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<td>Author(s)</td>
<td>Egawa, Gyohei; Kabashima, Kenji</td>
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<tr>
<td>Citation</td>
<td>Allergology International (2018), 67(1): 3-11</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2018-01</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2433/230801">http://hdl.handle.net/2433/230801</a></td>
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Invited Review Article

Barrier dysfunction in the skin allergy

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Article info

Article history:
Received 22 September 2017
Received in revised form 30 September 2017
Accepted 4 October 2017
Available online 16 November 2017

Keywords:
Atopic dermatitis
Barrier function
Cornified envelope
Stratum corneum
Tight junction

Abbreviations:
AD, atopic dermatitis; CE, cornified envelope; FLG, filaggrin gene; KLK, kallikrein; NMF, natural moisturizing factor; PCA, pyrrolidine carboxylic acid; SC, stratum corneum; SG, stratum granulosum; SPR, small proline-rich protein; TG, transglutaminase; TJ, tight junction; UCA, urocanic acid

Abstract

The skin is continuously exposed to external pathogens, and its barrier function is critical for skin homeostasis. Previous studies have shown that the barrier dysfunction is one of the most predisposing factors for the development of skin allergic diseases such as atopic dermatitis. In this article, we summarize how the physical barrier of the skin is organized and review its link to the pathomechanism of skin allergic diseases. We describe the formation of the SC barrier in terms of the following five categories: 1) filaggrin metabolism; 2) cornified envelope; 3) intercellular lipids; 4) corneodesmosome; and 5) corneocyte desquamation. New approaches to restoring the skin barrier function are also discussed.

Introduction

The skin covers the entire body and protects us from various kinds of external stimuli. An impaired epidermal barrier allows the enhanced penetration of external antigens and readily induces skin inflammation. This facilitates the interaction of external antigens with local immune cells and may lead to systemic immune responses.1 This is called the “outside-to-inside” hypothesis, and it explains the association between skin barrier dysfunction and an increased risk of developing allergic diseases, including atopic dermatitis (AD), asthma, food allergies, and allergic rhinitis.2,3 In addition, it is evident that persistent skin inflammation, in turn, causes further attenuation of the skin barrier, suggesting the existence of an exacerbation loop between the skin barrier and skin immunity (the “outside-to-inside-and-back-to-outside” hypothesis).4,5 These observations suggest that maintaining the skin barrier function is important not only for effective management of allergic diseases but also for preventing their development.

The barrier function of the skin is largely dependent on the stratum corneum (SC), the outermost layer of the epidermis (Fig. 1A). The SC is formed through a course of tightly regulated processes of keratinocyte differentiation called keratinization.6 Keratinization is achieved by keratinocytes passing through four cell layers of the epidermis: the stratum basale, the stratum spinosum, the stratum granulosum (SG), and the SC. In the SG, keratinocytes start to produce two membrane-circumscribed granules: keratohyalin granules and lamellar bodies (Fig. 1B). Keratohyalin granules contain intracellular components of the SC (such as filaggrin [FLG], loricrin, and keratin filaments), whereas lamellar bodies contain extracellular components (such as lipids, corneodesmosin, and kallikreins). In the SC, keratinocytes are flattened

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and denucleated (which are then called as corneocytes) and simultaneously, corneocyte cell membranes are replaced by a specific barrier structure called a cornified envelope (CE). At the transition from the SG to the SC, lamellar bodies are secreted into the intercellular space of corneocytes and fill it up with lipids. These structures are often described as bricks (corneocytes) and mortar (intercellular lipids) (Fig. 1C).

Here, we describe the formation of the SC barrier in terms of the following five categories to review their link to the pathogenesis of skin allergic diseases: 1) FLG metabolism; 2) CE; 3) intercellular lipids; 4) corneodesmosome; and 5) corneocyte desquamation. The genes involved in each process are listed in Table 1. This review is an updated version of a similar article that has published in the Journal of Allergy and Clinical Immunology.3

