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Review Article

A review of core immuno-inflammatory mechanisms and key regulatory targets in psoriasis

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Abstract: Psoriasis is a chronic immune-mediated inflammatory skin disease caused by dysregulated interaction between innate and adaptive immune cells. Of note, the IL-23/Th17 axiom is new central circuit amongst known pathways, while TNF-alpha, IL-17 family cytokines and IL-36 mediate the dysfunction of keratinocyte and tissue in inflammation. An interconnecting inflammatory network involves dendritic cells, T-cell populations, keratinocytes, neutrophils and fibroblasts that plate epidermal hyperproliferation and lesional immune-cell recruitment. Biologics targeting TNF-alpha and IL-17 and IL-23 are clinically transformative in the treatment of disease, but a large cohort of patients are left with incomplete response, resistance or challenges in long-term management. Other novel targets such IL-36R and AHR may extend the window of therapeutic opportunity. Molecular stratification and biomarker-driven treatment selection also merit investigation in parallel with further delineation of a specific therapeutic strategy.

Keywords: Psoriasis, immune inflammation, IL-23/Th17 axis, TNF-α, IL-17, immune cells, targeted therapy, precision medicine, emerging targets

Introduction

Psoriasis is one of the most common chronic inflammatory skin disease affecting ~ 2%-3% of population worldwide [1]. Histopathological findings occur with epidermal hyper-proliferation, vascular remodeling and infiltration of inflammatory cells whereas clinically manifests as a scaly erythematous plaque [2]. Disease heterogeneous as there are many disease types like plaque, guttate and pustular psoriasis and severe variants generalized pustular psoriasis/guttate lead to erythrodermic psoriasis [3]. Its etiology is multifactorial, but immune dysregulation is regarded as the principal pathomechanism.

Moreover, during the last decade mounting evidence has emerged that psoriasis can no longer be regarded as mediated by 1 single cytokine/cell type but instead a hierarchically organized network of dendritic cells, pathogenic T-cell subpopulations, keratinocytes, neutrophils and stroma. Accordingly, differentiating between core drivers and downstream amplifiers is key to understanding both disease mechanisms and therapeutic translation.

All of the above have provided more theoretic basis for targeted therapy [4], and as emerging aspects of psoriasis immune-inflammatory network being gradually uncovered, several pivotal proinflammatory cytokines such as IL-23/Th17 axis, TNF-α and IL-17 defined in pioneering works and along with their downstream signal transmission process (NF-κB, JAK/STAT/MAPK et al.) with been an increasingly concentration. Psoriasis is a chronic inflammatory autoimmune disease with incompletely understood pathophysiology, in particular the interplay between innate and adaptive immunologic processes. In early disease, injured KCs release self-nucleic acids and antimicrobial peptides (e.g., LL37), activate pDCs and mDCs which

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then induce IL-23 and TNF-α secretion [5]. Moreover, IL-23 promotes differentiation of Th17 cells that secrete IL-17A, IL-17F and IL-22. NF-κB and MAPK signaling pathways mediate these cytokines activating inflammatory process of KCs, thus resulting in a positive feedback loop. In contrast γδ T cells and neutrophils In turn also secrete mediators like IL-17 and IL-36 which aggravates tissue damage while undergoing neutrophil extracellular traps (NETs) have been shown to augment the severity of disease in inflammation [6].

KCs and FBs are not just 'innocent by standers' in this context, and ICAM-1 can also be induced via IL-17/IL-17R axis mediated activation along with several other chemokines like CCL20. MMP2hi FBs, for instance, have been shown to promote CD8+ Tcell retention mediated by the CD100-PLXNB2 axis that induces chronic inflammation [7]; while FXYD3 activates an IL-17A signaling - induced feed-forward loop accelerate epidermal hyperplasia [8]. Understanding of immune-inflammatory mechanisms has led to major advances in the treatment of psoriasis (biologic agents and small molecule inhibitors). Anti-TNF-α agents (etanercept, etc.) and anti-IL-12/23 monoclonal antibodies (ustekinumab) were the first effective drugs practically used for patients with moderate-to-severe illness, which have greatly changed the patient's prognosis. More recent targeted therapies such as IL-17A (secukinumab), IL-23p19 (guselkumab) and the JAK-STAT pathway (tofacitinib) [9] showed higher specificity.

In addition, there are new targets such as the IL-36 receptor (spesolimab), AHR (agonist Tapinarof), and the OX40/OX40L pathway on the horizon to treat refractory patients [10]. However, certain patients experience low efficacy or drug resistance, potentially involving imbalance of Th1/Th17/Treg cells and epigenetic modification (e.g., GLS1-dependent histone acetylation) as well as dysregulation of gut-skin axis. Psoriasis has seen great development in the treatment landscape, yet many remain challenging. Current standardized molecular subtyping is not unified across different types of patients, as targeted drugs require long-term safety evaluation (e.g., JAK inhibitors may induce cardiovascular risk). The clinical strategy of combination therapy (e.g., biologics and methotrexate(MTX)) for RA treatment still needs a firm evidence basis [11]. For basic research, single-cell sequencing and spatial transcriptomics are predicted as the tools that can reveal cellular heterogeneity of psoriatic inflammatory microenvironment, organoid models and artificial intelligence prediction would enhance the process from target discovery to clinical application.

This review outlines the mechanism of immune inflammation in psoriasis and highlights their mechanisms by providing insight on important immune cells (eg, DCs, Th17 and γδ T cells), cytokine network (IL-23/Th17 axis, TNF-α and IL-36) and signaling pathways (NF-κB and JAK/STAT). It also reviews the clinical progress of existing targeted treatment and future perspectives, aiming to provide theoretical reference for precision therapy in psoriatic patients.

Overview of psoriasis immune inflammation

Classical subtypes and clinical characteristics

Psoriasis is a widely prevalent chronic inflammatory skin disease of unknown etiology that clinically presents with papular and scaly skin lesions, and it belongs to the group of immune-mediated diseases. Its pathogenesis is multifactorial and heterogeneous. Typically presents as erythematous, scaly plaques on extensor surfaces of arms & legs and scalp There are several clinical subtypes of psoriasis [12] (plaque-type, guttate-type, pustular-type, erythrodermic-type). Plaque-type psoriasis is the most common of these, with erythema and silvery-white scale. Guttate psoriasis is observed more in teenage and frequently linked with streptococcal infection. Psoriasis with pustular type has sterile pustules in most cases: In case of Psoriatic arthritis, the involvement can be mono- or poly-articular involvement leading to joint swelling and pain. EP is features of diffuse erythema and large-scale peeling areas, but in severe cases it can be quickly progressive and life-threatening.

In patients with psoriasis vulgaris, generalized pustular psoriasis (GPP) is an infrequent but more severe subtype and categorized as autoinflammatory skin disease [13]. The key feature is isolated, sterile, visible pustules that can be accompanied by systemic symptoms like fever, chills and leukocytosis. In a minority of cases [14], systemic symptoms may be lacking. GPP

has a course of highly variable disease with frequently cyclical flares in which erythema and pustules alternate. It also plays a vital role in the clinical side of patient's life because this disease can be dangerous [15] and its diagnosis and treatment methods are often tedious.

Psoriasis is an immune-mediated skin disease with unequivocal establishment for its pathogenesis and the important role of IL-23/IL-17 signaling pathway mediated dysregulation beyond psoriasis to pustular type [16]. EP can also be used to describe a more severe and rare form with generalized eruptions involving almost total skin surface (widespread erythema and adherent scaling) [17]. The most clinical severe type of psoriasis, EP is associated with rapid progression of disease, multiple complications and higher mortality risk [18]. Psoriasis comprises multiple distinct subtypes that vary widely in their clinical appearance, pathology and pathophysiology. Increased clinical heterogeneity and recurrent flares among new rare essential PSD subtypes presented after GPP and EP must be noted - the early identification of these distinct subtypes for use as meaningful prognostic indicators along with optimal timely treatment is crucial.

In this sense, the current study is clinically relevant as careful characterisation of these subtypes is required to obtain additional insights concerning their prognosis and implement personalized therapeutic regimens.

Immune-inflammatory core role in psoriasis

Psoriasis is a chronic inflammatory skin disease, in which IL-17 signaling pathways play an important role. $CD8^+$ T cells induced by autoantigens are one of its main pathogenic factors in the pathogenesis of rheumatic diseases [19]. The immune-inflammation axis needs to be continuously activated in order for the disease to progress. DCs are stimulated by environmental inputs, like skin damage and generate various inflammation-driving T cell subsets (i.e. Th1, Th17 or Th22) that release pro-inflammatory cytokines such as IL-17, IL-23 and TNF-α. In addition to promoting the aberrant growth of KCs, these inflammatory mediators also increase local inflammatory response [20]. Psoriasis is a chronic and highly recurrent disease, and the theoretical basis for the targeted therapy provided by the positive feedback loop. At the mechanistic level, MMP2 phenotype FBs were identified to enhance $CD8^+$ T cell retention in skin by regulating the CD100-PLXNB2 signaling pathway hence supporting persistence and amplify local inflammation which triggers psoriasis reactivation [7]. Additionally, γδ T cells, which represent a significant source of the cytokine IL-17A (41), are critical for psoriatic inflammation. According to earlier reports, hyperforin blocks the MAPK/STAT3 signaling pathway which suppresses the function of γδ T cells and ameliorates IMQ-induced psoriasis-like inflammation [21]. The downstream IL-17 driven inflammatory mediators (e.g. IL-36G, S100A8, DEFB4A and DEFB4B) positively correlate with psoriasis clinical severity in KCs - indicating their potential role as novel disease activity biomarkers. Confirmation of this is also present in the change brought about by treatment with IL-23 inhibitors where significant changes are noted among the composite immune cells involved in psoriatic lesions acting on Psoriasis confirming multifarious hands that Th17 subgroups are critical for disease processes to occur.

Metabolic imbalance, too, contributes to immune-inflammatory dysregulation in psoriasis. Indeed, a study demonstrated that glutamine catabolism by GLS1 is pathologically activated in psoriasis and induced acetylation of histone H3 in the region of the IL-17A promoter. This promotes Th17 and γδ T17 cell differentiation and functional activation, thereby enhancing inflammation and immune dysregulation [22]. Exogenous infections such as those by clones of Group A Streptococcus (GAS) also induce psoriasis lesions. This mechanism of action may be mediated through activation of CD1a-restricted autoreactive GAS-induced psoriasis contributing T cells by GAS [23]. Additionally, TFAP2C also serves to activate and augment the Th17 and Th1 cells which initiate an inflammatory program through the induction of TEAD4 expression [24].

