

Beyond the Skin: Investigating Psoriasis, Its Systemic Associations, and the Future of
Therapeutics

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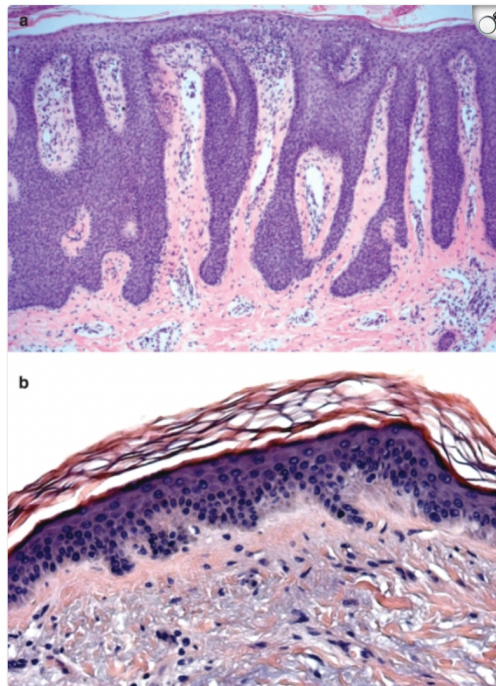
Abstract

This paper will highlight critical genetic factors that contribute to the phenotypes associated with psoriasis, examine potential causes, comorbidities, and currently available treatment options, and discuss future treatments in development. First, as psoriasis is an autoimmune disease, an examination of the immune system will be presented, along with a discussion of common causes and concerns, associated treatments, and future outcomes. The skin is the largest organ of the body. While many perceive skin disorders as cosmetic issues, this thesis aims to provide information that helps readers regard these conditions as serious problems affecting overall well-being rather than superficial concerns.

Key words: Psychobiology, Psoriasis, Immune System, Cytokines, Interleukins, JAK/STAT pathway, Nuclear factor kappa B (NF- κ B), Biologics, Monoclonal Antibodies, Artificial Intelligence

Introduction

Psoriasis is an autoimmune disease that affects 2-3% of the global population. In psoriasis, skin cells proliferate faster than normal, resulting in dry, scaly patches and plaque accumulation. Chronic inflammation prompts the immune system to attack healthy cells like pathogens. Skin cells mature and divide significantly more slowly in a healthy state than in psoriasis. Skin cells take about four weeks to mature, but in psoriasis, they mature within a few days, resulting in abnormal skin cell development. This accelerated maturation process produces skin cells lacking crucial components, which prevents proper differentiation and contributes to plaque formation and scaly skin, hallmark characteristics of psoriasis (Dhabale et al., 2022). Figure 1 presents histologic evidence of psoriatic epidermal skin in panel A, contrasting with healthy epidermal skin in panel B. The abnormal architecture of psoriatic skin is evident (Heidenreich et al., 2009).



Psoriasis histology. (a) H&E staining of psoriasis skin. Epidermal thickening with elongated rete ridges. Infiltration of neutrophils in the corneal layer. Lymphocytic infiltrate, few macrophages and mast cells in the dermis. Dilated and elongated capillaries in the papillary dermis. (b) Healthy skin with regular epidermis and orthokeratosis.

Figure 1. Histological Evidence of the Effects of Prolonged Maturation of Psoriatic Skin

*Note. Reprinted from “Angiogenesis drives psoriasis pathogenesis” by Regina Heidenreich, Martin Rocken, Kamran Ghoreschi. 2009. Retrieved from <https://doi.org/10.1111/j.1365-2613.2009.00669.x>

Types of Psoriasis

There are seven types of psoriasis: plaque-type psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, nail psoriasis, and psoriatic arthritis. Plaque psoriasis is the most common and consists of raised patches of skin and scaly, itchy, dry skin covering mainly the elbows, knees, scalp, and back. Guttate psoriasis primarily affects children and is caused by a bacterial infection, resulting in small drop-shaped spots across the trunk, arms, and legs. Fungal infections usually trigger inverse psoriasis and cause patches in folds of the skin, the groin, buttocks, and breasts. Pustular psoriasis mainly appears on the hands and consists of

blisters with pus. Erythrodermic psoriasis is the least common and consists of a peeling rash all over the body that burns and itches. Nail psoriasis affects the toe and fingernails and consists of abnormally grown nails with discoloration. Psoriatic arthritis is chronic and affects the joints and axial skeleton (Dhabale et al., 2022).

When providers diagnose psoriasis, they consider the total body surface area (BSA) and use the Psoriasis Area and Severity Index (PASI), provided by the American Academy of Dermatology, to classify psoriasis as mild, moderate, or severe. The American Academy of Dermatology defines mild psoriasis as less than 3% BSA, moderate psoriasis as 3-10% BSA, and severe psoriasis as 10% BSA. The Psoriasis Area Severity Index (PASI) defines the severity of the plaques on a scale of 0-72 (Kessler et al., 2022).

