

Paradigms and perspectives

Autoinflammatory keratinization diseases

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Among the genetic causes/predisposing factors for inflammatory keratinization disorders, several factors are associated with autoinflammatory mechanisms. Here we review these inflammatory keratinization disorders with autoinflammatory pathogenic mechanisms and advocate the novel and unique concept of autoinflammatory keratinization diseases (AIKD). We propose the following definition of AIKD. First, the primary and main inflammation sites are the epidermis and the upper dermis. Second, inflammation in the epidermis and upper dermis leads to hyperkeratosis, which is the main and characteristic phenotype of AIKDs. Third, AIKDs have primary genetic causative factors associated with the hyperactivation of innate immunity (autoinflammation), mainly in the epidermis and upper dermis. Finally, the concept of AIKDs encompasses diseases with mixed pathomechanisms of autoinflammation and autoimmunity. AIKDs have genetic abnormalities as causative factors, and hyperactivation of the innate immune system resulting from those genetic defects plays an important role in the pathogenesis.

Recently, a number of *CARD14* gain-of-function variants/mutations have been reported as predisposing factors for psoriasis vulgaris (plaque-type psoriasis) and psoriatic arthritis.^{1,2} Jordan et al¹ found a rare *de novo* gain-of-function variant in *CARD14*, p.Glu138Ala, in a sporadic case of severe early-onset generalized pustular psoriasis (GPP). Sugiura et al³ reported a rare variant in *CARD14*, p.Asp176His, to be a significant predisposing factor for GPP with preceding or concurrent psoriasis vulgaris lesions, and this variant underlies approximately 20% of patients with GPP with psoriasis vulgaris in the Japanese population. *CARD14* variants are also disease susceptibility factors for European palmoplantar pustular psoriasis (palmoplantar pustulosis).⁴

Caspase recruitment domain-containing protein 14 (*CARD14*) encoded by *CARD14* is expressed and localized mainly in the skin, especially in keratinocytes.¹ Psoriasis-causative *CARD14* mutations enhance nuclear factor κ B activation and upregulate a subset of psoriasis-associated genes in keratinocytes

(Fig 1).^{1,2} *CARD14* mutations in the keratinocytes are thought to be responsible for the disease pathology and clinical manifestations of inflammatory keratinization diseases with *CARD14* mutations. However, we cannot rule out the possibility that *CARD14* mutations in immune cells other than keratinocytes might be involved in the pathogenesis.

Deficiency in IL-36 receptor antagonist (IL-36Ra) because of mutations in *IL36RN* has been reported as a genetic cause of familial GPP with recessive inheritance in the Tunisian population.⁵ Onoufriadis et al⁶ reported that *IL36RN* mutations underlie 3 European patients with sporadic GPP. Later, it was elucidated that most patients with sporadic GPP without psoriasis vulgaris skin symptoms have *IL36RN* mutations as a cause of the disease.⁷ Hussain et al⁸ recommended that patients with GPP with the clinical triad of early-onset systemic inflammation and absence of concurrent psoriasis vulgaris should be screened for *IL36RN* mutations based on the results of their GPP cohort study. Mutations in *IL36RN* have been reported in patients with certain other psoriasis-related diseases, such as acrodermatitis continua of Hallopeau, severe acute generalized exanthematous pustulosis, and impetigo herpetiformis.

IL-36Ra expression is seen primarily in the skin. IL-36Ra works as an antagonist to the IL-1 family members IL-36 α , β , and γ (Fig 1). Thus deficiency of IL-36Ra caused by *IL36RN* loss-of-function mutations is thought to result in acceleration of IL-36-driven skin inflammation.

These facts clearly demonstrate that, among psoriasis and its related disorders, the rare subtypes, GPP, impetigo herpetiformis, and acrodermatitis continua with *IL36RN* mutations and GPP and palmoplantar pustular psoriasis (palmoplantar pustulosis) with *CARD14* variants, are thought to be able to be categorized as AIKDs.

