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REVIEW

Role of Interleukin 36 in Generalised Pustular Psoriasis and Beyond

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ABSTRACT

Generalised pustular psoriasis (GPP), a severe neutrophilic skin disease characterised by the sudden and widespread eruption of superficial sterile pustules, remains a challenging disease with limited treatment options. The recent discovery of genetic mutations associated with GPP and advances in understanding of the molecular mechanisms of autoinflammation have resulted in identification of key cytokines that drive the development and progression of GPP. Accumulating evidence demonstrates that interleukin (IL)-36 acts as a central node cytokine by orchestrating the hyperactivation of key pro-inflammatory cytokines and stimulating immune cells, including neutrophilic accumulations, a unique feature of GPP skin lesions. These findings are paving the way for the discovery and development of novel targeted GPP therapeutics that block the IL-36 pathway and neutralise the pathogenic immunologic mechanisms and pro-inflammatory cytokines. This article provides an overview of the current evidence that supports the role of IL-36 as a central node cytokine in GPP pathogenesis.

Keywords: Autoinflammatory keratinisation disease; Generalised pustular psoriasis; Inflammatory; Interleukin 36; Neutrophils; Pustules

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Key Summary Points

Generalised pustular psoriasis (GPP) is a severe neutrophilic skin disease characterised by the sudden and widespread eruption of superficial sterile pustules with or without systemic inflammation and is considered a distinct disease from plaque psoriasis

Gene mutations in the interleukin (IL)-36 cytokine family, such as loss-of-function mutations in the IL-36 receptor antagonist and overexpression of IL-36, have been discovered in patients with GPP. Such mutations drive an inflammatory cascade leading to the activation and accumulation of immune cells, particularly neutrophils in the skin

Advances in understanding of the underlying molecular mechanisms of GPP pathogenesis and clinical validation of novel pharmacological targets establish IL-36 as a central node that drives the development and progression of GPP

Innovative therapies targeting IL-36 for the treatment of GPP and other autoinflammatory skin disorders, that were historically considered unmet medical needs, are in development

DIGITAL FEATURES

This article is published with a Japanese translation, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19552333.

INTRODUCTION

Generalised pustular psoriasis (GPP) is a severe neutrophilic skin disease characterised by the sudden and widespread eruption of superficial sterile pustules with or without systemic inflammation [1]. Patients with GPP may or may not have a history of plaque psoriasis. The clinical course of the disease can be relapsing or persistent. GPP flares can be life-threatening if not treated due to severe systemic complications [2].

GPP is considered a distinct disease from plaque psoriasis. Typically, psoriasis is classified into several subtypes: plaque, inverse, guttate, erythrodermic and pustular psoriasis. In addition to these subtypes, certain patients with psoriasis may experience psoriatic arthritis, an inflammatory arthritis that may be associated with arthritis of the joints, enthesitis, dactylitis, psoriasis and nail involvement [3]. GPP is a form of pustular psoriasis [4, 5]. Due to the association between GPP and plaque psoriasis, GPP is classified as GPP alone or GPP with plaque psoriasis [6]. Most GPP cases that are not associated with plaque psoriasis (GPP alone) are mainly due to the presence of homozygous or compound heterozygous mutations of *IL36RN*, which encodes the interleukin (IL)-36 receptor antagonist (IL-36Ra). A small number of patients with GPP with plaque psoriasis have *IL36RN* mutations [7]. According to the Japanese guidelines for the management and treatment of GPP, a definitive diagnosis of GPP can be established based on the recurrence of systemic symptoms and multiple sterile pustules that could merge, forming lakes of pus and neutrophilic subcorneal pustules that are characterised histopathologically as spongiform pustules of Kogoj [8].

With advances in understanding of the molecular basis of GPP pathogenesis, the term "autoinflammatory keratinisation diseases" has been recently proposed to refer to diseases with mixed pathologic mechanisms that involve autoinflammation and autoimmunity and are linked to IL-36Ra-related pustulosis, CARD14-mediated psoriasis, pityriasis rubra pilaris type V and familial keratosis lichenoides chronica. GPP without plaque psoriasis can be considered an autoinflammatory keratinisation disease [9, 10].

