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The immunological role of certain cytokines in the inflammatory response to psoriasis and the relationship of the disease itself with the PSORS genes: a comprehensive review

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Abstract :

Psoriasis is a chronic inflammatory skin disease diagnosed with clearly defined scaly red plaques. It is a common skin disease that occurs in different areas of the body and is concentrated around the elbow, scalp and trunk, as well as on the knees. Psoriasis is associated with a number of comorbidities such as cardiovascular disease, metabolism and autoimmune diseases. Cytokine-targeting antibodies such as IL-23, IL-17A, and TNF-α, which are released by these cells, have shown promising results in treating psoriasis The occurrence of the disease is related to several factors, including genetic and environmental factors. Its genetic foundations have long been proven through studies of twins and family gatherings. Several studies have shown that psoriasis is associated with HAL genes and a correlation has been found at the allele site HLA-Cw6. In this review, psoriasis was defined, its different types were mentioned, and known genetic predispositions to the disease were described, in relation to immune genes and their specific pathways in susceptibility to psoriasis. These genes cover a range of functions, including antigen presentation (HLA-Cw6, ERAP1, ERAP2, MICA), cytokines IL17 and IL-23, development and polarization of T lymphocytes, the role of innate immunity as well as the contribution of some of these genetic products to psoriasis by targeting key immune components, such as the Th17/IL-23 axis, which has been highly successful in treating the disease. Unlike previous reviews, this work provides a comprehensive integration of PSORS gene variants with cytokine-mediated pathways, offering an updated immunogenetic perspective on psoriasis susceptibility.

Key words: Psoriasis, PSORS genes, Cytokines, IL17, IL23, HLA-Cw6.

الدور التآزري لجينات PSORS وبعض الحركيات الخلوية في الاستجابة المناعية والاستعداد الوراثي لداء الصدفية: مراجعة

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مستخلص:

الصدفية مرض جلدي التهابي مزمن، يُشخص بظهور لويحات حمراء متقشرة واضحة المعالم. وهو مرض جلدي شائع الحدوث حول الكوع وفروة الرأس والجذع، وكذلك على الركبتين. يرتبط الصدفية بعدد من الأمراض المصاحبة لأمراض القلب والأوعية الدموية، والأيض، والمناعة الذاتية. الصدفية اضطراب متعدد العوامل، يتأثر بالعوامل الوراثية والبيئية. وقد ثبتت أسسها الوراثية منذ فترة طويلة من خلال دراسات التوائم والتجمعات العائلية. وقد أظهرت العديد من الدراسات ارتباط الصدفية بأليل HLA-Cw6. في هذه المراجعة تم تعريف داء الصدفية وذكر انواعه المختلفة ووصف الاستعدادات الوراثية المعروفة لمرض الصدفية، وذلك فيما يتعلق بالجينات المناعية ومساراتها المحددة في قابلية الإصابة بالصدفية. وتغطي هذه الجينات مجموعةً من الوظائف، تشمل عرض المستضد (HLA-Cw6، ERAP1، ERAP2، MICA)، ومحور IL17/23، وتطور الخلايا التائية واستقطابها والمناعة الفطرية وكذلك مساهمة بعض هذه المنتجات الجينية في مرض الصدفية من خلال استهداف المكونات المناعية الرئيسية، مثل محور Th17/IL-23 الذي حقق نجاحًا كبيرًا في علاج المرض. على عكس المراجعات السابقة، يقدّم هذا العمل وصفا شاملاً لمتغيرات جينات PSORS مع المسارات المناعية الوسطية بالسايتوكينات، مما يوفر منظورًا محدّثًا حول الأسس المناعية–الوراثية لقابلية الإصابة بداء الصدفية.

الكلمات المفتاحية: داء الصدفية، جينات PSORS، الحركيات الخلوية، الجلد.

Introduction

Psoriasis is a chronic inflammatory skin disease, characterized by the appearance of elevated scaly red plaques (Joodi and AL-Saadi, 2024a). The disease affects about 2-3% of the world's population and is most prevalent in US, Canada and Europe (Dairov *et al*., 2024). Psoriasis affects both men and women, but is more common among non-Hispanic whites (Raharja *et al*., 2021). It is also associated with many comorbidities, suggesting that the underlying pathogen goes beyond just "skin". Psoriasis arises from chronic interactions between highly proliferating keratinocytes and active infiltrating immune cells (Saad *et al.*, 2024). The disease manifests itself in five main forms: plaque, guttate (or rash), inverse, pustular, and erythematosis. Certain external stimuli, such as wounds, stress, smoking, poor eating habits, certain medications, and alcohol intake, play an important role in the risk of developing infection (Liu *et al*., 2024). Cellular and molecular contributions to the hyperactive immune response interfere in psoriasis It has been found that T cells, especially Th1 and Th17, are densely present in psoriasis lesionsIn addition, inflammatory dendritic cells (TIP-DCs) producing TNFα HLA-Cw6 ability to attract other cytokines (Hu *et al*., 2021). Their activity leads to dermatitis and the activation and hyper-proliferation of keratinocytes. In addition, other cells and signaling pathways are involved in the pathogenesis of psoriasis, including Th9 cells, Th22 cells, CD8+ cytotoxic cells, neutrophils, γδ T cells, and cytokines and chymokines secreted by them (Sieminska *et al*., 2024). Psoriasis arises from the complex interaction of genetic and environmental factors, especially genetic predisposition in individuals carrying the risk allele HLA-C*06:02 (Li *et al*., 2025). Genetic factors in psoriasis are complex, with key susceptibility loci such as PSORS1 on chromosome 6p21.3 (HLA-Cw6 allele) and SNPs in genes like IL23R and TRAF3IP2 strongly linked to disease risk (Thamer and Yahya, 2022, Zalesak *et al.*, 2024). There is clear evidence of an important genetic factor in the etiology and development of psoriasis. On the other hand, the co-genetic effects

of psoriasis have been associated with a number of comorbidities. Although several genes associated with psoriasis risk has been identified (Babaie *et al*., 2022).