The immune system

To understand psoriasis, it is crucial to understand the immune system. The immune system protects the body from pathogens and invaders, but sometimes harms healthy cells. There are two parts of the immune system: innate and adaptive. The innate immune system, the focus of this paper, is the first line of defense against invaders. It consists of a variety of cell types located in the skin, cornea of the eyes, and mucous membranes such as the respiratory, intestinal, and gastrointestinal tracts. The adaptive immune system develops as the body is exposed to various pathogens and microbes. The adaptive immune system consists of multiple cells involved in pathogen defense, such as B cells, which produce antibodies for the body's defense against pathogens in the extracellular environment, and T cells, responsible for destroying cells infected with intracellular pathogens (Smith et al., 2018).

As mentioned above, one aspect of the immune system is fighting against pathogens. Some immune system cells produce cytokines, small proteins that bind to specific receptors and signal the immune system to fight pathogens. A category of cytokines is the interleukins (ILs). Interleukins are a superfamily of cytokines involved in immune cell adhesion, migration, maturation, proliferation, activation, and differentiation. Additionally, they have anti-inflammatory and pro-inflammatory qualities. Therefore, interleukins' main job is to control growth, differentiation, and activation during immunological and inflammatory reactions (Singh et al., 2021).

Within the interleukin superfamily, various proteins mediate autoimmune inflammation. The innate and adaptive immune systems play a role in the persistent skin inflammation associated with psoriasis. The overproduction of inflammatory cytokines, especially interleukin-17 (IL-17) and interleukin-22 (IL-22), plays a key role. Numerous immune cells, such as T helper 17 (Th17) cells, natural killer (NK) cells, and natural killer T (NKT) cells, generate these cytokines. By encouraging keratinocytes, specialized cells in the epidermis, to create more cytokines and chemokines, which draw more immune cells into the skin, IL-17 increases inflammation. By promoting their proliferation and interfering with the normal function of the epidermal barrier, IL-22 also has an impact on keratinocytes. Tumor necrosis factor (TNF), IL-17, IL-22, and interferon-gamma (IFN- γ) are released by innate immune cells, including NK and NKT cells, which contribute to psoriasis (Lowe et al., 2014). Amplifying cytokines IL-17, TNF, IFN- γ , and IL-22 is associated with the psoriasis phenotype.

Possible causes

Psoriasis is a chronic cycle of inflammation and an autoimmune disorder currently under investigation to understand its causes and develop a potential cure. In this discussion, we will explore the current understanding of its pathogenesis. As previously noted, researchers focus on mutations in key genes within the immune system to gain insights into the disease's pathogenesis.

Genetically, the concordance rate of psoriasis in monozygotic twins, identical twins who share their environment and all of their genes, is approximately 70%, and in dizygotic twins, who share their environment but only half their genes, it is 20%. Since the concordance rate is significantly higher in monozygotic twins than in dizygotic twins, genetic variables play a substantial role in developing psoriasis. However, environmental variables and epigenetic influences also contribute to the condition, as the concordance rate in monozygotic twins is not 100%. This suggests psoriasis is a complicated, multifaceted condition impacted by environmental triggers such as infections, stress, lifestyle choices, and a genetic predisposition. There are more than 30 single-nucleotide polymorphisms (SNPs) associated with psoriasis, however, two mutations have been discovered that are capable of causing psoriasis on their own, IL36RN and CARD14 (Lowe et al., 2014). These genes affect the skin and the immune system. Before describing these mutations, a vital pathway related to inflammation must be described.

The Nuclear factor kappa B (NF- κ B) is a key inflammatory pathway in psoriasis that regulates the immune system and inflammation. NF- κ B promotes the production of pro-inflammatory cytokines and plays a role in regulating T cell activation and differentiation. Many genes

associated with this pathway contribute to psoriasis by influencing TNF signaling, a key pathway in inflammation. TNFAIP3 and TNFRS1B mutations have been related to impairing TNF-mediated apoptosis, programmed cell death, and promoting chronic inflammation (Patel et al., 2023). Furthermore, a mutation in the IL36RN gene increases the production of cytokines downstream of NF- κ B by decreasing the effects of another gene, IL-IF9 (Patel et al., 2023). These two mutations provide part of the genetic basis for the phenotypes associated with psoriasis.

Caspase Recruitment Domain-Containing Protein 14 (CARD-14) is a gene that plays a significant role in NF- κ B signaling. A mutation in this gene has been linked to hyperactivity in the NF- κ B signaling pathway, resulting in excessive inflammation and psoriasis flares. Additional CARD-14 gene mutations and increased protein levels have been found in psoriasis patients, but not in healthy individuals. Mutations in the CARD-14 gene lead to altered CARD-14 protein, which may enhance NF- κ B activation (Lowes et al., 2014). An overactive NF- κ B pathway can cause an accumulation of excess immune cells, thickening the skin, and contribute to the phenotypic characteristics of psoriasis. Furthermore, the hyperactivity of the NF- κ B pathway results in elevated chemokines that recruit additional neutrophils, T cells, and inflammatory mediators. Psoriasis is characterized by a vicious cycle of inflammation and acanthosis, exacerbated by all these factors (Lowes et al., 2014, p. 12). Table 1 below provides a visual summary of the genes, highlighted as those specifically discussed in this thesis, that are known to be associated with psoriasis.

Table 1. Genetic mediators associated with psoriasis.