This feed-forward circuit between dendritic cells, pathogenic effector T-cell subsets, keratinocytes and innate immune effectors is depicted in **Figure 1** (the integrative immune-inflammatory network regarding psoriasis). The schema differentiates between central pathogenic nodes and downstream amplifiers, vertically aligning additional validated and novel

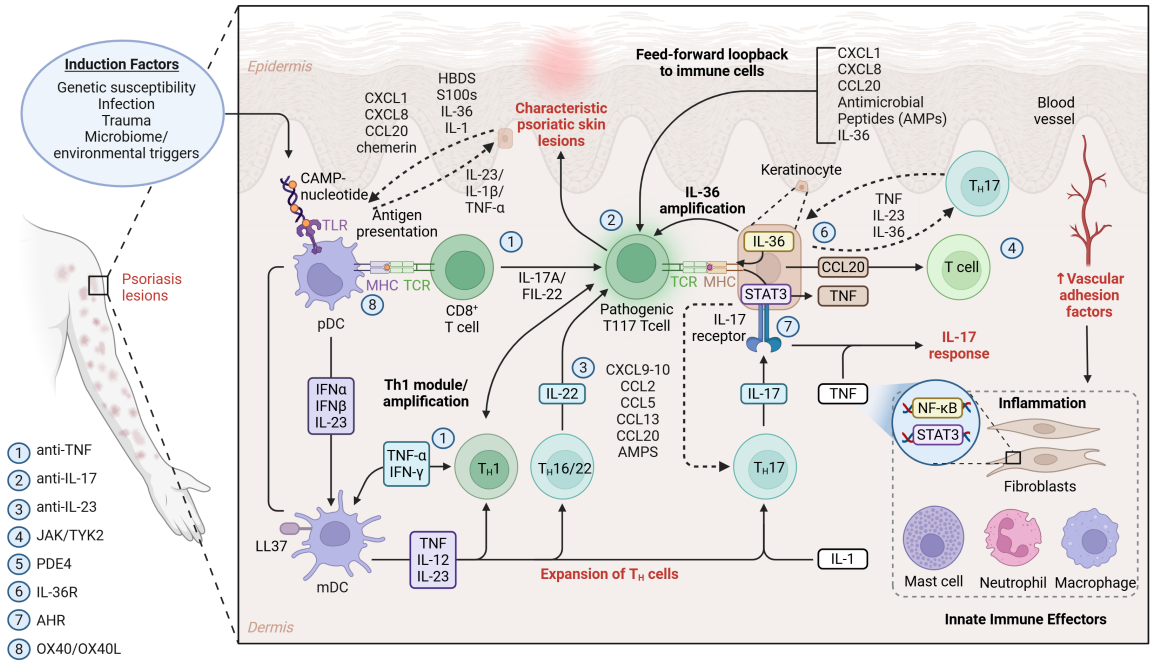

Figure 1. Central immune-inflammatory network and primary therapeutic targets in psoriasis. Psoriasis is caused by a combination of genetic susceptibility and environmental triggers (infection, trauma and perturbation to the microbiome) that promote epidermal stress and self-nucleic acid release. These signals stimulate plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs), which secrete type I interferons, IL-23, TNF-α, IL-1β and other inflammatory mediators. These pathways in turn promote the polarization and development of pathogenic T-cell subsets, especially T17/Th17 cells, along with some contribution from Th1-associated inflammatory responses. Effector cytokines (e.g., IL-17A/F and IL-22) signaling through keratinocytes induce chemokines, antimicrobial peptides, and IL-36, which initiate immune-cell recruitment and perpetuate lesional inflammation. IL-36-mediated signaling further amplifies keratinocyte activation and feed-forward inflammatory crosstalk within psoriatic skin. The major roles of stromal and innate immune effectors including fibroblasts, neutrophils, mast cells and macrophages are as tissue level amplifiers of chronic inflammation. Major validated or potential therapeutic targets that are mapped onto this network includes TNF-α, IL-17, IL-23, JAK/TYK2, PDE4, IL-36R, AHR and OX40/OX40L.

therapeutic targets within this operant framework.

Overview of major pathological changes: epidermal hyperplasia, vascular remodeling, and inflammatory infiltration

Psoriasis is one of the more prevalent chronic inflammatory skin disorders, and its pathogenic mechanisms are primarily related to dysregulated epidermal KCs proliferation, dermal vascular remodeling, and the infiltration of a variety of inflammatory cells. The main pathophysiological changes are synergistically linked causing marked epidermal thickening and the development of typical silvery scales. Meanwhile, the capillaries in the dermal papillary layer become dilated and proliferate and reach angiogenesis so as to enable inflammatory cells to migrate into the lesion site. Inflammatory cells include T cells, DCs, neutrophils and macrophages; they are mainly recruited at the epidermal-dermal junction to secrete a higher amount of inflammatory mediators like TNF-α, IL-17 and IL-23 which activate immune responses and support persistent chronic inflammation [25]. Studies have found that when Ovol1-deficient mice are administered with imiquimod (IMQ), pro-inflammatory cytokine IL-1α signaling is aberrantly activated in their skin, which dramatically promotes immune cell infiltration and epidermal hyperplasia. This pathway is regulated by OVOL1 to provide protection from psoriasis-like skin lesions [26]. The IMQ-induced psoriasis-like mouse study demonstrated that fisetin was significantly more effective than rapamycin in ameliorating skin inflammation with less infiltration of T cells and F4/80$^+$ macrophages as well as blocking Akt/mTOR signaling activity, thereby promoting KCs differentiation and autophagy [27].

In addition, GLS1 or MALT1 protease blockade markedly attenuates the differentiation of Th17 and γδT17 cells and decreases epidermal hyperplasia. Mechanistically, IL-17A instructs KCs to overexpress GLS1 by activating the MALT1/c-Jun signaling axis, which ultimately drives their hyper-proliferation and pro-inflammatory chemokine release [22]. Furthermore, FXYD3 behaves as a promoter of IL-17A signaling in KCs, establishing a positive feedback loop that worsens the advancement of inflammation [8]. PGE2 uses this PUN-mediated mechanism to exert its potent anti-inflammatory activity by inhibiting the activation of NF-κB pathway and cleavage of caspase-1; thus suppressing abnormal IL-1β and its mediators causing inflammatory cascade [28]. CXCR4^hi neutrophils, regulated by transcription factor CREB1, play an important role in the inflammation-associated vascular remodeling process. These cells significantly recruit and migrate within the vascular and inflammatory microenvironment, exacerbating local inflammation at the same time to contribute to disease progression [29].

At present, some natural or synthetic drugs exhibit a good prospect of application for psoriasis inflammation regulation. Inhibition of the NF-κB signaling pathway by daphnetin decreases HaCaT cell proliferation and inflammatory response which effectively mitigates skin lesions and inflammation in an IMQ mouse model [30]. Moreover, CS suppressed the expression of pro-inflammatory cytokines and chemokines by regulating the MAPK signaling pathway, which relieved metabolic disorder in psoriasis mice [31]. Resveratrol (Res) reduced macrophage infiltration and glycolysis levels to ameliorate psoriasis-like pathological changes [32]. Dexamethasone (DXM) is a glucocorticoid known to suppress keratinocyte hyperproliferation and inflammation thereby holding significant value in acute symptom management [33]. The main cellular components of psoriatic immune inflammation, along with their major mediators, biological functions, representative signaling pathways, pathogenic roles evidence levels as well as relevant therapeutic or experimental strategies are summarized in **Table 1**. This table organizes elements into a functional hierarchy axis that distinguishes primary pathogenic drivers - including dendrites, Th17 cells and keratinocyte-centric inflammatory circuits - from secondary amplifiers and emerging contributors. This integrative summary establishes a more unified structural framework with which to consider the immunopathological basis of psoriasis while laying the groundwork for continued conversation regarding disease evolution, mechanistic complexity and therapeutic translation.

Key immune cells and their functions

DCs

Subtypes and activation mechanisms: In non-erythrodermic stages of psoriasis, apoptotic keratinocytes release self-nucleic acids and antimicrobial peptides that activate pDCs through pattern-recognition pathways (eg, TLR7/TLR9). The first response consists of type I interferon production and dendritic cell subsets during the maturation of dermal and inflammatory dendritic cells. In matured lesions, cDC2 and inflammatory DCs are the main producers of IL-23 and TNF-α which mediates persistent pathogenic T-cell activation and a chronic inflammation [20].

PRR sensing and resulting downstream inflammatory networks fuel psoriasis-dependent DC activation, with the TLR7/c-Rel axis as a prominent player. Activated DCs promote Th17 polarization by inducing IL-6, IL-1β and costimulatory molecules that can enhance local tissue inflammation [34]. Therefore, in the context of psoriasis disease, DCs should better be considered as activating and polarizing cells not as single cell long-term effector.

Psoriasis of types DCs include such as: pDC (plasmacytoid DC), cDC (conventional DC), iDC (inflammatory DC) and LCs (Langerhans cells). More precisely, the pDCs recognize damaged nucleotides with TLR7/TLR9 while cDC2 and iDCs release IL-23 inducing Th17 differentiation; in response to stimulation, such as IL-1β, LCs also make IL-23 supporting the Th17 immune response. Collectively these subsets of DC connect innate sensing with adaptive T cell polarization, and their most oncogenic contribution appears to be the amplification of IL-23 driven Th17 responses [35].

Antigen presentation and T cell activation: DCs not only contribute to psoriasis through antigen presentation, but also by promoting T-cell

Table 1. Functional hierarchy of major cellular components in psoriatic immune inflammation and their translational relevance

Cellular component	Key mediators	Main biological function	Representative signaling pathway (s)	Pathogenic relevance in psoriasis	Representative therapeutic/experimental strategy	Evidence level	References
Th1 cells	IFN-γ; TNF-α	Promote inflammatory polarization and macrophage activation	JAK-STAT	Contribute to inflammatory polarization, plaque persistence, and phenotype heterogeneity rather than serving as the dominant central axis	TNF-α blockade; JAK-pathway modulation	Secondary but important	[157, 162]
Th17 cells	IL-17A; IL-17F; IL-22	Drive keratinocyte activation, epidermal hyperplasia, and neutrophil-oriented inflammatory amplification	STAT3; IL-23/Th17 axis	Dominant adaptive effector axis and central driver of chronic plaque inflammation	IL-17-targeted biologics (e.g., secukinumab)	Core	[163, 164]
γδ T cells	IL-17; IL-22	Rapid innate-like production of IL-17-family cytokines during early inflammatory amplification	IL-23-responsive signaling; context-dependent Notch-related regulation	Early inflammatory amplification, especially in selected phenotypes and acute lesional initiation	γδ TCR inhibitors (experimental)	Secondary/ phenotype-dependent	[165, 166]
DCs	IL-12; IL-23; TNF-α	Initiate innate immune sensing and polarize pathogenic T-cell responses	TLR/NF-κB; TLR7/c-Rel-related signaling	Bridge innate and adaptive immunity and act as primary upstream initiators of IL-23-dependent inflammation	IL-23-directed therapy (e.g., guselkumab); DC maturation/co-stimulatory pathway modulation	Core	[167, 168]
Macrophages	TNF-α; IL-1β	Amplify cytokine release, tissue inflammation, and dermal immune activation	MAPK; NF-κB	Secondary inflammatory amplifier contributing to dermal inflammation and cytokine-rich lesional maintenance	TNF-α-directed therapy	Secondary amplifier	[96, 112]
Neutrophils	ROS; LL-37; NET-related mediators	Form Munro microabscesses and amplify keratinocyte- and cytokine-driven inflammation	NETosis	Secondary but clinically characteristic lesional amplifier, particularly in neutrophil-rich inflammation	Antioxidant/NET-targeted experimental strategies	Secondary but clinically relevant	[169, 170]
KCs	IL-36; S100A7-9; chemokines and antimicrobial peptides	Act as both effector and amplifier cells by linking cytokine signaling to epidermal pathology	PI3K/Akt; IL-17-responsive signaling	Core downstream effector that sustains epidermal hyperplasia, barrier dysfunction, and feed-forward inflammatory loops	Barrier-restoring strategies; IL-36-related intervention	Core downstream effector	[171, 172]
ILC3	IL-17; IL-22	Provide T-cell-independent type 3 cytokine production and contribute to chronic inflammatory signaling	AHR pathway	Emerging contributor to chronic inflammation rather than a uniformly established core driver	AHR agonist-related strategies (context-dependent)	Emerging	[173, 174]
Mast Cells	Histamine; IL-31	Contribute to pruritus, vasodilation, and neuroimmune signaling	FcεRI signaling	Secondary neuroinflammatory and pruritus-related contributor	IL-31RA-related antipruritic strategies	Secondary/ symptom-linked	[175, 176]
Treg cells	IL-10; TGF-β	Maintain immune tolerance and suppress excessive effector T-cell responses	FOXP3-related regulatory signaling	Core regulatory defect contributing to loss of immune homeostasis	Immune-restorative strategies (experimental)	Core regulatory defect	[51, 53]
Endothelial Cells	VEGF; ICAM-1	Promote angiogenesis, vascular remodeling, and leukocyte recruitment	VEGF/PI3K-Akt	Secondary tissue-level amplifier contributing to vascular remodeling and inflammatory cell trafficking	Anti-angiogenic/VEGF-related experimental strategies	Secondary	[177, 178]
FBs	MMP-9; FGF; fibroblast-derived inflammatory mediators	Promote stromal remodeling, immune-cell retention, and keratinocyte-fibroblast crosstalk	TGF-β/Smad	Emerging stromal amplifier involved in lesional persistence and structural remodeling	MMP-related or stromal-targeted experimental strategies	Emerging	[179, 180]
NK cells	IFN-γ; perforin	Mediate cytotoxicity and modulate inflammatory immune responses	NKG2D/STAT4	Secondary immune contributor with context-dependent pro-inflammatory effects	NKG2D-related modulation (experimental)	Secondary/ context-dependent	[181, 182]
Neurons	CGRP	Mediate neurogenic inflammation and itch-related signaling	TRPV1/ERK	Secondary neuroimmune contributor, especially in pruritus-associated inflammation	Neuroimmune/antipruritic experimental strategies	Secondary/ symptom-linked	[183, 184]
Adipocytes	Leptin; adiponectin	Link metabolic dysregulation to inflammatory immune bias	AMPK/JAK	Context-dependent metabolic amplifier, particularly relevant to obesity-associated disease aggravation	Metabolic modulation/ leptin-related experimental strategies	Secondary/ comorbidity-linked	[185, 186]

polarization through co-stimulatory signaling and release of inflammatory cytokines. Mature DCs release mediators such as IL-12, IL-6 and IL-1β [35] that augment pathogenic T-cell stimulation. A number of modulators, such as plant-derived compounds rosmarinic acid and curcumin, also downregulate DC maturation and Th1/Th17 polarization [36].

