REVIEW ARTICLE

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Comprehensive Insights into Psoriasis: Disease Types, Underlying Mechanisms, and Effective Treatments

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Abstract

Psoriasis is a prevalent immune-mediated disorder characterized by inflammation of the skin and joints, impacting significant percentages of global populations. Psoriasis is inherited, and individuals' genetic backgrounds make some people more likely to get this illness. The prevalence of the disease is estimated to impact approximately 1–3% of the global population. However, psoriasis' prevalence exhibits variation among different populations owing to its genetic basis. Psoriasis is classified as a systemic illness due to the notable prevalence of comorbidities among affected individuals. These comorbidities include psoriatic arthritis, cardiovascular disease, metabolic syndrome, nonalcoholic fatty liver disease, inflammatory bowel disease, osteoporosis, and psychiatric disorders. Chronic plaque psoriasis, also referred to as psoriasis vulgaris (PV), is the prevailing form of psoriasis, constituting around 90% of the reported cases. Psoriasis was initially perceived as an illness primarily affecting epidermal keratinocytes, but it is now acknowledged as one of the most prevalent immune-mediated disorders. The pathophysiology of psoriasis is significantly influenced by tumor necrosis factor α, dendritic cells, and T cells. There are several treatment options available for psoriasis based on disease severity.

Keywords: Psoriasis; Psoriasis Vulgaris; pathophysiology; Treatment; Comorbidities.

1. Introduction

Psoriasis is an immune-mediated disease associated with skin and joint inflammation that affects large proportions of populations worldwide. It is a heritable disease: individuals' genetic backgrounds modulate their susceptibility **(Ogawa and Okada, 2020)**. The disease affects about 1-3% of the world's population **(Grozdeva et al., 2022)**, however, prevalence varies by population due to the genetic basis of psoriasis **(Ogawa and Okada, 2020)**. It has traditionally been considered a skin disease. Today, however, it is considered to be a systemic disease, as those patients present a high prevalence of associated comorbidities, such as psoriatic arthritis, metabolic syndrome, cardiovascular disease (CVD), nonalcoholic fatty liver disease, inflammatory bowel disease, osteoporosis, psychiatric diseases, smoking, and alcohol abuse **(Altemir et al., 2022)**.

Psoriasis has four major clinical phenotypes, which are distinguished by the morphological characteristics of their lesions: (i) psoriasis vulgaris, (ii) guttate psoriasis, (iii) pustular psoriasis, and (iv) erythrodermic psoriasis. The most common type of psoriasis is chronic plaque psoriasis (also known as psoriasis vulgaris: PV), which accounts for about 90 % of cases **(Griffiths and Barker, 2007)**. The disease exhibits a variable clinical presentation and is characterized by lesions in the form of circular, red papules and plaques with a grey or silvery-white, dry scale. Psoriatic lesions are generally distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and umbilicus (Dursun et al. 2018). Psoriasis is originally thought of as a disorder primarily of epidermal keratinocytes but is now recognized as one of the commonest immune-mediated disorders. Tumor necrosis factor α (TNF-α), dendritic cells (DCs), and T-cells all contribute substantially to its pathogenesis **(Griffiths and Barker, 2007)**. Therefore, the genetic factor affecting the regulation of T-cell responses may be associated with the susceptibility to psoriasis.

Psoriasis is a multifactorial genetic disease for which the genetic factors explain about 70% of disease susceptibility. Currently, the genetic background of psoriasis is a key target for developing psoriasis treatments **(Ogawa and Okada, 2020)**. Psoriasis treatments aim to stop skin cells from growing so quickly and to remove scales. Options include creams and ointments (topical therapy), light therapy (phototherapy), and oral or injected medications. The choice of the treatment depends on how severe the psoriasis is and how responsive it has been to previous treatment and self-care measures. You might need to try different drugs or a combination of treatments before you find an approach that works. Even with successful treatment, usually the disease returns **(Lee and Kim, 2023)**.

2. The Skin

The skin is a vital organ for human life. It plays a complex set of functions and is essential for maintaining homeostasis. The skin's most important function is to maintain the hydric balance of the organism and form an effective mechanical barrier against external injury whether physical, chemical, or biological. Apart from protection, the skin actively participates in thermoregulation and is involved in the immunological surveillance. It plays a critical role in the synthesis of vitamin D and functions as a sensory organ in detecting different stimuli **(Nguyen and Soulika, 2019)**.

2.1. Structure of the Skin

The structure of the skin consists of three layers: the epidermis, the dermis and hypodermis **(Figure 1)**.

2.1.1. The Epidermis

It is an avascular tissue that consists of four layers of keratinocytes in their various stages of differentiation. From the deepest layer to the more superficial, they are the basal cell layer, the spinous or squamous layer, the granular cell layer, and the stratum corneum. The first three compose the nucleated portion of the epidermis and are referred to collectively as Malpighian layer. The stratum corneum is composed of completely keratinized cells that are no longer alive but still play an important role in the homeostasis of the epidermis **(Cheng et al., 2021)**.

The interface between the two layers of the skin is known as the dermal-epidermal junction. The primary function of the dermal-epidermal junction is to promote adherence of the epidermis to the dermis, keeping the permeability required for the diffusion of nutrients and oxygen **(Bouwstra et al., 2003)**.

Keratinocytes of the basal layer are the least differentiated cells of the epidermis and form a single row of columnar cells with the major axis perpendicular to the dermoepidermal junction. They are the only keratinocytes of the epidermis with reproductive ability, functioning as cell reservoir and supplying continuously, through cell division, keratinocytes to higher layers (stratum spinosum, stratum granulosum, and stratum corneum **(Venus et al., 2010)**.

Depending on the body's anatomical area, Malpighian layer thickness varies. In general, the thickness of the epidermis varies from 0.04 mm on the eyelids to 1.6 mm on the palms and soles of the feet. The spinous layer is composed by larger keratinocytes than the basal cells, with a polyhedric shape, and they may be arranged in five to ten layers of cells **(Blair et al., 2020)**.

The stratum corneum consists of fully differentiated and keratinized anucleated keratinocytes. Corneocytes are embedded in intercellular matrix composed of cholesterol, free