	Type	Gene(s)
Interleukins	Pro-inflammatory	IL1B, IL2, IL6, IL15, IL17, IL18, IL20, IL23
	Anti-inflammatory	IL1RN, IL4, IL10, IL13, IL19
Interleukin receptor proteins		IL20RA, IL28RA, IL36RN
Mediators of HLA class I function		HLA-C, ERAP-1
NF- κ B pathway regulators		TNFAIP3, TNFRsF1B, TNIP1, TRAF1IP2, NFKBIA
Interferons and mediators		IFN-gamma, IFIH1
JAK/STAT pathway		STAT3, STAT4, JAK2, TYK2
Other		APOE, CTLA4, DEFB4, GBP6, LCE, MCP1, VDR, ZNF313

Note. Reprinted from “The Genetic Susceptibility to Psoriasis and the Relationship of Linked Genes to Our Treatment Options,” by Patel, H. et al., (2023, Aug. 1). Retrieved from <https://doi.org/10.3390/ijms241512310>

Another critical pathway for understanding the ongoing cycle of inflammation in psoriasis is the JAK/STAT pathway. The cytoplasmic tyrosine kinases, known as Janus Kinases (JAKs), are associated with this enzyme-linked signaling pathway, which phosphorylates and activates transcription regulators called signal transducers and activators of transcription (STATs). Figure 2 illustrates the steps in this pathway. Cytokine binding alters the arrangement of JAKs, bringing two JAKs close together so they can phosphorylate one another and enhance the activity of their tyrosine kinase domains. The JAKs then create phosphotyrosine docking sites for STATs by phosphorylating tyrosines on the cytoplasmic tails of cytokine receptors. Once STATs bind, they travel to the nucleus to directly influence gene expression. The JAK/STAT pathway involves numerous extracellular signaling proteins; however, we mainly focus on their relation to

macrophages, as these are associated with the immune system and thus psoriasis. JAK activation is a prerequisite for the results of an immune response triggered by T-helper (Th) cell lineage-defining cytokine signals (Ghoreschi et al., 2009). Tyk2, one of the four members of the JAK family (JAK1, JAK2, JAK3, and Tyk2), is essential to the pathophysiology of psoriasis because it relays signals from IL-12 and IL-23, two interleukins that promote Th1 and Th17 differentiation. These Th subsets contribute to the psoriatic phenotype by producing inflammatory cytokines such as IFN- γ , IL-17, and IL-22. Thus, Tyk2 is a crucial intracellular kinase that aids in transmitting cytokine signals, which in turn causes chronic inflammation, rather than being a cytokine in and of itself. Tyk2 is usually active or overactive in psoriasis, contributing to chronic inflammation as IL-12 and IL-23 are chronically active (Singh et al., 2021). Below is how these two cytokines, in conjunction with antimicrobial peptides, contribute to the inflammatory loop observed in psoriasis. Moreover, we will discuss how inhibitors of this pathway are a promising treatment for psoriasis.