Furthermore, co-stimulatory pathways play pivotal roles in DC maturation and ability to activate T cells. DC-T-cell co-stimulation has been found to be critical in sustaining psoriatic inflammation, such as through CTLA4Ig-sensitive signaling [37].

TSLP induces DC maturation and drives Th17 polarization via JAK/SYK-associated signaling pathways [38]. It is of interest primarily as an upstream regulatory and not as a bona fide pathogenic axis, such as IL-23/Th17.

Correspondingly, P2X7R is activated to enhance the maturation of DC and upregulates IL-23/IL-1β production that augments Th17-related inflammation. These results are consistent with the hypothesis that a purinergic signal amplifies DC immune activation in psoriasis [39].

Together, we should consider DCs as orchestrators of the pathogenic T-cell response in psoriasis. Likewise, the major importance lays not in their role on chronic lesional inflammation but rather on initiating immune polarization.

T lymphocytes

Th1/Th17/Th22 cells and their cytokine profiles: Within T-helper subsets involved in psoriasis pathogenesis, Th17 seem to be the predominant effector population and responsible for driving disease process, whilst Th1 is thought predominantly to mediate broad inflammatory skewing and phenotypic diversity of lesions as well as more functionally-altered/flexibly-differentiated secrete Th22 primarily amplifying keratinocytes dysenforcement/barrier rupture. These Th17-related cytokines such as IL-17A/F and IL-22, drive neutrophil recruitment, keratinocyte proliferation and chronic inflammation while the Th1 cytokines IFN-γ and TNF-α serve to sustain immune activation and plaque maintenance [40].

Regulatory circuitry influencing Th1 or Th17 or Th22 balance through complex upstream effectors miRNAs, transcription factors and MAPK/STAT-related pathways [41]. Examples of these are miR-125a-5p, TFAP2C-TEAD4 axis, and BML-111 [24, 42, 43]. However, these regulators should be further regarded as modulatory components and are not indicative of the fact that all T-helper subsets play similar roles in disease pathogenesis.

Moreover, cytokine profiles have also been associated with differences in immune responses between psoriasis and atopic dermatitis, where active Th1/Th17 cytokines directly correlate to impaired lipid barrier (as seen in psoriasis). Comparative studies further show that active Th1/Th17-type involved in psoriasis are more closely correlated with the disease compared to atopic dermatitis, especially with respect to barrier lipid defects [44]. Moreover, the role of LARP7-SIRT1 axis in inflammatory process suggests its potential involvement as a target with regulatory activity [45].

In conclusion, while relative contributions of Th1, Th17 and Th22 responses can differ between disease stages/clinical phenotypes, the most compelling evidence to date supports a Th17-centered inflammatory model in psoriasis.

Dysfunction of Tregs: The predominant IL-10-producing Treg population that can prevent psoriasis inflammation mediated by IL-17A$^+$ γδ T cells in the skin are those expressing peroxisome proliferator-activated receptor γ (PPARγ). Thus, Tregs are important for maintaining immune tolerance, regulating immune homeostasis, and limiting nonphysiological inflammation [46]. However, in psoriasis patients, Tregs' number is often decreased or their function is inhibited so that they cannot inhibit pathogenic T cell activation effectively such as Th17 cells. This results in dysregulation of the immune system and persistence of inflammatory responses [47]. Tregs in the joint cavity of patients with psoriatic arthritis are highly dysfunctional. In contrast with circulating Tregs, the relevant transcription factor Foxp3 is downregulated and pro-inflammatory markers such as CD161, RORγt and ICOS upregulate; CTLA-4 and TIGIT were not reduced in the key PsA study (and have been previously reported increased in synovial-fluid Tregs [48]). The instability of

Foxp3 expression is also one mechanism underlying peripheral immune tolerance collap se, allowing autoreactive T cells to escape into tissues and drive psoriasis inflammatory processes [49].

In addition, cytokines present in the inflammatory microenvironment, particularly IL-6 and IL-23, are able to trigger the transition of Tregs into an inflammatory phenotype exacerbating skin lesions and generating a sustained positive feedback loop [50]. Excessive function of Tregs not only promotes the maintenance of inflammatory response but also hinders the self-limitation and repair processes in skin lesions. Research has indicated that IL-17A is crucial to Treg impairment, and its excessive expression hinders the immunosuppressive capacity of Tregs. In addition, targeted therapy against IL-17A has been suggested to restore Treg function. IL-17A neutralizer secukinumab was shown to partially restore Treg suppressive function and exercise anti-psoriasis effects [51]. In a mouse model of psoriasis, etanercept inhibits the JAK/STAT3 pathway and decreases the Th17/Treg ratio while shifting macrophages to the anti-inflammatory M2 phenotype, and reduces inflammation [52]. Apelin is also shown to regulate Th17 differentiation and adjust the balance of Th17/Treg ratios, alleviating IMQ-induced psoriasis plaques in mice. Moreover, $Foxp3^+$ B cell-derived Tregs (Foxp3-Treg-of-B) can promote the selective conversion of macrophages into M2 subtypes through STAT6 pathway activation, offering a new cellular therapeutic approach for psoriasis [53].

Innate immune cells

Neutrophils: NET formation and tissue damage: Neutrophils are central innate immune system effector cells and important mediators of the psoriasis immune-inflammatory response. They have roles in the immune response such as cytokine and chemokine secretion and NET generation which recruit and amplify local inflammatory responses. NETs: a mix of fibrin, DNA and other enzymes expelled by neutrophils. Not only do these substances trap and kill pathogenic microbes, but they also contribute to the activation of other immune cells, such as macrophages and dendritic cells (DCs). In contrast, increased NET formation correlates with damage and disease flaring in psoriasis [54].

In psoriasis pathogenesis, neutrophils are excessively activated and aberrantly produce NETs, resulting in skin barrier damage and inflammation amplification. NET components (fibrin, DNA) directly damage KCs and contribute to skin hyperpermeability and potentiate inflammation. Moreover, the release of NET-derived enzymes (e.g., elastase and matrix metalloproteinases) destroys the extracellular matrix that contributes to local inflammation. NETs formation is closely related to the inflammation level in psoriatic lesions [55]. NETs induce a vicious cycle through IL-17, TNF-α and other inflammatory pathways that lead to aggregation and persistent activation of immune cells, which further drives the chronicity and relapse of psoriasis [56].

By targeting PAD4 to inhibit the formation of NET, JKSQD may help resolve the progression of psoriasis [57]. In addition, SHP2 is critical for both NET release and subsequent cell death, making it a potential novel therapeutic target in psoriasis [58]. Citrullinated but non-natural LL37 was found to activate IFN-γ responses in T cells and B cells from psoriasis patients, particularly those with high levels of circulating NETs and early disease onset, thus implying its role as an autoantigen [59].

Neutrophils amplify skin inflammation and inflammatory cascade by activating IL-36 and TLR4 signaling pathways further exacerbate tissue damage. Psoriasis could be treated with novel approaches that modulate neutrophil activity (e.g. NET regulation, etc.) [6]. Not only such approach will not more potentially mitigate damage on the skin although improve clinical symptoms, but also it may drive psoriasis therapies by targeting NET related molecules or interfering excess of neutrophil activation.

γδ T Cells and Natural Killer (NK) cells: As important innate immune cells, γδ T cells and NK cells are involved in the early stage of inflammation during the immune-inflammatory response of psoriasis. In addition to local tissue damage, immune evasion, γδ T cells can rapidly respond and directly recognize pathogens, tumor cells and damaged host cells; their immune surveillance function is independent of antigen-presenting cells [60]. The increase in γδ T cells and the increased activity of these cells closely correlate with damage to skin bar-

rier function and exacerbation of inflammatory responses, where it plays an important role.

GLS1-mediated glutamine metabolism drives the differentiation of γδ T17 cells, thereby promoting the development of psoriasis [22]. High-fat diet (HFD) induces a pro-inflammatory milieu that triggers the migration of γδ T cells to the skin and enhances IL-17 production in spleen, exacerbating skin inflammation. Moreover, dermal γδ T cells migrate into lymph nodes to differentiate into highly activated γδ T17 subpopulations dependent on CCR2/CCR6-mediated migration and induce glycolytic reprogramming through the AKT/mTOR/HIF-1α pathway [61]. This, in turn, drives IL-17 secretion and enhances skin inflammation. By inhibiting this metabolic pathway, D-mannose preferentially suppresses γδ T cell expansion and IL-17 secretion that alleviates psoriasis skin inflammation.

NK cells are also involved in the immune response to psoriasis, particularly at early stages of the immune response. NK cells can secrete IFN-γ, which activate other immune cells, and mediate direct killing of damaged or mutated cells in order to limit the expansion of lesions [62]. Nonetheless, the difficulty was that dysfunctional or overactive NK cells can induce persistent inflammation, which in turn exacerbates skin injury pathology. γδ T cells and NK cells cell interactions in psoriasis immune response. These cells independently effector the immune effects but also regulate themselves to promote or inhibit immune responses. IL-27 inhibits γδ T17-mediated inflammation, showing its immune-regulatory activity during psoriasis immune [63].

Therefore, regulation of immune mechanism of γδ T cells and NK cells may be a new target and strategy for the treatment of psoriasis.

Other cells: KCs and FBs in inflammation

KCs, which make up the majority of cells in the epidermis, are critical mediators of the immune-inflammatory response observed in psoriasis. They are not only target cells and cause the secretion of cytokines but also modulate immune response by interaction with immune cells. Our findings indicate that in the course of psoriasis pathogenesis lots of KCs, especially IL-17RC-positive spinous KCs associated with interleukin signaling, present high-level EMT activity as well, which might play important role in immune-mediated inflammatory response. In addition, KCs release chemokines (e.g., CXCL8) to recruit immune cells such as neutrophils and T cells that improve the local immune response [64].

FBs are also critical in the immune adaptive response psoriasis. The iFibs subpopulation greatly express cytokines such as IL-17 and TNF-α which promote the epidermal hyperplasia, additionally interact with KCs to further enhance the inflammatory reaction [64]. For instance, SFRP2+ FBs stimulate IL-36G in KCs that amplify the inflammatory response. The cross-talk between KCs and FBs during EMT deeply regulates the immune-inflame response in psoriasis by promoting immune cell recruitment and further aggravating local inflammation [65].

Daphnetin ameliorated skin lesions and inflammation in psoriasis mouse model by inhibiting NF-κB signaling pathway, which attenuates KC proliferation and inflammation [30], implying its potential use in the treatment of psoriasis. These findings acquired interesting implications for the potential of fibroblast-targeted intervention to ameliorate psoriatic immune inflammation as JAK inhibitor tofacitinib was able to restore fibroblast-like synoviocyte functionality and downregulate their pro-invasive and pro-inflammatory phenotypes in psoriatic arthritis [66]. MMP2-high expressing FBs are key players in the psoriatic inflammatory response. These cells promote CD8+ T cell residency through coordination of the CD100-PLXNB2 axis to amplify inflammation [7]. These mechanisms indicate that the interaction of KCs and FBs plays a critical role in the immune-inflammatory response of psoriasis, which highlights new insight and targeted options for psoriasis treatment.

