INVITED REVIEW ARTICLE

Nagoya J. Med. Sci. **86**. 1–15, 2024
doi:10.18999/nagjms.86.1.1

Diseases categorized as autoinflammatory keratinization diseases (AiKDs), and their pathologies and treatments

Masashi Akiyama

Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Whole-exome and whole-genome sequencing have become widespread in approximately the last 15 years, and the predisposing factors and pathomechanisms of inflammatory keratinization diseases, which have been unknown for a long time, have gradually been revealed. Hence, various inflammatory keratinization diseases are recognized to cause innate immunity hyperactivation. Therefore, we have been advocating for the clinical entity, "autoinflammatory keratinization diseases (AiKDs)" since 2017. AiKDs are inflammatory keratinization diseases caused by autoinflammatory-related pathomechanisms in the skin. The aberrant activation of innate immunity and the resultant autoinflammation in the epidermis and the superficial dermis in AiKDs cause hyperkeratosis in the epidermis. Our initially proposed concept of AiKDs included generalized pustular psoriasis and related conditions, pityriasis rubra pilaris type V, and familial keratosis lichenoides chronica. Since then, the number of diseases known to be AiKDs has increased as previously unknown disease-causing factors and pathogenetic mechanisms of inflammatory keratinization diseases have been clarified one by one. To date, porokeratosis, hidradenitis suppurative, keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome, and AiKDs associated with epidermal growth factor receptor (EGFR) deficiency or with hepatitis and autism have been recognized as AiKDs. The concept of AiKDs is considered extremely useful in our precise understanding of the pathogeneses behind inflammatory keratinization diseases and our appropriate treatment method selection. The number of AiKDs is expected to grow with the clarification of the pathomechanisms of further inflammatory keratinization diseases.

Keywords: hidradenitis suppurativa, keratosis lichenoides chronica, pityriasis rubra pilaris, porokeratosis, pustular psoriasis

Abbreviations:
AiKDs: autoinflammatory keratinization diseases
EGFR: epidermal growth factor receptor
GPP: generalized pustular psoriasis
KLC: keratosis lichenoides chronica
KLICK: keratosis linearis with ichthyosis congenita and sclerosing keratoderma
NLRP1: NLR family pyrin domain-containing protein 1
POMP: proteasome maturation protein
PRP: pityriasis rubra pilaris
TNF: tumor necrosis factor

Received: June 1, 2023; accepted: July 6, 2023
Corresponding Author: Masashi Akiyama, MD, PhD
Department of Dermatology, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
TEL: +81-52-744-2314, Fax: +81-52-744-2318, E-mail: makiyama@med.nagoya-u.ac.jp

INTRODUCTION: WHAT ARE AUTOINFLAMMATORY KERATINIZATION DISEASES (AiKDs)?

The concept of autoinflammatory diseases or syndromes, whose pathogeneses are closely associated with autoinflammation (innate immunity hyperactivation due to genetic factors), has long been well known.[1] Systemic autoinflammatory diseases contain several different types, including familial Mediterranean fever, cryopyrin-associated periodic syndrome, and tumor necrosis factor (TNF) receptor-associated periodic syndrome. Systemic autoinflammatory diseases or syndromes are usually monogenic diseases characterized by innate immunity hyperactivation as the pathogenic mechanism, and the majority exhibited recurrent fever.[2] Unlike autoimmune diseases, autoinflammatory diseases do not exhibit antigen-specific tolerance breakdown nor B-cell or T-cell hyperactivation but instead demonstrate upregulated innate immune responses, such as neutrophil infiltration, which play a crucial role in their pathogeneses.[1] Autoinflammatory diseases and syndromes affect various organs throughout the body, and various symptoms generally occur in the skin.[3]

In contrast, inflammatory reactions in the epidermis and the superficial part of the dermis affect the epidermal cell turnover and keratinization processes in a group of skin diseases termed inflammatory keratinization diseases, resulting in excessive keratinization (hyperkeratosis). Inflammatory keratinization diseases are a vast and diverse group of diseases, including relatively prevalent conditions, such as psoriasis and lichen planus, which affect a significant number of patients. The pathogenic mechanisms and causative factors of inflammatory keratinization diseases have long been unknown although they are prevalent disorders. However, whole-exome and whole-genome sequencing have become widespread in approximately the last 15 years, and the predisposing factors and pathomechanisms of inflammatory keratinization diseases, which had been long unknown, have gradually been revealed.[4-16] The pathogeneses of various inflammatory keratinization diseases have been closely related to genetic predispositions to innate immunity hyperactivation caused by genetic factors, ie, autoinflammation.

To date, *IL36RN* loss-of-function variants and *CARD14* gain-of-function variants have been identified as causative factors in pustular psoriasis and related disorders.[17] *CARD14* gain-of-function variants have been demonstrated as causative genetic factors of pityriasis rubra pilaris (PRP) type V.[11] Furthermore, familial chronic lichenoid keratosis (KLC) is caused by gain-of-function variants in *NLRP1*.[10] The pathogenesis-related genes for each of these diseases all encode molecules that play important roles in innate immunity in the skin, especially in the epidermis. Interleukin-36 (IL-36) binds to the IL-36 receptor, causing downstream inflammatory responses.[18,19] The IL-36 receptor antagonist, which is encoded by *IL36RN*, constrains the IL-36 binding to the IL-36 receptor and controls IL-36 pathway-mediated inflammatory responses. CARD14, which is encoded by *CARD14*, induces skin inflammation by activating NF-κB in epidermal keratinocytes.[6] *NLRP1* encodes NLR family pyrin domain-containing protein 1 (NLRP1), which is the major inflammasome sensor in keratinocytes. NLRP1 inflammasome activation causes IL-1β and IL-18 release from epidermal keratinocytes, resulting in skin inflammation.[10] Molecules that are predisposing factors for these various types of inflammatory keratinization diseases are important in innate skin immunity, and autoinflammation is considered to play a crucial role in the pathogenic mechanisms of inflammatory keratinization diseases.[20]

In 2017, we advocated for a new disease concept from newly obtained knowledge about the etiology of inflammatory keratinization diseases, the "autoinflammatory keratinization diseases (AiKDs)", which widely encompasses various inflammatory keratinization diseases mainly caused by autoinflammation.[21,22] AiKDs initially included pustular psoriasis and related diseases, PRP type V, and familial KLC during its proposal.[21] To date, hidradenitis suppurativa, porokeratosis,

keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome, and AiKDs associated with epidermal growth factor receptor (EGFR) deficiency or with hepatitis and autism have been added to AiKDs (Table 1).[16,17,20,22-26] Accurately understanding that the disease pathomechanisms included in AiKDs are autoinflammatory is of great significance. Such

Table 1 Diseases classified as AiKDs, with their predisposing factors and mechanisms of pathogenesis (adopted and modified from References No. 17, 20, 22 and 26)

