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Review article

Pustular psoriasis as an autoinflammatory keratinization disease (AiKD): genetic predisposing factors and promising therapeutic targets

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Running Head: Pustular psoriasis as AiKD

Abstract

Pustular psoriasis is a chronic inflammatory skin disease characterized by erythematous plaques with sterile pustules. It includes the distinct clinical entities generalized pustular psoriasis (GPP), acrodermatitis continua of Hallopeau (ACH) and palmoplantar pustular psoriasis (PPPP). Recently clarified pathomechanisms of pustular psoriasis indicate that hyperactivation of the skin innate immunity, including of the IL-1/IL-36 axis, plays an important role in the pathogenesis of pustular psoriasis. Autoinflammatory keratinization disease (AiKD) is the umbrella clinical entity for inflammatory keratinization disorders with genetic autoinflammatory pathomechanisms, and pustular psoriasis is a representative AiKD. To date, mutations/variants in five genes—*IL36RN*, *CARD14*, *AP1S3, MPO* and *SERPINA3*—have been reported to be genetic causative or predisposing factors for pustular psoriasis. The pathogenic mechanisms induced by the mutations/variants in these genes are all closely related to the excessive activation of skin innate immunity and autoinflammation. A number of biologics (e.g., tumor necrosis factor inhibitors, IL-17/IL-17 receptor inhibitors and IL-23 inhibitors) and granulocyte and monocyte adsorption apheresis are used to treat pustular psoriasis. Recently, based on novel information on the pathomechanisms of pustular psoriasis, which are mainly associated with autoinflammation, inhibitors of several pathogenic pathways, including of the IL-1, IL-36, IL-8 and granulocyte colony-stimulating factor signaling pathways, have been studied as emerging treatments.

Key words: AP1S3, CARD14, IL-36, *IL36RN*, MPO, SERPINA3

Abbreviations: ACH, acrodermatitis continua of Hallopeau; AGEP, acute generalized exanthematous pustulosis; AP-1, adaptor-related protein complex 1; AP1S3, adaptor-related protein complex 1, sigma-3 subunit; AiKD: autoinflammatory keratinization disease; CARD14: caspase recruitment domain family member 14; CTSG, cathepsin G; CTSS, cathepsin S; GPP: generalized pustular psoriasis; GPPASI, Generalized Pustular Psoriasis Area and Severity Index; GMA, granulocyte and monocyte adsorption apheresis; G-CSF, granulocyte colony-stimulating

factor; IL1RL2, IL-1 receptor-like 2; IL-17RA, IL-17 receptor A; IL-36Ra, IL-36 receptor antagonist; IH, impetigo herpetiformis; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; NE, neutrophil elastase; PPPP, palmoplantar pustular psoriasis; PPP, palmoplantar pustulosis; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PPPASI50, Palmoplantar Pustulosis Area and Severity Index 50% reduction; PRP, pityriasis rubra pilaris; PR3, proteinase 3; SERPINA3, serine protease inhibitor A3; TLR3: toll-like receptor 3; TNF, tumor necrosis factor

1. Introduction

Pustular psoriasis is a group of clinically and pathophysiologically heterogeneous subtypes of psoriasis. The group includes three clearly distinct clinical entities: generalized pustular psoriasis (GPP), acrodermatitis continua of Hallopeau (ACH) and palmoplantar pustular psoriasis (PPPP) (Table 1). These subtypes are occasionally associated with the lesions of plaque psoriasis or psoriasis vulgaris and are thought to be in the psoriasis spectrum; however, in terms of pathophysiology and phenotype, the subtypes of pustular psoriasis differ genetically from psoriasis vulgaris. Five genes—*IL36RN* [1], *CARD14* [2,3] *AP1S3* [4], *MPO* [5] and *SERPINA3* [6]—that are associated with autoinflammatory pathogenesis have been identified as predisposing factors. The recent elucidation of the pathogenesis and pathophysiology of pustular psoriasis associated with the hyperactivation of skin innate immunity has led us to the concept that pustular psoriasis is a representative clinical entity of autoinflammatory keratinization disease (AiKD) [7,8].

