Mechanisms and Etiopathogenesis of Psoriasis: An Integrative Review

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ABSTRACT

Background: Psoriasis is a chronic, immune-mediated inflammatory skin disease with systemic manifestations, affecting approximately 2–3% of the global population. It presents with well-demarcated, erythematous, scaly plaques that follow a relapsing-remitting course. While traditionally viewed as a dermatologic condition, psoriasis is now recognized as a systemic disorder with potential involvement of the joints (psoriatic arthritis), cardiovascular system, and metabolic pathways. The etiopathogenesis of psoriasis is multifactorial, involving a dynamic interplay between genetic susceptibility, environmental triggers, and immune dysregulation. Genome-wide association studies have identified numerous susceptibility loci, notably the HLA-C*06:02 allele and genes involved in IL-23/Th17 signaling. Epigenetic alterations, including DNA methylation changes and dysregulated microRNAs, further influence disease expression. Environmental factors—such as infections, trauma (Koebner phenomenon), stress, obesity, and certain medications—can trigger disease onset or exacerbate flares. Immunologically, the disease is driven by activated dendritic cells and T-helper cells (especially Th1 and Th17 subsets), which release proinflammatory cytokines including IL-17, IL-23, TNF-α, and IFN-γ. These cytokines stimulate keratinocyte hyperproliferation, abnormal differentiation, and promote angiogenesis and immune cell recruitment. Histopathology reveals acanthosis, parakeratosis, elongated rete ridges, and Munro microabscesses. Psoriasis is associated with a range of comorbidities, including psoriatic arthritis, metabolic syndrome, cardiovascular disease, and psychological disorders, reflecting systemic inflammation mediated by shared cytokine networks. Targeted therapies have emerged based on pathogenic insights. Biologics directed against TNF-α, IL-17, and IL-23 have transformed disease management, while small molecule inhibitors (e.g., JAK inhibitors) offer additional options. Personalized medicine approaches using genetic and immunologic profiling are evolving to optimize therapy selection and improve outcomes.

Conclusion: Understanding the complex mechanisms and systemic nature of psoriasis is critical for accurate diagnosis, effective management, and holistic patient care.

Keywords: Psoriasis, Mechanisms, etiopathogenesis

1. INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects both the skin and, in some cases, the joints. It is characterized by well-demarcated, erythematous plaques covered with silvery-white scales, most commonly seen on the scalp, elbows, knees, and lower back. The disease follows a relapsing-remitting course, with episodes of flare-ups and periods of remission. Psoriasis is more than just a skin condition—it is increasingly recognized as a systemic disease with potential involvement of joints (psoriatic arthritis), cardiovascular risk, and metabolic syndrome [1].

Psoriasis affects approximately 2–3% of the global population, with variations based on ethnicity and geographic location. It has a strong genetic component, and about one-third of patients report a positive family history. Environmental factors such as infections (e.g., streptococcal pharyngitis), stress, skin injury (Koebner phenomenon), smoking, obesity, and certain medications (like beta-blockers and lithium) are known to trigger or exacerbate the disease. The age of onset usually follows a bimodal distribution: early-onset (before 40 years) and late-onset (after 40 years), with early-onset being more common and often more severe [2].

The hallmark of psoriasis is the presence of red, raised, scaly plaques, which may vary in size and distribution. Lesions typically exhibit symmetrical patterns and are often pruritic. The Auspitz sign—pinpoint bleeding when scales are removed—is characteristic. Nail involvement is common and may manifest as pitting, onycholysis, or subungual hyperkeratosis. In about 20–30% of patients, psoriasis extends to the joints, resulting in psoriatic arthritis, a condition marked by joint pain, stiffness, and swelling [3].

The pathogenesis of psoriasis involves a complex interplay between genetic predisposition, environmental triggers, and immune dysregulation. Central to the disease is the activation of dendritic cells, which stimulate T-helper cells (especially Th17 and Th1 subsets). These cells release proinflammatory cytokines such as IL-17, IL-23, TNF-α, and interferon-γ, which drive keratinocyte proliferation and sustain chronic inflammation. Keratinocytes, in turn, produce antimicrobial peptides and cytokines, perpetuating the inflammatory loop. Angiogenesis and alterations in the extracellular matrix further contribute to lesion development [4].