Disease	Genetic causative or predisposing factor	Pathogenetic mechanism
Pustular psoriasis and related conditions		
Generalized pustular psoriasis (GPP) (including impetigo herpetiformis)	1) *IL36RN* loss-of-function variants	a) hyperactivation of the IL-36 pathway
	2) *CARD14* gain-of-function variants	b) upregulation of CARD14-NFκB signaling
	3) *AP1S3* loss-of-function variants	c) deficient AP1 endosomal translocation, defective autophagy
	4) *MPO* loss-of-function variants	d) hyperactivation of the IL-36 pathway, defective efferocytosis of neutrophils
	5) *SERPINA3* loss-of-function variants	e) hyperactivation of the IL-36 pathway
	6) *BTN3A3* loss-of-function variant(s)	f) disturbed IL-1/IL-36 axis (?), upregulation of the TNF-α pathway (?)
acrodermatitis continua	1) – 4) above	a) – d) above
palmoplantar pustular psoriasis (palmoplantar pustulosis)	1) – 3) above	a) – c) above
Pityriasis rubra pilaris (PRP) (mainly type V)	*CARD14* gain-of-function variants	upregulation of CARD14-NFκB signaling
Porokeratosis	loss-of-function variants in the mevalonate pathway-related genes *MVK, MVD, PMVK* and *FDPS*	disturbed mevalonate-isoprenylated protein pathway
Hidradenitis suppurativa	1) loss-of-function variants in the γ-secretase genes *NCSTN, PSENEN* and *PSEN1*	a) deficient γ-secretase, downregulated Notch signaling
	2) variants in *NOD2*, *LPIN2*, *NLRP3*, *NLRP12*, *PSMB8*, *MVK*, *IL1RN*	b) other autoinflammatory pathways
Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome	a single-nucleotide deletion in the 5′UTR of *POMP* (dysfunction of POMP)	proteasome maturation deficiency, ER stress and UPR
Familial keratosis lichenoides chronica	*NLRP1* gain-of-function variants (unknown)	hyperactivation of the NLRP1 inflammasome pathway
AiKD with EGFR deficiency	*EGFR* loss-of-function variants	hyperactivation of PLA2, NFκB, and JNK1 signaling
AiKD with hepatitis and autism	*JAK1* gain-of-function variants	hyperactivation of JAK1-STAT signaling

an understanding of disease etiology promises to contribute to novel therapeutic innovation targeting essential molecules or inflammatory pathways in AiKD pathogenic mechanisms.[20,26,27] For example, biologics focusing on the IL-36 axis are promising novel therapeutic agents for pustular psoriasis and related disorders.

AiKDs are characterized by four significant attributes.[21,22] (1) The primary etiological event is epidermal and superficial dermal inflammation. (2) This inflammation causes hyperkeratosis. (3) Genetic causative factors of AiKDs provoke innate immunity hyperactivation, causing epidermal and superficial dermal autoinflammation. (4) The main pathogenic mechanism of inflammation in AiKDs is autoinflammation, but autoimmune reactions sometimes play a crucial role.[21,22] Psoriasis vulgaris has both autoinflammatory and autoimmune pathogeneses. Thus, psoriasis vulgaris might well be included in AiKDs.[20] However, several patients have psoriasis vulgaris, but only a minority of whom have been revealed to have genetic predisposing factors. Hence, I have intentionally excluded psoriasis vulgaris. In the future, we cannot exclude the possibility of considering psoriasis vulgaris as an AiKD if a majority of patients with psoriasis vulgaris are demonstrated to have distinct genetic predisposing factors.

As previously described above, AiKDs included pustular psoriasis and associated disorders, PRP type V, hidradenitis suppurativa, porokeratosis, familial KLC, KLICK syndrome, and AiKDs associated with EGFR deficiency or with hepatitis and autism (Table 1, Figure 1).[16,17,20,22-26] Disorders and conditions contained in the AiKD category are anticipated to grow in number in recent years, with the clarification of the pathogeneses of inflammatory keratinization diseases.[20] The unique concept of AiKDs is expected to help precisely understand the pathogenesis of inflammatory keratinization disorders due to autoinflammation, causing novel treatment strategy innovation.[16,20,21-24,26]

Diseases included in AiKDs may be categorized into those that are purely genetic, such as KLICK syndrome, and those that have germline mutations associated with only some patients, such as generalized pustular psoriasis (GPP). However, distinguishing between them might be difficult because it may become clear in the future that a considerable number of patients do have genetic causative variants even in diseases in which genetic factors are not known to play

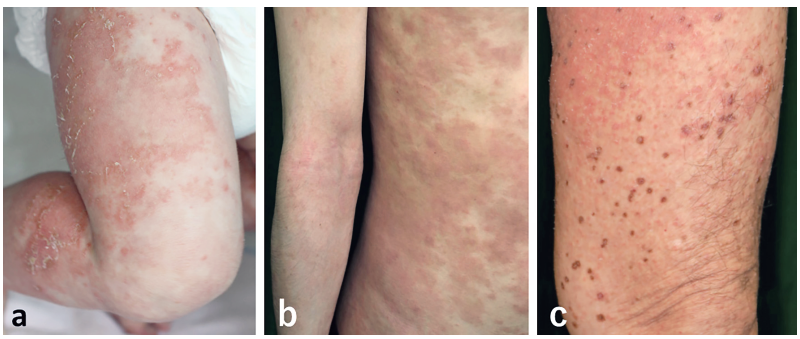

Fig. 1 Clinical features of patients with representative AiKDs

Fig. 1a: Pustular psoriasis characterized by irregularly shaped confluent erythema with multiple pustules on the leg of a patient with DITRA with a heterozygous *IL36RN* loss-of-function variant.

Fig. 1b: PRP type V characterized by keratotic papules and erythema on the trunk and arm of a patient carrying a heterozygous *CARD14* gain-of-function variant.

Fig. 1c: Porokeratosis (eruptive pruritic papular porokeratosis) characterized by inflammation at the typical disseminated superficial porokeratotic lesions and erythema expanding to the surrounding areas on the left thigh of a patient with eruptive pruritic papular porokeratosis carrying an *MVD* germline variant.

a crucial role in the majority of patients. Thus, categorizing AiKDs into purely genetic ones versus partly genetic ones might be premature.

Researchers have elucidated only a few AiKDs for which the immune cells associated with innate immunity play important roles in pathogenesis. Neutrophils have played crucial roles in the pathogenesis of skin lesions in GPP and hidradenitis suppurativa.[17,28] However, neither γδ T cells nor natural killer (NK) cells have been reported to play crucial roles in AiKD pathogeneses.

DISEASES INCLUDED IN AiKDs AND THEIR PATHOGENESIS

At present, AiKDs included many inflammatory keratinization diseases, and the number of disorders and conditions considered to be AiKDs remains increasing. The genetic causative factors and pathomechanisms of the disorders included in AiKDs widely vary, although they share autoinflammation as the main pathogenic mechanism. The diseases currently classified in AiKDs are summarized below.

