King's Research Portal

DOI:

[10.1016/j.jdermsci.2018.01.012](https://doi.org/10.1016/j.jdermsci.2018.01.012)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Akiyama, M., Takeichi, T., McGrath, J. A., & Sugiura, K. (2018). Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin. *Journal of Dermatological Science*. <https://doi.org/10.1016/j.jdermsci.2018.01.012>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Title: Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin

Authors: Masashi Akiyama, Takuya Takeichi, John A. McGrath, Kazumitsu Sugiura

PII: S0923-1811(18)30077-X
DOI: <https://doi.org/10.1016/j.jdermsci.2018.01.012>
Reference: DESC 3323

To appear in: *Journal of Dermatological Science*

Received date: 5-12-2017
Revised date: 20-1-2018
Accepted date: 23-1-2018

Please cite this article as: Akiyama Masashi, Takeichi Takuya, McGrath John A, Sugiura Kazumitsu. Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin. *Journal of Dermatological Science* <https://doi.org/10.1016/j.jdermsci.2018.01.012>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Journal of Dermatological Science

Manuscript ID JDermSci-2017-0300 Revised Version

Review Article

Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin

Masashi Akiyama^{a, *}, Takuya Takeichi^a, John A. McGrath^b, Kazumitsu Sugiura^c

^aDepartment of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

^bSt John's Institute of Dermatology, King's College London, Guy's Hospital, London, UK

^cDepartment of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan

*Corresponding Author:

Masashi Akiyama MD, PhD

Department of Dermatology

Nagoya University Graduate School of Medicine

65 Tsurumai-cho, Showa-ku, Nagoya

Aichi 466-8550, Japan

Tel: +81-52-744-2314, Fax: +81-52-744-2318

E-mail: makiyama@med.nagoya-u.ac.jp

HIGHLIGHTS

- The term autoinflammatory keratinization diseases has been proposed as an umbrella term for inflammatory keratinization disorders with autoinflammatory pathomechanisms.
- Integral diseases entities include *IL36RN*-related pustulosis, CARD14-mediated pustular psoriasis, pityriasis rubra pilaris type V and keratosis lichenoides chronica.

- Improved understanding of disease pathophysiology may lead to innovative targeted therapies.

ABSTRACT

Classifying inflammatory skin diseases is challenging, especially for the expanding group of disorders triggered by genetic factors resulting in hyperactivated innate immunity that result in overlapping patterns of dermal and epidermal inflammation with hyperkeratosis. For such conditions, the umbrella term “autoinflammatory keratinization diseases” (AIKD) has been proposed. AIKD encompasses diseases with mixed pathomechanisms of autoinflammation and autoimmunity, and includes IL-36 receptor antagonist (IL-36Ra)-related pustulosis, CARD14-mediated pustular psoriasis, pityriasis rubra pilaris (PRP) type V, and familial keratosis lichenoides chronica (KLC). Mechanistically, the entities include generalized pustular psoriasis (GPP) without psoriasis vulgaris, impetigo herpetiformis and acrodermatitis continua, which are IL-36Ra-related pustuloses caused by loss-of-function mutations in *IL36RN*; GPP with psoriasis vulgaris and palmoplantar pustular psoriasis which are CARD14-mediated pustular psoriasiform dermatoses with gain-of-function variants of *CARD14*; PRP type V which is caused by gain-of-function mutations in *CARD14*; and, familial KLC in which mutations in *NLRP1*, an inflammasome sensor protein predominantly expressed in skin, have been identified. It is likely that further inflammatory keratinization disorders will also fall within the concept of AIKD, as elucidation of novel pathogenic mechanisms of inflammatory keratinization diseases emerge. A better understanding of the pathophysiology of AIKD is likely to lead to innovative, targeted therapies that benefit patients.

Abbreviations used:

AIKD: autoinflammatory keratinization diseases

CAPS: cryopyrin-associated periodic syndrome

CARD14: caspase recruitment domain family member 14

FMF: familial Mediterranean fever

GPP: generalized pustular psoriasis

IL-36Ra: IL-36 receptor antagonist

KLC: keratosis lichenoides chronica

NLRP1: NLR family Pyrin domain-containing protein 1

PAPA syndrome: syndrome of pyogenic arthritis with pyoderma gangrenosum and acne

PRP: pityriasis rubra pilaris

PV: psoriasis vulgaris

TLR4: toll-like receptor 4

TRAPS: TNF receptor-associated periodic fever syndrome

Key words: autoinflammation, CARD14, IL-36 receptor antagonist, keratinization, keratosis lichenoides chronica, NLRP1, pityriasis rubra pilaris, psoriasis, psoriatic arthritis, pustular psoriasis

1. Introduction

Among the myriad diseases affecting the skin are a subset of disorders whose main pathobiology is inflammation, predominantly in the epidermis and the superficial dermis, that leads to hyperkeratosis, manifesting clinically as thickened scaly skin. These are designated as “inflammatory keratinization disorders”. The category includes many conditions that are poorly defined, although some, including psoriasis and lichen planus, are better categorized.