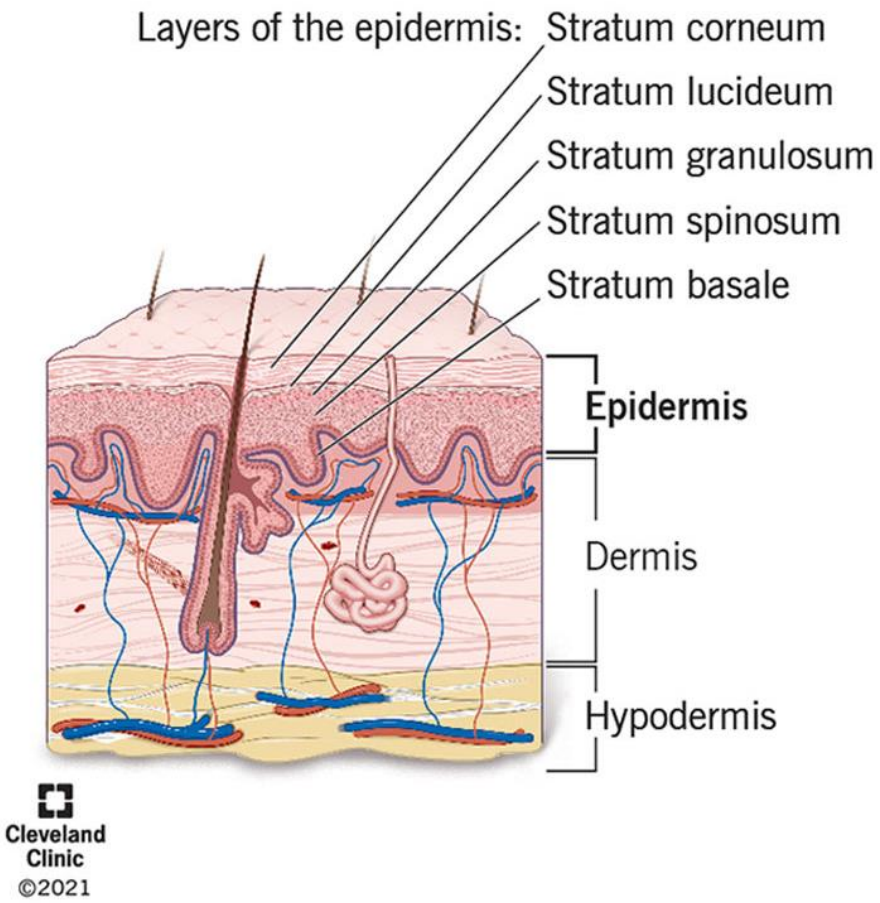

Figure 1. Layers of the skin. Available on: https://my.clevelandclinic.org/health/body/21901-epidermis

fatty acids, and glucosylceramides. This structure is essential for the stratum corneum to keep the skin's adequate moisture and simultaneously preserve the hydric barrier **(Elias, 2012)**.

Skin thickness depends on both the epidermis and the dermis thickness, which varies at different anatomical sites of the body. Hydration depends primarily on epidermis thickness and on the presence of cutaneous appendages **(Torres et al., 2023)**.

The epidermis exists in a dynamic state. Keratinocytes constantly divide and migrate upward from the basal cell layer toward the stratum corneum, in a vertically oriented path. As keratinocytes migrate, they progressively differentiate until complete keratinization at the stratum corneum. The maturation process of an undifferentiated basal cell to become a corneocyte lasts about 14 days. And, also, a corneocyte takes about 14 additional days to peel off the skin surface. Thus, in normal conditions, the epidermis, with the exception of cells that remained in the basal layer, is completely renewed every 4 weeks **(Lim, 2021)**.

2.1.2. The Dermis

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The dermis is divided into two portions, the papillary dermis and reticular dermis. An imaginary line, parallel to the skin surface, that joins the vessels of the superficial vascular plexus

limits these portions **(Prost-Squarcioni et al., 2008)**.

The papillary dermis is located more superficially. It has a relatively loose aspect because it is rich in amorphous interstitial substance and has more delicate, thinner, and less eosinophilic collagen bundles than those found in the reticular portion of the dermis. However, the papillary dermis has a higher density of fibroblasts than the reticular dermis. Fibroblasts are fusiform cells with oval nuclei that are immersed in the extracellular matrix of the dermis. The loose aspect of the papillary dermis facilitates the diffusion of oxygen and nutrients, which come out of the capillary vessels and reach the epidermis **(Venus et al., 2010)**.

2.1.3. The Hypodermis

The subcutaneous tissue hypodermis is the deepest layer, which in most instances consists largely of pads of adipose tissue. It is attached to the deep fascia or periosteum **(Arda et al., 2014) (Figure 2)**.

2.2. Immune Cells of the Skin

Skin-resident immune cells promote tissue function in homeostasis and act as sentinels by actively sampling environmental antigens. Both myeloid and lymphoid cell subsets are found in the skin in the steady state. Some of these resident immune cells migrate to lymph nodes to either induce peripheral tolerance to tissue self-antigens or initiate robust immune responses. In the event of a challenge, such as infections or tissue injury, immune cells resident in the skin and those infiltrating from the periphery interact to create an intricate defense network and restore the tissue to its original state **(Nguyen and Soulika, 2019)**.

3. Psoriasis

Psoriasis is a common immune-mediated skin disease with a strong genetic background, which affects approximately 0.5–1% of children and 2-3% of the adult population (>125 million people worldwide). Psoriasis may begin at any age, however, there are two peaks: at 20-30 years and 50-60 years. This means that 50% of the cases in psoriasis starts before the age of 25 **(Chovatiya and Silverberg, 2019)**.

Psoriasis is recognized as a skin disease with significant impact on quality of life and emotional well-being of patients suffering from it. Indeed, depression is very common among those patients. It waxes and wanes throughout the life of a patient **(Hepat et al., 2023)**.

Although the exact etiology of psoriasis is unknown, it is a widely held view that can be provoked by non-specific triggers such as mild trauma, drugs (lithium, IFN-alpha, antimalarial medications etc.), stress (which is probably the strongest environmental trigger of psoriasis) but also viral infections (e.g., HIV) can start the inflammatory processes which lead to the development of the disease. This chronically relapsing inflammatory disease is thought to be multifactorial, involving both environmental and genetic factors **(Raharja et al., 2021)**.

Psoriasis is characterized by aberrant interaction between keratinocytes and infiltrating immune cells, which leads to hyperproliferation and altered differentiation of the keratinocytes themselves and formation of psoriatic plaques. The severity of the psoriatic plaques is quantified by two major scoring systems: the psoriasis area and severity index (PASI) and the physician's global assessment (PGA). In addition, the Dermatology Life Quality Index (DLQI) represents a ten-question questionnaire which assesses how psoriasis is affecting well-being and quality of life of psoriasis patients **(Gordon et al., 2022)**.

The characteristic histological features of psoriasis are epidermal hyperplasia and inflammatory cell infiltration in both the dermis and the epidermis. The rapid proliferation of immature keratinocytes in psoriasis, which may increase more than ten times over the normal rate, is combined with an impaired cellular differentiation, while the retention of the keratinocytes' nuclei in the stratum corneum results in a phenomenon called "parakeratosis" **(Anaba et al., 2022)**.

Keratinocytes, once activated by different triggers (environment, injuries, stress, cytokines, viral infection etc.), have been shown to produce a large number of cytokines, which may induce further proliferation of these cells and have other pro-inflammatory and immunomodulatory effects **(Fernandes et al., 2023)**.

3.1. Clinical Classification

There are several types of psoriasis; Psoriasis Vulgaris (PV), Inverse Psoriasis, Gutta Psoriasis, Pustular Psoriasis and Erythrodermic psoriasis.