This article provides an overview of the role of IL-36 in the pathogenesis of GPP and its function as a central node that orchestrates the pathogenic role of downstream cytokines. This article is based on previously conducted studies

Table 1 Treatment options for GPP based on the Japanese guidelines

Medication class	Medication	Mechanism of action
Non-biologic oral therapy	Etretinate	Acts by suppressing keratinisation and epidermal cell proliferation and may inhibit the production of pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6 [57]
	Cyclosporin	Suppresses the production of inflammatory cytokines by T cells through inhibition of calcineurin [57]
	Methotrexate	Thought to suppress DNA synthesis and induce apoptosis of keratinocytes [2]. Findings in psoriasis suggest that it restores the immunosuppressive function of Tregs through inhibition of the mTOR pathway [58, 59]
Non-biologic oral or topical therapy	Corticosteroids	Stimulates the glucocorticoid receptor, activating transcription of genes with anti-inflammatory functions (e.g. IL-Ra and IκB-α) and repressing transcription of pro-inflammatory genes (e.g. cytokines, growth factors, adhesion molecules, nitric oxide, prostanoids and other autacoids) [60]
Non-pharmacologic therapy	Granulocyte and monocyte adsorption apheresis	Selectively depletes myeloid lineage leukocytes [61]
Non-biologic topical therapy	Topical activated vitamin D3	Acts through the vitamin D receptor on keratinocytes, which activates transcription of genes that regulate inflammation in keratinocytes [62]
Topical therapy	Psoralen and UVA radiation	Alters cytokine activity in psoriatic lesions [63]
	PUVA therapy	
	Narrow-band UVB radiation	Involves the controlled delivery of the narrow-band region of the UVB spectrum centred on 311 nm [64]
Systemic biological therapies	Infliximab	Monoclonal antibody that blocks TNF-α [21]
	Adalimumab	Monoclonal antibody that blocks TNF-α [65]
	Secukinumab	Monoclonal antibody that binds IL-17A [12]
	Ixekizumab	Monoclonal antibody that binds IL-17A [13]
	Brodalumab	Monoclonal antibody that binds IL-17 receptor [16]
	Guselkumab	Monoclonal antibody that binds to the p19 subunit of IL-23 [14]
	Risankizumab	Monoclonal antibody that binds to the p19 subunit of IL-23 [66, 67]

IκB, inhibitor of nuclear factor-kappaB; IL, interleukin; mTOR, mammalian target of rapamycin; PUVA, psoralen plus ultraviolet A; TNF, tumour necrosis factor; Treg, regulatory T cell; UV, ultraviolet

