DERMATOLOGICA SINICA 30 (2012) 142–146

Contents lists available at SciVerse ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

REVIEW ARTICLE

Pathomechanism of atopic dermatitis in the perspective of T cell subsets and skin barrier functions – "Which comes first, the chicken or the egg?"

Kenji Kabashima*

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan

ARTICLE INFO

Article history:
Received: Jun 30, 2012
Revised: Jul 11, 2012
Accepted: Jul 26, 2012

Keywords:
atopic dermatitis
dendritic cell
Langerhans cell
regulatory T cell
skin barrier
T cell

ABSTRACT

Atopic dermatitis (AD) is a common skin condition that is characterized by a complex, heterogeneous pathogenesis. The possible candidates for its pathogenesis include skin barrier abnormality and allergy/immunology aspects. It has long been asked, "Which comes first, the barrier dysfunction or the allergy/immunology abnormality?" Recently, direct evidence of a link between the incidence of AD and loss-of-function mutations in the gene encoding *Filaggrin* has been discovered. This finding suggests that barrier dysfunction is a primary cause of AD. It has also been widely recognized that T cells play an important role in the development of AD in the perspective of the Th1/Th2 paradigm. Recently, however, new T cell subsets, Th17, T22, and regulatory T cells have been identified. In this review, we will update the roles of T cell subsets in AD and ascertain how skin barrier abnormality and allergy/immunology interact in a highly interdisciplinary manner.

Introduction

Atopic dermatitis (AD) is a relapsing chronic inflammatory skin disease characterized by eczematous skin lesions and intense pruritus.[1] AD is one of the most frequent chronic inflammatory skin diseases and is increasingly prevalent, affecting at least 15% of children and 2–10% of adults in industrialized countries.[2] The skin is an active organ of the immune system and can, therefore, influence systemic immunity[3]; consequently, patients with AD often have other allergic disorders, such as food allergy, asthma, and allergic rhinitis,[2] which is called allergic (or atopic) march (Figure 1).[4] Therefore, it is important to evaluate the mechanism of AD. Thus far, the pathogenesis of AD has been attributed to a complex interaction among the environment and host susceptibility genes, altered skin barrier function and the immune system.[5] In this review, we will focus on the role of barrier functions and immune systems, especially in line with helper T (Th) cell subsets and regulatory T cells (Treg), in the development of AD.

Barrier

Outermost barriers are critical to avoid desiccation and to protect us from insult from foreign bodies. Mammalian skin consists of two sets of barriers: the stratum corneum and tight junctions (TJs). Thus far, several causes of xerosis have been considered: (i) a decrease in skin ceramides[6]; (ii) alterations of the stratum corneum pH[7]; (iii) overexpression of the proteases, including kallikreins (KLKs) and chymases[8]; and (iv) defects in *Filaggrin* (*FLG*). [9]

In Netherton syndrome, unregulated pH-sensitive KLK5 directly activates proteinase-activated receptor 2 and induces nuclear factor kappaB-mediated overexpression of thymic stromal lymphopoietin (TSLP), which aggravates AD-like skin lesions.[10]

The role of TJ in AD remains unknown. A knockout study of claudin-1, a TJ-specific integral membrane protein, demonstrated that TJs function as paracellular diffusion barriers in mammalian epidermis.[11] In humans, lack of claudin-1 lead to ichthyosis with scalp hypotrichosis, scarring alopecia, neonatal sclerosing cholangitis, and leukocyte vacuolization (NISCH syndrome),[12] but a precise description in terms of skin manifestation has not been provided, especially in relation to AD.

One of the characteristics of AD is dry skin that affects both lesional and non-lesional skin areas.[1] Dry skin in AD is in accord with increased transepidermal water loss, which suggests that the skin barrier is disrupted in AD. It has long been thought that the

* Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara, Sakyo, Kyoto 606-8507, Japan. Tel.: +8175 751 3310; fax: +81 75 761 3002.
E-mail address: kaba@kuhp.kyoto-u.ac.jp.

1027-8117/$ – see front matter Copyright © 2012, Taiwanese Dermatological Association. Published by Elsevier Taiwan LLC. All rights reserved.
http://dx.doi.org/10.1016/j.dsi.2012.07.003

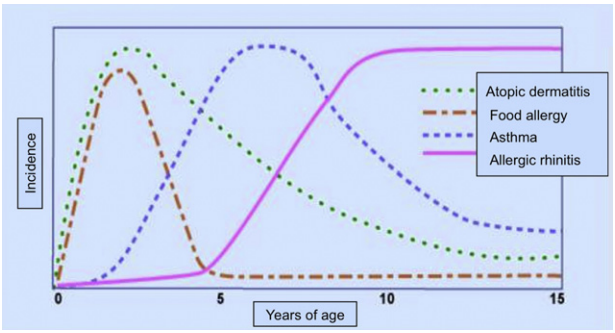

Figure 1 Allergic march. The allergic march is characterized by a typical sequence of sensitization and manifestation of symptoms that appear during a certain age period, persist over years or decades, and often show a tendency for spontaneous remission with age.

barrier abnormality in AD is not merely an epiphenomenon but rather the initiator of its pathogenesis.[13] As a result of the barrier disruption, the skin may permit the penetration of external stimuli, such as allergens, bacteria, and viruses.[14]

