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Review Article

Cytokine-Driven Immunopathogenesis of Psoriasis: Clinical Therapeutic Targets and Future Immunologic Directions

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Abstract

Background: *Psoriasis is a chronic inflammatory skin disorder affecting ~2% of the global population, characterized by erythematous, scaly plaques. It involves a complex interplay of immune dysregulation and genetic susceptibility.*

Pathogenesis: *The disease is driven by persistent activation of immune cells and overproduction of pro-inflammatory cytokines. Genome-wide association studies have identified polymorphisms in genes encoding cytokines, their receptors, and signalling molecules, highlighting their central role. Elevated serum cytokine levels and their overexpression in psoriatic lesions correlate with disease severity.*

Immunological Insights: *Initially considered a type-1 immune-mediated disorder due to the involvement of cytokines such as interferon-γ, interleukin-2 (IL-2), and interleukin-12 (IL-12), psoriasis understanding has evolved significantly. The discovery of T helper 17 cells (Th17 cells) and their associated cytokines has redefined its immunopathology and provided new therapeutic targets.*

Contributing Factors: *Psoriasis develops in genetically predisposed individuals through interactions between environmental triggers and immune responses.*

Therapeutic Advances: *Targeted cytokine-based therapies, including biologics, have improved disease management by specifically modulating key inflammatory pathways.*

Conclusion: Cytokine dysregulation is central to psoriasis pathogenesis, and continued exploration of cytokine networks offers promising avenues for more effective and personalized treatments.

INTRODUCTION

A chronic inflammatory autoimmune skin condition, psoriasis is influenced by both geneticand environmental factors. Psoriasis is recognized as a substantial burden on public health and is projected to affect approximately 125 million individuals worldwide and approximately 2–4% of people in Western nations [1]. Despite the low mortality rate, patients with psoriasis experience a severe reduction in quality of life and a heavy psychological load [2].

Immune cell entry into the skin and epidermal proliferation are hallmarks of psoriasis. Psoriasis has a complex pathophysiology that includes interactions between keratinocytes, immune cells, and other cells in the skin. Keratinocytes have been considered the sole executors of immune cell activity during psoriasis over the past 20 years, viewing psoriasis as an immunological cell-driven disease [3]. Additionally, the pathogenic Interleukin-23 (IL-23) /Interleukin-17 (IL-17) axis is what causes psoriasis. Myeloid cell types (mDCs) mature and produce Tumor Necrosis Factor- , InteleukinL-12(IL12), and IL-23 when plasmacytoid dendritic cells are activated, leading to Th (T helper) 1 or Th17 activation, followed by the release of inflammatory cytokines, such as IL-17, IL-21, and IL-22, These cytokines, particularly IL17, subsequently activate keratinocytes, which help to amplify inflammation by producing cytokines, chemokines, and antimicrobial peptides [4].

Numerous biologics that target TNF- α, IL-23, and IL-17 have show remarkable efficacy in the management of psoriasis. However, the adverse effects, safety, recurrence, and loss of efficacy following cessation of these biologics have motivated researchers to investigate new therapeutic methods Recent research has suggested that keratinocytes may be a trigger for psoriasis and a prospective target for psoriasis therapy [5].

TYPES OF PSORIASIS

GUTTATE PSORIASIS

This kind of psoriasis typically affects children and young adults. Damage that appears like tiny drops and occurs suddenly are less common.as psoriatic epidermal pimples, which often appear following streptococcal infections [6].

GENERALIZED PUSTULAR PSORIASIS

This is a common type of psoriasis that typically affects young people and causes pustules. It may appear as a side effect of psoriasis vulgaris or develop on its own. In this condition, lymphopenia, leukocytosis, and nitrogen equilibrium are improved. The pustules dry up after a few days, and new ones appear quickly thereafter. Erythroderma results from the propensity of peri-pustular erythematous spread. If the dispersed region is not treated promptly, the acute phase may lead to a fatal outcome [7].

PLAQUE PSORIASIS

The most common type manifests as elevated, red skin patches covered with silvery-white scales . The patches often form on the scalp, trunk, and limbs, particularly the elbows and knees, and develop symmetrically over the body [8].

INVERSE PSORIASIS

This variety manifests as red, smooth patches in skin folds, such as in the armpits, crotch, or under the breasts. Sweating and rubbing may exacerbate it.

Erythrodermic psoriasis

In this uncommon but severe type of psoriasis, the majority of the body has red, scaly skin. Severe sunburn or the use of certain drugs, such as corticosteroids, may cause it [8].

EPIDEMIOLOGLICAL DATA

It is believed that psoriasis affects 2–3% of people globally. The impact of this disease in a tropical or subtropical nation, such as India, is impossible to overstate, despite the fact that it is known to be more common in the world's polar regions. Owing to a variety of hereditary and environmental factors, the frequency of psoriasis may differ from one region to another in a multicultural nation like India. Only six studies from North India estimated the prevalence of this illness among adult dermatology patients, and these were primarily conducted in hospitals [9].

TABLE NO 1: PREVALENCE DATA OF PSORIASIS

Country/Region	Prevalence	Year	Approximate Number Affected	References
United State	2-3%	2023	Over 8 million	[9]
United Kingdom	1.7%	2024	Around 1.1, million	[9]
Germany	2%	2024	~2 million	[11]
Spain	2.3%	2022	Approximately 1.1 million	[12]
Norway	1.98%	2020	~104000	[13, 15]
East Asia	0.12%	2021	0.44-2.2	[14]
INDIA	2-3%	2024	2.8-33.6	[9, 10]

Pathogenesis of psoriasis: An Immunological Perspective

Psoriasis is characterized by persistent inflammation which results in incorrect differentiation and unchecked keratinocyte proliferation. Exogenous factors, such as infections, skin injuries, smoking, medications, and occupational risks, may serve the source of several triggers [16]. A robust familial genetic correlation exists between loci that are prone to psoriasis. Additionally, PSORS can be identified early on and contributes to the development of severe psoriasis [17]. If the illness is deemed to be acquired, it may result from specific underlying illnesses, such as predisposed metabolic syndrome, diabetes mellitus, and hypertension [18].