Table 2 Gene mutations in GPP

Gene	Mutations	Role in GPP pathogenesis
IL36RN	Several loss-of-function mutations have been discovered, including: c.80T>C (p.Leu27Pro) homozygous missense mutation [6]. Other mutations were identified in patients of Eastern Asian ancestry, including c.28C>T (p.Arg10X), c.104A>G (p.Lys35Arg), c.140A>G (p.Asn47Ser), c.227C>T (p.Pro76Leu), c.304C>T (p.Arg102Trp), c.305G>A (p.Arg102Gln), c.368C>G (p.Thr123Arg), c.368C>T (p.Thr123Met) and (p.Arg10ArgfsX1) c.115+6T>C [6]	Increased keratinocyte expression of the inflammatory cytokines, such as IL-8, IL-36α, IL-36β and IL-36γ [68] GPP alone, which is not accompanied by plaque psoriasis, is caused by homozygous or compound heterozygous mutations of *IL36RN* [68]
CARD14	c.526G4C c.349G>A (p.Gly117Ser) and c.349+5G>A heterozygosity in *CARD14* in European ancestry with psoriasis, and the c.413A>C (p.Glu138Ala) variant in a sporadic paediatric case with GPP [6]	*CARD14* encodes CARD14, which mediates the activation of TRAF2-dependent NF-κB signalling in keratinocytes [6] Significant risk factor for GPP with plaque psoriasis, but not for GPP alone in Japanese patients [69] The heterozygous variants c.349G>A (p.Gly117Ser) and c.349+5G>A were identified in European ancestry with psoriasis [6] The c.413A>C (p.Glu138Ala) variant was identified in a sporadic paediatric case of GPP [6]
AP1S3	Heterozygosity for the c.11T>G (p.Phe4Cys) and c.97C>T (p.Arg33Trp) missense mutations in *AP1S3* gene in 15 European patients with various forms of pustular psoriasis (i.e. PPP, ACH and GPP) and not harbouring *IL36RN* and *CARD14* gene mutations [6]	*AP1S3* encodes the core subunit σ1C of AP-1, and is responsible for stabilisation of AP-1 heterotetramers involved in vesicular trafficking between the trans-Golgi network and endosomes [6] Loss-of-function mutations of *AP1S3* are associated of GPP [6]
MPO	c.2031-2A>C homozygous mutation due to A–C transition at the 3' end of intron 11 in *MPO* in patients with GPP or APP [6]	*MPO* encodes myeloperoxidase, a lysosomal haemoprotein located in the azurophilic granules of neutrophils [6] In vitro functional analysis demonstrated that mutations in *MPO* cause an increase of neutrophil accumulation and activity, as well as a reduction in the number of apoptotic neutrophils induced by PMA, suggesting a role of MPO mutations in GPP pathogenesis [6]

Table 2 continued

Gene	Mutations	Role in GPP pathogenesis
SERPINA3	Heterozygous deletion c.966delT/p.Tyr322Ter was identified in two patients with GPP [20]	*SERPINA3* encodes serine protease inhibitor A3 (serpin A3), which inhibits several proteases in patients with GPP [20] Loss-of-function mutation in *SERPINA3* in GPP may impact the inhibitory effect of serpin A3 on cathepsin G [20]

ACH, acrodermatitis continua of Hallopeau; AP-1, adaptor protein complex 1; APP, annular pustular psoriasis; CARD14, caspase recruitment domain family member 14; GPP, generalised pustular psoriasis; IL, interleukin; NF-κB, nuclear factor-kappaB; PMA, phorbol myristate acetate; PPP, palmoplantar pustulosis

and does not contain any new studies with human participants or animals performed by any of the authors.

TREATMENT OF GPP

There are no approved GPP-specific treatments in the USA and Europe. Furthermore, the evidence that supports the current therapies is not well established and is mainly based on case reports and small open-label non-randomised trials [2, 11]. In Japan, several biologics are currently approved for the treatment of GPP, including the tumour necrosis factor (TNF)-blocking agents adalimumab, infliximab and certolizumab pegol; the monoclonal antibodies that antagonise IL-17/IL-17R, secukinumab, brodalumab and ixekizumab; and the IL-23 inhibitors risankizumab and guselkumab. In Taiwan and Thailand, brodalumab is the only approved biologic [8, 12–18]. A summary of current treatment options for GPP in Japan is provided in Table 1.

THE ROLE OF CYTOKINES IN GPP PATHOGENESIS

The pathogenic mechanisms of GPP are not clear. Recent studies identified several mutations linked to GPP, including those in *IL36RN*, *CARD14*, *AP1S3* and *MPO* (Table 2). These genes are involved in the regulation of key inflammatory and immune pathways, most notably the IL-1/IL-36–chemokines–neutrophil pathogenic axis [6, 19]. Additionally, a rare loss-of-function mutation was identified in *SERPINA3*, which encodes serine protease inhibitor A3 (serpin A3) that inhibits several proteases in patients with GPP. Specifically, the heterozygous deletion c.966delT/p.Tyr322Ter in two patients with GPP was confirmed by Sanger sequencing. This rare variant was significantly associated with GPP and may impact the inhibitory effect of serpin A3 on cathepsin G, which is involved in activation of IL-36 and downstream pro-inflammatory cytokines [20].

