Thesis

Eukaryotic initiation factor 4E as a potential therapeutic target in psoriasis

submitted by

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Affidavit

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 19.09.2024 Chiara Julia Reinprecht eh

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Zusammenfassung

Hintergrund: Etwa 3 % der Weltbevölkerung leiden an Psoriasis. Es ist bekannt, dass der eukaryotische Translations-Initiationsfaktor 4E (eIF4E) eine entscheidende Rolle bei wichtigen zellulären Prozessen wie Proliferation, Apoptose und Differenzierung spielt. In einer früheren Studie unserer Gruppe wurde eine Überexpression des eukaryotischen Translationsinitiationsfaktors 4E (eIF4E) in psoriatischen Hautläsionen nachgewiesen. Die Hypothese dieser Arbeit ist, durch die Hemmung von eIF4E mittels eines neuartigen eIF4E-Inhibitors kommt es zu einer Verringerung von eIF4E und seinen Interaktionspartnern eIF4A und eIF4G *in vitro*.

Zielsetzung: Die Entwicklung von Biologika, einschließlich der neuesten Klassen von Anti-IL-17- und Anti-IL-23-Antikörpern, hat die systemische Behandlung der Psoriasis revolutioniert, aber bei der topischen Behandlung wurden nur wenige Fortschritte erzielt. Steroide und Vitamin-D3-Analoga kommen am häufigsten als topische Therapie bei PatientenInnen mit leichten Formen der Psoriasis (die höchstens 3-5% der Körperoberfläche betreffen, aber dennoch mit einem hohen Leidensdruck verbunden sind) zur Anwendung. Obgleich diese Formen der Psoriasis etwa 90 % der PatientenInnen betreffen, wurden diese topischen Therapeutika, abgesehen von Änderungen in ihren pharmazeutischen Formulierungen in den letzten Jahren nicht weiterentwickelt. Daher ist die Entwicklung neuer topischer Behandlungsstrategien wünschenswert.

Methoden: HaCaT-Keratinozyten wurden mit einem neuen eIF4E-Inhibitor ("compound no. 31") behandelt. Die mRNA- und Proteinexpression von eIF4E, eIF4A, eIF4G und proinflammatorischen Zytokinen wurde mittels quantitativer Echtzeit-Polymerase-Kettenreaktion und Western Blot analysiert.

Ergebnisse: Die Hemmung von eIF4E in HaCaT-Zellen führte zu einer signifikanten Reduktion der mRNA- und Proteinspiegel von eIF4E und seinen Interaktionspartnern eIF4G und eIF4A. Insbesondere kam es zu einem bemerkenswerten Rückgang der Expression proinflammatorischer Zytokine wie IL-17, IL-22, IL-1b und Keratinozytenmoleküle wie S100A8 und FLG, die eine wichtige Rolle bei der Pathogenese der Psoriasis spielen. Diese Ergebnisse weisen auf die wichtige Rolle von eIF4E bei der Psoriasis und dem Ungleichgewicht der Translation hin.

Schlussfolgerung: Die direkte Inhibierung von auf eIF4E eröffnet eine Reihe neuer Möglichkeiten im Bereich der topischen Behandlung von Psoriasis.

Abstract

Background: Approximately 3 % of the world's population suffer from psoriasis. It is known that eukaryotic translation initiation factor 4E (eIF4E) plays a crucial role in important cellular processes such as proliferation, apoptosis and differentiation. A previous study by our group showed overexpression of eukaryotic translation initiation factor 4E (eIF4E) in psoriatic skin lesions. Here we reported that inhibition of eIF4E by a novel eIf4E inhibitor ("compound no. 31") leads to a reduction of eIF4E and its interaction partner's eIF4A and eIF4G *in vitro*.

Objective: The development of biologics, including the latest classes of anti-IL-17 and anti-IL-23 antibodies, has revolutionized the systemic treatment of psoriasis, but little progress has been made in topical treatment. Steroids and vitamin D3 analogs are most commonly used as topical agents in patients with mild forms of psoriasis (affecting a maximum of 3-5 % of the body surface areas, but still associated with a high level of suffering). Although these forms of psoriasis affect about 90 % of patients, these agents have not been further developed in recent years, apart from changes in their pharmaceutical formulations. Therefore, the development of new topical treatments is desirable.

Methods: A HaCaT-keratinocyte cell line was treated with a new eIF4E inhibitor. The mRNA and protein expression of eIF4E, eIF4A, eIF4G and proinflammatory cytokines was analyzed by quantitative real-time polymerase chain reaction and Western blotting.

Results: Inhibition of eIF4E in HaCaT cells resulted in a significant decrease in mRNA and protein levels of eIF4E and its interaction partners eIF4G and eIF4A. In particular, there was a remarkable decrease in the expression of proinflammatory cytokines IL -17, IL -22, IL -1b and keratinocyte molecules such as S100A8 and FLG, which play an important role in the pathogenesis of psoriasis. These results indicate the important role of eIF4E in psoriasis and translational imbalance.

Conclusion: Direct targeting of eIF4E opens up a range of new possibilities for the effective treatment of psoriasis.

Table of Contents

Abbreviations

4E-BPs	4E-binding proteins
AMP	Antimicrobial peptides
ATP	Adenosintriphosphat
BMI	Body Mass Index
BSA	Body surface area
cAMP	Cyclisches Adenosinmonophosphat
DC	Dendritic cells
DMEM	Dulbecco's Modified Eagle Medium
GTP	Guanosintriphosphat
H	Hours
HLA	Histocompatibility antigens
IL-17	Interleukin-17
MNK1	MAP Kinase interacting kinase 1
mTOR	mammalian target of rapamycin
MTX	Methotrexat
NGF	Nerve growth factor
NF-XX	Nuclear factor
PABP	Poly(A)-binding protein
PCR	Polymerase chain reaction
PDE4	Phosphodiesterase 4
PEG	Polyethylenglykol
PIC	Preinitiation complex
RRM	RNA recoginition motif

RNA	Ribonucleic acid
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

List of figures

List of tables

1. Introduction

1.1. Definition

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by (1) sharply defined papulosquamous, scaly plaques. Psoriasis can affect not only the skin but also the nails and may be associated with comorbidities. (2) The lesions cause itching, scaling, rash, pain and bleeding. (3) Since 2014, the World Health Organization has classified psoriasis as a non-communicable disease. (4)

1.2. Epidemiology

Psoriasis occurs worldwide and is equally common in men and women, regardless of ethnic background. (5) On average, it affects about 3 % of the world's population. (6,7) Prevalence varies by region from 0.09 % in the United Republic of Tanzania (8) to 11.4 % in Norway. (9) The disease appears to be more common in populations further from the equator. It is most common in Northern Europe (9,10) and least common in East Asia. (11) The prevalence of self-reported psoriasis may be increasing, but we cannot rule out the possibility that this is due to greater awareness of the disease or better access to the healthcare system. (9) Psoriasis can first appear at any age (1), with an average onset age of 33 years. (12) There are two peaks: the first at the age of 16 years (women) and 22 years (men) and the second at the age of 60 years (women) and 57 years (men). The onset of the disease is observed slightly earlier in women than in men. In addition, people with an earlier onset of the disease have a higher tendency to develop generalized disease. (13)

1.3. Genetic Factors

Histocompatibility antigens (HLA) are surface molecules that play a decisive role in the regulation of immune reactions. In the context of psoriasis, there is an association with a specific HLA antigen, namely HLA-Cw6, which is located on chromosome 6. The presence of HLA-Cw6 increases the risk of psoriasis by 13 % in Caucasians and 25 % in Japanese compared to individuals lacking this specific antigen. (14) Two different types of psoriasis have been defined based on the age at which the disease manifests. Type I affects patients with early onset, a positive family history and expression of HLA-Cw6. In contrast, individuals with late-onset psoriasis, no family history and no expression of HLA-Cw6 were categorized as type II. (15) In addition, several other gene loci have been identified as being involved in the development of psoriasis. For example, PSORS1-9 is associated with up to 50 % higher risk. (16)

A study conducted in Germany shows a correlation between the occurrence of psoriasis and family history. In cases where both parents had psoriasis, there was a 41 % chance that their offspring would develop the disease. In cases where only one parent was affected, the risk fell to 14 %. If a sibling also had psoriasis, the risk fell further to 6 %. (17) In addition, one study found a two- to three-fold increased risk of psoriasis in identical twins compared to fraternal twins. (18)

1.4. Trigger factors

1.4.1. Extrinsic Risk Factors

Mechanical irritation and injury have been identified as triggering factors for the formation of lesions on previously unaffected skin in people with psoriasis, a phenomenon commonly referred to as the Koebner phenomenon. (19) A comprehensive review of the existing literature has revealed a discernible correlation between the type, location, depth, and severity of trauma and the subsequent manifestation of Koebner phenomenon in psoriasis patients. (20) Nerve growth factor (NGF) is a neurotrophic factor found in both the central nervous system and peripheral organs. There is a hypothesis that suggests a link between NGF and the occurrence of the Köbner phenomenon. (21) In the early stages, an upregulation of NGF has been found, in contrast to patients who do not have psoriasis. This emphasizes the potentially important role of NGF in the pathogenesis of psoriasis. (22)

Certain medications have been identified as potential triggers or exacerbators of psoriasis. Definitive determination of whether a medication has triggered psoriasis can be challenging given the potential long latency periods. Consequently, psoriatic manifestations may persist even after the triggering medication has been discontinued. Drugs that may be considered primarily include β-blockers, lithium, antimalarials, interferons, imiquimod, angiotensin-converting enzyme inhibitors, terbinafine, tetracycline, nonsteroidal anti-inflammatory drugs and fibrates. It is known that β-blockers reduce the intraepidermal cAMP concentration, which leads to hyperproliferation of keratinocytes. In addition, it is worth noting that biologics used in the treatment of psoriasis can paradoxically exacerbate the disease. This phenomenon is known as a paradoxical reaction. To date, most documented paradoxical reactions have been associated with tumor necrosis factor TNF-α inhibitors. (23) Biologics targeting the IL-23 and IL-17 signaling pathways do indeed have the potential to

disrupt the balance of cytokines. If paradoxical reactions are suspected, it is advisable to discontinue the drug in question and consider alternative treatment. (24)

Many psoriasis patients are immunocompromised and therefore particularly susceptible to infections. Streptococcal infections in particular have been shown to trigger guttate psoriasis. In addition, certain fungi, including Malassezia and Candida, can play a role in exacerbating the disease. (25,26) Various viruses such as HIV, papillomaviruses, retroviruses, and endogenous retroviruses should also be considered as possible triggers. (25,27)In addition, vaccinations as well as certain behaviors such as smoking or alcohol consumption may have a bad influence on the clinical manifestation of psoriasis. (19)

1.4.2. Intrinsic risk factors

A large prospective cohort study also confirmed a positive correlation between body mass index (BMI) and psoriasis. (28) Obesity, characterized by the accumulation of white adipose tissue, triggers the release of various mediators from adipose tissue and promotes a state of low-grade inflammation that contributes significantly to the development of psoriasis. This inflammatory milieu is characterized by the production of pro-inflammatory adipokines, including TNF-α, IL-6, leptin, and adiponectin, which originate from adipose tissue. (29)

A meta-analysis has revealed an association between psoriasis and diabetes mellitus (30) The likelihood of developing type 2 diabetes is increased regardless of the severity of psoriasis or the age of the patient. (31)

In addition, a higher prevalence of hypertension was found in psoriasis patients. Psoriasis and hypertension share common risk factors such as obesity and smoking, but most studies indicate an independent association between psoriasis and hypertension, even when these common risk factors are taken into account. (32)

A link between psychological stress and psoriasis is suspected. It has been observed that stressors overlap with susceptibility factors. That is, individuals with higher levels of daily stress combined with an increased tendency to worry and scratch had significantly higher disease severity and more severe itching. Thus, an itch-scratch-itch cycle may develop and exacerbate the clinical findings of psoriasis. (27)

1.5. Clinical features

Psoriasis is a papulosquamous disease characterized by papules and plaques that may be accompanied by itching and pain. (33) The disease has been divided into several categories based on its external appearance: Psoriasis vulgaris, inverse, seborrheic, guttate, pustular, erythrodermic, psoriatic nail disease, and psoriatic arthritis. (1)

1.5.1. Psoriasis vulgaris (Plaque Psoriasis)

Psoriasis vulgaris is the most common subtype and accounts for around 90 % of all cases. It is characterized by papulosquamous plaques that are well demarcated from the surrounding skin, have a salmon color and are covered with gray-white, dry scales. (1) The plaques occur mainly on the extensor surfaces of the knees and elbows, but also on the scalp, trunk, limbs and buttocks. The lesions can be symmetrically arranged and less than one centimeter in diameter. Smaller plaques can coalesce to form extensive plaques, particularly on the legs and trunk. Accompanied by pain and severe itching, they can lead to a considerable impairment of quality of life. Painful cracks within the plaques can occur on the joints, palms of the hands or soles of the feet. (6)

