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REVIEW

The IL-36 Cytokine Rheostat: Hierarchical Regulation of Epithelial–Immune Crosstalk and Precision Therapy in Psoriatic and Related Dermatoses

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Abstract: The interleukin-36 (IL-36) cytokine subfamily—comprising IL-36α, IL-36β, IL-36γ, and their natural antagonists IL-36Ra and IL-38—has emerged as a central regulator of epithelial–immune communication and systemic inflammation. Acting through the IL-36 receptor complex (IL-1Rrp2/IL-1RAcP), IL-36 can be conceptualized as integrating protease-dependent molecular activation, multicellular amplification loops, and disease-specific network crosstalk within a unified hierarchical framework. At the molecular level, neutrophil-derived proteases license IL-36 activation, establishing a threshold that converts barrier stress into inflammatory signaling. Within cellular networks, keratinocyte-derived IL-36γ amplifies dendritic cell–Th17 interactions and neutrophil recruitment, while the antagonists IL-36Ra and IL-38 provide feedback restraint. Across the psoriatic spectrum, IL-36 acts as a driver cytokine in generalized pustular psoriasis (GPP), an amplifier in plaque psoriasis (PV), and a sustainer in psoriatic arthritis (PsA)—defining a gradient of cytokine dependency that is conceptually consistent with differential therapeutic responsiveness. Beyond psoriasis, IL-36 participates in neutrophilic, fibrosing, and atopic dermatoses, serving as a convergent inflammatory axis that bridges epithelial stress with systemic immune propagation. The successful clinical translation of IL-36R blockade—exemplified by spesolimab and imsidolimab—validates IL-36 as a tractable therapeutic target and underscores its role within the IL-17A/TNF-α/IL-23 cytokine network. Collectively, these advances position IL-36 as a cytokine rheostat capable of scaling immune intensity according to molecular and spatial context. Emerging multi-omic and spatial transcriptomic analyses are now redefining IL-36-high endotypes across inflammatory diseases, suggesting that IL-36 may serve as a reference axis for precision immunotherapy and as a conceptual model for hierarchical immune calibration in chronic inflammation.

Keywords: IL-36, cytokine rheostat, protease activation, psoriatic disease, epithelial immunity, endotype-driven therapy, precision inflammation

Introduction — IL-36 as a Bridge Between Barrier Stress and Systemic Inflammation

The interleukin-36 (IL-36) subfamily—comprising IL-36α, IL-36β, IL-36γ, and their natural antagonists IL-36Ra and IL-38—represents a central hub within the IL-1 cytokine family that bridges epithelial stress responses with systemic inflammation.[1–4] These cytokines bind to the IL-36 receptor complex (IL-1Rrp2/IL-1RAcP) and activate canonical MyD88-NF-κB/MAPK signaling, thereby regulating both innate and adaptive immune axes at the skin and joint interfaces.[5] Unlike classical IL-1β, which acts as a binary switch, IL-36 functions as a graded immunologic rheostat—a system capable of modulating inflammation intensity proportionally to barrier stress. Activation of IL-36 cytokines is tightly regulated by proteolytic cleavage from neutrophil elastase, cathepsin G, and proteinase-3.[6] This protease-

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dependent licensing defines the molecular threshold that governs sterile inflammation onset—representing the first conceptual level of IL-36 organizational framework.

At the cellular level, IL-36 shapes reciprocal feedback loops among keratinocytes, dendritic cells, neutrophils, and Th17 cells.[7–9] Upon epithelial damage, keratinocyte-derived IL-36γ stimulates IL-23/IL-17 production, sustaining chronic inflammation and neutrophil infiltration.[10] Conversely, IL-36Ra and IL-38 restrain this cascade, acting as negative rheostats that restore homeostasis.[11,12] These counter-regulatory circuits confer a second, cellular-amplification conceptual level of regulation.

At the tissue and systemic scales, IL-36 expression gradients across epidermal and synovial compartments define the spatial architecture of inflammation.[13,14] Transcriptomic analyses reveal that IL-36 marks a transition from local keratinocyte stress to systemic cytokine propagation, explaining why diseases like psoriasis and psoriatic arthritis display overlapping molecular signatures.[15]

Clinically, IL-36 activity correlates with the disease-dependency gradient: it acts as a driver cytokine in generalized pustular psoriasis (GPP) due to IL36RN mutations, as an amplifier cytokine in plaque psoriasis (PV), and as a sustainer cytokine in psoriatic arthritis (PsA).[16–19] The IL-36 blockade antibody spesolimab has validated this axis, producing rapid pustule clearance in GPP and defining a new era of cytokine-specific therapy.[20–22]

Emerging evidence further expands IL-36's influence beyond psoriasis. Elevated IL-36 expression has been documented in hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus, underscoring its role as a convergent inflammatory backbone.[23–25] The cytokine's dual nature—acting as both sensor and amplifier—makes it a pivotal node for immune calibration.