Nevertheless, the pathogenic mechanisms of most inflammatory keratinization disorders remain unresolved. However, new pathogenic mechanisms relating to autoinflammation have been demonstrated in some inflammatory keratinization disorders, providing unexpected mechanistic insights and new ideas for targeted therapies. In 2017, we proposed a new umbrella term,

“autoinflammatory keratinization diseases” (AIKD), to encompass inflammatory keratinization disorders with autoinflammatory pathogenic mechanisms [1]. We herein summarize the concept of AIKD, review the diseases included in this disease subgrouping, and discuss the clinical value of grouping conditions as AIKD.

2. What are AIKD?

Our initial concept paper on AIKD defined the disease entities as having four inclusion criteria [1]: (1) the primary and main inflammation sites are the epidermis and the upper dermis; (2) the inflammation 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 spectrum of AIKD encompasses diseases with mixed pathomechanisms of autoinflammation and autoimmunity. Of note, in AIKD, genetic abnormalities leading to hyperactivation of the innate immune system predominantly are implicated in disease pathogenesis. In contrast, in inflammatory keratinization diseases without autoinflammatory pathogenesis (inflammatory keratinization diseases, non-autoinflammatory), no apparent genetic background susceptibility has been identified in most cases and the innate immune system involvement is not as significant. Points of differentiation between AIKD and inflammatory keratinization diseases, non-autoinflammatory are summarized in Table 1. To date, disorders included in AIKD comprise: IL-36 receptor antagonist (IL-36Ra)-related pustulosis, caspase recruitment domain family member 14 (CARD14)-mediated pustular psoriasis, pityriasis rubra pilaris (PRP) type V and keratosis lichenoides chronica (KLC) (Table 2) [1, 2]. As the causes and predisposing factors for inflammatory keratinization diseases come to be clarified, further disorders are also likely to be included in the AIKD category. For example, lichen planus, which may be triggered by factors such as medications, trauma or viruses, is currently regarded as non-autoinflammatory, yet new data on inflammasome pathology in other lichenoid diseases may lead to future reassignment of

lichen planus to within the AIKD grouping. (See the discussion below on NLR family Pyrin domain-containing protein 1, NLRP1).

3. IL-36RA-related pustulosis

In 2011, Marrakchi et al. [3] reported that *IL36RN* mutations leading to IL-36Ra deficiency were present in nine Tunisian families with recessively inherited familial generalized pustular psoriasis (GPP). *IL36RN* mutations were also reported as a genetic cause in three sporadic European GPP patients [4] and a Japanese GPP patient [5] (Fig. 1A, B). Subsequently, it was established that most sporadic GPP patients without preceding or concomitant psoriasis vulgaris (PV) skin lesions have *IL36RN* mutations as genetic predisposing or causative factors for the disease [6, 7]. Patients with certain other psoriasis-related pustular diseases including acrodermatitis continua of Hallopeau [8], severe acute generalized exanthematous pustulosis [9] and impetigo herpetiformis [10], have been reported to have *IL36RN* mutations as a genetic predisposing or causative factor.

IL-36 α , IL-36 β and IL-36 γ are absent in non-inflammatory skin, but they are generated by stimuli of inflammatory cytokines including TNF- α and IL-17A [11]. IL-36 α , IL-36 β and IL-36 γ are activated differentially by the neutrophil granule-derived proteases cathepsin G, elastase and proteinase-3, resulting in up to a 500-fold increase in their biological activities [12]. IL-36 α , IL-36 β and IL-36 γ activate several pro-inflammatory signaling molecules including NF κ B [13]. The skin is the primary and main expression site of IL-36Ra. Mainly in the skin, IL-36Ra antagonizes the interleukin-1 family members IL-36 α , β and γ [14, 15]. In this context, IL-36Ra deficiency caused by loss-of-function mutations in *IL36RN* is considered to induce and accelerate IL-36-driven inflammation in the skin [15]. Recently, *IL36rn*^{-/-} mice treated with a toll-like receptor 4 (TLR4) agonist were reported to show autoinflammatory symptoms in the skin, joints and liver; such mice have been established as a model of IL36Ra-deficient GPP [16].

4. CARD14-mediated pustular psoriasis

Psoriasis, one of the most common inflammatory keratinization disorders, is a chronic multifactorial inflammatory disease involving the skin, nails and joints [17]. The most common plaque-type psoriasis is psoriasis vulgaris (PV). Various inflammatory keratinization disorders such as psoriatic arthritis, GPP and palmoplantar pustular psoriasis (palmoplantar pustulosis) are known to be psoriasis-related diseases [18]. Recently, Arakawa *et al.* [19] demonstrated that melanocyte antigens can trigger autoimmunity in chronic PV, indicating that psoriasis has autoimmunity aspects and that acquired immunity may play a pathogenic role in psoriasis. In addition, it is widely accepted that psoriasis is a Th17-mediated disease rather than an inflammasome-driven one. This categorization is convincingly demonstrated by the much greater clinical efficacy of Th17-targeted biologics than IL-1-neutralizing therapies in PV. In light of this, inflammatory keratinization in psoriasis is not completely autonomous. However, psoriasis has innate and adaptive immune mechanisms implicated in its pathogenesis. Christophers *et al.* [20] suggested that, chronologically, in early or highly active lesions of psoriasis, inflammation begins as IL-1-TNF-mediated, neutrophil-dominant inflammation that induces Th17-dominant, early T-cell infiltration that develops into a Th1-dominant psoriasis plaque. This perspective remains controversial. For example, one recent publication identified IL-12 as a psoriasis-protective factor [21]. Furthermore, psoriasis is a group of highly heterogeneous diseases. Thus, autoimmunity and autoinflammation might be relevant to the inflammatory processes to different degrees in each clinical subset of psoriasis [22].