The genetic regions on chromosomes that carry psoriasis genes are called PSORS (psoriasis predisposition) sites. There are at least 12 different sites for PSORS, identified mainly through association analysis of multiple psoriasis families. However, the genes of most PSORS sites responsible for predisposition to infection have not been adequately studied. The dominant function of a large proportion of these genes is therefore associated with immune system diseases (Mateu-Arrom and Puig, 2023).

Several epidemiological studies have shown that the prevalence of psoriasis differs across populations. In Western countries such as Europe and North America, psoriasis affects approximately 2–3% of the population (Parisi *et al.*, 2020), whereas studies from the Middle East, including Iraq and Gulf countries, report lower prevalence rates ranging between 0.5–1.5% (Daou *et al.*, 2021, Albreiki *et al.*, 2025). Moreover, the associated risk factors also vary; in Western populations, smoking, obesity, and alcohol consumption are among the most significant contributors, while in Middle Eastern populations, psychosocial stress, bacterial infections, and environmental factors appear to play a more prominent role (Michalski *et al.*, 2023). This comparison highlights the epidemiological and environmental diversity of psoriasis between populations and provides a broader global and regional context for the disease.

In this review, psoriasis was defined, its different types were mentioned, and known genetic predispositions to the disease were described, in relation to immune genes and their specific pathways in susceptibility to psoriasis. This review uniquely focuses on the synergistic role of PSORS genes and cytokine signaling pathways in psoriasis pathogenesis, providing an updated insight into heir immunogenetic interaction.

2. Disease definition and classification

Psoriasis is a systemic inflammatory disease, pro-inflammatory cytokines (Joodi and AL-Saadi, 2024b), such as interleukin-23 (IL-23) and interleukin-17 (IL-17), and tumor necrosis factor alpha (TNF-α), play a crucial role in initiating psoriasis and psoriasis can trigger a variety of external and internal risk factors (Menter *et al*., 2021). Psoriasis vulgaris is the most common phenotype, affecting between 85% and 90% of psoriasis patients. The most common areas of infection include lesion of the extensor surfaces of the elbows and knees, the sacrum and scalp, although lesions can affect any part of the skin. Furthermore, growing evidence suggests that psoriasis patients, compared to the general population, have a higher prevalence of other chronic and serious diseases, including arthritis, metabolic diseases, diabetes, cardiovascular disease, high blood pressure, depression or anxiety, liver disease, Crohn's disease, lymphoma or other types of cancer. Therefore, psoriasis is classified into cutaneous psoriasis and systemic psoriasis (Yan *et al*., 2021).

2.1 Cutaneous psoriasis

Several subtypes of cutaneous psoriasis have been described. Their clinical presentation varies in severity, distribution, and systemic involvement ((Kimmel and Lebwohl, 2018). A concise description of each subtype is provided below, and the main features with prevalence are summarized in Table (1) for clarity.

2.1.1 Plaque psoriasis (Psoriasis vulgaris):

This is the most common type, accounting for about 85–90% of cases. It presents as well-defined erythematous plaques with silvery scales, most often affecting the scalp, trunk, elbows, and knees (Gisondi *et al.*, 2020).

2.1.2 Guttate psoriasis: Characterized by small, drop-like papules that appear suddenly, usually after streptococcal infections. It is more common in children and adolescents, and up to one-third of cases may evolve into chronic plaque psoriasis (Leung *et al*., 2023).

2.1.3 Pustular psoriasis: Presents with sterile pustules on an erythem-

atous base. It can be localized (commonly on palms and soles) or generalized, the latter being more severe and sometimes associated with systemic symptoms (Rivera-Diaz *et al*., 2023).

2.1.4 Palmoplantar pustulosis: A chronic and recurrent form localized to the palms and soles. It is often resistant to treatment and follows a relapsing course (Freitas *et al*., 2020).

2.1.5 Erythrodermic psoriasis: A rare and severe form that affects more than 90% of the body surface area, associated with systemic complications such as fever, infection risk, and fluid imbalance (Yan *et al*., 2021).

2.1.6 Inverse psoriasis: Occurs in skin folds (axilla, groin, inframammary areas), presenting as shiny, smooth, red patches that are often misdiagnosed due to the absence of scaling (Nguyen *et al.,* 2022).

Table 1. Summary of psoriasis subtypes, clinical features, and prevalence.