Taken together, IL-36 embodies a multi-tiered cytokine rheostat that integrates: Molecular licensing via protease activation; Cellular amplification through epithelial-immune loops; Tissue compartmentalization guiding local vs systemic spread; Clinical dependency correlating with chronicity and therapeutic response.

Framing IL-36 within this hierarchical model provides a unifying concept linking epithelial stress to systemic inflammation and supports the view of IL-36 as a reference axis for endotype-driven precision immunotherapy (Figure 1).

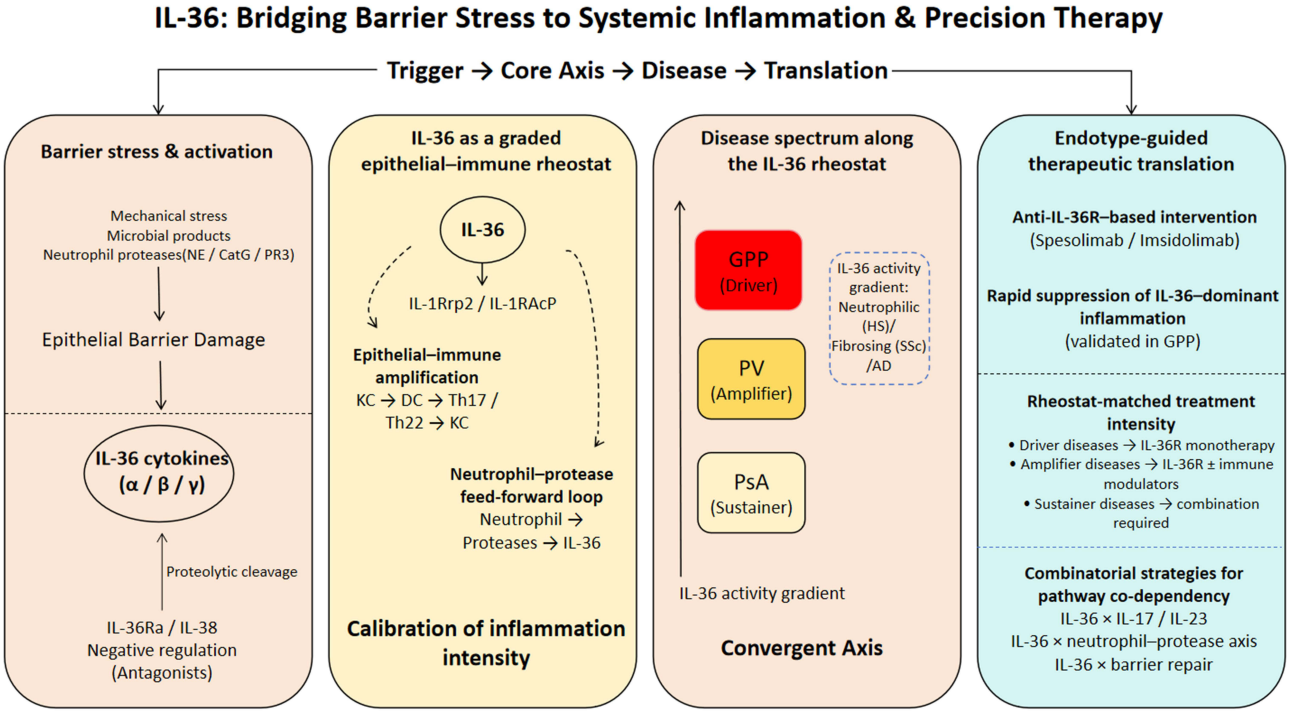

Figure 1 The IL-36 cytokine rheostat: a unified hierarchical framework integrating molecular activation, disease-specific roles, and precision therapeutic strategies.

Literature Search Strategy

This narrative review was based on literature retrieved from PubMed, Web of Science. Searches were conducted up to December 2025 using combinations of the following keywords: "IL-36", "psoriasis", "generalized pustular psoriasis", "keratinocytes", "neutrophils", "spesolimab", and "imsidolimab". Articles were selected based on relevance to molecular mechanisms, cellular interactions, and clinical translation. Priority was given to mechanistic studies, translational research, and clinical investigations that clarified IL-36 signaling biology and disease associations.