Based on clearly defined criteria (age of onset, heredity and clinical course of the disease), two types of non-pustular forms could be distinguished: a hereditary form with early onset and a non-hereditary, sporadic form that occurs later. (13)

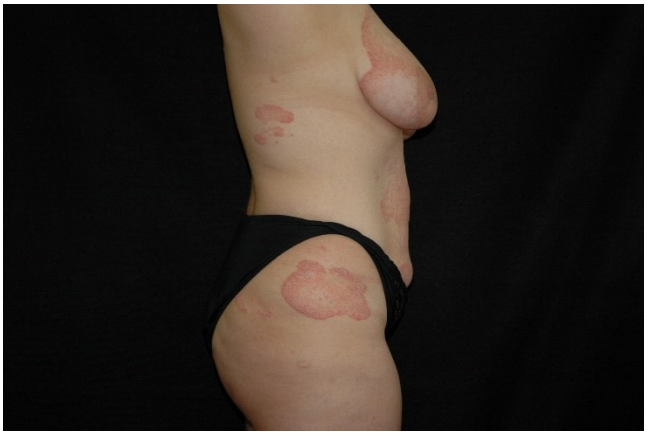


Figure 1 - A typical picture of chronic plaque psoriasis (38)

1.5.2. Inverse (Flexural or Intertriginous) Psoriasis

Inverse psoriasis is typically localized in intertriginous areas, bright red, shiny and typically without scales due to the moist environment. (1) Secondarily, they may impress with fissures or maceration. (34) Classic regions include eyebrows, nasolabial folds, postauricular and

presternal areas (1), submammary, groin, axillae, genitalia (34), perineal and intergluteal areas. (6)

1.5.3. Seborrheic Psoriasis

Due to its similar appearance and location, seborrheic psoriasis can easily be confused with seborrheic dermatitis. Affected areas include the nasolabial folds, medial cheeks, nose, ears, eyebrows, hairline, and scalp. (34)

1.5.4. Guttate Psoriasis

Children, adolescents and young adults can develop an acute form of psoriasis known as guttate psoriasis. The papules, which are less than one in diameter, develop in droplets about two weeks after a streptococcal infection (34) (pharyngitis or perianal) or a respiratory infection. (35) The trunk is most commonly affected. (34) Psoriasis guttata accounts for 2 % of cases. (6) Differential diagnoses include pityriasis rosacea, tinea corporis, secondary syphilis, pityriasis lichenoides chronica, nummular dermatitis and drug eruptions. (35)

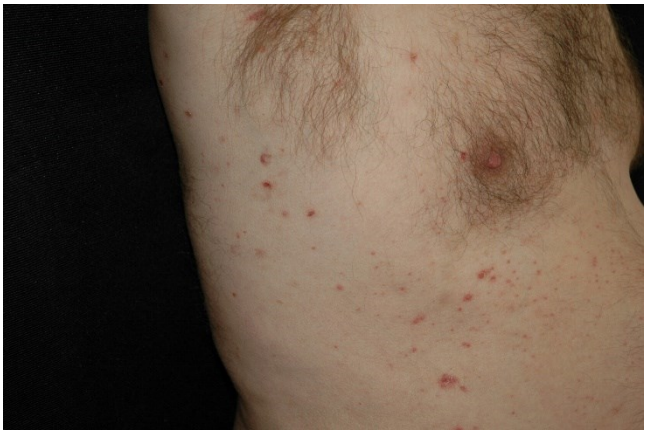


Figure 2 - Erruptive guttate psoriasis (38)

1.5.5. Pustular Psoriasis: 3 Subtypes

All types of psoriasis contain neutrophils in their horny layer. When these exceed a critical point and become clinically visible, it is referred to as pustular psoriasis. Pustular psoriasis is the second most common subtype and can be further subdivided into generalized pustular psoriasis, acrodermatitis continua of Hallopeau, and palmoplantar pustulosis. (1)

1.5.6. Generalized pustular psoriasis

Generalized pustular psoriasis, also known as psoriasis Zumbusch, usually has an acute eruption of monomorphic sterile pustules. (1) Accompanied by erythema and edema, the

patient has fever and shows signs of systemic infection. (36) The characteristic erythematous plaques of psoriasis vulgaris may have occurred before, during, or after an acute pustular event. (6)

A variety of precipitating factors cannot be excluded: intercurrent infections, (1) especially streptococcal infections (36), abrupt discontinuation of systemic or topical ultrapotent corticosteroids (1) pregnancy, hypocalcemia associated with hypoparathyroidism and medications. (36)

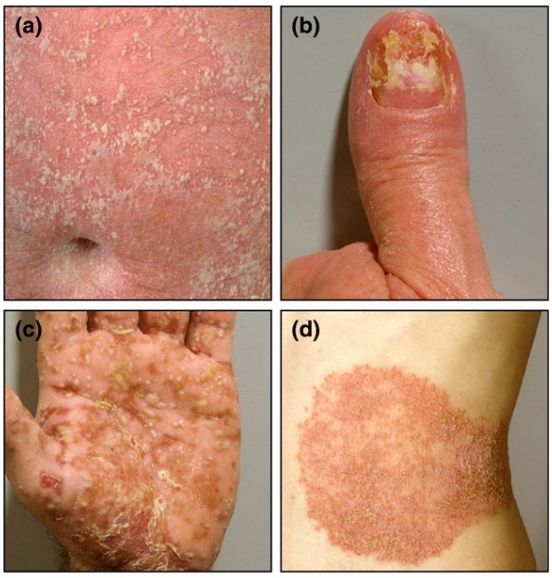


Figure 3 - Phenotypes of pustular psoriasis (37)

1.5.7. Acrodermatitis continua of Hallopeau

Hallopeau's acrodermatitis continua is a localized form of pustular psoriasis that begins on the acral extremities and affects the nails and nail beds. At an advanced stage, a classic perihelminthic swelling may be noted. (1)

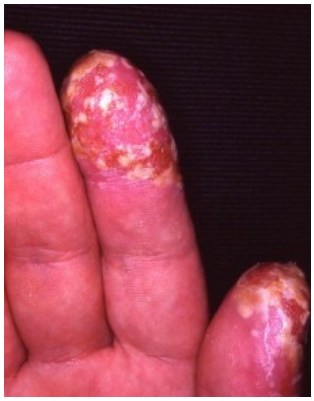


Figure 4 - Acrodermatitis continua (38)

1.5.8. Palmoplantar pustulosis

Palmoplantar pustulosis (syn.: Koenigsbeck-Barber type) is characterized by sterile yellow-brown pustules on the palms of the hands and soles of the feet. Palmoplantar pustulosis is still treated as a subtype of psoriasis in reference books (1), although genetic analyzes have found different causes for psoriasis vulgaris and palmoplantar pustulosis. It can therefore be considered a comorbidity. (37) About a quarter of those affected also have signs of chronic plaque psoriasis. Nine times more women are affected and there is an association with nicotine abuse. (1)

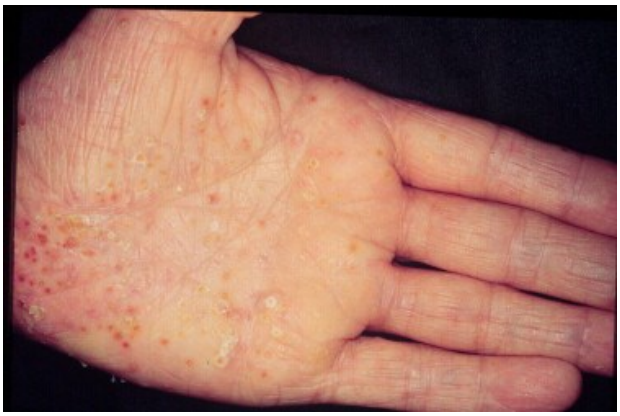


Figure 5 - Pustular lesions and scaling in palmoplantar pustulosis (38)

1.5.9. Erythroderma

Erythrodermic psoriasis may manifest slowly if it arises from chronic plaque disease, or it may appear suddenly with minimal previous psoriatic symptoms. (6) Erythroderma affects more than 90 % of the body surface. As a result, hypothermia, hypoalbuminemia and heart failure with high blood pressure may occur, leading to a life-threatening situation. (1) As the disease progresses, eczema, drug reactions, pityriasis rubra pilaris and cutaneous T-cell lymphoma may occur. Skin biopsies can be used as a diagnostic tool to improve accuracy. (38)

1.5.10. Psoriatic nail disease

The nails are affected in about 4.2 % - 69 % of all patients with psoriasis (39), in the form of nail spots (small depressions on the nail surface), onycholysis (detachment of the nail), oil spots (orange-yellow subungual discoloration), dystrophy (1) and subungual hyperkeratosis. (40)

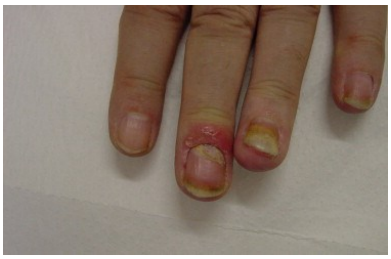


Figure 6 - Yellowish discoloration of fingernails and paronychia in psoriasis (38)

1.5.11. Psoriasis Arthritis

PsA is an inflammatory (41) destructive (42) disease of the musculoskeletal system classified as seronegative spondyloarthropathy. (6) Opinions vary widely as to how many people with psoriasis have joint involvement. The range is from 6 % to 42 %. (41) A large study of 1000 participants showed that 80 % of patients with PsA had skin lesions 12 years before the onset of Psa. (42,43) It has some similarity to rheumatoid arthritis, but it lacks the rheumatoid factors as well as the systemic symptoms (flu-like symptoms). (43) In addition, PSA can be said to have a better prognosis than Ra. (44)

Peripheral and axial joints, enthesitis, dactylitis (sausage fingers), skin and nails are affected. (41) A characteristic feature is the asymmetric involvement of the distal interphalangeal joints. (42) Symptoms range from swollen, tender, stiff and painful joints to debilitating joint destruction. (45) Radiologic features include joint erosions, new bone formation, joint space narrowing, periarticular periostitis and socket periostitis, osteolysis implying a ”pencil in the cup” deformity, spur formation, and spondylitis. (42,43) The hands are much more commonly affected in a 2:1 ratio. (43)

The axial skeleton, consisting of the sacroiliac joints and the spine, is affected in 50 % - 70 % of all cases. Axial PsA consists of back pain (improvement with movement), limited mobility and morning back/neck stiffness (longer than 30 minutes). (41)

Due to the wide clinical variety, it can be difficult to make a diagnosis. Classification criteria such as CASPAR (Classification Criteria for PsA) provide guidance for physicians. (46)

1.6. Histology

Histologic findings include acanthosis (thickening of the epidermis), parakeratosis, downward redness, hypogranulosis, and dilated capillaries. (6, 48) Pathognomonic findings

include abscess-like collections of neutrophilic leukocytes within the parakeratotic stratum corneum areas adjacent to the stratum spinosum (Munro's microabscesses) and Kogoj spongiform micropustules (accumulation of neutrophils in pustules). (47)

1.7. Diagnostic

There are many diagnostic instruments that are not used in clinical practice but in clinical studies. The most commonly used instrument to measure the severity of psoriasis is the "Psoriasis Area and Severity Index" (PASI). The severity of psoriasis can be classified according to the percentage of the body surface area affected, BSA: Body Surface Area, or according to the PASI score.

- Mild psoriasis: BSA < 2 %/PASI < 5
- Moderate psoriasis: BSA 2-10 %/PASI 5-20
- Severe psoriasis: BSA > 10 %/PASI > 20 (48)

It is also well suited to determine the effect of a drug by measuring the PASI before, during and after treatment. The lower the PASI value, the more effective the drug. (6)

Crucial to the clinician are the morphology, distribution and thickness of the lesions in conjunction with the medical history and the financial, physical and psychological impact. In conjunction with the body surface area (BSA) of the affected skin, the clinician can get a consistent picture of the overall situation and initiate appropriate treatment. (49)

Typical clinical signs include the candle wax phenomenon, the inguinal skin phenomenon, the Auspitz phenomenon and the Köbner phenomenon. The candle wax phenomenon describes that a scale resembles a scraped-off candle wax after its removal. After the scales have been removed, a final shiny layer of epidermis is visible in the area of the papilla tips. This is referred to as the final skin phenomenon. The "Auspitz phenomenon" occurs when the last skin is removed. There is punctual blood leakage from damaged and dilated capillaries. (49)

The characteristic Köbner phenomenon can be a clue to the diagnosis of psoriasis. Following trauma or other stimuli ("chemical stimulation, mechanical stress, iatrogenic stimulation and pathogenic infections"), psoriatic lesions may appear that are clinically and histologically identical to primary psoriatic lesions. This could explain the frequency of psoriatic lesions on the extensor muscles. (50) The Koebner phenomenon is not specific to psoriasis; it can also occur in lichen ruber and vitiligo. (49)

1.8. Differential diagnoses

Below you will find the most common differential diagnoses with their distinguishing features from psoriasis. The onset of pityriasis rosea is characterized by the so-called Herold's spot, an oval, slightly raised, scaly patch that can be mistaken for psoriasis guttate. The Herold's spot usually appears two to three weeks before the rash breaks out and can be easily recognized by the so-called Collarette scale of the Herold's spot.

