Skin Barrier-Related Molecules and Pathophysiology of Asthma

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ABSTRACT

The concept of “atopic march” has been well appreciated both by physicians and by dermatologists; eczema (atopic dermatitis) often precedes the development of airway diseases such as asthma and allergic rhinitis in atopic subjects. However, the underlying mechanisms for atopic march are less elucidated. It has been conceived that genetic susceptibility to atopy determines the phenotype of allergic diseases progressive from the skin to the airways, but recent discovery of filaggrin gene mutations that disturb the barrier function of the skin in patients with asthma and eczema now suggests the crucial role of epicutaneous sensitization as a precursory event for the development of asthma. In the present review, we describe updated genetic and immunological evidences that suggest the relationship between skin barrier-related molecules and the pathology of asthma.

KEY WORDS

atopic dermatitis, danger signal, filaggrin, IL-17, TSLP

INTRODUCTION

Atopic asthma develops often in childhood with the sensitization of host immune system to the specific allergens derived from insects, fungi, animals, low molecular weight chemicals, et al. The route for the allergen to evade into the body is variable from the airways, the gastrointestinal tract, to the skin (epicutaneous sensitization). Eczema (atopic dermatitis) often precedes airway diseases such as asthma and allergic rhinitis in a substantial proportion of patients, in whom epicutaneous sensitization should be a crucial precursory process for the development of airway diseases.

Intact epidermal barrier protects the immune system from the exposure to exogenous allergens that eventually cause unfavorable allergic reactions, while impaired skin barrier, either mechanically or functionally, can allow the allergens to penetrate into the sub-epidermal layer of the skin and make the host susceptible to atopic diseases. Recent progress in the genetics and the immunology further supports the role of skin barrier-related molecules in the pathophysiology of allergic diseases in the airways, such as asthma. In the present review, we focus on the role of genetic mutations in filaggrin, an essential protein for the skin barrier system, on the susceptibility to asthma, and also update the immunological aspects of epicutaneous sensitization in the development of allergic airway inflammation.

GENETIC EVIDENCES SUGGEST THAT THE MOLECULE(S) RELATED TO SKIN BARRIER FUNCTION IS ASSOCIATED WITH THE SUSCEPTIBILITY TO ASTHMA (Table 1)

It has been more than 20 years since Cookson and his colleagues published the first evidence that there is a linkage between specific genetic loci (chromosome 11) and atopy/asthma. A number of studies have been performed on the field of asthma genetics since then, however, our knowledge about asthma susceptibility genes is still limited. The reported associations between the “candidate” genes and asthma are not reproducible in many cases, while laborious, but less biased, genome-wide approaches have only suggested a few genes with unknown biological and pathological functions, such ADAM33, CYFIP2, DPP10, HLA-G, GPRA, and PHF11. ADAM33 on chromosome 20p13 has been one of the most extensively studied genes, but a number of the critical...
questions are still unanswered; which mutation(s) in ADAM33 is crucial for the development of asthma, what kind of changes in the gene expression or the protein function are caused by the mutation(s), what is the biological function of ADAM33, and how the mutant ADAM33 gene relates to the pathology of asthma.