Molecular Architecture and Proteolytic Activation of IL-36 Signaling

IL-36 subfamily represents a distinct signaling arm within the IL-1 cytokine family, comprising three agonists (IL-36α, IL-36β, IL-36γ) and two endogenous antagonists (IL-36Ra and IL-38). These cytokines bind to the IL-36 receptor complex (IL-1Rrp2/IL-1RAcP), recruiting the adaptor MyD88 and activating canonical NF-κB and MAPK pathways, which coordinate transcription of inflammatory mediators such as IL-6, CXCL8, and IL-23 across epithelial and immune compartments.[26–28]

Although IL-36 and IL-1β share downstream signaling frameworks, their activation checkpoints differ fundamentally.[29] IL-1β is processed intracellularly by caspase-1 within inflammasomes, whereas IL-36 cytokines are activated extracellularly by neutrophil-derived serine proteases, providing spatial control at barrier surfaces and inflamed tissues.[29,30] Each IL-36 isoform undergoes proteolytic activation with distinct enzyme preferences and magnitudes of activity enhancement.[29,31] IL-36γ is preferentially cleaved by neutrophil elastase, producing the most potent agonist activity (approximately 500-fold increase relative to the precursor), consistent with its dominance in neutrophil-rich epithelial sites such as skin and airway mucosa.[3] IL-36α is most efficiently processed by cathepsin G and proteinase-3, leading to roughly 300-fold activation, aligning with its expression in stromal and macrophage-enriched environments.[32] IL-36β, though less potent overall, is activated primarily by cathepsin G and elastase, yielding a more modest 100- to 150-fold enhancement.[33,34] This protease-specific activation creates an isoform hierarchy in which IL-36γ drives acute epithelial inflammation, IL-36α mediates sustained stromal responses, and IL-36β provides modulatory input, together forming a graded inflammatory spectrum.

Protease cleavage removes short N-terminal inhibitory sequences, converting latent precursors into high-affinity ligands for IL-36R.[35] This proteolytic licensing step acts as a molecular threshold: only when extracellular protease activity surpasses a critical level—such as during neutrophil infiltration—do active IL-36 cytokines accumulate and trigger robust inflammation. The process is further amplified through neutrophil extracellular traps (NETs), which provide a local protease-rich scaffold that can facilitate IL-36 processing and retention, establishing a self-reinforcing inflammatory loop.[36–38]

The endogenous antagonists IL-36Ra and IL-38 act as negative rheostats to limit signaling intensity.[39,40] IL-36Ra competes with agonists for receptor binding and can itself be modestly activated by protease truncation, creating a dynamic balance that mirrors agonist activation kinetics. IL-38 operates through partial receptor competition and suppression of NF-κB signaling independently of proteolytic processing.[41,42] Together, the receptor architecture, protease selectivity, and antagonist feedback constitute a protease-gated cytokine rheostat. The intensity and duration of IL-36 signaling are determined by the extracellular protease milieu and counter-regulatory mechanisms, ensuring minimal baseline activity in homeostasis but rapid amplification during acute tissue stress.[43] This multilayered control defines the first hierarchical level of IL-36-driven inflammation—molecular licensing—bridging epithelial damage sensing with systemic immune activation (Figure 2).

Cellular Circuits of IL-36: From Epithelial Sensors to Immune Amplifiers

IL-36 functions as a critical epithelial-immune interface that converts barrier stress into coordinated inflammatory amplification. Upon epidermal disruption, keratinocytes rapidly produce IL-36α and IL-36γ in response to pro-inflammatory stimuli such as TNF-α, IL-17A, and microbial components, establishing an early cytokine relay between epithelial and immune compartments.[44,45] These cytokines engage NF-κB and MAPK signaling in keratinocytes, leading to the induction of CXCL1, CXCL8, and CCL20, which orchestrate recruitment of neutrophils and $CCR6^{+}$ myeloid

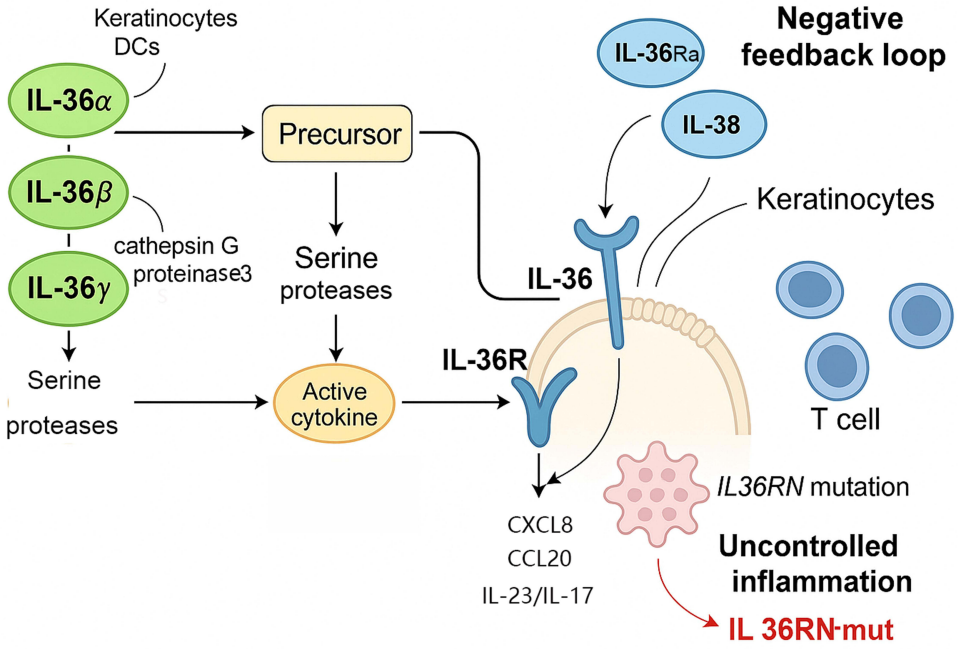

Figure 2 Activation and Amplification Mechanisms of IL-36 Signaling.