Recent findings further confirmed the role in GPP of sustained activation of IL-1 and IL-36, which induces neutrophil chemokine expression, infiltration and pustule formation [21]. The IL-36 subfamily of cytokines is part of the IL-1 superfamily. It is composed of three pro-inflammatory agonists, IL-36α, IL-36β and IL-36γ, which activate the IL-36 receptor (IL-36R), and one antagonist (IL-36Ra). IL-36 cytokines play a key role in signalling between epithelial cells, dendritic cells and neutrophils, which constitute the central cytokine node responsible for the initiation, continuation and exacerbation of inflammation [22].

The IL-1 ligand family members are present as a single cluster on human chromosome 2 and are likely to be formed through a series of gene duplications of the prototypical IL-1 family cytokine IL-1β. IL-36 is a member of the IL-1 family, which includes IL-1β, IL-1α, IL-36α, IL-

Table 3 Overview of the IL-1 family members involved in GPP pathogenesis

Cytokine	Receptor	Role in GPP pathogenesis
IL-1β	IL-1R1	IL-1β paracrine signalling network activates pro-inflammatory pathways [10]
IL-18	IL-18Ra	IL-18, a component of the inflammasomes expressed in epidermal keratinocyte, activates the paracrine pro-inflammatory signalling network in the epidermis and the superficial dermis [10]
IL-36α IL-36β IL-36γ	IL-36R (IL-1Rrp2)	The secretion of IL-36 by the keratinocyte results in the activation of neutrophils and dendritic cells in the dermis. Additionally, autocrine stimulation of keratinocytes results in the secretion of IL-36, IL-8, CXCL1, CXCL2 and CCL20, which further activates pro-inflammatory pathways [10]
IL-38	IL-36R (IL-1Rrp2)	IL-38 is a 17–18 kDa protein that shares 40% sequence similarity with IL-1Ra and IL-36Ra (antagonists of IL-1 and IL-36, respectively) and binds IL-36R to antagonise IL-36. IL-38 is expressed mainly in the skin and immune cells, and its expression is downregulated by inflammatory cytokines [70]
IL-1Ra	IL-1R1	Loss-of-function mutations in *IL1RN*, which encodes IL-1Ra, lead to a partial or complete absence of the IL-1Ra protein, causing uncontrolled activity of IL-1α and IL-1β [71, 72]
IL-36Ra	IL-36R	Deficiency in IL-36Ra caused by *IL36RN* loss-of-function mutations is thought to result in acceleration of IL-36-driven skin inflammation [10]

IL, interleukin

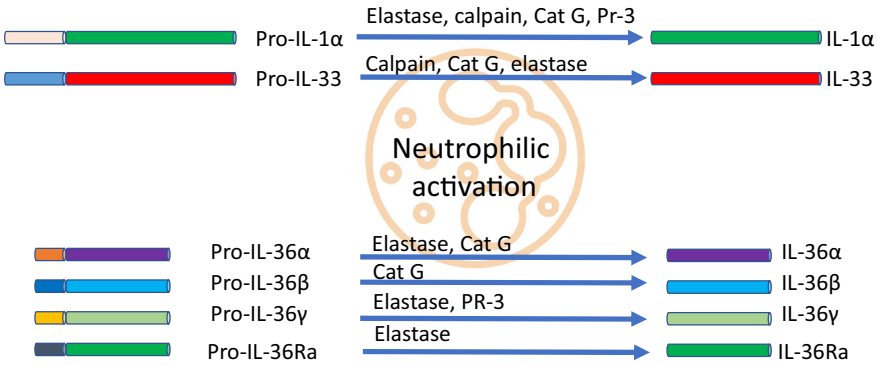

Fig. 1 IL-1/IL-36 neutrophilic activation [22, 26, 73, 74]. Cat G, cathepsin G; IL, interleukin; Pr-3, proteinase-3

