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## Editorial

## Barrier dysfunction in allergy

In *Allergology International* (AI) Vol. 67, Issue 1, we feature a set of review articles entitled “Barrier dysfunction in allergy” as well as original articles and letters to the editor. We believe that this issue will be of great help in understanding how barrier disruptions are associated with the onset of allergy in barrier organs, which may lead to the prevention of allergic diseases.

The barrier organs—such as the skin, lung, gut, and nasal cavity—cover the entire body and protect us from the external environment. When these barriers are impaired, external toxins penetrate the body and induce inflammation to defend against them. Over the last decade, many studies have demonstrated that barrier dysfunction is a critical component of allergy.<sup>1–3</sup> In particular, inherited defects in epidermal barrier proteins, such as filaggrin, facilitate the interaction of external antigens with skin-resident immune cells, driving local inflammation that can also lead to systemic immune responses.<sup>4,5</sup> This is the “outside-in” hypothesis of atopic dermatitis pathogenesis, and it helps to explain why atopic dermatitis sufferers have an increased risk of developing food allergies, asthma, and allergic rhinitis later in life, known as the “atopic (allergic) march”.<sup>6</sup> These observations suggest that maintaining the skin barrier function is important for both effectively managing atopic dermatitis and preventing subsequent allergic diseases.

In this review article series, Egawa and Kabashima summarize how the physical barrier of the skin is organized and review its link to the pathogenesis of skin allergic diseases, such as atopic dermatitis, from the perspective of the stratum corneum components: 1) filaggrin metabolism, 2) cornified envelope, 3) intercellular lipids, 4) corneodesmosome, and 5) corneocyte desquamation.<sup>7</sup> Gon and Hashimoto summarize the pathogenesis of bronchial asthma, characterized by the hyper-responsive, chronically inflamed airways. Damage to the barrier functions of the airway epithelium enhances mucosal permeability of foreign substances, leading to the release of epithelial cytokines (e.g. TSLP, IL-25, and IL-33), which then activates dendritic cells, Th2 cells, and type 2 innate lymphoid cells to cause allergic airway inflammation.<sup>8</sup> Fukuoka and Yoshimoto summarize the functions of tight junctions, a cell–cell junctional complex located on the apical side of epithelial cells. And they review an interesting observation that diesel exhaust particles, the main component of particulate matter 2.5 (PM<sub>2.5</sub>), exacerbated allergic rhinitis in a mouse model through tight junction disruption.<sup>9</sup> These findings suggest that controlling barrier functions is important to prevent allergies, which is in line with a paradigm shift away from avoidance and delayed

introduction of allergenic foods. Natsume and Ohya show the increased importance of preventing eczema/atopic dermatitis in infancy.<sup>10</sup> Two randomized controlled trials using emollients showed successful results in preventing infant atopic dermatitis.<sup>11,12</sup> Taken together, recent findings on barrier dysfunctions in allergy have revealed the pathogenesis of allergic diseases and pointed the way to novel strategies to control allergic diseases.<sup>13</sup>

During the 2015 enterovirus D68 epidemic, both an unusual cluster of children with acute flaccid paralysis and a high rate of hospitalization of asthmatic children were observed. Korematsu *et al.* report the results of a nationwide retrospective survey conducted by the Japanese Society of Pediatric Allergy and Clinical Immunology. Their analysis confirms the association between the unusual increase in acute asthma hospitalizations of children and the enterovirus D68 epidemic in September 2015 in Japan.<sup>14</sup> To verify a causative role for a respiratory virus in exacerbating asthma in children, surveillance systems for asthma and respiratory infectious pathogens have been shown to be essential.

The pathogenesis of mild persistent asthma in children, and optimal treatments for it, remain elusive. Nagao *et al.* performed a randomized, controlled trial of treatment of preschool children with mild persistent asthma using a leukotriene receptor antagonist (LTRA), montelukast, daily for 48 weeks [recommended by Japanese Guideline for Childhood Asthma (JGCA)]<sup>15</sup> or as-needed  $\beta_2$ -agonist(s) (recommended by GINA and EPR-3 guidelines).<sup>16–18</sup> LTRA significantly reduced acute exacerbations and the percentage of children needing step-up treatment. These results not only demonstrated the superiority of the JGCA guideline, but also suggested the involvement of cysteinyl leukotrienes in the exacerbation and progression of childhood asthma.

Oguma *et al.* report the first nationwide survey of allergic bronchopulmonary aspergillosis (ABPA) in Japan, one of the largest studies examining the clinical characteristics of this disease worldwide.<sup>19</sup> ABPA is an allergic pulmonary disease characterized by a hypersensitivity reaction to *Aspergillus* species colonizing the airways. They summarized 358 cases meeting the criteria for possible ABPA-central bronchiectasis (ABPA-CB) taken from 499 physician-diagnosed cases reported by 132 clinical centers. This survey identified several unique clinical characteristics of ABPA in Japan compared to other countries: late onset (median: 57 years); relatively lower serum IgE levels, particularly in late-onset patients; and frequent recurrences/flare (48%). These patients do not meet the current diagnosis criteria; therefore, some modification of these criteria is needed for this phenotype of ABPA.

Japanese cedar pollinosis, including allergic rhinitis and conjunctivitis, has been considered a national affliction in Japan,

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with a prevalence of >25%.<sup>20</sup> Fukuda *et al.* demonstrated that feeding mice suffering from allergic conjunctivitis caused by Japanese cedar with transgenic rice expressing two major allergens of Japanese cedar pollinosis, Cry j 1 and Cry j 2, ameliorated the disease.<sup>21,22</sup> The allergens of Japanese cedar pollinosis are expressed as fragmented and shuffled sequences in the transgenic rice in order to eliminate IgE reactivity, not to cause adverse anaphylactic reaction. The rice-based edible allergen vaccine for Japanese cedar pollinosis is potentially effective and safe for oral immunotherapy in people suffering from this condition.

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#### Conflict of interest

The authors have no conflict of interest to declare.

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