GPP is traditionally classified as the most severe subtype of pustular psoriasis (Table 1). It is a chronic, systemic inflammatory disease accompanied by diffuse erythema with multiple sterile pustules all over the body, high fever and general malaise. GPP often relapses over the lifetime and is occasionally fatal. Impetigo herpetiformis (IH) is thought to be a variant of GPP that is triggered by pregnancy. A number of cases of IH with *IL36RN* mutations have been reported [9,10]. Concerning the clinical course of IH after delivery, some patients have post-partum flare-ups, whereas others do not and they do not require biologics.

ACH is a localized form of pustular psoriasis. It clinically presents as sterile pustules and underlying erythema at the tips of the fingers and toes. ACH lesions often have their onset after

local trauma or infection, and ACH may progress to onychodystrophy, anonychia, osteitis and osteolysis of the distal phalanges.

Another subtype of localized pustular psoriasis is palmoplantar pustular psoriasis (PPPP). It is characterized by sterile pustules presenting various clinical features, such as fresh or eroded pustules, pustules with yellow crusts or dark brown lesions, in the palms and the soles. Palmoplantar pustulosis (PPP) is a clinical entity related to PPPP. PPP consists of two subtypes: Type A and Type B [11]. In Type-A PPP, vesicles precede pustules in the lesions and this type is an entity distinct from PPPP [11]. In contrast, Type-B PPP presents only pustules without vesicles and this type is associated with PPPP and is a variant of pustular psoriasis [11].

Recently, our understanding of the genetic predisposing factors and pathogenic mechanisms of pustular psoriasis have advanced greatly. However, the therapeutic management of pustular psoriasis still faces many challenges and much uncertainty. I briefly update our current understanding of the molecular pathomechanisms behind pustular psoriasis as an AiKD. In addition, current and emerging treatments for pustular psoriasis as an AiKD are summarized.

2. Pustular psoriasis as an AiKD

Inflammation induced by the hyperactivation of innate immunity triggered by genetic factors sometimes leads to inflammatory keratinization diseases of the skin. Those inflammatory keratinization diseases with genetic autoinflammatory pathomechanisms are termed "autoinflammatory keratinization diseases" (AiKDs) [7,8]. AiKDs also include disorders that have mixed autoinflammatory and autoimmune pathomechanisms. AiKDs have primary genetic factors causative of autoinflammation, predominantly in the epidermis and the superficial

dermis, resulting in the hyperkeratosis and various skin inflammatory phenotypes seen in AiKDs [7,12]. The clinical features of AiKDs are varied, although common phenotypes are hyperkeratotic lesions with inflammation.

In 2011, *IL36RN* mutations were described as genetic causative factors in GPP cases [1,13]. Moreover, *CARD14* and *AP1S3* mutations/variants were reported to be associated with GPP [2-4]. Disease-related variants/mutations in *IL36RN*, *CARD14* and *AP1S3* have also been reported in patients with ACH and in those with PPPP [14]. Variants/mutations in the three genes are considered to induce the hyperactivation of innate immunity (see below: "3. Updated pathogenesis of pustular psoriasis"). Two additional genes—*MPO* and *SERPINA3*—associated with autoinflammation have recently been reported to confer susceptibility to pustular psoriasis [5,6].

Furthermore, evidence that the IL-1/IL-36-chemokine-neutrophil axis plays a central role in the development of pustular psoriasis is expanding not only in patients with *IL36RN* variants/mutations, but also in patients with other genetic predisposing factors [15]. From these data, pustular psoriasis, including cases with GPP, ACH and PPPP, is thought to be chiefly characterized by innate immune inflammation and is considered to be an AiKD [12,15].

3. Updated pathogenesis of pustular psoriasis

In familial cases of GPP, rare mutations in *IL36RN* were identified in 2011 [1,13]. After that, as I described above, variants/mutations in the five genes associated with the activation of innate immunity and the induction of autoinflammation (*IL36RN*, *CARD14*, *AP1S3, MPO* and *SERPINA3*) were reported as genetic predisposing factors for pustular psoriasis. I summarize the updated information on genetic predisposing factors for pustular psoriasis below (Table 2, Fig. 1).

