON3—paraoxonase 3; rHDL—reconstituted high-density lipoprotein; ROS—reactive oxygen species; S1P—sphingosine-1-phosphate; Tg—transgenic; TLR—Toll-like receptor; TLR1—Toll-like receptor 1; TLR2—Toll-like receptor 2; TLR3—Toll-like receptor 3; TLR4—Toll-like receptor 4; TLR7—Toll-like receptor 7; TLR8—Toll-like receptor 8; TLR9—Toll-like receptor 9; TRAM—TRIF-related adaptor molecule; TRIF—TIR-domain-containing adapter-inducing interferon-β.

3.4. HDL and Neutrophil Function

Neutrophils, the most abundant innate immune cells, are related to chronic inflammation and autoimmune diseases, such as rheumatoid arthritis [190] or psoriasis [191]. Neutrophils are also associated with obesity [192], atherosclerosis [193] and acute coronary events [194,195], with their presence being identified in atherosclerotic lesions [196,197]. Neutrophils can become activated in hyperlipidemia. The severity of the disease is directly correlated with superoxide release and CD11b expression [198–200]. Neutrophil activation can be directly triggered by cholesterol loading [201]. The main offensive functions of these cells include the respiratory burst, which is linked to the generation of reactive oxygen species, degranulation and the formation of neutrophil extracellular traps (NETs) [202,203]. NETs are a key component of pathological thrombi and drive cardiovascular, inflammatory and thrombotic diseases in humans and mice [204] and were shown to promote atherosclerosis and carotid thrombosis in *ApoE*$^{-/-}$ mice [205–208]. Moreover, myeloid deficiency of ABCA1 and ABCG1 leads to macrophage and neutrophil inflammasome activation, which in turn promotes atherosclerotic plaque development and NETs forming in plaques [209].

3.4.1. Effects of HDL and HDL-Associated Apolipoproteins on Neutrophil Function

ApoA-I rapidly inhibits neutrophil activation and CD11b expression through ABCA1, while mature HDL suppresses effector responses apparently independent of receptors [210]. ApoA-I was also shown to diminish neutrophil degranulation and superoxide production in response to surface-bound immunoglobulin G and N-formyl-L-methionyl-L-leucyl-phenylalanine (fMLP) [211]. Moreover, apoA-I suppressed neutrophil activation associated with reductions in cellular adhesion, degranulation and oxidative burst [211,212]. At the same time, apoA-I was also able to decrease IL-1β release in LPS stimulated neutrophils [213]. Both apoA-I and HDL attenuated neutrophil adhesion and spreading to activated platelet monolayers [210,212]. Interestingly, also apoA-IV potently decreased neutrophil chemotaxis upon IL-8 stimulation [29].

HDL was shown to stimulate the biogenesis of microRNA-223-3p in neutrophils [214]. MicroRNA-223-3p regulates neutrophil development, hyperactivity and recruitment during infection [214]. Another recent study proposed that dysfunctional HDL may contribute to the systemic inflammation in uremic patients via modulation of polymorphonuclear cells' functions, such as attenuation of apoptosis [215]. Moreover, both apoA-I and HDL decreased neutrophil membrane lipid rafts, which is likely a key event since lipid raft abundance has been correlated with CD11b activation [76]. In fact, many studies have described the importance of lipid rafts not only in neutrophil activation but also in the release of inflammatory mediators [216–219]. Cholesterol loading of neutrophils is priming their activation and is increasing their endothelium adhesiveness [201].

ApoA-II decreased producing of IL-8 released by neutrophils stimulated either with the acute phase protein SAA or with LPS [213]. The addition of recombinant SAA caused an increase in the basal liberation of TNF-α, IL-1β and IL-8 by human blood neutrophils. In contrast, HDL-associated SAA did not show these activities [220].

3.4.2. Effects of HDL-Associated Lipids on Neutrophil Function

Modification of HDL by secretory phospholipase A2 (sPLA2) results insaturated lysophosphatidylcholines forming. Interestingly, sPLA2 modified HDL (HDL enriched with lysophosphatidylcholines) depicted a dramatically increased ability to suppress agonist-induced neutrophil activation, including shape change, CD11b activation, NET formation, adhesion under flow and migration of neutrophils, when compared to control HDL [71]. This NETosis-preventing effect may be due to the potent lipid raft disrupting capacity of sPLA2-modified HDL and the suppression of intracellular Ca^{2+} rise [71]. Moreover, the HDL-associated lysophosphatidylcholine 16:0 and lysophosphatidylserine 18:0 could inhibit neutrophil shape change, whereas unsaturated lysophosphatidylcholine 18:1 showed no effect [71].

In addition, in a mouse model of myocardial ischemia/reperfusion injury, HDL-associated sphingosylphosphorylcholine reduced infarct size and polymorphonuclear neutrophil recruitment to the infarcted area via the S1P receptor 3 [221]. Similarly, HDL-associated S1P reduced infarct size in a mouse model of myocardial ischemia/reperfusion by inhibiting cardiomyocyte apoptosis and neutrophil recruitment to the infarct area dependent on nitric oxide and the S1P receptor 3 [164]. Moreover, smaller myocardial infarcts and reduced neutrophil infiltration into the infarcted area were observed in apoM (major plasma carrier of S1P) transgenic mice [222].