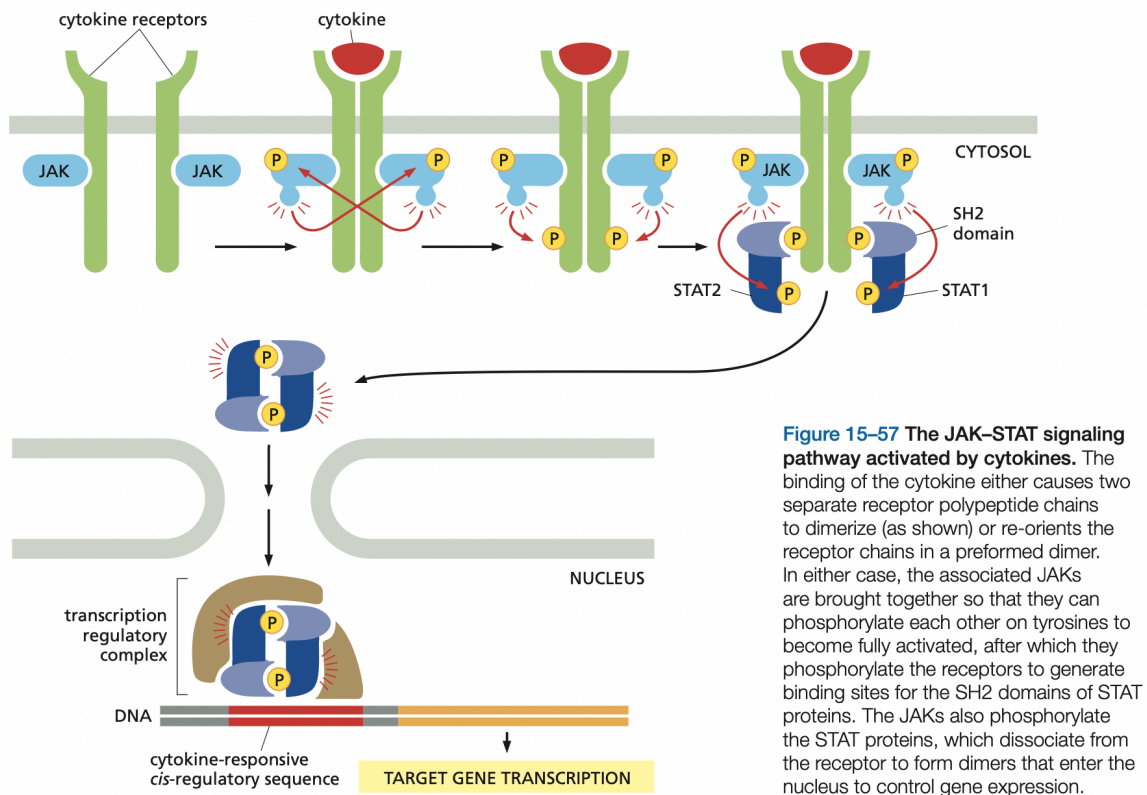


Figure 2. JAK/STAT Signaling Pathway

*Note. Reprinted from “Molecular Biology of the Cell 7th Edition: Alberts, B., Heald, R., Johnson, A., Morgan, D., Raff, M., Roberts, K. P. Walter. 2022. Molecular Biology of the Cell, Seventh Edition. New York: W.W. Norton and Co.”

Researchers have found that the pathogenesis of psoriasis is linked to antimicrobial peptides (AMPs) produced by keratinocytes in response to damage in dendritic cells, which serve as a crucial connection between the innate and adaptive immune systems. The AMPs related to psoriasis include LL37, β -defensins, and S100 proteins. Each plays a vital role in creating the inflammatory loop associated with psoriasis; however, we will specifically focus on LL37. When LL37 binds to DNA, it induces the formation of toll-like receptors (TLRs), which activate plasmacytoid dendritic cells (pDCs), further producing interferons such as $INF-\alpha$ and $INF-\beta$. The

generation of these interferons enables myeloid dendritic cells (mDCs) to stimulate the maturation and differentiation of type 1 helper T cells (Th1) and type 17 helper T cells (Th17). Th1 cells produce IFN- γ and TNF- α , while Th17 cells produce IL-17, IL-22, and additional TNF- α , the three genes discussed earlier that are involved in forming psoriasis phenotypes. Additionally, activated mDCs can further stimulate dendritic cells, creating the autoinflammatory loop associated with psoriasis. Furthermore, mDCs can directly migrate to the lymph nodes and secrete inflammatory cytokines such as TNF- α and IL-12, which produce Th1 cells from natural T cells, as well as IL-23, which facilitates the survival of Th17 and Th22 cells (Singh et al., 2021). Using cytokines such as IL-17, IL-22, IL-12, and IL-23, which are markers of psoriatic pathology, this pathway illustrates how antimicrobial peptides like LL37 initiate a cascade that stimulates dendritic cells and Th cells, ultimately leading to IL-mediated inflammation. Figure 3 below provides a visual description of this entire inflammatory process.

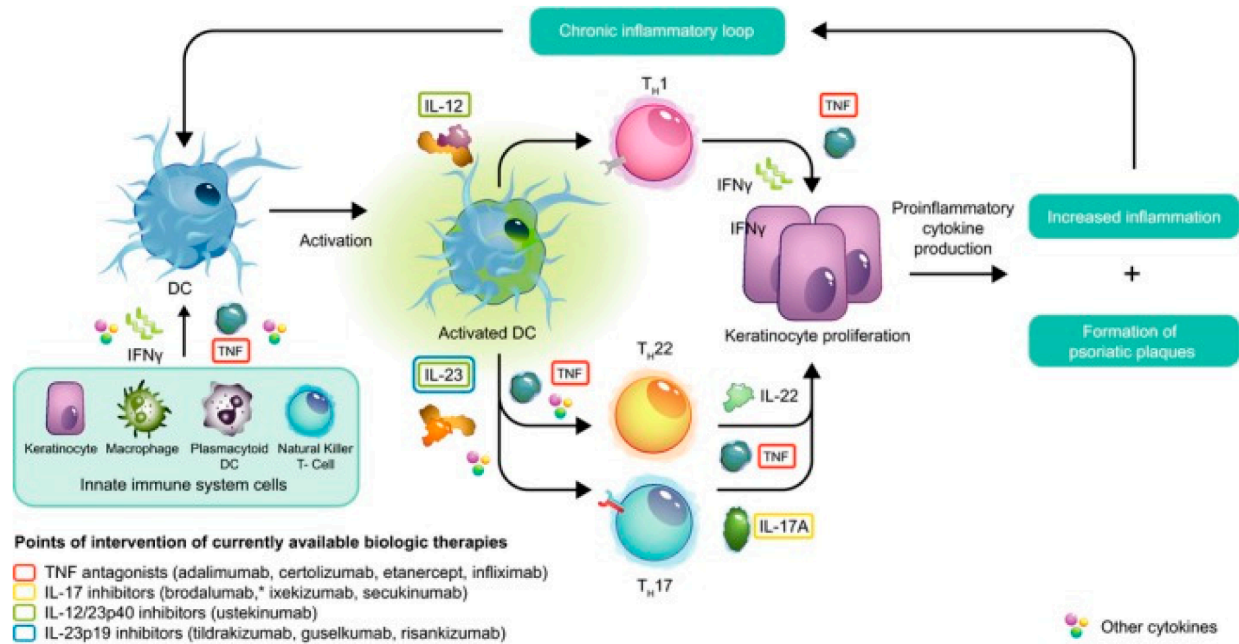


Figure 3. Inflammatory Process in Psoriasis

*Note. Reprinted from “The Cytokine Mediated Molecular Pathophysiology of Psoriasis and Its Clinical Implications, by Singh, Rohan et al. (2021, Nov.26). Retrieved from <https://doi.org/10.3390/ijms222312793>