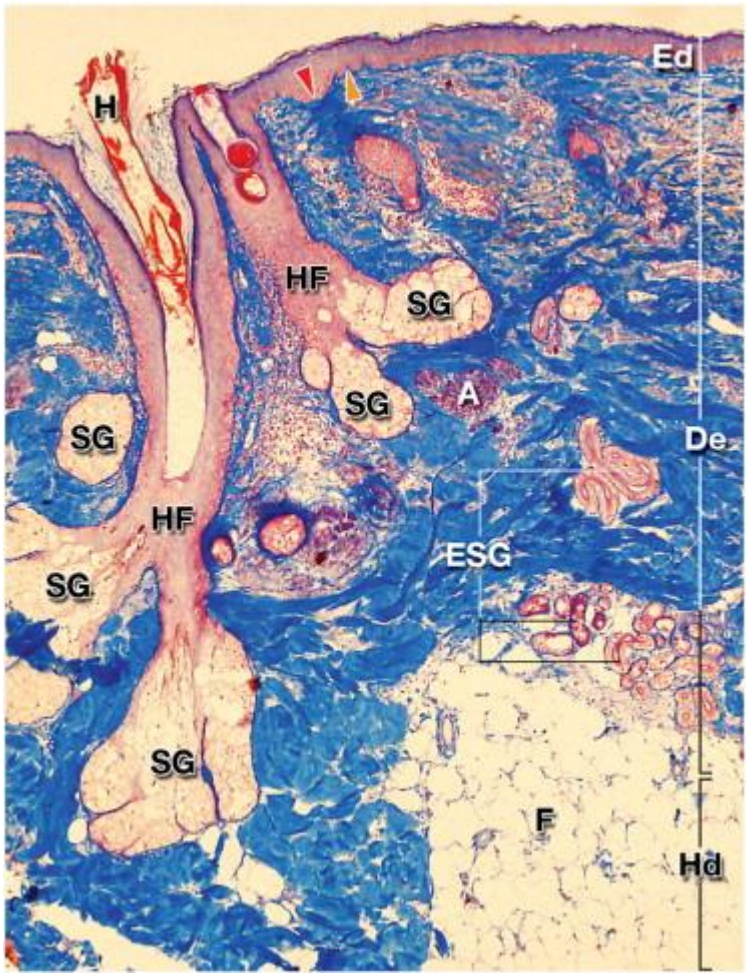

Figure 2. Thin skin. Light micrograph of a longitudinal section of female cheek showing layers of thin skin. Red arrowhead, epidermal ridge; orange arrowhead, dermal papilla; Ed, epidermis; De, dermis; Hd, hypodermis; HF, hair follicle; SG, sebaceous gland; ESG, eccrine sweat glands; A, arrector pili muscle; F, fat tissue; X2.52, Heidenhain azan **(Arda et al., 2014)**.

Clinical manifestations and treatment options are somewhat different for each subtype. PV is also called plaque-type psoriasis and is the most prevalent type. The terms psoriasis and PV are used interchangeably in the scientific literature; nonetheless, there are important distinctions among the different clinical subtypes **(Rendon and Schäkel, 2019)**.

3.1.1. Psoriasis Vulgaris

About 90% of psoriasis cases correspond to chronic plaque-type psoriasis. The classical clinical manifestations are sharply demarcated, erythematous, pruritic plaques covered in silvery scales. The plaques can coalesce and cover large areas of skin. Common locations include the trunk, the extensor surfaces of the limbs, and the scalp **(Koca, 2016) (Figure 3)**.

3.1.2. Inverse Psoriasis

Also called flexural psoriasis, inverse psoriasis affects intertriginous locations and is characterized clinically by slightly erosive erythematous plaques and patches. Inverse psoriasis is considered to be a rare variant of plaque-type psoriasis and is associated with significantly impaired quality of life **(Göblös et al., 2021)**.

3.1.3. Guttate Psoriasis

Guttate psoriasis is a variant with an acute onset of small erythematous plaques. It usually affects children or adolescents and is often triggered by group-A streptococcal infections of tonsils. About one-third of patients with guttate psoriasis will develop plaque psoriasis throughout their adult life **(Ko et al., 2010)**.

3.1.4. Pustular Psoriasis

Pustular psoriasis is characterized by multiple, coalescing sterile pustules. Pustular psoriasis can be localized or generalized. Two distinct localized phenotypes have been described: psoriasis pustulosa palmoplantaris (PPP) and acrodermatitis continua of Hallopeau (ACH). Both affect the hands and feet; PPP is restricted to the palms and soles, while ACH is more distally located at the tips of fingers and toes and affects the nail apparatus. Generalized pustular psoriasis presents with an acute and rapidly progressive course characterized by diffuse redness and subcorneal pustules and is often accompanied by systemic symptoms **(Navarini et al., 2017) (Figure 3)**.

3.1.5. Erythrodermic Psoriasis

Erythrodermic psoriasis is an acute condition in which over 90% of the total body surface is erythematous and inflamed **(Dogra and Mehta, 2022) (Figure 4)**.

3.2. Comorbidities in Psoriasis

In a simplified way, the comorbidities associated with psoriasis may be classified as classic, emerging and related to lifestyle **(Srivastava et al., 2021) (Table 1)**.

Table 1. Comorbidities associated with psoriasis (Oliveira et al., 2015)

Classic	Psoriatic arthritis
	Inflammatory bowel disease
	Psychological and psychiatric disorders
	Uveitis
Emerging	Metabolic syndrome and its components
	Cardiovascular diseases
	Atherosclerosis
	Nonalcoholic fatty liver disease
	Lymphomas
	Sleep apnea
	Chronic obstructive pulmonary disease
	Osteoporosis
	Parkinson's disease
	Celiac disease
	Erectile dysfunction
Related to Lifestyle	Smoking habit
	Alcoholism
	Anxiety

Psoriasis typically affects the skin, but may also affect the joints, and has been associated with several diseases. Inflammation is not limited to the psoriatic skin and has been shown to affect different organ systems. Thus, it has been postulated that psoriasis is a systemic entity rather than a solely dermatological disease. When compared to control subjects, psoriasis patients exhibit increased hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and increased body mass index. The metabolic syndrome, which comprises the aforementioned conditions in a single patient, was two times more frequent in psoriasis patients **(Rendon and Schäkel, 2019)**.

Coronary plaques are also twice as common in psoriasis patients when compared to control subjects. Several large studies have shown a higher prevalence of diabetes and CVD correlating with the severity of psoriasis. There are divided opinions regarding the contribution of psoriasis as an independent cardiovascular risk factor; however, the collective evidence supports that psoriasis independently increases risk for myocardial infarction, stroke, and death due to CVD. In addition, the risk was found to apply also to patients with mild psoriasis to a lower extent **(Egeberg et al., 2017)**.

Psoriatic inflammation of the joints results in psoriatic arthritis. The skin manifestations generally precede psoriatic arthritis, which shares the inflammatory chronicity of psoriasis and requires systemic therapies due to a potential destructive progression. Psoriatic arthritis develops in up to 40% of psoriasis patients; around 15% of psoriasis patients are thought to have undiagnosed psoriatic arthritis. It presents clinically with dactylitis and enthesitis in oligoarticular or polyarticular patterns. The polyarticular variant is frequently associated with nail involvement **(Villani et al., 2015)**.

Nails are specialized dermal appendages that can also be affected by psoriatic inflammation. Nail psoriasis affects more than half of psoriasis patients and can present as the only psoriasis manifestation in 5–10% of patients. The clinical presentation of nail psoriasis depends on the structure affected by the inflammatory process. Nail matrix involvement presents as pitting, leukonychia, and onychodystrophy, whereas inflammation of the nail bed presents as oil-drop discoloration, splinter hemorrhages, and onycholysis **(Rendon and Schäkel, 2019) (Figure 5)**.