dendritic cells (DCs) into the inflamed dermis.[11,36,46,47] In parallel, IL-36 signaling cooperates with IL-17A and TNF-α pathways to enhance epithelial expression of IL-23 and IL-6, thereby promoting Th17-skewed immune polarization through activation of recruited myeloid DCs. This cascade represents the cellular amplification layer in IL-36-mediated inflammation, transforming localized epithelial stress into an organized multicellular immune response.

Within the DC compartment, plasmacytoid DCs (pDCs) infiltrate early lesions and release type I interferons upon sensing nucleic acid–antimicrobial peptide complexes, facilitating maturation of myeloid DCs (cDC1/cDC2) and inflammatory DC subsets (iDCs).[48–51] Activated myeloid DCs produce IL-23 and TNF-α, polarizing naïve CD4+ T cells into Th17 and Th22 subsets. Th17 cells secrete IL-17A/F to sustain neutrophil chemotaxis, while Th22 cells, enriched for IL-22, drive keratinocyte proliferation and epidermal remodeling.[52–54] Together, these interactions form a self-reinforcing epithelial–DC–Th loop that maintains psoriatic inflammation even after the initial trigger subsides.

At the innate interface, neutrophils function as both executors and amplifiers of IL-36 signaling, integrating proteolytic activation with cytokine propagation.[55] Upon stimulation by IL-36γ or upstream pro-inflammatory cues, neutrophils undergo chemotactic activation and degranulation, releasing neutrophil elastase, cathepsin G, and proteinase-3, which are essential proteases that convert latent IL-36 precursors into their bioactive forms.[6,19,34] This protease-driven processing amplifies IL-36 activity in neutrophil-rich microenvironments, establishing a feed-forward axis that sustains epithelial inflammation.[26] Moreover, NETs serve as localized protease reservoirs enriched in elastase and cathepsin G, providing a matrix that may facilitate continued IL-36 activation and cytokine retention; although direct biochemical evidence for NET-associated IL-36γ remains limited, this mechanism is consistent with the spatial co-localization of proteolytic enzymes and IL-36 cytokines observed in psoriatic tissue.[56]

Beyond the epidermis, fibroblast-like synoviocytes (FLS) and macrophages expressing IL-36R act as peripheral amplifiers linking skin-localized inflammation to systemic disease manifestations.[57] In PsA, IL-36α stimulation of FLS induces robust production of IL-6 and IL-8 through NF-κB and p38 MAPK pathways, enhancing leukocyte recruitment and synovial inflammation.[2] Additional studies suggest that IL-36 signaling may also up-regulate other pro-inflammatory mediators, further propagating the cutaneous-articular inflammatory axis characteristic of PsA.[18,19] Together, these interactions delineate a hierarchical extension of IL-36-driven inflammation from epithelial foci to systemic immune amplification.

Yet, the IL-36 network is not purely feed-forward—counter-regulatory mechanisms modulate its amplitude.[58] IL-10–producing DCs, regulatory T cells (Tregs), and the antagonists IL-36Ra and IL-38 restrain excessive signaling by competing for IL-36R binding or suppressing DC activation, thereby preventing runaway cytokine amplification.[39,59,60]

Collectively, these cellular interactions define the second hierarchical tier of the IL-36 rheostat—cellular amplification and regulation—where balanced cross-talk among keratinocytes, DCs, neutrophils, and Th subsets determines whether epithelial stress resolves or evolves into chronic systemic inflammation.

Hierarchical Roles Across the Psoriasis Spectrum

IL-36 signaling operates as a graded inflammatory rheostat across the psoriasis spectrum, reflecting a progressive shift from epidermal stress response to systemic immune propagation.

This hierarchy—from generalized pustular psoriasis (GPP) to plaque psoriasis (PV) and psoriatic arthritis (PsA)—illustrates how IL-36 transitions from a driver to an amplifier and finally to a sustainer cytokine, defining disease severity, chronicity, and therapeutic responsiveness (Table 1).