Subtype	Key Clinical Features	Prevalence / Notes
Plaque psoriasis (Psoriasis vulgaris)	Most common form (≈85–90% of cases); well-defined erythematous plaques with silvery scales, mainly on scalp, trunk, elbows, and knees.	Most frequent worldwide.
Guttate psoriasis	Small drop-like scaly papules (0.3–0.5 cm); often triggered by streptococcal infections; common in children/adolescents.	~30% may progress to chronic plaque psoriasis.
Pustular psoriasis	Sterile pustules on erythematous base; can be localized (palms/soles) or generalized.	Rare but severe.
Generalized pustular psoriasis (GPP)	Widespread pustules, systemic symptoms (fever, malaise, risk of organ failure).	Life-threatening if untreated.
Palmoplantar pustulosis	Recurrent pustules on palms/soles; resistant to treatment; chronic course.	Rare, chronic.
Erythrodermic psoriasis	Generalized erythema (>90% BSA), scaling, systemic complications (fever, infection risk).	Very rare (<2% of cases), severe.
Inverse psoriasis	Smooth, shiny red patches in skin folds (axilla, groin, under breasts).	Commonly coexists with other types.

2.2 Systemic psoriasis

In addition to psoriasis lesions, other systemic diseases may appear first, either simultaneously or sequentially. Evidence suggests that psoriasis is an important systemic inflammatory disease, the symptoms of which are shared with other chronic inflammatory diseases. After treatment, psoriasis lesions improve, and systemic symptoms generally improve (Tashiro and Sawada, 2022).

2.2.1 Psoriatic arthritis

Psoriatic arthritis develops in approximately 30% of psoriasis patients. In addition to psoriatic lesions, psoriatic arthritis can affect any joint in the body, from large joints such as the elbow and knees, to small joints such as the fingers, toes, spine and sacroiliac joints. This disease develops gradually, and may cause swelling and pain in the affected joints, resulting in oligoarticular or polyarticular arthritis, limiting movement, and leading to joint damage and deformation in severe cases. It is important to note that the blood test for rheumatoid factor is often negative. Characteristic features of psoriatic arthritis on X-rays include swelling of soft tissues, varying degrees of joint wear, narrowing of the joint space, bone proliferation, including periarticular periarthrosis and trunk inflammation, as well as osteolysis. Up to 90% of psoriatic arthritis patients suffer from nail psoriasis (Crespo-Rodríguez *et al*., 2021). Psoriatic arthritis can be divided into several subtypes: distal subtype (damage to the proximalous and distal phalangeal joints of the hands and feet), oligoarthritis (arthritis affecting up to four joints), polyarticular arthritis (arthritis affecting five or more joints), deformal arthritis (absorption and shortening of finger bones), axial/ankylosing spondylitis, osteitis, and inflammation of the fingers (Krakowski *et al*., 2019).

2.2.2 Psoriasis with metabolic syndrome

Moderate to severe psoriasis is often associated with metabolic disorders, especially metabolic disease syndrome. Metabolic syndrome may combine several interrelated metabolic disorders, including obesity, insulin resistance, blood sugar disorder, atherosclerosis lipidemia, hypertension, lung disease, hepatitis, iris, lupus ery-

thematosus, and cancer (Mustață *et al*., 2024).

2.4 Components of autoimmune psoriasis

Immunogenesis is triggered by circulating inflammatory cytokines, including tumor necrosis factor (TNF-α), interleukin (IL-17) and interferon (IFN) types 1 and 2, including IFNα/β and IFNγ. These cytokines are produced by T helper (Th) cells and activated dendrites (DCs) that infiltrate the skin and remain as memory T cells in the affected skin (Hawkes *et al*., 2017), supporting this psoriasis lesion frequently recur in the same anatomical area. Increased regulation of these molecular pathways stimulates keratinocyte hyperproliferation and inflammation caused by T cells. This important inflammatory burden plays an important role in increasing the risk of multiple concomitant inflammatory diseases (Menter *et al*., 2021).

2.4.1 Cytokines

Cytokines are intracellular signaling proteins. This term generally includes interleukins (ILs), interferons, and growth factors, such as tumor necrosis factor alpha (TNF-α), which are typically polypeptides or glycoproteins with relatively small molecular weights (usually between 6 to 70 kDa), regulating the function, differentiation, and proliferation of target cells, apoptosis, and survival (Yi *et al*., 2024). In the complex immune system, inflammatory cytokines and their receptors form a comprehensive regulatory framework that can exert a significant influence on the onset and progression of disease. Thus, inflammatory factors can form an essential part of diagnosis, prediction and treatment in autoimmune diseases (Bhol *et al*., 2024). Abnormal cutaneous and systemic expression of adipokines and cytokines may affect the activation, proliferation and differentiation of keratinocytes, as well as immune cells that contribute to the development of psoriatic lesions (Sabri and Ibraheem, 2023). Although the majority of inflammatory agents produced by adipose tissue and keratinocytes remain in the tissues, a small percentage of these biomarkers can also be identified in the systemic circulation (Zhou *et al*., 2022). T cells, along with innate immune cells, produce a key effect, IL-17, which in turn stimulates epidermal

modulation. The emergence of a detailed concept of pathogens in the past decade has promoted the development of targeted therapies. Thus, therapies have moved from immunosuppression in general to interference with T cells and the IL-23/IL-17 pathway, and now to later acting molecules such as IL-17 and its cellular targets (Chi *et al*., 2024).