Recently, it has been documented that *CARD14* gain-of-function variants/mutations may be risk factors for PV and psoriatic arthritis [23, 24]. Of note, the heterozygous *CARD14* mutation, p.Gly117Ser, was identified in a large family with familial PV [23]. In addition, the rare *de novo* gain-of-function *CARD14* variant p.Glu138Ala was reported in a sporadic patient with severe early-onset GPP [23]. Another rare *CARD14* variant, p.Asp176His, was revealed to be a

significant risk factor for GPP with preceding or concomitant PV lesions, and was shown to underlie approximately 20% of GPP cases with PV in the Japanese population (compared to 3.0% in Japanese controls) [25]. In addition, concerning palmoplantar pustular psoriasis (palmoplantar pustulosis), *CARD14* variants are thought to be a disease risk factor in European patients [26]. Autosomal dominant familial GPP caused by a *CARD14* mutation was recently reported [2]. These data show that various phenotypes are seen in patients carrying *CARD14* variants/mutations, with clear pathogenic implications for these findings in psoriasis and related diseases.

CARD14 encodes the CARD family member CARD14. CARD14 is regarded as a scaffold protein regulating the signaling pathway of NF- κ B [23, 27, 28]. CARD14 is mainly expressed and localized in epidermal keratinocytes [23, 27]. In reports by Jordan *et al.*, [23, 24] transfection experiments and studies using keratinocyte cell lines from patients with *CARD14* mutations revealed that psoriasis-predisposing *CARD14* mutations hyperactivate NF- κ B and accelerate the expression of certain psoriasis-associated genes in keratinocytes. Recently, CARD14 has been reported to form a signaling complex with BCL10 and the paracaspase MALT1, and psoriasis-associated *CARD14* mutations were revealed to enhance this process in keratinocytes [29, 30]. These findings support the notion that, in inflammatory keratinization diseases associated with *CARD14* mutations, the *CARD14* mutations are involved in disease pathology in epidermal keratinocytes, although we cannot completely rule out the possibility that effects of *CARD14* mutations in immune cells may be partly responsible for disease pathogenesis.

5. Pityriasis rubra pilaris (PRP)

In addition, the concept of AIKD can also be applied to *CARD14* mutation-driven inflammatory keratinization diseases, such as PRP type V. PRP is an inflammatory keratinization disease that shows general follicular plugging and perifollicular erythema with confluent configurations [31]. Pityriasis capitis and palmoplantar keratoderma are also seen in PRP [31]. In 1980, PRP was

classified into five subgroups, types I to V, based on clinical criteria (age of onset, distribution of lesions, disease course) [31]. The types are classical adult type (type I), atypical adult type (type II), classical juvenile type (type III), circumscribed juvenile type (type IV) and atypical juvenile type (type V). A further subtype, associated with HIV infection (PRP type VI), has been reported [32]. Patients with PRP are mostly sporadic cases [33]. However, familial cases have also been reported, mainly in PRP type V [33]. Indeed, this particular subtype of PRP differs somewhat from the other variants. Patients with type V PRP show skin symptoms from infancy or early childhood and usually have a chronic course without any long-standing resolution of the skin features. In 2012, gain-of-function mutations in *CARD14* were reported to underlie familial PRP cases with autosomal dominant inheritance [27]. We recently reported that all PRP type V patients in our series of PRP cases had *CARD14* mutations (Fig. 1C-E) [34]. Furthermore, the symptoms and disease course of PRP patients who were reported to have *CARD14* mutations were scrutinized, and notably, all the previously reported PRP patients harboring *CARD14* mutations were clinically classified as PRP type V [34]. In contrast, among patients with the other types of PRP, no *CARD14* mutations were found, although a few *CARD14* variants were observed in some patients [34]. Currently, nine heterozygous *CARD14* mutations have been reported in type V PRP patients [27, 34-37]. In light of the above, PRP type V, the atypical juvenile type, is thought to be a distinct variant of PRP with *CARD14* mutations [34], and we propose that PRP type V is an AIKD.

6. Familial keratosis lichenoides chronica (KLC)

KLC is an infrequently seen inflammatory keratinization disorder. Kaposi first described KLC in 1895, but the term KLC was formally proposed by Margolis in 1972 [38]. Patients with KLC show multiple small papules with confluent, linear and reticulate configurations on the trunk and extremities. KLC patients may also have seborrheic dermatitis-like eruptions on the face, palmoplantar keratoderma and hypertrophic nail deformities. These skin lesions are usually asymptomatic, but typically show chronic and frequently progressive courses.

Histopathologically, lichenoid interface dermatitis with numerous necrotic keratinocytes and parakeratosis are seen in lesional skin [38]. For a long time, the cause of KLC was unknown. Very recently, a gain-of-function mutation in *NLRP1*, the gene that encodes the inflammasome sensor protein NLRP1 was reported to underlie familial KLC in one family (Fig. 1F, G) [39]. Thereafter, one family and one sporadic patient with *NLRP1* mutations were reported to have autoinflammation symptoms including follicular keratosis in the skin, as well as polyarthritis [40].