Core cytokine networks

The IL-23/Th17 axis

Psoriasis is an IL-23/Th17 driven disease. Other inflammatory cytokines produced by activated antigen presenting cells (APCs) such as dendritic cells, IL-23 promote stabilization and maintenance of pathogenic Th17 responses, whereas IL-17A/F and IL-22 induce a change in keratinocytes to secrete pro-inflammatory mediators, antimicrobial peptides, epidermal hypertrophy/chronic tissue inflammation [67].

Multiple upstream modulators feed into this pathway. Inhibition of IL-23-mediated psoriasiform inflammation by regulatory B cells [68] with microbiota associated signals e.g. Malassezia globosa, promoting keratinocyte-derived IL-23 to drive pathogenic Th17 differentiation of the CD4 T helper cells [69].

Another, likely more experimental, set of regulators - e.g., Jak/STAT3-associated signaling, STING-related pathways and MST1 and CARD14-MALT1-dependent signaling - may engage the IL-23/Th17 axis in a modulated or potentiated manner (through interaction with cytokine orchestrators) but might be better regarded as upstream or parallel pathway modifiers than equivalent hub cytokine drivers [70-73].

In particular, especially for IL-23/Th17 axis, it is notable by not only mechanistic primacy and high disease relevance but also therapeutic translatability evidenced by the clinical efficacy of agents targeting IL-17 and IL-23.

TNF-α and the Th1 pathway

Although TNF-α/Th1 is known to play a significant role in the pathogenesis of psoriasis, due recently considered one of several inflammatory pathways collaborating in the development of psoriatic lesions, current evidence indicates thateven if dominant for some pathogenic mechanisms, it represent only part of an extensive TNF/IL-23/IL-17 network where IL-23 and Th17 pathway generally are seen as predominant. On the contrary, TNF-α stimulates immune cell activation and inflammatory machinery in keratinocytes as well as downstream signaling cascade [25]; these are associated with an increase in Th1-related responses.

There are many pro-inflammatory cytokines contributing to the synergistic aggravation in psoriasis among which TNF-α derived from partially Th1 mediated infiltration. Th1 inducible IFN-γ could upregulate antigen presenting cells as well directly modulating keratinocyte inflammatory programs, perpetuating lesional inflammation. In general, this interaction could be considered as an enhancing inflammatory cycle instead of classical overlapped principal pathogenic axis [74].

This axis is additionally supported by multiple lines of experimental evidence attesting to its pathogenic relevance. Agents embodying these ideas of interaction include BML-111 and hispidulin (HPD) which attenuate psoriasiform inflammation via downregulating Th1/Th17-dependent responses, while the TFAP2C-mediated signal pathway has been documented to drive activation of Th1/Th17, thus promoting inflammatory response; on top of that, hyperuricemia for example can also worsen the TNF-α-/IL-17-mediated inflammation in a metabolism dysfunction way [24, 43, 75, 76]. These findings should be interpreted more as demonstrating pathway amplification and modulation than a rewriting of the existing hierarchy of psoriatic inflammation.

There is probably a difference in how psoriasis patients are treated (especially TNF-α inhibitors such as adalimumab and infliximab), which are still present in clinical practice as one of the first biologic drugs. However, in the setting of IL-17 and IL-23 directed therapies, newer agents typically have higher skin response rates so that TNF-α blockers still retain an important role for selected patients based on patient features or other clinical characteristics. Long-term usage also takes into consideration risk of infection, immunogenicity, and secondary loss of response [77].

In conclusion, TNF-α/Th1 signaling is a clinically relevant amplification axis in psoriasis and Newton et al.'s findings add (as described already above) a novel mechanistic insight into how blockade of this pathway ameliorates the cutaneous features of this condition. Although it is a major contributor to the maintenance of inflammation and response to therapy, it does not substitute for the key pathogenic function of the IL-23/Th17 axis.

The IL-17 family and lesion maintenance

In psoriasis, the IL-17 family among the downstream effector cytokines is of central importance in sustaining chronic skin inflammation. IL-17 primarily targets keratinocytes with high expression of IL-17 receptors, potentiating chemokines, antimicrobial peptides and inflammatory mediators and connecting pathogenic T-cell responses with persistent epidermal activation and chronic inflammatory amplification [78].

In addition to lesion initiation, IL-17A also sustains chronic local inflammation in established

psoriasis [79]. Keratinocyte IL-17 receptor signaling enhances this maintenance function by activating downstream NF-κB and MAPK pathways that induce pro-inflammatory mediators. Other drivers such as diet-altered disturbance of the gut microbiome and FXYD3-driven strengthening of IL-17R signaling are likely to amplify this process [8].

Continuous signaling from IL-17 sustains a pathogenic cytokine network in psoriasis and facilitates keratinocyte inflammatory activation, resulting in chronic immune amplification [80]. However, it is important to mention that the focused experimental interventions on JAK/STAT3-related signaling or those directly diminishing IL-17-associated downstream pathways have demonstrated anti-psoriatic effects in animal models of disease [81, 82]. This has been primarily interpreted as providing support for therapeutic truncation of IL-17-dominated signaling rather than reconstitution of the psoriatic inflammatory axis.

In summary, the IL-17 family is widely viewed as a downstream effector module in psoriasis; thus its function is particularly meaningful for lesion persistence. Its importance is that it transduces this immune polarization into persistence of keratinocyte-mediated inflammation and also accounts for the (more than perhaps expected) clinical efficacy of targeting the IL-17 axis.

Emerging inflammatory mediators: IL-22, IL-36, and others

In addition, in addition to the IL-23/Th17 but also TNF-α-targeted pathways other inflammatory mediators contribute to disease amplification and the subtype-specific pathology of psoriasis. IL-22 and IL-36 among these are of particular interest due to their high relevance for keratinocyte dysregulation, epidermal remodelling and severe inflammatory phenotypes.

Psoriasis: IL-22 as a keratinocyte-targeted amplifier It stimulates epidermal hyperplasia as well as atypical differentiation and proinflammatory mediator release via IL-22R-dependent activation of JAK/STAT3 and MAPK signaling [83]. In addition, the evidence of regulatory interactions between IL-22BP and the miR-21-3p/IL-22 axis supports its relevance in the psoriatic pathophysiology [84]. Relative to IL-23/Th17 signaling, we expect that a better role for IL-22 will be as a downstream amplifier of epidermal aberrancy than an upstream driver.

In the case of IL-36 signaling, this has now been shown to be a central pathway mediating another major inflammatory pathway in psoriasis, specifically pathogenic inflammatory phenotypes and pustular disease. Keratinocyte activation and local cytokine release following IL-36 is enhanced with MyD88-dependent NF-κB/MAPK signaling, thereby promoting feedforward inflammatory loops [85]. Importantly, the IL-36 axis should not be viewed as equivalent on a pathological basis in all aspects of psoriasis, but rather seems to play an especially crucial role in pustular psoriasis and hyperinflammatory foci [86].

Interestingly, IL-22 and IL-36 showed mutual regulation in a synergistic fashion to enhance psoriatic inflammation. IL-36 can induce IL-22 mediated inflammation, and conversely, IL-22 can also induce expression/activity of IL-36 which would amplify the cutaneous inflammatory cascade. This concept of bidirectional interaction hints at a potential key histological passage and drug target in psoriasis [87].

Together, these cytokines highlight aspects of psoriasis pathogenic wiring beyond the IL-23/Th17 core axis centered on epidermal compartment dysfunction and subtype-specific inflammation maintenance. This is a bona fide addition to the mechanistic palette so far defined by this review - and needs to remain properly conditional as only amplifiers or phenotype-specific intermediaries incomparable with more central players such as IL-23/Th17 [88, 89].

Positive feedback and negative regulatory networks among cytokines

The pathogenesis and evolution of psoriasis involves extensive cytokine networks activating positive feedback pathways driving inflammation as well as negative regulatory elements promoting immune homeostasis which we can envision a barrier model describing how these biological effects might interact. So important are these regulatory terrains that they have become the purview of non-stop dynamical studies hunting for diseases and new thera-

peutic targets. These results imply that some of the identified SNPs are activating both the IL-23/IL-17 signaling cascade and the JAK-STAT signaling pathway leading to aberrant activation of macrophages and KCs leading to psoriasis as well as psoriatic arthritis [90].

In this setting, IL-23 promotes Th17 cells to produce IL-17, which leads to KCs secreting proinflammatory mediators such as IL-6, IL-8 and granulocyte colony-stimulating factor (G-CSF). This creates a typical inflammatory positive feedback loop that amplifies local immune responses. Moreover, granzyme K (GzmK) is able to upregulate IL-23 expression and enhance KC proliferation through the protease-activated receptor 1 (PAR-1), which also aggravated skin lesions [91].

In addition, the ACT1/TRAF6/TAK1/NF-κB signaling cascade is synergistically activated in KCs and macrophages on IL-23 stimulation which potentiates the IL-23/IL-17-mediated inflammatory responses within psoriatic skin [92]. While positive stimuli predominate, there are several negative regulatory pathways within the psoriatic inflammatory network to inhibit hyperactivation of T-cells and ensure homeostasis. For example, calcium/calmodulin-dependent protein kinase IV (CaMK4) promotes inflammation due to inhibition of the anti-inflammatory cytokine IL-10 expression, but deletion of CaMK4 markedly alleviates psoriasiform skin pathology [93].

Interleukin 10 (IL-10) is an important immunoregulatory cytokine in psoriasis. It blocks the secretion of IL-17 and TNF-α from Th17 cells, attenuates T cell activation, and down-regulates KCs production of proinflammatory cytokines. IL-10 downregulation usually signifies dysregulated inflammation. In addition, TLR2 signaling may reduce inflammation by facilitating the expansion of Tregs and increasing IL-10 production, which potentially makes it an attractive therapeutic target [94]. Levels of IL-10 are significantly reduced and TNF-α, IFN-γ and IL-2 concentrations increased in patients with active psoriasis indicating feedback regulation imbalance [95].

Orientin, a flavonoid that showed strong anti-inflammatory effects in psoriasis animal models and in vitro studies. It suppresses the release of numerous pro-inflammatory CD4+ T-helper cytokines (including IL-1β, IL-17 and IL-23), increases the expression of anti-inflammatory cytokine IL10 and restores GSH alterations by inhibiting MAPK pathway [96]. **Table 2** delivers a multi-dimensional cartography of the master cytokine network substrate of psoriatic immunoinflammation, elucidating the inter-network association between central dispositions or effectors and their opposite regulators in a milieu of immune effector actions. Given this comprehensive nature, here we aim to offer a theoretical basis for our improved understanding of psoriasis immunopathological pathways. Guided reading this article highlights the direct comparison of psoriasis proinflammatory and anti-inflammatory pathways.

Abundant Th17 and/or IL-23 signaling establishes self-propagating feedback loops resulting in the signature, phenotype, of psoriasis defining an IL-23/IL-17-dominated immunological dialog between immune cells and keratinocytes. There are anti-inflammatory mediators such as IL-10 that serve to counteract these responses, and there is also the ongoing crosstalk among macrophages with both Th17 cells and keratinocytes which further determines a lesional immune network. These mechanisms underpin IL-17/IL-23-directed therapy and other immunomodulatory strategies [97].

Major signaling pathways and molecular mechanisms

The NF-κB pathway

NF-κB as a Master Regulator of the Immune Response in Psoriasis It is also involved in many immune cells kcs mediated pathological processes, mainly by altering pro-inflammatory cytokines expression such as IL-1β and IL-6 to promote epidermal hyperproliferation, immune cell infiltration. The signaling pathways of NF-κB are composed of canonical (IκB-dependent) and non-canonical (mediated through NIK) activation cascades; this pathway's signal transduction is mainly contributed by a group of proteins termed as Rel family, which includes RelA, RelB and c-Rel.