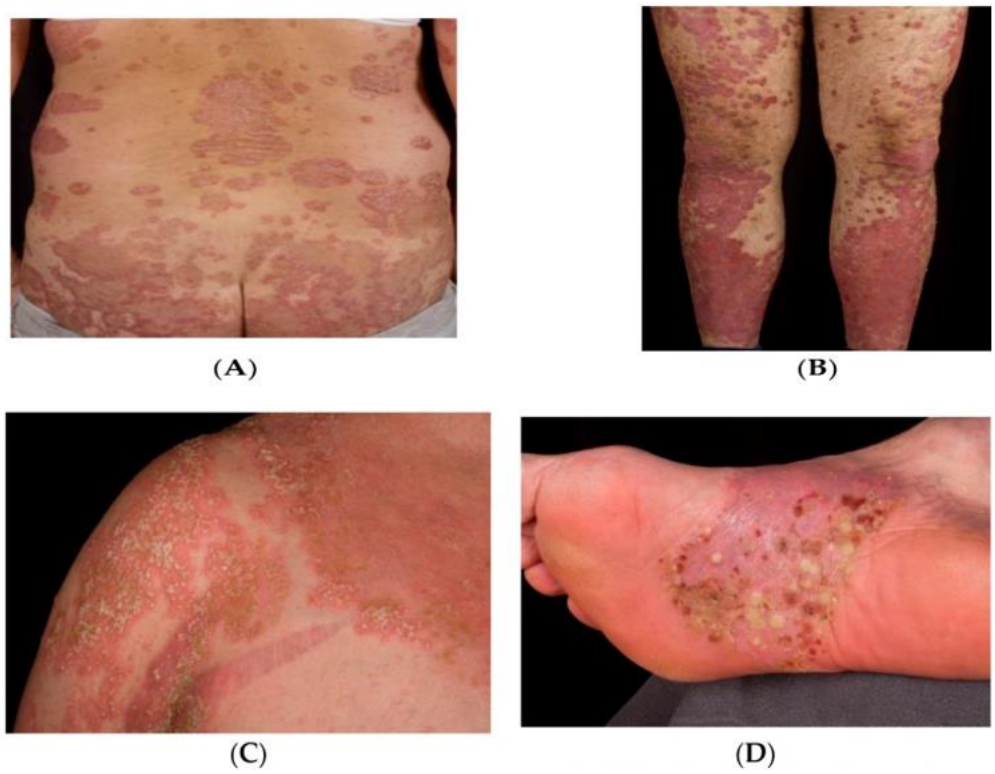

Figure 3. Clinical manifestations of psoriasis. (A, B) Psoriasis vulgaris presents with erythematous scaly plaques on the trunk and extensor surfaces of the limbs. (C) Generalized pustular psoriasis. (D) Pustular psoriasis localized to the soles of the feet **(Rendon and Schäkel, 2019)**.

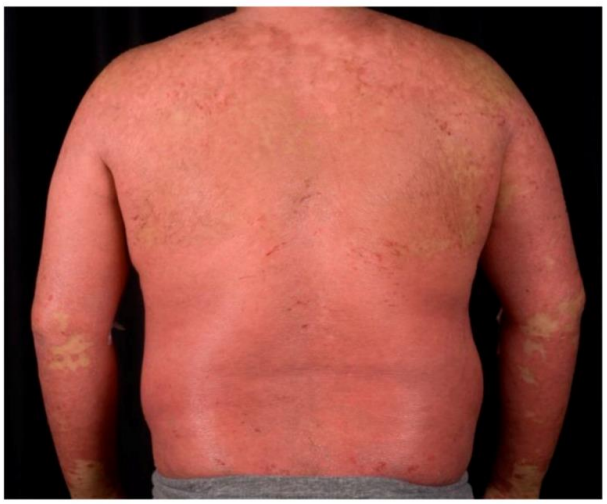

Figure 4. Erythrodermic psoriasis (Rendon and Schäkel, 2019).

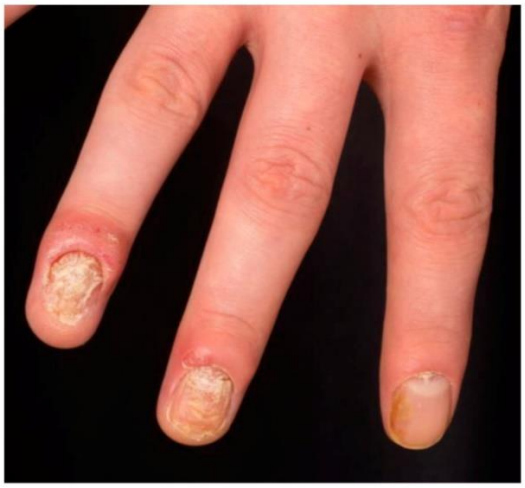

Figure 5. Onycholysis and oil drop changes on psoriatic nail involvement (Rendon and Schäkel, 2019).

Additionally, psoriasis has been associated with a higher prevalence of gastrointestinal and chronic kidney disease. Susceptibility loci shared between psoriasis and inflammatory bowel disease support this association in particular regarding Crohn's disease. An association with mild liver disease, which correlates with imaging studies, has been reported. Psoriasis might be a risk factor for chronic kidney disease and end-stage renal disease, independent of traditional risk factors (demographic, cardiovascular, or drug-related) **(Wan et al., 2013)**.

Taken together, the different factors contributing to psoriasis as a systemic disease can have a dramatic effect on the quality of life of patients and their burden of disease. Psoriasis impairment to psychological quality of life is comparable to

cancer, myocardial infarction, and depression. The high burden of disease is thought to be owed to the symptoms of the disease, which include pain, pruritus, and bleeding, in addition to the aforementioned associated diseases. The impact of psoriasis on psychological and mental health is currently an important consideration due to the implications of the disease on social well-being and treatment. Patients with psoriasis have an increased prevalence of depression and anxiety and suicidal ideation. Interestingly, psoriasis treatment leads to improvement in anxiety symptoms **(Fleming et al., 2016)**.

3.3. Triggering Factors of Psoriasis

Both external and systemic factors can elicit psoriasis in genetically predisposed individuals.

3.3.1. External Triggering Factors

Koebner's phenomenon: Psoriatic lesions often develop at the site of injury. It is also known as "isomorphic phenomenon". It refers to induction of lesions by cutaneous trauma. It is observed in approximately 25% of patients with psoriasis. Epidermal trauma alone does not induce the lesions, it should also involve the papillary dermis. Psoriatic lesions can also be induced by other forms of cutaneous injury, e.g., Sunburn, morbilliform drug eruptions, viral exanthems, and tattoo marks. The lag time between the trauma and the appearance of skin lesions is usually 2-6 weeks. Lesions of psoriasis may also appear within pre-existing dermatoses such as contact dermatitis and leprosy **(Xhaja et al., 2014)**.

3.3.2. Systemic Triggering Factors

3.3.2.1. Seasonal Variations

Most patients have experienced worsening of their skin lesions during winter. High humidity is usually beneficial. Sunlight may worsen psoriasis in some, but improves it in many **(Unissa et al., 2019)**.

3.3.2.2. Infections

Infections, particularly bacterial infections may aggravate psoriasis. Streptococcal infections are the most common offenders. These streptococcal infections often lead to a flare of guttate psoriasis, especially in children and adolescents, but may also precipitate pustular psoriasis or exacerbate plaque type psoriasis. Less often, even infections of sinuses and respiratory, gastrointestinal or genitourinary tracts may be responsible for a disease flare **(Ladizinski et al., 2013)**.

3.3.2.3. HIV

Exacerbation or even the initial manifestation of psoriasis has been observed in patients with HIV infection. Though the frequency is unchanged, the severity of the disease is greater in this population **(Arbune et al., 2021)**.

3.3.2.4. Endocrine Factors

Various endocrinal factors act as trigger for generalized pustular psoriasis. Hypocalcemia, pregnancy may alter disease activity. Pregnant women may develop pustular psoriasis, referred to as impetigo herpetiformis, sometimes in association with hypocalcemia **(Wang and Jin, 2021)**.

3.3.2.5. Drugs

Many drugs can precipitate psoriasis, particularly beta-blockers, lithium, antimalarials, IFN, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors. Intracellular cyclic adenosine monophosphate (cAMP) levels are decreased within psoriasis lesions and drugs that decrease (cAMP) levels such as β- blockers and lithium may worsen psoriasis **(Kamat and Dogra, 2019)**.