NLR proteins patrol the cytosol and initiate inflammasome assembly, pyroptotic cell death, and pro-inflammatory cytokine release upon ligand binding [41, 42]. Aberrant activation of inflammasomes is known to be pathogenic in a group of autoinflammatory syndromes with germline-activating mutations in inflammasome sensor proteins [43]. Another member of the NLR family of inflammasome sensor proteins, NLRP3 is well known as the causative molecule of the autoinflammatory syndrome cryopyrin-associated periodic syndrome (CAPS) [44].

NLRP1 was revealed to be one of the most highly produced inflammasome sensor proteins in the skin, and other components of inflammasomes, such as CASP1, ASC, IL-1 β and IL-18, are also expressed in epidermal keratinocytes [39]. It was elucidated that wild-type NLRP1 retains its form as an inactive monomer by the combined action of the pyrin domain and a leucine-rich repeats domain. The KLC-causing mutation reported disrupts the leucine-rich repeats domain and part of the linker region, leading to constitutive NLRP1 self-oligomerization and inflammasome activation [39]. Excessive activation of inflammasomes and IL-1 secretion has been demonstrated in patient keratinocytes, and inflammasome-dependent IL-1 cytokines have been shown to cause the inflammatory familial KLC [39]. Thus, autoinflammation is thought to work in the pathogenesis of KLC, at least in that of familial KLC. Further studies are expected to yield information on similar pathogenic mechanisms associated with inflammasome signaling in sporadic KLC cases.

7. Therapies based on the pathomechanisms of AIKD

Recently, various therapies based on the pathomechanisms of AIKD have achieved sufficient efficacy in several kinds of AIKD.

Neutrophils are thought to be frequently involved in the inflammatory reaction induced in AIKD (Fig. 2). Thus, granulocyte and monocyte adsorption apheresis is expected to be effective for AIKD cases. Indeed, the treatment efficacy of granulocyte and monocyte adsorption apheresis was reported in a GPP case that resulted from an *IL36RN* mutation [45].

Concerning molecularly targeted therapies for GPP patients with IL-36Ra-related pustulosis, a successful therapy with the IL-1 receptor antagonist anakinra was reported in a patient with GPP caused by *IL36RN* mutations [46]. The IL-1 pathway is generally involved in the pathogenesis of AIKD (Fig. 2). In GPP with *IL36RN* mutations, the IL-1 pathway is downstream of the inflammatory reaction induced by IL-36 (Fig. 2). Thus, it is conceivable that the blockade of IL-1 signaling is effective against GPP resulting from *IL36RN* mutations. TNF- α is also generally involved in the inflammatory pathways in the pathogenesis of AIKD (Fig. 2), and infliximab, a monoclonal anti-human TNF- α antibody, was reported to be effective in sibling cases of GPP with *IL36RN* mutations [47].

Furthermore, IL-12/IL-23 and IL-17 are thought to be involved in the inflammatory cascades that have been implicated in the pathogenesis of AIKD, including GPP with *IL36RN* mutations and PRP with *CARD14* mutations (Fig. 2). In fact, the therapeutic efficacy of ustekinumab, a monoclonal anti-human IL-12/IL-23 p40 antibody, was suggested in GPP patients with and without *IL36RN* mutations [48]. Beneficial effects of ustekinumab were reported also in patients with PRP caused by *CARD14* mutations [35, 37]. In addition, response to IL-17 inhibition was observed in an adolescent GPP patient with IL-36Ra deficiency [49].

Although sufficient information has not been obtained concerning treatments for KLC resulting from *NLRP1* mutations, anakinra seems to have some effectiveness in patients with *NLRP1*-associated autoinflammation with arthritis and dyskeratosis [40]. KLC-causative *NLRP1* mutations are known to overactivate inflammasomes and IL-1 secretion, resulting in the KLC phenotype [39] (Fig. 2). Thus, the IL-1 receptor antagonist anakinra is assumed to be effective as a treatment for KLC with *NLRP1* mutations.

In light of the above-mentioned findings, molecularly targeted therapies directing chemokines/cytokines and signal molecules involved in the inflammatory pathways of AIKD pathogenesis are promising, novel treatments for AIKD [16]. In this context, understanding the pathophysiology of severe inflammatory keratinization diseases with autoinflammatory pathogenesises, based on the recognition that they are AIKD, may give us significant clues to innovate highly effective, novel targeted therapies.

8. Conclusions and future perspectives

In 2017, the disease terminology AIKD was proposed for inflammatory keratinization disorders with autoinflammatory mechanisms as their main etiology (Fig. 2) [1]. The clinical entity of AIKD contains certain PRP type V, KLC, and subgroups of psoriasis-related diseases as described above (Table 2).

