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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, unique concept of "autoinflammatory keratinization diseases" (AIKD). We propose the following definition of AIKD. (1) The primary and main inflammation sites are the epidermis and the upper dermis. (2) The inflammation in the epidermis and the upper dermis leads to hyperkeratosis, which is the main and characteristic phenotype of AIKD. (3) AIKD have primary genetic causative factors associated with the hyperactivation of innate immunity (autoinflammation), mainly in the epidermis and the upper dermis. (4) The concept of AIKD subsumes diseases with mixed pathomechanisms of autoinflammation and autoimmunity. AIKD 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 al.*[1] 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 al.*[3] 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 GPP cases with psoriasis vulgaris in the Japanese population. *CARD14* variants are also disease susceptibility factors of European palmoplantar pustular psoriasis (palmoplantar pustulosis).[4]

CARD14 encodes the CARD family member "caspase recruitment domain family, member 14" (CARD14). CARD14 is expressed and localized mainly in the skin, especially in keratinocytes.[1] Psoriasis-causative *CARD14* mutations enhance NF-κB activation and upregulate a subset of psoriasis-associated genes in keratinocytes (Fig 1).[1, 2] The *CARD14* mutations in the keratinocytes are thought to be responsible for pathogeneses 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 may be involved in the pathogenesis.

Deficiency in interleukin 36 receptor antagonist (IL-36Ra) due to mutations in *IL36RN* has been reported as a genetic cause of familial GPP with recessive inheritance in the Tunisian population.[5] Onoufriadis *et al.*[6] reported that *IL36RN* mutations underlie three sporadic European GPP patients. Later, it was elucidated that most sporadic GPP patients without psoriasis vulgaris skin symptoms have *IL36RN* mutations as a cause of the disease.[7] Hussain *et al.*[8] recommended that GPP patients with the clinical triad of early onset, systemic inflammation and absence of concurrent psoriasis vulgaris 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, 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 interleukin-1 family members IL-36 α, β and γ (Fig 1). Thus, deficiency of IL-36Ra due to *IL36RN* loss-of-function mutations is thought to result in the acceleration of IL-36-driven skin inflammation.

These facts clearly demonstrate that, among psoriasis and its related disorders, 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 catagorizable as AIKD.

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 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 three patients with PRP type V 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, eight 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 that is caused by *CARD14* mutations[9] and should be regarded as an AIKD.

Keratosis lichenoides chronica (KLC) is a rare inflammatory keratinization disorder of unknown pathomechanism. Characteristic clinical features of KLC are tiny papules on the trunk and extremities, which 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 as the cause in a family with KLC.[10]

NLRP1 is considered to be the most prominently expressed inflammasome sensor in human skin, and keratinocytes express all other inflammasome components, including CASP1, ASC, IL-1β and IL-18.[10] Evidence for spontaneous inflammasome activation by the KLC-causing *NLRP1* mutation in patients' keratinocytes has been provided, and inflammasome-dependent IL-1 cytokines have been demonstrated 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 etiology, 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 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 AIKD. As the causes/predisposing factors for inflammatory keratinization disorders come to be successively elucidated, a larger number of disorders will be categorized into AIKD.

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Figure legend

FIG 1. Pathways and processes of inflammatory responses induced by CARD14 gain-of-function mutations and IL-36Ra deficiency.

Mutant CARD14 hyperactivates NFκB (red arrows with *), leading to the 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 *) causes up-regulation of IL-36 signaling, also leading to the secretion of chemokines/cytokines from the keratinocytes. Up-regulated 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; ⊥：inhibition.

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

Disease	Genetic causative factor (frequency)	Pathogenic inflammatory mechanisms and pathways in keratinocytes
IL36Ra-related pustulosis		
generalized pustular psoriasis (GPP) without PV	*IL36RN* mutations (prevalent)	IL-36→MyD88→NFkB/MAPK →TNF, IL-1, IL-8, IL-17, IL-36, CXCL1, CXCL2, CCL20
impetigo herpetiformis	*IL36RN* mutations (prevalent)	
acrodermatitis continua	*IL36RN* mutations (not rare)	
CARD14-mediated pustular psoriasis		
GPP with PV	*CARD14* variants (not rare)	
palmoplantar pustular psoriasis (palmoplantar pustulosis)	*CARD14* variants (not rare)	CARD14→NFkB→IL-36, IL-8, CXCL1, CXCL2, CCL20
Pityriasis rubra pylaris (PRP)		
PRP type V	*CARD14* mutations (prevalent)	
PRP other types	*CARD14* variants (rare)	
Keratosis lichenoides chronica (familial)	*NLRP1* mutation (unknown)	NLRP1→inflammasome →caspase-1→IL-1 →TNF, GM-CSF, IL-36