Filaggrin metabolism

FLG and its metabolites are key components for maintaining normal skin barrier function (Fig. 2).8,9 In the SG, FLG is produced as FLG polymer (profilaggrin), in which 10–12 repeats of FLG monomer are linked, and stored in keratohyalin granules. At the transition from the SG to the SC, profilaggrin is cleaved to generate FLG monomers by proteases such as CAP1/Pss8 and SASPase/ASPRV1.9,10 FLG monomers bind to keratin filaments and this keratin–FLG bundle is a fundamental structure in corneocytes. At the upper layer of the SC, FLG is re-dissociated from keratin filaments to further metabolism. In this process, the citrullination of FLG and keratin1 by peptidylarginine deiminase is considered essential.11 The released FLG monomers are degraded to free amino acids, including glutamine, arginine, and histidine, and then converted into urocanic acid (UCA) and pyrrolidine carboxylic acid (PCA). This process is mediated by other sets of proteases, including caspase14, calpain1, and bleomycin hydrolase.12,13 UCA is an important ultraviolet-absorbing chromophore in the SC and also contributes to maintaining the acidic pH of the skin.14 Recent study has shown that UCA significantly reduced costimulatory molecule expression on dendritic cells and increased their ability to induce a regulatory T cells.15 In contrast, PCA is a major constituent of natural moisturizing factors (NMFs), which are responsible for retaining water in the SC. Therefore, FLG and its metabolites assume a manifold role in the barrier function of the SC. Gene targeting studies have revealed that FLG-deficient mice demonstrate a reduced SC barrier function with enhanced sensitization.16 Furthermore, on a proallergic BALB/c background, FLG-deficient mice develop spontaneous dermatitis.17

Filaggrin deficiency in the skin allergy

AD is the most common inflammatory skin disease, and has multiple etiologies. Over the last decade, data from both experimental models and patients have highlighted the primary pathogenic role of skin barrier deficiency in AD.18–20 Particularly, loss-of-
function mutations in the FLG gene are strongly associated with the development of AD as well as with ichthyosis vulgaris. The prevalence of FLG mutations in AD patients ranges from 25 to 50% in the Northern European and Asian populations. In addition, genome-wide association studies (GWAS) among individuals with European, African, Japanese, and Latino ancestry have identified 31 risk loci of AD, to date, and among them, the mutation in FLG is proved to be the strongest risk factor. These observations indicate the major contribution of FLG-deficiency in AD pathogenesis.

Although mutations in FLG are common in Northern European and Asian subjects, FLG mutations are less common in Southern Europe and are even absent in some African countries. A recent study showed that the expression of another skin barrier protein, FLG2, is reduced in the epidermis of AD patients. Further, a nonsense mutation in the FLG2 gene was shown to be associated with persistent AD patients of African ancestry. The biological function of FLG2 remains to be elucidated, but its structure, pattern of expression, and biological properties are very similar to FLG. Therefore, FLG2 may also play important roles in skin barrier integrity. We must also note the possibility that FLG deficiency might be compensable under a tropical climate.

### Formation of the cornified envelope

The cornified envelope (CE) is a specific barrier structure formed beneath the cell membrane of corneocytes (Fig. 3). The CE consists of highly crosslinked insoluble proteins and the extracellular lipids anchoring on it. This structure acts as a vital physical barrier to the SC. The assembly of the CE starts in the upper layer of the stratum spinosum. In response to the elevation of intracellular Ca^2+ levels, keratinocytes produce enpokrakin, periplakin, and involucrin. Enpokrakin and periplakin form heterodimers, and, together with involucrin, they accumulate beneath the plasma membrane. These three proteins are crosslinked to each other by transglutaminase (TG) 1 and TG5. Involucrin acts as a scaffold of the CE.
Ceramides replace the lipid bilayer of the plasma membrane. This ceramide lipid adds onto the scaffold of involucrin, and eventually, the CE protein consists of loricrin. TG1 also combines extracellular CE, this crosslinking is repeated and as the result, up to 80% of the conversion into PCA and UCA.

While plakin dimers act as a binding site of keratin filaments and combine them with desmosomal proteins. Importantly, since plakin proteins are tightly crosslinked to the involucrin scaffold, desmosomes and keratin filaments are rigidly linked on the CE, which confers mechanical stability to corneocytes.

In the SG, loricrin and small proline-rich (SPR) protein families are produced. These proteins are crosslinked by TG3 and translocate to the cell periphery; next they crosslink onto the pre-existing scaffold of involucrin by TG1 and TG5. To reinforce the CE, this crosslinking is repeated and as the result, up to 80% of the CE protein consists of loricrin. TG1 also combines extracellular ceramide lipids onto the scaffold of involucrin, and eventually, the ceramides replace the lipid bilayer of the plasma membrane. This step is further described in section “Formation of intercellular lipid lamellae”.