Beta blockers like propranolol, practolol, metaprolol and oxprenolol induce papulosquamous eruptions resembling psoriasis. Severe psoriasis is associated with depression. However, treatment of depression with lithium compounds in these patients may destabilize and exacerbate psoriasis **(Dika et al., 2006)**. Lithium causes decrease in cAMP and inositol which causes low intracellular calcium levels, leading to lack of differentiation and increased proliferation of keratinocytes, enhanced chemotaxis, and phagocytic activity of polymorphonuclear leucocytes **(Basavaraj et al., 2010)**.

3.3.2.6. Psychogenic Stress

Psoriasis is more stress sensitive than any other skin disease. The disease itself can cause a reactive anxiety and depression in patients which could further exacerbate psoriasis. There is sufficient literature implicating stressful life situations in

precipitating and exacerbating psoriasis. Estimates of proportion of psoriasis patients whose disease is affected by stressful events vary from 40% to 80% depending on how stress is defined (acute or chronic) and measured **(Torales et al., 2020)**.

3.3.2.7. Alcohol and Smoking

Smoking more than 20 cigarettes daily is associated with a two-fold increased risk of severe psoriasis and may play a role in its onset as well. There is a strong association between smoking and pustular psoriasis **(Torales et al., 2020)**.

3.3.2.8. Obesity

Increased adiposity and weight gain are strong risk factors for incident psoriasis. Obese patients are more likely to present with severe psoriasis **(Czarnecka et al., 2023)**.

3.3.2.9. Genetics

Psoriasis is significantly more likely to occur in first- and second-degree relatives of patients with psoriasis than in the general population, and concordance is greater in monozygotic than in dizygotic twins pointing to a strong genetic influence on the disease **(Babaie et al., 2022)**.

In fact, the heritability of psoriasis has been estimated to be higher than 60%, even though psoriasis is not a monogenic disease, but a complex and multifactorial disease involving multiple susceptibility genetic loci. Early analyses on this topic were carried out by family-based linkage disequilibrium studies, since genetic variants or loci which are in situated closely on the same chromosome are less prone to separation by recombination during meiosis, thus they are more likely to be inherited together and exhibit correlation in the population **(Dand et al., 2020)**.

Areas thought to harbor psoriasis-related genes with psoriasis susceptibility were primarily named PSORS (psoriasis-susceptibility) loci. There are at least 12 distinct PSORS loci that were mainly identified through linkage analysis of multiply affected psoriasis families. Loci in the major histocompatibility complex (MHC) I, on the short arm of chromosome 6, were among the first and most repetitive genetic susceptibility regions found in psoriasis. In fact, the first loci linked to psoriasis susceptibility, PSORS 1, was the human leukocyte antigen (HLA)-Cw6, situated at chromosomal position 6p21.3 **(Harden and Krueger, 2015)**.

3.4. Immunopathogenesis of Psoriasis

The precise initiation of psoriasis remains elusive, but it's postulated that a confluence of environmental and genetic factors instigates stress in keratinocytes, subsequently activating plasmacytoid DCs. The early activation of plasmacytoid DCs is pivotal in the pathogenesis of psoriasis. The maintenance phase of psoriasis is characterized by a sustained immune response, involving a dynamic interplay between keratinocytes, cytokines, and immune cells, and leading to the chronic nature of the disease **(Benhadou et al., 2018)**.

3.4.1. Pathophysiology Overview

The skin pathology in PV is characterized by vast proliferation and dysregulated differentiation of keratinocytes, infiltration of immune cells of both innate and adaptive lineage, changes to the dermal vasculature in the area, and local production of proinflammatory cytokines **(Rendon and Schäkel, 2019) (Figure 6)**. This essentially creates a pathophysiological “feed-forward” cycle that increases the inflammation intensity and sustains it **(Armstrong and Read, 2020)**. The initial trigger event in psoriasis is still not completely characterized, and it is possible that multiple different factors may unleash the subsequent pro-inflammatory cascade. Emotional stress, different medications, infectious agents and even physical trauma (Koebner phenomenon) have all been associated and observed in the initiation of the disease. Extensive studies have highlighted that DCs, or plasmacytoid DCs, steer the initiation of the disease but less is known about events leading up to DC activation **(Kim et al., 2014)**.

3.4.2. The Role of T Cells

Since the 1980s, psoriasis has been characterized as a T cell-mediated pathology due to the pronounced accumulation of T cells in psoriatic skin lesions. The significant therapeutic efficacy of T cell blockade further confirms their central role in psoriatic pathogenesis. In the immune cascade, DCs initiate the response by presenting antigens to naive T cells in the lymph nodes. Upon receiving antigenic stimuli, these T cells differentiate into specific subsets, namely T helper (Th)17, Th1, and Th22 **(Lande and Gilliet, 2010)**.