Psoriasis manifests in various clinical forms. The most common is plaque psoriasis (psoriasis vulgaris), accounting for over 90% of cases. Other types include guttate psoriasis, often seen in children following streptococcal infection; inverse psoriasis, affecting body folds; pustular psoriasis, characterized by sterile pustules; and erythrodermic psoriasis, a severe, potentially life-threatening form involving widespread erythema and desquamation. Psoriatic arthritis is a distinct clinical entity with musculoskeletal involvement and may occur with or without visible skin lesions [5].

Psoriasis is primarily diagnosed clinically based on characteristic skin lesions and distribution. Dermoscopy and skin biopsy may aid diagnosis in atypical cases. Histologically, psoriasis shows parakeratosis, acanthosis, elongation of rete ridges, Munro's microabscesses, and a diminished granular layer. Severity is assessed using standardized tools such as the Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA) involvement, and the Physician’s Global Assessment (PGA). Nail and joint involvement are also evaluated for comprehensive disease management [6].

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by keratinocyte hyperproliferation, abnormal differentiation, angiogenesis, and immune cell infiltration, primarily involving the IL-23/IL-17 axis [1]. Genetic predisposition, environmental triggers, and immune

dysregulation contribute to disease development and progression [2]. The interaction between T-helper 17 (Th17) cells, dendritic cells, and keratinocytes results in a self-sustaining cycle of inflammation, with IL-17, IL-22, and TNF-α playing critical roles [3,4].