The data summarized indicate that certain subsets of psoriasis and diseases related to it have genetic causes and predisposing factors associated with autoinflammatory mechanisms, such as *CARD14* variants/mutations and *IL36RN* mutations. AIKD featured the hyperactivation of innate immunity (autoinflammation) resulting from genetic causative/predisposing factors as the predominant pathogenic mechanism. The concept of AIKD includes diseases with mixed

autoinflammation and autoimmune mechanisms, as opposed to purely autoinflammatory diseases such as familial Mediterranean fever (FMF) and CAPS (Table 3). In light of this, we think that rare subtypes of psoriasis and disorders related to it [50] (i.e., GPP, impetigo herpetiformis and acrodermatitis continua with *IL36RN* mutations) and GPP and palmoplantar pustular psoriasis (palmoplantar pustulosis) with *CARD14* variants all fit within the category of AIKD. Furthermore, regarding the content of AIKD, although autoinflammatory mechanisms play a significant role in the inflammatory keratinization of the epidermis, we do not think that all the inflammatory processes need to manifest completely in epidermal keratinocytes in order for a disease to be categorized as an AIKD.

Most conventional autoinflammatory diseases/syndromes are known to have skin symptoms. Their skin manifestations are various and include urticarial eruptions, erythema nodosum-like lesions and pustular acne. FMF shows erysipelas-like erythema, and CAPS often has urticarial eruptions. TNF receptor-associated periodic fever syndrome (TRAPS) shows migratory, urticarial erythema and purpuric macules. Blau syndrome/early onset sarcoidosis has granulomatous dermatitis, and the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA syndrome) shows pustular acne and pyoderma gangrenosum. However, inflammatory eruptions with hyperkeratosis are uncommon in patients with conventional autoinflammatory diseases/syndromes. Therefore, while AIKD have autoinflammatory pathogenic mechanisms, AIKD are thought to cause distinctive inflammation that encompasses epidermal keratinocytes, leading to hyperkeratosis (Table 3).

Recent advances in medical genetics have revealed genetic causes/predisposing factors for a number of inflammatory keratinization disorders of the skin whose etiology has long been unknown. Such new insights into the pathogeneses of these inflammatory keratinization disorders has established the novel disease concept of AIKD. We expect that more inflammatory keratinization disorders will be classified as AIKD in the future, as better elucidation of novel

pathogenic mechanisms of inflammatory keratinization diseases emerges. The identification of further genetic causes and disease susceptibility factors and the correct evaluation of their significance to disease pathogenesis promise to provide clues for further understanding the pathophysiology of AIKD and for developing innovative and more targeted therapies for the protean collection of autoinflammatory syndromes.

Funding sources: No external funding

Conflict of interest

The authors declare no conflict of interest.

Conflicts of interest: None declared

Acknowledgements

This work was supported by funding from Advanced Research and Development Programs for Medical Innovation (AMED-CREST: JP17gm0910002) to M.A. from Japan Agency for Medical Research and Development (AMED), and by a Grant-in-Aid for Scientific Research (B) 15H04887 to M.A. from the Japan Society for the Promotion of Science (JSPS).

REFERENCES

- [1] M. Akiyama, T. Takeichi, J.A. McGrath, K. Sugiura. Autoinflammatory keratinization diseases, *J. Allergy Clin. Immunol.* 140 (2017) 1545-1547.
- [2] T. Takeichi, A. Kobayashi, E. Ogawa, Y. Okuno, S. Kataoka, M. Kono, et al., Autosomal dominant familial generalized pustular psoriasis caused by a CARD14 mutation, *Br. J. Dermatol.* 177 (2017) e133-e135.
- [3] S. Marrakchi, P. Guigue, B.R. Renshaw, A. Puel, X.Y. Pei, S. Fraitag, et al., Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis, *N. Engl. J. Med.* 365 (2011) 620-628.
- [4] A. Onoufriadis, M.A. Simpson, A.E. Pink, P. Di Meglio, C.H. Smith, V. Pullabhatla, et al., Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis, *Am. J. Hum. Genet.* 89 (2011) 432-437.
- [5] K. Sugiura, T. Takeichi, M. Kono, Y. Ogawa, Y. Shimoyama, Y. Muro, M. Akiyama, A novel IL36RN/IL1F5 homozygous nonsense mutation, p.Arg10X, in a Japanese patient with adult-onset generalized pustular psoriasis, *Br. J. Dermatol.* 167 (2012) 699-701.
- [6] K. Sugiura, A. Takemoto, M. Yamaguchi, H. Takahashi, Y. Shoda, T. Mitsuma, et al., The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist, *J. Invest. Dermatol.* 133 (2013) 2514-2521.
- [7] T. Takeichi, Y. Togawa, Y. Okuno, R. Taniguchi, M. Kono, H. Matsue, et al., A newly revealed IL36RN mutation in sibling cases complements our IL36RN mutation statistics for generalized pustular psoriasis, *J. Dermatol. Sci.* 85 (2017) 58-60.
- [8] N. Setta-Kaffetzi, A.A. Navarini, V.M. Patel, V. Pullabhatla, A.E. Pink, S.E. Choon, et al., Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes, *J. Invest. Dermatol.* 133 (2013) 1366-1369.