In fact, the entire pathophysiology of psoriasis is still unknown, and the "Psoriatic Universe" is still undefined and unexplored [19]. The four primary stages of psoriasis development are the initiation of the disease, a responsive innate immune response, a stimulated adaptive immune response, and excessive epidermal proliferation (Figure 1). There is strong evidence that during the early stages of psoriasis, plasmacytoid dendritic cells (pDCs) are stimulated by nucleic acid complexes, such as the antimicrobial peptide chains (AMP) of cathelicidin LL-37 in the outermost layer of the epidermis. Interferon Gamma (IFN-γ), TNF-α, IL-12, and IL-23 are among the cytokines that pDCs produce to interact with marrow dendritic cells (mDCs). Subsequently, these cytokines instruct CD4+ and CD8+ T cells to divide clonally and release IL-17 and IL-22. In order to form chemoattractant and innate immune mediators, CD8+ T cells move and attach to the keratinocytes' Major Histocompatibility (MHC) I receptors [20]. Additionally, mDCs promote the development of T helper (Th)1, Th22, and Th17 cells. Th1 cells release Interleukin 2(IL-2), TNF-α, and IFN-γ, which trigger keratinocytes and DCs to produce inflammatory factors. In contrast, Th22 cells generate IL-22, which causes keratinocyte-derived T cell-recruiting chemokines to be released and results in an altered dermal phenotype, including parakeratosis, acanthosis, and epidermal hyperplasia. After migrating to the dermis, Th17 cells activated by Interleukin 1(IL-1), IL-23, IL-12, and TNF-α produce IL-17 [21]. keratinocytes- are then signalled to express TNF-α and chemokine (CC)ligand 20 (CCL20) by released IL-17. TNF-α and IL-17 work together to assemble neutrophils and produce Munro's micro abscesses. Granular substances, such as neutrophil elasticity (NE), proteinase 3, LL-37, reactive oxygen species (ROS), α-defensin with antibacterial properties, lipocalin, C-X-C-motif ligand (CXCL)8, Interleukin 6 (IL-6), and CCL20, can be produced by neutrophils through degranulation [22-23].

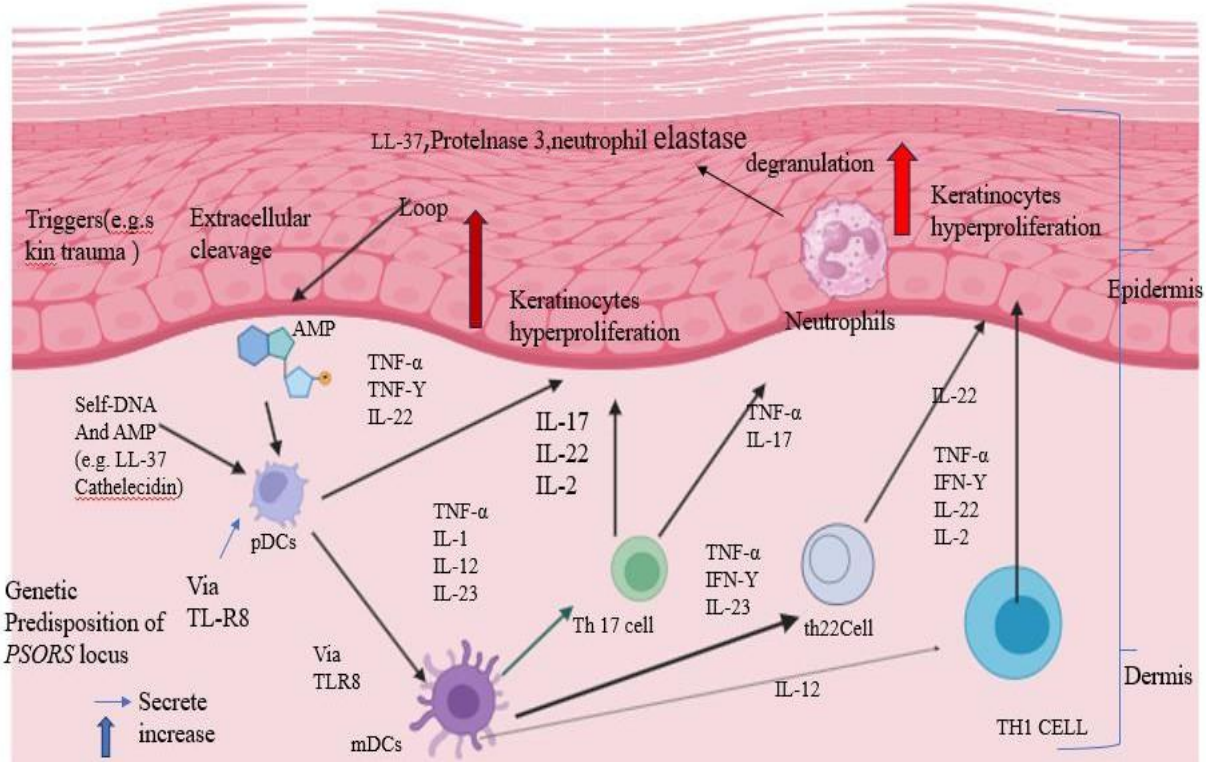

Figure. No 1: Molecular pathogenesis of psoriasis

Role of immune cells

CD4+ HELPER T CELLS IN PSORIASIS

CD4 glycoprotein is expressed on the surface of CD4+ helper T cells; thus, it is named CD4. When MHC class II molecules expose these cells to peptide antigens, they become activated. are surface-expressed on antigen-presenting cells, which subsequently generate cytokines that support or modulate the immune system. Studies have shown that people with psoriasis have CD4+ helper T cells in their dermal skin. When cells from patients with psoriasis are introduced into graft sites on mice with severe combined immunodeficiency disease (SCID), the effects of CD4+ helper T cells in psoriasis may be demonstrated. These changes in the skin illustrate how CD4+ helper T cells work in psoriasis [24]. These CD4+ helper T cells, which have distinct roles, may be divided into Th1, Th2, Th17, and Th22 cells. Th1 cells can enhance cytotoxic T cells and macrophages, which are immune-mediated reactions by producing tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), two important factors in the onset of psoriasis [25] Studies have shown that the cytokines released by T cells linked to psoriasis are not Th2 type cytokines [Interleukin-4(IL4) and Inteleukin-10(IL-10)],[26] but rather almost Th1 linked ones (IL-2, IFN-γ, and TNF-α). According to the study, Th1 cells are the main factor influencing psoriasis. However, psoriasis treatment with humanized monoclonal antibody therapies that target IFN-γ did not work as well as anticipated. This implies that IFN- g could play a more intricate part in psoriasis than earlier believed [27]. A subset of pro-inflammatory T helper cells known as T responder 17 cells (Th17 cells) secretes IL-17 but not IFN-g [28]. IL-1 and IL-6 stimulate the development of Th17 cells from naïve CD4+ T cells. Cells as well as preserve the IL-23 generated via macrophages, dendritic cells, Langerhans cells, and keratinocytes.