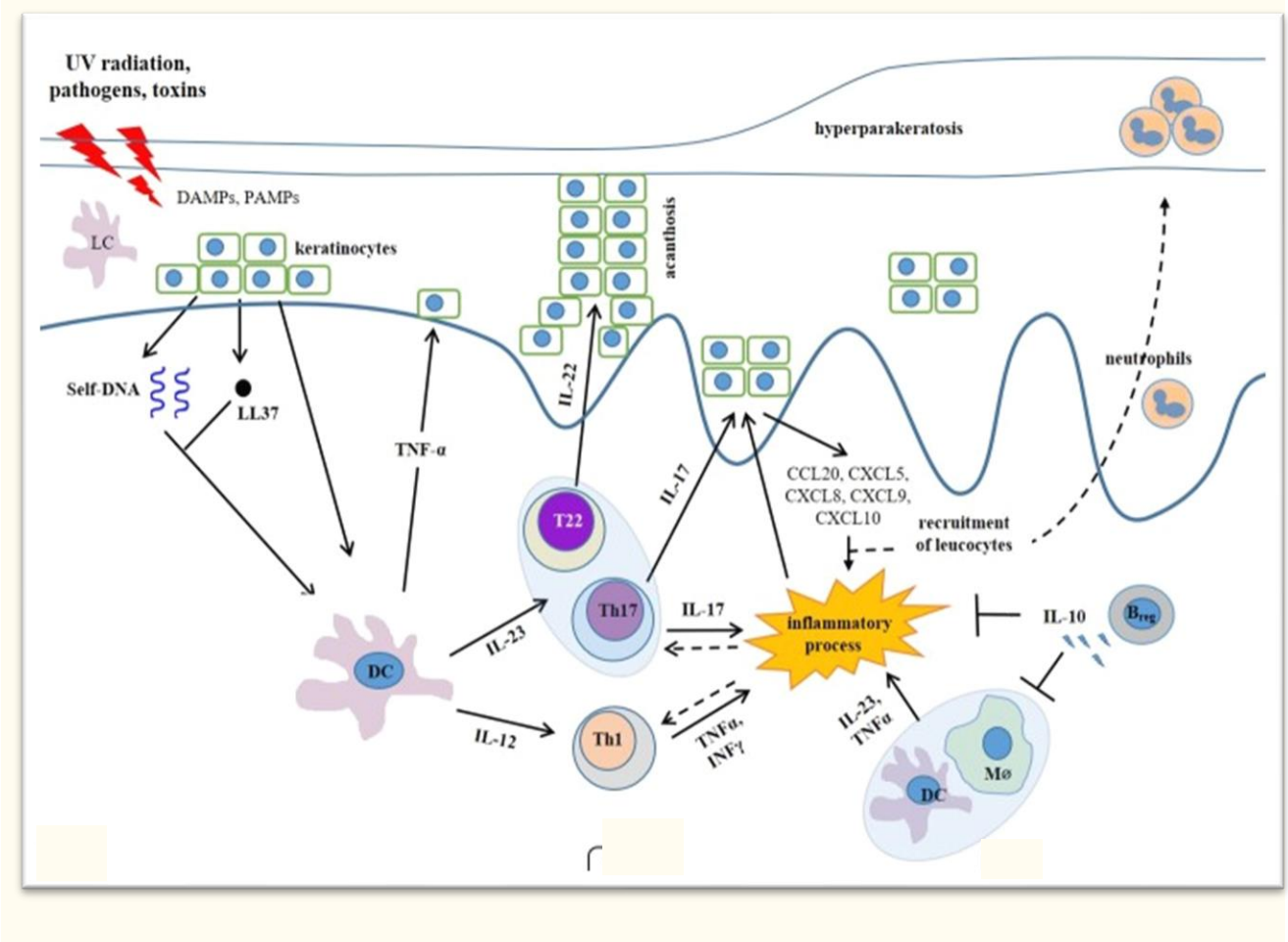

Fig.1: The pathogenesis of Psoriasis [5].

Immunopathogenesis of Psoriasis

The immunopathogenesis of psoriasis involves a complex interplay between innate and adaptive immune responses, with a central role played by dendritic cells, T lymphocytes, and various pro-inflammatory cytokines. Environmental triggers, such as trauma (Koebner phenomenon), infections, or stress, activate plasmacytoid dendritic cells (pDCs), leading to the production of interferon-alpha (IFN-α), which stimulates myeloid dendritic cells (mDCs) to mature and present antigens to naïve T cells in regional lymph nodes [5].

These activated mDCs secrete interleukin-12 (IL-12) and interleukin-23 (IL-23), promoting the differentiation of naïve CD4+ T cells into Th1 and Th17 effector subsets, respectively. Th1 cells release interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), while Th17 cells secrete interleukin-17 (IL-17), IL-22, and IL-21, all of which contribute to keratinocyte hyperproliferation, angiogenesis, and the recruitment of additional inflammatory cells [6].

Keratinocytes, far from being passive targets, actively participate in the inflammatory loop by producing antimicrobial peptides (AMPs) like LL-37, cytokines (e.g., IL-1, IL-6), and chemokines (e.g., CCL20), which further perpetuate the recruitment of immune cells to the skin [7]. Moreover, IL-17 and IL-22 induce keratinocyte proliferation and impair differentiation, leading to the hallmark histological features of psoriatic lesions—acanthosis, parakeratosis, and loss of the granular layer [8]. Additionally, the IL-23/Th17 axis has been identified as a critical therapeutic target, with biologic agents such as secukinumab, ixekizumab, and ustekinumab showing efficacy in modulating this pathway and significantly improving clinical outcomes [9].

Genetic and Epigenetic Factors

Psoriasis has a strong genetic component, as evidenced by its higher concordance rates among monozygotic twins and familial aggregation. Genome-wide association studies (GWAS) have identified more than 60 susceptibility loci, many of which are involved in immune regulation and skin barrier function [10]. The most prominent genetic association is with the major histocompatibility complex (MHC), particularly the HLA-C*06:02 allele, which is strongly linked to early-onset psoriasis [11].

Beyond the MHC, non-MHC loci such as IL12B, IL23R, TNIP1, and STAT3 further implicate the IL-23/Th17 axis and NF-κB signaling in disease pathogenesis [12]. These genetic variants contribute to aberrant immune activation, heightened cytokine responses, and dysregulated keratinocyte behavior. Importantly, these discoveries have directly informed the development of targeted therapies.