Pityriasis rubra pilaris (PRP) is an inflammatory erythematous keratinization disorder showing perifollicular erythema, often with confluent configurations, follicular plugging, pityriasis capitis, and palmoplantar hyperkeratosis. Most PRP cases are regarded as sporadic cases, although familial occurrence is also seen, particularly in one subtype, type V (atypical juvenile type). Notably, the skin eruptions in patients with type V PRP first appear in infancy or early childhood and tend to run a chronic course with no sustained clearance of the skin. Gain-of-function mutations in *CARD14* were identified in some autosomal dominant familial cases of PRP. In our recent study of 22 patients with PRP, all 3 patients with type V PRP were found to have *CARD14* mutations.⁹ In addition, detailed clinical features of the reported PRP cases with *CARD14* mutations in the literature were reviewed, and it was confirmed that all the PRP cases with *CARD14* mutations in the literature were affected with type V PRP.⁹ To date, 8 heterozygous mutations in *CARD14* have been reported in patients with type V PRP. We propose that PRP type V, the atypical juvenile type, is a distinct variant of PRP caused by *CARD14* mutations⁹ and should be regarded as an AIKD.

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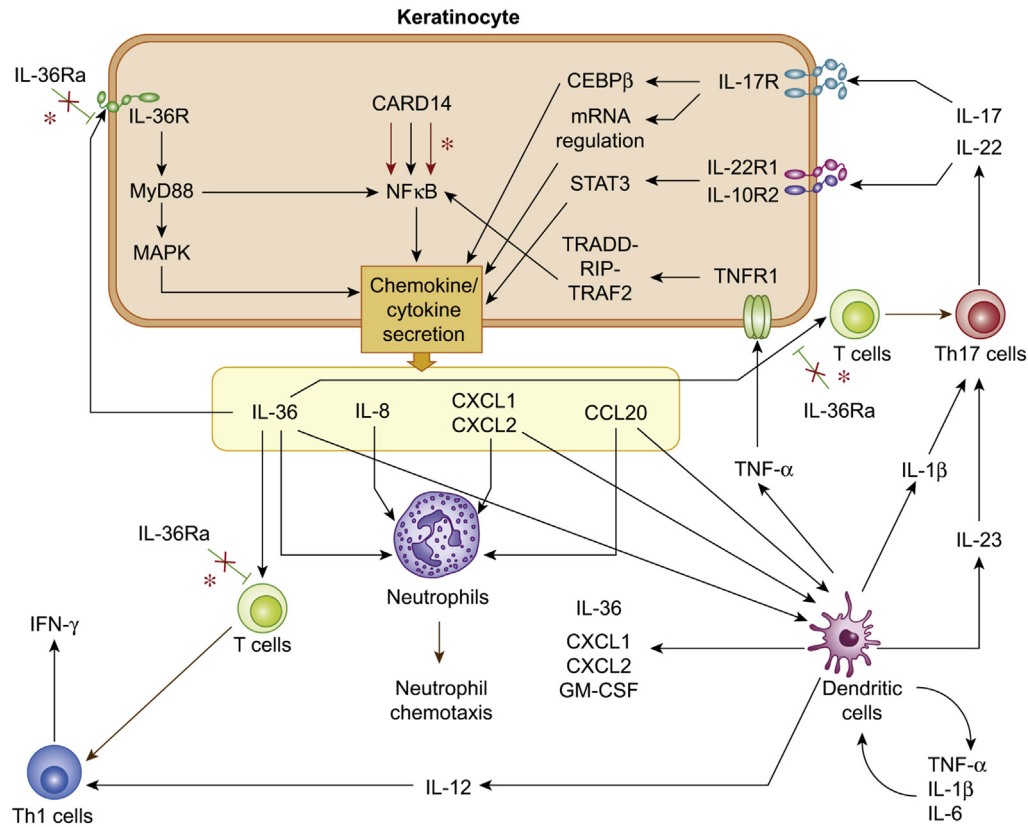