Epigenetic influences

As mentioned above, the concordance rate for monozygotic twins was not 100%, indicating that epigenetic factors may also contribute to the severity of psoriasis. Epigenetics refers to changes in DNA that do not alter the DNA sequence by turning genes on and off. Unlike the mutations in CARD14 genes described above, epigenetic modifications are not inherited and cannot be easily identified with gene sequencing analysis. These changes usually occur in response to diseases and environmental factors, including diet, smoking, and alcohol consumption. Through chemical modifications to DNA and histones, epigenetic mechanisms alter gene expression by changing chromatin structure and activating specific transcription factors. This leads to the translation of new mRNA without altering the DNA sequence (Dopytalska et al., 2021). One type of epigenetic change is due to DNA methylation. DNA methylation regulates gene expression by adding

methyl groups to cytosine bases, particularly in CpG islands, which are regions rich in cytosine and guanine nucleotides. The enzyme DNA methyltransferase (DNMT) catalyzes this reaction, converting cytosine into 5-methylcytosine (5-mC). Increased DNA methylation results in more significant chromatin condensation, making it more difficult for transcription factors to bind to DNA and regulate gene expression and development. Studies have identified abnormal DNA methylation in patients with psoriasis. According to a study, the promoter regions of two genes, PDCD5 and TIMP2, had higher levels of methylation, a chemical alteration that can shut down genes, in psoriatic skin. Lower mRNA levels were associated with this increased methylation, indicating that these genes were less active than normal skin. These genes are significant because they affect the growth of keratinocytes, the cells that make up the skin. If PDCD5 expression is suppressed due to hypermethylation, then the apoptosis of keratinocytes decreases; therefore, an excessive buildup of cells is observed, leading to skin cells growing and dividing too quickly. Meanwhile, TIMP-2 regulates degradation and repair, and if this gene is suppressed, the enzymes responsible for tissue degradation and repair are overexpressed, resulting in heightened inflammation in the skin (Dopytalska et al., 2021). Moreover, many other studies have shown that psoriatic patients exhibit increased hypermethylation in psoriatic skin lesions, which is detrimental as it dysregulates keratinocyte regulation.

Psoriasis Systemic Effects

Metabolic Syndrome

To understand the broader effects of psoriasis, we will explore three comorbidities associated with psoriasis; however, there are many more. Psoriasis is associated with metabolic syndrome (MetS), known as the most common comorbidity, which contributes to premature mortality in patients. MetS is a group of conditions, and its most common forms include obesity,

hypertension, and diabetes. The connection between metabolic syndrome and psoriasis has not been studied extensively; thus, the current understandings relate to cell signaling and dysfunction (Hao et al., 2021). Proinflammatory cytokines are a part of the immune response that regulates growth, cell activation, differentiation, and involvement in controlling intracellular pathogens. Proinflammatory cytokines link psoriasis with MetS. Th17, discussed extensively above, plays a role in the pathogenesis of psoriasis and indicates an increased risk of psoriasis. Insulin resistance is the primary correlation between type 2 diabetes (T2D) and MetS. Two well-known adipokines, leptin and adiponectin, are endocrine hormones that operate on certain receptors in distant target organs. By interacting with the insulin receptors AdipoR1 and AdipoR2, adiponectin acts as an insulin sensitizer that enhances insulin sensitivity and regulates glucose and lipid metabolism. Studies have indicated that low levels of adipokines in patients with psoriasis contribute to MetS. Leptin is a hormone that regulates metabolism; when increased levels are present, it exacerbates the severity of psoriasis (Hao et al., 2021).

Atherosclerosis

Several studies have demonstrated the correlation between psoriasis and cardiovascular disease. However, the specific pathways and mechanistic processes addressing this correlation have not been studied. Atherosclerosis is a buildup of fats, cholesterol, and other substances around the artery walls and contributes to cardiovascular disease. Some similarities between psoriasis and cardiovascular disease conditions are known: psoriasis causes inflammation that drives keratinocyte proliferation and plaque buildup, while atherosclerosis is an accumulation of inflammatory cells at sites of epithelial injury, leading to plaque buildup. In a recent analysis of the increased susceptibility of atherosclerosis with psoriasis, researchers used bioinformatics to discover two proteins directly linked between the two conditions, IFN- γ and TNF- α . Then

researchers used IFN- γ and TNF- α to stimulate primary aortic endothelial cells, specific cells isolated from human aorta for research purposes, and *ex vivo*, outside of the living body, atherosclerotic tissue. They discovered that these two substances enhanced monocyte and T-cell chemoattractants, endothelial cell surface adhesion molecule expression, and endothelial barrier integrity *in vitro*, increasing permeability (Mehta et al., 2017). Expression of IFN- γ was higher in psoriatic skin compared to healthy skin, while TNF- α was higher in atherosclerosis lesions compared to healthy coronaries.