3.1. Deficiency of IL-36 receptor antagonist

IL36RN mutations are well known as causative genetic defects for pustular psoriasis [16]. Among pustular psoriasis subtypes, the prevalence of *IL36RN* mutations is higher in patients with GPP (23.7%) and in those with ACH (17.4%) than in those with PPPP (5.1%) [14]. Not only do individuals with homozygous or compound heterozygous *IL36RN* mutations develop pustular psoriasis, but so do those with heterozygous *IL36RN* mutations [14,17]. GPP patients and ACH patients are more likely than PPPP patients to harbor biallelic *IL36RN* mutations [14]. Significantly, patients with early-onset GPP without preceding plaque psoriasis frequently have *IL36RN* mutations [14,17-19]. Hussain et al. reported that GPP patients with *IL36RN* mutations show a more severe autoinflammatory phenotype with a high risk of systemic inflammation [20]. In their series of IH patients, Adachi et al. reported that three of four IH patients with *IL36N* mutations had post-partum flare-ups and that three of five IH patients without *IL36N* mutations did not need biologics treatment after delivery [21]. *IL36RN* mutation status might give us a clue to predict the occurrence of post-partum flare-ups in IH [10].

IL36RN encodes the anti-inflammatory cytokine interleukin 36-receptor antagonist (IL36Ra). Deficiency and/or malfunction of IL36Ra results in the upregulation of IL-1 family cytokine signals, the accelerated secretion of inflammatory cytokines and a hyperactive innate immune reaction, leading to the development of pustular psoriasis.

3.2. CARD14 gain-of-function variants

Variants in *CARD14*, which encodes caspase recruitment domain family member 14 (CARD14), are associated with both plaque psoriasis and GPP, and severe gain of function of CARD14 leads to GPP [22,23]. In addition, gain-of-function mutations in *CARD14* were identified as the cause of pityriasis rubra pilaris (PRP) type V [24,25]. *CARD14* variants were reported to be associated with GPP [2]. An autosomal dominant familial GPP pedigree due to a *CARD14* mutation was also reported [3]. However, pustular psoriasis patients with *CARD14* variants/mutations account

for only a minority of pustular psoriasis patients [14]. Most GPP patients with *CARD14* variants/mutations have concomitant psoriasis vulgaris [2]. *CARD14* variants/mutations have been observed in PPPP patients [16].

CARD14 is predominantly expressed in epidermal keratinocytes and it predominantly works there. CARD14 is a scaffold protein which activates NF-κB and upregulates the NF-κB signaling pathway. *CARD14* pathogenic gain-of-function mutations/variants were revealed to upregulate NFκB activities excessively, inducing pathogenic inflammatory responses within the epidermis [23]. The CARD14-mediated pathway is considered to play an important role in the pathogenesis of general psoriasis patients without *CARD14* mutations.

3.3. AP1S3 loss-of-function mutations

Variants in *AP1S3*, which encodes adaptor-related protein complex 1, sigma-3 subunit (AP1S3), have been found in patients with all subtypes of pustular psoriasis, i.e., GPP, PPPP and ACH [4,14,16,26]. Fewer pustular psoriasis patients with *AP1S3* variants have been reported than those with *IL36RN* variants/mutations.

AP1S3 is predominantly expressed in keratinocytes [26]. Adaptor-related protein complex 1 (AP-1) is a heterotetramer containing AP1S3, which traffics various molecules between the trans-Golgi network and the endosomes. Setta-Kaffetzi et al. reported that *AP1S3* silencing disrupts the endosomal translocation of the innate pattern-recognition receptor Toll-like receptor 3 (TLR-3) and affects Toll-like receptor homeostasis in keratinocytes [4]. Furthermore, AP1S3 works in the formation of autophagosomes from the trans-Golgi network, particularly in keratinocytes. Mahil et al. demonstrated that the loss of function of AP1S3 causes malfunctioning autophagy and the aberrant accumulation of p62 in keratinocytes [26]. p62 works in NFκB activation, and p62 accumulation is considered to result in excessive NFκB activation, the consequent upregulation of IL-1 signaling and the overexpression of IL-36α [26]. These pathogenetic mechanisms that have been suggested in pustular psoriasis and are associated with *AP1S3* variants further support the idea that pustular psoriasis is an AiKD.