In atopic dermatitis, there is no clear demarcation of the lesions from healthy skin, as is the case with psoriasis, and it typically occurs in the flexural areas. The lesions of seborrhoeic dermatitis tend to be greasier and stickier. Secondary syphilis can also be confused with psoriasis. It is characterized by pink patches or papules, particularly on the soles of the hands and feet. Tinea corporis consists of marginal scaling. Other differential diagnoses that may be mentioned are lichen planus, subacute cutaneous lupus erythematosus, nummular eczema and pityriasis rubra pilaris. (47)

1.9. Comorbidities

Intensive research in recent years has shown that psoriasis affects far more than just the skin. A study conducted from 1972 to 2002 in the General Practice Research Database in the United Kingdom showed that patients with severe psoriasis have a shorter life expectancy. No increase in the overall mortality rate was observed in people with mild psoriasis. (51) Other studies have shown that patients with psoriasis have a higher risk of developing cardiovascular disease because they are more likely to have obesity, diabetes, high blood pressure and higher laboratory levels of low-density lipoprotein cholesterol. In addition, patients with psoriasis are more likely to smoke than non-psoriasis patients, which further increases the risk of cardiovascular disease. (52) This group of patients therefore has a higher risk of suffering a heart attack, according to a study of the General Practice Research Database in the United Kingdom between 1987 and 2002. (53)

An analysis of a clinical study in Italy has shown that patients with psoriasis are more likely to develop metabolic syndrome. This syndrome includes a bundle of risk factors such as obesity, dyslipidemia, atherosclerosis, hypertension and glucose intolerance. Even those with mild psoriasis showed an increased susceptibility to metabolic syndrome. Above all, the degree of obesity proved to be a particularly decisive factor in this context. (54) People suffering from metabolic syndrome are more susceptible to cardiovascular disease. (6) In addition, psoriasis has been associated with psychiatric/psychological comorbidities such as

mood disorders (depression). (55) In an Italian study of 2,391 patients, depressive symptoms were found in over 60 % of participants. (56)

Disfigurement, social withdrawal and stigmatization contribute to reduced self-esteem. The WHO emphasizes that it is not the psoriasis itself that leads to this problem, but the reaction of society itself, and this can be changed. (4,57,58) In addition, these patients have higher healthcare costs. (59) Even if only a relatively small body surface area (BSA) is affected, this has a major impact on quality of life. (60,61)

1.10. Pathogenesis of psoriasis

The hallmark of psoriasis is the excessive proliferation of keratinocytes and impaired differentiation. The characteristic feature of the skin, the plaques, are not caused solely by a dysfunction of the keratinocytes, but by the interaction with many other cell types and the vascular system under the influence of the innate and adaptive immune system. (62)

In the past, it was generally believed that DC4+ and TH1 helper cells play a central role in the development of psoriasis. However, current research has shown that interleukin-17 plays an important role in this process. Specifically, IL-17 is produced by dendritic cells and its activity is enhanced by interleukin-23. This updated view emphasizes the fundamental contribution of IL-17 to dermatologic pathogenesis. (63)

1.10.1. Th17 and Th17 cytokines

Th17 was classified as a separate subtype of T helper cells due to its deviation from the conventional Th1/Th2 paradigm. The cytokine interleukin-17, which consists of six known members (IL-17A to IL-17F), has a crucial function in the maintenance and mobilization of neutrophils. IL-17A is mainly synthesized by CD4+ memory T cells, while CD8+ cells, γδ-T cell receptor cells and natural killer T cells have low production. (63)

At the mRNA level, elevated levels of IL-17 were detected in lesional skin. In contrast, no increased levels of IL-17 were found in non-lesioned skin. In keratinocytes, interleukin-17 was observed to upregulate the expression of interleukin-6 and interleukin-8, recognized proinflammatory cytokines that further exacerbate the manifestations of psoriasis. Imiquimod, a Toll-like receptor (TLR)7/8 ligand, together with IL-17A and IL-17F, were also defined as activators of inflammation in psoriasis. These results strongly suggest that the IL-17 family plays a central role in the pathogenesis of psoriasis. In addition, a clinical trial using both cyclosporin A (CsA) and anti-tumor necrosis factor-alpha (anti-TNF-α)

agents resulted in a significant decrease in the levels of interleukin-17A, interferon-gamma, interleukin-23p19 and chemokine ligand 20 in psoriasis lesions. At the same time, the clinical appearance also improved. (63,64)

Interleukin-22 is mainly synthesized by Th17 cells, with limited production occurring in T22 cells. Keratinocytes show increased expression of the IL-22 receptor, leading to hyperproliferation and hyperplasia. Elevated levels of IL-22 have also been found in the circulatory system of people with psoriasis, in contrast to observations in healthy controls. (63)

1.10.2. Dendritic cells, IL-23 and TNF-α

Interleukin-23, consisting of two subunits (IL-23p19 and IL-12p40), is synthesized by various immune cells, including dendritic cells, activated monocytes, macrophages, T cells, and B cells. Its central role is to control the development and persistence of the Th17 cell population by facilitating the expansion of Th17 cells. In mouse models, the absence of IL-23 led to a decrease in Th17-mediated inflammation, highlighting the role of IL-23 in Th17. (63)

IL-23 was found mainly in the papillary dermis and induced to acanthosis and hyperkeratosis in mouse models, by producing TNF-α, IL-12p40, IL-23p19, and IL-20R2 (IL-20 receptor subunit) (63,65)

In the gastrointestinal tract, the role of IL-17 appears to be different than in the skin. Here, IL-17 appears to exert a protective influence on the epithelial barrier. Remarkably, its secretion appears to be at least partially independent of IL-23 (66). This discrepancy may explain the exacerbation of Crohn's disease symptoms observed in psoriasis patients receiving treatment with IL-17, a phenomenon not previously reported in the context of IL-23 blockade. (67)

Dendritic cells play a decisive role in the initial phase of psoriasis. (68) They are crucial for the differentiation of naïve T cells into mature T cells. (64) These antigen-presenting cells are thought to be activated by the recognition of antimicrobial peptides and secreted by keratinocytes. (68) Activated DC migrate from the skin to the neighboring draining lymph nodes, where they present antigens and initiate the activation of T cell responses. In lesional skin, an increase in TNF and inducible nitric oxide synthase-producing DC producing TNF-α was detected. (63)

Tumor necrosis factor-α is a pro-inflammatory cytokine that plays a key role in the pathogenesis of psoriasis through activation of the nuclear factor (NF)-κB pathway. In lymphocytes and keratinocytes, TNF-α leads to proliferation and anti-apoptotic effects. By stimulating keratinocytes, they produce IL-8, which triggers the formation of microabscesses and stimulates Th17 to produce proinflammatory cytokines. It is therefore a popular drug target. (63)

1.10.3. Antimicrobial peptides (AMPs)

AMPs protect the host by killing harmful pathogenic microorganisms such as bacteria, protozoa, fungi and viruses. They are involved in the mechanisms of alerting, mobilizing and enhancing the innate and adaptive immune system. (69) When AMPs are reduced, the likelihood of infectious diseases increases. Studies have shown that AMPs are increasingly expressed in psoriatic lesions. In particular, β-defensins, S100 proteins and cathelicidin are highly overexpressed. They are expressed by keratinocytes, neutrophils and macrophages, leading to the production of cytokines and inflammation. (62) Defensins can be divided into three categories: Defensins α, β and θ. (70) The α-defensins are further subdivided into 6 subtypes, also known as human neutrophil peptides (HNPs) 1 – 6. The β-defensins can be divided into four subtypes, human β-defensins (hBDs) 1 – 4, which have been detected in psoriasis scales. HBDs 2 and 3 are produced by TNFα and IFNα, respectively, which have been detected in psoriasis scales. IL-17A and IL-22 secrete hBDs 2, which can be found in keratinocytes. (63) A more detailed understanding of the exact pathomechanism is still pending. (69)

1.10.4. Microbiota and IL-33/31 Axis

In psoriasis and other chronic inflammations such as atopic dermatitis, a link between microbial changes and disease development has been demonstrated Studies have demonstrated upregulation of IL-31 and IL-33, leading to the formulation of the "IL-33/ IL-31 axis hypothesis" (71) and several researchers are currently investigating the link between autoimmune diseases and the cytokines IL-31 and IL-33. (72) This approach holds potential for future therapeutic targeting.

IL-31, which belongs to the gp130/IL-6 family, is secreted not only by activated Th2 cells but also by mast cells, macrophages, dendritic cells, eosinophils, and basophils. Several researchers suggest that it is involved in cell proliferation and tissue remodeling. IL-31 exerts its biological effects through three different signaling pathways: JAK/STAT (Janus-activated

kinase/signal transducer and activator of transcription), PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase), and MAPK (mitogen-activated protein kinase). (73,74)

IL-33 belongs to the IL-1 family. It is thought to have multiple functions in maintaining tissue homeostasis, facilitating growth and participating in tissue repair processes. IL-33 is constitutively expressed in several cell types, including endothelial cells, epithelial cells in barrier tissues, fibroblast-like cells and myofibroblasts. (75) IL-33 acts via two mechanisms: extracellularly, where it acts as a cytokine to stimulate the immune system, and intracellularly, where it acts as a nuclear factor to regulate gene expression. In terms of signaling pathways, IL-33 interferes with several pathways, including JNK (c-Jun N-terminal kinase), NF-κB (nuclear factor κB), and MAPK. (76)

The remarkable prevalence of Crohn's disease and periodontitis in psoriasis patients supports the hypothesis of an underlying link (77). However, a review by Daniel J. Lewis, Warren H. Chan, Tiffany Hinojosa, Sylvia Hsu and Steven R. Feldman found no clear association between microbiota and psoriasis. It is important to remember that microbial changes can also occur as a result of the inflammatory microenvironment. (78)

1.11. Treatment of Psoriasis

The active substances can be classified according to their points of action:

1) Inhibitors of effector cytokines (mainly TNF-alpha)
2) Inhibitors of T-cell proliferation
3) Inhibitors of T-cell activation
4) Inhibitors of T cell migration
5) Modulators of the immune response
6) Inhibitors of keratinocyte proliferation.

1.11.1. Topical treatment

Patients suffering from mild psoriasis affecting less than 5 % of the body surface receive topical treatment. (79) By adding certain substances, a keratolytic (salicylic acid, lactic acid, uric acid), antiseptic (chlorhexidine, triclosan) or antipruritic (policadonol) effect can be achieved. (49) Topical therapeutics include: topical corticosteroids, topical cholecalciferol analogs, topical retinoids, tar, calcineurin inhibitors and anthralin (dithranol, cignolin). Patients in whom more than 5 % of the body surface is affected or less than 5 % but susceptible areas such as the scalp, intriginous areas, genitals, hands and feet receive

additional systemic therapy. Certain forms of psoriasis (erythrodermic, pustular or guttate) are also treated systemically. (79)

1.11.1.1. Vitamin D analogs

Topical vitamin D analogs (calcipotriol, calcitriol) act by inhibiting keratinocyte proliferation and modulating keratinocyte differentiation by binding to T-cell receptors or receptors on keratinocytes. (45,49) In keratinocytes, vitamin D promotes apoptosis and simultaneously inhibits the production of IL-8. In addition, increased levels of IL-10 are observed in these cells. (63,80)

When taking vitamin D, kidney function should be monitored regularly. The maximum daily dose for children is 50 g per week and for adults 100 g per week. It is recommended to use a maximum of 30 % of the body surface area, otherwise there is a risk of percutaneous absorption. Common side effects are skin irritation (erythema), burning, which occurs in 35 % of cases, but decreases after prolonged use. (45,49)

1.11.1.2. Retinoids

Retinoids inhibit the proliferation of keratinocytes and mediate cell differentiation. It can be applied topically or systemically. Topical tazarotene has a keratolytic effect and facilitates the breakdown of thick plaques by influencing gene transcription and thereby reducing the proinflammatory cytokines IL-6 and migration inhibitory factor-related protein 8. (63,81,82) Numerous studies have shown that symptoms decrease after treatment with tazarotene gel at concentrations of 0.1 % or 0.05 %. Affected individuals reported burning and irritation as common side effects. (81)

1.11.1.3. Dithranol (anthralin)

Dithranol plays a multifaceted role in influencing multiple facets of psoriasis pathogenesis, including the stimulation of free radical production. The stability and limited reactivity of these radicals suggest that the likelihood of causing skin irritation and promoting tumor formation is relatively low. (83) Treatment usually starts with a lower concentration and is gradually increased depending on individual tolerance and response. (84) To avoid skin irritation, a slow reduction in dosage is recommended. It is worth noting that brown discoloration of the skin and clothing may occur with this treatment.