Multiple recent studies revealed apparently complex interplay between the NF-κB pathway and its upstream regulators. Consequently, the small molecule inhibitors H-151 attenuate psoriasiform skin inflammation through STING/

Table 2. Multidimensional analysis of the core cytokine network in psoriasis immuno-inflammation

Cytokines	Main Sources of Cytokines	Main Functions	Associated Pathways	Role in Psoriasis	Potential Targets	References
IL-17A	Th17 Cells; KCs	Pro-inflammatory; Pro-keratinization	NF-κB Pathway	Worsen inflammation; Exacerbate lesion inflammation	IL-17A receptor; NF-κB p65	[30, 187]
IL-22	Th22/Th17 Cells	Pro-keratinization, Pro-inflammatory; Promoting Proliferation and Anti-apoptosis	JAK2-STAT3	Worsen skin lesions; Inhibit KC apoptosis	IL-22R blocker; IL-22/IL-22R1	[100, 188]
CXCL-1	KCs	Recruitment of Neutrophils	NF-κB-miR-27a-3p-galectin-3	Exacerbate inflammation; Chemotaxis/Antimicrobial/Pro-inflammatory	galectin-3	[189, 190]
IL-23	DCs/Macrophages	Maintenance of TH17 Cells; Driving Th17/Tc17 Differentiation	IL-23/STAT3	Drive inflammation; Promote inflammation to sustain relapse	p19/p40	[191, 192]
TNF-α	Macrophages/Lymphocytes	Pro-inflammatory; Activate MSCs to enhance their immune regulatory capacity	TNF-IRF7/NF-κB/IFN-α; TSG-6/STAT1/CXCL1	Block and subsequently induce psoriasis; Alleviate inflammation and ameliorate psoriatic-like lesions	TNF-α; TSG-6	[193, 194]
IL-9	T Cells/Th9 Cells	Pro-inflammatory/Th17 Amplification	IL-9/IL-9R/STAT; IRF4/STAT5/PU.1	Exacerbate inflammation	IL-9	[195, 196]
IL-1α	Intestinal Epithelium/Immunity; Stratum Granulosum KCs	Pro-inflammatory	IL-1R/NF-κB	Drive inflammation	IL-1R	[26, 197]
IL-17A/IL-17F	T17 Cells	Pro-inflammatory/Cytotoxic; Promoting KC Proliferation	IL-23R-STAT3; Hippo-YAP-AREG	Drive plaque inflammation; Drive epidermal hyperplasia	IL-17A/IL-17R; YAP-AREG axis	[198, 199]
IL-1β	Macrophages/KCs; $CD14^+$ DC3	Pro-inflammatory chemotaxis; Promote Th17/Inflammation amplification	STAT3/NF-κB; STAT2-FOSL2-XBP1	Exacerbate inflammation; Drive lesions	NRF2; $CD14^+$ DC3	[100, 200]
IL-6	Macrophages and Other Immune Cells; CD8 T Cells/KCs	Pro-inflammatory and proliferative signaling; Promote inflammation and Th17 differentiation	IL-6/JAK/STAT3	Drive KC proliferation; Amplify inflammation and lesions	STAT3; IL-6R	[201, 202]
IL-18	Macrophages/KCs	Pro-inflammatory and immune response regulation; Promote inflammation and Th17 cell development	Th1/Th17 axis; Inflammasome activation pathway	Induce inflammatory response; Promote inflammatory response	IL-18	[203, 204]
CXCL16	DCs; Monocytes/KCs	Chemotaxis of neutrophils; Chemotaxis and lipid phagocytosis	TLR7-MyD88; NF-κB	Promote neutrophil infiltration; Promote inflammation and lipid metabolism disorders	CXCR6	[205, 206]
IL-12/IL-23	DCs	Promote Th1/Th17 cell differentiation	JAK/STAT pathway; IL-12/IL-23-p40 pathway	Drive the inflammatory response	JAK inhibitor; IL-12/IL-23 p40	[207, 208]
IL-36	KCs, Macrophages	Promote KC proliferation and regulate immune cell activation	IL-36R signaling pathway; NF-κB, MAPK signaling pathways	Cause excessive proliferation of KCs, exacerbate the inflammatory response	IL-36; IL-36R	[209, 210]
IL-10	Tregs; DCs	Inhibit inflammatory response and maintain immune balance	TLR2 signaling pathway; FOXP3 signaling pathway	Reduce inflammation, alleviate skin lesions; Reflect compensatory response to chronic inflammation	TLR2; FOXP-3gene mutation	[94, 211]

NF-κB axis antagonism [98], indicating their putative therapeutic value in psoriasis. In addition, protein phosphatase SHP2 amplifies the activation of NF-κB pathway and worsens skin inflammation by dephosphorylating TLR7 at Tyr1024, which promotes its trafficking from Golgi apparatus to endosomes as well as increasing its ubiquitination [99].

Also a member of the NF-κB family, c-Rel is necessary for immune homeostasis. Reduced p65 levels prevent the assembly of any active NF-κB complex and inhibitory homodimers bind to IL-1β and IL-6 promoter regions, preventing expression. Notably, this disruption diminishes the viability of DCs in promoting Th17 differentiation, which is believed to be important for the immunopathogenesis of psoriasis [34].

Natural bioactive compounds are promising candidates for modulating NF-κB activity. One of the representative compounds, sulforaphane (SFN), is known to activate antioxidant genetic pathways such as KEAP1-NRF2 while damping down activity of NF-κB and STAT3. This corresponds to a double action in the reduction of IL-1β, IL-6 and CCL2 expression, managing to minimize psoriatic inflammation [100].

At the genetic level, NF-κB1 has previously been associated as a susceptibility gene for psoriasis. It aggravates IMQ-induced psoriasiform lesions through the expansion of $V\gamma4^+$ $V\delta4^+$ γδT17 cells, implicating a central role in the pathogenesis of certain T cell subpopulations [101].

Non-coding RNAs also play a role in the tightly controlled regulation of the NF-κB pathway. miR-155 induces pro-inflammatory program in HaCaT KCs through the IRF2BP2/KLF2/NF-κB axis, causing damage of viable cells and promoting psoriatic disease [102].

Therapeutically, MTX is a traditional immunosuppressive agent that alleviates inflammation partly by inhibiting Th17 cell differentiation and NF-κB signaling activity simultaneously [103]. The polyphenol punicalagin derived from plant source, showed a significant anti-inflammatory activity by simultaneously inhibiting NF-κB binding to the promoter region of IL-1β and interfering with caspase-1 mediated IL-1β secretion shedding new light on natural product-based treatment approaches in psoriasis [28].

Collectively, these advances highlight the key role of the NF-κB pathway in the initiation and maintenance of psoriatic inflammation. Natural compounds, small molecule inhibitors and non-coding RNAs have emerged targeting their interplay with pivotal signaling pathways including STING, TLRs and STAT3 to modulate this pathway. Insights gained from deep understanding of NF-κB regulatory networks in these systems may pave the way towards multi-targeted therapeutics and precision medicine strategies for psoriasis.

The JAK/STAT pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is centrally involved in regulating the immunoinflammatory mechanisms driving psoriasis. This is known to be extensively implicated in cytokine-mediated signal transduction, negatively regulating the differentiation of T cells, KC activation and promoting inflammatory cytokines expression. Based on this regulated network, the KP (kuding polysaccharide) can negatively modulate IFN-γ-dependent JAK/STAT pathway through enhancing binding of IFN-γ receptor 1 (IFN-γR1), suppressor of cytokine signaling 1 (SOCS1) and blocking phosphorylation of STAT and transcription of a downstream target gene. Moreover, KP suppresses the abundance of DCs and γδT17 cells with very significant amelioration of IMQ-induced psoriasiform dermatitis in mice, indicating multi-target systemic anti-inflammatory activity [104].

The JAK/STAT pathway consists of four Janus kinases (JAK1, JAK2, JAK3 and TYK2) and seven signal transducers and activators of transcription (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6). Canonical activation of these pathways occurs in response to the binding of cytokines including IL-6, IL-12, IL-23 and IFN-γ to their receptors, which induces transphosphorylation of receptor-associated Janus kinases (JAKs), phosphorylation of tyrosine residues within the cytoplasmic domain of receptors, recruitment and phosphorylation of signal transducer and activator of transcription proteins (STATs) - which then dimerize and translocate to the nucleus to determine target gene transcription [105].

In psoriasis, this pathway not only drives Th1 and Th17 cell polarization and effector functions but also stimulates KCs to secrete antimicrobial peptides and numerous chemokines, fueling a chronic inflammatory loop. Ethanol extracts containing flavonoids (FFE) have been shown in experimental studies to dramatically inhibit JAK1 and STAT3 phosphorylation, showing good anti-psoriatic activity both in vitro and by-in-vivo confirming natural product-based prevention strategies [106]. In addition, by targeting lipocalin-2 (LCN2) and blocking the activity of JAK/STAT signaling, miR-383 also relieves inflammation in the skin of rats from psoriasis models [107].

The chronic drive of IL-23/IL-17 axis signalling is an important pathogenic feature in psoriasis, and signalling through this pathway depends strongly on JAK2- and TYK2-driven phosphorylation of STAT3. Stimulation of IL-23 induces Th17 cells to secrete IL-17A, IL-17F, and IL-22 that synergistically amplify inflammatory responses. STAT3 is also highly expressed in KCs, where it induces expression of S100 family proteins, β-defensins and CXCL chemokines that augment local inflammatory responses and T cell recruitment. Conversely, IFN-γ induces pro-inflammatory mediators including IRF1, CXCL9 and CXCL10 by activating the JAK1/JAK2→STAT1 pathway and strengthens Th1 responses. Based on supplementation studies, baicalin (a flavone glycoside) was able to ameliorate psoriasiform and atopic dermatitis - like lesions induced by DNCB via acting on Th1/Th2 balance, restoring skin barrier function and gut microbiota homeostasis and inhibiting activation of both the NF-κB and JAK/STAT signaling axes [108].

Enhanced JAK/STAT pathway activation, particularly STAT1 and STAT3 phosphorylation, has been reported in psoriatic lesions which suggests continued pathway engagement throughout the progression of disease. Additionally, functional cross-talk of JAK/STAT signaling with several other inflammatory cascades such as NF-κB and MAPK pathway [70] further promotes upregulation of pro-inflammatory genes and activates epidermal immune response in inflammation.

The JAK/STAT pathway is critically positioned to transduce cytokine-driven signals of inflammation and has therefore become a key therapeutic target in psoriasis. Because of its unique location at the intersection of extracellular cytokine signals and intracellular transcriptional programs, it is particularly accessible for targeted manipulations and precision medicine approaches in inflammatory skin disease [109].

The MAPK family (ERK, p38, JNK)

Mitogen-activated protein kinase (MAPK) pathway is one of the most conserved signal transduction pathways in mammalian cells that consists of many genes and metabolites involved in regulating cell proliferation, apoptosis and differentiation or production of inflammatory mediators and cytokines during inflammation. MAPK signaling serves as a central intracellular nexus of convergence in psoriasis, connecting external pro-inflammatory signals to both epidermal and immune pathology. In classical configurations, there are three main branching points in the pathway - ERK, JNK and p38 MAPK - which ultimately lead to phosphorylation of their respective downstream effectors through a hierarchical cascade consisting of MAPKKK-MAPKK-MAPK [41].

In psoriasis, MAPK signaling is dysregulated downstream of inflammatory mediators such as IL-17, TNF-α, and IL-22 leading to aberrant responses in keratinocytes, dendritic cells (DCs), and T lymphocytes. Among its most prominent branches, ERK is associated with keratinocyte hyperproliferation, p38 regulates expression of pro-inflammatory cytokines and chemokines while JNK mediates inflammatory and stress-response via AP-1-dependent transcriptional programs [41].

Many natural compounds have been demonstrated to confer anti-psoriatic effects through the mitogen activated protein kinase (MAPK) signaling pathway, leading to potential support for therapeutic intervention. For instance, JFG stimulates p38α MAPK and enhances nuclear translocation of PPARγ thus inhibits NF-κB/STAT3 signaling pathways in KCs while inhibiting BMDC maturation and activation to ameliorate inflammatory responses [110]. Orientin has a potent broad-spectrum inhibition of MAPK signaling, and significantly alleviates psoriasiform dermatitis symptoms [96]. ReA specifically abrogates the IL-17A-mediated axis of signaling via TRAF6/MAPK, thereby significantly dampening the inflammatory responses

in HaCaT KCs [111]. PUN also alleviates IMQ-induced inflammatory lesions by modulating the MAPK/ERK and NF-κB pathways and inhibiting ROS production [112].