Pustular psoriasis and related conditions

Pustular psoriasis is considered a subtype of psoriasis and is characterized by sterile pustules. Pustular psoriasis is divided into generalized and localized types.[17] The generalized types are characterized by skin lesions seen almost in the entire body. The GPP types include acute GPP (von Zumbusch), infantile GPP, impetigo herpetiformis (GPP caused by pregnancy), generalized acrodermatitis continua of Hallopeau, and annular pustular psoriasis.[29] Localized types are characterized by skin lesions seen only in limited areas, such as the tips of the extremities and the palms and soles. The localized types include acrodermatitis continua of Hallopeau and palmoplantar pustular psoriasis.[29] In general, all pustular psoriasis subtypes are included in AiKDs.[17] In particular, GPP is considered a representative AiKD.[30] Patients with early-onset GPP without plaque psoriasis typically have *IL36RN* loss-of-function mutations as genetic causative factors (Figure 1a).[31,32]

IL36RN encodes the IL-36 receptor antagonist. Epidermal keratinocytes mainly produce the IL-36 receptor antagonist, which competitively prevents the binding of IL-36α, β, and γ to the IL-36 receptor.[18] TNF-α and IL-17 inflammatory pathways induce IL-36α, β, and γ production. IL-36α, β, and γ bind to IL-36 receptors, which activates NFκB, thereby increasing cytokine/chemokine production and lesional epidermal inflammation of pustular psoriasis (Figure 2a).[33] IL-36 receptor antagonists competitively inhibit IL-36 signaling and repress the IL-36-induced inflammation amplification. IL-36 pathway-induced inflammation is exacerbated in patients with impaired IL-36 signaling inhibition due to loss-of-function variants in *IL36RN*.[5] Intensive inflammatory responses due to IL-36 receptor antagonist malfunction are the major pathogenic mechanisms in patients with pustular psoriasis harboring loss-of-function variants in *IL36RN*.

Stephenson et al[34] proposed the 15-item DITRA/Autoinflammatory Diseases Activity Index (DITRA/AIDAI), which consists of the AIDAI[35] plus three additional skin-focused items: skin rash (pustular), skin rash (plaque type with keratinization), and geographic tongue, to score the severity of deficiency of IL-36 receptor antagonist (DITRA)/AiKDs due to IL36RN variants.

Variants in five other genes, including *CARD14*, *AP1S3*, *MPO*, *SERPINA3*, and *BTN3A3*, in addition to *IL36RN* variants, have been recognized as predisposing factors for pustular psoriasis.[17,36]

CARD14, which is encoded by *CARD14*, works in NFκB signaling activation in epidermal keratinocytes.[6] Thus, variant CARD14 hyperactivates NFκB in keratinocytes and induces skin lesion inflammation in patients with GPP and palmoplantar pustular psoriasis due to *CARD14* gain-of-function variants (Figure 2b).[37]

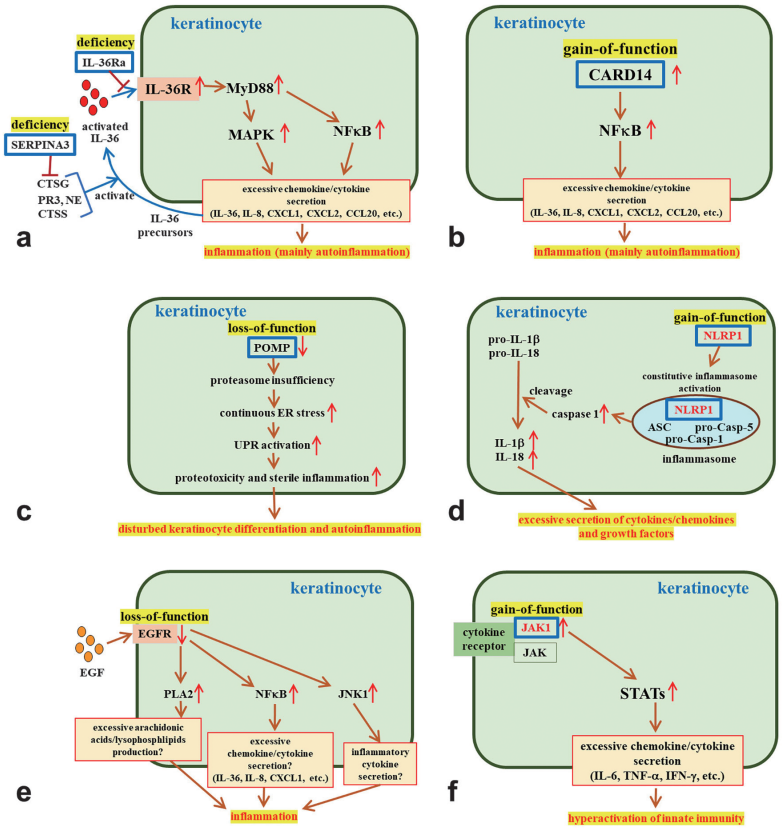

Fig. 2 Genetic causative defects and pathogenic pathways/mechanisms of autoinflammatory keratinization diseases (AiKDs) (adopted and modified from References No. 17, 21, 22, and 26)

Fig. 2a: *IL36RN* loss-of-function variants in pustular psoriasis characterized by excessive IL-36 signaling due to IL-36 receptor antagonist deficiency causing autoinflammation in the skin.

Fig. 2b: *CARD14* gain-of-function variants in pustular psoriasis and PRP type V characterized by *CARD14* gain-of-function variants overactivating the CARD14-NFκB pathway and causing cutaneous inflammation.

Fig. 2c: *POMP* mutation (1-bp deletion in the 5′UTR) in KLICK syndrome characterized by POMP deficiency causing proteasome insufficiency and ER stress, thereby hyperactivating UPR and autoinflammation in the skin.

Fig. 2d: *NLRP1* gain-of-function variants in familial KLC characterized by the aberrant NLRP1 inflammasome activation causing the upregulated IL-1β and IL-18 secretion, resulting in skin autoinflammation.

Fig. 2e: *EGFR* loss-of-function variants in AiKD with epidermal growth factor (EGFR) deficiency characterized by EGFR deficiency causing phospholipase A2 (PLA2), NFκB, and JNK1 upregulation, resulting in skin inflammation.

Fig. 2f: A *JAK1* gain-of-function variant in AiKD with hepatitis and autism characterized by the hyperactivated JAK1-STAT pathway increasing chemokine and cytokine secretion.

Red up arrows: upregulation.
⊥: inhibition.