The cytokine IL-23 is made up of two chains (t19 and p40), which IL-12 also shares. Mounting evidence indicates that psoriasis is significantly influenced by the IL-23/Th17 axis and associated cytokines. IL-23 expression levels are higher in psoriatic skin than in healthy skin. When IL-23 is administered intradermally to animal models, aberrant keratinocyte proliferation and epidermal hyperplasia occur [29]. Biologically active IL-12/-23 and IL-23-targeting medications have proven successful in treating psoriasis [30]. Conversely, in addition to releasing IL-17, TNF- α and IL-6, the IL-21, and IL-22 can also be released by Th17 cells, contributing to in psoriasis development. Randomized clinical trials on psoriasis have demonstrated that targeted IL-17 A and IL-17F antibody therapies may benefit from the use of these two cytokines [31].

Th22 cell s, a recently identified subtype of T cells, generate IL-22. Not IFN-g, IL-4, or IL-17[32] but 13. Comparable to Th1/17 cells, patients with psoriasis

had higher levels of Th22 cells. Additionally, a variant of psoriasis known as generalized pustular psoriasis (GPP) is distinguished by the entry of neutrophils into the epidermis, which causes excruciating symptoms in individuals deficient in MPO in a stable state; their transcriptomes can be examined using single-cell RNA sequencing. Multilingual comparison mapping of the single-cell RNA sequencing data allowed for the identification of cell types. The findings showed that whereas the number of naive CD4+ T cells was significantly reduced in GPP, the fraction of CD4+ lymphocytes that are cytotoxic along with other CD4+ effector lymphocytes was higher [33].

CD8+ cytotoxic T cells in psoriasis

Psoriasis has long been considered a skin condition mediated by Th1 cells. There is mounting evidence that the IL-22/Th22 pathway and the IL-23/Th17 axis are essential for psoriasis [34, 35]. While CD8+ T lymphocytes are mostly identified in the epidermis of psoriatic wounds on the skin, CD4+ T cells are localized in the upper dermis [36]. Cytotoxic CD8+ T cells, also known a Tc1, It17, and Tc22 cells, may secrete IL-2, IFN-g, TNF-α, IL-17, and the IL-22 cytokines, in addition to CD4+ T lymphocytes. Tc1 cells in psoriasis emit TNF-α, IL-2, and IFN-g, each of which has a distinct function in the progression of psoriasis [37]. IFN-g can activate antigen-presenting cells early in the psoriatic cascade. keratinocytes and Antigen presenting Cells (APC)s to produce IL-22 and IL-1b, hence intensifying a storm of in psoriasis [38]. In psoriasis, TNF-α can activate DCs to release cytokines such as IL-23 and control APCs. Additionally, TNF-α can work in combination with other cytokines, such as IL-17A, to enhance the inflammatory cascade and encourage T cell proliferation and chemotaxis to the lesional sites [39]. Researchers used single-cell transcriptomics to identify two pathogenic lethal type 17 T- cell (Tc17) subgroups of CD8+ T cell subsets in the psoriatic skin of five healthy control subjects and eleven psoriasis patients. people [40]. Unlike Th17 cells in the body, Tc17 cells

Cytokines associated with Th1 (TNF-α), Th17 (IL-17/–21/–22), and Th1 (IFN-γ) have been found in psoriatic materials. Additionally, Tc17 cells express CCR6, which is the receptor for CCL20 and is required for all CD8+ T cells to nominate epidermally. In addition to secreting cytokines, CD8+IL-17+ T cells in psoriatic lesions may also generate cytotoxic molecules, such as granzyme B, and reduce target cells in a manner that is reliant on the T-cell receptor (TCR) and CD3 [41]. However, the precise process by which cytotoxic target cells are killed remains unknown.

Another newly identified CD8+ T cell subgroup in psoriasis is Tc22 cells, which are predominantly observed in the psoriatic epidermis. In the absence of IFN-g and IL-17, Th22 cells exclusively secrete Interleukin-22(IL-22) Skin with psoriasis [42]. Additionally, Th17- and Thc17derived cells cannot express IL-17A; instead, they evolve into T-lymphocytes that exclusively produce IL-22. Peripheral arthritis, a condition called, and dactylitis are the hallmarks of PsA, which can develop in approximately30% of those with psoriasis [43]. Research has indicated that the growth of memory People with PsA have significantly more CD8+ T lymphocytes in their joints than in their bloodstreams. Furthermore, CD8+ T cells have been found in Psoriatic arthritis (PsA) patients' synovial fluid in earlier research [44]. The joint fluid composed of PsA has a higher concentration of CD8+T cells, according to single-cell sequencing. individuals with CXCR3 expression, a receptor that facilitates tissue homing. Furthermore, it was shown that the CXCR3 ligands, CXCL9 and CXCL10, were expressed at increased levels, offering a mechanistic explanation of the cellular immunological mechanism underlying PsA [45].

Tissue-Resident Memory T Cells (TRM Cells) in Psoriasis

Tissue-resident memory T cells (TRM cells) in psoriasis Tissue-resident memory T (TRM) cells are a specialized subset of long-lived memory T cells that permanently reside in non-lymphoid tissues, including the skin, mucosa, lungs, brain, and gastrointestinal tract. These cells are transcriptionally and functionally distinct from circulating central and effector memory T lymphocytes [46]. TRM cells are commonly identified by the surface expression of markers such as CD49a, CD69, and CD103, with CD69 and CD103 serving as key indicators of tissue retention [47].Although biologic therapies targeting TNF-α, IL-12/IL-23, IL-17A, and IL-17 receptors have demonstrated superior clinical efficacy compared with conventional treatments, disease relapse frequently occurs after treatment discontinuation [48]. Notably, psoriatic plaques often recur at the same anatomical locations, suggesting the presence of localized immune memory. Accumulating evidence implicates skin-resident TRM cells as central drivers of psoriasis persistence and recurrence [49].Among the TRM subsets, $CD8^+CD103^+$ TRM cells are particularly pathogenic and secrete psoriasis-associated cytokines, such as IFN-γ, IL-17A, and IL-22. In contrast, $CD4^+CD103^+$ TRM cells and $CD8^+CD103^-$ TRM cells exhibit limited cytokine production [50]. $CD8^+CD103^+$ TRM cells can be further subdivided into $CD49a^-IL\text{-}17A^+$ and $CD49a^+IFN\text{-}\gamma^+$ populations, which are preferentially associated with psoriasis and vitiligo,

respectively. Importantly, persistent IL-17A expression by epidermal TRM cells has been detected in clinically resolved psoriatic skin and is strongly linked to early disease recurrence, underscoring the critical role of TRM cells in maintaining long-term disease memory [50].