In addition to genetic predisposition, epigenetic modifications—including DNA methylation, histone modifications, and non-coding RNAs—are increasingly recognized as important contributors to psoriasis. These changes can regulate gene expression without altering the DNA sequence and are often influenced by environmental factors such as infections, trauma, and stress [13].

For example, reduced methylation at promoters of inflammatory genes such as TNF-α and IL-17 has been observed in psoriatic skin, correlating with increased gene expression [14]. Moreover, microRNAs (miRNAs), particularly miR-21 and miR-146a, are dysregulated in psoriasis and have been shown to modulate inflammatory signaling and keratinocyte proliferation [15].

Together, genetic susceptibility and epigenetic dysregulation form a complex, dynamic foundation for the development and persistence of psoriasis, underscoring the disease's multifactorial nature.

Environmental Triggers and Risk Factors

Although psoriasis is strongly influenced by genetic and immunological factors, environmental triggers play a pivotal role in initiating and exacerbating disease flares. These triggers interact with an individual's genetic predisposition to induce or worsen the psoriatic process [16].

Infections, particularly streptococcal pharyngitis, are well-known triggers for guttate psoriasis, especially in children and adolescents. Streptococcal antigens may act as superantigens or mimic

keratinocyte peptides, activating autoreactive T cells and provoking psoriatic lesions [17]. Viral infections such as HIV are also associated with severe and treatment-resistant forms of psoriasis, likely due to dysregulated immune activation [18].

Skin trauma, known as the Koebner phenomenon, is another well-established trigger. Physical injury, sunburn, tattoos, or surgical scars can precipitate lesions at the site of damage, likely due to the release of cytokines and self-DNA, which activate plasmacytoid dendritic cells and initiate inflammation [19].

Certain medications are implicated in psoriasis onset or flare-ups, including beta-blockers, lithium, antimalarials, and some biologics like anti-TNF agents. These drugs may alter cytokine profiles, impair T cell regulation, or affect keratinocyte signaling [20]. Additionally, abrupt withdrawal of systemic corticosteroids can trigger a rebound of severe pustular psoriasis.

Lifestyle-related factors also contribute. Obesity is associated with increased disease severity and poor therapeutic response, likely due to the chronic low-grade inflammation driven by adipokines such as leptin and resistin [21]. Smoking and alcohol consumption have both been linked to increased psoriasis risk and severity, possibly through oxidative stress and modulation of immune responses [22].

Lastly, psychological stress is a commonly reported aggravating factor, capable of enhancing sympathetic nervous activity and upregulating proinflammatory cytokines like TNF-α and IL-6, thereby fueling disease activity [23].

Pathophysiology of Skin Lesions and Histological Features

The psoriatic skin lesion results from a dynamic interaction between immune cells and keratinocytes, leading to characteristic epidermal and dermal changes. The core features include hyperproliferation of keratinocytes, altered differentiation, neoangiogenesis, and a dense inflammatory infiltrate [24].

Keratinocyte hyperproliferation is driven largely by cytokines such as IL-17, IL-22, and TNF-α, which stimulate mitotic activity in basal and suprabasal layers, shortening the epidermal turnover time from the normal 28 days to approximately 3–5 days [25]. This accelerated cycle results in acanthosis (epidermal thickening), parakeratosis (retention of nuclei in the stratum corneum), and loss of the granular cell layer.

Histologically, psoriatic plaques exhibit Munro microabscesses—collections of neutrophils in the stratum corneum—and spongiform pustules of Kogoj in the upper epidermis [26]. Vascular changes are also prominent, including dilated, tortuous capillaries in the dermal papillae, which account for the erythematous appearance of lesions and the Auspitz sign (pinpoint bleeding on scale removal) [27].

Dermal infiltration by T cells, dendritic cells, macrophages, and neutrophils sustains the inflammatory loop. IL-23 and IL-17 released by these cells promote further recruitment and activation of both innate and adaptive immune elements, while keratinocytes respond by releasing antimicrobial peptides and additional chemokines [28].