3.4.3. Effects of Reconstituted HDL and Mimetic Peptides on Neutrophil Function

Reconstituted HDL containing apoA-I and phosphatidylcholine potently decreased cell adhesion via blockage of LPS activity and modification of CD11b/CD18 upregulation [223]. Interestingly, phosphatidylcholine alone was shown to be sufficient for lipopolysaccharide-binding protein catalyzed neutralization of LPS [224]. Infusion of reconstituted HDL in type 2 diabetes mellitus patients reduced neutrophil adhesion to the fibrinogen matrix [104]. In peripheral vascular disease patients, infusion of reconstituted HDL attenuated neutrophil activation [210]. Administration of apoA-I or reconstituted

HDL containing apoA-I (or the 5A apoA-I mimetic peptide) complexed with phosphatidylcholine showed potent antiatherogenic effects and reduced the collar-mediated increase in endothelial expression of the cell adhesion molecules VCAM-1 and ICAM-1 in New Zealand white rabbits. In addition, it suppressed the production and expression of the catalytic NADPH oxidase-4 subunits of NADPH oxidase and markedly impaired the infiltration of circulating neutrophils into the carotid intima-media [225–227]. ApoA-I promoted atherosclerosis regression in diabetic mice by suppressing myelopoiesis and plaque inflammation [105].

Administration of the apoA-I mimetic peptide 5A in an experimental murine model of house dust mite-induced asthma resulted in a significant reduction of airway inflammation, hyperreactivity and remodeling, as well as in a reduction of bronchoalveolar lavage fluid neutrophils [228]. Administration of the 5A peptide to ovalbumin-challenged apoA-I knockout mice suppressed increases in neutrophilic airway inflammation [229], while administration of L-4F to wild-type mice receiving inhaled LPS reduced the number of bronchoalveolar lavage fluid neutrophils [230]. Moreover, L-4F inhibited the activation of isolated human leukocytes and neutrophils by acute respiratory distress syndrome serum and LPS in vitro [231]. In addition, infusion of recombinant apoA-I-Milano in a transient middle cerebral artery occlusion stroke rat model significantly reduced infarct volume through inhibition of platelet aggregation. Still, it did not reduce hemorrhagic transformation and activation of neutrophils [232].

Intranasal administration of full-length human apoA-I to house dust mite-challenged mice lead to a reduction in airway inflammation, with decreased number of bronchoalveolar lavage fluid neutrophils [31]. ApoA-I suppressed the expression of ICAM-1 on endothelium, thus diminishing neutrophil adherence and transendothelial migration and the subsequent myocyte injury in an experimental rat model of ischemia/reperfusion injury [233]. In an experimental mouse model of LPS-induced inflammation and lethality, apoA-I gene transfer resulted in a significantly attenuated LPS-induced infiltration of neutrophils into the lungs, as well as in reduced lung edema and mortality [234]. A single low dose infusion of apoA-I administered after the onset of acute inflammation in carotid arteries of normocholesterolemic New Zealand White rabbits decreased neutrophil infiltration and inhibited their activation [227]. Infusion of lipid-free apoA-I or discoidal reconstituted HDL containing phosphatidylcholine and apoA-I decreased neutrophil infiltration and VCAM-1 and ICAM-1 expression in a model of acute vascular inflammation in New Zealand White rabbits [235].

The effects of HDL, reconstituted HDL, HDL-associated apolipoproteins, lipids and enzymes, as well as mimetic peptides on neutrophil function, in human studies and studies utilizing animal models are summarized in Table 3.

Table 3. Effects of HDL, reconstituted HDL, HDL-associated apolipoproteins, lipids and enzymes or mimetic peptides on neutrophil function in human studies utilizing primary neutrophils and in studies utilizing animal models.

HDL, HDL-Associated Protein/Lipid/Enzyme, rHDL, Mimetic Peptide	Human Study/Animal Model	Effect on Neutrophils	References
Human studies			
HDL	Uremic patients, human neutrophils	Decreased apoptosis	[215]
rHDL-containing apoA-I and PC	Type 2 diabetes patients	Decreased adhesion	[104]
rHDL	Peripheral vascular disease patients	Decreased activation	[210]
rHDL-containing apoA-I and PC	Human polymorphonuclear and endothelial cells	Decreased adhesion via LPS blocking and modification of CD11b/CD18	[223]
L-4F-peptide	Human neutrophils	Decreased activation	[231]

Table 3. *Cont.*

HDL, HDL-Associated Protein/Lipid/Enzyme, rHDL, Mimetic Peptide	Human Study/Animal Model	Effect on Neutrophils	References
Secretory PLA2-modified HDL	Human neutrophils	Decreased shape change, chemotaxis, adhesion, CD11b activation, NET formation	[71]
Animal studies			
apoA-I, rHDL-containing apoA-I, 5A-peptide complexed with PC	New Zealand white rabbits	Decreased infiltration of circulating neutrophils into carotid intima-media	[225–227]
apoA-I, rHDL-containing apoA-I and PC	New Zealand white rabbits	Decreased neutrophil infiltration, VCAM-1 and ICAM-1 expression	[235]
apoA-I/HDL overexpression	Diabetic mice	Decreased neutrophil production and NETs	[105]
5A-peptide	Asthma mouse model	Decreased bronchoalveolar lavage fluid neutrophils	[228]
5A-peptide	OVA-challenged apoA-I$^{-/-}$ mice	Decreased neutrophilic airway inflammation	[229]
L-4F-peptide	LPS-challenged WT mice	Decreased bronchoalveolar lavage fluid neutrophils	[230]
HDL-SPC	S1P3$^{-/-}$ myocardial ischemia/reperfusion mice	Decreased infarct size and neutrophil apoptosis/recruitment	[221]
HDL-S1P	Mouse model of ischemia/reperfusion	Decreased neutrophil recruitment in the infarcted area	[164]