FIG 1. Pathways and processes of inflammatory responses induced by *CARD14* gain-of-function mutations and *IL-36Ra* deficiency. Mutant *CARD14* hyperactivates nuclear factor κB ($\text{NF-}\kappa\text{B}$; red arrows with asterisks), leading to secretion of chemokines/cytokines, IL-36, IL-8, CXCL1, CXCL2 and CCL20, from the keratinocyte and resulting in the activation of neutrophils and dendritic cells in the dermis. In addition, Th1 and Th17 cells are induced, and Th1 cytokines and IL-17 are secreted. *IL-36Ra* deficiency (red x-mark with asterisks) causes upregulation of IL-36 signaling, also leading to secretion of chemokines/cytokines from keratinocytes. Upregulated IL-36 signaling finally activates neutrophils and dendritic cells and promotes Th1 and Th17 cell polarization. Black arrows, Secretion or activation; brown arrows, cell differentiation or chemotaxis; $\perp$, inhibition. *CEBP β* , CCAAT/enhancer binding protein β ; *MAPK*, mitogen-activated protein kinase; *MyD88*, myeloid differentiation primary response 88; *RIP*, receptor interacting protein; *STAT3*, signal transducer and activator of transcription 3; *TNFR1*, TNF receptor 1; *TRADD*, TNF receptor 1-associated death domain protein; *TRAF2*, TNF receptor-associated factor 2.

TABLE I. Inflammatory keratinization disorders included in AIKDs and their pathogeneses

Disease	Genetic causative factor (frequency)	Pathogenic inflammatory mechanisms and pathways in keratinocytes
IL36Ra-related pustulosis		
GPP without PV	<i>IL36RN</i> mutations (prevalent)	IL-36 $\rightarrow$ MyD88 $\rightarrow$ $\text{NF-}\kappa\text{B}$ /MAPK $\rightarrow$ TNF, IL-1, IL-8, IL-17, IL-36, CXCL1, CXCL2, CCL20
Impetigo herpetiformis	<i>IL36RN</i> mutations (prevalent)	
Acrodermatitis continua	<i>IL36RN</i> mutations (not rare)	
CARD14-mediated pustular psoriasis		
GPP with PV	<i>CARD14</i> variants (not rare)	
Palmoplantar pustular psoriasis (palmoplantar pustulosis)	<i>CARD14</i> variants (not rare)	CARD14 $\rightarrow$ $\text{NF-}\kappa\text{B}$ $\rightarrow$ IL-36, IL-8, CXCL1, CXCL2, CCL20
PRP		
PRP type V	<i>CARD14</i> mutations (prevalent)	
PRP other types	<i>CARD14</i> variants (rare)	
KLC (familial)	<i>NLRP1</i> mutation (unknown)	NLRP1 $\rightarrow$ inflammasome $\rightarrow$ caspase-1 $\rightarrow$ IL-1 $\rightarrow$ TNF, GM-CSF, IL-36

MAPK, Mitogen-activated protein kinase; $\text{NF-}\kappa\text{B}$, nuclear factor κB ; PV, psoriasis vulgaris.

Keratosis lichenoides chronica (KLC) is a rare inflammatory keratinization disorder of unknown pathobiology. Characteristic clinical features of KLC include tiny papules on the trunk and extremities that become confluent, resulting in linear and reticulate patterns, and seborrheic dermatitis-like eruptions on the face. The lesions have a chronic and often progressive course. Recently, a distinct gain-of-function mutation in the inflammasome sensor protein, NLR family, pyrin domain containing protein 1 (NLRP1) was found to be the cause in a family with KLC.¹⁰

NLRP1 is considered the most prominently expressed inflammasome sensor in human skin, and keratinocytes express all other inflammasome components, including caspase-1, apoptosis-associated speck-like protein containing a CARD (ASC), IL-1 β , and IL-18.¹⁰ Evidence for spontaneous inflammasome activation by the KLC-causing *NLRP1* mutation in patients' keratinocytes has been demonstrated, and inflammasome-dependent IL-1 cytokines have been shown to cause familial KLC.¹⁰ In this context we now consider that autoinflammatory mechanisms play an important role in the pathogenesis of KLC, at least in that of familial KLC.

Here we advocate for the new disease category AIKD, which describes inflammatory keratinization disorders with autoinflammatory mechanisms as their predominant cause, including minor subsets of psoriasis and related diseases, PRP type V and KLC, as mentioned above (Table I). Inflammatory hyperkeratotic skin lesions are not common in patients with conventional autoinflammatory diseases. Thus although AIKD is thought to have autoinflammatory pathogenic mechanisms, unique pathomechanisms with inflammation that involves epidermal keratinocytes and results in hyperkeratosis are assumed in

patients with AIKDs. As the causes/predisposing factors for inflammatory keratinization disorders come to be elucidated, a larger number of disorders will be categorized as AIKDs.

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