Diabetes

Furthermore, as mentioned above, Psoriasis is also associated with diabetes. Psoriasis increases susceptibility for developing diabetes (Brazzelli et al., 2021). In a study analyzing the correlation between diabetes and psoriasis, Brazeelli and colleagues found a gene contributing to both psoriasis and diabetes, TNF- α . TNF- α is an inflammatory cytokine contributing to the systemic inflammation associated with psoriasis and the pathogenesis of insulin resistance. This gene reduces a vital tyrosine kinase insulin receptor in metabolism and cell differentiation.

Furthermore, the authors conducted a study with diabetes patients, psoriatic patients, and healthy individuals. Many tests were performed to measure each patient's psoriasis area and severity index (PASI), body mass index, insulin-resistant parameter, blood glucose, and more. Results demonstrated that fasting plasma glucose and insulin resistance parameters were higher in diabetics with psoriasis than in other subjects. Since psoriasis is an inflammatory disease, the authors hypothesized that insulin resistance was higher due to systemic inflammation caused by psoriasis. Furthermore, psoriasis patients and diabetics had similar inflammatory cytokines and adipocytokines related to insulin resistance and released by adipocytes (Brazzelli et al., 2021).

Therefore, it is crucial for practitioners to monitor psoriasis patients thoroughly, as this disease is damaging not just to the skin but to all aspects of physical health.

Psychological Affects

Mental Health

Although biological and physical aspects are important to discuss, psoriasis also affects many mental aspects of a patient's life, such as confidence, stress levels, and other aspects of social life. To measure patients' health status with the disease, a questionnaire measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression was conducted using the EQ-5D. Specifically, skin irritation and self-confidence were analyzed for psoriasis. One-on-one interviews were conducted where patients reported physical problems such as skin irritation, limitation in clothing choice, scratching, and bleeding, which lead to pain/discomfort, difficulty bathing, and mental issues, such as feeling unattractive, explaining to others the disease is not contagious, negative impact on social relationships, and the overall stress of psoriasis controlling what products they use, wear, etc. (Rencz et al., 2022). In another study, participants stated “they were willing to accept a 40% shorter life expectancy to avoid uncontrolled disease” (Swinburn et al., 2013). Although psoriasis is mainly treated with medication, multiple studies attest that mental health should also be considered when treating such patients.

Stress

Research demonstrates that stress can negatively impact mental health and sometimes exacerbate health conditions. Patients with psoriasis have to deal with the stress of staying consistent with treatment and the financial costs of treatment, and some may have to deal with the stress of needles. Stress can impact treatment outcomes and worsen patients' mental health. Furthermore, research has found that stress can trigger or exacerbate psoriasis symptoms by hyperactivating

the hypothalmo-pituitary-adrenal axis (HPA). HPA axis is a neuroendocrine pathway maintaining physiological homeostasis by releasing certain hormones, glucocorticoids, to the adrenal cortex, which maintain homeostasis and also cause changes in gene expression in the NF- κ B pathway. Hyperactivity of the HPA axis is known to cause deleterious changes in the skin by increasing the proliferation of pro-inflammatory cytokines, thus exacerbating psoriasis symptoms (Sheng et al., 2021).

Treatments

Topical Corticosteroids

Psoriasis is treated according to the severity of the condition. Topicals are usually the first line of treatment, offering relief to some patients but not all. Topical treatments are available in different formulations such as gels, emollients, etc (Uva et al., 2012). Topical corticosteroids remain a cornerstone of treatment for psoriasis because of their immunosuppressive, anti-inflammatory, and anti-proliferative qualities. However, they have side effects, including atrophy, skin barrier, striae, and/or telangiectases, breakdown due to long-term use, and potential systemic adverse effects. Whether used alone or in conjunction with systemic therapy, corticosteroids continue to be the first-line treatment for all grades of psoriasis. Stoughton and Cornell categorized the potency of corticosteroids in 1985 based on their vasoconstrictive characteristics. Lower potency corticosteroids, such as triamcinolone acetonide, hydrocortisone, and betamethasone valerate, are recommended for application on the face, groin, and axillary areas and are suitable for infants and children. In contrast, mild- and higher potency corticosteroids are commonly employed as initial therapy for all other areas in adults (Uva et al., 2012). Higher potency drugs should not be used for more than two weeks, and patients should be monitored during their use.

One way corticosteroids function is through a glucocorticoid receptor (GR), a cytoplasmic protein. The glucocorticoid receptor is activated by cortisol, and when cortisol is absent, GR binds with helper proteins HSP90 and HSP70, forms a complex, and accumulates in the cytoplasm. When cortisol is present, the complex breaks and GR moves to the nucleus. In the nucleus, two GR molecules pair up and bind to specific DNA sequences called glucocorticoid response elements (GREs). This binding triggers the transcription of specific anti-inflammatory genes. GR can also reduce the activity of genes that promote inflammation, such as those for cytokines and other signaling molecules. In this process, GR interacts with another protein called NF- κ B, which usually activates inflammatory genes. GR represses NF- κ B, lowering inflammation. Topical glucocorticoids are antimitotic, increasing skin cell turnover (Sevilla et al., 2019). Most topical corticosteroids are covered by insurance or available over the counter at relatively low prices.