Cornified envelope formation in the skin allergy

Despite the ubiquitous presence of involucrin, envoplakin, and periplakin in the CE, single knockout mice of these genes do not show any obvious skin abnormalities. The triple knockout of these three genes results in abnormal CE formation with reduced lipid content and decreased mechanical integrity, but the skin barrier function is normal (possibly compensated by reduced desquamation of corneocytes). Similarly, loricrin-deficient mice exhibit only a subtle phenotype, with shiny skin at birth and reduced CE stability. These studies suggest that CE proteins are redundant and indicate the existence of strong compensatory mechanisms. In accordance with this notion, no mutations of the CE genes of component have been linked to the pathogenesis of skin allergic diseases thus far.

The CE is abnormal or even absent with TG1-deficiency, in which severe ichthyosiform erythroderma (autosomal recessive congenital ichthyosis) [ARCI] develops. In addition, TG5 deficiency causes peeling skin syndrome 2, which represents as superficial acral skin peeling occurring at the junction between the SG and the SC. These facts suggest the non-redundant role of TGs in the formation of CE; however, the association between genetic mutation in TGs and skin allergic diseases has not been reported.

Formation of intercellular lipid lamellae

The intercellular lipids (the “mortar”) are also an integral component of the SC barrier. They consist of a heterogeneous mixture of ceramides, free fatty acids, and cholesterol in a roughly 1:1:1 M ratio. These lipids are produced in the SG and stored in lamellar bodies, and are subsequently secreted into extracellular space in the transition to the SC. In the ceramide fraction alone, over 300 distinct species have been identified from human SC. Among them, omega-hydroxyceramide is indispensable because it is conjugated to the involucrin scaffold by TG1 and covers the surface of corneocytes. Using this ceramide as a template, periodic sheets of lipid lamellae are formed in the intercellular space of corneocytes.

Intercellular lipid lamellae formation in the skin allergy

Several defects in ceramide-processing enzymes have been linked to the etiology of barrier-deficient skin diseases. 12R-lipoxygenase (encoded in the ALOX12B gene) and epidermal lipoxygenase-3 (encoded in the ALOXE3 gene) are both essential for the generation of omega-hydroxyceramide. Defect in these proteins causes congenital ichthyosis (ARCI2, and ARCI3, respectively). The skin manifestations of ARCI2 and ARCI3 are less severe than those of ARCI1, probably because the protein layer of the CE is formed in these diseases.

The transmembranal transport of lamellar bodies is conducted by a lipid transporter called ATP-binding cassette subfamily A member 12 (ABCA12). Mutations of this gene result in moderate (ARCI4A) to severe (ARCI4B, also known as harlequin ichthyosis) congenital ichthyosis, suggesting an essential role of lamellar body contents in normal cornification. Recently, transmembrane protein 79/matriptin (Tmem79/Matt) was identified to be involved in the secretion of lamellar body contents. Tmem79 is a five-transmembrane protein that is localized to lamellar bodies, and Tmem79-deficient mice exhibit spontaneous dermatitis with elevated serum IgE, which resembles human AD manifestations. In addition, a meta-analysis of AD patients revealed that a missense mutation of the Tmem79 gene has a small but significant association with AD. These findings suggest that the abnormality of the lamellar body function of subsequent intercellular lipid layer dysformation might result in barrier deficiency in some AD patients.

Structure of corneodesmosome

The cell adhesion of corneocytes is dependent on the desmosome apparatus, called the corneodesmosome (Fig. 3). The
Corneodesmosome is composed of three protein families: desmosomal cadherin, armadillo proteins, and plakins. In the corneodesmosome, desmoglein 1 and desmocollin 1 (cadherin family) interact with plakoglobin and plakophilins (armadillo proteins), which attach to envoplakin and periplakin. As described above, envoplakin and periplakin heterodimers are crosslinked to the involucrin scaffold, and bind keratin filaments on its C-terminus. The corneodesmosin is another important modulator of corneodesmosomal adhesion. It is stored in the lamellar bodies and secreted into the intracellular space of the SC, and interacts with cadherin proteins to support their adhesion.

Corneodesmosomal adhesion in the skin allergy

Abnormality of the corneodesmosome is prone to cause hyperdesquamation of corneocytes, which may lead to skin barrier defect and subsequent skin inflammation. A recent study revealed that the homozygous mutation of desmoglein 1 results in severe dermatitis (erythroderma), accompanied by palmoplantar keratoderma, hypotrichosis, and increased serum IgE (EPKHE, also known as severe dermatitis, multiple allergies, and metabolic wasting [SAM] syndrome). Importantly, EPKHE patients often have multiple food allergies. In contrast, the homozygous mutation of the corneodesmosin causes peeling skin syndrome 1, characterized by dermatitis, severe pruritus, food allergies, repeated episodes of angioedema and urticaria, asthma, and increased serum IgE.