AP1S3 encodes adapter-related protein complex 1 subunit sigma 3 (AP1S3), and *AP1S3* variants have been identified in patients with all types of pustular psoriasis.[8,38-40] AP1S3 is involved in adapter-related protein complex 1 (AP-1) formation. AP-1 participates in clathrin-mediated vesicular transport from the Golgi or endosomes. *AP1S3* silencing reportedly disturbs the endosomal translocation of Toll-like receptor 3, thereby affecting the homeostasis of the

Toll-like receptor system in keratinocytes.[8] Furthermore, AP1S3 loss-of-function was reported to cause defects in autophagy and the aberrant p62 accumulation, causing NFκB hyperactivation and IL-1 signaling upregulation and excessive IL-36α production in the skin.[38]

Additionally, defects in the neutrophil heme-containing enzyme myeloperoxidase, which is encoded by *MPO*, have been associated with GPP development.[13,14]

Neutrophil elastase, cathepsin G, and proteinase 3, which are neutrophil serine proteases, and monocyte protease cathepsin S cleave IL-36 precursors, causing the formation of active IL-36 forms. Defective myeloperoxidase activity in neutrophils causes the upregulated activity of neutrophil serine proteases, the decreased neutrophil extracellular trap formation, and an abundance of soluble neutrophil proteases, causing the excessive IL-36 cytokine activity.[13] Furthermore, myeloperoxidase deficiency disturbs neutrophil efferocytosis, thereby extending the persistence of infiltrating neutrophils at inflammation sites in the skin.[13]

Additionally, in 2020, loss-of-function variants in *SERPINA3*, which encodes serine protease inhibitor A3 (SERPINA3), were reported as predisposing factors for GPP.[15] The loss of SERPINA3 function is believed to cause the IL-36 pathway upregulation because SERPINA3 reduces the activity of various neutrophilic proteases that activate IL-36.[15]

In 2023, gene burden testing indicated that *BTN3A3* correlates with GPP.[36] Further studies revealed the significant association between one loss-of-function variant, c.513G>A (p.Trp171*), in *BTN3A3* and GPP.[36] BTN3A3 is a member of the butyrophilin (BTN) 3 subfamily, and its function remains to be elucidated. Zhang et al[36] indicated that BTN3A3 expression is related to inflammatory imbalances in patients with GPP and demonstrated that BTN3A3 deficiency in HaCaT cells significantly suppresses *IL36RN* mRNA expression.

Pityriasis rubra pilaris

PRP is commonly recognized as an inflammatory keratinization disease characterized by keratotic papules and scales primarily on the trunk and the extensor sides of the extremities (Figure 1b). Hyperkeratosis and erythema are often observed on the palms. At present, PRP is categorized into six types following onset age, clinical presentation, and disease course.[41,42] PRP type V has its onset in infancy or early childhood and has a chronic disease course without improvement for a lifetime. Many patients with PRP type V have *CARD14* variants as a genetic predisposing factor, and PRP type V is believed to be an AiKD.[11,21] *CARD14* gain-of-function variants activate NFκB excessively in keratinocytes in patients with PRP, causing autoinflammation in the epidermis and the superficial dermis (Figure 2b). PRP caused by gain-of-function *CARD14* variants is considered an AiKD.[11,21]

Porokeratosis

Porokeratosis is a keratinization disease characterized histopathologically by the presence of cornoid lamellae, which are towering columns of parakeratotic cells in the stratum corneum from the spinous cell layers, at the margin of brown keratotic plaques and macules.[43] Porokeratosis has been historically categorized following the clinical features into various subtypes, including classic porokeratosis (porokeratosis of Mibelli), superficial disseminated porokeratosis, and superficial disseminated actinic porokeratosis.[43] Porokeratosis lesions are usually asymptomatic, but they can be accompanied by intense inflammation such as in eruptive pruritic popular porokeratosis (Figure 1c).[44] Some familial cases of porokeratosis have exhibited autosomal dominant inheritance. Variants in four genes (*MVD*, *MVK*, *PMVK*, and *FDPS*) that encode enzymes involved in the mevalonate pathway have been described as disease-related genes for porokeratosis.[7,45] Porokeratosis has been considered an AiKD caused by variants in mevalonate pathway genes.[46] Abnormal epidermal morphology was reported in *Mvda*-deficient zebrafish (*Mvda* being the zebrafish

homolog to human *MVD*).[47] Furthermore, peripheral T-cell subset alterations and proinflammatory cytokine dysregulated production by T cells are found in patients with porokeratosis who harbor *MVD* variants as well as those with *MVK* variants.[48] These findings might help elucidate the pathogenesis of porokeratosis as an AiKD.[48]

Hidradenitis suppurativa

Hidradenitis suppurativa is characterized by chronic, recurrent, intractable multiple abscesses and pustular drainage, primarily in the groins, axillae, buttocks, and vulva.[49,50] It had been considered an infectious disorder but has recently been recognized as an AiKD.[12,51-53] Familial cases of hidradenitis suppurativa exhibit a more robust tendency to possess AiKD characteristics than nonfamilial cases.[51] Some hidradenitis suppurativa cases demonstrated variants in genes that encode NCSTN, PSENEN, and PSEN1, which are the proteins that form the γ-secretase complex.[51] Hair follicle epithelial hyperkeratosis is seen in hidradenitis suppurativa cases with variants in these genes, thereby occluding hair follicles and plugging keratin. Such occlusion and plugging are major steps in hidradenitis suppurativa pathogenesis.[12,51] Notch1 and Notch2 signaling dysfunction was indicated in the skin lesions of patients with hidradenitis suppurativa with variants in γ-secretase complex genes.[53,54]

Some patients with various systemic autoinflammatory diseases/syndromes, including familial Mediterranean fever, arthritis suppurativa, pyoderma gangrenosum, acne (PAPA) syndrome, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) syndrome, demonstrated hidradenitis suppurativa-like cutaneous symptoms. Innate immunity hyperactivation in the skin is assumed to be the pathogenesis of hidradenitis suppurativa-like cutaneous symptoms in systemic autoinflammatory diseases and syndromes,[51] and these hidradenitis suppurativa-like cutaneous symptoms indicate the significance of autoinflammatory pathomechanisms in hidradenitis suppurativa.

Additionally, patients with hidradenitis suppurativa have demonstrated variants in several autoinflammation-related genes (*NOD2*, *LPIN2*, *NLRP3*, *NLRP12*, *PSMB8*, *MVK*, and *IL1RN*).[51] Recently, patients with biallelic *MVK* variants have shown both hidradenitis suppurativa and hyper-IgD syndrome (an autoinflammatory syndrome).[55] These cases further support the idea that hidradenitis suppurativa should be included in the AiKDs. Adalimumab, which is a monoclonal anti-TNFα antibody used to treat pustular psoriasis, has recently been used in patients with hidradenitis suppurativa, considering the pathogenesis of hidradenitis suppurativa as an AiKD.[56,57] Additionally, brodalumab, which is an IL-17 receptor A antibody, was reported to be effective for hidradenitis suppurativa as an AiKD.[58]

KLICK syndrome

KLICK syndrome is a very rare inflammatory keratinization disease. Patients present hyperkeratosis and scaling over wide body surface areas, including the palmoplantar areas.[59] Linearly arranged hyperkeratotic papules are seen on the cubital fossae and the wrists while hyperkeratotic plaques on the axillae and the neck.[59] Hyperkeratosis, acanthosis with papillomatosis, and hypergranulosis are histopathologically seen in the lesional epidermis, and nonspecific inflammatory cell infiltration is observed in the dermis of the skin lesions.[59] A homozygous single-nucleotide deletion in the 5′UTR of *POMP*, which encodes proteasome maturation protein (POMP), which is a key chaperone for proteasome maturation, causes KLICK syndrome.[4] Deficiency in such maturation caused by POMP dysfunction boosts endoplasmic reticulum stress and provokes unfolded protein response (Figure 2c).[4,60,61] KLICK syndrome is thought to be an AiKD, considering the pathomechanism by which autoinflammation causes hyperkeratosis.[23] Notably, heterozygous frameshift variants in the penultimate exon of POMP have been reported to cause a systemic

autoinflammatory disease called proteasome-associated autoinflammatory syndrome 2 (PRAAS2), which is also known as POMP-related autoinflammation and immune dysregulation disease.[61,62]