In addition, many bioactive compounds show multitarget regulatory effects on multiple signaling pathways. TRYP simultaneously inhibits both NF-κB (IκB and p65) and MAPK (JNK, ERK1/2, and p38) with activating the Nrf2 antioxidant pathway for dual benefits to ameliorate inflammation as well as oxidative stress [113]. SeP has a wide anti-inflammatory potential by inhibiting JNK and p38 phosphorylation and preventing NF-κB nuclear translocation, which in turn suppresses pro-inflammatory cytokine expression in HaCaT KCs as well as RAW264. 7 macrophages [114]. Inhibition of LPS induced KC hyperproliferation by Eupatilin through p38 MAPK/NF-κB axisEupatilin [115]. The MAPK pathway has well-established extensive interactions and co-activation with a number of inflammatory signaling networks, including NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), JAK/STAT (Janus kinase-signal transducer and activator of transcription), and PI3K/AKT1 (phosphatidylinositol 3-kinase/mammalian target of rapamycin) pathways (Barbasa et al., 202123), creating an intricate network among interconnected psoriasis inflammatory pathways. Not only does this pathway diversity crosstalk complement and amplify microenvironmental inflammatory programs, but it also contributes to heterogeneity and challenges for therapeutic intervention. Thus, the canonical and non-canonical MAPK cascades (MEKKs), MKK 2 or isoforms of p38α and ERK1/2) have emerged as promising targets in both diagnostics and precision treatment of psoriasis.

MAPK sub-branches have different functional roles, and therefore future studies to determine the contributions of sub-branches on immunoinflammatory mechanisms in psoriasis will be essential. This will lay the theoretical groundwork for the creation of highly efficient, safe, and target-directed therapeutics, including both novel pharmaceuticals as well herbal medicine-career solutions.

The PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway is a highly conserved intracellular signaling cascade that regulates proliferation, apoptosis, metabolism, autophagy and inflammatory response. Dysregulated activation of this pathway in psoriasis has been associated with keratinocyte hyperproliferation, immune dysregulation/immune imbalance, chronic inflammation and epidermal metabolic reprogramming [116].

In a mouse model of psoriasis, the expression of long non-coding RNA MEG3 is decreased. MEG3 overexpression effectively inhibits inflammation, promotes autophagy and PI3K/Akt/mTOR pathway activity in keratinocytes under IL-6 stimulation in vivo. Similar effects are observed with TNF-α-treated KCs, providing evidence that MEG3 primarily functions to repress this signaling axis [117].

Alternatively, E3 ubiquitin ligase TRIM22 strongly promoted cell proliferation, inflammatory response and downregulated autophagic flux in M5-stimulated HaCaT KCs through activation of the PI3K/Akt/mTOR pathway. These observations suggest TRIM22 overexpression as a crucial instigator of psoriasiform inflammation, and targeting TRIM22 may provide a unique therapeutic option [118].

Traditional Chinese medicine also demonstrated great potential in modulating this pathway. Liu Jun Zi decoction formula (LXJDF) alleviates psoriatic symptoms and associated dyslipidemia through inhibition of PI3K/Akt/mTOR cascade and its phosphorylation events, supporting the ecosystem of LXJDF as a multi-target synergistic therapy [119]. SCP suppresses the activation of PI3K, Akt and mTOR. A molecular docking analysis substantiates its binding to core proteins of the pathway with high affinity, promoting an anti-inflammatory and anti-proliferative effect in psoriasis through modulation on this axis signalling [120].

Furthermore, polysaccharides of Rosa rugosa and their nano-fiber membrane formulations have also exhibited anti-inflammatory and immunomodulatory effects through the inhibition of PI3K/Akt/mTOR pathway activity, offering a novel, safe, effective alternative treatment for psoriasis [121]. Likewise, we found that the co-activation of PI3K/Akt/mTOR and p38 MAPK pathways during IL-22/TNF-α/LPS-induced HaCaT cells is strongly inhibited by Portulaca oleracea ethanol extract (MCEO). To downregulate inflammatory cytokine expression and

ameliorate IMQ induced psoriasiform skin lesions in mouse. Nonetheless, since MCEO does not significantly suppress IL-17A expression, its targeted inhibition of the PI3K/Akt/mTOR pathway remains substantial in anti-inflammatory potential [122].

Overall, the PI3K/Akt/mTOR signaling pathway has complex and multilayer regulatory effects in psoriasis. Not only does it play a critical role in pathological KC proliferation and abnormal differentiation, but it also involved in T cell differentiation and immune homeostasis. Tackling this pathway, especially by modulating its activation state or interfering with crosstalk with other signaling cascades such as NF-κB, MAPK and JAK/STAT, provides a good theoretical basis and strategic reference for the design of multi-targeted precision therapies against psoriasis.

Wnt/β-catenin and notch pathways in skin barrier regulation

Psoriasis pathogenesis relies on classical inflammatory pathways: NF-κB, JAK/STAT and MAPK; as well yeast signaling cascades regulating skin barrier homeostasis, including the Wnt/β -catenin and Notch pathways. The Wnt/β-catenin pathway facilitates the nuclear localization of β-catenin and transcriptional activation of downstream target genes (e.g., c-Myc, Cyclin D1), resulting in aberrant KC proliferation and differentiation. The pathway is consistently activated in psoriatic lesions [123, 124]. Previous studies have demonstrated that upregulation of miR-145-5p can efficiently activate the Wnt/β-catenin pathway and suppress the development of psoriasiform lesions.

The traditional Chinese medicinal formula Huanglian Jiedu Decoction has been proven to be effective in reducing skin erythema and epidermal thickness. Its mechanism of action involves downregulating the expressions of Wnt1, β-catenin, and c-Myc; as well as the upstream receptors for Wnts (Frizzled2 & LRP5/LRP6). At the same time, it downregulates downstream transcription factors such as TCF4 and LEF1, as well as target genes that include Cyclin D1, TBX3 and EPHB2; conversely up- regulates negative regulators including GSK-3β, APC and Axin2. These multi-level effects lead to the inhibition of Wnt/β-catenin signaling pathway by HLJDD and produce antipsoriatic consequences [124]. Additionally, previous work has demonstrated the dual targeting of Ang-2 and VEGFA by miR-205-5p can synergistically inhibit the Wnt/β-catenin and MAPK signaling pathways to ameliorate epidermal thickening and abnormal neovascularization in IMQ-induced mouse models of psoriasis [125].

After γ-secretase cleavage, Notch intracellular domain (NICD) is released and translocates to the nucleus where it forms a complex with CSL to promote target down-regulated genes such as Hes1. Notch signaling is required for KC terminal differentiation and maintenance of epidermal barrier homeostasis. Notch signaling antagonism is a major hallmark of psoriatic lesions that seems dysregulated and associates with altered KC maturation, epidermal disorganization and increased proinflammatory cytokines [126, 127]. Notch seems to play a role in psoriasis, but unfortunately that role appears somewhat context dependent. However, Notch signaling is also downregulated during impaired keratinocyte differentiation and barrier dysfunction; in several interventional studies of percutaneous drug delivery, blockade of additional Notch-dependent signaling pathways improved barrier function. This variability may be stage of disease or cell type dependent, experimental setting dependent or pathway crosstalk dependent and should therefore be interpreted with caution. Tanhsinone IIA strongly inhibits the development of psoriasiform lesions induced by IMQ through Notch signaling repression and modulating M1 macrophage polarization while alleviating pathological phenotypes [126]. Natural flavonoid quercetin, owing to their remarkable properties has demonstrated protective effects against the psoriatic inflammation by Down Regulation of Notch, PI3K/Akt and Glut1 signaling pathways [127]. Notch signaling confirms this: KCs with high levels of Notch1, Akt, and Glut1 induce KC apoptosis and promote differentiation.

Therefore, Notch signaling inhibition/activation does not follow a linear pathway in psoriasis. Subject to epidermal context, inflammatory status and crosstalk with other signaling pathways, it appears pertinent. The context-dependent role of Notch signaling in keratinocyte differentiation, proliferation and vascular dysfunction in psoriasis is summarized in **Figure 2**.

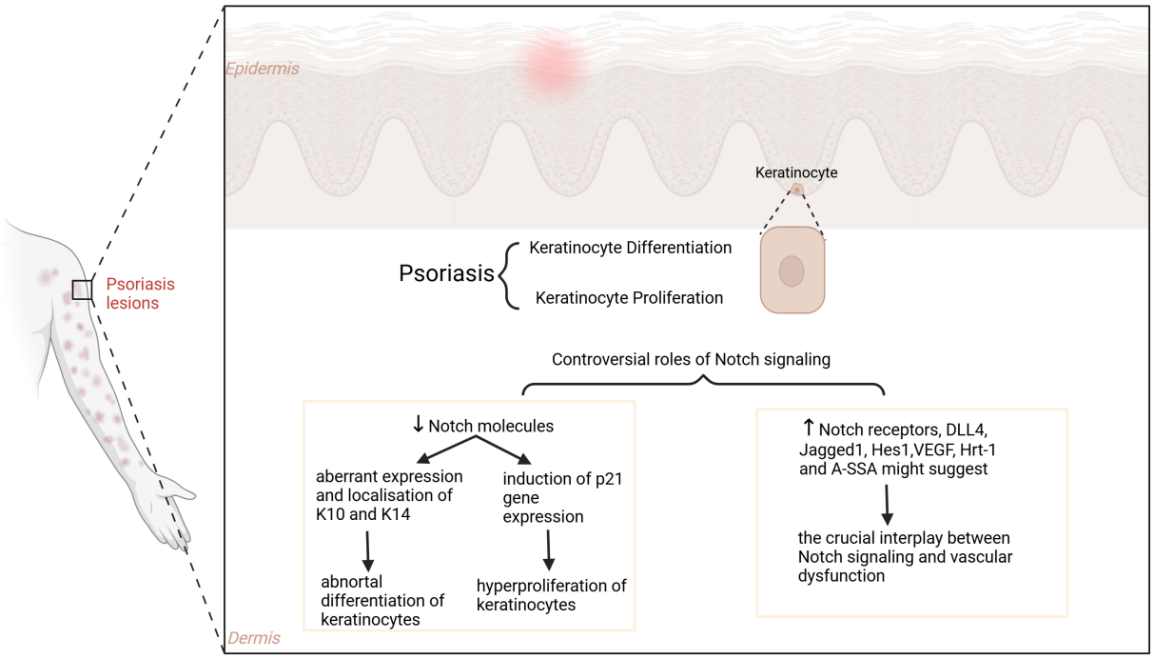

Figure 2. Notch signaling pathway in the pathogenesis of psoriasis. A schematic illustration depicting how mechanisms leading to inflammation and KC hyperproliferation in psoriasis leading the mention of controversial Notch signaling pathway. Notch signaling also promotes the differentiation and proliferation of dysregulated KCs leading to development of psoriatic lesions. Aberrant Notch components alongside mislocalized KC lineage markers K10 and K14 implicate dysfunctional KC maturation. Thus, mutational inactivation of Notch can further promote the persistent hyperproliferation of KCs. Key molecules are Notch receptors, DLL4, Jagged1 and Hrt-1 in the pathogenesis of psoriasis.

Notably, cross-talk exists between the Wnt and Notch pathways. Dysregulation of this equilibrium is the hallmark of psoriasis and excessive Wnt5a signaling coupling low Notch1 leads to pathogenic keratinocyte proliferation and skin plaques [128].

In summary, the Wnt-Notch axis needs to be considered as a context-sensitive regulatory module rather than pheno-typified widely as confirmed core driver of psoriasis.

Key therapeutic targets and advances

Biologic agents

Anti-TNF-α therapies: TNF-α is the key pro-inflammatory cytokine of psoriasis, correlating with immune-cell activation and keratinocyte inflammatory responses as well as amplification of downstream signaling. In terms of psoriasis, anti-TNF agents were the first biologics to demonstrate considerable efficacy in moderate-to-severe disease and continue to have clinical significance. However, in the age of IL-17- and IL-23-directed therapy to this date time-tested new biologics are generally much more specific towards the respective cytokines (if not target ligand/subunit blockers) with up higher rates of skin clearance achievable in many contexts [77].

Several other anti-TNF-α biologics (infliximab, adalimumab and golimumab) have also been approved for psoriasis [129]. As a powerful TNF-α blocker, tiamaurin fumarate (TF) was able to significantly inhibit the NF-κB and MAPK signaling pathways activated by TNF-α in HaCaT KCs and can dramatically ameliorate symptoms of psoriasiform dermatitis mouse models [129]. The TNF-α antagonist etanercept also markedly inhibits LPS-mediated proliferation and inflammatory responses in HaCaT cells. It calms the cell cycle maturation and apoptosis defects, thereby resolving inflammation in psoriasiform mouse models. In addition, etanercept also has intrinsic immunomodulatory properties through the inhibition of JAK/STAT3 signaling pathway that can augment therapeutic benefits [52, 130].