The Involvement of B Cells in Psoriasis

In contrast, because B cells are rarely observed in lesional psoriatic skin, their role in psoriasis has been disregarded. Research on psoriasis-related cells, as previously hypothesized, isstill in the active discovery phase. They may contribute to the elucidation of any tenable mechanism by filling in the cellular gaps [51].

Researchers have recently proposed novel theories on the relationship between B cells and psoriasis, claiming that B cells play a critical role in regulating the anti-inflammatory cytokine IL-10 by connecting with a nuclear factor of activated T cells (NFATc1), which is a protein transcription factor [52]. In contrast to imiquimod-induced wild-type mice and pups treated with a moisturizing cream as controls, animals bred with decreased B cells or possessing IL- 10-deficient B cells showed very catastrophic indications and symptoms when administered with imiquimod, which cream to create psoriasis-like inflammation. The most harmful psoriasis-like skin was shown in mice with decreased B cells or IL-10-deficient B cells at the conclusion of the seven-day period. inflammation as a result of the absence of IL-10 suppressing effects. In the imiquimod-induced psoriasis-like animals, pro-inflammatory cytokines produced by T cells decreased concurrently with an increase in B10 cells that produce IL-10. The latter was proposed as a result of massive splenic B cells differentiating into cells that produce antibodies. in vitro results on these spleen B cell types with ablated NFATc1 expression showed that such cells might hasten the onset of skin inflammation with repeated topical administration of imiquimod coincided with experiment. Via the B cell receptors (BCR) signals, NFATc1 might inhibit splenic B cells that were purportedly secreting IL-10 [53]. Pro-inflammatory components of psoriasis are somewhat greater than anti-inflammatory components due to an imbalance caused by decreased anti- inflammatory regulation and decreased IL-10. B cells' NFATc1 can attach to the IL10 gene and inhibit its release. Consequently, this referenced study proposed that a protein called in B cells might be considered the most recent treatment Psoriasis research. This discovery is considered to be among the first few studies linking B cells to psoriasis, which inspired several researchers to further investigate B cells and their function in psoriasis, as well as following the activation processes inside Guanylate Cyclase (GC).

Supporting evidence also showed that in certain mouse models, the loss of B cells that regulate (Bregs), a subset of B cells, might worsen other autoimmune conditions such scleroderma, lupus erythematosus systemic (SLE), and encephalomyelitis by reducing the amount of IL-10 it produces [54]. The deletion of the phosphatidylinositol 3 kinase (PI3K)-Akt pathway is the cause of this dysfunction. The PI3K-Akt pathway, which can stimulate cell proliferation, is thought to stimulate the production of IL-10 in order to reduce inflammation. Once compromised, Akt activation may be reduced, which would, in turn, reduce the production of IL-10 (Since the Th17 differentiation process cannot be blocked, loss of Brags can also lead to increased IL-23 production) [55].According to later clinical studies, individuals receiving B cell–depleting monoclonal antibodies, including rituximab, for conditions such as autoimmune diseases and lymphoproliferative disorders have been reported to develop psoriasiform skin lesions without any prior history of psoriasis [56].Regulatory B cells (Bregs) have been shown to be downregulated in the peripheral blood of patients with psoriasis, including pustular psoriasis, suggesting a potential loss of their protective immunoregulatory function in disease pathogenesis.

B cells may exert multiple immunomodulatory roles: (i) inhibiting the pathogenic effects of Th1 and Th17 cells, such as the release of TNF-α and IL-17; (ii) enhancing the regulatory functions of T cells, particularly through the secretion of IL-10; and (iii) neutralizing currently unidentified antigens.

Collectively, these findings indicate that B cells may represent an important and emerging factor in the pathogenesis of psoriasis.As understanding the natural mechanisms and roles of B cells may potentially exacerbate psoriasis, there is increasing interest in the relationship between B cells and psoriasis. recent studies have shown that psoriasis may have its own autoantigens, which may arise from a variety of factors, including genetic predisposition and modifications to the cellular surroundings [57]. GC contributes to immunological tolerance disruption, which affects the body's ability to distinguish between self and on-self or even immune cell activation, all of which can fuel inflammation [58]. Events in the GC may cause B cells to become activated in autoimmune diseases, such as psoriasis, which produces antibodies directed against autoantigens as a result of the reaction. B lymphocytes can therefore be autoreactive and detect autoantigens, resulting in the production of autoantibodies that cause inflammation, tissue damage, and disruption of regular cellular processes. Furthermore, B cells can produce pro-inflammatory cytokines, such as IL-17, to accelerate inflammation, which plays a crucial role in the development of psoriatic skin conditions.

Additionally, B cells have immunomodulatory properties that allow them to regulate other immune cells, including T cells, dendritic cells, and macrophages. Inflammatory responses in psoriasis may be caused by disruption of these regulatory processes. Additionally, GC is essential for B cell maturation and activation and can develop in psoriasis in both classical (inside lymphoid tissues) and ectopic (outside the lymphatic tissues [59] manners. The suggested synopsis of GC's functions in autoimmune disorders, including an example of psoriasis. The mechanism of B cells may also be reflected in psoriasis, as shown by other autoimmune illnesses, leading to the development of novel research hypotheses. Experimenting using immune system cells in psoriasis is challenging because skin biopsies and plasma samples are insufficient to gauge immune cell development. However, doing research on psoriasis is challenging. without the use of an actual human sample. Therefore, in vivo psoriasis-like animal models or the use of secondary lymphoid organs, such as the spleen and lymph nodes, controlled in vitro cell experiments, such as hybridoma cells, can accurately replicate the most authentic psoriasis microenvironment.