KLC

KLC is a rare inflammatory keratinization disorder. Patients show multiple keratotic papules and nodules on the extensor sides of the extremities and the trunk. Patients with KLC show seborrheic dermatitis-like lesions on the face, hyperkeratotic lesions on the palms and the soles, and thickening deformities of the nails.[63] Lichenoid tissue reaction is histopathologically observed in the skin lesions.[63] Patients with KLC with a family history have occasionally been reported. An *NLRP1* gain-of-function variant, which encodes NLR family pyrin domain-containing protein 1 (NLRP1), had been a genetic causative factor in familial KLC in 2016.[10] NLRP1 is an inflammasome sensor, and the causal *NLRP1* variant excessively activates NLRP1 inflammasomes, primarily in keratinocytes.[10] NLRP1 inflammasome activation in the epidermis in increased IL-1β secretion causes epidermal and superficial dermal autoinflammation (Figure 2d).[10,64] Thus, familial KLC caused by *NLRP1* gain-of-function variants is considered an AiKD.[21,22]

AiKDs with epidermal growth factor deficiency

We indicated skin inflammatory symptoms due to germline *EGFR* variants to be included in AiKDs.[25] Several facts indicated that inflammatory skin symptoms caused by *EGFR* variants demonstrate characteristic AiKD features. Hyperkeratosis was clinically and histopathologically seen in the skin lesions of a patient with a homozygous loss-of-function variant who demonstrated neonatal inflammatory skin and bowel disease[9] and in patients with fatal neonatal nephrocutaneous syndrome caused by *EGFR* variants.[65] The majority of patients carrying *EGFR* variants demonstrated ichthyosiform skin desquamation, which is a characteristic of AiKDs. Furthermore, the patient with neonatal inflammatory skin and bowel disease had neutrophilic infiltration in the follicular epithelium, causing folliculitis.[9] The patient's skin mRNA expression patterns revealed the upregulation of inflammatory and innate immune response pathways, especially NF-κB, c-Jun N-terminal kinase 1 (JNK1), and phospholipase A2.[9] EGFR-ablated mice demonstrated the overexpression of the cytokines/chemokines CCL5, CCL11, CCL2, CCL22, IL-1β and TNF-α in the skin.[66] These data indicated patients with *EGFR* loss-of-function variants and skin symptoms to be having an AiKD (Figure 2e).

AiKDs with hepatitis and autism

A unique AiKD case suffering from severe early-onset hepatitis and autism has been reported with a *JAK1* gain-of-function variant.[16] The female patient presented with mild erythema and dry skin over a wide body area since birth, and she had erythema on the cheeks and ichthyotic lesions on the trunk at 8 years of age. Janus kinase 1 (JAK1), which is encoded by *JAK1*, plays crucial roles in various cytokine signaling, such as IL-6 and interferons.[67] Indeed, heterozygous *JAK1* variants had been associated with a disease characterized by multiorgan immune dysregulation.[68,69] Thus, the heterozygous gain-of-function variant in *JAK1* is considered to cause multiorgan immune dysregulation, causing the unique AiKD: AiKD with hepatitis and autism, in AiKD with hepatitis and autism due to a *JAK1* variant (Figure 2f).[16]

TREATMENTS FOR AiKDs

Novel therapeutic strategies and new drugs that target key molecules and pathways in the autoinflammatory pathomechanisms of AiKD have already been developed or are expected to be

innovated by precisely elucidating the autoinflammation-related pathogenetic mechanisms of various AiKDs.[26] Additionally, the repurposing of drugs already used for other inflammatory diseases as novel AiKD treatments is thought to be a promising strategy for innovative AiKD medications.

Treatments targeting the IL-36 pathway

GPP is representative of AiKD, and *IL36RN* variants are known as a significant predisposing factor for GPP. The IL-36 pathway is thought to be crucial in GPP pathogenesis. Thus, the IL-36 pathway is a promising target for novel treatments.[28] Individuals carrying loss-of-function variants in *IL1RL2*, which encodes the IL-36 receptor interleukin-1 receptor-like 2 (IL1RL2), were investigated in terms of safety.[70] Individuals with abolished IL-36 receptor functions demonstrated no immune function deficits. Therefore, IL-36 signal inhibition did not significantly disturb the host defense, and such inhibition was considered a possibly safe treatment.[70] Two biologics against the IL-36 receptor, including spesolimab (BI655130) and imsidrimab (ANB019), demonstrated potential as a treatment for several diseases. The Food and Drug Administration in the USA and Japan has recently approved spesolimab as a GPP treatment.

Spesolimab is a biologic that acts against the IL-36 receptor and blocks the IL-36 pathway,[71] thereby reducing T-cell stimulation and proinflammatory process inhibition. Additionally, spesolimab has been assumed to, directly and indirectly, reduce several IL-36 family members and other cytokines production, including IL-17C, thereby contributing to Th cell activity suppression.[72] A phase I, open-label, proof-of-concept study of spesolimab revealed that adult patients with biologic-naïve GPP with moderate flares demonstrated rapid improvement in skin symptoms after a single intravenous administration of 10 mg/kg of spesolimab.[73] Spesolimab had good efficacy in patients with GPP with or without GPP-associated *IL36RN*-variants.[73] These results verify the significant involvement of the IL-36 axis in GPP pathogenesis among patients without IL-36 receptor antagonist deficiency. A phase II study revealed that a single dose of 900 mg of intravenous spesolimab met the primary endpoint of "GPP Physician Global Assessment (GPPGA) pustule subscore 0 (no pustules visible)" and the secondary endpoint of "GPPGA total score 0 or 1 (clear or nearly clear skin)" 1 week after administration.[74,75]

Hidradenitis suppurativa might be the next indication for "trunk" molecule IL-36-targeted therapies among AiKDs.[28] The greatly upregulated IL-36α, β, and γ expression has been observed in the skin lesions and sera of patients with hidradenitis suppurativa.[76-78] IL-36γ activates NFκB in keratinocytes, causing IL-8 secretion and neutrophil recruitment into the hidradenitis suppurativa lesions.[78] Furthermore, IL-36 has upregulated the granulocyte colony-stimulating factor levels, thereby recruiting and extending the survival of neutrophils in the lesions of hidradenitis suppurativa.[79] These data indicate the involvement of IL-36 in keratinocytes and immune cell interactions, especially neutrophils, thereby participating in the hidradenitis suppurativa pathogenesis.[78] Therefore, the NIH site ClinicalTrials.gov revealed clinical trials of spesolimab for hidradenitis suppurativa.