As discussed above, CARD14 mutations were found to be a genetic cause of psoriatic inflammation. Researchers have found that inhibiting a protein, MALT1, causes inhibition in CARD14, thus reducing inflammation. MALT1 has primarily been investigated in innate immunity cells, such as mast cells, dendritic cells, natural killer cells (NK), and adaptive immune cells. In these cells, it promotes the production of proinflammatory genes downstream of many cell-surface receptors. In the T cell receptor (TCR) signaling context, MALT1 is most well-known for mediating nuclear factor κ B signaling, as discussed above, which triggers T cell activation and proliferation. MALT1 was long thought to serve only as a scaffold for assembling other signaling proteins, a necessary step in activating NF- κ B. The finding that MALT1 also possesses proteolytic activity, which causes the cleavage of a small range of proteins,

fundamentally altered this perspective. It was proposed that MALT1 is a prospective therapeutic target in autoimmunity and cancer when it was discovered that MALT1 proteolytic activity is necessary for T cell activation and B cell lymphoma proliferation. Therefore, drugs targeting this protein also inhibit CARD14 and the NF- κ B pathway and lead to an overall reduction in inflammation. These drugs have not been used yet, but researchers are excited for the future of therapeutics with this discovery (Liu et al., 2024).

Small Molecule Inhibitors

A small molecule inhibitor is another form of treatment, which consists of a drug usually administered orally and that is small in size. Although not discussed in detail above, another enzyme involved in the ongoing inflammation observed in psoriasis is phosphodiesterase-4 (PDE-4). Researchers have discovered that this enzyme also contributes to the production of pro-inflammatory cytokines when it degrades cyclic adenosine phosphate (cAMP) to adenosine monophosphate (AMP) (Milakovic et al., 2021). PDE-4 inhibitors function by preventing cAMP from breaking down, lowering inflammation. PDE-4 inhibitors can decrease superoxide production and chemotaxis and prevent the production and secretion of inflammatory cytokines such as IFN- γ , TNF- α , IL-2, IL-12, and IL-23. Additionally, by activating CREB, PDE-4 inhibitors increase the number of anti-inflammatory cytokines, such as IL-10. The only oral PDE-4 inhibitor authorized for treating psoriasis is apremilast, a small molecule inhibitor. When comparing apremilast therapy to placebo trials, researchers found significant improvement in signs and symptoms of psoriasis and one of its comorbidities, psoriatic arthritis, compared to the placebo (Jiand et al., 2023).

TNF- α inhibitors are another form of small molecule inhibitors that improve signs and symptoms while helping control the effects of comorbidities associated with conditions such as cardiovascular diseases. Targeting TNF- α proteins will help reduce the amount of proinflammatory cytokines, as they attract immune cells to inflamed areas and trigger inflammation. Blocking this process will help reduce inflammation. However, these medications must be dosed according to the patient's weight (Jiang et al., 2023).

Tofacitinib is another oral small-molecule JAK Kinase inhibitor specifically targeting JAK1 and JAK3. The US Food and Drug Administration (FDA) initially authorized tofacitinib, a JAK inhibitor, in November 2012 to treat rheumatoid arthritis, an immune-mediated condition. Furthermore, it was discovered that JAK3 inhibition can dramatically lower the inflammation associated with psoriasiform illness, another inflammatory condition, in mice. Therefore, tofacitinib is also thought to be able to treat human psoriasis by targeting JAK3 to prevent the signaling of cytokines, given the similarities between human and mouse psoriasis. According to a meta-analysis, people with psoriatic arthritis or plaque psoriasis should take 5 mg of tofacitinib BID. Adverse events were shown to be significantly increased by higher dosages or longer durations of tofacitinib. Therefore, the suggested course of treatment for the two primary clinical symptoms of psoriatic illness is 5 mg tofacitinib BID for 12 weeks (Wang et al., 2024).

Biologics

Biologic medications target specific parts of the immune system, such as T cells, unlike traditional treatments, which target the immune system. Biologics are used when topical treatments are not helping the patient or are causing adverse side effects. Injections or IVs are

usually the route of administration for biological medications, and the patient must be screened before beginning them. Patients must be up to date on all vaccinations, screened for hepatitis, and screened for Tuberculosis (Smith et al., 2018). Some popular biological treatments include Humira, Skyrizi, and Tremfya. If not covered by insurance, these treatments are relatively expensive and range from \$8,000 to \$48,000 a year.