Despite the remarkable results that antitumor necrosis factor (TNF)-α treatments have achieved - particularly in regard to symptomatic resolution among moderate-to-severe psoriasis patients - and the advent of biologics with this indication, long-term administration is not without challenges. These include drug resistance, increased risk for infections due to immunosuppression and possible side effects of drugs. Indeed, both combination therapy approaches and new anti-TNF-α biologics are the focus of research strategies to enhance efficacy and limit side effects.

TNF inhibition is a clinically validated strategy, but long-term therapy must be balanced against risks of infection, although immunogenicity or secondary loss of response. Therefore, TNF inhibitors should be regarded as an established class of important biologics but not the preferred targeted therapy in all patients.

Anti-IL-23/IL-17 drugs: Biologics directed at targets within the IL-17/IL-23 axis represent some of the most immediate clinical translations of the central pathogenic paradigm of psoriasis and are current leading therapy for moderate-to-severe plaque psoriasis. Therefore, agents targeting the IL-23p19 subunit (e.g., guselkumab, tildrakizumab and risankizumab) directly inhibit the upstream pathogenic circuit with maximal selectivity while ustekinumab inhibits Shared IL-12/23 p40 subunit and represents an earlier generation of pathway-directed biologic therapy [131].

Another reality: the IL-17-targeted drugs have also strong clinical value. Inhibiting IL-17A & IL-17F as bimekizumab will (secukinumab is an IL-17A antibody) leads to a more impeded inflammatory cascade transduction [132]. In contrast, agents targeting IL-17 are often associated with rapid clinical response but IL-23-directed therapies offer a tantalizing long-term maintenance profile because of durable responses and convenient dosing paradigms [133]. But still treatment remains expensive, not a long-lasting response is achieved in some cases and durability of therapy, for that matter also stays foremost un-answered queries.

Small-molecule inhibitors

JAK inhibitors: JAK inhibitors are a novel and exciting class of oral small molecule therapies that we have available for our patients with psoriasis. These potent drugs primarily work by suppressing the immunoinflammatory responses in psoriasis through inhibition of surface receptor associated JAK kinases and blockade of cytokine receptor mediated signaling leading to decreased activation within pathways responsible for amplification of pro-inflammatory cytokines and cellular immune response.

The members of JAK family (mainly JAK1, JAK2, JAK3 and TYK2) are key mediators in the pathogenesis of psoriasis. They initiate the JAK-STAT signaling pathway resulting in immune cell activation and KC proliferation, contributing to skin damage and disease progression. There are two general classes of JAK inhibitors, selective and non-selective. Selective inhibitors - tofacitinib, baricitinib and upadacitinib - possess broad selective inhibition activity on different JAK isoforms effectively leading to marked improvement of psoriatic lesions as well as clinical manifestations [134-137].

These agents are administered and absorbed systemically which provides a certain degree of therapeutic efficacy; additionally, they provide a much greater convenience and adherence to the treatment regimen especially in patients with inability to tolerate conventional therapy or essential biological agent. It has been shown that Janus Kinase (JAK) inhibitors reduce psoriatic skin disease symptoms, improving quality of life in patients by altering immune response and without therapeutic detriment arising from impaired barrier function. The therapeutic JAK-inhibitor tofacitinib is efficacious in psoriasis-related indications, demonstrating its translational relevance of blocking the JAK-pathway [134]. Moreover, other JAK inhibitors such as CS12192 or deucravacitinib also demonstrated promising therapeutic merits in preclinical and clinical studies [135, 137].

If active, the safety profile of this drug class should be considered. Lengthy use can raise the likelihood for infections and likewise cause hematologic, lipid and hepatic dysfunction. Therefore, clonal testing to guide intensive clinical surveillance and baseline risk stratification is needed during treatment.

Thus, the JAK inhibitors diversify treatment options beyond biologic agents particularly in

cases where an oral agent is favored or in patients deemed poor candidates for parenteral agents. They are potentially clinically useful but must be employed in a stratified risk manner not as improved system didactic.

PDE4 inhibitors: Phosphodiesterase 4 (PDE4) inhibitors are newly developed novel small-molecule therapeutic agents that have emerged to treat psoriasis. PDE4 has emerged as a therapeutic target of significant interest due to its potential in modulating immune and inflammatory responses via selective hydrolysis of cyclic adenosine monophosphate (cAMP). These agents elevate intracellular cAMP levels via PDE4 inhibitory action whereby changes in immune cell function and processes of inflammation are decreased directly related to psoriasis immunoinflammatory pathogenesis.

Apremilast, a selective phosphodiesterase (PDE4) inhibitor of intracellular cAMP signaling is used to target pathways driving psoriatic inflammation in enhanced IL-17-associated responses and modulation of immune regulatory networks [138-140]. It is an approved, oral small-molecule drug that offers a non-biologic systemic choice for some patients.

PDE4 inhibition, overall, is less broad in activity than that of biologics and some novel targeted agents but remains an important oral non-biologic choice with respect to its ease of administration and differentiated place in therapy. However, in clinical practice, gastrointestinal intolerance and variability of clinical response has to be still taken into consideration at the time of apremilast placement [140].

Emerging therapeutic targets

Translational maturity for psoriasis treatment targets is highly heterogeneous. We identify pathways (e.g., IL-36R and AHR) that have clinical implications already and others that are more experimental. Therapeutically, clinical actionability vs mechanistic interest is a very large consideration and if we balance all conceivable targets (that can include immature [developmentally] things that will not be relevant during human development) becomes of huge importance.

The most advanced candidate in this pipeline is spesolimab, a humanized mAb that inhibits the activity of IL-36R. Generalized pustular psoriasis (GPP), which is most relevant for therapeutics, can quickly manage skin lesions and avoid systemic inflammatory manifestations [141]. However, the extension of this unusual role for IL-36 blockade into psoriasis therapy will have to be confirmed by final clinical trial results but has relevant conclusions in that it first establishes IL-36R blockade as a subtyperelevant therapy and not as a universal treatment dogma/hypothesis that can just be forcibly applied in all forms of psoriasis.

AHR pathway as another clinically relevant novel target. The topical AHR agonist, Tapinarof demonstrated impressive efficacy in psoriasis with excellent tolerability [142], further supporting the therapeutic efficacy of targeting inflammation and repair simultaneously. Meanwhile, other supplementary pathways such as co-application with Galactomyces ferment filtrate or IL-33/AHR/IL-37-dependent regulation [143, 144] appear to be questionable if at all substantiated (data-core) evidence-wise. Mechanistic rationale, salient clinical value, translational maturity status and principal limitations or future priorities for validated and up-and-coming therapeutic modalities currently under active investigation in psoriasis are summarised in **Table 3**. The table distinguishes these targets by stage of translation and clinical development, facilitating the differentiation between leader strategies vs. expanded or even still “experimental” modalities in relation to this condition effectively providing a clear construct for understanding both an emerging treatment landscape as well as future pathways towards psoriasis management.

New pharmacological pathways have introduced novel therapeutic targets to the treatment armamentarium for psoriasis, but their clinical translation is not equal. But IL-36R and AHR are currently the most translationally relevant scoring high on our validation spectrum. Future progress will depend on the precise target selection, subtype-specific delivery and long-term safety evaluation.

Combination therapy and personalized treatment strategies

Novel targeted therapeutics for psoriasis have significantly improved in recent years but challenges remain to circumvent interindividual

Table 3. Comparative overview of validated and emerging therapeutic targets in psoriasis

Target class	Mechanistic rationale	Main clinical value	Representative agents	Translational maturity	Key limitations/future priorities	References
TNF-α	Broad suppression of inflammatory amplification and immune-cell activation	Established efficacy in moderate-to-severe psoriasis	Etanercept; certolizumab	Validated/established	Long-term safety, infection risk, and positioning versus newer biologics	[77, 212]
IL-17A/IL-17F	Direct suppression of the dominant downstream effector cytokine program	Rapid lesion clearance and strong suppression of downstream inflammation	Bimekizumab; secukinumab	Validated/leading biologic class	Long-term safety, durability, and phenotype-specific comparative efficacy	[132, 213]
IL-17/IL-23 axis-directed biologics	Pathway-specific intervention within the central IL-23/Th17 framework	High efficacy with pathway-aligned immune suppression	Guselkumab; risankizumab	Validated	Optimal sequencing, long-term maintenance, and head-to-head comparison	[133, 214]
IL-23p19	Upstream suppression of the central IL-23/Th17 circuit	Durable disease control and maintenance of remission	Guselkumab; tildrakizumab; risankizumab	Validated/leading biologic class	Early intervention strategies, long-term durability comparison, and subtype-specific validation	[17, 192]
IL-23/IL-12p40	Earlier pathway-directed blockade affecting both IL-12 and IL-23 signaling	Broad inflammatory control with established efficacy	Ustekinumab	Validated but less prioritized in the current biologic landscape	Comparative positioning versus p19-directed agents; long-term monitoring	[215, 216]
JAK/STAT pathway	Broad inhibition of cytokine signaling across multiple inflammatory pathways	Oral systemic option with broad cytokine suppression	Tofacitinib; TYK2/JAK-pathway agents	Clinically relevant/expanding	Long-term safety, cardiovascular and infection risk stratification, and class refinement	[217, 218]
PDE4	Increase intracellular cAMP and dampen inflammatory mediator production	Non-biologic oral anti-inflammatory option with modest efficacy	Apremilast	Validated but lower-efficacy tier	Response variability, tolerability, and niche positioning	[140, 219]
STING-related signaling	Modulation of innate inflammatory sensing and NF-κB-linked inflammatory amplification	Experimental anti-inflammatory proof-of-concept	H-151 (experimental)	Experimental	Homeostatic duality, tissue specificity, and delivery feasibility	[98, 220]
IL-17A/IL-23p19	Blocking Key Pro-inflammatory Cytokines	Reduction of Inflammatory Cells, Ixekizumab Acts More Quickly	Ixekizumab; guselkumab	All Approved for Moderate to Severe Plaque Psoriasis	Comparative Study of Long-Term Efficacy and In-Depth Mechanistic Research	[221, 222]
IL-17A	Blocking IL-17A Inflammatory Signaling	Inhibition of Inflammation-Related Pathophysiological Mechanisms	Secukinumab	Approved for Multiple Inflammatory Diseases	Expansion of Real-World Follow-up	[223, 224]
TNF-α	Neutralization of TNF-α to Block Inflammation	Improvement of Psoriasis Symptoms, Achieving Long-Term Remission	Infliximab	Approved for Moderate to Severe Plaque Psoriasis	Impact of Biosimilars, Comorbidities, and Other Factors on Long-Term Efficacy	[225, 226]
JAK	JAK Inhibition	Treatment of Psoriatic Arthritis	upadacitinib	Upadacitinib is a Potential Therapeutic Agent	Experimental Validation	[227, 228]
IL-23 p19	Specific Targeting of the p19 Subunit	Significant Improvement in Psoriasis, High PASI Response Rate	tildrakizumab	FDA Approved for Moderate to Severe Psoriasis	Studies with Larger Sample Sizes and Longer Follow-up	[229, 230]
IL-23/IL-17A; IL-23 p19	Blocking IL-23/IL-17A, Regulating Th17 Subpopulations; Specific Binding to the p19 Subunit of IL-23	Reduction of Inflammatory Response, Improvement of Psoriasis Symptoms; Inhibition of IL-23 Signaling Pathway, Improvement of Psoriatic Arthritis Symptoms	Secukinumab, Risankizumab	Used for Psoriasis Treatment; Approved for Psoriasis, Demonstrates Efficacy in Psoriatic Arthritis (PsA) Research	Head-to-Head Trials and Other Disease Studies; Evaluation of Long-Term Efficacy and Safety	[231, 232]
IL-23p19	Inhibition of IL-23, Potentially Preventing PsA Progression	Prevention of Psoriatic Arthritis Onset; Reduction of Multiple Inflammatory Cytokine Levels	Guselkumab	Approved for Use in Psoriasis and Psoriatic Arthritis (PsA)	Study on the Preventive Potential of Drugs Targeting Different Pathways	[233, 234]

variability, incomplete responses, drug resistance and adverse events. Therefore, combination therapy and individualizing treatment are two complementary strategies for optimizing durable control of disease.