36β, IL-36γ, IL-36Ra, IL-37, IL-38 and IL-1Ra (Table 3) [23]. These findings are supported by a study by Yamamoto et al., which demonstrated that the levels of serum cytokines IL-1β, IL-1Ra, IL-6, IL-10, IL-12p70, IL-18, IL-22, interferon (IFN)-γ and vascular endothelial growth factor were positively correlated with GPP clinical markers, including severity scores of GPP, white blood cell counts and serum C-reactive protein levels [24]. The activation of IL-36 cytokines requires proteolytic cleavage by proteases released from activated neutrophils. Cathepsin

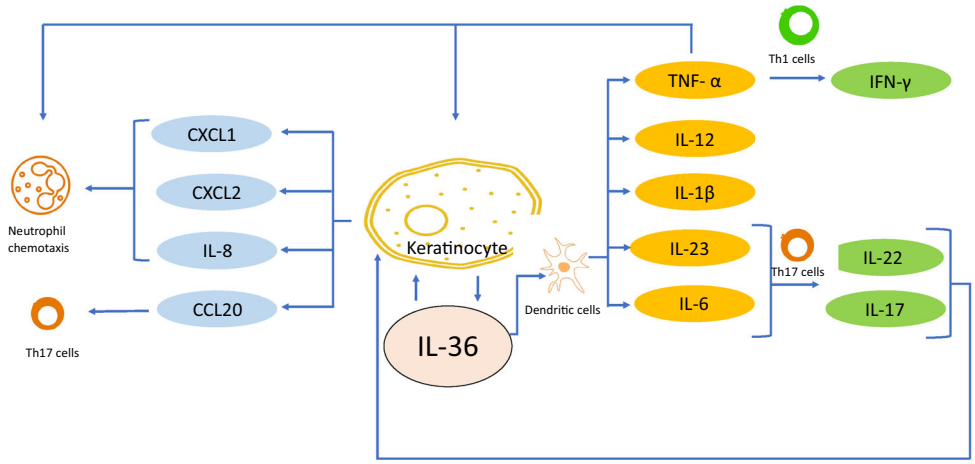

Fig. 2 IL-36 is a central node in GPP pathogenesis. IL-36 acts as a central node cytokine in the pathogenesis of GPP. The overexpression or unopposed activation of IL-36 due to *IL36RN* mutations results in hyperactivation of the IL-36 pathway in GPP [9, 10]. GPP, generalised pustular psoriasis; IFN, interferon; IL, interleukin; Th17, T-helper type 17; TNF, tumour necrosis factor

G, elastase and proteinase-3 differentially process and activate all three IL-36 family members. Therefore, neutrophil-derived proteases can amplify inflammation through the processing of extracellular cytokines (Fig. 1) [25]. These observations were further confirmed by a study by Clancy et al. that showed that proteases released by activated neutrophils into the extracellular space are potent modulators of IL-1α, IL-1β, IL-33, IL-36α, IL-36β and IL-36γ activation states. Thus, neutrophils play a key role in modulating inflammatory responses through the processing of multiple IL-1 family cytokines (Fig. 1) [26].

Several studies have established IL-36 as a central node in GPP pathogenesis. The sustained unopposed activation of IL-36R leads to activation of the transcription factor NFκB, which results in massive production of several key inflammatory cytokines, including CXCL8, TNF-α, IL-1 and IL-23 [21, 27–29]. Moreover, the serum and mRNA levels of IL-17 are substantially higher in pustular psoriasis [30]. The pathogenic role of IL-17A, the most potent member of the IL-17 family, was confirmed by the demonstrated efficacy of several IL-17A inhibitors in patients with GPP (Fig. 2). [15, 31].

IL-36 FAMILIAL MUTATIONS AND GPP

The first observation of the familial incidence of GPP was described in 1972 by Landry and Muller. In this report, a patient, his maternal uncle, another uncle and grandmother experienced symptoms of GPP with disease onset early in childhood. The symptoms were aggravated by streptococcal infections [32]. More recently, a significant linkage to an interval of 1.2 megabases on chromosome 2q13-q14.1 and a homozygous missense mutation in *IL36RN* was identified in patients with GPP, which further confirms the clinical relevance of the IL-36 pathway in the pathogenesis of GPP [33]. Homozygous and heterozygous *IL36RN* mutations were also discovered in cases of impetigo herpetiformis, a rare pustular dermatosis that affects pregnant women and shares clinical and histologic features of GPP [6]. A recent case report by Sawabe et al. described the diagnosis of a patient with GPP with co-existing mutations in *IL36RN* and *CARD14*, suggesting that concurrent mutations in *IL36RN* and *CARD14* may also be a predisposing factor of GPP [34]. Another report further confirmed the potential