1.11.1.4. Corticosteroids

Corticosteroids have a broad spectrum of action due to their numerous points of action. They have anti-inflammatory, antiproliferative and local vasoconstrictive effects by inhibiting the

production of cytokines and immune cells. They can be applied topically or systemically. The effect depends on which class (from I to VII) is used. Class I, also known as superpotent, has the strongest effect and class VII the weakest. Superpotent (class I to III) corticosteroids are preferred for the trunk and thick plaques. If the face, intertriginous or inframammary areas are affected, low-potency corticosteroids (class IV to VII) are used. (45,49)

Limitations of topical steroid use include striae, telangiectasia, purpura, acne, and skin atrophy. When administered systemically, possible inhibition of the hypothalamic-pituitary-adrenal axis should be considered. Other adverse effects include increased susceptibility to infection, delayed wound healing, weight gain, manifestation or derailment of diabetes mellitus, high blood pressure, spontaneous bone fractures, glaucoma, cataracts and psychosis. Special care should be taken with children. Generous topical therapy may be absorbed systemically due to the smaller body surface to skin ratio. (45,49)

1.11.1.5. Salicylic acid

A concentration of 5 % to 10 % salicylic acid has keratolytic properties and has the potential to alleviate the severe scaling associated with the condition. Traditionally, salicylic acid is dissolved in an oily phase, making the product difficult to wash off after application to the scalp. (84)

1.11.1.6. Coal tar

Coal tar is known for its anti-inflammatory, anti-proliferative and antipruritic properties. It is often used in a shampoo in combination with corticosteroids. However, its use is hampered by undesirable side effects, including unpleasant odor, hair dryness, hair discoloration and concerns about possible carcinogenicity (84). Coal tar is contraindicated in pregnancy (49) and banned by the European Union in cosmetic products. (84) Recent studies have shown that there is no increased risk of cancer after treatment with coal tar. (85)

1.11.2. UV - Therapy

Phototherapy has immunosuppressive functions and is used as a treatment method for moderate to severe psoriasis. Available options include narrow-band UV-B, broad-band UV-B and psoralen plus UV-A (PUVA) therapy. (45)

UV radiation comes in three different forms. UVC (200 - 280 nm) is effectively absorbed by the ozone layer in the European atmosphere. UVB (280 - 320 nm) is able to penetrate to the basal layer of the epidermis, which can lead to skin tanning and sunburn. Finally, UVA (320 - 400 nm) is able to penetrate window glass and contributes to skin aging. (49)

Before starting phototherapy, the minimum erythema dose (MED) or, in the case of PUVA treatment, the minimum phototoxic dose (MPD) should be determined. Contraindications include increased photosensitivity due to a genetic predisposition or the use of photosensitizing agents (such as tetracyline, hydrochlorothiazide or meladiene) and the presence of malignant skin tumors or multiple dysplastic nevus cell nevi. Adverse effects include erythema, skin aging and malignant tumors. (49)

1.11.2.1. Psoralen and ultraviolet A

During PUVA treatment, a compound is introduced into the DNA double helix. This process leads to the formation of highly mutagenic photoproducts that distort the DNA structure. These changes effectively inhibit the rapid proliferation of psoriatic epidermis. (86) To achieve this effect, the so-called psoralen is taken/applied locally or systemically, which enhances the effect of UVA rays and allows the use of lower UV doses. (49)

1.11.2.2. UVB therapy

UVB radiation is used in broadband and narrowband applications. Among these, narrowband UVB therapy shows the most pronounced therapeutic efficacy with the most favorable side effect profile. (45,87) NB-UVB induces apoptosis of T cells in the epidermis. This process leads to a faster resolution of psoriatic lesions, a lower incidence of excessive erythema, and a longer duration of remission. (87,88) Excimer light therapy (308 nm) is a subtype of UVB therapy and allows treatment of a specific area without irradiating the surrounding tissue. (89)

1.11.3. Small molecules: PDE 4 inhibitor

Phosphodiesterase 4, an isoenzyme, is mainly localized in immune cells, which include lymphocytes, granulocytes and monocytes/macrophages, as well as in epithelial cells. (63,91) In addition, PDE-4 is also expressed in the lungs, brain, liver and kidneys. (92) Inhibition of PDE4 leads to an intracellular increase in cAMP concentration, which subsequently inhibits NF-κB signaling. This signaling pathway, which is typically upregulated in psoriasis, is downregulated, thereby attenuating the inflammatory response by suppressing the production of pro-inflammatory cytokines. (63,91) The following agents are available: Apremilast, roflumilast and cisaborole. PDE-4 inhibitors can cause gastrointestinal symptoms, including diarrhea, weight loss and nausea. In addition, their use can lead to upper respiratory tract infections, headaches and abdominal pain. Adverse effects may also manifest as burning or stinging at the application site. (92)

1.11.4. Biologics

Biologics are classified as "biological response modifiers" and include antibodies, fusion proteins or cytokines. They are recombinant proteins and are produced by genetic engineering. They can only be administered parenterally. When prescribing biologics, it should be noted that before these substances were used, the established forms of therapy (MTX, CsA, PUVA) were either ineffective, unavailable, contraindicated or could not be administered due to side effects. (6,43)

1.11.4.1. TNF-α inhibitors

TNF-α inhibitors include adalimumab, etanercept, infliximab, certolizumab-pegol, and golimumab. Golimumab is only approved for PsA. (93)

1.11.5. JAK inhibitors

Another therapeutic approach is the inhibition of Janus kinases (JAKs) to prevent the signaling cascade downstream of IL-23 and IL-6. The drug tofacitinib blocks JAK1, JAK2, and JAK3, but has some serious side effects, including cytopenias. Therefore, research has recently shifted its focus to the selective variant as a potential target. (7)

1.12. Protein synthesis in Eukaryotes

Protein synthesis is a fundamental cellular process in which new proteins are formed by linking amino acids. Protein biosynthesis consists of two main phases: Transcription and translation. During transcription, the RNA is synthesized following the example of a DNA segment. This is followed by a post-transcriptional modification in which the immature RNA is converted into mRNA. In contrast to transcription, translation takes place in the cytoplasm and is the translation of base sequences of the RNA into amino acid building blocks. Translation takes place on the ribosome and is divided into three phases: Initiation, elongation and termination. (94) Initiation is characterized by its complexity and requires numerous protein factors.

The mRNA is recruited to the 40S ribosome, the start codon is placed and together with the 60S subunit it forms the functional 80S ribosome. Three bases, called codons, are read on the mRNA. Each codon is recognized by a corresponding transfer RNA (tRNA) molecule that carries a specific amino acid and forms a chain of amino acids. When the stop codon is reached, translation is terminated, and the protein sequence is complete. The polypeptide chain is then released into the cytoplasm where it undergoes further modifications to fold into its functional, mature protein structure. Finally, the ribosome is recycled and divided into its subunits to transform back into an 80S ribosome and begin the cycle again. (95)

1.12.1. Translation initiation

The initiation of translation is the rate-limiting step, which is controlled by countless factors and can take between 4s and 233s, depending on the study. Initiation takes place in five phases: [1] binding of the mRNA by the eIF4F cap-binding complex; [2] formation of the 43S preinitiation complex (PIC); [3] recruitment of the mRNA to the ribosome; [4] localization of the initiation codon; [5] assembly of the 60 S ribosome. (95)

1.12.2. Eukaryotic translation initiation complex 4F

The initiation of translation in eukaryotes begins with the binding of the eIF4F complex to the cap. The hetero-trimeric eIF4F complex consists of eIF4E, the modulating caffolding protein eIF4G and the DEAD-box helicase eIFEA. The function of eIF4E is determined by its binding partners. (95)

1.12.3. The role of the Eukaryotic Translation Initiation factor eIF4E

Protooncogenes encode proteins that are important for physiological cell division and differentiation. When protooncogenes are irreversibly damaged, oncogenes are formed. (96) eIF4E is a strong oncogene. Overexpression of eIF4E has been found in cancer in various organs, including cervical, bladder, head, colon, breast, prostate, lung and blood cancers. (95)

The eIF4E component of eIF4F is generally regarded as the rate-limiting factor in the initiation of translation. The eIF4E-binding proteins (4E-BPs) regulate the activity of eIF4E. These proteins serve as competitive inhibitors that effectively prevent the binding of eIF4E to eIF4G. The PI3K-AKT signaling pathway (mTOR) in turn influences the eIF4E-binding proteins. Activation of mTOR complex 1 (mTORC1) triggers the release of eIF4E from its inhibitory binding partners, the 4E-BPs, thus facilitating the translation of a subset of mRNAs. Consequently, overexpression of eIF4E leads to increased translation of highly structured mRNAs associated with cell proliferation and survival. Remarkably, this increased translational capacity is involved in the transformation of immortalized cells and the development of tumors in mouse models. Nevertheless, the exact mechanism underlying the selective control exerted by the availability of eIF4E on the initiation of translation of mRNAs with structured 5'-UTRs is still unclear. (97)

The eIF4E bound to eIF4G abolishes auto-inhibition, whereupon eIF4G stimulates the helicase activity of eIF4A. In addition, previous studies have shown that binding of eIF4E leads to structural modification of eIF4G, resulting in increased susceptibility to cleavage by viral proteases. (95)

In eIF4e-overexpressing cells, upregulation of neoplastic angiogenesis by increased production of VEGF has been described. This process is thought to be mediated by the activation of Ras, a GTPase-activating protein. Ras is often associated with the development of tumors. It has also been shown that c-myc, a tumor regulator, leads to activation of eIF4E transcription. (98)

1.12.4. Eukaryotic Translation Initiation factor eIF4A

In mammals, there are three isoforms: eIF4AI, eIF4AII and eIF4AIII. (99) eIF4A is an ATP-dependent RNA helicase, a component of the eIF4F cap-binding complex, and unwinds the secondary structure in the 5′ UTR of mRNA. (100) EIF4G and the accessory protein eIF4B significantly enhance the ATP-dependent RNA unwinding activity of eIF4A. (101) It belongs

to the DEAD or DEAH box helicase family (consisting of aspartic acid, glutamic acid, alanine, and histidine. (100) These proteins are involved in various processes beyond translation, including pre-mRNA splicing, ribosome biogenesis and development, including spermatogenesis and oogenesis. (99) Additional domains of eIF4A facilitate its interaction with eIF4B and eIF4H, eIF4G, PDCD4, RNA and ATP. It can be assumed that dysregulation of eIF4 expression is associated with malignant transformation. Overexpression of EIF4A has been found in malignant hepatomas and melanomas. Overall, eIF4G and eIF4E are reported to be associated with most malignant transformation. (100)

1.12.5. Eukaryotic Translation Initiation factor eIF4G

There are two isoforms of eIF4G: eIF4GI and eIF4GII. These isoforms show 46 % similarity in their amino acid sequences and have a predicted molecular weight of 171 kDa and 176 kDa, respectively. eIF4G has binding sites for eIF4E, eIF4A, eIF3 and PABP and serves as a bridge between ribosomes and mRNA. (100) A characteristic feature of all eIF4Gs is an RNA recognition motif (RRM)-like RNA binding domain. In addition, the C-terminal region contains a binding site for MAP kinase-interacting kinase-1 (MNK1; also known as MAP kinase signal-integrating kinase 1). The polypeptide binding site for eIF4E is located in the N-terminal half of the eIF4G protein. In addition, there are two eIF4A binding sites on eIF4GI and eIF4GII in the middle region and another one in the carboxy-terminal region. (99) Overexpression of 4G can lead to breast cancer, cervical cancer, squamous cell carcinoma and nasopharyngeal carcinoma. (100)

1.13. Eukaryotic Translation Initiation Factors

Dysregulated mRNA translation plays an important role in the etiology and pathogenesis of malignant diseases. This can lead to tumor growth and cell transformation. In normal cells, this signaling pathway is sensitive to cellular environmental conditions such as nutrient availability, energy status and stress, which affects ribosome production and gene expression. Studies have shown that various cancers are associated with increased expression of eIF4A, eIF4E and eIF4G and decreased expression of 4E-BPs or phosphorylation of eIF2. (100)

1.13.1. Eukaryotic translation initiation factor 1 (eIF1 and eIF1A or eIF1AX)

EIF1 and eIF1A are encoded on chromosome X and are therefore also referred to as x-linked eIF1a or eIF1AX. They play an important role in the initiation of protein translation in mRNA screening as well as in the delivery of tRNA. They are also required for recognition

of the start codon. EIF1 binds to the region near the ribosomal P site and eIF1A binds near the ribosomal A site. (100)