3.4. MPO loss-of-function mutations

Recently, Haskamp *et al.* performed whole-exome sequencing in 31 GPP patients and revealed the effects of *MPO* mutations [5]. They found eight *MPO* loss-of-function mutations in patients with GPP, ACH and acute generalized exanthematous pustulosis (AGEP) [5]. The allele frequencies of functionally relevant *MPO* variants were significantly higher in affected individuals than in control subjects, and it was indicated that deficiency of the neutrophilic heme-containing enzyme myeloperoxidase (MPO), encoded by *MPO*, contributes to GPP susceptibility [5]. Phenotypic analyses in subgroups of GPP patients with and without *MPO* mutations demonstrated that patients with *MPO* mutations had concomitant PPPP more frequently [5].

Vergnano *et al.* reported a homozygous mutation in *MPO* in one GPP patient and one acral pustular psoriasis patient [27]. The frequency of the *MPO* mutation in their European GPP case cohort was significantly higher than that in the non-Finnish European exomes sequenced by the gnomAD consortium [27]. In addition, they found biallelic MPO mutations in two AGEP patients: One had a homozygous mutation; the other had compound heterozygous mutations [27]. An analysis of UK Biobank data revealed that four *MPO* variant alleles were associated with the phenotype of increased neutrophil abundance in the general population [27]. Recently, Haskamp *et al.* [28] reported that no association was observed between *MPO* variants and either psoriasis vulgaris or psoriatic arthritis in patients from Germany.

MPO oxidizes Cl^-/Br^- with H_2O_2 to the highly reactive radicals HOCl/HOBr. The neutrophil serine proteases cathepsin G (CTSG), elastase (NE) and proteinase 3 (PR3), and the monocytic protease cathepsin S (CTSS) are known to proteolyze IL-36 precursors, leading to the activation of IL-36 cytokines. Haskamp et al. demonstrated that *MPO* loss-of-function mutations in GPP, ACH and AGEP patients lead to MPO deficiency in neutrophils and monocytes and that the activity of the neutrophil serine proteases is increased in MPO-deficient neutrophils [5]. Thus, MPO deficiency is considered to correlate with the hyperactivation of IL-36 signals. In addition,

the formation of neutrophil extracellular traps (NETs) is reduced in MPO-deficient cells, resulting in the predominance of soluble neutrophil proteases activating IL-36 precursors compared with NET-bound proteases [5]. Furthermore, the phagocytosis of neutrophils by monocytes (efferocytosis of neutrophils) was impaired in MPO-deficient patients and *Mpo*$^{-/-}$ mice, suggesting the prolonged persistence of neutrophils at the cutaneous inflammatory sites [5]. These findings indicate that MPO works as a modulator of neutrophil-associated inflammation in the skin and that loss-of-function mutations in *MPO* induce pustular psoriasis via IL-36 hyperactivation and the impaired efferocytosis of neutrophils [5].

3.5. SERPINA3 loss-of-function mutations

Frey *et al*. found a loss-of-function mutation, c.966delT (p.Tyr322*), in *SERPINA3* in two independent GPP patients, and based on their additional experimental data, they proposed that *SERPINA3* loss-of-function mutations might be a predisposing factor for GPP [6]. *SERPINA3* encodes serine protease inhibitor A3 (SERPINA3), and the expression of *SERPINA3* is shown in the liver, skin, trachea and lung [6]. SERPINA3 inhibits several proteases, but it interacts more robustly with CTSG than with any other protease. Neutrophilic serine proteases, including CTSG, were shown to cleave IL-36 precursors, resulting in the activation of IL-36 cytokines. Thus, considering the inhibitory effect of SERPINA3 on CTSG, it is speculated that loss-of-function mutations in *SERPINA3* might reduce the inhibitory effects of SERPINA3 on serine proteases including CTSG and might lead to the excessive activation of IL-36 cytokines, resulting in the development of GPP [6]. Further genetic studies of large patient cohorts and supporting evidence by experimental studies are needed to elucidate clearly the role of SERPINA3 deficiency in pustular psoriasis pathogenesis.

4. Current treatments for pustular psoriasis involving biologics and granulocyte and monocyte adsorption apheresis (GMA)

Concerning treatments for pustular psoriasis, based on its mixed autoinflammatory and autoimmune pathogenic mechanisms, therapeutic strategies targeting molecules working in autoinflammatory and autoimmune cascades of pathomechanisms have been successfully used for pustular psoriasis as an AiKD, as follows.