This self-amplifying cytokine network not only drives the development of skin lesions but also contributes to systemic inflammation, which is increasingly linked to comorbid conditions such as cardiovascular disease and insulin resistance [29].

Psoriatic Comorbidities and Systemic Inflammation

Psoriasis is increasingly understood as a systemic inflammatory disease with multiple comorbidities extending beyond the skin. Chronic immune activation—particularly involving the IL-23/Th17 axis—drives systemic inflammation, contributing to a range of associated conditions including psoriatic arthritis (PsA), metabolic syndrome, cardiovascular disease, and psychological disorders [30].

Psoriatic arthritis affects up to 30% of patients with psoriasis and can lead to joint damage and disability if not promptly diagnosed and treated. The pathophysiology overlaps with that of skin psoriasis, with IL-17, IL-23, and TNF-α playing central roles in synovial inflammation and bone remodeling [31]. Enthesitis and dactylitis are hallmark features, and imaging often reveals bone erosion and new bone formation.

Cardiovascular disease is a leading cause of morbidity and mortality in psoriasis. Chronic systemic inflammation promotes endothelial dysfunction, atherogenesis, and insulin resistance. Elevated levels of C-reactive protein (CRP), oxidized LDL, and proinflammatory cytokines have been reported in patients with moderate-to-severe psoriasis, correlating with increased risk for myocardial infarction and stroke [32].

Metabolic syndrome is significantly more prevalent in psoriasis patients and includes components such as obesity, type 2 diabetes, dyslipidemia, and hypertension. Adipose tissue secretes proinflammatory adipokines like leptin and resistin, further amplifying systemic inflammation and potentially reducing treatment efficacy [33].

Mental health comorbidities are also prominent. Depression, anxiety, and reduced quality of life are common due to the visible and chronic nature of the disease. Elevated levels of proinflammatory cytokines such as IL-6 and TNF-α have been implicated in the pathogenesis of depression in psoriasis, linking inflammation to psychological outcomes [34].

These findings highlight the need for a multidisciplinary approach to psoriasis management, integrating dermatological, rheumatological, cardiometabolic, and psychological care to reduce the long-term burden of the disease.

Therapeutic Implications Based on Pathogenesis

Advancements in understanding the immunopathogenesis of psoriasis have revolutionized its treatment, shifting from broad immunosuppressants to targeted biologic therapies. Therapeutic strategies now aim to disrupt key inflammatory pathways—particularly the IL-23/Th17 axis and TNF-α signaling—that are central to disease development and progression [35].

TNF-α inhibitors such as etanercept, infliximab, and adalimumab were among the first biologics approved for moderate-to-severe psoriasis. These agents reduce systemic inflammation and skin lesion severity but carry risks of infections and paradoxical psoriasis flares [36].

Subsequent focus shifted to IL-12/23 inhibitors like ustekinumab, which block the p40 subunit shared by both cytokines. However, more selective IL-23p19 inhibitors (e.g., guselkumab, tildrakizumab, risankizumab) have shown improved efficacy and safety profiles, offering longer-lasting remissions with fewer adverse effects [37].

IL-17 inhibitors (e.g., secukinumab, ixekizumab, brodalumab) directly target IL-17A or its receptor and provide rapid and robust improvement in plaque psoriasis. These agents are particularly effective in treating difficult-to-manage areas like the scalp and nails [38].

Janus kinase (JAK) inhibitors, such as tofacitinib, represent a newer class of oral agents that modulate intracellular signaling pathways involved in cytokine receptor activity. While they offer convenience and efficacy, concerns about thromboembolic events and lipid elevation necessitate careful patient selection [39].

Personalized medicine is gaining traction, using biomarkers and genetic profiling to predict treatment response and optimize therapy. Moreover, non-biologic treatments like phototherapy, methotrexate, and cyclosporine remain important in certain clinical scenarios, especially in resource-limited settings or where comorbidities contraindicate biologics [40].

This paradigm shift underscores the importance of understanding psoriasis as an immune-mediated systemic disease, enabling clinicians to select therapies based on underlying pathogenic mechanisms rather than just clinical severity.