IL-36 as a "Driver Cytokine" in Generalized Pustular Psoriasis (GPP)

GPP represents the prototypical IL-36-driven autoinflammatory disease, in which aberrant activation of the IL-36 pathway drives neutrophil-dominant cutaneous inflammation.[61] Loss-of-function mutations in IL36RN, encoding the natural antagonist IL-36Ra, abolish receptor inhibition and lead to sustained IL-36R signaling; producing the distinct DITRA phenotype characterized by sterile pustules and systemic inflammation.[62] Lesional transcriptomic and immunohistochemical studies confirm marked up-regulation of IL-36α/γ, neutrophil proteases (elastase, cathepsin G), and downstream NF-κB / p38 MAPK signatures; these pathways form a self-amplifying epithelial–neutrophil circuit that is largely autonomous, requiring minimal cooperation from secondary cytokines such as IL-17A or TNF-α.[20,63]

Clinical validation of this mechanistic axis comes from IL-36R blockade: the monoclonal antibody spesolimab produces rapid pustule clearance—often within 48 hours—in GPP patients, establishing direct proof of IL-36 dependency.[64] Notably, some plaque-psoriasis patients who develop intermittent pustular flares show transient IL-36γ and neutrophil up-regulation, suggesting a pathogenic continuum between PV and GPP rather than strict clinical segregation.

Together, these findings position IL-36 as the driver cytokine defining the upstream tier of psoriatic inflammation, where protease-licensed, self-sufficient IL-36 signaling initiates the cascade of epidermal neutrophilic activation and pustule formation.

Table 1 Distinct Functional Roles and Therapeutic Targeting Potential of the IL-36 Pathway Across Psoriasis Subtypes

Characteristic Dimensions	PV	GPP	PsA
Expression of IL-36 agonists	↑↑	↑↑↑	↑
Expression of antagonists (IL-36Ra)	Normal or mild↓	Significant↓	Normal or mild↓
Upstream inducing factors	TNF-α, IL-17A	Genetic mutations + TNF	IL-17, IL-1β
Primary cellular sources	Keratinocytes	Keratinocytes, Neutrophils	Synovial fibroblasts
Downstream effects	Th17 activation, epidermal hyperproliferation	Pustule formation, neutrophil storm	Synovial hyperplasia, bone erosion
Core role in disease pathogenesis	No (Inflammatory amplifier)	Yes (inflammatory driver)	No (Synergistic factor)
Approved targeted therapies	None	Spesolimab	None
Therapeutic target potential	Moderate	High	Low to Moderate

Notes:↑ indicates increased expression/activity; ↓ indicates decreased expression/activity.

IL-36 as an "Amplifier Cytokine" in Plaque Psoriasis (PV)

PV, IL-36 operates as a cytokine amplifier that integrates with TNF-α and IL-17A signaling to sustain epithelial–immune feedback. Keratinocyte-derived IL-36γ is consistently elevated in lesional epidermis and co-expressed with IL-17A/F and IL-23, forming a feed-forward inflammatory module.[7,65]

Mechanistically, IL-17A and TNF-α enhance IL-36γ transcription via NF-κB and p38 MAPK pathways, while IL-36γ reciprocally promotes IL-23 and IL-6 production by myeloid DCs, thereby reinforcing the IL-23/IL-17 axis.[8,10] This reciprocal signaling loop converts transient cytokine stimuli into persistent inflammatory activation of keratinocytes, DCs, and Th17 cells.

Functionally, IL-36 cooperates with IL-17A and TNF-α to up-regulate epithelial chemokines CXCL8 and CCL20, enhancing neutrophil recruitment and $CCR6^{+}$ cell infiltration.[66] This cytokine synergy underlies the chronic, self-sustaining inflammation typical of PV. Notably, lesions with micropustular or erythrodermic features often exhibit further amplification of IL-36γ and neutrophil-related signatures,[8] supporting the existence of a continuum between pustular and plaque psoriasis rather than strictly distinct disease entities. In this context, IL-36 functions as an amplifier cytokine—transforming cytokine crosstalk into chronic inflammation through integrated feedback among keratinocytes, DCs, Th17 cells, and neutrophils.

IL-36 as a "Sustainer Cytokine" in Psoriatic Arthritis (PsA)

In PsA, IL-36 signaling extends beyond the epidermis into the synovium, where it links cutaneous inflammation with systemic immune amplification.[18,67] Fibroblast-like synoviocytes (FLS) in the PsA synovium express IL-36R and respond to IL-36α stimulation by producing IL-6 and IL-8 through canonical NF-κB and p38 MAPK activation, thereby driving leukocyte recruitment and perpetuating local inflammation.[57]

Transcriptomic profiling further demonstrates elevated IL-36α/γ and reduced IL-36Ra expression in PsA synovial tissue, correlating with increased neutrophil infiltration and clinical joint activity. Within macrophage-enriched synovial regions, IL-36 signaling reinforces TNF-α and GM-CSF expression—cytokines central to the psoriatic inflammatory loop—suggesting cooperative amplification that sustains chronic leukocyte recruitment.

Emerging spatial and single-cell analyses indicate that psoriatic skin activity parallels synovial IL-36 expression, reflecting a shared immunologic program across tissue interfaces.[68] Shared T-cell clonotypes and mirrored inflammatory transcriptional signatures between lesional skin and synovium support a coordinated cutaneous–articular IL-36 network, bridging local stress sensing with systemic propagation.[57]

Thus, in the psoriatic disease spectrum, IL-36 transitions from a driver (in GPP) to an amplifier (in PV) and ultimately to a sustainer cytokine in PsA—acting not as the initiator of inflammation but as its stabilizer, maintaining chronic immune activation across epithelial and mesenchymal compartments.