- [9] A.A. Navarini, L. Valeyrie-Allanore, N. Setta-Kaffetzi, J.N. Barker, F. Capon, D. Creamer, et al., Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis, *J. Invest. Dermatol.* 133 (2013) 1904-1907.
- [10] K. Sugiura, N. Oiso, S. Inuma, H. Matsuda, M. Minami-Hori, A. Ishida-Yamamoto, et al., IL36RN mutations underlie impetigo herpetiformis, *J. Invest. Dermatol.* 134 (2014) 2472-2474.
- [11] Y. Carrier, H.L. Ma, H.E. Ramon, L. Napierata, C. Small, M. O'Toole, et al., Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. *J. Invest. Dermatol.* 131 (2011) 2428-2437.
- [12] C.M. Henry, G.P. Sullivan, D.M. Clancy, I.S. Afonina, D. Kulms, S.J. Martin, Neutrophil-derived proteases escalate inflammation through activation of IL-36 family cytokines, *Cell Rep.* 14 (2016) 708-722.
- [13] J.E. Towne, K.E. Garka, B.R. Renshaw, G.D. Virca, J.E. Sims, Interleukin (IL)-1F6, IL-1F8, and IL-1F9 signal through IL-1Rrp2 and IL-1RAcP to activate the pathway leading to NF-kappaB and MAPKs, *J. Biol. Chem.* 279 (2004) 13677-13688.
- [14] C. Dinarello, W. Arend, J. Sims, D. Smith, H. Blumberg, L. O'Neill, et al., IL-1 family nomenclature, *Nat. Immunol.* 11 (2010) 973.
- [15] K. Sugiura, The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants, *J. Dermatol. Sci.* 74 (2014) 187-192.
- [16] A. Shibata, K. Sugiura, Y. Furuta, Y. Mukumoto, O. Kaminuma, M. Akiyama, Toll-like receptor 4 antagonist TAK-242 inhibits autoinflammatory symptoms in DITRA, *J. Autoimmun.* 80 (2017) 28-38.
- [17] M.A. Lowes, M. Suárez-Fariñas, J.G. Krueger, Immunology of psoriasis, *Annu. Rev. Immunol.* 32 (2014) 227-255.
- [18] S. Noda, J.G. Krueger, E. Guttman-Yassky, The translational revolution and use of biologics in patients with inflammatory skin diseases, *J. Allergy Clin. Immunol.* 135 (2015) 324-336.

- [19] A. Arakawa, K. Siewert, J. Stöhr, P. Besgen, S.M. Kim, G. Rühl, et al., Melanocyte antigen triggers autoimmunity in human psoriasis, *J. Exp. Med.* 212 (2015) 2203-2212.
- [20] E. Christophers, G. Metzler, M. Röcken, Bimodal immune activation in psoriasis, *Br. J. Dermatol.* 170 (2014) 59-65.
- [21] P. Kulig, S. Musiol, S.N. Freiburger, B. Schreiner, G. Gyölvézi, G. Russo, et al., IL-12 protects from psoriasiform skin inflammation, *Nat. Commun.* 7 (2016) 13466.
- [22] M. Sticherling, Psoriasis and autoimmunity, *Autoimmun. Rev.* 15 (2016) 1167-1170.
- [23] C.T. Jordan, L. Cao, E.D. Roberson, K.C. Pierson, C.F. Yang, C.E. Joyce, et al., PSORS2 is due to mutations in CARD14, *Am. J. Hum. Genet.* 90 (2012) 784-795.
- [24] C.T. Jordan, L. Cao, E.D. Roberson, S. Duan, C.A. Helms, R.P. Nair, et al., Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis, *Am. J. Hum. Genet.* 90 (2012) 796-808.
- [25] K. Sugiura, M. Muto, M. Akiyama, 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.* 134 (2014) 1755-1757.
- [26] R. Mössner, Y. Frambach, D. Wilschmann-Theis, S. Löhr, A. Jacobi, A. Weyergraf, et al., Palmoplantar pustular psoriasis is associated with missense variants in CARD14, but not with loss-of-function mutations in IL36RN in European patients, *J. Invest. Dermatol.* 135 (2015) 2538-2541.
- [27] D. Fuchs-Telem, O. Sarig, M.A. van Steensel, O. Isakov, S. Israeli, J. Nussbeck, et al., Familial pityriasis rubra pilaris is caused by mutations in CARD14, *Am. J. Hum. Genet.* 91 (2012) 163-170.