1.13.2. Eukaryotic translation initiation factor 2 (eIF2α eIF2β eIF2γ)

eIF2 is a complex enzyme that consists of three parts (eIF2α, eIF2β and eIF2γ) and plays a crucial role in the initiation of translation, a process essential for protein synthesis. When eIF2α is phosphorylated, it becomes inactive in its GDP-bound form, leading to a reduction in translation. This reaction is an important cellular stress response in all eukaryotes and helps cells conserve energy and overcome stress. Certain stressors such as oxidants, nutrient deprivation, heat shock, heavy metals, high salt concentrations and hypoxia have been reported to lead to phosphorylation of eIF2α. The eIF2 complex, particularly eIF2α, appears to be critical for translation and plays a role in cell proliferation, survival, malignant transformation, tumor development, progression and metastasis. The role of eIF2α in the regulation of various carcinomas is emphasized by the fact that overexpression of the non-phosphorylatable mutant of eIF2α (eIF2α S51A) increases the amount of TC, leading to unimpeded translation initiation and resulting in the transformation of normal cells into malignant cells. While dephosphorylation of eIF2α alone is not sufficient to trigger malignant transformation, it can lead to cell transformation when combined with oncogenic stimuli. (100)

1.13.3. Eukaryotic translation initiation factor 3 (eIF3)

Mammalian eIF3 is the largest eIF protein complex with a weight of about 804 kDa and consists of 13 non-identical subunits (eIF3a-m) with different masses. The interaction between eIF3 and the 40S ribosomal subunits is stabilized by eIF3j. This binding can occur early in the translation process, as has been shown in tumor cells in which the eIF3-40S complexes lack Met-tRNAi and mRNA. Importantly, eIF3 binds to eIF4G, which plays a crucial role in the recruitment of the 40S subunit to the mRNA. The eIF3 complex and its subunits play a critical role in organizing key components of the translational machinery to ensure its proper function. Specifically, the eIF3 complex binds to eIF5 and eIF2β, eIF3c binds to eIF1 and eIF5, and eIF3g binds to eIF4B. Despite the ability of eIF3 to interact with other initiation factors, the eIF3a and eIF3d subunits bind to the initial region of the ribosome on the mRNA, indicating premature dissociation of the mRNA. However, it is still unclear how the subunits of eIF3 coordinate these processes. Alterations in the expression of eIF3 and/or its subunits may contribute to various malignant transformations. (100)

1.13.4. Eukaryotic translation initiation factor 4B (eIF4B)

The exact role of eIF4B in the initiation of translation remains unclear. EIF4B does contribute to bringing the ribosome to the mRNA, but its importance appears to be less than that of eIF4A, which is essential for the process. This suggests that eIF4B may have a secondary, supporting function, as initiation complexes can be formed without it. Overexpression of 4H is associated with ovarian granulosis, B-cell lymphoma and leukemia. (100)

1.13.5. Eukaryotic translation initiation factor 4H (eIF4H)

EIF4H acts as a co-factor alongside eIF4A. Both EIF4H and eIF4B show a similar ability to enhance the RNA helicase activity of eIF4A when eIF4G is not present. However, when eIF4G is present, eIF4B stimulates eIF4A more effectively than EIF4H, indicating a potentially different role in translation initiation. EIF4H and eIF4B bind to the same domain of eIF4A120, and their interaction is enhanced in the presence of ATP. Overexpression of 4H is associated with colon and esophageal cancer. (100)

1.13.6. Eukaryotic translation initiation factor 5 (eIF5)

EIF5 serves both as an N-terminal GTPase-activating protein (GAP) responsible for promoting GTP hydrolysis by eIF2 and as an independent GDP dissociation inhibitor that facilitates the controlled recycling of eIF2. In addition, EIF5 acts as an inhibitor of eIF2B and functions as a guanine nucleotide exchange factor that promotes recycling of eIF2. The multifactor complex in which eIF5 is involved includes the TC (eIF2-GTP-Met-tRNAi), eIF1A, eIF1 and eIF3. EIF1 binds to eIF5 to modulate its GAP activity and thus helps in the precise recognition of the start codon. eIF5A has two isoforms: eIF5A1 and eIF5A2. The EIF5A gene (17 kDa) encodes the eIF5 protein. EIF5A1 is expressed in all tissues and cells, especially in rapidly proliferating cells. In contrast, eIF5A2 is expressed in a tissue-specific manner and is normally barely detectable. In a recent study, it was discovered that eIF5A2 promotes chemoresistance to doxorubicin in colorectal cancer cells by regulating epithelial-mesenchymal transition. This suggests that targeted inhibition of eIF5A2 may be a novel strategy to combat drug resistance in colorectal cancer therapy. Aberrant expression of eIF5A1 was found in glioblastoma, cervical cancer and colorectal cancer, of eIF5A2 in colorectal cancer, bladder cancer, hepatocellular carcinoma, ovarian cancer and non-small cell lung cancer, and of eIF5B in hepatocellular carcinoma. (100)

1.13.7. Eukaryotic translation initiation factor 6 (eIF6)

eIF6 regulates translation by reducing its speed. By blocking the interaction of the ribosomal subunits 40S and 60S, it serves as a ribosomal anti-association factor during translation initiation. This leads to binding to the 60S ribosomes and thus to an inhibition of translation initiation. It is assumed that the initiation factor eIF6 plays a role in the development of tumors. EIF6 shows increased expression in various types of cancer, with the strongest expression (up to ten times higher) occurring in colorectal carcinomas. Similar overexpression has also been observed in malignant mesothelioma, serous ovarian carcinoma, acute promyelocytic leukemia, head and neck carcinoma and lung metastases. Reducing eIF6 expression by half led to a significant 90 % reduction in oncogenic transformation mediated by activated Ras and Myc. (100)

1.14. mTOR pathway

Cellular processes are controlled by a protein called mammalian target of rapamycin (mTOR), a type of enzyme found in many species including humans. This enzyme cooperates with another protein pathway, the phosphoinositide 3-kinase PI3K/AKT, the murine thymoma viral oncogene homolog AKT. These processes, which are important for the normal function of the body and may also play a role in diseases such as cancer, obesity, type 2 diabetes and neurological disorders, include the production of proteins and lipids, the control of gene utilization and the assembly of ribosomes. They influence cell growth, metabolism, survival, mortality, apoptosis and immune response. (102)

mTORC1 plays a critical role in the control of cap-dependent initiation of translation, a key process for the production of many cancer-causing proteins such as cyclin D1, c-Myc, Mcl-1 and Snail. It adds a phosphate group to two important proteins: the p70 ribosomal protein S6 kinase (p70S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). These phosphorylation processes lead to activation, which subsequently contributes to the development and progression of cancer.(102)

mTORC2 consists of several proteins, including mTOR, rictor, mLST8, DEPTOR, mSin1 and protor. It phosphorylates Akt, serum and glucocorticoid-induced kinase and protein kinase C. One of its functions is the regulation of the cytoskeleton and cell survival. However, the exact mechanism of mTORC2 is not yet fully understood. (102)

Nevertheless, abnormalities in the mTOR signaling pathway are frequently observed in cancer, making it an attractive target for cancer therapy. Rapamycin and its analogs

(rapalogs) act as specific inhibitors of the mTOR signaling pathway. Rapalogs paradoxically increase eIF4E phosphorylation (Ser209) in various types of cancer cells while inhibiting mTORC1 signaling. (102)

In summary, eIF4B, eIF4G and many other components of the mTOR signaling pathway are regulated by the mTOR signaling pathway by altering their phosphorylation state. This shows how important the mTOR signaling pathway is for the control of translation. (101)

1.15. Aim of the diploma thesis

The aim of my diploma thesis in collaboration with Graz College of Technology is to contribute developing a compound for the topical treatment of psoriasis. Under the supervision of Prof. Breinbauer, Leo Krammer, and Alexander Wolf a significant progress was made, which led to the production of compound 31. The term "compound 31" is a name generated by the Technical College that refers to a specific chemical entity resulting from a series of carefully planned and executed synthetic steps. Further research and optimization of the compound is underway to improve its therapeutic properties and minimize potential side effects. The interdisciplinary efforts and innovative approaches used in this project demonstrate the potential for significant advances in the treatment of psoriasis.

2. Material and Methods

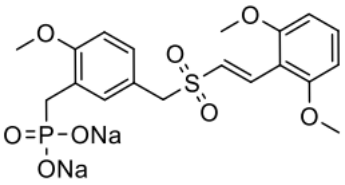
2.1. Cell culture

HaCaT cells of the keratinocyte cell line were grown in Dulbecco´s modified Eagle´s medium (DMEM) (#11960-044, Gibco, Waltham, Massachusetts, USA). DMEM was supplemented with 10 % fetal bovine serum (FBS) and 1 % penicillin-streptomycin (100 µg/ml) at 37 °C and 5 % CO2. Cells were monitored by regulatory control and confirmed to be free of mycoplasma.

1.5 ml of trypsin was applied to the cells for five minutes at 37 °C. The progress of enzymatic dissolution was checked regularly under the microscope (with phase contrast device). When the adherent cells dissolved in the supernatant, the reaction was stopped with 5 ml DMEM. Finally, the cell suspension was placed in 6-well plates together with 2 ml DMEM per well.

2.2. Treatment

24 h after seeding the 6-well plates were treated with the new eIF4E inhibitor. Figure 7 shows the structural formula of the new eIF4E inhibitor. The compound 31 was dissolved in water at concentrations of 20 nM, 40 nM, 60 nM, and 80 nM. The cells were treated with ddH_2O, as a negative control.



$C_{19}H_{21}Na_2O_8PS$ [486.38 g/mol]

Figure 7 - Composition of the new eIF4e inhibitor

2.3. Cell harvesting

After 24 h, 48 h, and 72 h, the cells were mechanically removed from the surface using a cell scraper. After washing twice with cooled DPBS, the cells were stored at – 80 °C for further use.

2.4. RNA isolation

Total RNA isolation was performed according to a Trizol protocol. Frozen cells were thawed, 500 µl Trizol (#15596018, Life technologies, Carlsbad, California) was added, vortexed to dissolve the pellet, and incubated for 10 minutes at room temperature. For separation of

RNA, 100 µl of chloroform (#STBK3742, Sigma Aldrich, St. Louis, Missouri, USA) was added, shaken for 10 seconds, then incubated at room temperature for 3 minutes and centrifuged at 14,800 rpm at 4 °C for 15 minutes (Thermo Fischer Scientific, Massachusetts, USA).

After centrifugation, two distinct phases can be seen, a lower red phenol-chloroform phase containing the proteins, an intermediate phase containing the DNA, and a colorless upper phase containing the RNA. After precipitation of the RNA, the aqueous phase is transferred to a fresh tube and 250 µl isopropanol (#LC-7377.4, Einhausen, Germany) is added. After vigorous shaking by hand and incubation at room temperature for 10 minutes, the mixture was centrifuged at 14,800 rpm for 20 minutes at 4 °C. The supernatant was removed and the pellet was washed with 250 µl of 80 % ethanol (#1.00983.2511; Merck, Darmstadt, Germany) and centrifuged at 14,800 rpm for 20 min at 4 °C.

After discarding the ethanol, the pellet was dried at 37 °C for 5 min. The pellet must not be allowed to dry out completely, as this reduces its solubility. Depending on the size of the pellet, ≥ 12 µl of distilled water (RNase-free water, Fresenius Kabi, Bad Homburg, Germany) was added and incubated for 10 min at 58 °C. The RNA concentration was determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Massachusetts, USA) and stored at - 80 °C until use.

2.5. Reverse transcription

Reverse transcription was first performed using the transcription kit (#4368814, Applied Biosystems, Thermo Fischer Scientific, Massachusetts, USA) in a reaction volume of 20 µl according to the manufacturer's instructions. According to the manufacturer's instructions, a 20 µl reaction mix was prepared by adding 10 µl RNA (200 ng RNA).

Table 1 - Components of the reverse transcription Master Mix for one reaction

Component	Volume
10x RT Buffer	2.0 µl
25x dNTP Mix	0.8 µl
10x RT Random Primers	2.0 µl
Multi Scribe Reverse Transcriptase	1.0 µl
RNase Inhibitor	1.0 µl
Nuclease-free water	3.2 µl
Total per Reaction	**10.0 µl**

Table 2 - PCR program used for PCR Transcription

	Temperature [C°]	Time [min]
Step 1	25	10
Step2	37	120
Step 3	85	5
Step 4	4	∞

2.6. Quantitative real-time PCR (qPCR)

The cDNA was diluted 1: 20 in RNase/DNAse-free water for quantitative real-time PCR. ratio. The qRT-PCR was performed using Power SYBR Green PCR Master Mix (#4309155, Applied Biosystems, Thermo Fisher Scientific, Massachusetts, USA). GAPDH was used as a stable housekeeping gene. Fold-change values were analyzed using the $2^{-\Delta\Delta CT}$ method. The thermal cycler settings for PCR amplification can be found in table 5.