Cytokine Synergy and Molecular Dependency Gradient

Accumulating transcriptomic and mechanistic evidence delineates a molecular dependency gradient of IL-36 signaling across the psoriasis spectrum.

This gradient mirrors therapeutic responsiveness: IL-36R blockade demonstrates curative efficacy in GPP, partial benefit in pustular or erythrodermic PV, and limited effects in PsA—reflecting progressive loss of IL-36 exclusivity and increasing cytokine co-dependency across the psoriatic continuum.

From an immunologic systems perspective, IL-36 functions as a hierarchical cytokine rheostat, whose intensity and interacting partners determine inflammatory topology. GPP exemplifies high-intensity, self-propagating IL-36 activation; PV embodies cytokine-cooperative amplification with IL-17A and TNF-α; and PsA reflects a multi-node sustainment network integrating IL-36 with TNF-α and GM-CSF. This integrative model reconciles molecular and clinical heterogeneity, positioning IL-36 dependency as both a mechanistic biomarker and a conceptual framework for endotype-driven immunotherapy.

Beyond Psoriasis: IL-36 as a Convergent Axis in Neutrophilic and Fibrosing Dermatoses

The biological reach of IL-36 extends beyond the psoriatic spectrum, emerging as a convergent inflammatory axis in diverse neutrophilic, fibrosing, and systemic dermatoses. Across these diseases, IL-36 operates as a molecular bridge—linking epithelial stress, neutrophil activation, and tissue remodeling—and defines a shared transcriptional architecture characterized by CXCL8, IL1B, and S100A8/A9 enrichment.[69]

IL-36 in Neutrophilic Dermatoses

Hidradenitis suppurativa (HS) and Sweet's syndrome (acute febrile neutrophilic dermatosis) exemplify IL-36–dominant neutrophilic inflammation.[70,71] Keratinocytes and macrophages in HS lesions exhibit strong IL-36α and IL-36γ expression, particularly at follicular rupture sites, where neutrophil elastase and cathepsin G co-localize and may proteolytically activate latent IL-36 precursors.[70,72] IL-36R and downstream NF-κB targets (CXCL1, CXCL8, IL-6) are markedly upregulated in HS tunnels and perilesional epidermis, correlating with disease severity and neutrophil infiltration.

Similarly, Sweet's syndrome—an archetypal neutrophilic dermatosis—shares a transcriptional footprint with IL-36–driven inflammation. Early transcriptomic and emerging evidence suggest IL-36 involvement in neutrophilic amplification. These data imply that IL-36 may participate in amplifying the neutrophil-dominated inflammatory loop observed in Sweet's syndrome, analogous to the protease-cytokine circuits in GPP and HS.[73]

In both disorders, IL-36 orchestrates neutrophil chemotaxis and degranulation, leading to NET formation and further IL-36 activation—establishing a self-reinforcing "protease–cytokine feedback circuit" observed across neutrophilic dermatoses.

IL-36 in Fibrosing and Barrier-Repair Dermatoses

Beyond acute inflammation, IL-36 signaling has been increasingly implicated in chronic tissue remodeling and fibrosis across autoimmune and connective-tissue dermatoses. Elevated serum and lesional IL-36α expression in systemic sclerosis (SSc) has been demonstrated in both clinical and experimental studies, correlating with increased IL-6, CCL20, and CCL2 production in dermal and epithelial cells via MAPK-dependent signaling.[74,75] Although IL-36 does not directly induce extracellular matrix deposition in isolated fibroblasts, its activation in keratinocyte-fibroblast co-culture models enhances fibroblast responsiveness to inflammatory cues, indicating a paracrine mechanism linking epithelial stress to stromal activation. At the mechanistic level, IL-36R engagement activates NF-κB, p38 MAPK, and ERK1/2 pathways that converge on fibroblast proliferation, myofibroblast differentiation, and cytokine release. Animal and in-vitro models show that pharmacologic blockade of IL-1RAP —the shared co-receptor for IL-1, IL-33, and IL-36—attenuates dermal and pulmonary fibrosis, underscoring IL-36's role in fibro-inflammatory crosstalk.[76] In parallel, IL-36R expression has been detected in chronic cutaneous lupus erythematosus (CLE) lesions, where lesional keratinocytes and infiltrating immune cells express IL-36γ together with IL-6 and CXCL8, supporting a role for IL-36 in sustained inflammation and aberrant tissue repair.[4]

Collectively, these findings support a dual role for IL-36 as both a pro-inflammatory and pro-fibrotic mediator, coordinating epithelial and mesenchymal responses to chronic injury. Through its ability to couple inflammatory cytokine circuits with fibroblast activation, IL-36 bridges the transition from inflammation to fibrosis, representing a potential therapeutic node in disorders characterized by persistent barrier damage and tissue scarring.

