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Invited review article

New concept of the pathogenesis of atopic dermatitis: Interplay among the barrier, allergy, and pruritus as a trinity

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ABSTRACT

Atopic dermatitis (AD) is a common skin condition, characterized by a complex, heterogeneous pathogenesis, including skin barrier dysfunctions, allergy/immunology, and pruritus. When the skin barrier is disrupted by, for example, the filaggrin gene mutation and/or environmental factors, the skin is predisposed to being penetrated by external stimuli. Foreign antigens can be subdivided into two subsets by size: haptens (including metals) and protein antigens. It is known that a single hapten challenge provokes Th1 initially, but that repeated elicitation with haptens results in a shift toward Th2-dominated responses. On the other hand, exposure to protein antigens directly induces Th2-dominant conditions via the thymic stromal lymphopoietin (TSLP) receptor on Langerhans cells. Recently, it has been revealed that Th2 cells produce IL-31, which provokes pruritus, and that Th2 cytokines decrease filaggrin expressions by keratinocytes. These findings suggest that Th2 conditions lead to pruritus and barrier dysfunctions. In this review, we will examine the highly complex interplay among skin barrier abnormality, allergy/immunology, and pruritus as a trinity in the development of AD.

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1. 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 its prevalence is increasing, affecting at least 15% of children and 2–10% of adults in industrialized countries [2]. Patients with AD often have other allergic diseases, including food allergies, asthma, and allergic rhinitis [2]; these often begin early in life and progress in a typical fashion—this is called the allergic (or atopic) march [3]. The skin is an active immune system organ that influences systemic immunity [4].

AD can be categorized into two types: extrinsic or intrinsic. Extrinsic or allergic AD exhibits 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 without filaggrin gene mutations [5]. The skin barrier is perturbed in the extrinsic, but not intrinsic type. The pathogenesis of AD has been attributed to a complex interaction of the environment and host susceptibility genes, altered skin barrier function, the immune system, and pruritus [6,7]. Thus far, each component has been studied independently; however, recent findings have suggested that they interact in a highly complex manner in the development of AD. In this review, we focus on the role of barrier functions, immune systems, and pruritus in AD, and we discuss their interplay in the development of AD.

2. Barrier functions in AD

2.1. Stratum corneum and tight junction

Outermost barriers are critical to avoid desiccation and to protect against foreign insults. Mammalian skin consists of two sets of barriers: stratum corneum and tight junctions (TJs). Thus far, at least four causes of xerosis have been considered: (1) decrease in skin ceramides [8], (ii) alterations of the stratum corneum pH [9], (iii) overexpression of the proteases, including kallikreins (KLKs) and chymases [10], and (iv) defect in *Filaggrin* (FLG) [11] (Fig. 1).

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

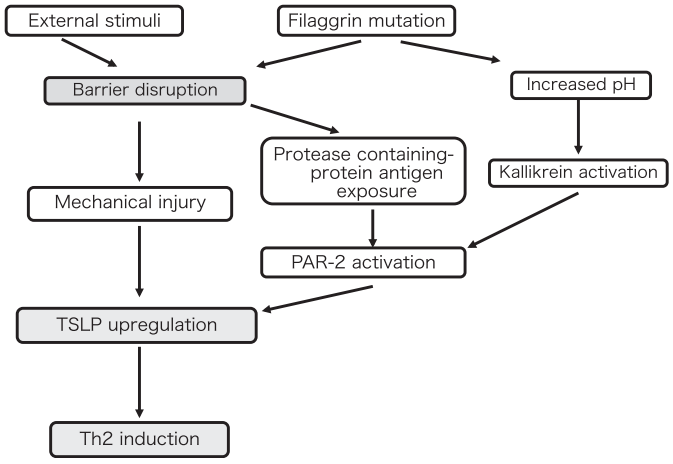

Fig. 1. Effect of barrier dysfunction on Th2 induction. Barrier dysfunction in line with filaggrin deficiency will lead to Th2 skewing conditions, which may play an important role in the development of AD.

manifestations in flaky tail (Flg^{ft}) mice, which is a mouse model of AD, as described below [12,13].

The role of TJs 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 [14]. In humans, lack of claudin-1 leads to ichthyosis with scalp hypotrichosis, scarring alopecia, neonatal sclerosing cholangitis, and leukocyte vacuolization (NISCH syndrome) [15], although a precise description of skin manifestation from the perspective of AD has not been reported.

One of the characteristics of AD is dry skin that affects both lesional and non-lesional skin areas [1]. Dry skin in AD parallels increased transepidermal water loss, which suggests that the skin barrier is disrupted in AD. It has long been thought that the barrier abnormality in AD is not merely an epiphenomenon, but is instead the initiator of its pathogenesis [16]. As a result of barrier disruption, the skin may permit the penetration of external stimuli, such as allergens (which may contain proteases), bacteria, and viruses [17].

2.2. Filaggrin

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 [11]. FLG protein is localized in the granular layers of the epidermis (Fig. 2). Profilaggrin, a 400 kDa polyprotein, is the main component of keratohyalin granules [18,19]. In the differentiation of keratinocytes, profilaggrin is dephosphorylated and cleaved into 10–12 FLG molecules (with 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 [18]. These FLG monomers are further degraded into natural moisturizing factors (NMFs) by caspase 14, peptidylarginine deiminases, or bleomycin hydrolase. Filaggrin-derived NMFs are important to maintain skin hydration and low pH (Fig. 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 [20].

2.3. Filaggrin in mouse and human AD

Flaky tail (Flg^{ft}) mice, deficient in *Flg* and *matted* (*ma*), have been used to investigate the role of filaggrin in AD [21]. There have been four recent studies using Flg^{ft} mice as a model of filaggrin deficiency: Fallon et al. [22] used Flg^{ft} mice in which the *ma* mutation had been eliminated with four additional backcrosses to B6 mice, and the others used the commercially available Flg^{ft} mice [12,23,24].

The first report showed only a histological abnormality without clinical manifestations [22]. The second report demonstrated spontaneous eczematous skin lesions after 28 weeks of age [23]. The third report did not indicate any spontaneous dermatitis in Flg^{ft} mice [24]. The fourth report observed spontaneous dermatitis as early as five weeks of age with gradual exacerbation with age [12]. This time course differs from that of humans since most cases of AD resolve with age in humans. In addition, the cutaneous manifestations only occur in homozygous Flg^{ft} mice, but heterozygous carriers of a loss-of-function mutation of the *FLG* gene predispose humans to AD. The discrepancies among these results seem to be related to the presence or absence of the *ma* mutation and/or variation in the genetic backgrounds of the different strains used and to environmental factors. Recently, Flg null mutation mice have been generated that demonstrated that antigens penetrated the Flg null stratum corneum more efficiently, leading