A summary of the effects of HDL, reconstituted HDL or HDL-associated apolipoproteins, lipids and enzymes, along with apoA-I mimetic peptides on neutrophil activation and functional properties is given, as described from human studies, studies utilizing primary neutrophils or studies utilizing animal models. Abbreviations: apoA-I—apolipoprotein A-I; CD—cluster of differentiation; HDL—high-density lipoprotein; ICAM-1—intercellular adhesion molecule 1; LPS—lipopolysaccharide; NET—neutrophil extracellular trap; OVA—ovalbumin; PC—phosphatidylcholine; PLA2—phospholipase A2; rHDL—reconstituted high-density lipoprotein; S1P—sphingosine-1-phosphate; S1P3—sphingosine-1-phosphate receptor 3; SPC—sphingosylphosphorylcholine; VCAM-1—vascular cell adhesion molecule 1.

3.5. HDL and Eosinophil Function

Eosinophil-rich inflammation has long been associated with allergic inflammation, asthma and parasitic infestation. Eosinophils release basic proteins that are cytotoxic and lipid mediators, such as cysteinyl leukotrienes, which cause bronchial epithelial damage and airflow obstruction [236]. Evidence from animal models of asthma and clinical studies demonstrated a causal role of eosinophils in the pathogenesis of asthma, including airway hypersensitivity, remodeling and elevated mucus production [237]. The number of eosinophils increases in several diseases, including helminth infections, hypereosinophilic syndrome, allergies [237] and acute myocardial infarction [238], while eosinophil levels have emerged as a strong predictor of mortality in acute heart failure [239] and coronary artery disease patients [240]. Granules of mature eosinophils contain basic proteins, such as eosinophil cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin [241]. In contrast, deposition of granules released from eosinophils in tissues comprises a common finding in eosinophil-associated diseases and potentially contributes to their pathogenesis [242–245]. Recently, however, it was recognized that eosinophils are crucial for local immunity and repair, with an increasing number of regulatory and homeostatic roles attributed to them. An important function of eosinophils is their antitumor effect in colorectal cancer [246]. Eosinophils show hepatoprotective activity [247] and cardiac protective function after myocardial infarction [248]. Of particular interest, a robust inverse correlation between eosinophil numbers and coronavirus disease 2019 (COVID-19) infection severity was observed most recently [249]. Taken together, these new findings point to an unmet need to target eosinophil overactivation without completely depleting

this multifunctional immune cell type. Therefore, it is important to investigate whether HDL or an HDL-associated component could serve as a potential new target to reduce eosinophil activation.

3.5.1. Effects of HDL and HDL-Associated Components on Eosinophil Function

In coronary artery disease patients, an inverse association of absolute eosinophil count and HDL cholesterol and a positive association with the prevalence of coronary artery disease was reported [250]. Both HDL and HDL apolipoproteins were recently shown to effectively inhibit eosinophil chemotaxis [29] and to attenuate eosinophil activation [251]. In a study involving atopic dermatitis patients, patients'-derived HDL showed an impaired ability to inhibit agonist-induced eosinophil shape change and migration compared to HDL isolated from healthy controls [34]. In contrast, an increased ability of isolated HDL derived from allergic rhinitis patients to suppress eosinophil effector responses upon eotaxin-2/CCL24 stimulation was demonstrated [28]. Importantly, apoA-IV applied at very low concentrations, decreased eosinophil shape change, chemotaxis, CD11b expression and Ca^{2+} flux. The molecular mechanism involved the activation of Rev-ErbA-α followed by the induction of a phosphatidylinositol-3-kinase (PI3K)/phosphoinositide-dependent-kinase 1 (PDK1)/protein kinase A (PKA)-dependent signaling cascade [29]. In addition, apoA-IV could accelerate eosinophil apoptosis of allergic donors, while apoA-I was less effective [29]. Interestingly, besides apoA-IV and apoA-I, apoC-III effectively and dose-dependently suppressed agonist-induced eosinophil shape change [34]. Moreover, intranasal administration of full-length human apoA-I to house dust mite-challenged mice lead to a reduction in airway inflammation, with decreased number of bronchoalveolar lavage fluid eosinophils [31]. Another study evaluated the role of HDL in lung-allergic inflammation of ovalbumin-challenged endothelial lipase knockout mice. A reduction in the number of eosinophils in bronchoalveolar lavage and in the expression of VCAM-1, as well as an attenuation of hyperresponsiveness, was shown in endothelial lipase knockout mice. This indicated that targeted inactivation of endothelial lipase attenuated lung-allergic inflammation. At the same time, the protective effects were associated with high plasma HDL levels, downregulation of VCAM-1 and loss of the direct ligand-binding function of endothelial lipase [252].