Table 3 - SYBR Green Master Mix used for Real-Time PCR

Master Mix Components	Volume [µl]
Power SYBR Green PCR Master Mix (2x)	15
Forward Primer [10 pm]	1
Reverse Primer [10 pm]	1
Nuclease-free H2O	8
Total Volume per Reaction	25

Table 4 - Primer used for qRT-PCR

Gene	Primer	Sequence (5´-3´)	Length	Tm[°C]
eIF4A	Fwd	CCTCCCAGTCCACTCGAGCTG	21	65
	Rev	GCTTGGGTGTCTCTCCCGAGG	21	65
eIF4G	Fwd	CCCGAAAAGAACCACGCAAG	20	62
	Rev	TTCCCCTCGATCCTTATCAGC	21	61
eIF4E	Fwd	GACCTGACCTCCCGCGGACAA	21	65
	Rev	TGCCCATCTGTTCTGTAGGGGATG	24	64

Table 5 - Program settings used for qRT-PCR (40 cycles)

Step	Hold	Denature	Anneal/Extent
Temperature [C°]	95	95	60
Time	10 min	20 sec	2 min

2.7. Protein isolation and Western Blot

2.7.1. Protein isolation

Frozen cells were lysed with 100 µl NP-40 lysis buffer (0.05 M Tris-HCl, 0.15 mM NaCl, 0.5 % NP-40, 0.1 M Pefabloc, 1 mM DTT, complete Mini (#05892970001, Roche Diagnostics, Mannheim, Germany), PhosSTOP (#04906545001, Roche Diagnostics, Mannheim, Germany). The pellet was pipetted up and down 20 times and centrifuged at 14.800 rpm for 10 min at 4 °C. The supernatant was transferred into a new tube, diluted with Laemmli buffer 1:1 (0.125 M Tris/HCI, glycerol, SDS 2.3 % bromophenol blue 0.25 %, ddH_2O), and stored at – 80 °C.

2.7.2. Western Blot

The protein samples were incubated for 10 minutes at 95 °C to dissolve the secondary structure of the proteins. 20 to 45 µl of each sample was loaded onto an 8 – 16 % sodium dodecyl sulfate polyacrylamide gel (SDS gel) (#4561106, Mini-Protean TGX Precast Gel, Bio Rad, California, USA) and subjected to electrophoresis in mini-vertical electrophoresis units, and blotted with a Semi Dry Blotting Unit (SCIE-PLAS; Cambridge, England) onto PVDF membranes (#LC2002, Immobilin-P Transfer Membrane, Carlsbad, USA). The membranes were blocked with TBS tween (TBST) containing 5 % non-fat milk (AppliChem; Darmstadt, Germany) for 1 hour at room temperature with gentle agitation to prevent non-specific binding of the primary and secondary antibodies. The primary antibodies were diluted in TBST, 5 % BSA (#2323, Santa Cruz Biotechnolog) and applied overnight at 4 °C. The antibodies, GAPDH, eIF4E, eIF4G and eIF4A were diluted 1:1000 in 10 ml 1xTBST buffer with 5 % bovine serum albumin (BSA). Information on the antibodies can be found in supplementary table 6.

Membranes were washed 3 times with TBST, followed by incubation with a secondary antibody against rabbit immunoglobulin G (IgG) with horseradish peroxidase (#17635091 anti-rabbit 1:5000; GE Healthcare Life Sciences, Buckinghamshire, UK) at room temperature for 1 h, followed by 3 washes with TBST for 5 min. The chemiluminescent substrate SuperSignal West Femto Chemiluminescent Substrate (#34095, Thermo Fisher Scientific, USA) was used. The blots were photographed with the Fusion FX Vilber Lourmat (Peqlab Life Science, Darmstadt, Germany) imaging system.

Table 6 - Primary antibodies used for Western blot analysis

Primary antibody	Company	Dilution	Secondary antibody
GAPDH	Cell Signaling	1:3000	Rabbit
eIF4E	Cell Signaling	1:1000	Rabbit
eIF4A	Cell Signaling	1:1000	Rabbit
eIF4G	Cell Signaling	1:1000	Rabbit

2.7.3. Quantification of Western Blots

We used Image J software to obtain quantitative Western blot results (National Institutes of Health, USA). Signals were normalized to GAPDH, an internal control (housekeeping gene). Statistical analyzes were performed using GraphPad Prism software (version 9).

3. Results

3.1. Expression analysis via quantitative realtime PCR

The mRNA expression of eIF4E was significantly decreased in HaCaT cells at the concentrations of 40 nM, 60 nM and 80 nM of compound 31 after 24 h ($p < 0.0001$). The expression of 20 nM and 80 nM of compound 31($p < 0.0001$) showed downregulation of eIF4E at 48 h and 72 h, respectively. At the 72 h time point, mRNA expression of eIF4E was significantly decreased at 60 nM of compound 31 ($p < 0.0001$) (Figure 7a).

Expression of 20 nM, 40 nM and 60 nM ($p < 0.0001$) showed down-regulation of eIF4A at the mRNA level after 24 h. At the 48 h time point, inhibition of mRNA expression for eIF4A was still evident in the 20 nM and 40 nM samples ($p < 0.0001$). In contrast, upregulation of eIF4A was observed in the 40 nM, 60 nM and 80 nM samples ($p < 0.0001$) after 72 h of treatment (Figure 7b).

Expression of 60 nM ($p < 0.0001$) showed downregulation of eIF4G after 24 hours. The mRNA expression of eIF4G was significantly decreased in HaCaT cells at concentrations of 20 nM, 40 nM and 60 nM ($p < 0.0001$) after 48 h. After 72 h, the mRNA expression of eIF4G was significantly decreased at 40 nM and 80 nM ($p < 0.0001$) (Figure 7c).

The mRNA expression level of *IL-1b* was significantly ($p < 0.0001$) decreased in HaCaT cells at concentrations of 40 nM, 60 nM and 80 nM after 24 hours. After 72 h, the mRNA expression of *IL-1b* was significantly decreased at 20 nM, 60 nM and 80 nM ($p < 0.0001$) (Figure 7d).

The mRNA expression of *IL-17* was significantly decreased in HaCaT cells at concentrations of 20 nM, 40 nM and 60 nM ($p < 0.0001$) after 24 h, 48 h and 72 h, respectively. The expression of *IL-17* at 80 nM ($p < 0.0001$) showed significant upregulation after 24 h. After 48 h and 72 h, the mRNA expression of IL-17 at 80 nM ($p < 0.0001$) was significantly decreased (Figure 7e).

Expression of 20 nM, 40 nM, 60 nM and 80 nM ($p < 0.0001$) showed down-regulation of *Il-22* at the mRNA level after 24 h. At 48 h, mRNA expression of *IL-22* was significantly decreased at 20 nM and 40 nM ($p < 0.0001$). The expression of 20 nM and 60 nM ($p < 0.0001$) showed down-regulation of *IL-22* after 72 h (Figure 7f).

The mRNA expression of *KRT16* was significantly decreased in HaCaT cells at concentrations of 20 nM, 40 nM and 60 nM ($p < 0.0001$) after 24 h. The expression of 20

nM and 40 nM ($p < 0.0001$) showed downregulation of *KRT16* after 48 h. At 72 h, mRNA expression of *KRT16* was significantly decreased at 80 nM ($p < 0.0001$) (Figure 7g).

The mRNA expression of TNF-α was significantly reduced in HaCaT cells at concentrations of 40 nM, 60 nM and 80 nM ($p < 0.0001$) after 24 h. TNF-α mRNA expression was significantly reduced in all samples after 48 h ($p < 0.0001$). After 72 h, the mRNA expression of TNF-α was significantly decreased at 20 nM, 40 nM and 60 nM ($p < 0.0001$) (Figure 7h).

Expression of 40 nM and 60 nM ($p < 0.0001$) showed down-regulation of S100A8 at the mRNA level after 24 h. At the 48 h time point, inhibition of mRNA expression for S100A8 was observed in the 20 nM, 40 nM, 60 nM and 80 nM samples ($p < 0.0001$). At the 72 hour time point, mRNA expression of S100A8 was significantly decreased at 20 nM and 60 nM ($p < 0.0001$) (Figure 7i).

The expression of 20 nM and 60 nM ($p < 0.0001$) showed down-regulation of FLG after 24 h. The mRNA expression of FLG was significantly decreased in HaCaT cells at concentrations of 20 nM, 40 nM, 60 nM and 80 nM ($p < 0.0001$) after 48 h. After 72 h, mRNA expression of FLG ($p < 0.0001$) was significantly decreased in all samples (Figure 7j).

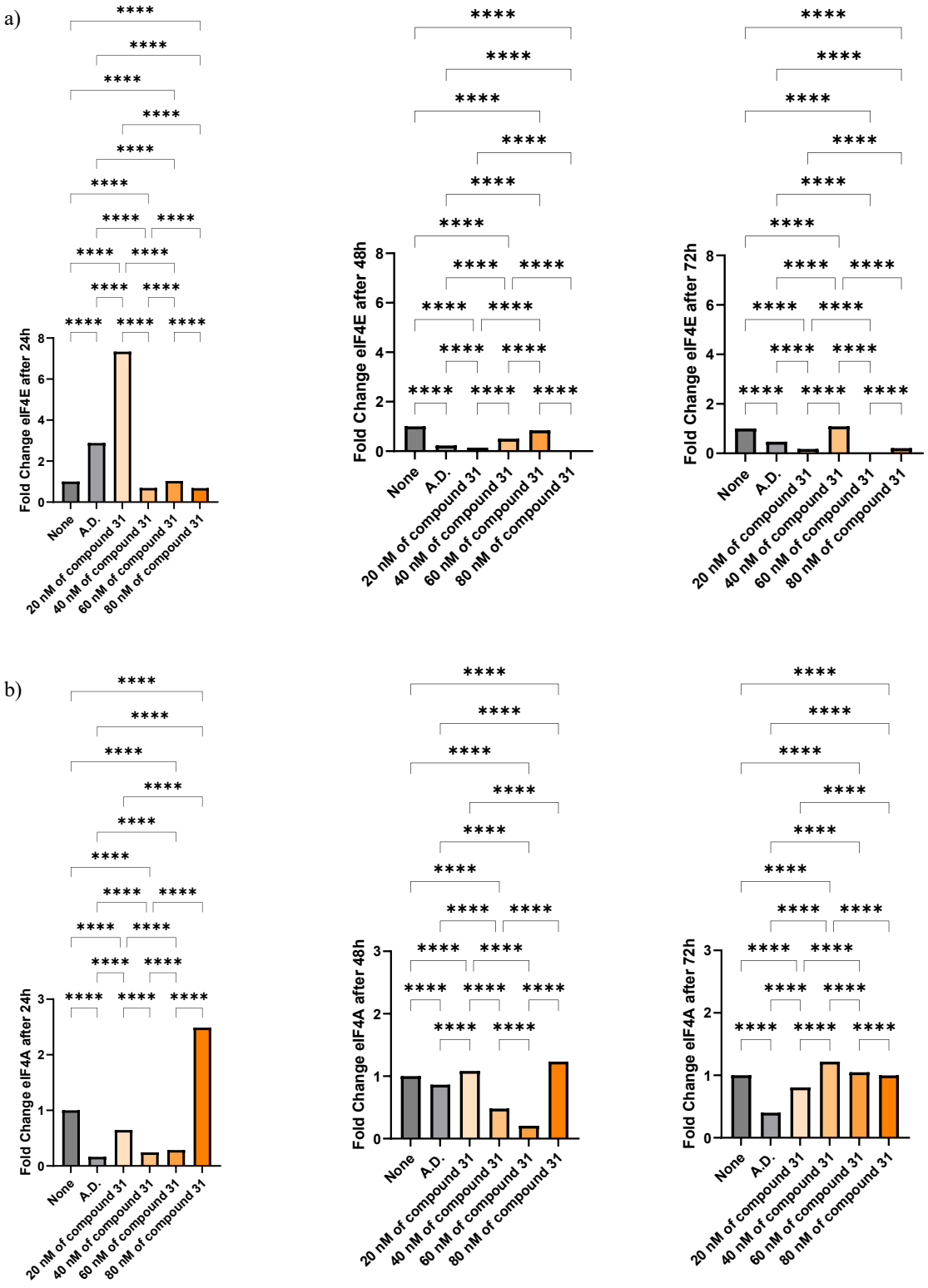


Figure 8 - mRNA expression of eIF4E and eIF4A

Effects of compound 31 on mRNA expression of eIF4E, eIF4A, and eIF4G. a) mRNA expression of eIF4E after 24h, 48h, and 72h. b) mRNA expression of eIF4A after 24h, 48h, and 72h. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Two-Way ANOVA.