Imsidolimab is another IL-36 receptor antagonist that exhibited a sufficient safety profile in a phase I study (https://www2.anaptysbio.com/wp-content/uploads/ANB019-Phase-1-Study-Poster-EAACI-2018.pdf). Several phase II clinical trials of imsidolimab for the AiKDs GPP and hidradenitis suppurativa are found on the same NIH site: ClinicalTrials.gov (NCT03619902; NCT04856930; NCT05352893; NCT05366855).

Treatment target pathways other than the IL-36 axis

Various autoinflammation-related genes/molecules and pathways, in addition to the IL-36 pathway, are thought to play important roles in various AiKD pathogeneses. Understanding the genetic predisposing factors, disease-related genes/molecules, and pathways that induce innate

immunity hyperactivation and precisely recognizing AiKD pathophysiology are essential for novel therapeutic strategy innovation. The precise elucidation of AiKD pathogeneses is expected to contribute to drug repurposing and the establishment of precision medicines for patients with AiKDs. One good example is the repurposing of adalimumab, which is an anti-TNF-α biologic for psoriases, including pustular psoriasis, which is a representative AiKD, as a treatment for hidradenitis suppurativa, which is another AiKD. In Japan, adalimumab has been approved for hidradenitis suppurativa. Furthermore, JAK inhibitors, as drugs that target disease-related molecules, might be effective against AiKD with hepatitis and autism caused by a JAK1 gain-of-function variant.[16] Excellent etiological treatment strategies targeting disease-related molecules and pathways of autoinflammation are expected to be established for more diseases and greater numbers of patients as more inflammatory keratinization disorders are recognized as AiKDs.[20]

CONCLUSION

Inflammatory keratinization disorders, with autoinflammation as the main inflammatory pathway, are considered AiKDs,[21] and their mechanisms of pathogenesis involve innate immunity hyperactivation by disease-related gene variants.[22] The accurate recognition of the pathogenesis and pathophysiology of each AiKD is expected to contribute to novel therapeutic strategy innovation, drug repurposing, and precision medicine establishment for various AiKDs.[20] The systemic administration of drugs targeting disease-related molecules, biologics for disease-related immune pathways, and immunosuppressants will be considered novel AiKD treatments.

The etiological mechanisms of various inflammatory keratinization disorders with unknown pathogeneses are expected to be identified. Some of the inflammatory keratinization disorders with newly clarified etiologies will probably be included in AiKDs. Thus, an increased number of disorders is expected to be realized as AiKDs. I hope that safe, novel, and effective treatment methods will be established for many AiKDs based on a precise and detailed recognition of pathogenetic autoinflammation mechanisms.

ACKNOWLEDGEMENTS

I thank Dr Takuya Takeichi for providing me with the patients' photos for the figure.

The author is supported by Grant-in-Aid for Scientific Research (B) 21H02941 from the Japan Society for the Promotion of Science (JSPS) and by a grant from the Ministry of Health, Labor and Welfare of Japan (Health and Labor Sciences Research Grant for Research on Intractable Diseases: 23FC1039).

DISCLOSURE STATEMENT

The author has received research grants from Boehringer Ingelheim, Novartis Japan, and Maruho. The author has received payment for lectures from Maruho, Sanofi, and Boehringer Ingelheim.

REFERENCES

1 Broderick L, Hoffman HM. IL-1 and autoinflammatory disease: biology, pathogenesis and therapeutic

targeting. *Nat Rev Rheumatol.* 2022;18(8):448–463. doi:10.1038/s41584-022-00797-1.
2 Delplanque M, Fayand A, Boursier G, Grateau G, Savey L, Georgin-Lavialle S. Diagnostic and therapeutic algorithms for monogenic autoinflammatory diseases presenting with recurrent fevers among adults. *Rheumatology (Oxford).* 2023;62(8):2665–2672. doi:10.1093/rheumatology/keac712.
3 Wu D, Shen M, Yao Q. Cutaneous manifestations of autoinflammatory diseases. *Rheumatol Immunol Res.* 2021;2(4):217–225. doi:10.2478/rir-2021-0030.
4 Dahlqvist J, Klar J, Tiwari N, et al. A singlenucleotide deletion in the POMP 5′ UTR causes a transcriptional switch andaltered epidermal proteasome distribution in KLICK genodermatosis. *Am J Hum Genet.* 2010;86(4):596–603. doi:10.1016/j.ajhg.2010.02.018.
5 Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med.* 2011;365(7):620–628. doi:10.1056/NEJMoa1013068.
6 Jordan CT, Cao L, Roberson ED, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet.* 2012;90(5):796–808. doi:10.1016/j.ajhg.2012.03.013.
7 Zhang SQ, Jiang T, Li M, et al. Exome sequencing identifies MVK mutations in disseminated superficial actinic porokeratosis. *Nat Genet.* 2012;44(10):1156–1160. doi:10.1038/ng.2409.
8 Setta-Kaffetzi N, Simpson MA, Navarini AA, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet.* 2014;94(5):790–797. doi:10.1016/j.ajhg.2014.04.005.
9 Campbell P, Morton PE, Takeichi T, et al. Epithelial inflammation resulting from an inherited loss-of-function mutation in EGFR. *J Invest Dermatol.* 2014;134(10):2570–2578. doi:10.1038/jid.2014.164.
10 Zhong FL, Mamaï O, Sborgi L, et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell* 2016;167(1):187–202. doi:10.1016/j.cell.2016.09.001.
11 Takeichi T, Sugiura K, Nomura T, et al. Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. *JAMA Dermatol.* 2017;153(1):66–70. doi:10.1001/jamadermatol.2016.3601.
12 De Vita V, McGonagle D. Hidradenitis suppurativa as an autoinflammatory keratinization disease. *J Allergy Clin Immunol.* 2018;141(5):1953. doi:10.1016/j.jaci.2018.01.010.
13 Haskamp S, Bruns H, Hahn M, et al. Myeloperoxidase modulates inflammation in generalized pustular psoriasis and additional rare pustular skin diseases. *Am J Hum Genet.* 2020;107(3):527–538. doi:10.1016/j.ajhg.2020.07.001.
14 Vergnano M, Mockenhaupt M, Benzian-Olsson N, et al. Loss-of-function myeloperoxidase mutations are associated with increased neutrophil counts and pustular skin disease. *Am J Hum Genet.* 2020;107(3):539–543. doi:10.1016/j.ajhg.2020.06.020.
15 Frey S, Sticht H, Wilsmann-Theis D, et al. Rare loss-of-function mutation in SERPINA3 in generalized pustular psoriasis. *J Invest Dermatol.* 2020;140(7):1451–1455. doi:10.1016/j.jid.2019.11.024.
16 Takeichi T, Lee JYW, Okuno Y, et al. Autoinflammatory keratinization disease with hepatitis and autism reveals roles for JAK1 kinase hyperactivity in autoinflammation. *Front Immunol.* 2022;12:737747. doi:10.3389/fimmu.2021.737747.
17 Akiyama M. Pustular psoriasis as an autoinflammatory keratinization disease (AiKD): Genetic predisposing factors and promising therapeutic targets. *J Dermatol Sci.* 2022;105(1):11–17. doi:10.1016/j.jdermsci.2021.11.009.
18 Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev.* 2018;281(1):8–27. doi:10.1111/imr.12621.
19 Sugiura K. Role of interleukin 36 in generalised pustular psoriasis and beyond. *Dermatol Ther (Heidelb).* 2022;12(2):315–328. doi:10.1007/s13555-021-00677-8.
20 Akiyama M. Autoinflammatory keratinization diseases (AiKDs): Expansion of disorders to be included. *Front Immunol.* 2020;11:280. doi:10.3389/fimmu.2020.00280.
21 Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases. *J Allergy Clin Immunol.* 2017;140(6):1545–1547. doi:10.1016/j.jaci.2017.05.019.
22 Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases: An emerging concept encompassing various inflammatory keratinization disorders of the skin. *J Dermatol Sci.* 2018;90(2):105–111. doi:10.1016/j.jdermsci.2018.01.012.
23 Takeichi T, Akiyama M. KLICK syndrome linked to a POMP mutation has features suggestive of an autoinflammatory keratinization disease. *Front Immunol.* 2020;11:641. doi:10.3389/fimmu.2020.00641.
24 Akiyama M, De Vita V, Sugiura K. Editorial: Autoinflammatory keratinization diseases (AiKD). *Front Immunol.* 2020;11:1753. doi:10.3389/fimmu.2020.01753.
25 Takeichi T, Akiyama M. Systemic inflammatory diseases due to germ line EGFR mutations, with features suggestive of autoinflammatory keratinization diseases. *J Dermatol.* 2021;48(1):e24-e25. doi:10.1111/1346-