In addition to HDL apolipoproteins, the major HDL-associated saturated lysophosphatidylcholine species 16:0 and 18:0 were shown to effectively and dose-dependently inhibit agonist-induced shape change and migration of eosinophils [34]. Along with this, another study demonstrated that lysophosphatidylcholines suppressed multiple eosinophil effector responses, such as CD11b upregulation, chemotaxis, degranulation and downstream signaling and suppressed eosinophil migration in vivo [72]. In an experimental murine model of house dust mite extract-induced asthma, apoA-IV could repress the infiltration of eosinophils into the bronchoalveolar space and protected mice from the airway and systemic eosinophilia [29], while lysophosphatidylcholine 18:0 treatment markedly reduced immune cell infiltration into the lungs in a mouse model of allergic cell recruitment [72]. Interestingly, the stable lysophosphatidylcholine analog miltefosine also showed very similar properties, suppressing human eosinophil activation and ameliorating murine allergic inflammation in vivo [253].

3.5.2. Effects of Mimetic Peptides on Eosinophil Function

It has been reported that the apoA-I/ABCA1 pathway may have a protective effect on asthma, supporting the concept of advancing inhaled apoA-I mimetic peptides to a clinical trial of asthma [254]. Specifically, administration of the 5A apoA-I mimetic peptide in an experimental murine model of house dust mite-induced asthma resulted in a significant reduction of bronchoalveolar lavage fluid eosinophils [228]. Similarly, intranasal administration of D-4F, another apoA-I mimetic peptide, reduced airway eosinophilia and airway resistance in ovalbumin-challenged mice [255].

The effects of apoB-depleted serum, isolated HDL, HDL-associated apolipoproteins and lipids, as well as mimetic peptides on eosinophil function, both in human studies and in studies utilizing animal models are summarized in Table 4.

Table 4. Effects of apoB-depleted serum, HDL, HDL-associated apolipoproteins and lipids or mimetic peptides on eosinophil function in human studies utilizing primary eosinophils and in studies utilizing animal models.

ApoB-Depleted Serum, HDL, HDL-Associated Protein/Lipid, Mimetic Peptide	Human Study/Animal Model	Effect on Eosinophils	References
Human studies			
apoB-depleted serum, HDL	Allergic rhinitis patients, human eosinophils	Inhibited shape change and chemotaxis	[28]
HDL	Atopic dermatitis patients, human eosinophils	Decreased ability to inhibit shape change and chemotaxis	[34]
HDL, apoA-I, apoA-IV	Allergic patients, human eosinophils	Decreased chemotaxis, accelerated apoptosis	[29]
Stable LPC analog Miltefosine	Human eosinophils	Inhibited shape change, CD11b expression, chemotaxis, degranulation, CD63 expression and Ca^{2+} flux	[253]
Animal studies			
apoA-I, apoA-IV, 5A-peptide	House dust mite-induced asthma mouse model	Decreased bronchoalveolar lavage fluid eosinophils	[29,31,228]
D-4F	OVA-challenged mouse model	Decreased airway eosinophilia	[255]
LPC 18:0	Allergic cell recruitment mouse model	Decreased infiltration into the lungs	[72]
Stable LPC analog Miltefosine	Allergic cell recruitment; allergic lung inflammation mouse models	Suppressed eosinophil migration into the bronchoalveolar lavage; reduced eosinophil numbers, improved lung resistance	[253]

A summary of the effects of apoB-depleted serum, HDL, HDL-associated apolipoproteins and lipids, as well as apoA-I mimetic peptides on eosinophil activation and functional properties is given, as described from human studies utilizing primary eosinophils or studies utilizing animal models. Abbreviations: apoA-I—apolipoprotein A-I; apoA-IV—apolipoprotein A-IV; apoB—apolipoprotein B; CD—cluster of differentiation; HDL—high-density lipoprotein; LPC—lysophosphatidylcholine; OVA—ovalbumin.

3.6. HDL and Dendritic Cell Function

Dendritic cells comprise a heterogenous family of bone marrow-derived immune cells of both lymphoid and myeloid stem cell origin that populate all lymphoid organs, including the spleen, thymus and lymph nodes, as well as almost all nonlymphoid organs and tissues [256]. They are responsible for the process and presentation of antigens to naïve, memory and effector T cells [73,256]. At the same time, they are implicated in the pathogenesis of autoimmune diseases, such as psoriasis [257,258] and systemic lupus erythematosus [256], as well as allergies, including allergic rhinitis [259], allergic asthma [260] and atopic dermatitis [261]. It was suggested that dendritic cells are critically involved in the progression and destabilization of atherosclerotic plaques [262,263]. In contrast, in atherosclerotic plaques, it has been shown that plasmacytoid dendritic cells stimulate T cells against viral antigens [264]. The exact mechanisms of action of dendritic cells, along with their role in immunity and their implication in diseases, have been described in detail elsewhere and are not in the focus of the current review [256,265].