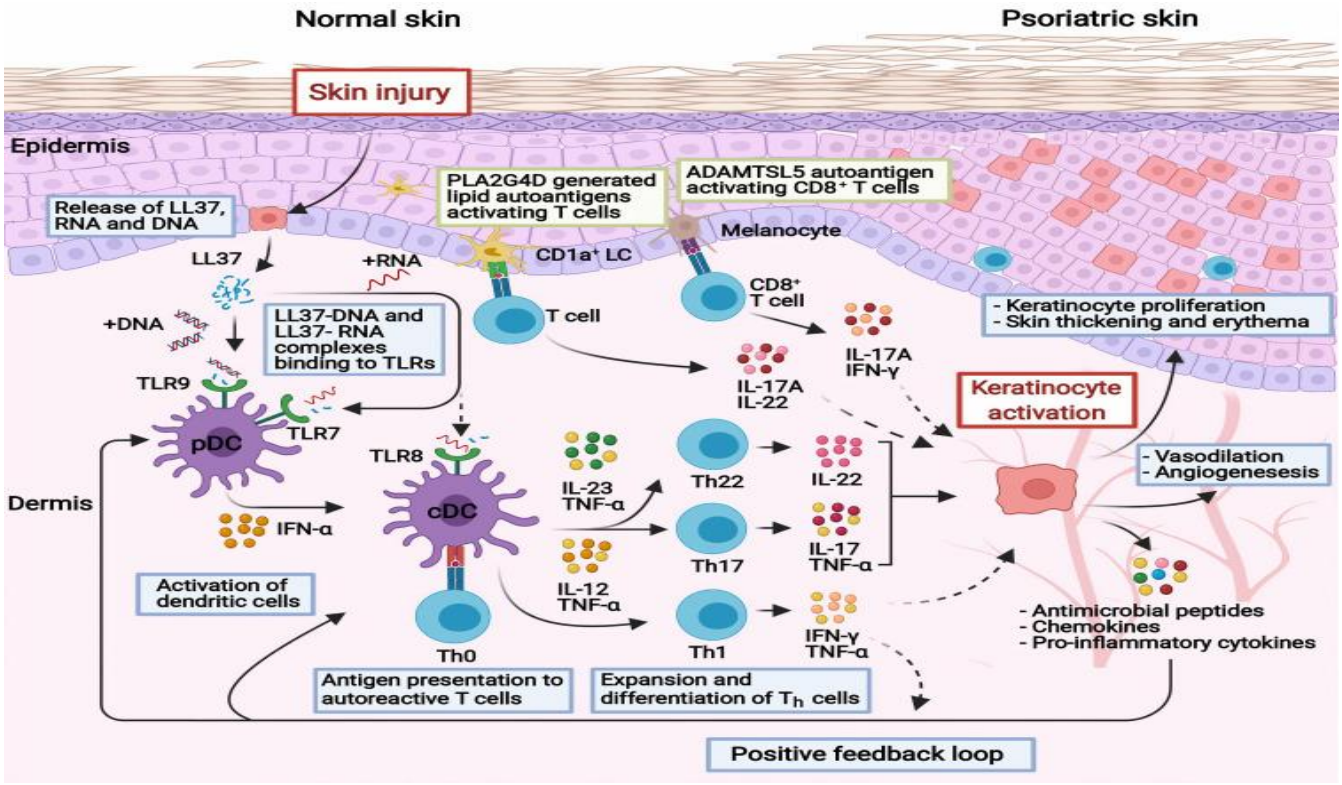

Figure 6. Pathophysiology of psoriasis. In response to skin injury, damaged keratinocytes release LL-37 which forms complexes with self-DNA/RNA. The complexes bind to TLRs and activate dendritic cells, which in turn promote the expansion and differentiation of autoreactive T cells through antigen presentation and secretion of cytokines. IL-23 promotes the differentiation of Th17 and Th22 cells, whereas IL-12 promotes Th1 cells. The activated Th22 and Th17 cells secrete TNF-α, IL-17 IL-22 that stimulate the keratinocytes to proliferate and produce inflammatory cytokines, chemokines, and antimicrobial peptides which further activate immune cells, enabling a positive feedback loop. Other concepts with autoantigens as triggers include; ADAMTSL5 in melanocytes which bind and activate autoreactive CD8+ T cells with subsequent release of IL-17 and IFN-γ; or PLA2G4D producing neolipid autoantigens expressed on CD1a+ dendritic cells, which upon presentation activate lipid-specific T cells secreting IL-17A and IL-22. ADAMTSL5, a disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like 5; cDC, conventional dendritic cells; IFN, interferon; IL, interleukin; LC, Langerhans cell; LL37, cathelicidin; pDC, plasmacytoid dendritic cells; PLA2G4D, phospholipase A2 group IVD; Th, T helper cell; TLR, toll-like receptor; TNF, tumor necrosis factor **(Ben Abdallah et al., 2021)**.

The cytokines play a crucial role in this differentiation: Interleukin (IL)-12 primarily drives Th1 differentiation, while IL-23 induces Th17 differentiation. Th1 effector cells release IFN-γ and TNF-α, intensifying skin inflammation. Th17 cells, vital in psoriasis, produce pro-inflammatory cytokines, especially IL-17A. This cytokine prompts keratinocyte abnormalities leading to the formation of psoriatic plaques **(Krueger et al., 2021)**.

Concurrently, Th22 cells secrete IL-22, influencing keratinocyte proliferation and boosting the production of antimicrobial peptides. The diverse range of chemokines and adhesion molecules directs a plethora of immune cells, including neutrophils, T lymphocytes, innate lymphoid cells, and monocytes, to infiltrate the epidermis and dermis. The monocytes can locally differentiate into DCs or macrophages **(Strober et al., 2023)**.

Notably, even after the inflammation subsides, resident memory T cells (TRM) remain in skin lesions, primed for a rapid response upon antigen re-exposure, emphasizing the recurrence of psoriatic episodes. In addition to infiltration, these effector T cells undergo proliferation within the psoriasis-affected epidermis. During the maintenance phase of psoriasis, the function of Tregs, which are essential immune modulators, appears compromised or overwhelmed, perpetuating inflammation in the condition **(Strober et al., 2023)**.

3.4.3. Cytokine/Chemokine Network

The chronicity of the lesions in this phase is maintained by a complex network of mediators. The IL-23/IL-17 axis acts as the central pathway in psoriasis pathogenesis, a fact highlighted by the effectiveness of biological treatments targeting it. In the IL-23/Th17 axis of psoriasis, activated DCs and keratinocytes release IL-23, stimulating Th17 cells to produce key cytokines such as IL-17A, IL-17F, and IL-22. IL-22 induces keratinocyte proliferation and aberrant differentiation. While Th17 cells are primary IL- 17A producers. Mast cells, T cells, and innate lymphoid cells also play significant roles **(Chen et al., 2022)**.

Additionally, both IL-17A and IL-17F can activate keratinocytes, recruit neutrophils, and promote inflammation. IL-17F concentrations in psoriatic lesional tissues and serum are consistently higher, averaging 30 times more than IL-17A levels, but IL-17A is substantially more active than IL-17F. IL-17A, has multiple roles in psoriasis pathogenesis, boosts the antimicrobial peptide LL37 and the chemokine CXCL1, amplifying inflammation. IL-17A also synergizes with other cytokines, such as TNF-α and IL-22, stimulating the production of antimicrobial peptides, chemokines, and cytokines by targeting various cells like keratinocytes, endothelial cells, and fibroblasts **(Wan et al., 2021)**.

These mediators further recruit Th17 cells and DCs, amplifying the IL-23/IL-17A axis and skin inflammation. IFN-γ, a type II IFN primarily secreted by Th17 and Th1 cells, exhibits pronounced presence within psoriatic skin and serum. While psoriasis skin shows a distinct IFN-γ signature, its precise role in inflammation remains ambiguous. One key function is IFN-γ's enhancement of responses to other cytokines, termed IFN-γ-priming **(Kumar et al., 2021)**. Preliminary exposure to IFN-γ in keratinocytes is imperative for inflammasome activation and subsequent proinflammatory cytokine release, highlighting its central role in initiating inflammasome activation in vitro. There's mounting evidence to support the role of IFN-γ in enhancing cellular reactions to other cytokines **(Ramessur et al., 2022)**.

3.4.4. Activation of Keratinocytes

Cytokines IL-17 and IL-22, produced by Th17 cells, along with other proinflammatory cytokines, synergistically stimulate keratinocytes to an "activated status." In psoriasis, these activated keratinocytes display significant proliferation, with growth rates in psoriatic lesions increasing nearly 50-fold, leading to the disease's characteristic thick, scaly plaques. Furthermore, the activated keratinocytes release a wide array of inflammatory cytokines and chemokines **(Chiricozzi et al., 2011)**.

Concurrently, the production of keratins K6, K16, and K17, primarily found in the skin's suprabasal layer, is crucial for hyperproliferation, immune activation, and strengthening the skin's barrier. This interaction establishes a reinforcing feedback loop between resident skin cells and immune cells, resulting in the sustained inflammation characteristic of psoriasis **(Zhang et al., 2019)**.

3.5. Autoimmunity in Psoriasis

In addition to the TNF-α/IL-23/IL-17-shifted immune deviation, psoriasis is likely to be associated with an autoimmune background. Several studies have revealed the presence of autoreactive T cells in psoriasis **(Prinz, 2017)**.

The antimicrobial peptide LL37 is over-expressed in psoriatic epidermis. LL37 not only triggers the TNF-α/IL-23/IL-17 axis by activating DCs but also works as an autoantigen to activate the T-cell adaptive immune system. LL37 is recognized as an autoantigen by circulating T cells in 46% of psoriasis patients and more frequently (75%) in moderate-to-severe psoriasis. These LL37-specific T cells express cutaneous lymphocyte antigen (CLA) and produce variable amounts of IFN-γ, IL-17 and IL-22 but not IL-4. The frequency of LL37-specific T cells is significantly correlated with disease severity and is reduced by anti-TNF-α therapy **(Furue et al., 2018)**.

In addition to the autoreactive T-cell response, several autoantibodies have been demonstrated in patients with psoriasis, including anti-stratum corneum antibody, anti-squamous cell carcinoma antigen and anti-heatshock protein 65. However, the clinical significance of the autoantibody production remains elusive **(Sticherling, 2016)**.