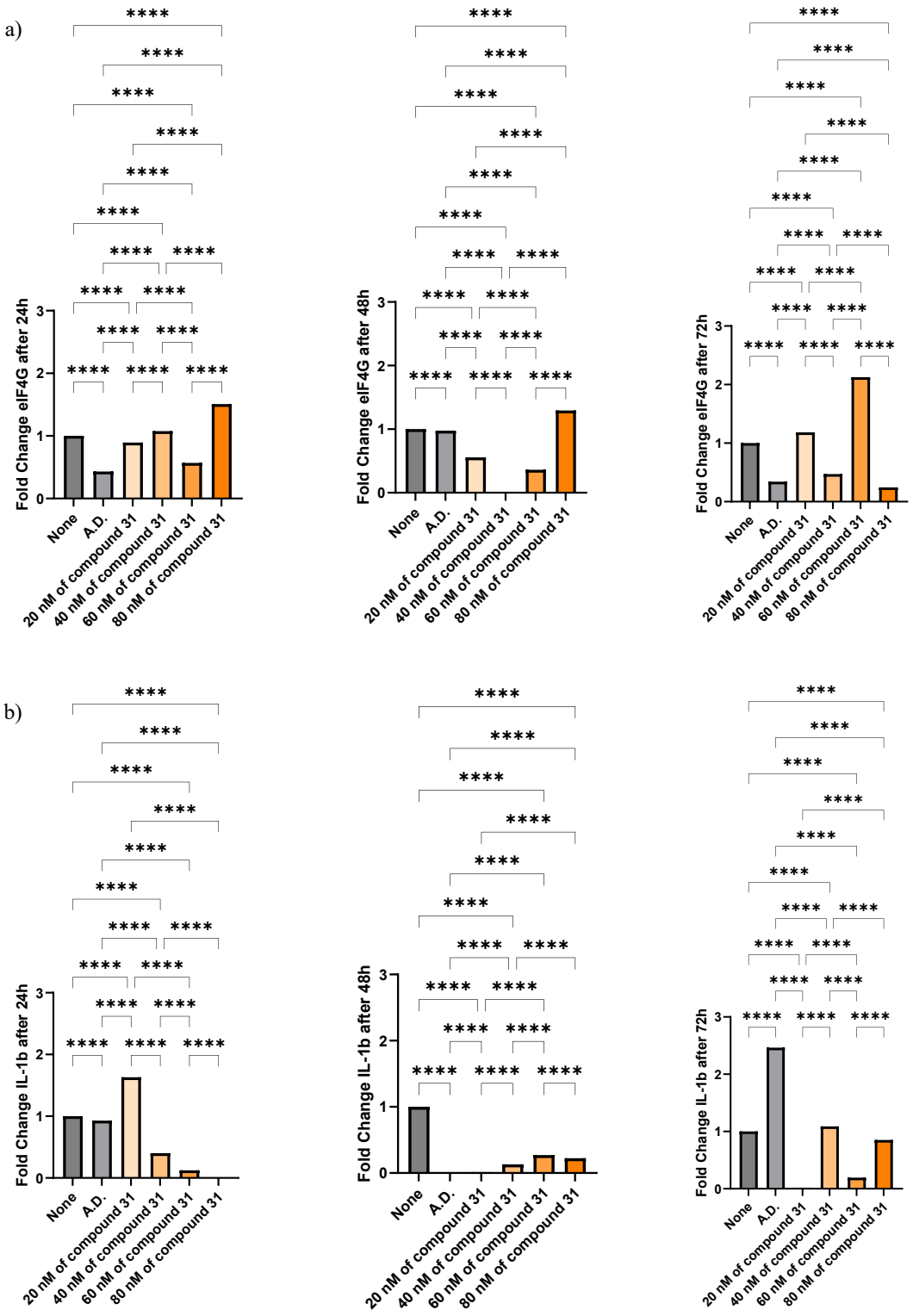


Figure 9 - mRNA expression of eIF4G and IL-1b

Effects of compound 31 on mRNA expression of eIF4E, eIF4A, and eIF4G. a) mRNA expression of eIF4G after 24h, 48h, and 72h. b) mRNA expression of IL-1b after 24h, 48h, and 72h. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Two-Way ANOVA.

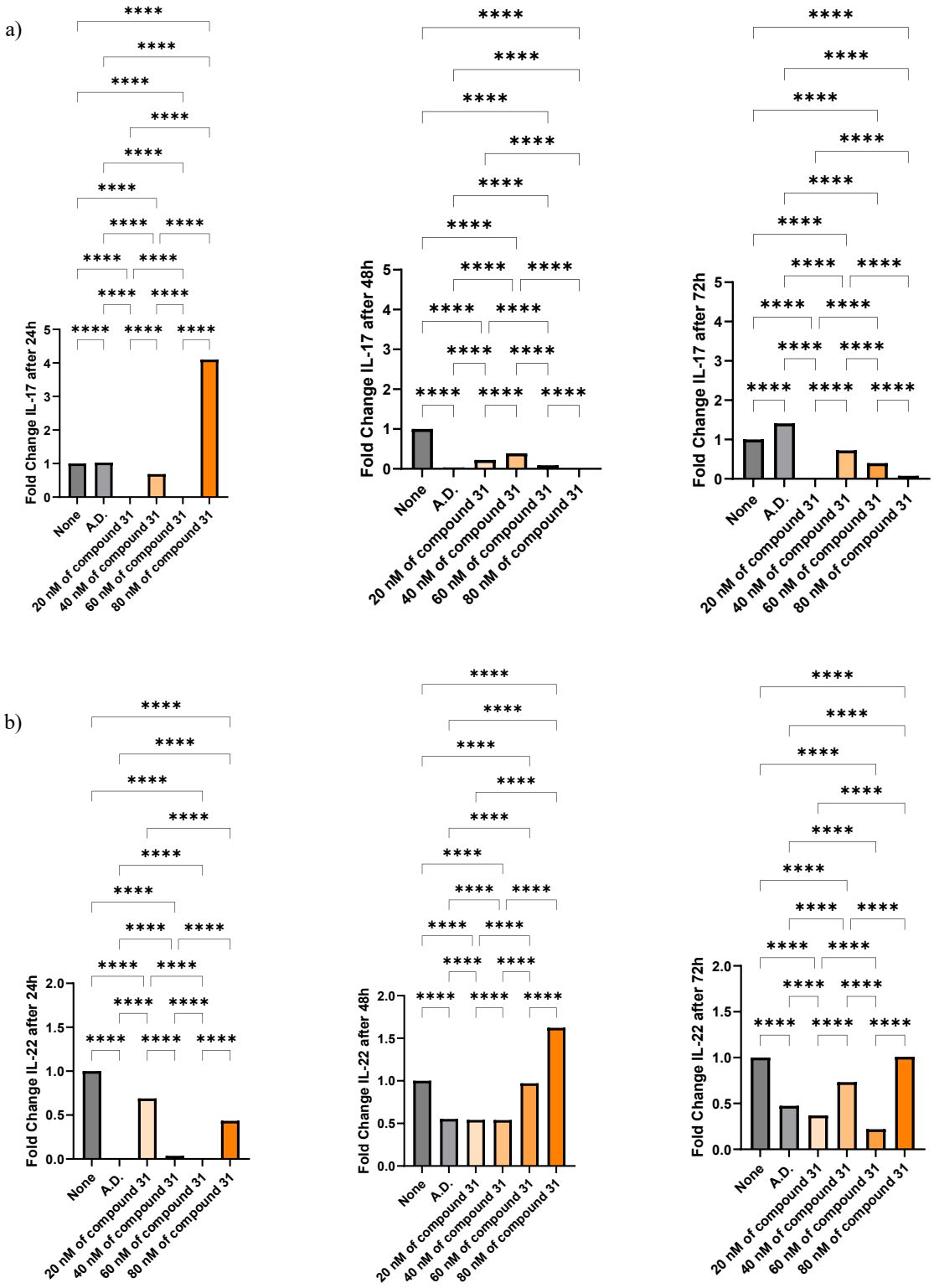


Figure 10 - mRNA expression of IL-17 and IL-22

Effects of compound 31 on mRNA expression of eIF4E, eIF4A, and eIF4G. a) mRNA expression of IL-17 after 24h, 48h, and 72h. b) mRNA expression of IL-22 after 24h, 48h, and 72h. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Two-Way ANOVA.

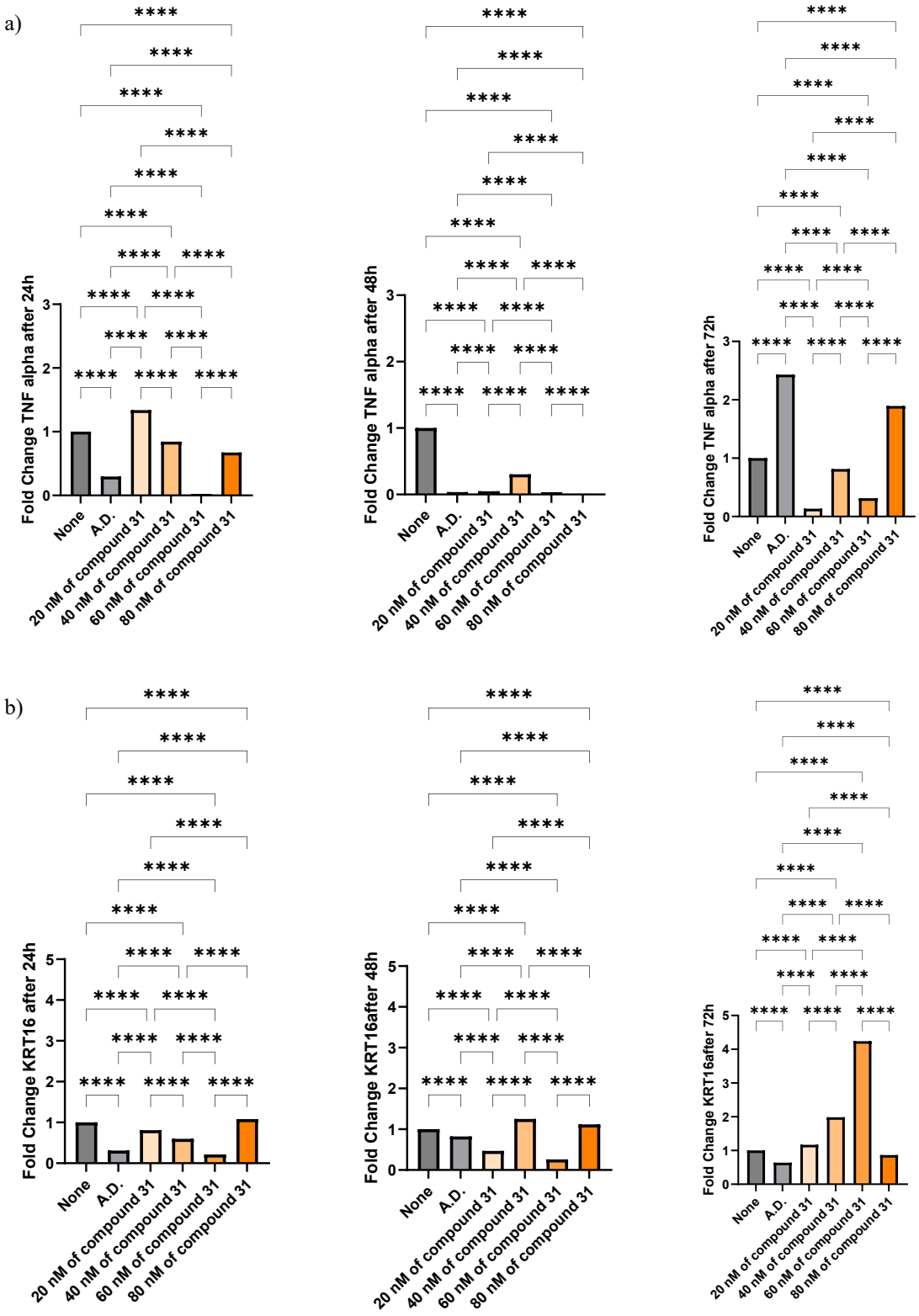


Figure 11 - mRNA expression of TNF-alpha and KRT16

Effects of compound 31 on mRNA expression of eIF4E, eIF4A, and eIF4G. a) mRNA expression of TNF-alpha after 24h, 48h, and 72h. b) mRNA expression of KRT16 after 24h, 48h, and 72h. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Two-Way ANOVA.