Effects of HDL and HDL-Associated Components on Dendritic Cell Function

It has been shown that hyperlipidemia altered dendritic cell function, specifically by inhibiting cell migration. At the same time, HDL and HDL-associated PAF-AH restored

this process [266]. HDL, along with some of its components, were shown to interfere with certain steps of dendritic cells' activity and maturation. Specifically, apoA-I impaired adaptive immunity via inhibition of maturation, differentiation and function of dendritic cells [267–269] by inducing prostaglandin E2 and IL-10, two known inhibitors of dendritic cell function and differentiation, and by inhibiting the ability of dendritic cells to secrete IL-12 when stimulated with anti-CD40 and IFN-γ [268]. HDL was also able to reduce IL-12 production in stimulated mature dendritic cells, thus decreasing their ability to stimulate T cells [268,270]. Moreover, upon LPS-mediated TLR4 stimulation, HDL inhibited the ability of dendritic cells to induce Th1 response. At the same time, the phospholipid HDL fraction was identified as the most active in inhibiting dendritic cell maturation [270]. Specifically, HDL-associated 1-palmitoyl-2-linoleoyl-phosphatidylcholine and 1-stearoyl-2-linoleoyl-phosphatidylcholine were shown to have direct immunoregulatory functions by impairing the ability of dendritic cells to activate a Th1 response of T cells [270]. Moreover, reconstituted HDL particles could trigger immunogenic cell death and promoted dendritic cell maturation in an experimental model of hepatocellular carcinoma [271]. At the same time, it has been shown that oxidized HDL may promote the maturation and migration of bone marrow-derived dendritic cells in vitro [272].

The effects of HDL, HDL-associated enzymes, as well as reconstituted or synthetic HDL on dendritic cell function, both in human studies and in studies utilizing animal models are summarized in Table 5.

Table 5. Effects of HDL, reconstituted HDL, synthetic HDL or HDL-associated enzymes on dendritic cell function in human studies utilizing monocyte-derived dendritic cells and in studies utilizing animal models.

HDL, HDL-Associated Enzyme, rHDL, sHDL	Human Study/Animal Model	Effect on Dendritic Cells	References
Human studies			
HDL	Human dendritic cells	Impaired ability to activate T cells, decreased IFN-γ, IL-12 and TNF-α secretion	[270]
Animal studies			
HDL, HDL-PAF-AH	ApoE/LDL-deficiency mouse model	Increased migration, restored immunologic priming	[266]
rHDL-containing apoA-I and PC	Mouse BMDCs	Decreased MHC class II, CD40, CD80 and CD86 expression and IL-6, IL-8, IL-12, IL-23, TNF-α and IL-10 secretion; decreased Myd88 mRNA levels	[269]
sHDL	BMDCs from a hepatocellular carcinoma mouse model	Decreased tumor burden triggered immunogenic cell death and induced maturation of dendritic cells	[271]

A summary of the effects of HDL, reconstituted and synthetic HDL, as well as HDL-associated enzymes on dendritic cell activation and functional properties is given, as described from human studies utilizing monocyte-derived dendritic cells or studies utilizing animal models. Abbreviations: apoA-I—apolipoprotein A-I; apoE—apolipoprotein E; BMDCs—bone marrow-derived dendritic cells; CD—cluster of differentiation; HDL—high-density lipoprotein; IFN-γ—interferon γ; IL—interleukin; LDL—low-density lipoprotein; MHC—major histocompatibility complex; PAF-AH—platelet-activating factor acetylhydrolase; PC—phosphatidylcholine; rHDL—reconstituted high-density lipoprotein; sHDL—synthetic high-density lipoprotein; TNF-α—tumor necrosis factor α.

S1P is a major regulator of both dendritic cell activation and maturation [273]. S1P effectively diminished the ability of dendritic cells to capture antigens via macropinocytosis, while most studies supported that extracellular S1P presence on dendritic cells leads to an IL-6, IL-23, STAT3-dependent T helper type 17 inflammatory profile; although at least in part Th1 was attenuated [273]. Topical application of S1P was shown to be beneficial in atopic dermatitis treatment [274]. At the same time, S1P homeostasis dysregulation has been discussed in the pathogenesis of the disease. However, in systemic inflammatory syndromes, such as bacterial sepsis and viral hemorrhagic fever, S1P promoted the

dissemination of inflammation by contributing to the coagulation-induced activation and trafficking of dendritic cells in the lymphatics [275].

3.7. Role of HDL and HDL-Associated Components on T Cell Function

The allergic response is engineered by CD4+ T lymphocytes secreting Th2 cytokines upon activation by allergen-derived peptides [276]. At the same time, immune-mediated skin diseases may be mediated mainly by T cells through uncontrolled, unspecific inflammation and via the humoral immune system [277]. Importantly, T cell activation plays a critical role in the pathogenesis of psoriasis [278], which is T17/T22 cell-dominated, and atopic dermatitis, a T2 cell-dominated disease [277].

HDL-induced cholesterol efflux from macrophages affected antigen presentation to T cells, along with T cell receptor signaling [267,279,280]. At the same time, the HDL concentration regulated cellular contact between stimulated T cells and monocytes [281]. HDL-associated apoA-I inhibited producing of IL-1β and TNF-α by blocking the contact-mediated activation of monocytes by T lymphocytes through its binding to stimulated T cells [282], while HDL potently reduced reactive oxygen species production induced in polymorphonuclear neutrophils upon contact with stimulated T cells [283].

ApoA-I was shown to control the cholesterol-associated T-lymphocyte activation and proliferation in peripheral lymph nodes of diet-fed LDLr$^{-/-}$, apoA-I$^{-/-}$ mice [284] and to suppress inflammation through stimulation of regulatory T cells (Tregs) in the lymph nodes and through inhibition of effectors, such as memory T cells [285]. Tregs could specifically internalize HDLs from their microenvironment and use them as an energy source, a fact likely attributable to the increased SR-BI cell expression. At the same time, HDLs could significantly decrease the apoptosis of human Tregs in vitro [286].