2.4.2 IL-17 and IL-23

The IL-17 and IL-23 pathways are key in psoriasis (Figure 1). TNF-α is the target of four approved psoriasis therapies and plays an indirect role in the pathogenesis of disease by enhancing the adaptive immune effects of the IL-23/IL-17 axis. The role of IL-23 in the onset and persistence of psoriasis is attributed to its effect on IL-17, a key cytokine that affects future inflammatory cycles that perpetuate inflammation. These signaling episodes represent the hallmarks of innate immune responses in inflammatory and infectious diseases associated with rashes, fever, arthritis, dermatitis, bone disease, and central nervous system damage (Chiricozzi et al., 2018). IL-17 more directly affects the distribution and activation of dendritic cells than TNF-α; however, the synergy between IL-17A and TNF-α modifies keratinocyte gene responses in psoriatic lesions (Furue *et al.*, 2020). This reaction is amplified by IL-17C, the most abundantly expressed isoform of IL-17 in psoriatic lesions. While IL-17A is mainly secreted by Th17 cells and acts as a key driver of keratinocyte activation and immune cell recruitment, IL-17C is produced predominantly by keratinocytes and functions in an autocrine/paracrine loop to amplify local inflammation. This distinction indicates that IL-17A serves as a central effector cytokine, whereas IL-17C acts as a keratinocyte-derived amplifier of psoriatic lesions (Vidal *et al.*, 2021).

In mammals, IL-17 consists of six homologues that are considered to be homologous diodes. Th17 cells produce IL-17 interleukin in response to stimulation of IL-23 and other cytokines. In addition to Th17 cells, innate lymphocytes (ILCs), mast cells, neutrophils, and γδ T cells may be independent sources of IL-17A production in patients with psoriasis. IL-17A is released from neutrophils and mast

cells during immunomediated specialized cell death, where proteins bind to chromatin filaments to form extracellular traps (Huangfu *et al*., 2023). In response to increased expression of IL-17A, cells with high concentrations of IL-17 receptors release antimicrobial chemokines, cytokines, and antimicrobial peptides that stimulate inflammation. The effects of immunocytokines as transcription activators of keratinocyte gene products, and autoantigen stimulation of T cell responses, create frontal feeding inflammatory circuits that perpetuate T cell activation and psoriasis-related inflammation (McGeachy *et al*., 2019). Keratinocyte stimulation by IL-17A stimulates the production of C–C motif 20 chemokine bind, while other chemical attractions recruit CCR6+ T cells, including T cells that produced IL-17 (T17), mature myelodendritic cells, and other inflammatory cells. This creates a cycle of ongoing inflammatory responses. IL-17A also stimulates keratinocytes to produce IL-19, leading to increased keratinocyte proliferation (Furue *et al*., 2020). Besides skin psoriasis, IL-17 is also involved in other immune-related diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, uveitis, Crohn's disease, multiple sclerosis, and asthma (de Morales *et al*., 2020). IL-23 is a dichotogeneous asymmetric cytokine that shares a common subunit of p40 with IL-12 and a common subunit of p19 with IL-23 and IL-39. Gene expression of p40 and p19 units of IL-23 increases in psoriasis plaques, and differences in genes that code p19 and its receptors are associated with an increased risk of psoriasis. Interleukin-23 is produced by many types of cells, including dermal dendritic myeloid cells, phagocytes, and human Langerhans cells (Floss *et al*., 2020). This interleukin is regulated by toll-like receptor signaling and is enhanced by tumor necrosis factor alpha (TNF-α), gamma interferon (IFN-γ) and transcription factors. The interleukin-23 receptor (IL-23R) is expressed on memory T cells, natural killer cells, neutrophils, mast cells, endogenous lymphocytes (ILCs), and phagocytes. The binding of interleukin-23 to its similar receptor forms a compound of interleukin-23/interleukin-23R, which stimulates the differentiation of endogenous lympho-

cytes (ILCs), and stimulates CD4+, CD8+ and γδ T cells to synthesize interleukin-17 and other pro-inflammatory cytokines (Mezghiche *et al*., 2024 IL-23 induces phagocytes to produce TNF-α, promotes keratinocyte proliferation… and enhances IL-23R expression (Menter *et al*., 2021).