To our surprise, a major breakthrough in the genetics of asthma has been brought by a simple case-control study for atopic dermatitis with a candidate gene, filaggrin, on chromosome 1q21. Two null mutations in this gene, R501X and 2282del4, had been identified as the susceptibility gene for ichthyosis vulgaris using classic linkage analysis and positional cloning.7 R501X mutation replaces the nucleotide sequence coding arginine with stop codon, and 2282del4 mutation causes frame shift, also resulting in the premature termination of translation. The researchers who identified these mutations noticed that the heterozygous carriers of filaggrin gene mutations were more likely to exhibit atop dermatitis. Using three modest size of cohorts from Iceland, Scotland, and Netherlands, they demonstrated that R501X and 2282del4 mutations were more common in the subjects with atopic dermatitis than in control subjects with the OR of 3.4.8 Surprisingly, more than 20 studies have already replicated the association between atopic dermatitis and filaggrin gene mutations with the OR of 3.12 (95% confidence interval, 2.57-3.79).9 The original work has suggested that filaggrin gene mutations are more common in patients with the combination of atop dermatitis and asthma.8 Successive studies have further confirmed a strong association between filaggrin gene mutations and atopic asthma accompanied with eczema. A meta-analysis of 14 studies demonstrates that the OR of filaggrin gene mutations is 1.48 (95% confidence interval, 1.32-1.66) for asthma, and 3.29 (95% confidence interval, 2.84-3.82) for eczema-associated asthma, whereas there is no association with asthma unaccompanied with eczema (OR 1.11, 95% confidence interval, 0.88-1.41).9 The association is more evident in childhood asthma; the risk developing asthma at later stage is higher in children with eczema in the first year of life and the combined filaggrin mutations.10 Another report demonstrates that filaggrin variants increase the risk of developing recurrent wheeze and asthma within the first one and half year of life.11 Filaggrin gene mutations also affect the severity of asthma; individuals with filaggrin null alleles carry a significantly increased risk of exacerbations requiring hospital admissions, courses of oral steroids, or experiencing school absences11,12. Filaggrin is required for the maintenance of skin barrier function in the cornified layer of the skin as discussed in detail in the review by Osawa et al. in this journal. The association with filaggrin gene mutations is the first solid evidence that skin barrier function is important for the development of asthma in the childhood. Another pediatric asthma-susceptibility gene, ORMDL3 on chromosome 17q21, has been identified by a genome-wide association study.13 A meta-analysis suggests the OR of 1.44 (95% confidence interval, 1.35-1.54) for the association between ORMDL3 and asthma.14 Recent studies using yeasts and cultured cells have clarified the functions of ORMDL3 as the regulator of sphingolipid synthesis and unfolded protein response in endoplasmic reticulum.15,16 Interestingly, integrity of skin barrier depends on the presence of adequate amount of ceramide and sphingosine, implying that ORMDL3 mutations may also be associated with disturbance of skin barrier function.  

**IMMUNOLOGICAL INTERACTIONS OF ALLERGENS AND DANGER SIGNALS WITH THE SKIN MODIFY THE DEVELOPMENT OF ATOPY AND ASTHMA (Table 2)**

It has long been speculated that the proteases in allergens such as mites, fungi, or pollen digest the epithelial barrier-related protein and assist allergenic protein/peptide to enter into the sub-epithelial layer. In fact, proteolytic enzymes often act as the key components of allergens, for example, a cysteine protease (Der p1) in house dust mite (*Dermatophagoides pteronyssinus*),17,18 serine proteases (Asp f13 and f18), an aspartic protease (Asp f10), and a metalloprotease (Asp f5) in *Aspergillus fumigatus*. Protease activities in
Table 2  The immune responses induced by the combination of allergen, danger signal, and route of allergen entry

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Danger signal</th>
<th>Route of allergen entry</th>
<th>Th2</th>
<th>Th17</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA</td>
<td>alum</td>
<td>airway</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>OVA</td>
<td>lipopolysaccharide</td>
<td>peritoneal cavity</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>OVA</td>
<td>protease</td>
<td>airway</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>HDM / Fungus</td>
<td>机械损伤?</td>
<td>skin</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
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OVA, ovalbumin; HDM, House dust mite extract.

Fig. 1 Interaction of allergen, danger signals, and barrier-related molecules during the sensitization and following immunological responses to allergen. Simple antigen (such as ovalbumin) application does not provoke asthmatic phenotypes. Co-administration of danger signals such as protease, LPS, or mechanical damage of epithelial/epidermal layer (1) and the altered skin barrier functions due to the genetic mutation of barrier-related molecules (filaggrin et al.) (2) induces the release of inflammatory mediators including TSLP and activates antigen-presenting cells (3), leading to Th2 and Th17 cell differentiation and activation (4). Th2 and Th17 cells (5) contribute to the development of airway hyperresponsiveness.