Systemic and Atopic Disorders: IL-36 as an Immune Amplifier

Beyond neutrophilic and fibrosing dermatoses, the IL-36 axis has emerged as a context-dependent amplifier across systemic and atopic inflammatory diseases.[40] In atopic dermatitis (AD), transcriptomic and immunohistochemical analyses demonstrate significant upregulation of IL-36α and IL-36γ in lesional epidermis, particularly within keratinocytes and dermal macrophages.[77,78]

Microbial colonization—particularly by Staphylococcus aureus—has been shown to potentiate IL-36 expression indirectly through epithelial stress and Toll-like receptor activation, reinforcing local inflammation and epidermal

hyperplasia.[79,80] Although direct induction of IL-36γ by S. aureus superantigens remains unconfirmed, microbial and cytokine synergy within AD lesions promotes Th17-skewed inflammation, consistent with elevated IL-36γ in "mixed Th2/Th17" AD endotypes.

Functionally, IL-36 signaling enhances the expression of epithelial alarmins such as IL-33 and TSLP in keratinocytes under inflammatory stress, indicating that IL-36 participates in a secondary amplification loop within type 2-dominant microenvironments. These findings position IL-36 as a mediator that integrates microbial stimuli, type 2 cytokines, and epithelial activation into a unified inflammatory cascade.

In systemic lupus erythematosus (SLE), elevated serum and lesional IL-36α/γ levels correlate with disease activity and neutrophil activation markers, supporting its role in systemic immune amplification.[81] Dysregulated IL-36 signaling, characterized by increased agonist-to-antagonist (IL-36α/γ: IL-36Ra) ratios, has been observed in lupus patients and linked to heightened type I interferon and NET formation.[36]

Collectively, these findings delineate a broadened immunologic spectrum for IL-36, extending its role from epithelial sentinel to auxiliary immune amplifier in systemic autoimmunity and allergic inflammation. By integrating microbial, cytokine, and protease inputs, IL-36 contributes to chronic immune activation across barrier and systemic interfaces—positioning it as a potential biomarker and therapeutic target in inflammatory diseases beyond psoriasis.

Across diverse dermatoses—from neutrophilic (hidradenitis suppurativa, Sweet's syndrome) to fibrosing and autoimmune forms (systemic sclerosis, cutaneous lupus)—IL-36 functions as a convergent inflammatory backbone.

A conserved cascade—epithelial induction → protease activation → neutrophil recruitment → secondary cytokine propagation → tissue remodeling—recurs across these contexts, positioning IL-36 as a modular node within the IL-1 network that calibrates inflammation to tissue milieu and stress.

Its graded, context-dependent activation, shifting from neutrophil- to fibroblast-dominant circuits, exemplifies the hierarchical rheostat paradigm and unifies seemingly distinct skin diseases under a shared cytokine topology.

Therapeutic Landscape and Resistance Networks

The therapeutic targeting of IL-36 signaling has rapidly advanced from conceptual rationale to clinical reality, particularly in GPP.[82] IL-36 receptor antagonism with monoclonal antibodies has shown robust efficacy in acute flares and in reducing flare risk, validating IL-36 as a tractable clinical target.[83] Spesolimab, a humanized anti-IL-36R monoclonal antibody, has demonstrated marked efficacy and acceptable safety in treating GPP flares, leading to regulatory approval for this indication in the United States and other regions. In clinical trials, spesolimab significantly reduced GPP symptom severity and prevented subsequent flares over extended follow-up periods compared with placebo, representing a paradigm shift in the management of this rare but life-threatening disease.[61]

Parallel clinical development of imsidolimab, another IL-36R-targeting antibody, has yielded similarly promising results. Phase 1/2 studies in GPP patients reported rapid and sustained resolution of pustular eruptions and favorable tolerability, and positive topline results from Phase 3 GEMINI trials underscore its potential as an effective IL-36-directed therapy.[84]

Beyond GPP, early investigations of IL-36 blockade in related pustular phenotypes such as palmoplantar pustulosis (PPP) have been conducted, with mixed outcomes.[85] Phase II studies of spesolimab in moderate-to-severe PPP demonstrated the feasibility of IL-36R inhibition in this refractory condition, though further work is needed to clarify its role in non-GPP pustular subsets.