B cell Maturation and activation Antigen presentation

T cell Regulation Autoantibody production

Tolerance breakdown Immunomodulators

Cytokine secretions Aberrant responses caused inflammation

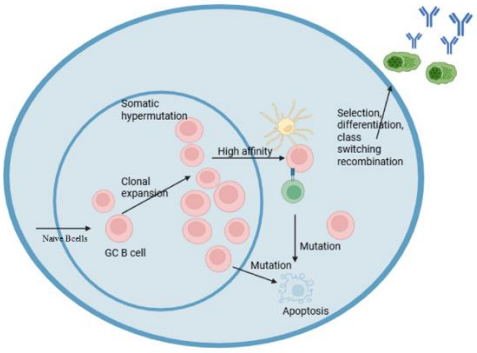

Figure No 2: The role of germinal center (GC) in autoimmune diseases, that is psoriasis, FDC, follicular dendritic cell

Key Cytokines in the Etiopathogenesis of psoriasis

Tumor necrosis factor (TNF)

Tumor necrosis factor (TNF) is a pleiotropic cytokine belonging to the TNF superfamily and plays a central role in regulating cell proliferation, differentiation, activation, and programmed cell death (apoptosis) [60-63].

TNF in psoriasis

The contribution of TNF-α to psoriatic lesion development has been extensively studied; however, some variability in findings exists. Multiple investigations have demonstrated significantly increased TNF-α expression in lesional psoriatic skin compared with non-lesional and healthy skin [64–66]. TNF-α is overexpressed in the epidermis and perivascular regions of the superficial dermis, with macrophages, keratinocytes, and epidermal Langerhans cells identified as the principal cellular sources. In contrast, mast cells, endothelial cells, and dermal Langerhans cells are not considered major contributors to TNF-α production in psoriasis [67].

TNF exerts its biological effects through two receptors, TNFRI and TNFRII. TNFRI is expressed on epidermal keratinocytes and on a network of dendritic cells in both lesional and non-lesional psoriatic skin. In psoriatic plaques, TNFRI expression is detected in the parakeratotic stratum corneum and is markedly increased around superficial dermal blood vessels. Conversely, TNFRII expression in healthy skin is largely confined to dermal dendritic cells and eccrine sweat ducts and is minimally present within the dermis [67]. Corneal lysates from psoriatic epidermis with predominant TNFRI expression contain significantly elevated levels of soluble TNFRI and TNFRII. Moreover, plasma concentrations of soluble TNFRI are substantially higher in patients with psoriasis than in healthy individuals [66].

Most studies have reported elevated plasma TNF levels in patients with active psoriasis [68]. In vitro analyses have further demonstrated that peripheral blood mononuclear cells (PBMCs) from individuals with psoriasis produce significantly higher amounts of TNF than PBMCs from healthy controls. Although TNF production decreases during disease remission, it remains higher than baseline levels observed in individuals without psoriasis [69]. Notably, TNF concentrations are considerably higher in pressure blister fluid than in serum or plasma, suggesting that TNF is predominantly produced at local sites of inflammation [70]. A positive correlation has also been observed between serum TNF levels and the Psoriasis Area and Severity Index (PASI) score [71]. Following effective anti-psoriatic treatments, such as psoralen plus ultraviolet A (PUVA) therapy, ultraviolet B (UVB) irradiation combined with topical corticosteroids, and dithranol therapy, a marked reduction in tumor necrosis factor (TNF) levels has been documented [72]. In contrast, TNF protein expression appears largely unaffected by treatments, such as cyclosporine A, acitretin, or the Goeckerman regimen [73]. Among all cytokine-targeted therapies for psoriasis, TNF antagonists remain the most extensively studied and widely used

in clinical practice for the treatment of both psoriasis and psoriatic arthritis [74].

Etanercept is a recombinant, soluble TNFRII fusion protein that neutralizes TNF by preventing its interaction with cell surface receptors. Initially approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis, etanercept has since been authorized for the management of psoriatic arthritis and plaque psoriasis [74]. Until 2006, it was the only TNF antagonist approved by the U.S. Food and Drug Administration (FDA) for cutaneous psoriasis [75]. Clinical improvement in joint symptoms is often observed within two weeks of treatment initiation, whereas improvement in skin lesions occurs more gradually. Approximately 60% of patients achieve significant improvement after 12 weeks of subcutaneous etanercept therapy at a dose of 50 mg weekly, with sustained efficacy and no significant increase in adverse effects reported during one-year follow-up (74). Recent clinical studies also suggest that etanercept exerts early inhibitory effects on Th17 cells, which are now recognized as key contributors to psoriatic inflammation [76].

Infliximab is a chimeric monoclonal antibody composed of a human IgG1 constant region fused to the TNF-binding domain of a murine antibody. By binding both soluble and membrane-bound TNF, infliximab prevents TNF interaction with its receptors and induces apoptosis of activated T cells, a mechanism distinct from that of etanercept [77]. Infliximab has been approved by the FDA for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, ulcerative colitis, psoriatic arthritis, and plaque psoriasis. Phase III clinical trials have confirmed its high efficacy in moderate-to-severe psoriasis [78-79].

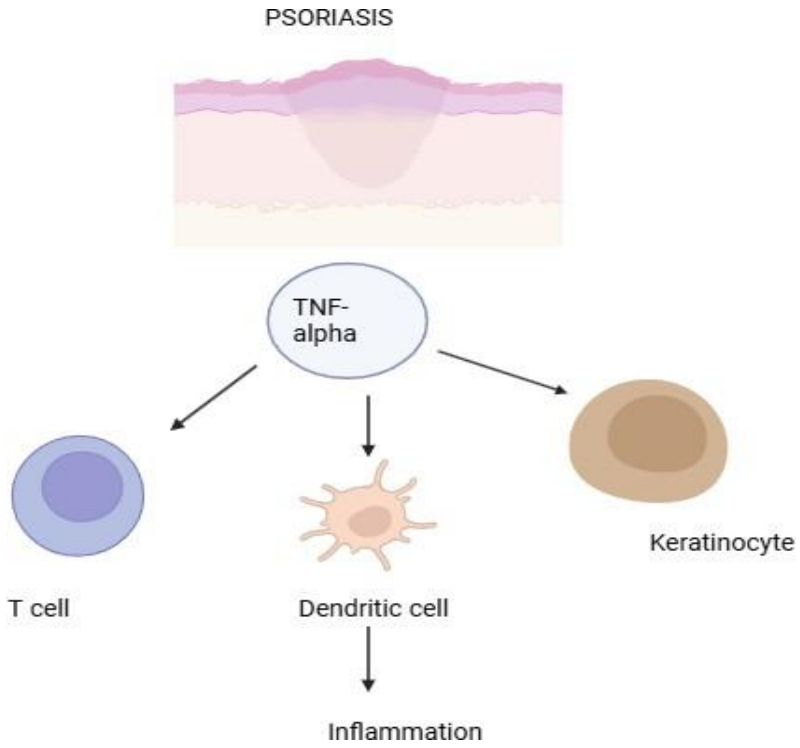

FIGURE NO 3: TNF-ALPHA PATHOGENESIS IN PSORIASIS

INTERLEUKIN-17 (IL-17A)

Interleukin-17A (IL-17) is a potent pro-inflammatory cytokine that plays a key role in coordinating innate and adaptive immune responses. IL-17 induces the expression of intercellular adhesion molecule-1 (ICAM-1/CD54) on fibroblasts and enhances the production of inflammatory mediators, such as IL-6, IL-8, granulocyte–macrophage colony-stimulating factor (GM-CSF), and prostaglandin E2 (PGE2), in epithelial, vascular, and fibroblastic cells [80].