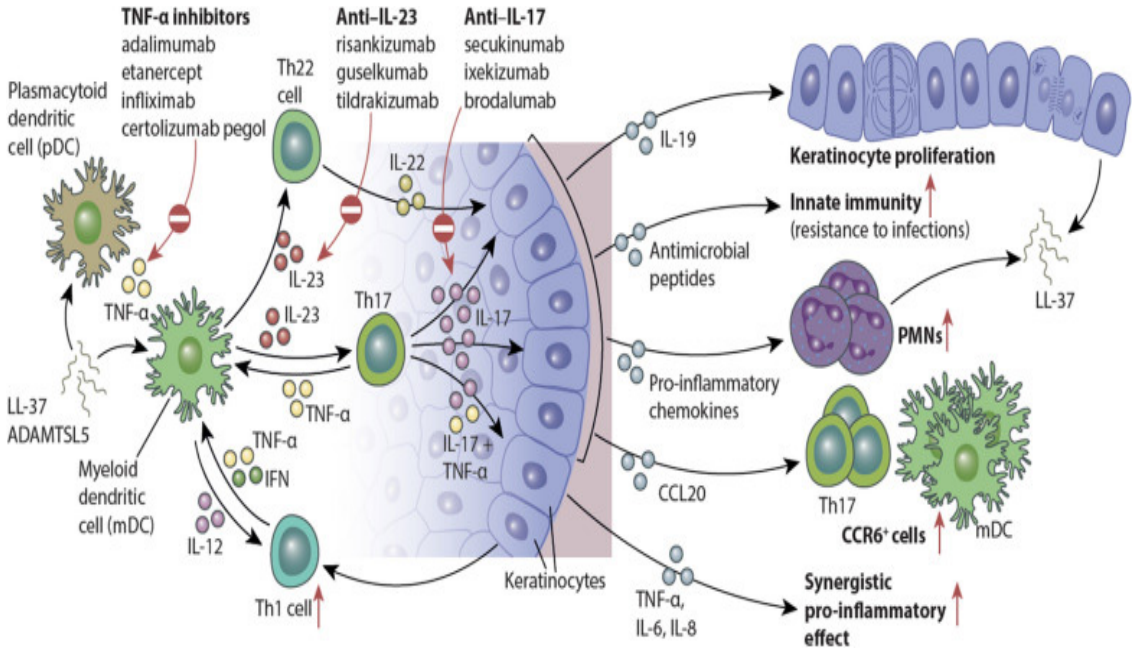

Figure 1. Effects induced by the IL-23/IL-17 axis on human keratinocytes in psoriasis skin (Menter *et al*., 2021).

2.4.3 T cell polarization

The crucial role of T cells in psoriasis was initially discovered by observing improvement of the disease when general T cell inhibition agents were used. Conventional T cells, such as CD4+ helper T cells and CD8+ cytotoxic T cells, recognize peptide antigens presented by MHC molecules. CD4+ helper T cells can be polarized into distinct subsets depending on the immune context. Initially, T cells were classified into Th1 and Th2, but current research has expanded this classification to include additional subsets such as Th17, Th22, Th9, and regulatory T cells (Zhang *et al*., 2023).

Among these, Th1, Th17, and Th22 cells are especially relevant in psoriasis. Th1 cells produce IFN-γ and

TNF-α, which contribute to keratinocyte activation and recruitment of inflammatory cells. Th17 cells secrete IL-17A, IL-17F, and IL-22, making them central drivers of keratinocyte proliferation, neutrophil infiltration, and sustained inflammation (Hasan *et al.*, 2021). Th22 cells mainly release IL-22 and TNF-α, which further enhance keratinocyte hyperproliferation and epidermal thickening. This coordinated T-cell activity amplifies the inflammatory cycle characteristic of psoriatic lesions (Zalesak *et al.*, 2024).

To avoid redundancy, overlapping descriptions of T-cell subsets have been streamlined. A comparative diagram (Figure 2) has also been included to illustrate the distinct cytokine profiles of Th1, Th17, and Th22 cells and their immunological roles in psoriasis, thereby improving clarity (Shin *et al.*, 2023).

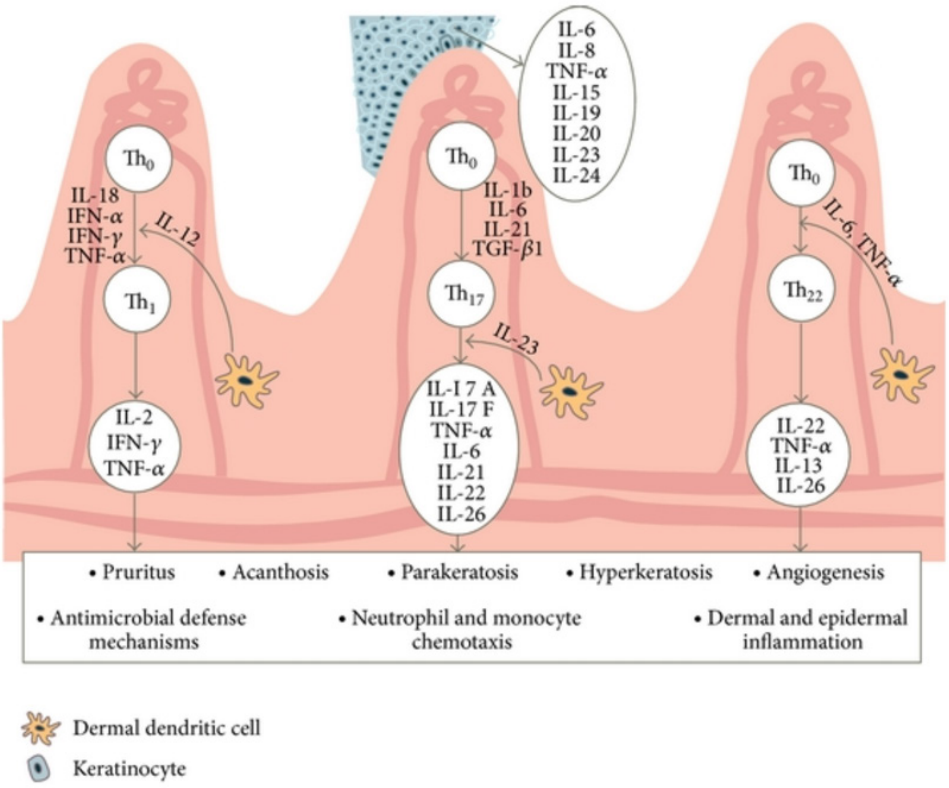

Figure 2: Th1, Th17, and Th22 cytokines in the pathogenesis of psoriasis (Michalak-Stoma *et al.*, 2013).