3.6. Disease Severity

Disease severity of psoriasis may be estimated in several ways. Over the years, clinicians have used various scoring systems to evaluate the severity of psoriasis using both quantitative as well as

qualitative measures, including percent body surface area (BSA), the Psoriasis Area and Severity Index (PASI) **(Manchanda et al., 2023)** and the Dermatology Life Quality Index (DLQI) which represents a ten-question questionnaire that assesses how psoriasis is affecting well-being and quality of life of psoriasis patients **(Gordon et al., 2020)**.

The total percentage of affected BSA remains a useful guide and may be readily estimated during the clinical encounter. The clinician may use the patient's own palmar handprint as a measurement tool, such that in general each handprint would represent 0.8% of total BSA for men, 0.7% for women, and 0.94% for children. In general, aggregate percent BSA categories of less than 5%, between 5% and 10%, and over 10% may represent mild, moderate-to-severe, and severe disease, respectively. In addition, involvement of certain areas of the body, such as the periorbital region or the palms and soles, may pose particular challenges and also elevate the estimation of severity **(Fleming et al., 2015)**.

The PASI provides a mechanism for delineating mild, moderate, and severe disease. Calculators for this instrument are available online, and combine estimates of severity (erythema, induration, and desquamation) with percentage of BSA for the head, trunk, arms, and legs. A PASI score below 7 indicates mild disease, a score of 7–12 implies moderate disease, and a score above 12 strongly suggests severe disease. The strengths of the PASI scoring system include its history as a validated instrument, now ubiquitous use in clinical trials ("gold standard"), high correlation with objective outcome measures, and ease of use, while limitations include the lack of a clear correlation to quality-of-life measures and patients' views on their disease, the lack of a linear relationship to cutaneous disease severity, and lack of applicability in measuring disease course over time **(Schmitt and Küster, 2015)**.

3.7. Treatment

3.7.1. Treatment for Mild Psoriasis

There is no consensus on the definitions of mild and moderate-to-severe psoriasis. Mild psoriasis is generally described as affecting less than 3% to 5% of the total BSA. There are several treatment options available for mild psoriasis, including topical corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytics, and targeted phototherapy. The choice of treatment depends on factors such as the location and severity of the lesions, presence of comorbidities, and individual patient preferences **(Lee and Kim, 2023)**.

3.7.1.1. Topical Corticosteroids

Topical corticosteroids are commonly used as the primary therapy for patients with mild or localized psoriasis. They work by reducing inflammation, inhibiting cell proliferation, and constricting blood vessels through the downregulation of inflammatory pathways. The selection of corticosteroid strength and formulation should be based on the location of the lesions to minimize adverse effects. Combined formulations of corticosteroids with vitamin D analogs or keratolytic agents, such as halobetasol propionate and tazarotene, are often more effective and have fewer side effects compared to using them individually. Additionally, they can also be used as proactive treatments applied twice a week when lesions show improvement **(Blauvelt et al., 2020)**.

3.7.1.2. Topical Vitamin D

Topical vitamin D analogs function by inhibiting the proliferation of keratinocytes and promoting their differentiation. They can be applied liberally unless the patient has renal impairment. Adverse effects may include a burning sensation and irritation, but these usually decrease over time **(Soleymani et al., 2015)**.

3.7.1.3. Topical Calcineurin Inhibitors

Topical calcineurin inhibitors like tacrolimus and pimecrolimus are used primarily for psoriatic lesions in facial and intertriginous areas by blocking T cell activation and inhibiting the synthesis of IL-2 and IFN-γ. The main side effects of topical calcineurin inhibitors, similar to topical vitamin D analogs, are a burning sensation and skin irritation. These side effects can be more pronounced in areas with severe inflammation, and applying topical corticosteroids first can help reduce the likelihood of these side effects **(Amiri et al., 2023)**.

3.7.1.4. Topical Keratolytics

Topical keratolytics such as tazarotene and salicylic acid, aid in the breakdown of thick scales on psoriasis plaques. Tazarotene, a retinoid, inhibits keratinocyte proliferation, while salicylic

acid reduces scaling. Adjusting the concentration, formulation, or frequency of application or combining them with topical corticosteroids can help minimize adverse effects such as burning and irritation **(Gold et al., 2018)**.

3.7.1.5. Targeted Phototherapy

Targeted phototherapy such as excimer light therapy, utilizes specific wavelengths of light to treat localized plaque psoriasis. It has a low potential for carcinogenicity and can lead to significant improvement after approximately two months of treatment. Adverse effects may include a burning sensation and blistering, which are preventable with an appropriate treatment schedule **(Fritz and Salavastru, 2018)**.

3.7.2. Treatments for Moderate-to-Severe Psoriasis

Moderate psoriasis is usually defined as psoriasis affecting from 3~5% to 10% of the BSA. Severe psoriasis is typically characterized by a BSA coverage of 10% or more. Systemic treatments are the primary approach for moderate-to-severe psoriasis, and these can also be used for localized disease or when topical therapies are ineffective. Both the U.S. and European guidelines recommend biologics, oral agents, and phototherapy in combination for these patients. Biologics have shown higher efficacy compared to oral medications or phototherapy. Topical therapies can be used as supplementary treatments but not as standalone therapy for moderate-to-severe psoriasis **(Lambert et al., 2020)**.

3.7.2.1. Phototherapy

Phototherapy, including narrowband ultraviolet (UV)-B, broadband UV-B, and psoralen ultraviolet light A (PUVA), has been used to treat moderate-to-severe psoriasis. Narrowband UV-B is preferred over the broadband form due to its higher effectiveness and better safety profile. UV-B phototherapy reduces DNA synthesis, leading to apoptosis of keratinocytes and decreased production of pro-inflammatory cytokines. Adverse effects may include erythema, pruritus, blistering, photoaging, and photocarcinogenesis. Narrowband UV-B is more commonly used due to its greater efficacy, longer remission duration, lower potential for skin cancer, and reduced erythema compared to broadband UV-B. Combining narrowband UV-B with systemic retinoids may enhance efficacy and reduce the potential for skin cancer **(Elmets et al., 2019)**.

The PUVA therapy involves the use of psoralens, such as methoxalen, to suppress DNA synthesis followed by UV-A irradiation. Although oral PUVA is more effective than UV-B, it is no longer preferred due to the increased risk of skin cancer with long-term use. Adverse effects may include gastrointestinal upset, burning, pruritus, hypertrichosis, and photoaging. Topical PUVA therapy is commonly used for palmoplantar psoriasis, involving soaking hands and feet in water with psoralen followed by UV-A irradiation. The main challenge with phototherapy is the need for patients to travel to undergo office-based sessions. Home phototherapy is a convenient option but may be limited by insurance and space constraints **(Lee and Kim, 2023)**.

3.7.2.2. Oral Systemic Treatments

Before the introduction of biologics, oral agents were commonly used to treat moderate-to-severe plaque psoriasis. The available oral treatment options for plaque psoriasis include methotrexate, apremilast, acitretin, and cyclosporine. Compared to biologics, the efficacy of oral treatments is generally low, except for that of cyclosporine. However, oral medications may still be considered for patients who have limited access to biologics or prefer non-injectable treatments. The adverse effect profiles differ significantly among the oral options, and careful consideration is necessary when selecting an oral agent due to various contraindications and precautions associated with them **(Menter et al., 2020)**.