8138.15612.
26 Akiyama M. Autoinflammatory keratinization diseases: The concept, diseases involved, and pathogeneses. *Dermatol Sin.* 2022;40(4):197–203. doi:10.4103/1027-8117.365590.
27 Peña-Rosado A, Riera-Martí N, Expósito-Serrano V, Romaní J. Autoinflammatory keratinitzation diseases (AIKDs)[in English, in Spanish]. *Actas Dermosifiliogr (Engl Ed).* 2021;112(10):891–900. doi:10.1016/j.ad.2021.05.015.
28 Fukaura R, Akiyama M. Targeting IL-36 in inflammatory skin diseases. *BioDrugs.* 2023;37(3):279–293. doi:10.1007/s40259-023-00587-5.
29 Takeichi T, Akiyama M. Generalized pustular psoriasis: Clinical management and update on autoinflammatory aspects. *Am J Clin Dermatol.* 2020;21(2):227–236. doi:10.1007/s40257-019-00492-0.
30 Neuhauser R, Eyerich K, Boehner A. Generalized pustular psoriasis-Dawn of a new era in targeted immunotherapy. *Exp Dermatol.* 2020;29(11):1088–1096. doi:10.1111/exd.14171.
31 Sugiura K, Takemoto A, Yamaguchi M, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. *J Invest Dermatol.* 2013;133(11):2514–2521. doi:10.1038/jid.2013.230.
32 Akiyama M. Early-onset generalized pustular psoriasis is representative of autoinflammatory keratinization diseases. *J Allergy Clin Immunol.* 2019;143(2):809–810. doi:10.1016/j.jaci.2018.11.009.
33 Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol.* 2017;140(1):109–120. doi:10.1016/j.jaci.2016.08.056.
34 Stephenson C, Prajapati VH, Hunter C, Miettunen P. Novel use of autoinflammatory diseases activity index (AIDAI) captures skin and extracutaneous features to help manage pediatric DITRA: A case report and a proposal for a modified disease activity index in autoinflammatory keratinization disorders. *Pediatr Dermatol.* 2020;37(4):670–676. doi:10.1111/pde.14155.
35 Piram M, Koné-Paut I, Lachmann HJ, et al. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. *Ann Rheum Dis.* 2014;73(12):2168–2173. doi:10.1136/annrheumdis-2013-203666.
36 Zhang Q, Shi P, Wang Z, et al. Identification of the BTN3A3 gene as a molecule implicated in generalized pustular psoriasis in a Chinese population. *J Invest Dermatol.* 2023;143(8):1439–1448. doi:10.1016/j.jid.2023.01.023.
37 Sugiura K, Muto M, Akiyama M. CARD14 c.526G>C (p.Asp176His) is a significant risk factor for generalized pustular psoriasis with psoriasis vulgaris in the Japanese cohort. *J Invest Dermatol.* 2014;134(6):1755–1757. doi:10.1038/jid.2014.46.
38 Mahil SK, Twelves S, Farkas K, et al. AP1S3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *J Invest Dermatol.* 2016;136(11):2251–2259. doi:10.1016/j.jid.2016.06.618.
39 Mössner R, Wilsmann-Theis D, Oji V, et al. The genetic basis for most patients with pustular skin disease remains elusive. *Br J Dermatol.* 2018;178(3):740–748. doi:10.1111/bjd.15867.
40 Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol.* 2019;143(3):1021–1026. doi:10.1016/j.jaci.2018.06.038.
41 Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol.* 1980;5(1):105–112. doi:10.1111/j.1365-2230.1980.tb01676.x.
42 Auffret N, Quint L, Domart P, Dubertret L, Lecam JY, Binet O. Pityriasis rubra pilaris in a patient with human immunodeficiency virus infection. *J Am Acad Dermatol.* 1992;27(2 Pt 1):260–261. doi:10.1016/s0190-9622(08)80734-7.
43 Sertznig P, von Felbert V, Megahed M. Porokeratosis: present concepts. *J Eur Acad Dermatol Venereol.* 2012;26(4):404–412. doi:10.1111/j.1468-3083.2011.04275.x.
44 Kanzaki T, Miwa N, Kobayashi T, Ogawa S. Eruptive pruritic popular porokeratosis. *J Dermatol.* 1992;19(2):109–112. doi:10.1111/j.1346-8138.1992.tb03190.x.
45 Zhang Z, Li C, Wu F, et al. Genomic variations of the mevalonate pathway in porokeratosis. *Elife.* 2015;4:e06322. doi:10.7554/eLife.06322.
46 Takeichi T, Akiyama M. Familial or sporadic porokeratosis as an autoinflammatory keratinization disease. *J Dermatol.* 2019;46(4):e125-e126. doi:10.1111/1346-8138.14666.
47 Wong W, Huang Y, Wu Z, et al. Mvda is required for zebrafish early development. *Biol Res.* 2021;54(1):17. doi:10.1186/s40659-021-00341-7.
48 Tao L, Huang YK, Yan KX, Li CH, Shen L, Zhang ZH. A preliminary study of peripheral T-cell subsets in porokeratosis patients with *MVK* or *MVD* variants. *Skin Health Dis.* 2021;2(1):e82. doi:10.1002/ski2.82.
49 Jemec GB. Clinical practice. Hidradenitis suppurativa. *N Engl J Med.* 2012;366(2):158–164. doi:10.1056/