- [28] A. Howes, P.A. O'Sullivan, F. Breyer, A. Ghose, L. Cao, D. Krappmann, et al., Psoriasis mutations disrupt CARD14 autoinhibition promoting BCL10-MALT1-dependent NF- κ B activation, *Biochem. J.* 473 (2016) 1759-1768.
- [29] I.S. Afonina, E. Van Nuffel, G. Baudelet, Y. Driege, M. Kreike, J. Staal, et al., The paracaspase MALT1 mediates CARD14-induced signaling in keratinocytes, *EMBO Rep.* 17 (2016) 914-927.
- [30] E. Van Nuffel, A. Schmitt, I.S. Afonina, K. Schulze-Osthoff, R. Beyaert, S. Hailfinger, CARD14-mediated activation of paracaspase MALT1 in keratinocytes: implications for psoriasis, *J. Invest. Dermatol.* 137 (2017) 569-575.
- [31] W.A. Griffiths, Pityriasis rubra pilaris, *Clin. Exp. Dermatol.* 5 (1980) 105-112.
- [32] N. Auffret, L. Quint, P. Domart, L. Dubertret, J.Y. Lecom, O. Binet, Pityriasis rubra pilaris in a patient with human immunodeficiency virus infection, *J. Am. Acad. Dermatol.* 27 (1992) 260-261.
- [33] N.A. Ross, H.J. Chung, Q. Li, J.P. Andrews, M.S. Keller, J. Uitto, Epidemiologic, clinicopathologic, diagnostic, and management challenges of pityriasis rubra pilaris: a case series of 100 patients. *JAMA Dermatol.* 152 (2016) 670-675.
- [34] T. Takeichi, K. Sugiura, T. Nomura, T. Sakamoto, Y. Ogawa, N. Oiso, et al., Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. *JAMA Dermatol.* 153 (2017) 66-70.
- [35] O. Eytan, O. Sarig, E. Sprecher, M.A. van Steensel, Clinical response to ustekinumab in familial pityriasis rubra pilaris caused by a novel mutation in CARD14, *Br. J. Dermatol.* 171 (2014) 420-422.
- [36] N. Inoue, T. Dainichi, A. Fujisawa, H. Nakano, D. Sawamura, K. Kabashima, CARD14 Glu138 mutation in familial pityriasis rubra pilaris does not warrant differentiation from familial psoriasis, *J. Dermatol.* 43 (2016) 187-189.

- [37] S.M. Lwin, C.K. Hsu, L. Liu, H.Y. Huang, N.J. Levell, J.A. McGrath, Beneficial effect of ustekinumab in familial pityriasis rubra pilaris with a new missense mutation in CARD14, *Br. J. Dermatol.* (Mar 16) (2017) doi: 10.1111/bjd.15462. [Epub ahead of print].
- [38] A.I. Böer, Keratosis lichenoides chronica: proposal of a concept, *Am. J. Dermatopathol.* 28 (2006) 260-275.
- [39] F.L. Zhong, O. Mamaï, L. Sborgi, L. Boussofara, R. Hopkins, K. Robinson, et al., Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation, *Cell* 167 (2016) 187-202.e17.
- [40] S. Grandemange, E. Sanchez, P. Louis-Pence, F. Tran Mau-Them, D. Bessis, C. Coubes, et al., A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (*NLRP1*-associated autoinflammation with arthritis and dyskeratosis), *Ann. Rheum. Dis.* 76 (2017) 1191-1198.
- [41] E. Latz, T.S. Xiao, A. Stutz, Activation and regulation of the inflammasomes, *Nat. Rev. Immunol.* 13 (2013) 397-411.
- [42] L. Broderick, D. De Nardo, B.S. Franklin, H.M. Hoffman, E. Latz, The inflammasomes and autoinflammatory syndromes, *Annu. Rev. Pathol.* 10 (2015) 395-424.
- [43] D.L. Kastner, I. Aksentijevich, R. Goldbach-Mansky, Autoinflammatory disease reloaded: a clinical perspective, *Cell* 140 (2010) 784-790.
- [44] H.M. Hoffman, J.L. Mueller, D.H. Broide, A.A. Wanderer, R.D. Kolodner, Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome, *Nat. Genet.* 29 (2001) 301-305.
- [45] K. Sugiura, K. Haruna, Y. Suga, M. Akiyama, Generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist successfully treated with granulocyte and monocyte adsorption apheresis, *J. Eur. Acad. Dermatol. Venereol.* 28 (2014) 1835-1836.

- [46] U. Hüffmeier, M. Wätzold, J. Mohr, M.P. Schön, R. Mössner, Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations, *Br. J. Dermatol.* 170 (2014) 202-204.
- [47] K. Sugiura, K. Endo, T. Akasaka, M. Akiyama, Successful treatment with infliximab of sibling cases with generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist, *J. Eur. Acad. Dermatol. Venereol.* 29 (2015) 2054-2056.
- [48] A. Arakawa, T. Ruzicka, J.C. Prinz, Therapeutic efficacy of interleukin 12/interleukin 23 blockade in generalized pustular psoriasis regardless of IL36RN mutation status, *JAMA Dermatol.* 152 (2016) 825-828.
- [49] K.M. Cordoro, D. Ucmak, M. Hitraya-Low, M.D. Rosenblum, W. Liao, Response to interleukin (IL)-17 inhibition in an adolescent with severe manifestations of IL-36 receptor antagonist deficiency (DITRA), *JAMA Dermatol.* 153 (2017) 106-108.
- [50] M. Akiyama, CARD14 alterations and psoriasis: are psoriasis and related disorders genetic autoinflammatory disease? *Br. J. Dermatol.* 174 (2016) 262.

Short biography of Prof. Masashi AKIYAMA

Masashi Akiyama (M.D., Ph.D.) is a Professor and Chairman of the Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan from 2010. He received the M.D. in 1986 and Ph.D. in 1991 from Keio University, Tokyo, Japan. He was assigned as a Senior Research Fellow at University of Washington, Seattle (1992-1994) and an Associate Professor at Teikyo University Ichihara Hospital, Chiba, Japan (1999-2001). He served as an Assistant Professor (2001-2007) and an Associate Professor (2007-2010) at Hokkaido University, Sapporo, Japan.

His research is in the field of genodermatosis, genetic and autoinflammatory keratinization diseases, skin barrier function and its related allergic diseases.

Figure legends

Fig. 1. Clinical features of AIKD patients.