Tumor necrosis factor (TNF) inhibitors, infliximab (a monoclonal anti-human TNF-α antibody), adalimumab (a monoclonal anti-TNF-α antibody), etanercept (a fusion protein containing human TNF-α receptor) and certolizumab pegol have been successfully used to treat GPP patients [29,30]. In addition, GPP patients successfully treated with IL-17/IL-17 receptor inhibitors, secukinumab (a monoclonal anti-IL-17A antibody), ixekizumab (a monoclonal anti-IL-17A antibody) and brodalumab (a monoclonal anti-IL-17 receptor A (IL-17RA) antibody) have been reported [29,30]. Furthermore, the efficacy of IL-23 inhibitors, ustekinumab (a monoclonal anti-IL-12/IL-23 p40 antibody), guselkumab (a monoclonal anti-IL-23 p19 antibody) and risankizumab (a monoclonal anti-IL-23 p19 antibody) has been demonstrated for GPP [29,30].

In addition, GMA is an extracorporeal treatment to remove increased, activated myeloid lineage leukocytes in the blood by using a cellulose acetate bead column [31]. GMA was first used for ulcerative colitis [31]. For skin disorders, GMA was initially applied to pyoderma gangrenosum [31]. A multicenter open-label study supported the efficacy and safety of GMA for GPP [32]. Successful treatments with GMA have been reported for a number of GPP cases as an AiKD [33]. Recently, it was suggested that the time to remission for GPP was shorter with intensive GMA (twice a week) than with conventional GMA (once a week) [34]. Also, IH patients including those with *IL36RN* mutations and *CARD14* mutations have been successfully treated with GMA [35]. In addition, several cases of PPP were reported to be successfully treated with GMA [36].

5. Novel, emerging treatment strategies for pustular psoriasis as an AiKD

The recognition of innate causative/predisposing factors and the precise assessment of their roles in the pathogenesis of pustular psoriasis may contribute to innovations of more precise, targeted, causal therapies for pustular psoriasis as an AiKD. Indeed, various treatments against pathogenic pathways and their key molecules have proven effective for pustular psoriasis cases, as described below. The novel therapeutic strategies may be able to achieve dramatic improvements in treatments for pustular psoriasis in the near future.

5.1. Treatments targeting IL-1 signaling

The IL-1 receptor antagonist anakinra has been reported as a treatment for GPP, PPPP and PPP [30]. A randomized placebo-controlled trial of anakinra for PPP demonstrated no evidence for the superiority of anakinra compared with the placebo group, although no serious adverse events were seen [37]. Treatments with another IL-1 receptor antagonist, gevokizumab, were reported to partially improve GPP lesions in two patients [38]. It was reported that one GPP patient was successfully treated with the monoclonal anti-IL-1β antibody canakinumab [39]. From these reports, IL-1 inhibitors might be effective against pustular psoriasis as an AiKD. However, the evidence is too limited to recommend their use [30,40].

5.2. Treatments targeting IL-36 signaling

Arakawa *et al.* [41] reported that induced *IL36RN* levels are lower in GPP patients with or without *IL36RN* mutations, and proposed "*IL36RN* insufficiency" in GPP. The IL-36 axis is a significant driver of inflammation in the pathogenesis of pustular psoriasis, irrespective of the presence or absence of *IL36RN* mutations. Thus, inhibitors of the IL-36 pathway are considered to be good candidates for therapeutic agents against pustular psoriasis.

As for safety, studies in individuals harboring loss-of-function mutations in *IL1RL2*, which encodes the IL-36 receptor IL-1 receptor-like 2 (IL1RL2), revealed that patients with loss of function of the IL36 receptor do not show defective immune function, and these studies suggest

that inhibition of the IL-36 pathway can be a safe therapy that does not cause significant immune deficiency in patients [42].

Two anti-IL36 receptor humanized monoclonal antibodies, spesolimab and imsidolimab, have been studied as novel agents for pustular psoriasis therapy.