Combination therapy is therapeutic and acts on multiple levels of inflammation, can halve the effect as synergistic effects will prevent resistance. Combination regimens of standard systemic agents and biologics might be effective in some settings; there are reasonable short-term tolerability for certain system - biologic combinations on the basis of pediatric data [145]. However, data from combination strategies should be taken with caution as evidence is heterogeneous across regimens, age groups and clinical settings.

Because of their preclinical and clinical effects, JAK/STAT inhibitors in combination with other biologics may have clinically relevant efficacy for patients who fail monotherapy. However, these strategies also raise concerns for cumulative immunosuppression, drug-drug interactions and long-term safety and cost, thus they should be embraced as evolving alternatives rather than endorsed broadly as standards.

Individualized treatment approaches are designed to tailor therapy according to a patient's clinical phenotype, immunologic profile, genetic background, concomitant diseases and the response of previous treatments. Biomarkers related to inflammation level may also include correlation with IL-17, IL-23, TNF-α and JAK/STAT signaling thereby enabling more tailored therapy in order to avoid unnecessary toxicity [16].

Indeed, it is plausible that alongside numerous genetic and pharmacogenomic investigations to date, traits of treatment response linked with susceptibility loci like IL12B/IL23R and TNF may constitute considerable actors that enables the final destination of precision medicine in an advantageous long term frame. Among patients with "relevant comorbidities", including metabolic syndrome and hepatic or renal impairment, factors in treatment selection may need to emphasize safety, dosing flexibility and tolerability for combination therapy. Any discussion of methotrexate based combinations should be either on a regimen-specific data or a generalization [146].

We will see more combination strategies used for the treatment of psoriasis in the future guided by biomarker driven determinants for selection. But henceforth these approaches need to be viewed as a means to an end (not endpoints in and of themselves), since we are not yet there, where more powerful comparative evidence, validated biomarkers and adequate long-term safety data will make such routine use widely applicable.

Future directions and challenges

Key knowledge gaps and technical bottlenecks in mechanistic research

While the exploration of psoriasis pathogenesis has advanced considerably, many mechanistic questions remain to be addressed. A significant critique, however, was that the literature still favored Th17/IL-23 axis targeting treatment even if molecular signatures of psoriasis subtypes are yet to be determined. For example, pustular psoriasis and plaque psoriasis not only display different degree of inflammation severity but can also have different dominant cellular programs, cytokine architecture, or overall immune cell organization at the tissue level [147]. For that reason, the mechanistic framework has to be far more subtype driven.

Psoriasis and Role of Non-Coding RNAs and Epigenetic Regulation Another major breach is the role of non-coding RNA and epigenetic regulation in psoriasis. Such as miR-21-3p and lncRNA MEG3 is link to inflammation signaling or show co-express with autophagy pathway [148]; however, their specific contribution in a hierarchical fashion in context of cell-type, disease stage relevance were not determinate. This is an emerging and promising field, but current data remains fragmentary and subject to the limitations of interpreting high-dimensional datasets.

Microbiome-immune cross talk is also not fully characterized. Evidence to date are in accord with an association between gut dysbiosis and microbial triggers, and IL-17-associated inflammation but the causal pathways underlying these associations involving specific taxa or microbial products with pathogenic T-cell acti-

vation in psoriasis remain incompletely understood [149]. Future studies should consider a shift from descriptive microbiome profiling to mechanism-driven validation.

The second bottleneck stems from the lower spatiotemporal resolution of the existing mechanistic studies. Although transcriptomics and proteomics have generated considerable insights, neither of these approaches sufficiently describes dynamic cellular trafficking, the evolution of lesions or local immune-cell interactions over time. The combination of single cell sequencing, spatial transcriptomics and intravital imaging could address these challenges, at least for migratory immune populations such as γδT17 cells [150].

Nonetheless, mechanistic knowledge gaps remain in psoriasis research, including subtype-biased biology; epigenetic regulation; microbiota-immune crosstalk and spatiotemporal dynamics of immune-cell networks as hallmarks of the system's psoriasis (patente) development. As they are going to need integrative models, higher resolution tissue analytics and mechanistically informative experimental systems as opposed to more isolated descriptive observations.

Validation of novel targets and translational medicine

Psoriasis treatment has progressed significantly, however translational validation of new mechanistic targets has been somewhat variable. Some of the steps, are already clinically, well validated and others, too promising, in absence of validation. Thus distinguishing clinical actionable targets instead of mechanistically compelling exploratory routes is vital [151].

One mechanistically tantalizing but early stage candidate target is GLS1. Although GLS1 inhibition can attenuate pathogenic Th17 activity, some critical questions remain with respect to its more systemic immunologic effects and whether it would be directed to the tissue [22]. So far, however, GLS1 should be regarded as a potential rather than near-clinical target.

Such targets like STING and the TLR7/c-Rel axis highlight at least some of the native challenge to developmental translation in psoriasis. Although these pathways can be inhibited experimentally to reduce dendritic-cell activation and pro-inflammatory signalling [71], the roles that such pathways play in tissue homeostasis and host defence preclude their straightforward translation to the clinic. As a result, these targets require broader and context-specific validation prior to therapeutic justification.

Compounds that hit multiple targets (multitarget drugs) such as quercetin can provide useful proof-of-concept for pathway modulation i.e. Notch-associated, PI3K/Akt-, and metabolism-related signaling. However, these compounds should be carefully exalted in a translational perspective, as their pleiotropic effects limit the well-targeted patient selection according to a described mechanism and the consequent clinical applicability [127].

Another main concern with translation medicine, Redundancy in Targeted Now, an immune pathway may be of therapeutic interest but not necessarily selective enough such that an intervention also perturbs other immune circuits and poses a risk for off-target effects. A good example here is JAK inhibition, which can block the signaling of pathogenic pathways and also inhibit general cytokine responses that can predispose to adverse events.

And therefore target translation in psoriasis relates not just mechanistic plausibility, but also selective activity and tissue relevant delivery to site of pathology which when combined with safety determines clinical benefit that is reproducible. Novelty per se is not enough; future studies must better differentiate experimental promise from therapeutic readiness.

Long-term efficacy, safety, and resistance mechanisms

Besides novel therapeutic agents, there are three major drivers where long-term control of psoriasis is once again affected: the durability of response; off-target safety; primary or secondary resistance. These issues can affect both biologics and small-molecule agents, although the mechanisms of these effects and their clinical consequences vary by drug class [152].

One concern for long-term efficacy is relapsed disease after prior disease control. That secondary therapy resistance likely mirrors alterations in adaptive immunity, altered cytokine hierarchies, anti-drug antibodies or compensatory inflammation circuits [153]. Combination approaches do reduce certain forms of treatment failure, but introduce new aspects to the data regarding safety and tolerability.

Long-term safety is the second broad topic, and varies by different therapeutic classes. Further broad immune-modulating agents may cause an increased risk of infection or laboratory abnormalities while other agents were constrained by organ-selective issues or tolerability concerns [154]. Therefore, the assessment of safety in psoriasis must not only focus on short-term reporting of adverse events but also long term surveillance, comorbidity profile and cumulative treatment burden.

Drug resistance in psoriasis is increasingly reported as a multi-dimensional phenomenon that includes immune modulation, pathway escape, change in cellular source of inflammatory mediators and patient specific pharmacological deviation. Future efforts should define mechanisms of resistance, refine predictive biomarkers and treatment sequencing and prevent the idea that any given targeted class will have persistence [155].

Summary to integrate long-term psoriasis management sustained efficacy, safety and resistance and treatment paradigm are to be considered for patient-centred care. These findings--which in future research should help shape a safer long-term strategies, biomarker-guided monitoring and effort to restrict short term lesion clearance as the major outcome need to be tailored for a more striking therapeutic strategy.

Patient stratification and precision medicine

The future of psoriasis treatment looks to be in disease stratification and therapy guidance. Depending on accurately classifying patients and delivery of personalized treatment regimen, it is essential to address the heterogeneous nature in clinical presentation and immune responses.

More recently, characterizations based on immune profile (eg, Th17-dominant or Th1/Th17 mixed subtypes) and molecular biomarkers (eg IL-17A levels and IL-23 receptor gene polymorphisms) are emerging as one of the approaches in which you can personalize treatment regimens based on evidence. For example, IL-17 targeting therapies (secukinumab) have been shown to provide better response in patients with higher Th17 activity [156], while TNF-α inhibitors (etanercept) are more effective in cases of predominant Th1 activities [157].

Other mutations in innate immune response genes (i.e., CARD14 and IL36RN, which encodes an interleukin-1 family cytokine) have also been shown to potentially contribute to the pathophysiology of eczema psoriasis subtypes such as generalized pustular psoriasis (GPP), adding support for a targeted therapies rationale [158]. Precision medicine is a catch-all term for vastly more than immune cell subtyping and gathers together genomic profiles, microbiome composition and environmental exposures. Natural immune control and now even rare genetic variants of susceptibility to certain psoriasis phenotypes, as demonstrated through association with distinct HLA-Cw6 genotypes in individual patients might have given rise to epigenetic phylogenetic induction of the psoriatic disease pathobiome and its progression towards IL-23 signalling via epigenetically influenced HLA class I alleles.

Innovations in multi-omics technologies (transcriptomics, proteomics and metabolomics) along with AI/ML facilitated integration of these facets for accurate disease risk prediction heralds the way to efficacy based patient stratification/target intervention. Single-cell RNA sequencing (scRNA-seq) of psoriatic skin identified pathogenic subsets of Tc17 cells and their distinct interactions with other immune compartments [19]. Simultaneously, machine learning models are being trained on integrative clinical data with genomic variants and drug metabolism profiles to predict therapeutic response [159].

But despite this promise, there are some low culture tensions in the clinical implementation of precision medicine in psoriasis. Different stratification methods previously targeted individual immune cell types or biomarkers and ignored the complexity of immune networks involved. Because of dynamic nature of immunopathology in psoriasis immune profile is not

constant and can differ throughout disease course which needs different therapeutic strategies through tuning adaptive response rather than static one-size-fits-all therapies. Apart from this, technical and economic challenges remain vast. More advanced diagnostic and stratification tools carry increasing cost, with repercussions for equitable access to health care. Also, using precision stratification in standard of care requires infrastructure and education. Psoriasis precision stratification remains along the trajectory to introduction, and should be considered as potential yet inchoate schema rather than clinical gold standard when widespread verification of biomarkers, infrastructure and expense and cross platform reproducibility are key barriers that remain [160].

The management of psoriasis is transitioning toward precision stratification and personalized treatment, which are not yet fully achieved in routine practice. Future advancement will require a replicable, cost-effective platform for the integration of immune phenotyping, genomic data, and biomarker validation with clinically informative decision-support technologies.

Conclusion

Psoriasis is a chronic immune-mediated inflammatory skin disease, whose whole immune-inflammatory network contributes to psoriasis pathogenesis, whose central core of pathogenicity is the IL-23/Th17 axis and the activated TNF-α/IL-17 family cytokines and IL-36 regulate epidermal and immunity dysfunction. Dendritic cells induce inflammatory skewing, pathogenic T-cell subsets sustain this polarization while keratinocytes and fibroblasts amplify the lesional milieu through positive feedback signaling circuits.

At present, biological inhibition of TNF-α, IL-17 and IL-23 offers the most translational supporting evidence where considerable improvements in moderate-to-severe psoriasis have been observed [25]. Novel small-molecule agents, in particular JAK- and PDE4-directed therapies, help broaden treatment options, and creative mechanisms targeting IL-36R and AHR reinforce the idea that mechanism-based calculus can inform drug development. However, several important issues remain unresolved pertaining to the incomplete response or resistance and the long-term safety of therapy and correct sequencing of the treatment.

Advancements in psoriasis will not come from identifying new opportunistic avenues, but with precision modeling of disease heterogeneity, subtype-specific mechanisms, biomarker-guided stratification and long-term translational evaluation with a wary eye toward collateral damage [161].

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None.

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