ApoA-II was shown to suppress IFN-γ production by concanavalin A-stimulated human CD4 T cells and to attenuate concanavalin A-induced hepatitis. Therefore, apoA-II could be an effective therapeutic agent for CD4 T cell-dependent autoimmune or viral human hepatitis [287].

In a study evaluating PON1 activity in individuals infected with human immunodeficiency virus (HIV) type-1, it has been shown that the enzyme activity was correlated with the number of CD4+ T cells, suggesting an association of PON1 with the immune status of HIV type-1 infected individuals [288]. Along with this, another group demonstrated impaired PON1 activity in HIV patients compared to controls. At the same time, HIV infection was associated with functional and compositional HDL alterations associated with CD4+ T cell counts [289].

Importantly, the S1P gradient and the cell surface residence of S1P receptor 1 on T cells are two key factors that mediate lymphocyte egress from peripheral lymphoid organs and the thymus [290–292]. In addition, S1P was reported to reduce T cell apoptosis [293]. The S1P receptor 1 expression was associated with T cell activation status [294,295] and lineage determination [296]. Specifically, S1P inhibited forkhead box P3 (FoxP3)+ Tregs differentiation, while it reciprocally promoted Th1 development [296]. S1P receptor antagonized transforming growth factor-beta receptor function through inhibition of small mother against decapentaplegic homolog 3 (SMAD3) activity to control Tregs and Th1 dichotomy [296]. Finally, FTY720, a synthetic S1P analog, was shown to inhibit atherosclerosis via modulation of lymphocyte and macrophage function, which is consistent with the notion that S1P contributes to the antiatherogenic potential of HDL [297,298].

4. Conclusions

HDL composition, function and plasma levels have been associated with altered immune responses. Accumulating evidence suggests an important modulatory ability of HDL particles, purified HDL-associated proteins, and lipids in the activation state and function of immune cells. It has long been known that HDL plays an anti-inflammatory role in inflammation and infection. At the same time, more recent studies also provided evidence for the role of HDLs in allergy and atopic skin diseases. In addition, alterations

in the ability of HDL to modulate immune cell apoptosis, activation, chemotaxis, expression of cell surface markers and pro-inflammatory cytokine secretion were observed. Such alterations could have a major impact on disease progression and affect the risk for infections and cardiovascular disease. Several groups over the years have attempted to demonstrate, both in in vitro and in vivo experiments, which HDL components are primarily responsible for the anti-inflammatory and anti-allergic effects. Of particular interest, purified apoA-I, apoA-IV and lysophosphatidylcholine could suppress neutrophil activation, adhesion and chemotaxis. At the same time, apoA-I, apoA-IV, apoC-III and lysophosphatidylcholine effectively inhibited eosinophil activation and function. ApoA-I was also shown to promote macrophage M2 polarization and cholesterol efflux. Moreover, it suppressed reactive oxygen species production, TLR expression and activation of inflammatory response in macrophages, along with dendritic cell maturation, differentiation and function. Although apoC-III effectively suppressed eosinophil shape change, it induced adhesion and inflammasome activation on monocytes. At the same time, it increased vascular adhesion molecules expression of endothelial cells. Moreover, HDL-associated paraoxonase was shown to affect monocyte and macrophage expression of cell surface markers, adhesion, chemotaxis and inflammatory cytokine release. A summary of the effects of HDL-associated or purified apolipoproteins, lipids and enzymes in immune cell activation and function in vitro is given in Figure 1.

Along with this, apoA-I mimetic peptides, including the 5A-peptide and the 4F-peptide, were shown to decrease activation, infiltration, neutrophilic airway inflammation and airway eosinophilia as well as to attenuate monocyte/macrophage TLR cell surface expression and signaling pathway. A summary of the different apolipoprotein mimetic peptides known to affect immune cell function and, therefore, mentioned in this review is given in Table 6.

Table 6. Summary of apolipoprotein mimetic peptides known to have an effect on immune cell function.

Specific Apolipoprotein Mimetic Peptides	Number of Residues	Amino Acid Sequence	References
ApoA-I mimetic peptides			
4F peptide	18	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	[299,300]
D-4F peptide	18	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	[301]
L-4F peptide	18	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	[302]
5A peptide	37	D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-P-D-W-A-K-A-A-Y-D-K-A-A-E-K-A-K-E-A-A	[301]
ApoE mimetic peptides			
Ac-hE18A-NH_2	28	Ac-L-R-K-L-R-K-R-L-L-R-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	[106]

Summary of the apolipoprotein mimetic peptides known to have an effect on immune cell function. Abbreviations: apoA-I—apolipoprotein A-I; apoE—apolipoprotein.

Importantly, apart from the aforementioned mimetic peptides, administration of apoA-I_{Milano} nanoparticles has gained much attention for treating heart failure and coronary artery disease [303–305]. Briefly, apoA-I_{Milano} is an apoA-I mutant resulting from an arginine 173 to cysteine mutation [306,307], leading to a higher life expectancy in heterozygotes and a lower atherosclerosis rate [304]. MDCO-216 is a form of reconstituted HDLs consisting of purified recombinant dimer apoA-I_{Milano} complexed with 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine [308]. In mice with pre-existing heart failure, treatment with MDCO-216 induced regression of interstitial fibrosis, normalization of lung weight, improved isovolumetric relaxation and increased relative myocardial vascularity [303]. The efficacy of MDCO-216 was also demonstrated in a mouse model of hypertension-associated heart failure with preserved ejection fraction [305].