Characteristic clinical features of GPP with *IL36RN* mutations (A, B), PRP type V with *CARD14* mutations (C-E) and familial KLC caused by *NLRP1* mutations (F, G). Pustules and scaly hyperkeratosis are seen on erythrodermic skin on the chest and abdomen of an 18-month-old male (A) and on the lower leg of a 61-year-old male (B). Diffuse erythema with fine scaling is observed on the trunk (C) and on the legs (D) of a 20-year-old male. Severe hyperkeratosis with erythema is present on the palm of a 24-year-old female (E). A 10-month-old male infant shows seborrheic dermatitis-like eruptions on the face (F). A 10-year-old female patient has multiple small hyperkeratotic papules of reticulate configuration on the wrist (G).

Fig. 2. Inflammatory pathways involved in the pathogenesis of AIKD.

Causative inflammatory pathways in the patients with IL-36Ra deficiency and gain-of-function mutations in *CARD14* and *NLRP1* are summarized. Up-regulated IL-36 signaling due to IL-36Ra deficiency (red starburst patterns) and gain-of-function mutant *CARD14* (red arrows with blue starburst pattern) accelerate NF κ B activity, resulting in the secretion of the chemokines/cytokines IL-36, IL-8, CXCL1, CXCL2 and CCL20 by keratinocytes. The chemokines/cytokines induce the activation of neutrophils and dendritic cells in the superficial dermis. In addition, gain-of-function mutants of *NLRP1* hyperactivate NLRP1 inflammasomes (blue starburst pattern) in keratinocytes, leading to the secretion of IL-1 β and IL-18 and resulting in the activation of the paracrine signaling network in the epidermis and the superficial dermis. Black arrows: secretion or activation; green arrows: cell differentiation or chemotaxis; $\perp$: inhibition.

Table 1 Summary of the differences between autoinflammatory keratinization diseases (AIKD) and inflammatory keratinization diseases, non-autoinflammatory

Points of differentiation between the two concepts	Autoinflammatory keratinization diseases (AIKD)	Inflammatory keratinization diseases, non-autoinflammatory
Pathogeneses		
Genetic causative factors	<i>CARD14, IL36RN, NLRP1</i>	none or unknown
Pathogenic mechanisms and pathways	mainly autoinflammation (hyperactivation of innate immunity) (mixture of autoinflammation and autoimmunity)	mainly autoimmunity (hyperactivation of acquired immunity) (Th17-mediated inflammation in psoriasis)
Clinical features		
Family history	common	rare
Disease course	often persistent for life	transient, or persistent for life
Extracutaneous symptoms	occasional (arthritis, cholangitis)	occasional (arthritis)
Treatments	Systemic treatments including immunosuppressants and biologics are often necessary.	Topical treatments are often effective. Systemic treatments are needed in some cases.
Representative diseases	GPP, PRP type V, KLC	psoriasis (the majority of cases), lichen planus

Table 2 Inflammatory keratinization diseases classified as AIKD to date

Disease	Genetic causative or predisposing factor (frequency)
IL36Ra-related pustulosis	
generalized pustular psoriasis (GPP) without PV	<i>IL36RN</i> mutations (predominant)
impetigo herpetiformis	<i>IL36RN</i> mutations (predominant)
acrodermatitis continua	<i>IL36RN</i> mutations (occasional)
CARD14-mediated pustular psoriasis	
GPP with PV	<i>CARD14</i> variants (occasional)
palmoplantar pustular psoriasis (palmoplantar pustulosis)	<i>CARD14</i> variants (occasional)
Pityriasis rubra pilaris (PRP)	
PRP type V	<i>CARD14</i> mutations (predominant)
PRP other types	<i>CARD14</i> variants (infrequent)
Keratosis lichenoides chronica (familial)	<i>NLRP1</i> mutation (unknown)

Table 3 Summary of the differences between autoinflammatory keratinization diseases (AIKD) and autoinflammatory diseases/syndromes

Points of differentiation	Autoinflammatory keratinization diseases (AIKD)	Autoinflammatory diseases/syndromes
Pathogeneses		
Main sites of inflammation	skin (epidermis and upper dermis)	all organs (but mainly joints, bones, eyes, muscles, mucous membranes, gastrointestinal tract, nervous system and skin (dermis))
Pathogenic mechanisms	hyperactivation of innate immunity and related activation of acquired immunity (autoinflammation + autoimmunity)	hyperactivation of innate immunity (autoinflammation)
Main inflammation pathways involved	CARD14/IL-36-driven NF κ B/MAPK activation, NLRP1-inflammasome-IL-1 pathway	inflammasome-driven IL-1 pathway
Phenotypes		
Skin symptoms	hyperkeratosis with/without pustulosis (main phenotype)	urticarial eruptions, erysipelas-like erythema, erythema nodosum-like lesions, pustular acne, pyoderma gangrenosum, granulomatous dermatitis
Extracutaneous symptoms	arthritis, cholangitis, fever (additional phenotypes)	recurrent or persistent fever, arthritis, fatigue, conjunctivitis, neurosensory deafness, aseptic meningopathy, osteomyelitis
Representative diseases	GPP, PRP type V, KLC	FME, TRAPS, CAPS, PAPA syndrome