Concerning spesolimab, a phase I open-label proof-of-concept study for GPP demonstrated that all seven patients with GPP flare-ups of moderate severity treated with a single intravenous dose (10 mg/kg) of spesolimab showed rapid improvement of the skin symptoms [43]. A 79.8% reduction of the mean value of patients' GPP Area and Severity Index (GPPASI) was observed four weeks after the administration, and the effect was maintained for 20 weeks [43]. No serious adverse events were seen in the patients [43]. Three of these seven patients were homozygous for *IL36RN* mutations, including one who also had a heterozygous *CARD14* variant, and the other four had no variant/mutation in *IL36RN*, *CARD14* or *AP1S3*. No apparent difference in the efficacy of spesolimab was observed between patients with versus without *IL36RN* mutations [43]. The efficacy of spesolimab regardless of the presence of the *IL36RN* mutation further supports the idea that the interleukin-36 pathway may play a major pathogenic role in patients with GPP due to different genetic backgrounds, including the absence of target mutations, as an AiKD [43]. Considering that GPP is an AiKD, it is interesting that, in the skin and serum of the patients, the innate immune responses and neutrophilic pathway reactions were promptly downregulated after spesolimab administration [43]. A Phase II study of a single 900-mg intravenous dose of spesolimab has been performed [44].

A Phase II study of spesolimab (300 mg or 900 mg every four weeks) has been reported for PPP [45]. At week 16, 31.6% of the patients in both spesolimab groups achieved a PPP Area and Severity Index (PPPASI) 50% reduction (PPPASI50) [45]. This result suggests a potential therapeutic effect for spesolimab against PPP, although the primary endpoint of significant improvement in the rate of patients achieving PPPASI50 was not met [45]. Another study on

spesolimab for PPP was completed recently (https://clinicaltrials.gov/ct2/show/NCT04015518). Further studies are needed to confirm the efficacy and safety of spesolimab against PPP [46].

As for imsidolimab, another humanized monoclonal antibody for the interleukin-36 receptor, a Phase I study indicated a favorable adverse event profile (https://www2.anaptysbio.com/wp-content/uploads/ANB019-Phase-1-Study-Poster-EAACI-2018.pdf). A Phase II study for patients with GPP (https://clinicaltrials.gov/ct2/show/nct03619902) and a Phase II study for patients with PPP (https://clinicaltrials.gov/ show/nct03633396) were recently completed.

Other therapeutic candidates targeting the IL-36 axis are under investigation [47]. The blockade of the IL-36γ signal with the small-molecule IL-36γ inhibitor oxypyrimidine A-552 was reported to inhibit IL-36γ signals and to reduce inflammation induced by IL-36γ experimentally *in vivo* and *in vitro* [48].

5.3. Treatments targeting IL-8 signaling

The fully human anti-IL-8 monoclonal antibody HuMab 10F8 binds an epitope on IL-8 overlapping the receptor binding site. HuMab 10F8 therapy was well tolerated by patients and significantly reduced the clinical disease activity of PPP [49]. However, this agent has never been approved for any clinical use, and no further reports on the antibody as a treatment for pustular psoriasis have been published.

In 2019, Campbell et al. reported CXCR2 (IL-8B receptor) and CCR6 as novel targets for therapies against GPP [50]. Ligands for the chemokine receptors CXCR2 and CCR6 were increased in GPP patients' skin and in IL-36α-treated skin [50]. An optimized small-molecule antagonist CCX624 targeting CXCR2 and CCR6 significantly reduced the infiltration of T cells, neutrophils and inflammatory dendritic cells in IL-36α-treated skin [50]. RIST4721, also called AZD4721, is an oral formulation that blocks CXCR2 (IL-8B receptor) signals on the inflammatory cells. A randomized double-blind placebo-controlled Phase IIa trial of this agent for PPP was recently completed (https://clinicaltrials.gov/ct2/show/nct03988335).

5.4. Treatments targeting granulocyte colony-stimulating factor signaling

GMA has been established as a treatment for GPP (see above). A phase I multicenter open-label study of the monoclonal anti-granulocyte colony-stimulating factor (G-CSF) receptor antibody CSL324 is under way for PPP, as well as for hidradenitis suppurativa (https://clinicaltrials.gov/ct2/show/nct03972280) [45].