NEJMcp1014163.
50 Saunte DML, Jemec GBE. Hidradenitis suppurativa: Advances in diagnosis and treatment. *JAMA*. 2017;318(20):2019–2032. doi:10.1001/jama.2017.16691.
51 Nomura T. Hidradenitis suppurativa as a potential subtype of autoinflammatory keratinization disease. *Front Immunol.* 2020;11:847. doi:10.3389/fimmu.2020.00847.
52 Frew JW. Hidradenitis suppurativa is an autoinflammatory keratinization disease: A review of the clinical, histologic, and molecular evidence. *JAAD Int.* 2020;1(1):62–72. doi:10.1016/j.jdin.2020.05.005.
53 Takeichi T, Matsumoto T, Nomura T, et al. A novel NCSTN missense mutation in the signal peptide domain causes hidradenitis suppurativa, which has features characteristic of an autoinflammatory keratinization disease. *Br J Dermatol.* 2020;182(2):491–493. doi:10.1111/bjd.18445.
54 Xiao X, He Y, Li C, Zhang X, Xu H, Wang B. Nicastrin mutations in familial acne inversa impact keratinocyte proliferation and differentiation through the Notch and phosphoinositide 3-kinase/AKT signalling pathways. *Br J Dermatol.* 2016;174(3):522–532. doi:10.1111/bjd.14223.
55 Guillem P, Mintoff D, Kabbani M, et al. Case Report: Comorbid Hyper-IgD Syndrome and Hidradenitis Suppurativa - A New Syndromic Form of HS? A Report of Two Cases. *Front Immunol.* 2022;13:883811. doi:10.3389/fimmu.2022.883811.
56 Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422–434. doi:10.1056/NEJMoa1504370.
57 Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol.* 2019;80(1):60–69.e2. doi:10.1016/j.jaad.2018.05.040.
58 Frew JW, Navrazhina K, Grand D, et al. The effect of subcutaneous brodalumab on clinical disease activity in hidradenitis suppurativa: An open-label cohort study. *J Am Acad Dermatol.* 2020;83(5):1341–1348. doi:10.1016/j.jaad.2020.05.007.
59 Vahlquist A, Pontén F, Pettersson A. Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK-syndrome): a rare, autosomal recessive disorder of keratohyaline formation? *Acta Derm Venereol.* 1997;77(3):225–227. doi:10.2340/0001555577225227.
60 Ding WX, Yin XM. Sorting, recognition and activation of the misfolded protein degradation pathways through macroautophagy and the proteasome. *Autophagy.* 2008;4(2):141–150. doi:10.4161/auto.5190.
61 Poli MC, Ebstein F, Nicholas SK, et al. Heterozygous truncating variants in POMP escape nonsense-mediated decay and cause a unique immune dysregulatory syndrome. *Am J Hum Genet.* 2018;102(6):1126–1142. doi:10.1016/j.ajhg.2018.04.010.
62 Brehm A, Liu Y, Sheikh A, et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J Clin Invest.* 2015;125(11):4196–4211. doi:10.1172/JCI81260.
63 Böer A. Keratosis lichenoides chronica: proposal of a concept. *Am J Dermatopathol.* 2006;28(3):260–275. doi:10.1097/00000372-200606000-00052.
64 Murase Y, Takeichi T, Koseki J, et al. UVB-induced skin autoinflammation due to *Nlrp1b* mutation and its inhibition by anti-IL-1β antibody. *Front Immunol.* 2022;13:876390. doi:10.3389/fimmu.2022.876390.
65 Mazurova S, Tesarova M, Zeman J, et al. Fatal neonatal nephrocutaneous syndrome in 18 Roma children with EGFR deficiency. *J Dermatol.* 2020;47(6):663–668. doi:10.1111/1346-8138.15317.
66 Mascia F, Lam G, Keith C, et al. Genetic ablation of epidermal EGFR reveals the dynamic origin of adverse effects of anti-EGFR therapy. *Sci Transl Med.* 2013;5(199):199ra110. doi:10.1126/scitranslmed.3005773.
67 O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: Impact on human disease and therapeutic intervention. *Annu Rev Med.* 2015;66:311–328. doi:10.1146/annurev-med-051113-024537.
68 Del Bel KL, Ragotte RJ, Saferali A, et al. JAK1 gain-of-function causes an autosomal dominant immune dysregulatory and hypereosinophilic syndrome. *J Allergy Clin Immunol.* 2017;139(6):2016-2020.e5. doi:10.1016/j.jaci.2016.12.957.
69 Gruber CN, Calis JJA, Buta S, et al. Complex autoinflammatory syndrome unveils fundamental principles of JAK1 kinase transcriptional and biochemical function. *Immunity.* 2020;53(3):672-684.e1-e11. doi:10.1016/j.immuni.2020.07.006.
70 Mahil SK, Catapano M, Di Meglio P, et al. An analysis of IL-36 signature genes and individuals with *IL1RL2* knockout mutations validates IL-36 as a psoriasis therapeutic target. *Sci Transl Med.* 2017;9(411):eaan2514. doi:10.1126/scitranslmed.aan2514.
71 Blair HA. Spesolimab: First Approval. *Drugs.* 2022;82(17):1681–1686. doi:10.1007/s40265-022-01801-4.
72 Baum P, Visvanathan S, Garcet S, et al. Pustular psoriasis: Molecular pathways and effects of speso-

limab in generalized pustular psoriasis. *J Allergy Clin Immunol.* 2022;149(4):1402–1412. doi:10.1016/j.jaci.2021.09.035.

73 Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. *N Engl J Med.* 2019;380(10):981–983. doi:10.1056/NEJMc1811317.

74 Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. *N Engl J Med.* 2021;385(26):2431–2440. doi:10.1056/NEJMoa2111563.

75 Choon SE, Lebwohl MG, Marrakchi S, et al. Study protocol of the global Effisayil 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare. *BMJ Open.* 2021;11(3):e043666. doi:10.1136/bmjopen-2020-043666.

76 Thomi R, Kakeda M, Yawalkar N, Schlapbach C, Hunger RE. Increased expression of the interleukin-36 cytokines in lesions of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2017;31(12):2091–2096. doi:10.1111/jdv.14389.

77 Di Caprio R, Balato A, Caiazzo G, et al. IL-36 cytokines are increased in acne and hidradenitis suppurativa. *Arch Dermatol Res.* 2017;309(8):673–678. doi:10.1007/s00403-017-1769-5.

78 Hessam S, Sand M, Gambichler T, Skrygan M, Rüddel I, Bechara FG. Interleukin-36 in hidradenitis suppurativa: evidence for a distinctive proinflammatory role and a key factor in the development of an inflammatory loop. *Br J Dermatol.* 2018;178(3):761–767. doi:10.1111/bjd.16019.

79 Wolk K, Brembach TC, Šimaitė D, et al. Activity and components of the granulocyte colony-stimulating factor pathway in hidradenitis suppurativa. *Br J Dermatol.* 2021;185(1):164–176. doi:10.1111/bjd.19795.