the allergens appear to be crucial for the allergic sensitization process; repeated administration of mite or fungus extracts into the airway easily induces airway hyperresponsiveness and eosinophilic inflammation,19-22 whereas an innocent extrinsic protein without proteolytic activity such as ovalbumin (OVA) fails to cause these phenotypes in the absence of adjuvant. In contrast, epicutaneous exposure to OVA alone followed by airway exposure, without alum or other adjuvant, induces elevated serum IgE levels, Th2 cytokine production, nasal symptoms, and airway hyperresponsiveness.23-25

In the last decade, however, another hypothesis on the interaction between the proteases and epithelial/epidermal barrier during allergic sensitization has emerged. An intraperitoneal injection of OVA, although epidermal barrier is bypassed, is insufficient for the sensitization, and the co-injection of an adjuvant, alum, is required to provoke a strong Th2-type inflammation and airway hyperresponsiveness. In this setting, alum acts as a danger signal that alarms the antigen-presenting cells such as dendritic cells,
resulting in the formulation of NLRP3 inflammasome and activation of caspase-1 that matures IL-1β and IL-18 into the biologically-active forms.26,27 Proteases in the allergens may similarly serve as a danger signal to facilitate the immune response. Other than alum or proteases, addition of small amount of lipopolysaccharide or Der p2 in house dust mite that is structurally related to LPS promotes the sensitization.28,29

Mechanical damage of the skin such as scratching may serve as the danger signal during the epicutaneous sensitization, but little is known about this process. Meanwhile, the molecules that may transduce the signals from the skin to the airways following epicutaneous sensitization are getting clarified in the past few years (Fig. 1). The airway responses induced by epicutaneous sensitization (without alum) are mediated by Th2 cytokines, CCR3 chemokines, and STAT6 signaling, similarly to the response caused by intraperitoneal sensitization (with alum).30,31 However, the contribution of IL-4 and IL-13, which is critical for the intraperitoneal sensitization protocol, is less important for the epicutaneous sensitization.24,32,33 As we previously reported, OVA-specific IgG1 response occurs more robustly in Th2-prone BALB/c mice, but airway inflammation and hyperresponsiveness is more prominent in C57BL/6 mice when sensitized through the skin.24 One of the characteristic features for the epicutaneous exposure of allergens is successive Th17-type response with the increased production of IL-17A and IL-23 in the skin, lymph nodes, and spleen, in addition to Th2-type reaction.34 Importantly, flaky tail mice with a mutation in the filaggrin gene demonstrate an exaggerated Th17 response in response to epicutaneous application of ovalbumin to shaved skin.35 There are lines of evidence suggesting that IL-17A and Th17-type response may be related to the development of severe asthma; expression of IL-17A in the airway of asthma patients is proportional to the severity of the disease.19,36 Th17 cells instilled into the airways promote the airway hyperresponsiveness synergistically with Th2 cells.37 Taken together, Th17 cytokines are essential for the airway pathology induced by epicutaneous sensitization.

Thymic stromal lymphopoietin (TSLP) is another mediator possibly released from the skin or other organs upon epithelial/epidermal damage. Disruption of epithelial barrier, either mechanically or functionally, causes TSLP release.38-40 Once it is released from epithelial/epidermal cells, TSLP leads to Th2-deviated inflammation through antigen presenting cells, T cells, B cells or mast cells.41,42 Cutaneous injection of TSLP alone causes Th2-mediated lung inflammation and airway hyper-responsiveness.39,43 It is, however, still undetermined how the impaired skin barrier is related to the modulation of TSLP synthesis.

CONCLUSION

Although asthma can now be controlled with inhaled corticosteroids and other medications in most cases, some asthmatics, including patients with early-onset atopic asthma, develop the disease refractory to current treatment. Furthermore, even an early introduction of therapy with inhaled corticosteroids in childhood is unable to cure or prevent the development of asthma, showing another limitation of the current treatment strategy of asthma. The discovery of filaggrin gene mutations in patients with eczema-associated asthma re-vitalized the old concept of “atopic march”. We hope that detailed analysis of the pathway for the allergic phenotypes to shift from the skin to the airways would possibly leads to the identification of novel tactics to prevent and treat allergic airway diseases.

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