Corneocyte desquamation

At the surface layer of the SC, corneocytes are constantly shed. This phenomenon is called desquamation, and it is an important process to maintain the SC homeostasis. Corneocyte desquamation is mainly regulated by a proteolytic cascade of kallikrein (KLK)-related peptidases, such as KLK5, KLK7, and KLK14. The activity of these proteases is pH-dependent and is enhanced when the pH in the SC is elevated. Their activity is also strictly regulated by a cocktail of protease inhibitors, including lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI) encoded by the serine protease inhibitor Kazal-type 5 (SPINK5). KLKs and LEKTI are stored in lamellar bodies and secreted into the intracellular space at the SG-SC interface.

Corneocyte desquamation in the skin allergy

In AD patients, the skin surface pH is increased, at least partially due to the decreased production of UCA derived from FLG (Fig. 2). As such, KLK activity is often enhanced in the AD skin. This condition is thought to induce an adverse effect on the SC barrier through a multimodal mechanism (Fig. 4). First, KLKs cleave corneodesmosomal cadherins and promote corneocyte desquamation. Second, KLKs activate protease-activated receptor (PAR)-2, a G-protein-coupled receptor on keratinocytes. Upon activation, PAR-2 signals lead to suppression of lamellar body secretion via the downregulation of lipid processing enzymes. Finally, activated KLKs increase the generation of interleukin (IL)-1α and IL-1β, whose preforms are abundantly stored in the cytosol of corneocytes. Indeed, IL-1 cytokines are increased in the SC of AD patients and their enhanced production is associated with FLG deficiency.

Two genetic polymorphisms that result in increased KLKs activity have been linked to AD pathogenesis: gain-of-function mutations in KLK7 and loss-of-function mutations in SPINK5. The 4bp insertion polymorphism of KLK7 was first reported in the UK, but their association with AD was not found in a French AD cohort study. SPINK5 is known as the gene responsible for Netherton syndrome in which patients display a broad range of allergic manifestations, such as AD-like dermatitis, food allergies, asthma, hay fever, and
markedly elevated serum IgE levels. A significant association of polymorphism in SPINK5 with AD was reported in the UK and Asian populations, but not found in the French population.

**Tight junction in the skin allergy**

In addition to the SC, tight junctions (TJs) are structures that are essential to the integrity of the skin barrier. In the skin, TJs seal adjacent keratinocytes in the SC (Fig. 1A) and act as a barrier for water and solutes. TJs are composed of transmembrane proteins, such as the claudin and occludin family, and several cytosolic scaffolding proteins, including zonulae occludens (ZOs). The indispensable role of TJs in skin homeostasis was first demonstrated by claudin1-deficient mice that died within 24 h of birth with severe dehydration. Importantly, these mice had no abnormalities in the production of SC components. A recent study with AD model mice showed that the expression of TJ proteins was suppressed with skin dehydration. CLAUDIN1 deficiency mice that died within 24 h of birth with severe dehydration.8 Importantly, these mice had no abnormalities in the production of SC components. A recent study with AD model mice showed that the expression of TJ proteins was suppressed with skin dehydration, but was not affected by FLG deficiency. 

In humans, the claudin1 expression is reduced in the non-lesional skin of AD patients, and the association of claudin1 polymorphism with AD susceptibility has been reported. These observations suggest that an impairment in TJs contributes to the barrier dysfunction observed in AD patients. Since most of the skin is covered with the SC, TJs seem to act as the second line of defense against external pathogens; however, TJs must be the primary barrier structure in skin appendages, such as hair follicles and sweat glands, because the SC is absent in these areas. Indeed, it is well known that hair follicles are important shunt routes into the skin for drugs and chemicals. In accordance with this notion, widespread eruptive infections with herpes simplex virus or molluscum contagiosum virus, which enter the body through hair follicles, sometimes occur as a complication of AD. These facts suggest that the skin appendages are the “security holes” of the skin, particularly in AD patients with TJ deficiency.

**Immunological modulation of skin barriers**

Accumulating evidence suggests that immune cells influence skin integrity through the production of cytokines. Although complex interaction of immune cells creates AD skin lesions, the immunopathogenesis of AD is characterized by Th2-skewed responses. Previous studies have shown that IL-4 and IL-13, the two major Th2 cytokines, downregulate the production of 1) FLG and keratin, 2) the CE components (loricrin and involucrin), 3) cell adhesion molecules (desmogleins, ZO-1), and 4) ceramide lipids. IL-31, another Th2 cytokine dominantly produced by Th2 cells, also downregulates FLG expression. Furthermore, a recent study has shown that IL-33, an alarmin that is abundantly stored in keratinocytes, has the potency to downregulate FLG expression as well. The original purpose of these immunological modulations against skin integrity may be to facilitate the desquamation and replacement of damaged corneocytes; however, to achieve this, dysregulation of the skin barrier is essential. A series of these modulations may cause problems, particularly in AD patients. The exacerbation loop between congenital barrier deficiency and immunogenic barrier deficiency leads to the formation of chronic, persistent skin inflammation in AD.

