Allergology International 66 (2017) 398–403

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review article

Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies

Masutaka Furue [a, b, c, *], Takahito Chiba [a], Gaku Tsuji [a, b], Dugarmaa Ulzii [a], Makiko Kido-Nakahara [a], Takeshi Nakahara [a, c], Takafumi Kadono [d]

[a] Department of Dermatology, Kyushu University, Fukuoka, Japan
[b] Research and Clinical Center for Yusho and Dioxin, Kyushu University, Fukuoka, Japan
[c] Division of Skin Surface Sensing, Department of Dermatology, Kyushu University, Fukuoka, Japan
[d] Department of Dermatology, St. Marianna University School of Medicine, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 8 November 2016
Accepted 16 November 2016
Available online 2 January 2017

Keywords:
Atopic dermatitis
Filaggrin
IgE autoreactivity
Th2
Th22

List of abbreviations:
AD, atopic dermatitis; α-NAC, α-nascent polypeptide-associated complex; AHR, aryl hydrocarbon receptor; CLA, cutaneous lymphocyte antigen; FcεRI, high affinity Fc IgE receptor; FLG, filaggrin; H4R, histamine H4 receptor; IFN, interferon; IL, interleukin; T22, interleukin-22 producing T; JAK, Janus kinase; Th, T helper; TrkA, tropomyosin receptor kinase A; TSLP, thymic stromal lymphopoietin

ABSTRACT

Atopic dermatitis (AD) is a chronic or chronically relapsing, eczematous, severely pruritic skin disorder mostly associated with IgE elevation and skin barrier dysfunction due to decreased filaggrin expression. The lesional skin of AD exhibits Th2- and Th22-deviated immune reactions that are progressive during disease chronicity. Th2 and Th22 cytokines further deteriorate the skin barrier by inhibiting filaggrin expression. Some IgEs are reactive to self-antigens. The IgE autoreactivity may precipitate the chronicity of AD. Upon activation of the ORAI1 calcium channel, atopic epidermis releases large amounts of thymic stromal lymphopoietin (TSLP), which initiates the Th2 and Th22 immune response. Th2-derived interleukin-31 and TSLP induce an itch sensation. Taken together, TSLP/Th2/Th22 pathway is a promising target for developing new therapeutics for AD. Enhancing filaggrin expression using ligands for the aryl hydrocarbon receptor may also be an adjunctive measure to restore the disrupted barrier function specifically for AD.

Introduction

Atopic dermatitis (AD) is a common eczematous skin disorder affecting 2–20% of the general population with age and ethnic differences.[1,2] AD is characterized by chronic cutaneous inflammation and dry skin with epidermal barrier dysfunction.[3–5] Intense pruritus is the major and burdensome symptom of AD.[6,7] Itch-induced scratching appears to exacerbate skin inflammation by accelerating cellular damage in the lesional skin.[8]

Approximately 80% of AD patients exhibit elevated levels of serum IgE.[9,10] In contrast to normo-IgE and non-allergic intrinsic AD patients, extrinsic AD patients with hyper IgE levels are associated with increased disease severity,[11,12] mutations in the *FLG* gene,[13] and impaired skin barrier function.[12,14] Recent genome-wide association studies and immunochip analyses indicate at least 19 significant susceptibility loci for AD, which emphasize the potential engagement of T helper 2 (Th2) cytokines (*KIF3A/IL-4/IL13*), IL-1 family receptors (*IL1RL1/IL18R1/IL18RAP*) and skin barrier proteins (*FLG*).[15–20]

With regards to immune abnormalities, AD is currently considered as a biphasic T cell-mediated disease. A Th2 signal predominates in the acute phase, whereas a Th2 to Th1 switch promotes disease chronicity.[21,22] However, recent studies have proposed a significant role for interleukin (IL)-22-producing T (T22)

* Corresponding author. Department of Dermatology, Kyushu University, Maidashi 3-1-1, Higashiku, Fukuoka 812-8582, Japan.
E-mail address: furue@dermatol.med.kyushu-u.ac.jp (M. Furue).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.12.002

cells, and to a less extent IL-17-producing Th17 cells, in the initiation and maintenance of AD.[22–24] Infiltrations of CD3+ T cells, CD11c+ dendritic cells and CD1c+ dendritic cells are accompanied with acute AD, and more intense infiltrations are associated with chronic AD.[22]

In addition to the involvement of cellular immunity towards Th2 and T22 differentiation, elevated IgE is likely to be engaged in the development and severity of AD by manifesting IgE autoreactivity.[25–27] Total IgE levels are strongly correlated with the prevalence of IgE autoreactivity.[28–30] Some reports indicate a correlation between autoreactivity and disease severity in AD.[28,31] In addition, numerous cells infiltrated in the lesional skin of AD are positive for IgE or the high affinity Fc IgE receptor (FcεRI).[22,32–35]

Based on the pathogenetic role of barrier and immune abnormalities in AD, standard therapeutics include topical emollients for barrier dysfunction and topical steroids and calcineurin inhibitors for skin inflammation.[6] These conventional treatments are more or less effective in reducing atopic inflammation and itch; however, patient satisfaction is generally low in daily clinics. Several targeting therapies are now emerging and being assessed in clinical trials.[6]