Monoclonal antibodies

Monoclonal antibodies, a subdivision of biologic therapy, have been proven to be a successful therapeutic for many diseases as they coat the protein in an antibody (Ab), which blocks the signaling cascade from continuing to function. As discussed above, Psoriasis follows a specific signaling cascade leading to excessive proliferation of skin cells, as shown in Figure 3 for more information. IL-17A and IL-17F are two critical cytokines produced by Th17 cells, which contribute to the inflammatory loop associated with psoriasis. Monoclonal antibodies inhibit this inflammatory loop by binding to these cytokine receptors and thus inhibiting the pathway from progressing. Although many monoclonal antibody treatments are available for psoriasis, Bimekizumab is the latest FDA-approved. Bimekizumab is the first monoclonal antibody binding to IL-17A, IL-17F, and IL-17A/F heterodimers, inhibiting activation of their receptor complexes. Furthermore, IL-17F and IL-17A have recently been discovered as promising targets for developing treatments for psoriasis, as researchers have found “dual-neutralization” of these cytokines leads to more significant suppression of inflammatory processes (Adama et al., 2020). Both cytokines have been found elevated in psoriasis patients and are considered responsible for psoriatic lesions. Furthermore, in vitro research showed that blocking both IL-17A and IL-17F simultaneously reduced the inflammatory response in psoriasis more successfully than blocking either isoform separately, unlike what past monoclonal antibodies have done (Tanaka et al.,

2023). Many treatment options are currently available to treat psoriatic lesions. However, patients experience adverse side effects. New treatments, such as bimekizumab, aim to have minimal impact on patients' well-being with higher improvement in disease outcomes.

Bimekizumab resulted in fewer adverse side effects with better long-term effects than previous treatments (Tanaka et al., 2023). The FDA has approved a specific dosage of Bimekizumab: 320mg, administered as two subcutaneous injections of 160mg each every four weeks, then every eight weeks thereafter (19).

Tumor necrosis factor (TNF) inhibitors are administered similarly to Bimekizumab, a subcutaneous injection. However, these proteins specifically target inflammation. In psoriasis, excessive inflammation causes the resulting phenotypes. Therefore, TNF- α inhibitors can work to reduce that inflammation. Similarly to Bimekizumab, they prevent the binding of TNF- α to its receptor, thus preventing the activation of an inflammatory response (American College of Rheumatology n.d).

Thermal therapy modulation

Research on psoriasis continually seeks improved and more effective treatment options. One approach under investigation is thermal therapy modulation. This treatment entails patients consuming heated water and bathing in it to alleviate the severity of psoriasis. The study aimed to integrate research on the gut and skin microbiomes. Drinking this water affects the gut microbiome, while bathing in it influences the skin microbiome. The experiment aimed to analyze how balneotherapy impacts psoriasis patients' skin and gut microbiomes. Before thermal treatment, researchers collected samples from both unaffected and affected areas in psoriasis patients, specifically from the elbow and ear. Various bacteria were found to be abundant in both

unaffected and affected regions. *Finegoldia* and *Ornithinimicrobium* were significantly more prevalent bacteria in affected areas than in unaffected ones before thermal therapy. In general, greater diversity of bacteria is associated with better health. However, the cause or effect is unknown. Following thermal treatments, there was an increased abundance of *Staphylococcus* on the elbow in both affected and unaffected skin, contrasting with previous studies. *Finegoldia* and *Ornithinimicrobium* significantly decreased after thermal treatment. *Micrococcus* and *Aggregatibacter* appear to be negatively associated with improvements in psoriasis and may hinder clinical treatments. In conclusion, while the study did not yield successful results, it highlights the observation of healthy bacterial growth in the skin following treatments.

Enhancing Healthcare with AI Technology

The medical field is constantly evolving and advancing. Artificial intelligence (AI) has significantly contributed to developing treatments and research within this field. Since dermatology primarily relies on diagnostic imaging, AI can facilitate efficient and accurate diagnoses. There are various types of AI, but in dermatology, the most beneficial is machine learning (ML), which detects patterns and generates predictions from input data, thereby enabling faster diagnoses as ML can identify skin conditions by analyzing skin features. Relying on the subjective classifications of dermatologists can result in inconsistencies in disease diagnosis; therefore, these new technologies support quicker diagnoses and treatment regimens. Moreover, developing drugs for psoriasis is costly and time-consuming, so AI can enhance treatment development efficiency (Liu et al., 2023).

Companies like Canfield Scientific Inc. are developing more efficient ways to diagnose skin disorders, leading to earlier detection and treatment before the condition worsens. Their new

whole body 3D imaging system, called the VECTRA 360, allows a patient's entire skin to be scanned and lesions identified on a macroscopic level in one body scan. Their company also developed a microscope called the DermaGraphix, which allows providers to view specific details about skin lesions to create more accurate diagnoses and thus start a patient on the correct treatment plan (Canfield Scientific n.d.). Technology allows for easier and more efficient methods of diagnosing and treating patients, hoping to give patients a better quality of life.

To summarize, the presented literature aimed to portray the current understandings of psoriasis and its effects on an individual's overall well-being and quality of life. The current understandings of the immune system, psoriasis causes, and essential pathways involved in pathogenesis and treatments were analyzed. Common comorbidities were discussed to shed light on skin disorders affecting multiple body systems. Although no cure for psoriasis has been developed, this new shift with artificial intelligence allows dermatologists to diagnose and treat psoriasis earlier. Early detection can help with better patient outcomes and improve patients' quality of life. The future of medicine is bright with new technological advancements, and I am certain we will be able to improve patient outcomes efficiently and successfully in the future.

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