role of the IL-36 pathway. Exosome sequencing of five unrelated patients with GPP revealed that loss of function of *IL36RN* constitutes the genetic basis of GPP and implicates innate immune dysregulation in this severe episodic inflammatory disease, thereby highlighting IL-1 signalling as a potential therapeutic target [35].

The unopposed IL-36 signalling hyperactivation stimulates antigen-mediated and possibly pathogenic T-helper type 17 (Th17) responses in GPP, promoting antigen-driven Th17 responses, which in the absence of exogenous triggers may trigger autoimmune reactions [36]. The central role of the IL-36 pathway in driving the pathogenesis of GPP was further confirmed by the development of IL-36 pathway inhibitors (e.g. spesolimab and imsidolimab). Efficacy of the anti-IL36R monoclonal antibody spesolimab has been shown in an open-label proof-of-concept trial in seven patients with a GPP flare and in a randomised, placebo-controlled double-blind trial (Effisayil^{TM} 1) in 53 patients with a GPP flare, suggesting that the IL-36 pathway may play a pathogenic role among patients with GPP of broad genetic backgrounds [37]. An interim analysis from an open-label trial of imsidolimab (also an anti-IL36R monoclonal antibody) in eight patients with GPP also supports IL-36 as a central player in the pathogenesis of GPP [38].

IL-36 AS A CENTRAL NODE IN GPP PATHOGENESIS

Recent evidence demonstrated that IL-36 signalling plays a key role in the development of psoriatic lesions based on in vivo pre-clinical studies in transgenic and knockout mice. IL-36 knockout mice (*IL-36R*$^{-/-}$:K5.Stat3C mice) had a downregulated gene expression of psoriasis-related cytokines, including IL-23/IL-17 axis cytokines. Additionally, IL-36-deficient keratinocytes were resistant to stimulation by D-glucan, which usually upregulates the expression of IL-36 members, S100A8, S100A9 and IL-17C, in vitro. These findings established that IL-36 signalling plays a role as a gatekeeper that potentially links innate immunity to the pathogenesis of psoriasis [39]. These observations were further supported by a study by Wang et al. [40], which showed that IL-36γ inhibits differentiation and induces inflammation of keratinocytes via the Wnt signalling pathway in psoriasis. These findings are clinically relevant. A retrospective immunohistochemical study of psoriatic lesions of 40 patients with psoriasis and matched controls demonstrated that IL-36γ was strongly expressed (in four or more layers) in the nuclei of suprabasal epidermal keratinocytes, while, in all controls, weak cytoplasmic expression was detected in the basal layer. Additionally, the elevated IL-36γ expression was significantly associated with psoriasis severity [41].

IL-36 cytokines play a central role in the recruitment and activation of neutrophils and Th17 cells in psoriatic skin. IL-36 cytokines induce chemokines, and cytokines that interfere with differentiation/cornification programmes in the epidermis and promote pathological angiogenesis and endothelial cell activation. IL-36 cytokines are upregulated in the psoriatic epidermis, and their expression is strongly induced by TNF-α and IL-17 [42]. These findings can be translated into the discovery of novel therapies for GPP. A small-molecule high-throughput screen identified A-552, but not the closely related family member IL-36α, as a potent antagonist of human IL-36γ. A-552 suppressed IL-36γ-induced responses in mouse and human disease models of psoriasis [43]. In addition to the pathogenic role of IL-36 in the skin, its potential role in the extracutaneous disease manifestations associated with GPP and plaque psoriasis was demonstrated in recent studies. Patients with GPP had a prominent IFN type-I signature, which correlates with abnormal IL-36 activity [44]. Pre-clinical in vivo studies in a mouse model of deficiency of IL-36 receptor antagonist (DITRA) also demonstrated an essential role for the IL-36 pathway in the pro-inflammatory responses in the skin and epithelial barrier function in the intestine [45].