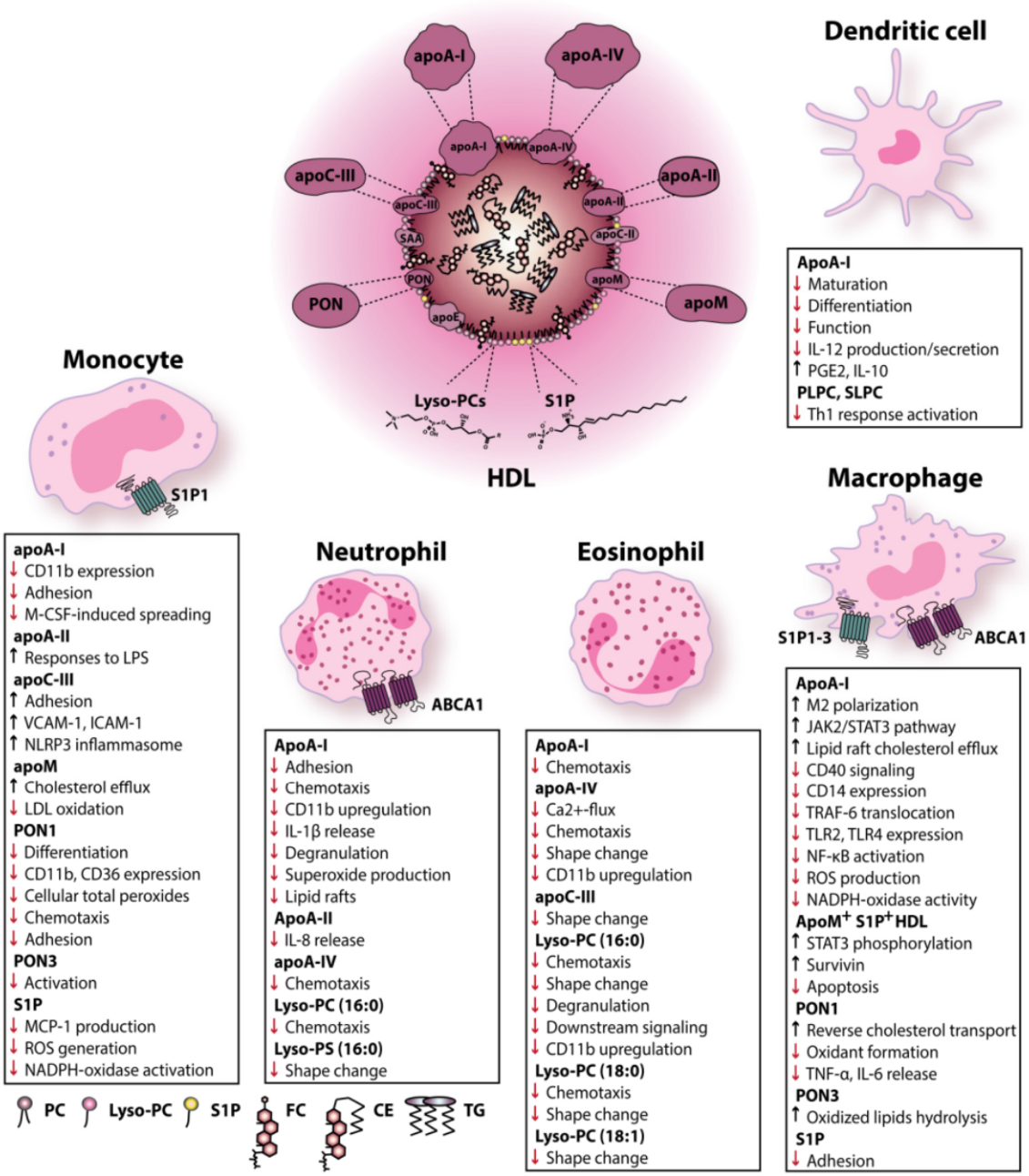

Figure 1. Effects of HDL-associated or purified apolipoproteins, lipids and enzymes in immune cell activation and function in vitro. Abbreviations: ABCA1—ATP-binding cassette subfamily A member 1; apoA-I—apolipoprotein A-I; apoA-II—apolipoprotein A-II; apoA-IV—apolipoprotein A-IV; apoC-II—apolipoprotein C-II; apoC-III—apolipoprotein C-III; apoE—apolipoprotein E; apoM—apolipoprotein M; CD—cluster of differentiation; CE—cholesteryl ester; FC—free cholesterol; HDL—high-density lipoprotein; ICAM-1—intercellular adhesion molecule 1; IL—interleukin; JAK2—Janus kinase 2; LDL—low-density lipoprotein; LPS—lipopolysaccharide; MCP-1—monocyte chemoattractant protein-1; M-CSF—macrophage colony-stimulating factor; NADPH—nicotinamide adenine dinucleotide phosphate; NLRP3—nod-like receptor family pyrin domain-containing 3; PC—phosphatidylcholine; PGE2—prostaglandin E2; PLPC—1-palmitoyl-2-linoleoyl-phosphatidylcholine; PON—paraoxonase; ROS—reactive oxygen species; S1P—sphingosine-1-phosphate; S1P1—sphingosine-1-phosphate receptor 1; S1P2—sphingosine-1-phosphate receptor 2; S1P3—sphingosine-1-phosphate receptor 3; SAA—serum amyloid A; SLPC—1-stearoyl-2-linoleoyl-phosphatidylcholine; STAT3—signal transducer and activator of transcription 3; TG—triglyceride; Th1—T helper type 1; TLR—Toll-like receptor; TNF-α—tumor necrosis factor α; TRAF-6—TNF receptor-associated factor 6; VCAM-1—vascular cell adhesion molecule 1.