2.4.2 Innate immunity

In psoriasis, an intense cross-reaction occurs between innate immune cells (such as dendritic cells, phagocytes, neutrophils), adaptive immune cells (B and T cells), and resident skin cells (e.g. keratinocytes, melanocytes, and endothelial cells). These reactions appear to amplify and perpetuate chronic inflammation (Grän *et al*., 2020). Many genes in the NF-κB pathway are associated with psoriasis. NF-κB is a key transcription factor in immune responses and plays an important role in almost all types of immune cells. NF-κB is preserved in the cytoplasm of the cell, bound to its IκB inhibitor. Many cellular receptors for immune signals include innate immune pattern recognition receptors and cytokine receptors, such as TNFα. When NF-κB signaling is initiated, IκB is phosphorylated by IκB kinase (IKK) and then targeted for proteolysis. IκB releases NF-κB to move to the nucleus, thereby stimulating inflammatory gene expression (Yoshinaga and Takeuchi, 2019). NF-κB is a two-unit transcription factor, which can consist of combinations of several different subunits, namely p50, p52, RelA (p65), c-Rel, and Rel-B. The expression of different subunits varies depending on the type of cell. The NF-κB pathway is known to be active in psoriasis skin, and decreases with successful treatment. Single nucleotide polymorphisms (SNPs) within the region containing an NF-κB component gene, c-Rel, are associated with a predisposition to psoriasis. C-Rel can also regulate keratinocyte growth and directly advance the cell cycle (Msweli *et al*., 2024). Single nucleotide polymorphism (SNP) in TRAF3IP2 (TRAF3 reaction protein 2, also known as Act1) is also associated with psoriasis. The TRAF3IP2 interacts with TRAF6, which is important for activating NF-κB after IL-17 receiver signals. It is also an important TRAF3IP2 for the production of CCL20 of keratinocytes in response to IL-17. A change in TRAF3IP2 coding is associated with both common psoriasis and psoriatic arthritis. This is likely to lead to increased NF-κB activation and increased production of inflammatory products (Harden *et al*., 2015) (Figure 3).

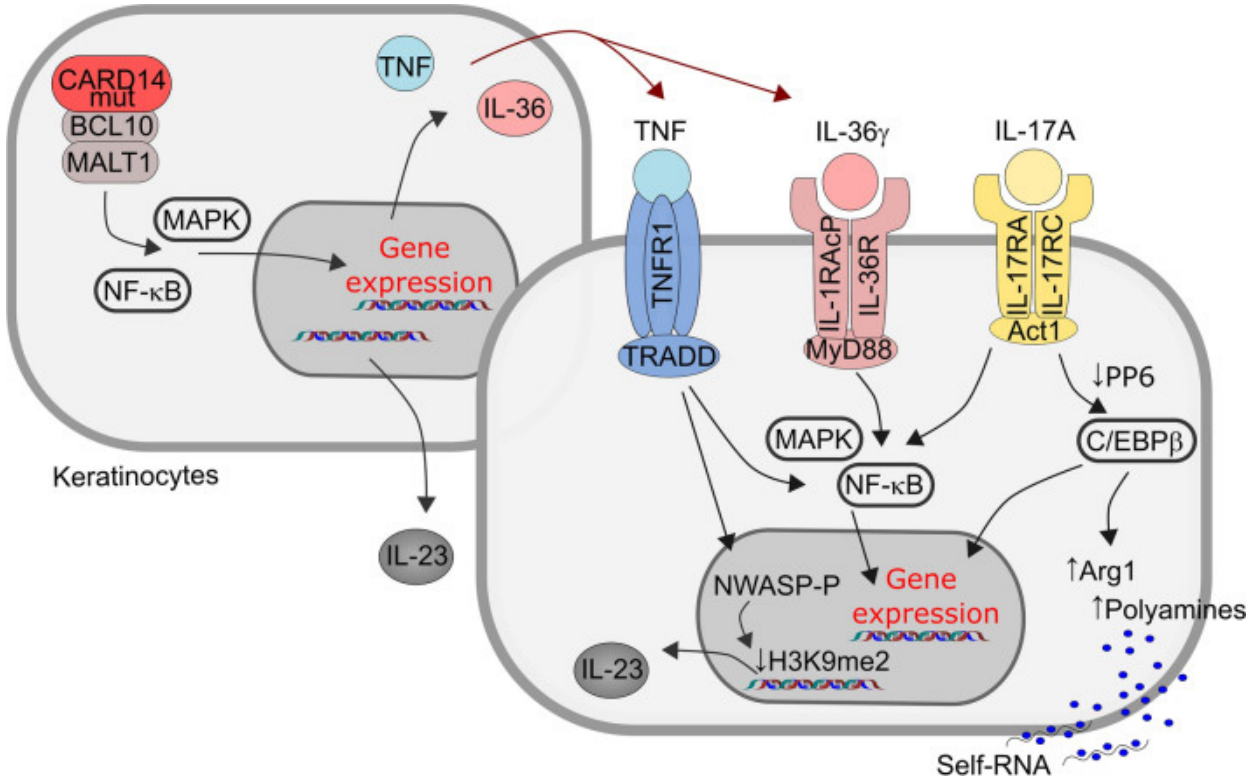

Figure 3: Major inflammatory signaling pathways in psoriasis-causing keratinocytes (Afonina *et al.*, 2021).