Moreover, recent findings in mice showed that the activation of toll-like receptor 4 (TLR4) signalling is attenuated by IL-37, an antagonist of IL-1 family cytokines [46]. Shibata et al. demonstrated that, in *IL36RN*$^{-/-}$ mice (a model of autoinflammatory syndromes associated with

DITRA), blocking TLR4 signalling using the TLR4 antagonist TAK-242 resulted in the resolution of the cutaneous, articular and hepatic autoinflammatory symptoms, which further highlights the central role of the IL-36 pathway and demonstrates a novel therapeutic strategy to treat GPP [46, 47].

ROLE OF THE IL-36 PATHWAY IN OTHER SKIN DISORDERS

The IL-1 family members IL-36α (IL-1F6), IL-36β (IL-1F8) and IL-36γ (IL-1F9) and the receptor antagonist IL-36Ra (IL-1F5) play a central role in regulating inflammatory skin activity. Furthermore, IL-36α-treated monocyte-derived dendritic cells (MO-DCs) enhanced allogeneic CD4+ T-cell proliferation, demonstrating that IL-36 can stimulate the maturation and function of DCs and drive T-cell proliferation. These data indicate that IL-36 cytokines actively propagate skin inflammation via activation of keratinocytes, antigen-presenting cells (APCs) and, indirectly, T cells [48]. IL-36 also seems to play a role in infectious dermatoses. Microbial triggers, especially *Staphylococcus aureus* infection, increase the production of pro-inflammatory IL-36 cytokines and initiate/promote the inflammation of skin lesions [29].

The enhanced expression of IL-36 family members has been shown to play a key role in the pathogenesis of Netherton syndrome, a rare autosomal recessive skin disease caused by loss-of-function mutations in *SPINK5*, which encodes lympho-epithelial Kazal-type-related inhibitor protein that results in the unopposed activity of epidermal kallikrein-related peptidases (KLKs), mainly KLK5, KLK7 and KLK14 [49].

In addition to its role in psoriasis, the role of IL-36 has been investigated in the pathogenesis of allergic contact dermatitis (ACD). Gene expression of all three IL-36 agonists, but not IL-36Ra, was enhanced in ACD-affected skin. In addition, an ex vivo model showed that the addition of recombinant IL-36Ra in skin explants causes the reduction of IL-36α, IL-36β and IL-36γ gene expression [50].

The role of neutrophil extracellular traps, web-like structures composed of neutrophil DNA, in the pathogenesis of psoriasis is not clear; however, recent studies suggest that neutrophil extracellular traps are induced in a psoriasis model of IL-36Ra-deficient mice, which suggests a potential role in the pathology of psoriasis-like lesions [51]. Mutations in *MPO*, which encodes the neutrophilic enzyme myeloperoxidase (MPO), that result in MPO deficiency in neutrophils and monocytes were found to be associated with GPP [6]. MPO-deficient mouse and human cells are characterised by altered neutrophil function and impaired clearance of neutrophils by monocytes (efferocytosis), promoting prolonged neutrophil persistence in inflamed skin [6]. These findings suggest a potential role in other neutrophil-driven diseases such as Sweet syndrome (acute febrile neutrophilic dermatosis) and pyoderma gangrenosum, as MPO deficiency has been described in a single individual with pyoderma gangrenosum [52]. The potential role of *MPO* mutations in other inflammatory skin conditions was further confirmed by the findings of *MPO* screening in conditions phenotypically related to GPP, which further revealed disease alleles in one subject with acral pustular psoriasis and in two individuals with acute generalised exanthematous pustulosis. A subsequent analysis of UK Biobank data demonstrated that the c.20312A>C and c.1705C>T (p.Arg569Trp) disease alleles were also associated with increased neutrophil abundance in the general population [53].