Moreover, reconstituted forms of HDL have already been applied in clinical use to attenuate atherosclerotic vascular disease and to reduce cardiovascular risk [309]. At the same time, their potent anti-inflammatory properties can also be exploited to reduce inflammation in diseases such as rheumatoid arthritis and type 2 diabetes [310]. Specifically, reconstituted HDL particles, mainly apoA-I and phosphatidylcholine, could effectively decrease neutrophil activation and adhesion in type 2 diabetes and peripheral vascular disease patients. At the same time, they also effectively decreased monocyte CD11b expression in type 2 diabetes patients. In addition, they effectively inhibited macrophage reactive oxygen species production, pro-inflammatory cytokine secretion and TLR expression. At the same time, they promoted cholesterol efflux from macrophages.

On the other hand, most diseases strongly influence the metabolism, composition and subsequent functionality, such as immunomodulatory functions of HDL. This leads in most cases to impaired HDL functionality, such as cholesterol efflux capacity, the ability of HDL to modulate immune cell activation, chemotaxis, expression of cell surface markers and pro-inflammatory cytokine secretion. Such alterations could have a major impact on disease progression and affect the risk for infections and cardiovascular disease.

To conclude, HDL and its associated components appear to have a major impact on the modulation of immune cell activation status and various aspects of immune cell function and comprise a promising tool for future therapeutic interventions.

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Abbreviations

ABCA1	ATP-binding cassette subfamily A member 1
ABCC1	ATP-binding cassette subfamily C member 1
ABCG1	ATP-binding cassette subfamily G member 1
apo	Apolipoprotein
ATP	Adenosine triphosphate
BMDCs	Bone-marrow-derived dendritic cells
CCL	C–C motif chemokine ligand
CD	Cluster of differentiation
Cdc42	Cell-division control protein 42 homolog
CE	Cholesteryl ester
CETP	Cholesteryl ester transfer protein
COVID-19	Coronavirus disease 2019
ERK	Extracellular-regulated kinase
FC	Free cholesterol
fMLP	N-formyl-L-methionyl-L-leucyl-phenylalanine
FoxP3	Forkhead box P3
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICAM-1	Intercellular adhesion molecule 1
IFN-γ	Interferon γ
IL	Interleukin

JAK2	Janus kinase 2
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low-density lipoprotein
LPC	Lysophosphatidylcholine
Lp-PLA2	Lipoprotein-associated phospholipase A2
LPS	Lipopolysaccharide
LXR	Liver X receptor
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony-stimulating factor
MHC	Major histocompatibility complex
NADPH	Nicotinamide adenine dinucleotide phosphate
NET	Neutrophil extracellular trap
NF-κB	Nuclear factor-κB
NLRP3	Nod-like receptor family pyrin domain-containing 3
NO	Nitric oxide
Nox2	Nicotinamide adenine dinucleotide phosphate oxidase 2
OVA	Ovalbumin
PAF	Platelet-activating factor
PAF-AH	Platelet-activating factor acetylhydrolase
PC	Phosphatidylcholine
PDK1	Phosphoinositide-dependent-kinase 1
PI3K	Phosphatidylinositol-3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PLPC	1-palmitoyl-2-linoleoyl-phosphatidylcholine
PLTP	Phospholipid transfer protein
PON	Paraoxonase
PON1	Paraoxonase 1
PON3	Paraoxonase 3
rHDL	Reconstituted high-density lipoprotein
ROS	Reactive oxygen species
S1P	Sphingosine-1-phosphate
S1P1	Sphingosine-1-phosphate receptor 1
S1P2	Sphingosine-1-phosphate receptor 2
S1P3	Sphingosine-1-phosphate receptor 3
SAA	Serum amyloid A
sHDL	Synthetic high-density lipoprotein
SLPC	1-stearoyl-2-linoleoyl-phosphatidylcholine
SMAD3	Small mother against decapentaplegic homolog 3
SPC	Sphingosylphosphorylcholine
SPHK	Sphingosine kinase
SPHK1	Sphingosine kinase 1
sPLA2	Secretory phospholipase A2
SR-BI	Scavenger receptor class B type 1
STAT3	Signal transducer and activator of transcription 3
TG	Triglyceride
Tg	Transgenic
Th1	T helper type 1
Th2	T helper type 2
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor α
TRAF-6	TNF receptor-associated factor 6
TRAM	TRIF-related adaptor molecule
TRIF	TIR-domain-containing adapter-inducing interferon-β
Tregs	Regulatory T cells
VCAM-1	Vascular cell adhesion molecule 1

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