CARD proteins are important supporting proteins in NF-κB activation and CARD proteins are characterized by a specific cellular distribution, with CARD9 found mainly in myeloid cells, CARD10 in non-hematopoietic cells, and CARD11 in hematopoietic cells. CARD14 has been described as the gene that causes PSORS2 syndrome. In this case, rare mutations with a high-penetration dominant effect, with a functional acquisition, lead to psoriasis with or without psoriatic arthritis. A new mutation in CARD14 has led to general pustular psoriasis (Sundberg *et al.*, 2019). Since the hallmark of psoriasis is the proliferation and differentiation of keratinocytes, one of the genes that increase psoriasis activity is the CARD14 gene, which is abundantly expressed in keratinocytes found in the skin epidermis, and encodes the nuclear factor activator NF-kB. Although CARD14 is expressed in placental tis-

sue and mucous membranes, it was later found to be expressed mainly in mucosal tissues and keratinocytes. Psoriasis-related mutations in CARD14 lead to increased NF-κB signaling, producing numerous inflammatory cytokines and chymokines in both keratinocytes and endothelial cells. This suggests that CARD14 mutations increase the ability of both keratinocytes and endothelial cells to recruit and activate immune cells. CARD14 is one of only two genes in which a rare mutation can independently lead to psoriasis; the other gene, IL36RN, mutates in pustular psoriasis (Singh *et al*., 2024).

2.5 Psoriasis pathogenesis

It is clear from the above that both the adaptive and innate immune systems play an important role in causing psoriasis. The different cell types observed in psoriasis lesions include keratinocytes (KC), dendrites (DC), monocytes, phagocytes, and T and B lymphocytes. Several studies have supported the relationship of T cells to psoriasis. These studies suggest that inhibition of T cells, either using cyclosporine, T-cell immunosuppressant, or other biological material, such as CD4 antibodies, leads to an improvement in psoriasis suppurations (Singh *et al*., 2024; Schön, 2019).

Psoriatic lesions contain different subsets of T cells, including T-helper cells type 1 (Th1), cytotoxic T cells (T) and type 17 T cells. Research confirms the crucial role of T cells in psoriasis, suggesting that different types of T cells are found at different anatomical sites of the affected skin – with type 1 (Th1) and type 17 cells being found mainly in the upper dermis, while type 2 T (T) cells are mainly found in the epidermis. The main influencers of the innate immune response involved in the pathogenesis of psoriasis include: phagocytes, natural killer T cells (KC), dendritic cells, mast cells, neutrophils, natural killer (NK) cells, and natural killer T cells (NKT) (Sieminska *et al*., 2024). Various innate cytokines, such as IL-12, IFN-γ, IL-17, Il-23, IL-6, IL-8, and TNF-α, play an important role in causing psoriasis by recruiting pro-inflammatory cells into psoriasis lesions (Al-Naqqash *et al.*, 2021). It has also been suggested that signals from pathogen recognition receptors, such as TLR3, -4, -7 and -9, may create

an inflammatory environment in which autoantigen-specific T cells are active. This may promote the development of psoriasis (Sabri and Ibraheem, 2024).

2.6 PSORS genes and their relationship to psoriasis

Genetic studies have identified multiple chromosomal loci predisposing individuals to psoriasis, collectively termed PSORS (Psoriasis Susceptibility Regions). These loci encompass a variety of immune-related genes that regulate antigen presentation, cytokine signaling, and keratinocyte differentiation. The strongest association has been observed at PSORS1, located on chromosome 6p21.3, within the major histocompatibility complex (MHC) region. This locus, particularly the HLA-Cw6 allele, represents the most significant genetic determinant of psoriasis susceptibility (Ikeda *et al.*, 2023). Additional PSORS regions, including PSORS2, PSORS4, and others distributed across various chromosomes, harbor genes implicated in immune activation, epidermal barrier maintenance, and inflammatory signaling (Puig *et al.*, 2014). A concise summary of these loci and their corresponding candidate genes is provided in Table (2).

2.6.1 *PSORS1* Gene

The PSORS1 locus, located within the MHC region on chromosome 6p21.3, accounts for the majority of the genetic contribution to psoriasis (Owczarek, 2022). The HLA-Cw6 allele is the most consistently associated variant, present in up to 50% of psoriasis cases depending on population background. This allele encodes a class I MHC molecule that presents autoantigens to CD8+ T cells, contributing to the activation of psoriatic immune pathways (Harden *et al.*, 2015).

Other genes located within or linked to the PSORS1 region—such as *ERAP1, ERAP2*, *CCHCR1*, *CDSN*, and MICA-interact with HLA-Cw6 to influence antigen processing, immune activation, and keratinocyte function. These combined effects reinforce the pivotal role of antigen presentation and immune regulation in psoriasis pathogenesis (Capon, 2017).

2.6.2 Other PSORS Genes

Beyond PSORS1, several additional susceptibility loci contribute to psoriasis risk through immune or epidermal mechanisms: PSORS2 (17q24–q25)

involves mutations in the CARD14 gene, which enhances NF-κB activation in keratinocytes and leads to inflammatory cytokine overproduction. PSORS3 (4q) and PSORS7 (1p) include genes such as *IRF2*, *PTPN22*, and *IL-23R*, known to regulate immune signaling and cytokine responses (Puig *et al.*, 2014).