Role of Filaggrin in skin barrier

The direct evidence for a primary structural abnormality of the stratum corneum in AD is a recently discovered link between the incidence of AD and loss-of-function mutations in the gene encoding *FLG*. Individuals carrying the *FLG* null allele variants tend to develop AD.[9] FLG protein is localized in the granular layers of the epidermis (Figure 2). Profilaggrin, a 400-kDa polyprotein, is the main component of keratohyalin granules.[15,16] In the differentiation of keratinocytes, profilaggrin is dephosphorylated and cleaved into 10–12 FLG molecules (a molecular mass of 37 kDa in human and 27 kDa in mice), which aggregates in the keratin cytoskeleton system to form a dense protein-lipid matrix in humans.[15] These FLG monomers are further degraded into natural moisturizing factors by either caspase 14 or bleomycin hydrolase, which are important for maintaining hydration and keeping the skin pH low (Figure 2). Intriguingly, it has recently been reported that intragenic copy number variation (20–24 copies in one person) within a *FLG* gene contributes to the risk of AD with a dose-dependent effect.[17]

Flaky tail (Flg^{ft}) mice, essentially deficient in Filaggrin, have been used to investigate the role of Filaggrin in AD.[18] There have been four recent studies using Flg^{ft} mice as a model of Filaggrin deficiency: Fallon et al[19] used Flg^{ft} mice from which the *ma* mutation had been eliminated with four additional backcrosses to B6 mice, and others used commercially available Flg^{ft} mice.[20–22]

The first report showed only a histological abnormality without clinical manifestations,[19] the second report demonstrated spontaneous eczematous skin lesions after 28 weeks of age,[20] the third report did not indicate any spontaneous dermatitis in Flg^{ft} mice,[21] and the fourth report observed spontaneous dermatitis as early as 5 weeks of age, with gradual exacerbation with age.[22] Humans and mice differ in this respect, since most AD resolves with age in humans and the cutaneous manifestations occurred only in homozygous Flg^{ft} mice. The discrepancies between these results seem to be related to the presence or absence of the *ma* mutation, variation in the genetic backgrounds of each mouse strain, and environmental factors.

Human AD can be categorized into the extrinsic and intrinsic types. Extrinsic or allergic AD shows high total serum IgE levels and the presence of specific IgE for environmental and food allergens, whereas intrinsic or non-allergic AD exhibits normal total IgE values and the absence of specific IgE.[23] The skin barrier is perturbed in the extrinsic, but not the intrinsic, type. *FLG* gene mutations are not a feature of extrinsic, but not intrinsic, AD.[24]

Dendritic cells as an initiator for skin immune responses

Dendritic cells (DCs) play an important role in the initiation of acquired immune responses. In the skin, there exist two populations of DCs; epidermal Langerhans cells (LCs), and dermal DCs. According to their expression of Langerin, dermal DCs are divided into at least two populations: Langerin-positive dermal DCs and Langerin-negative dermal DCs.[25–27] LCs have long been regarded as essential antigen presenting cells for the establishment of sensitization in hapten induced-contact hypersensitivity, but this concept is now being challenged by recent analyses using LC ablation murine models.[28] Langerin-negative DCs play a major role in the

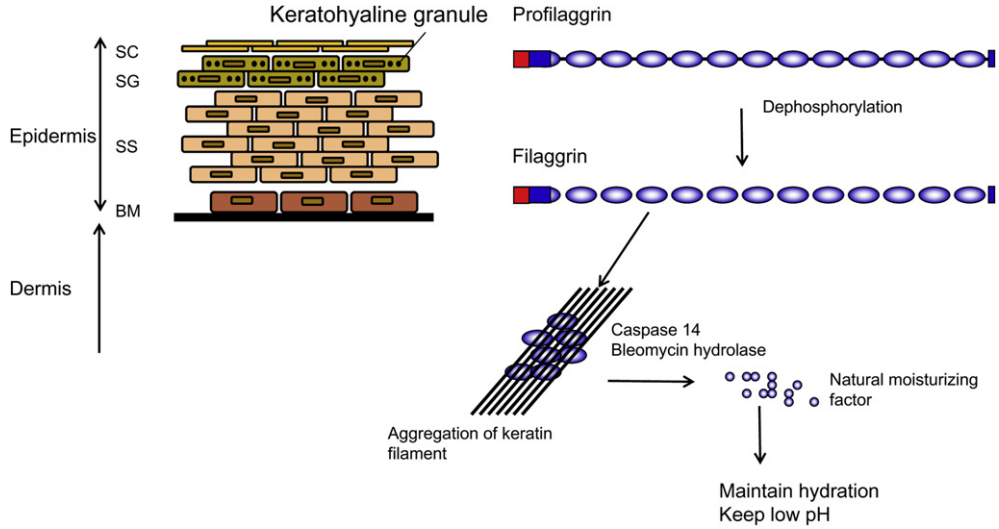

Figure 2 Role of Filaggrin. FLG protein is localized in the granular layers of the epidermis. Profilaggrin is the main component of keratohyaline granules. In the differentiation of keratinocytes, profilaggrin is dephosphorylated and cleaved into 10-12 FLG molecules, which aggregates in the keratin cytoskeleton system to form a dense protein-lipid matrix. These FLG monomers are further degraded into natural moisturizing factors, which are important to maintain hydration and keep the skin pH low.