3.7.2.3. Biological Treatment of Moderate-to-Severe Plaque Psoriasis

A. TNF-α Inhibitors

TNF-α inhibitors are a class of medications that target TNF-α, a cytokine involved in inflammation. Three commonly used TNF-α inhibitors are etanercept, infliximab, and adalimumab **(Figure 7)**. The response to TNF-α inhibitors is typically observed after 12 to 16 weeks of continuous treatment, except for infliximab, where response is experienced after 8 to 10 weeks. Their efficacies and long-term safety profiles have been demonstrated in moderate-to-severe psoriasis. However, many severe adverse events were reported, such as serious infections, reactivation of

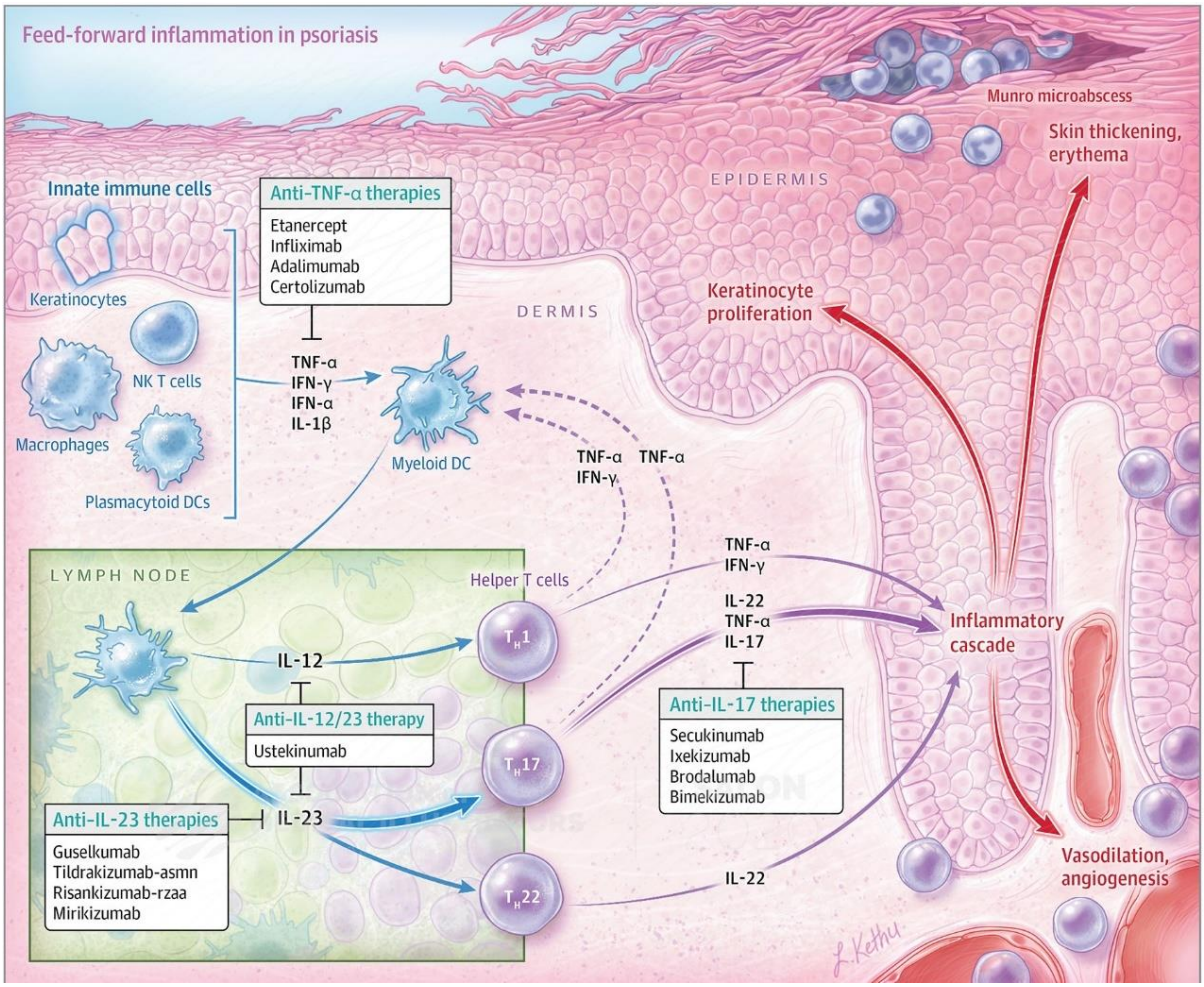

Figure 7. Pathophysiological cycle in psoriasis, therapeutic targets and drugs. The pathophysiology of psoriasis involves excessive feed-forward activation of the adaptive immune system. Activated myeloid dendritic cells secrete excess IL-12 and IL-23. IL-12 induces differentiation of naive T cells to T-helper cells type 1 (TH1). IL-23 is central to the survival and proliferation of TH17 and TH22 cells. TH17 cells (and a multitude of other inflammatory cells) secrete IL-17; TH1 cells secrete tumor necrosis factor α (TNF-α); and TH22 cells secrete IL-22. These secreted cytokines activate intracellular signal transduction in keratinocytes to bring about gene transcription of cytokines and chemokines. This results in an inflammatory cascade that leads to psoriatic disease manifestations. DC indicates dendritic cell; IFN, interferon; NK, natural killer **(Rendon and Schäkel, 2019)**.

hepatitis B and C, tuberculosis, drug-induced lupus, and demyelinating central nervous system disorders. TNF-α inhibitors may be beneficial for patients with a history of inflammatory bowel disease, and certain inhibitors are approved for its treatment **(Menter et al., 2017)**.

B. IL-23 Inhibitors

Ustekinumab, guselkumab, risankizumab, and tildrakizumab are effective IL23 inhibitors used in the treatment of psoriasis (Figure 7). Mirikizumab is for use in late-phase development. Ustekinumab is the only biologic that targets both IL-12 and IL-23 by inhibiting their shared p40 subunit **(Lee and Kim, 2023)**.

Other IL-23 inhibitors also demonstrate robust efficacy and convenient dosing regimens. Safety profiles are similarly acceptable, with no increased risk of serious infections or malignancies. Common side effects included nasopharyngitis, upper respiratory tract infection, headache, and fatigue **(Menter et al., 2019)**.

C. IL-17 Inhibitors

The IL-17 inhibitors target either the IL-17 ligand or its receptor. Secukinumab and ixekizumab inhibit IL-17A, while bimekizumab inhibits both IL-17A and IL-17F. Brodalumab targets IL-17 receptor α. IL-17 inhibitors have a rapid onset of action, strong response, and sustainable efficacy for plaque psoriasis **(Foulkes and Warren, 2019)**.

The IL-17 inhibitors are also approved for psoriatic arthritis. In addition, secukinumab and ixekizumab have been reported to be particularly effective in treating nail psoriasis. The safety profile of IL-17 inhibitors is acceptable, with no increased risk of serious infections or malignancy. However, mucocutaneous candidiasis and exacerbation of inflammatory bowel disease have been reported. Common adverse reactions include upper respiratory tract infections and injection site reactions **(Reich et al., 2017)**.

5. Conclusion

Psoriasis is a complex, chronic inflammatory skin disease characterized by a range of clinical manifestations, from mild, localized plaques to severe, widespread forms impacting a patient's quality of life and overall health. Understanding the different types of psoriasis and the underlying pathophysiological mechanisms has shed light on the pivotal role of immune dysregulation, particularly involving T cells and cytokines, in disease onset and progression. Severity in psoriasis varies widely and is influenced by genetic predispositions, immune factors, and environmental triggers, highlighting the importance of a tailored, patient-centered approach to management. While treatments have evolved substantially from topical agents to advanced biologics no universal cure exists, and response to treatment can vary significantly. Ongoing research continues to reveal new therapeutic targets and improve personalized treatment strategies, promising hope for better disease management, reduced symptoms, and improved quality of life for patients.

Conflict of interest

None of the authors have any conflicts of interest.

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