In keratinocytes, IL-17 acts either independently or synergistically with cytokines, such as IFN-γ, IL-4, and tumor necrosis factor-α (TNF-α), to stimulate the expression of IL-6, growth-regulated oncogene-α (GRO-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and ICAM-1 [81]. Through these mediators, IL-17 promotes leukocyte recruitment, retention, and activation within the epidermis, thereby sustaining cutaneous inflammation [82].

Role of Interleukin-17

Under normal physiological conditions, the IL-17 signaling pathway plays a crucial role in host

defenses against bacterial and extracellular fungal infections. Among its members, IL-17A functions as a key immunological bridge linking innate and adaptive immune responses. At mucosal surfaces, IL-17A induces the production of chemokines that facilitate antibody responses and establish chemotactic gradients responsible for neutrophil recruitment [83-84]. Activated neutrophils subsequently release IL-17, thereby amplifying the inflammatory response and promoting further neutrophil infiltration, resulting in a self-sustaining inflammatory loop [85].

IL-17 exerts pathogenic effects through multiple downstream targets, including keratinocytes, endothelial cells, and various immune cell populations. In keratinocytes, IL-17 signaling induces hyperproliferation and stimulates the production of chemokines, antimicrobial peptides, and pro-inflammatory cytokines characteristic of psoriatic inflammation. These keratinocyte-derived mediators further promote the recruitment and expansion of IL-17-producing immune cells, thereby reinforcing a positive feedback inflammatory loop. Although IL-17A and IL-17F independently act as potent pro-inflammatory mediators, their combined activity results in enhanced inflammatory responses. In vitro studies have demonstrated that the dual neutralization of IL-17A and IL-17F leads to greater suppression of inflammatory markers than the inhibition of either cytokine alone [86,-87]. Additionally, IL-17E contributes to innate immune activation by upregulating chemotaxis-related genes, further intensifying the inflammatory cascade. IL-17 also potentiates macrophage and dendritic cell activation and induces procoagulant activity in endothelial cells [88].

Interleukin-23 (IL-23)

Interleukin-23 (IL-23) is a critical cytokine involved in shaping T-cell-mediated immune responses. It plays a decisive role in determining the nature of type 1 immune responses and preferentially promotes proliferation and interferon (IFN)-γ production in memory T cells [87-88]. This function highlights the importance of IL-23 in host defense against bacterial infections. IL-23 also contributes to cytotoxic T-cell responses against antigens, such as viral DNA, further underscoring its role in cellular immunity [89].

Recent studies have identified IL-23 as a key mediator of inflammation in peripheral tissues [90]. Unlike IL-12, IL-23 promotes the immunological expression of tolerogenic peptides by antigen-presenting cells (APCs), suggesting a distinct role in immune regulation and autoimmune disease development [91]. Importantly, IL-23 differs from IL-12 in that it drives the expansion of a unique T-cell population that produces IL-17 as its primary effector cytokine. In contrast, IL-12 can inhibit IL-23-mediated IL-17 production, highlighting the regulatory interplay between these cytokines [92].

ROLE OF IL-23 IN PSORIASIS

Activated T cells and dendritic cells central contributors to psoriasis pathogenesis, and IL-23 is a pivotal cytokine in this process. IL-23 production in psoriasis is induced through interferon-γ (IFN-γ) signaling and activation of signal transducer and activator of transcription-1 (STAT1), leading to the transcription of multiple inflammatory genes [93]. Studies have demonstrated significantly higher expression of both IL-23 subunits, p19 and p40, in psoriatic lesional skin compared with normal skin. The localization of these subunits within epidermal cells suggests that keratinocytes may serve as a source of IL-23 [94].Recent investigations have reported markedly elevated IL-23 protein levels and more than tenfold increases in the mRNA expression of the p19 and p40, but not the p35, subunits in psoriatic skin [95]. These findings identify the shared p40 subunit of IL-12 and IL-23 as an attractive therapeutic target for psoriasis [96 -97], as demonstrated in a phase I, open-label clinical study in which a single intravenous administration of a humanized monoclonal antibody targeting the IL-12p40 subunit resulted in dose-dependent regression of psoriatic lesions and was generally well tolerated. Consistent with these findings, narrowband ultraviolet B (NB-UVB) therapy reduces interleukin (IL)-23 signaling in psoriatic skin [98-100].

Anti-inflammatory Cytokines

INTERLEUKIN-10

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that plays a critical role in immune regulation suppressing the synthesis of pro-inflammatory cytokines, such as IFN-γ, IL-2, IL-3, TNF-α, and granulocyte–macrophage colony-stimulating factor (GM-CSF). IL-10 is produced not only by regulatory T lymphocytes but also by B lymphocytes, dendritic cells, and macrophages [101].