REFERENCES

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496–509.
2. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;20(6):1475.
3. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol. 2014;32:227–255.
4. Sabat R, Philipp S, Höflich C, et al. Immunopathogenesis of psoriasis. Exp Dermatol. 2007;16(10):779–798.
5. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496–509.
6. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol. 2014;32:227–255.
7. Tsoi LC, Spain SL, Knight J, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet. 2012;44(12):1341–1348.
8. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014;71(1):141–150.
9. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of secukinumab in plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol. 2017;31(6):1006–1014.

10. Tsoi LC, Spain SL, Knight J, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. Nat Commun. 2015;6:7001.
11. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006;78(5):827–851.
12. Capon F, Bijlmakers MJ, Wolf N, et al. Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. Hum Mol Genet. 2008;17(13):1938–1945.
13. Zhang P, Su Y, Chen H, et al. Epigenetics and psoriasis: pathogenesis and treatment. J Eur Acad Dermatol Venereol. 2017;31(8):1270–1278.
14. Roberson ED, Liu Y, Ryan C, et al. A subset of methylated CpG sites differentiate psoriatic from normal skin. J Invest Dermatol. 2012;132(3):583–592.
15. Meisgen F, Xu N, Wei T, et al. MiR-21 is up-regulated in psoriasis and suppresses T cell apoptosis. Exp Dermatol. 2012;21(4):312–314.
16. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019;80(4):1073–1113.
17. Tervaert WC, Esseveld H, Poppema S. Streptococcal infection and psoriasis: a review of the literature. J Dermatol Treat. 1990;1(3):147–153.
18. Cedeno-Laurent F, Gómez-Flores M, Mendez N, et al. New insights into HIV-1-primary skin disorders. J Int AIDS Soc. 2011;14:5.
19. Raychaudhuri SP, Jiang WY, Raychaudhuri SK. Revisiting the Koebner phenomenon: role of NGF and its receptor system in the pathogenesis of psoriasis. Am J Pathol. 2008;172(4):961–971.
20. Wolkenstein P, Revuz J. Drug-induced psoriasis. Clinical features and mechanisms. Am J Clin Dermatol. 2001;2(3):159–165.
21. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case–control study. J Invest Dermatol. 2005;125(1):61–67.
22. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med. 2007;167(15):1670–1675.
23. Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. J Invest Dermatol. 2006;126(8):1697–1704.
24. Schön MP, Boehncke WH. Psoriasis. N Engl J Med. 2005;352(18):1899–1912.
25. Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol. 2004;135(1):1–8.
26. Nickoloff BJ, Wrone-Smith T. Injection of pre-psoriatic skin with CD4+ T cells induces psoriasis. Am J Pathol. 1999;155(5):145–158.
27. Braverman IM, Yen A. Ultrastructure of the capillary loops in the dermal papillae of psoriasis. J Invest Dermatol. 1977;68(1):53–60.
28. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007;445(7130):866–873.
29. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010;31(8):1000–1006.
30. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol. 2017;76(3):377–390.

31. Gladman DD, Chandran V. Observational cohort studies: lessons learnt from the University of Toronto Psoriatic Arthritis Program. Rheumatology (Oxford). 2011;50(1):25–31.
32. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735–1741.
33. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA Dermatol. 2013;149(1):84–91.
34. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol. 2010;146(8):891–895.
35. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386(9997):983–994.
36. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of etanercept, infliximab, and adalimumab in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis. Br J Dermatol. 2012;166(3):552–561.
37. Blauvelt A, Papp KA, Griffiths CEM, et al. IL-23 inhibitors in the treatment of psoriasis: current perspectives. J Eur Acad Dermatol Venereol. 2019;33(10):1670–1680.
38. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014;371(4):326–338.
39. Papp KA, Menter MA, Raman M, et al. A review of safety and efficacy of tofacitinib in psoriasis. J Am Acad Dermatol. 2020;82(4):1037–1046.
40. Nast A, Spuls PI, van der Kraaij G, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277–2294.