PSORS4 (1q21.3) resides within the Epidermal Differentiation Complex (EDC), containing over 60 genes vital for skin barrier integrity, including *LCE3B* and *LCE3C*, whose deletion weakens epidermal defense mechanisms. Other loch, such as *PSORS5* (3q21), *PSORS6* (19p), *PSORS8* (16q), and *PSORS9* (4q28-32), harbor genes linked to keratinocyte differentiation, cytokine activity, and inflammation modulation (Chandran, 2010). Collectively, these loci highlight the multifactorial genetic architecture of psoriasis, integrating immune dysregulation and epidermal barrier dysfunction.

2.6.3 Single Nucleotide Polymorphisms (SNPs) Associated with Psoriasis

Genome-wide association studies (GWAS) and immunochip analyses have identified over 60 SNPs linked to psoriasis susceptibility (Owczarek, 2022). Many of these variants are located in genes associated with the IL-23/IL-17 axis, including IL12B, IL23A, IL23R, and TRAF3IP2, which play a central role in promoting chronic inflammation and keratinocyte proliferation. Additional polymorphisms within the MHC class I region (e.g., rs2507971, rs9260313, rs66609536, rs380924) further emphasize the immunogenetic complexity of psoriasis (Suleiman *et al.,* 2019).

Table 2. Summary of PSORS loci, chromosomal positions, associated genes, and main functions

PSORS Locus	Chromosome Position	Key Associated Genes	Main Functions / Pathways
PSORS1	6p21.3	*HLA-Cw6, CCHCR1, CDSN, ERAP1, ERAP2, MICA*	Antigen presentation; peptide processing for MHC-I; immune activation of CD8+ T cells.
PSORS2	17q24–q25	*CARD14, RUNX1, RAPTOR*	NF-κB signaling; keratinocyte activation; immune synapse regulation.
PSORS3	4q	*IRF2*	Interferon regulatory factor; antiviral and inflammatory immune response.
PSORS4	1q21.3	*LCE3B, LCE3C, Filaggrin, S100 genes*	Epidermal differentiation and skin barrier integrity.
PSORS5	3q21	*SLC12A8, Cystatin A, ZNF148*	Keratinocyte ion transport and skin homeostasis.
PSORS6	19p	*JunB*	Transcription regulation of inflammatory and cell proliferation genes.
PSORS7	1p	*PTPN22, IL23R*	Cytokine signaling; Th17/IL-23 pathway regulation.
PSORS8	16q	*CX3CL1, CX3CR1, NOD2/CARD15*	Chemokine signaling; innate immunity.
PSORS9	4q28–32	*IL15*	T-cell activation and cytokine-mediated inflammation.
PSORS10	18p11	*Unknown / candidate genes*	Possibly linked to immune regulation and keratinocyte proliferation.

2.7 Possible therapeutic interactions for psoriasis based on genetic and immunological patterns

Recent therapeutic advances in psoriasis have introduced a diverse range of targeted agents. Biologics primarily act by blocking specific cytokines such as TNF-α, IL-17, or IL-23, whereas small-molecule drugs interfere with intracellular signaling pathways, including PDE4 and JAK kinases (Wu *et al.,* 2023 Al-Thwani, 2021; Ferrara *et al*., 2024). Table (3) summarizes key differences between these drug classes, highlighting their mechanisms, administration routes, and clinical consideration.

Table 3. Comparison between Biologic and Small-Molecule Therapies Used in Psoriasis Treatment

Drug Class	Examples	Target / Mechanism of Action	Administration Route	Therapeutic Advantages	Limitations / Adverse Effects
TNF-α Inhibitors	Infliximab, Adalimumab, Etanercept	Neutralize TNF-α, reducing systemic inflammation	Intravenous or subcutaneous	Long clinical experience; effective for skin and joint symptoms	Risk of infection (e.g., TB, hepatitis); loss of efficacy over time
IL-17 Inhibitors	Secukinumab, Ixekizumab, Brodalumab	Block IL-17A or IL-17 receptor to suppress keratinocyte activation	Subcutaneous	Rapid onset; high efficacy for plaque psoriasis	May worsen IBD; injection-site reactions
IL-23 Inhibitors	Guselkumab, Tildrakizumab, Risankizumab	Inhibit IL-23 p19 subunit, reducing Th17 cell activation	Subcutaneous	Durable remission; less frequent dosing	High cost; delayed onset compared to IL-17 blockers
Small-Molecule PDE4 Inhibitors	Apremilast	Inhibits phosphodiesterase-4 → decreases proinflammatory cytokine release	Oral	Convenient oral use; suitable for mild–moderate psoriasis	Nausea, diarrhea, weight loss; lower efficacy than biologics
JAK Inhibitors (Emerging)	Tofacitinib, Deucravacitinib	Block Janus kinase signaling involved in cytokine-mediated inflammation	Oral	Promising for resistant cases; systemic immune modulation	Risk of infections, lipid elevation, cardiovascular events

Overall, biologic agents have demonstrated superior efficacy and durability, whereas small-molecule therapies offer the advantages of oral administration and broader accessibility

Conclusions

Psoriasis is a multifactorial autoimmune disease with significant genetic and immune contributions, although we are increasingly aware of the mechanism of the disease and the identification of genetic risk factors predisposing to it, which are single nucleotide polymorphism (SNPs). In addition, many of these immune genetic associations are shared with other autoimmune diseases, including PSORS genes. Genetic variants associated with a particular disorder have the ability to highlight genes or pathways that may contain reliable drug treatment targets. This is clearly seen in the IL-17/IL-23 axis and Th-17 cells, where biological drugs targeting IL-17 have shown strong efficacy.

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