TABLE 2: CYTOKINES AND THEIR ROLES IN PSORIASIS

Cytokine	Cellular Source/ Level in Psoriasis	Biological Effects in Psoriasis	Clinical Evidence	Preclinical Evidence
IL-1β	Activated macrophages, DCs, KCs, T cells/ ↑ Lesional skin	Activates keratinocyte inflammatory response Promotes perivascular DC clustering Stimulates Th17 differentiation Induces γδ T cell proliferation Supports T cell survival [102]	Elevated IL-1 levels are found in lesional skin and serum and IL-1 pathway inhibitors have been explored but show limited benefit in psoriasis; interest remains for IL-36/IL-1 family targeting [103].	IL-1β contributes to psoriasiform inflammation in mouse models; IL-1R signaling drives dermal IL- 17–producing cells and keratinocyte activation.[104]
IL-2	DCs, activated T cells, macrophages/ ↑ Lesional skin	Drives T cell differentiation into effector/memory subsets Supports Th1/Th17 activity [105]	Low-dose IL-2 has been trailed in psoriasis and small studies/reports show Treg expansion and clinical improvement (PASI responses reported in recent studies).[106]	In animal and ex vivo studies IL-2 promotes effector T-cell expansion; low-dose IL-2 expands regulatory T cells in preclinical models [107].
IL-4	Th2 cells, basophils, mast cells, ILC2/ ↓ Psoriatic epidermal T cells	Enhances Th2 response Suppresses Th1/Th17 pathways Inhibits IL-18 & IL-6 by keratinocytes Lowers IL-23 by DCs [108]	IL-4/IL-13 blockade (dupilumab) is effective in atopic dermatitis; in psoriasis dupilumab shows limited benefit and has been associated with paradoxical induction or flares of psoriasis in rare cases [109].	IL-4 suppresses Th1/Th17 pathways in preclinical models and can downregulate keratinocyte inflammatory responses [109].
IL-6	DCs, endothelial cells, KCs, T cells/	Stimulates Th17 differentiation Weakens Treg function Induces	Anti-IL-6 therapies effective in rheumatology have shown	Preclinical models show IL-6 promotes Th17 differentiation and psoriasis form inflammation
	↑ Lesional skin & serum	angiogenesis via VEGF [110]	inconsistent results in psoriasis and in some reports have induced psoriasis- like eruptions; IL-6 remains of research [111]	IL-6 is elevated in lesional skin and relates to pustular phenotypes [111]. .
IL-7	Hair follicle keratinocytes/ ↑ Lesional skin	- Maintains CD4+/CD8+ skin-resident memory T cells [112]	Clinical data are limited; IL-7 is implicated in persistence of TRM that	- IL-7 maintains skin-resident memory T cells (TRM) survival in murine and

			underlie relapse, but no approved IL-7 targeted therapy for psoriasis exists [113].	human skin models, supporting local disease memory in psoriasis [113].
IL-8 (CXCL8)	Neutrophils, KCs/ ↑ Serum & lesional skin	- Attracts neutrophils - Causes keratinocyte hyperproliferation - Stimulates angiogenesis [114]	Elevated serum and lesional IL-8 correlate with disease severity; no direct anti-IL-8 therapy is approved for psoriasis [115].	Keratinocytes and neutrophils produce IL-8 in psoriatic lesions; IL-8 drives neutrophil recruitment and NET formation in preclinical studies [115].
IL-9	Th9, Th22 cells/ ↑ Lesional skin & plasma	- Boosts IL-17A from CD4+ T cells - Enhances Angiogenesis [116]	Higher IL-9 levels are reported in psoriasis patients (Associations with severity/MetS); IL-9 is under investigation as a potential target [117].	Th9/IL-9 amplifies IL-17A production and angiogenesis in preclinical models; anti-IL-9 antibodies reduced inflammation in mouse psoriasis models [117].
IL-10	Th cells, macrophages, DCs/ ↑ Serum & lesional skin	modest benefit Downregulates IL-8/CXCR2 signaling - Reduces keratinocyte proliferation - Suppresses type	Recombinant IL-10 was trialed in pilot and phase II studies for psoriasis — generally safe with mixed clinical efficacy;	IL-10 is anti-inflammatory in animal models, reduces keratinocyte proliferation and inflammation in
		inflammation [118]	some trials showed reduced relapse rates or clinical benefit [119]	preclinical studies [119]
IL-11	Fibroblasts, epithelial cells/ ↑ Lesional skin	- Decreases keratinocyte proliferation - Reduces T cell infiltration - Shifts immunity towards Th2[120]	Small clinical studies suggested rhIL-11 can ameliorate psoriasis lesions and downregulate type-I cytokine expression, but development did not progress to large phase III trials for psoriasis.	Recombinant IL-11 (rhIL-11) reduced keratinocyte proliferation and inflammation in early human and animal Studies [119]
IL-12	DCs, macrophages,	- Blocks γδT17 infiltration	Ustekinumab (anti-IL-12/23	Preclinical models show

	monocytes, B cells/ ↑ IL-12p40/p70 in lesions & serum	- Supports Th1 differentiation - Stimulates IFN-γ Production [120]	p40) is approved and highly effective in plaque psoriasis and psoriatic arthritis — strong clinical evidence from pivotal trials.	IL-12 contributes to Th1 polarization; blockade of IL-12/23 p40 reduces psoriasiform inflammation in mice [121]. .
IL-13	Th2 cells, mast cells, basophils/ ↑ Lesional skin	Promotes Th2 activity Suppresses type 1 inflammation Exact role in psoriasis unclear [120]	IL-13/IL-4 blockade (dupilumab) is approved for AD but shows limited benefit in psoriasis and has been associated with paradoxical psoriasiform reactions in some patients	IL-13 is linked to Th2 activity and can suppress Th1 responses in preclinical models; role in psoriasis is complex and less dominant than Th17 cytokines [122].

Transforming growth factor β and psoriasis

An essential regulator for preserving immunological homeostasis is TGF-β. Abnormalities in TGF-β significantly affect a autoimmune illnesses, chronic inflammatory problems, parasite infections, neurological diseases, cancer, and persistent transplant rejection.expression or TGF-β response [123]. When TGF-β is administered, symptoms of autoimmune diseases are suppressed. In contrast, anti-TGF-β antibodies accelerate the course of the illness. A phenotype typical of autoimmune disorders is caused by mutations in TGF-β genes [124]. Although macrophages may produce TGF-β, it limits their function. Additionally, it suppresses neutrophil activity, promotes fibroblast growth and extracellular matrix synthesis by these cells, and initiates angiogenesis [125]. The T lymphocyte population can also be controlled by TGF-β. By utilizing peripheral FOXP3+Treg, it stimulates the formation of a Th17 response while suppressing the growth of Th1 and Th2 lineages [126]. Furthermore, Th3 is generated in the TGF- microalgae at high concentrations, and with full maturity They modulate immunoreactivity by secreting high quantities of TGF-β [127] It has been shown that TGF-β suppresses T cells, B cells, and macrophages in addition to having an impact on T cell functional memory transformation. Additionally, it suppresses the immune system response in conjunction with CTLA-4 and prevents leukocyte adherence to endothelial cells by blocking the production of adhesion molecules [128-129].There is still much to learn about the involvement of TGF-β in psoriasis. Its receptor in the skin's outer layer has been shown to decline significantly [130]. Because TGF-β1 is a strong growth regulator of keratinocytes, keratinocyte hyperproliferation is increased when its signaling is inhibited. Psoriasis [131] found that patients with psoriasis had greater levels of TGF- β1 expression in their blood and epidermis, as well as a link between TGF-β1 and PASI [132]. Furthermore, a decrease in TGF-β1 serum was observed following successful therapy. Furthermore, even in the context of increased TGF-β expression, aberrant TGF-β signaling seen in psoriasis promotes the overproduction of psoriatic cell types [133]. Stromal cells may be the mechanism underlying the increase in TGF-β levels in the blood of patients with psoriasis [134].