**Barrier dysfunction is leading pathogenesis of skin allergy**

It is now evident that epicutaneous antigens are strong sensitizers of allergic disorders. Mouse studies have demonstrated that food allergy and asthma can be induced via epicutaneous sensitization and are enhanced under disrupted skin barrier. In human, sequential acquisition of allergic diseases (atopic march) are frequently observed in both AD and some genodermatoses, as Netherton syndrome (mutation in SPINK5), peeling skin syndrome 1 (Corneodesmosin) and SAM syndrome (Desmoglein1) (Table 1, bold), which strongly suggests that skin barrier deficiency contributes to the development of atopic march. Eosinophilic esophagitis is another chronic immune disorder that is associated with hypersensitivity to food, and has recently been linked to the mutations in Capalin 14 (CAPN14), a protease specifically expressed in the esophagus. An in-vitro experiment showed that overactivation of CAPN14 results in loss of Desmoglein1. These studies demonstrate that barrier deficiency in mucosal epithelium also contribute to the induction of allergic disorders. Recent clinical trials have shown that epicutaneous antigen exposure induces
sensitization while oral antigen consumption induces immune tolerance.79,80

In the presence of barrier defects in the SC, foreign antigens readily penetrate into the epidermis and activate innate immune receptors and pattern recognition receptors. This results in the production of Th2-promoting cytokines, such as IL-33, IL-25 and thymic stromal lymphoproteins (TSLP), which are produced by skin resident cells. Animal studies have demonstrated an essential role for TSLP in the epicutaneous induction of food allergy with AD-like skin lesions. Increased TSLP in the epidermis elicits the accumulation of basophils into the skin that promote Th2-cytokine responses.81 In addition, TSLP signaling on epidermal Langerhans cells may be important for IgE production during the epicutaneous sensitization to food allergens.82 The suppressive effect of TSLP on FLG expression was also confirmed by the human skin engrafted on immunocompromised mice.83

It is noteworthy that cytokine profiles in patients with ichthyosis vulgaris, who are carrying FLG mutation, have an IL-17-dominant and low expression level of Th2-related cytokines.84 This immune profile resembles to psoriasis patients, rather than AD. These findings suggest that barrier dysfunction alone might not induce Th2 immune profiles.

Conclusion – therapeutic approach to restore skin barrier function

Skin barrier deficiency and excessive immune responses are two sides of the same coin in skin allergic diseases, and each is highly relevant to the other.85 Therefore, therapeutics targeting the skin barrier function, as well as immunosuppressive drugs, can be considered important in the effective management of skin allergy. Recently, two groups investigated whether protecting the skin barrier with a moisturizer during the neonatal period prevents the development of AD.86,87 They reported that moisturizer treatment at an early stage of life resulted in 32–50% less AD prevalence. These results suggest that to avoid percutaneous sensitization in the neonatal period by reinforcing the skin barrier function is a promising strategy to prevent AD.

The potency of FLG replacement therapies has been demonstrated. This approach includes the application of 1) read-through drugs, 2) drugs that enhance FLG production, 3) the FLG monomer itself, and 4) FLG metabolites. Read-through drugs are able to skip the nonsense mutation of the FLG gene, which may be applicable to both heterozygous and homozygous FLG mutation carriers. Candidate drugs are antimicrobial peptides, such as gentamicin and PTC124 (Ataluren). These drugs are currently tried in clinical trials for other genetic diseases.88,89 In contrast, the drugs that enhance FLG production are only considered applicable to patients with heterozygous FLG mutations. Candidates include agonists of peroxisome proliferator-activated receptors (PPARs),90 a serine-rich diet,91 apigenin,92 JTC801,93 JTE-052,94 and urea.95 All of these drugs have been demonstrated to induce keratinocyte differentiation and increase FLG levels. Further studies are necessary, however, because their efficacy has only been assessed in vitro or in animal models.

Intensive research to identify promising candidates to enhance the skin barrier function is ongoing90 and is expected to lead to better management of skin allergic diseases, including AD, in the near future.

Acknowledgement

This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Conflict of interest

The authors have no conflict of interest to declare.

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