6. Conclusions

Mutations/variants in *IL36RN*, *CARD14, AP1S3, MPO* and *SERPINA3* have been identified as predisposing factors for pustular psoriasis. These data have provided new insights into the pathogenetic mechanisms of pustular psoriasis, specifically the various cytokine pathways, especially the IL-36 pathway, that are involved in the pustular psoriasis pathogenesis. Our newly obtained knowledge on the molecular pathomechanisms of pustular psoriasis supports the concept of pustular psoriasis as a representative clinical entity of AiKD and has opened up a new era of novel therapeutic strategies for pustular psoriasis. Although further clinical studies are needed to assess the efficacy of molecular targeting agents, recently obtained information on inflammation pathways in pustular psoriasis suggest that the inhibition of cytokine pathways, including of the IL-36 axis, might be a promising therapeutic strategy to improve the quality of life of pustular psoriasis patients in the near future. Precise information on the pathomechanisms and the genetic background of pustular psoriasis promise to contribute to the establishment of personalized treatments for patients with pustular psoriasis.

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Declaration of competing interests

The author declares that he has no competing interests.

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Fig. 1. Genetic causative/predisposing factors and downstream pathways of inflammation, mainly autoinflammation, in pustular psoriasis as an AiKD

Pathogenic inflammatory pathways in pustular psoriasis patients with mutants/variants of five causative/predisposing molecules—IL-36Ra, CARD14, AP1S3, SERPINA3 and MPO—are summarized. These molecules are highlighted in yellow. Upregulated IL-36 signaling due to IL-36Ra deficiency (red X) and the gain-of-function mutant *CARD14* (red arrows with red +) accelerate NFκB activity. p62 accumulation caused by defective autophagy (red arrows with red +) due to AP1S3 deficiency (red X) also accelerate NFκB activity (red arrows with red +). Upregulated NFκB activity results in the accelerated secretion of chemokines/cytokines including IL-36, IL-8, CXCL1, CXCL2 and CCL20 by keratinocytes. These chemokines/cytokines induce the activation of neutrophils and dendritic cells. Loss-of-function mutants/variants in SERPINA3 lead to a failure of sufficient inhibition of CTSG activity (red X), resulting in the hyperactivation of IL-36 precursors and increased IL-36 signals. Furthermore, the loss-of-function of MPO causes a failure of adequate inhibition of neutrophil proteases (red X) and increases soluble proteases via the defective formation of NETs (red X), also leading to the excessive activation of IL-36 precursors and increased IL-36 signals. Increased IL-36 signals further activate the paracrine cytokine/chemokine signaling network excessively in the epidermis and the superficial dermis in pustular psoriasis lesions. In addition, MPO deficiency leads to the impaired phagocytosis of neutrophils by monocytes (red X), resulting in the prolonged persistence of neutrophils in the skin inflammatory lesions in pustular psoriasis.
Black arrows: secretion or activation; green arrows: cell differentiation or chemotaxis; ⊥: inhibition.

Journal of Dermatological Science

Review article

Pustular psoriasis as an autoinflammatory keratinization disease (AiKD): genetic predisposing factors and promising therapeutic targets

Masashi Akiyama

Highlights

- Autoinflammation is predominantly involved in pustular psoriasis pathogenesis.
- Pustular psoriasis is an autoinflammatory keratinization disease (AiKD).
- *IL36RN*, *CARD14*, *AP1S3, MPO* and *SERPINA3* are associated with pustular psoriasis.
- The IL-36 axis plays an important role in the pathogenesis of pustular psoriasis.
- Several cytokine pathways, including IL-36 signaling, are novel treatment targets.