Immune deviation towards Th2 and T22 expansion in AD

Historically, acute AD lesions have a significantly greater number of Th2 cytokine (IL-4, IL-5 and IL-13) mRNA-expressing cells compared with normal skin or uninvolved AD skin.[6,36] Compared with acute lesions, chronic AD lesions have fewer IL-4 and IL-13 mRNA-expressing cells but greater numbers of interferon (IFN)-γ mRNA-expressing Th1 cells.[6,36] The Th2 to Th2/Th1 shift is also exemplified in an atopic patch test elicited by house dust mite antigen.[37,38] In addition, the importance of Th2 deviation in AD is evidenced by the fact that the disease severity of AD is significantly correlated with IL-4/IL-13-related molecules, such as CCL17, periostin and galectin-9.[39–41] Although the potential role of IL-17-producing Th17 cells is proposed in AD,[42] controversial results have been reported.[43,44]

In addition to Th2 deviation, a series of recent studies by Guttman-Yassky *et al.* have stressed a critical role of IL-22 producing T22 cells in AD (Fig. 1).[22,24,45] Unlike murine Th17 cells, which coproduce IL-22, human T cells harbor distinct T22 cells that lack IL-17 expression.[45,46] Nograles *et al.* first demonstrated a significant accumulation of T22 cells in the lesional skin of AD compared with psoriasis and normal controls.[43] The infiltrated T22 cells included CD4+ helper (Th22) and CD8+ cytotoxic (Tc22) cells. Of note, the clinical severity of AD is correlated with the number of Tc22 cells rather than that of Th22 cells.[43] In a study comparing nonlesional skin with acute and chronic lesions in 10 patients with AD, the acute lesions exhibit a striking upregulation of genes related to Th2 (*IL4*, *IL10*, *IL31* and *CCL11*) and T22 (*IL22*, *S100A7*, *S100A8*, *S100A9*, *S100A12* and *IL32*).[22] The increased Th2/T22 signatures in acute AD lesions are further enhanced in chronic lesions intermingled with upregulation of Th1-related genes (*IFNG*, *CXCL9*, *CXCL10* and *CXCL11*).[22] Multicolor flow cytometric analyses have revealed that circulating cutaneous lymphocyte antigen-positive (CLA+; skin homing receptor) Th2 cells are markedly expanded in both children (aged 5–70 months) and adults (aged 18–74 years) with AD compared with normal control subjects.[24] The number of CLA+Th1 cells is significantly decreased in childhood AD but not adult AD, whereas the number of both CLA+Th22 and CLA+Tc22 is significantly increased in adult but not childhood AD patients compared with normal controls.[24] The comparative study enrolling early (aged 0–3 years) and late (aged 3–6 years) childhood AD patients has elucidated a significant elevation of CLA+Th2 and a significant decrease of CLA+Th1 population in the early but not in late childhood AD patients compared with normal age-matched control subjects.[47] No significant difference is observed in the number of CLA+Th22 cells between AD patients and normal controls in either early or late childhood AD.[47] In parallel with the pivotal participation of Th2/T22 cells, the upregulation of chemokines and

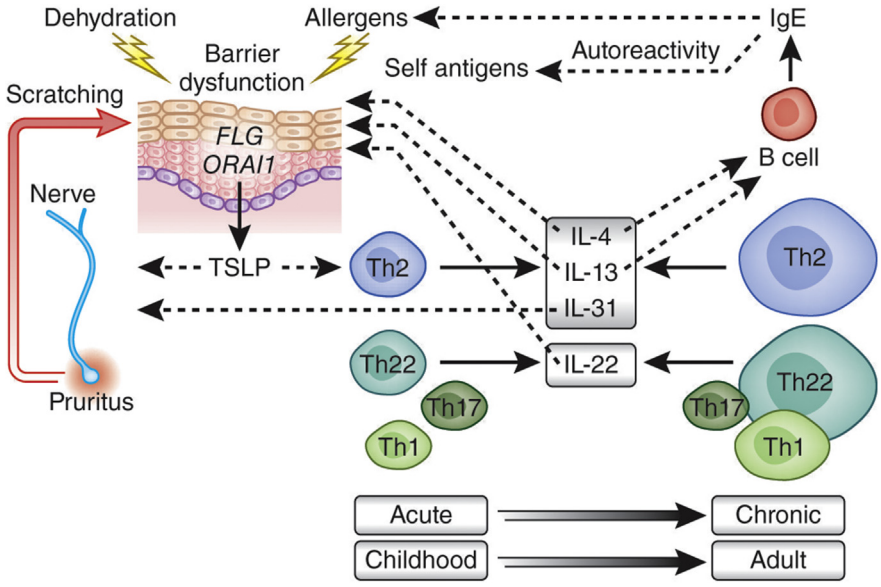

Fig. 1. Pathogenesis of atopic dermatitis (AD). Skin barrier dysfunction and Th2/Th22-deviated immune reactions are the fundamental abnormality in AD. Genetic mutations in filaggrin (*FLG*) cause barrier disruption and dehydration, which make the external allergens permeable. The barrier-disrupted epidermis abundantly releases thymic stromal lymphopoietin (TSLP), which triggers the Th2/Th22 immune response. The Th2/Th22 deviation is further accelerated during disease progression, for example, from acute to chronic or childhood to adult AD. In addition, Th1 but not Th17 cells tend to participate in the chronic phase of AD. Th2 cytokines (IL-4 and IL-13) stimulate B cells to produce IgE antibodies to allergens. Some IgEs react to self-antigens. IgE autoreactivity also contributes to disease activity. In addition, IL-4, IL-13 and IL-22 are strong suppressors of *FLG* expression. Pruritus is evoked by TSLP and Th2-derived IL-31, and the subsequent scratching further worsens skin barrier dysfunction. The release of TSLP from keratinocytes is dependent on calcium influx regulated by the ORAI1 channel. Targeting TSLP/Th2/Th22 as well as ORAI1 pathways is a promising strategy to overcome atopic inflammation.