Cytokine Crosstalk and Amplification Loops

CROSSTALK IMMUNE CELLS TO KERATINOCYTE

Interleukin (IL)-17 is a key factor in the pathophysiology of psoriasis. Additionally, keratinocyte proliferation and aberrant differentiation are induced by IL-17 [135]. As discussed later, keratinocytes induced with IL-17 and tumor necrosis factor (TNF)-α generate a variety of inflammatory chemokines, cytokines, and antimicrobial peptides (AMPs) [136]. Additionally, keratinocytes are activated by IL-22, which leads to their proliferation and the generation of these inflammatory chemicals. In this section, we focus on immune cells that affect keratinocytes in psoriasis.

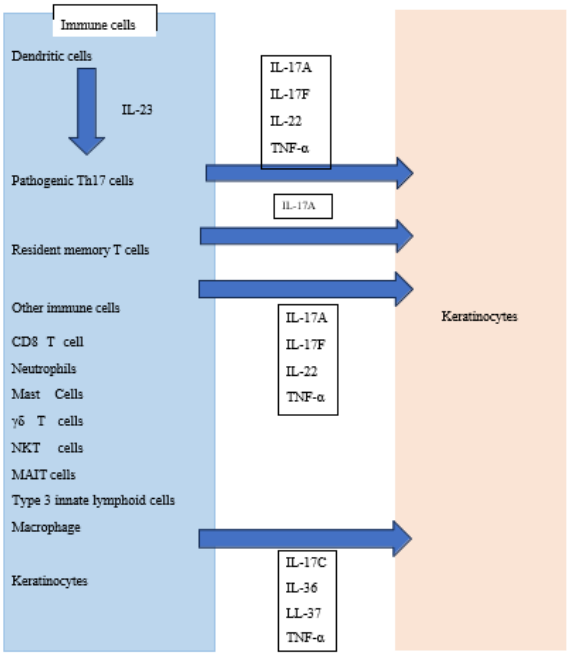

Figure No: 4 In psoriasis, immune cells and keratinocytes interact. In psoriasis, keratinocytes are impacted by a range of immune cells. TNF, MAIT, or mucosal- associated invariant T; NKT, or natural killer T; and IL, or interleukin.

Crosstalk keratinocytes to immune cells

Keratinocytes also produce a variety of chemicals that influence immune cells. This section focuses on these compounds and their effects on immune cells.

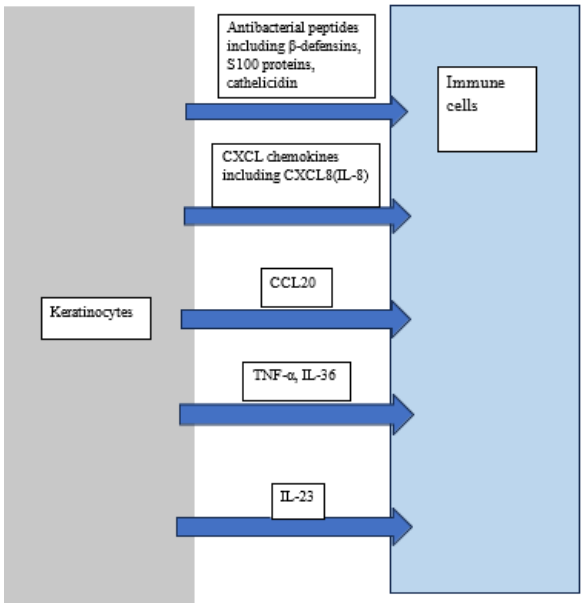

Figure N0:5 In psoriasis, immune cells and keratinocytes interact .in psoriasis, keratinocytes are impacted by a range of immune cells. TNF, or tumor necrosis Factor MAIT, or mucosal -associated in variant T; NKT or natural killer T; and IL, or interleukin.

Conclusion: Psoriasis is now recognized as a chronic immune-mediated disorder in which dysregulated cytokine networks particularly the IL-23/IL-17 axis supported by TNF-α-drive persistent cutaneous inflammation, keratinocyte hyperproliferation, and systemic comorbidities. The strong clinical efficacy of biologics targeting TNF-α, IL-23, and IL-17 has validated these pathways; however, variable responses, treatment costs, relapse after discontinuation, and long-term immunosuppression remain important limitations.

Future therapeutic progress will depend on a deeper immunological resolution of disease-specific T-cell subsets (including resident memory T cells and cytotoxic $CD8^+$ populations), keratinocyte-initiated cytokine signalling, and metabolic and neuro-immune contributors to inflammation. Precision immunology, biomarker-based patient selection, and emerging technologies, such as single-cell profiling, spatial transcriptomics, and computational drug design, offer the opportunity to personalize treatment, predict the durability of response, and identify new cytokine targets beyond the current IL-23/IL-17 paradigm.

Ultimately, shifting from the control of plaques to long-term immune re-education and true disease modification should define the next generation of psoriasis therapeutics.

Author Contributions

A.: Conceptualization, investigation, data curation, and writing original draft. **R.K.G.:** initiation, conceptualization, review manuscript, and supervision. **A.K.K.:** formal analysis, review manuscript, and project administration. **S.P.S.:** formal analysis and review manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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Abbreviations

TNF-α - Tumor Necrosis Factor - alpha
IL – Interleukin
IL1-Interleukin 1
IL2-Interleukin 2
IL4-Interleukin 4
IL6-Interleukin 6

IL10-Interleukin 10
IL-12-Interleukin 12
IL-17-Interleukin 17
IL22-Interleukin 22
IL-23- Interleukin 23
mDCs - Myeloid dendritic cells
pDCs - Plasmacytoid dendritic cells
TNF- Tumor Necrosis Factor
AMPs -Antimicrobial peptide
IFNγ -Interferon Gamma
MHC-Major Histocompatibility Complex
APCs-Antigen -presenting Cells
Psa- Psoriasis Arthritis
GC- Guanylate Cyclase

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