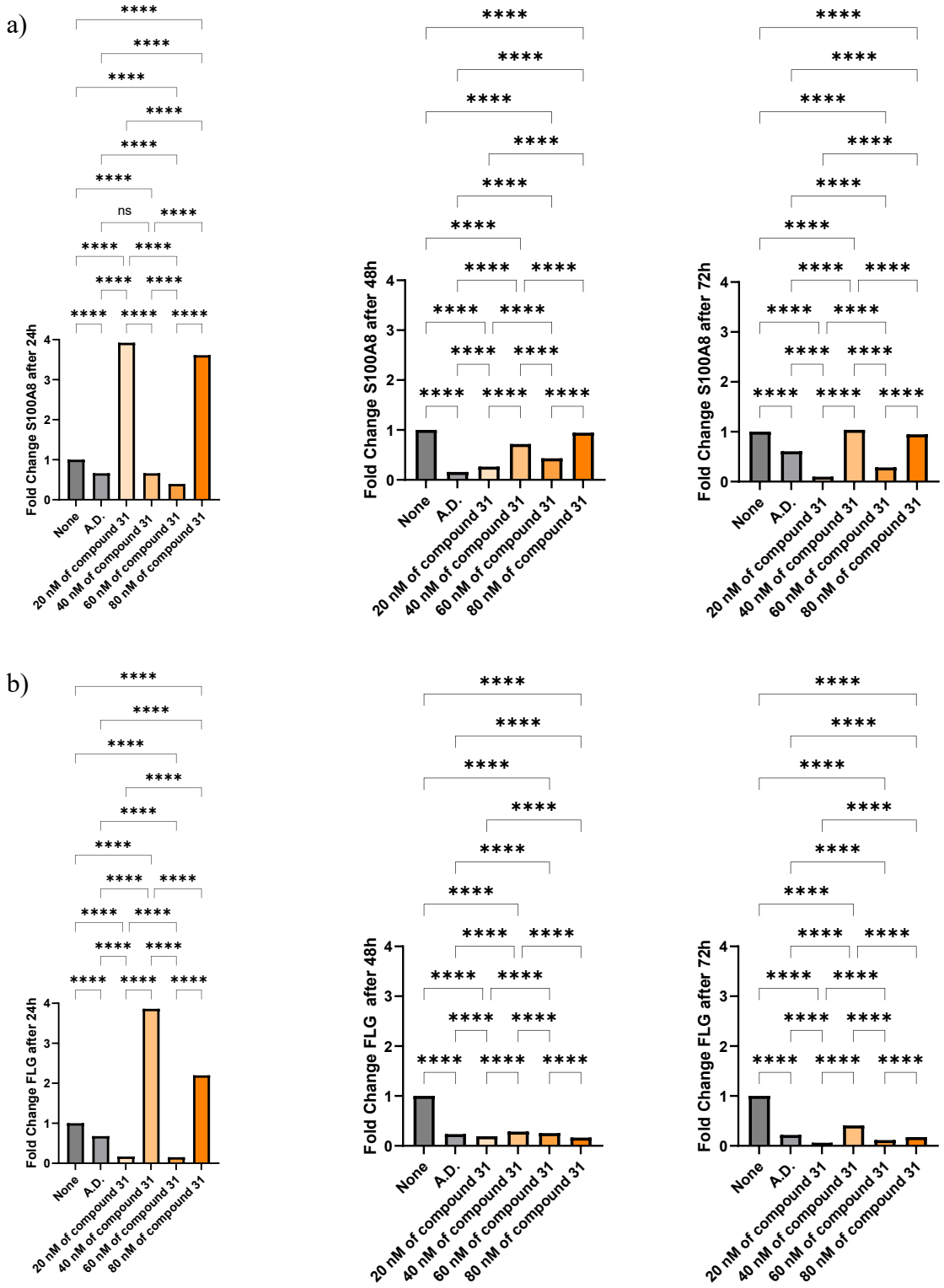


Figure 12 - mRNA expression of S100A8 and FLG

Effects of compound 31 on mRNA expression of eIF4E, eIF4A, and eIF4G. a) mRNA expression of eIF4E after 24h, 48h, and 72h. b) mRNA expression of eIF4A after 24h, 48h, and 72h. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Two-Way ANOVA.

3.2. Western Blot

The protein expression of eIF4E was significantly reduced at 20 nM, 40 nM, 60 nM and 80 nM compared to untreated cells and cells treated with aqua dest at all three time points (24 h, 48 h and 72 h).

The protein expression of eIF4A was significantly reduced at 20 nM, 40 nM, 60 nM and 80 nM compared to the untreated cells and the aqua dest treated cells after 24 h. The expression of 20 nM and 40 nM showed a down-regulation of eIF4A at the protein level after 48 h. The protein expression of eIF4A was significantly reduced at 60 nM and 80 nM and slightly reduced at 20 nM and 40 nM after 72 h.

The protein expression of eIF4G was significantly reduced at 20 nM, 40 nM, 60 nM and 80 nM compared to the untreated cells and the aqua dest treated cells at all three time points.

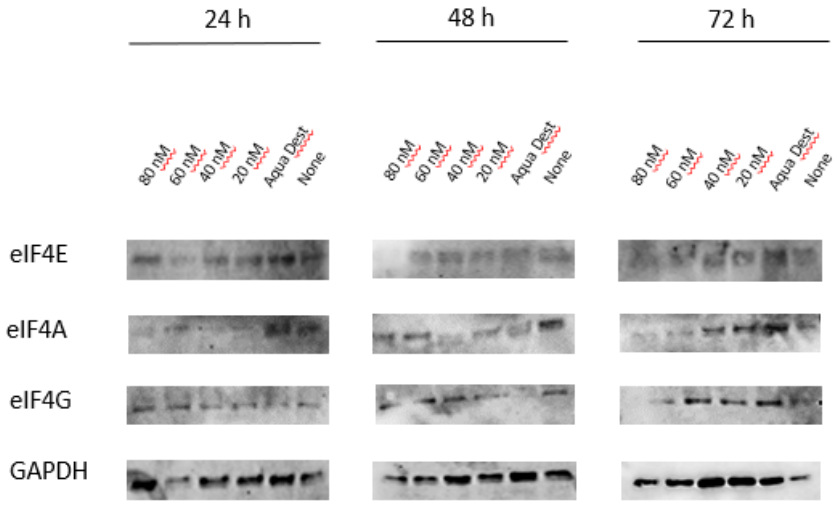


Figure 13 - Protein expression of eIF4E, eIF4A, eIF4G in untreated and treated HaCaT cells after 24, 48, and 72 h. GAPDH serves as a loading control group.

4. Discussion

In our study, we were able to demonstrate significantly reduced expression of eIF4E and eIF4G at both the mRNA and protein levels. These results are particularly important considering that eIF4E plays an essential role in cap-dependent initiation of translation, which is largely dependent on its interaction with eIF4G. This interaction is critical for the formation of the eIF4F complex, a crucial step in the initiation of the translation process. The regulation of this interaction is finely modulated by a category of proteins known as eIF4E inhibitor proteins. Among them, the 4EBP proteins are some of the best-studied inhibitors. These proteins exert their inhibitory effect by binding to eIF4E when it is not paired with eIF4G. This binding prevents eIF4E from interacting with eIF4G and thus hinders the formation of the eIF4F complex. As a result, the translation of certain mRNAs that normally require large amounts of available eIF4E for their translation is effectively repressed. The significance of our results is that we have shown that targeted interventions at the level of eIF4E and eIF4G expression can effectively disrupt this critical interaction. This could provide a new way to control the translation of mRNAs associated with various diseases. By reducing the availability of eIF4E and eIF4G, our new target could mimic the action of eIF4E inhibitor proteins such as the 4EBP proteins, providing a new strategy for suppressing the translation of mRNAs that contribute to disease progression. This approach emphasizes the importance of understanding the molecular mechanisms that control translation initiation and offers potential therapeutic opportunities for diseases in which overactive translation plays a key role in particular for psoriasis. (107–109)

Treatment with this novel eIF4E inhibitor led to a significant reduction in mRNA and protein expression of eIF4A, a result that is closely related to the broader context of translation initiation and the role of the eIF4F complex. eIF4A belongs to the DEAD-box family of proteins and is known for its role in ATP-induced RNA binding, RNA-dependent ATPase and helicase activities that are critical for cleavage of RNA secondary structures during the initiation phase of translation. This protein can exist independently or as a component of the eIF4F complex, where it plays a central role. The incorporation of eIF4A into this complex is facilitated primarily by its interaction with eIF4G, suggesting a tightly regulated mechanism of action. This incorporation is important because eIF4A is thought to be recycled from the eIF4F complex during initiation of translation, emphasizing its importance in this critical phase of protein synthesis. The significant decrease in eIF4A levels upon treatment with the new eIF4E inhibitor suggests an effect on the formation and function of

the eIF4F complex. Given the role of eIF4E in this complex - particularly its interaction with eIF4G, which is essential for the incorporation of eIF4A - targeting eIF4E could disrupt this interaction network. This disruption could lead to a reduction in the interaction of eIF4A with the eIF4F complex or affect its stability and function within the complex, which in turn affects its helicase activity, which is crucial for the initiation of translation. This observation highlights the complex relationships and dependencies within the eIF4F compartment and shows how the impairment of one component can affect the entire machinery of translation initiation. It provides a basis for understanding why treatment with the novel eIF4E inhibitor leads to a reduction in eIF4A expression and offers insights into possible mechanisms by which the inhibitor affects translational regulation. (107–109)

Our new eIF4E inhibitor shows that its use reduces the inflammatory milieu, leading to a significant decrease in IL-17 and IL-22 levels. Both cytokines are produced by T cells and stimulate keratinocytes to proliferate and trigger inflammation. This intervention highlights the potential of targeting specific molecular mechanisms to reduce inflammatory responses in affected tissues. (7)

TNF-α plays a central role in the development of psoriasis, although its exact mechanism of action is not yet fully understood. Together with IL-17A and IL-17C, it is a key component of the cytokine storm. Th-17 cells are known to produce significant amounts of TNF-α. (7) In our study, we observed a significant decrease in both mRNA and protein levels of TNF-α after administration of the new eIF4E inhibitor. IL-17 induces the production of TNF-alpha, which leads to acanthosis and hyperkeratosis in mouse models. (63,65) We hypothesize that the use of a novel eIF4E inhibitor affects TH-17-mediated inflammation, which may explain the observed reduction in TNF-alpha levels.

Our results have shown a significant reduction in IL-1β at both protein and mRNA levels, suggesting downregulation of this critical inflammatory marker. This reduction is particularly important in the context of skin inflammation and the progression of psoriasis, in which the IL-1/β-IL-1R signaling axis plays a central role. This axis is important for the regulation of IL-17-producing cells in the dermis and forces keratinocytes to increase the inflammatory response, thereby influencing the progression of psoriasis. Furthermore, the functionality of IL-1β, together with its IL-1 family counterpart, IL-18, is closely linked to post-translational modifications. In particular, caspase-1 cleaves the precursor protein into its active form. The activation of caspase-1 and thus the conversion of pro-IL-1β into its

active form is facilitated by the initiation of inflammasome complexes. These complexes are triggered by cellular stress, infection or localized danger signals, highlighting the complex interplay of cellular mechanisms in skin inflammation. (110,111)

Damage to keratinocytes triggers the release of antimicrobial peptides (AMPs), a process known as the Koebner phenomenon. AMPs such as S100A8 are part of this response. In particular, genes from the S100 family have been found to be significantly elevated in psoriasis. (62) Administration of the novel eIF4E inhibitor resulted in a significant decrease in mRNA and protein levels of S100A8, highlighting the potential of this treatment in modulating the expression of genes associated with skin inflammation and damage in psoriasis.

KRT16 is overexpressed in certain pathological conditions such as psoriasis, which contributes to the characteristic symptoms of the disease. Therefore, reducing KRT16 expression by inhibiting eIF4E is a potential therapeutic strategy. By modulating the pathological overexpression of KRT16, it is possible to alleviate the symptoms and progression of diseases such as psoriasis. Our study contributes to this promising therapeutic landscape by demonstrating that the use of a novel eIF4E inhibitor leads to a significant reduction in KRT16 levels at the mRNA and protein level. This finding suggests that interfering with eIF4E not only affects general protein synthesis but can also be used to target specific pathologic expressions of proteins such as KRT16. (112)

The characteristic features of psoriasis include rapid proliferation of keratinocytes leading to plaques, severe inflammation due to the involvement of the immune system, increasing neovascularization and the presence of specific cytokines that exacerbate the disease. Therapies that intervene in the pathogenesis of psoriasis are promising. Our study contributes to this promising therapeutic landscape by demonstrating that the use of a new eIF4E inhibitor leads to a remarkable reduction in cytokine levels, which are critical for the progression of the development of psoriasis. This finding underscores the potential of targeting specific molecular signaling pathways in the treatment of psoriasis. However, further research is needed to deepen our understanding of these mechanisms and refine our therapeutic approach. Our results have shown a significant reduction in the components of the eIF4F complex, along with a reduction in the cytokine-rich environment. These results indicate a step in the right direction for the topical treatment of mild forms of psoriasis. However, predicting the extent of the effects of the new eIF4E inhibitor in clinical use is

challenging due to the potential side effects. This underscores the complexity of translating laboratory successes into safe and effective clinical treatments and highlights the need for further research and careful assessment of the potential risks.

The protein complex eukaryotic translation initiation factor 4F (eIF4F) plays a critical role in the initiation of translation and serves as the linchpin for translational control, which is crucial under most conditions. In this work, we have explored the intriguing potential of eukaryotic initiation factor 4E (eIF4E) as a target for treatment by a specific new compound (no. 31). In doing so, we have uncovered new opportunities for therapeutic strategies and highlighted the need for further investigation in this area. Although we have observed a reduction in pro-inflammatory cytokines, our understanding of eIF4E and its cofactors is still in its infancy.

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