Animal studies also demonstrated a central role for IL-36Ra in wound healing. In *IL36*$^{-/-}$ mice, wound healing was delayed; however, treatment with a TLR4 antagonist normalised the impact on wound healing [54]. Moreover, in *IL36*$^{-/-}$ mice, cutaneous ischaemia–reperfusion injury was exacerbated; however, treatment with a TLR4 antagonist or PAD4 inhibitor normalised the impact on cutaneous ischaemia–reperfusion injury [55]. Additionally, recent studies in animal models suggest a potential role of IL-36 in the pathogenesis of ACD based on the finding that IL-36Ra deficiency might be involved in T-cell priming in the lymph nodes [56]. Further studies in the

well-established 1-fluoro-2,4-dinitrobenzene mouse model of contact hypersensitivity also demonstrated that IL-36α, IL-36β and IL-36γ did not impact disease phenotype, and their role may be limited to the amplification of priming and/or inflammatory responses [56].

DISCUSSION

GPP remains a challenging disease with few well-validated treatment options. The recent advances in understanding of the molecular mechanisms in inflammatory diseases and the characterisation of genetic mutations associated with GPP have demonstrated novel pharmacological targets to manage and treat GPP. Among the most notable mutations discovered in patients with GPP is the loss of function of *IL36RN*, a gene that encodes IL-36Ra. The unopposed activation of IL-36 pathway has established IL-36, a central node in the pathogenesis of GPP, as a critical pharmacological target for the treatment of GPP. Targeting IL-36 has been validated clinically in a proof-of-principle clinical trial of the anti-IL-36R monoclonal antibody spesolimab, which demonstrated efficacy within 1 week of treatment in patients with GPP flares [37]. An interim analysis of an open-label trial of imsidolimab (also an anti-IL36R monoclonal antibody) in eight patients with GPP also supports the central role of IL-36 in the pathogenesis of GPP [38].

Collectively, advances in understanding of the underlying molecular mechanisms of GPP pathogenesis and the clinical validation of novel pharmacological targets establish IL-36 as a central node that drives the development and progression of GPP (Fig. 2). The secretion of IL-36 by keratinocytes or inflammatory cells, and the subsequent stimulation of autocrine and paracrine pathways leads to an amplified autoinflammatory and autoimmune response mediated by several key cytokines, including IL-8, CXCL1, CXCL2, CCL20, IL-12, IL-1β, IL-23, IL-6 and TNF-α. These cytokines further activate T cells, leading to the secretion of IL-22, IL-17 and IFN-γ. Additionally, chemotaxis of activated neutrophils establishes GPP as a neutrophilic skin disorder as these further amplify the inflammatory mechanism through neutrophil-mediated cleavage and activation of pro-inflammatory cytokines.

The emerging role of the IL-36 pathway in other autoinflammatory skin disorders further confirms IL-36 as a central node that orchestrates a pathogenic autoinflammatory mechanism. Accumulating evidence implicates IL-36 cytokines in the activation of keratinocytes and APCs, and the proliferation of T cells [48]. These findings provide a plausible explanation for the susceptibility of a patient with *IL36RN* mutations to triggers of flares such as *Staphylococcus aureus* infections. IL-36 cytokines have been also found to play a role in the pathogenesis of the rare inflammatory skin disease Netherton syndrome [49]. Furthermore, IL-36 cytokines were found to play a potential role in the pathogenesis of ACD [50]. These discoveries may lead to the identification of novel treatments for ACD and rare conditions that are driven by neutrophil extracellular traps such as acute febrile neutrophilic dermatosis and pyoderma gangrenosum. Further characterisation of the regulatory mechanisms of IL-36 cytokines in wound healing mechanisms, such as the role of TLR4, may also lead to the development of novel pharmacological treatments beyond targeting IL-36R.

CONCLUSION

In summary, recent advances in understanding of the genetic and molecular basis of GPP pathogenesis, including the discovery of IL-36 as a central node, are driving the development of innovative treatments for GPP and other autoinflammatory skin disorders that were historically considered unmet medical needs.

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