Despite these advances, therapeutic limitations and emerging resistance networks warrant consideration.[64] The relatively small sample sizes of GPP trials and their focus on acute flares leave open questions about long-term disease control, especially in patients with overlapping plaque psoriasis or other comorbid inflammatory phenotypes, where IL-36 blockade alone may be insufficient. Case series suggest that some patients with concomitant chronic plaque psoriasis may require additional or alternative biologic therapies (eg, IL-17 or IL-23 inhibitors) to achieve optimal disease control, highlighting disease context and network redundancy as determinants of response.[19]

Mechanistically, resistance to IL-36 inhibition may emerge from cytokine co-dependency and compensatory signaling pathways. Inflammatory networks involving TNF-α, IL-17, and IL-23 remain active in many patients and can sustain immune activation even when IL-36 signaling is blocked, implying that monotherapy may be insufficient in multi-node

inflammatory circuits. Although direct evidence detailing resistance mechanisms to IL-36 blockade remains limited, analogous pathways have been implicated in tolerance and breakthrough inflammation in other cytokine targeted therapies, suggesting that combinatorial blockade or stratified endotype-guided approaches may improve durability of response.[22]

In summary, IL-36R blockade has established a new class of therapeutics with clear efficacy in acute GPP and potential in broader pustular and neutrophilic conditions. However, the heterogeneity of inflammatory networks and tissue-specific co-drivers necessitates integrated therapeutic strategies that anticipate resistance patterns and leverage combinatorial targeting for sustained clinical benefit.

Future Perspectives — IL-36 as a Reference Axis for Endotype-Driven Therapy

The collective evidence presented across preceding sections establishes IL-36 axis as a central rheostat of epithelial and systemic inflammation, integrating molecular activation, cellular amplification, and clinical heterogeneity into a unified hierarchical framework.[72,86] From its autonomous activation in GPP to cooperative amplification in PV and sustaining activity in PsA, IL-36 illustrates how cytokine intensity and network context—rather than anatomical site—define inflammatory endotypes.

Clinically, the success of IL-36R blockade through spesolimab and imsidolimab validates IL-36 as a mechanistically precise therapeutic target.[82,84] These biologics have transformed GPP management and demonstrated that targeting an epithelial stress cytokine can yield systemic benefit. However, heterogeneous responses in PV and limited efficacy in mixed phenotypes highlight the persistence of cytokine co-dependency within the IL-17A/TNF-α/IL-23 network. This underscores a fundamental gap: the need to understand how IL-36 dependency varies across molecular and spatial disease contexts.[87]

To address this, future studies should integrate multi-omic profiling and spatial transcriptomics to define IL-36–dependent molecular circuits with cellular resolution. Such datasets can reveal reproducible "IL-36-high" inflammatory signatures across epithelial and systemic diseases, enabling stratification of patients most likely to respond to IL-36R blockade or combinatorial cytokine inhibition. Moreover, correlating IL-36 expression, protease activation states, and IL-36Ra/IL-38 regulatory balance with therapeutic outcomes may yield predictive biomarkers of treatment responsiveness.

Conceptually, the IL-36 axis delineates a scalable framework for immune calibration—a hierarchical system in which cytokine dependency dictates therapeutic logic rather than clinical taxonomy.

In IL-36-dominant endotypes (eg, GPP), selective IL-36R antagonism can achieve near-complete circuit deactivation, reflecting monogenic-level dependency. In cytokine-cooperative networks (such as PV or hidradenitis suppurativa), IL-36 acts as an amplifier embedded within the IL-17/TNF matrix, where synergistic dual blockade may be required to dismantle self-sustaining inflammatory loops. In fibrosing or systemic contexts (eg, SSc, SLE), IL-36 signaling integrates with GM-CSF and type I interferon axes, suggesting that context-aware modulation—rather than full inhibition—could optimize immune homeostasis.

Within the evolving paradigm of precision inflammation, IL-36 thus stands as more than a disease-specific mediator: it embodies a reference axis for endotype-driven immunotherapy. As multi-layered datasets continue to bridge molecular, spatial, and clinical dimensions, IL-36 offers a conceptual and experimental model for how cytokine hierarchies can be dissected, quantified, and therapeutically recalibrated—transforming it from a target of intervention into a paradigm for hierarchical immune regulation and precision immunotherapy.

Conclusion

IL-36 cytokines represent a critical epithelial–immune interface linking barrier stress with graded inflammatory amplification. Protease-dependent molecular licensing, multicellular feedback circuits, and disease-specific dependency patterns collectively define the functional architecture of IL-36 signaling across inflammatory disorders.

Therapeutic validation through IL-36R blockade establishes IL-36 as a clinically actionable pathway, while emerging multi-omic analyses increasingly highlight IL-36-high inflammatory endotypes. Conceptualizing IL-36 biology within

a cytokine rheostat framework offers a useful interpretive model for understanding disease heterogeneity and therapeutic responsiveness. This narrative synthesis is inherently limited by qualitative evidence integration and evolving mechanistic data. Future studies combining molecular profiling with clinical outcomes will clarify the predictive utility of IL-36-centered stratification strategies.

AI Use Disclosure

AI-assisted tools were used solely for language refinement and improvement of readability. All scientific content, interpretation, and conclusions were independently developed and verified by the authors.

Data Sharing Statement

No primary datasets were generated or analyzed for this review. All information was derived from published literature.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, comprehensive literature search, conceptual framework generation, or drafting and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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