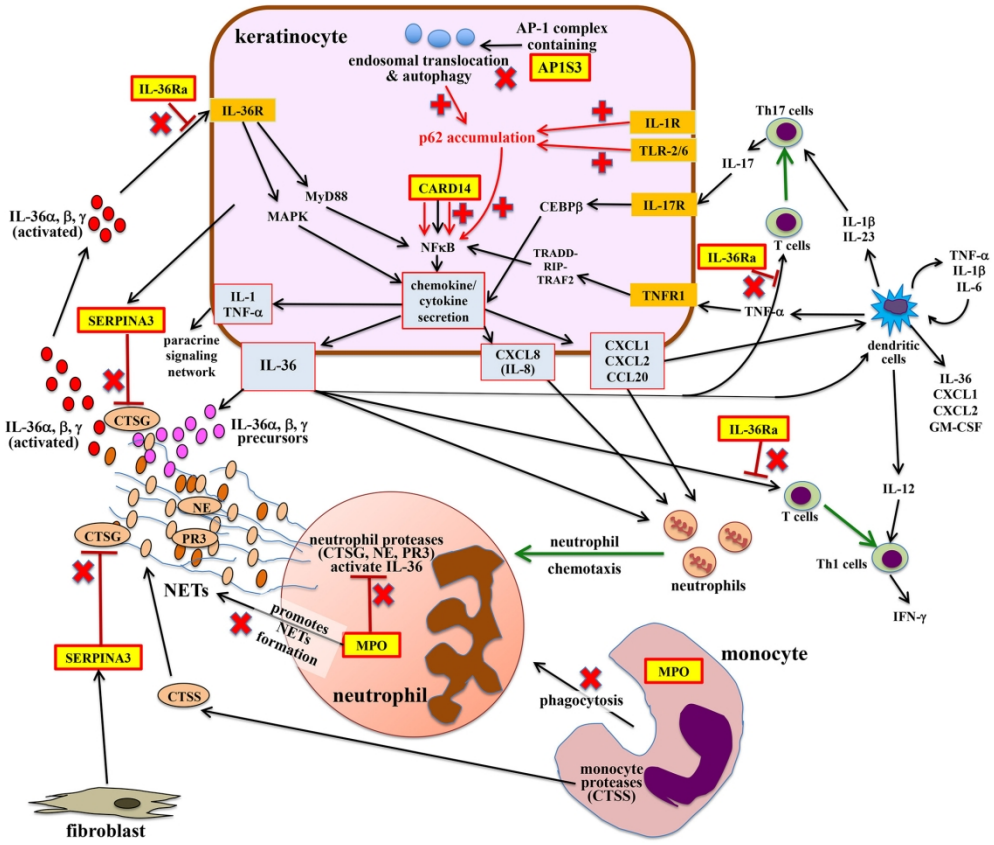

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Table 1. Classification and subtypes of pustular psoriasis

Generalized/Localized	Disease	Subtypes
Generalized	Generalized pustular psoriasis	Acute (von Zumbusch) Infantile (early-onset) generalized pustular psoriasis Impetigo herpetiformis Generalized acrodermatitis continua of Hallopeau
	Annular pustular psoriasis (circinate erythematous psoriasis)	
Localized	Acrodermatitis continua of Hallopeau	
	Palmoplantar pustular psoriasis (including Type B palmoplantar pustulosis)	

Table 2. Genetic causative/predisposing factors for pustular psoriasis as an AiKD

Disease-related gene (molecule)	Variant/mutation	Pathogenic autoinflammatory mechanism/pathway	Pustular psoriasis subtype
IL36RN (IL-36 receptor antagonist (IL36Ra))	loss-of-function mutation/variant	IL36Ra↓→IL-36↑→MyD88↑ →NFκB/MAPK↑→TNF, IL-1, IL-8, IL-17, IL-36, CXCL1, CXCL2, CCL20↑	GPP, ACH, PPPP
CARD14 (caspase recruitment domain family member 14 (CARD14))	gain-of-function mutation/variant	CARD14↑→NFκB↑→IL-36, IL-8, CXCL1, CXCL2, CCL20↑	GPP, ACH, PPPP
AP1S3 (adaptor-related protein complex 1, sigma-3 subunit (AP1S3))	loss-of-function mutation/variant	AP1S3↓→AP1 complex↓ →disrupted endosomal translocation & defective autophagy →p62 accumulation →IL-36, IL-1, TNFα↑	GPP, ACH, PPPP
MPO (myeloperoxidase (MPO))	loss-of-function mutation/variant	1) MPO↓→neutrophil & monocyte protease (CTSG, NE, PR3, CTSS) activity↑ →IL-36 activation↑→IL-36 pathway↑ 2) MPO↓→NET formation↓ →neutrophil soluble protease↑ →IL-36 activation↑→IL-36 pathway↑ 3) MPO↓→phagocytosis of neutrophils by monocytes↓→persistence of neutrophils in skin lesions	GPP, ACH
SERPINA3 (serine protease inhibitor A3 (SERPINA3))	loss-of-function mutation/variant	SERPINA3↓→CTSG↑ →IL-36β activation↑ →IL-36 pathway↑	GPP

GPP, generalized pustular psoriasis; ACH, acrodermatitis continua of Hallopeau; PPPP, palmoplantar pustular psoriasis; CTSG, cathepsin G; NE, elastase; PR3, proteinase 3; CTSS, cathepsin S; NET, neutrophil extracellular trap