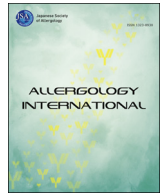




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Editorial

Innate lymphoid cells open a new window on allergic diseases



In *Allergy International* (AI) Vol. 64 No. 3, we offer a set of review articles entitled “Innate lymphoid cells open a new window on allergic diseases” as well as original articles and letters to the editor. We believe that this review series will provide you with the latest concepts in the area of group 2 innate lymphoid cells, recently emerged as important in the pathogenesis of allergic diseases.

The first evidence of “innate” type 2 immune response was observed 15 years ago, when interleukin (IL)-25 administered in mice was found to increase the eosinophil numbers and type-2 cytokines (IL-4, IL-5, IL-13) independently of T and B cells.¹ Kondo and colleagues, in 2008, also reported that IL-33 could induce eosinophilic inflammation in the airways in the absence of lymphocytes, mast cells, basophils, and other known immune cells.² These findings suggested the presence of an unidentified innate immune cell population that produces type-2 cytokines in response to IL-25 and IL-33 without antigen presentation.

The new era of research on “innate-type allergy” began in 2010 when Moro and colleagues discovered a new type of cells in a mesenteric lymphoid cluster and named them natural helper (NH) cells.³ NH cells express neither antigen-specific receptors nor lineage markers on the cell surface, but produce large amounts of IL-5 and IL-13 in response to IL-25 or IL-33. In 2013, innate lymphoid cells were classified into three subsets: group 1 cells that produce IFN- γ ; group 2 cells that produce IL-4, IL-5, and IL-13; and group 3 cells that produce IL-17 and/or IL-22.⁴ NH cells, nuocytes, and innate helper 2 cells are classified as group 2 innate lymphoid cells (ILC2s).

Although ILC2s were first described as a part of the innate immune system essential for eliminating intestinal parasites, two important findings have suggested possible roles for ILC2s in the pathophysiology of allergic airway and skin diseases. First, IL-25 and IL-33 can be synthesized in the epithelial and endothelial cells of these organs in response to non-parasitic microorganisms (viruses and fungi), protease allergens, or other damage-associated molecular patterns such as uric acid. Secondly, ILC2s are present in the upper and lower respiratory tracts and the skin where these pathologies occur. The review series “Innate lymphoid cells open a new window on allergic diseases” includes three updated and detailed review articles about ILC2s and their relationship with allergic airway diseases, especially asthma and rhinosinusitis. First, Kita provides information about the role of ILC2s in allergic airway inflammation and allergic diseases caused by fungal allergens.⁵ Kabata *et al.* discuss the similarities and differences between

ILC2s in mice and humans and review their role in a murine model of asthma and in human asthma.⁶ Matsushita *et al.* review the role of ILC2s in two allergic upper respiratory diseases, chronic rhinosinusitis with nasal polyps and allergic rhinitis.⁷

However, there remain many unresolved questions about ILC2s and their relationship to allergic diseases. Researchers have yet to elucidate (1) the interrelationship between ILC2-mediated innate immune responses and Th2 cell-mediated adaptive immunity; (2) the homeostatic functions of ILC2s that reside in the respiratory and digestive organs or the skin, as well as in the brain, heart, muscle, liver, and adipose tissue; (3) the precise distribution and functions of human ILC2s and their relationship to human diseases; or (4) the possibility of targeting ILC2s to treat allergic diseases.

Two articles regarding eosinophilic gastrointestinal disorders (EGID) appear in this issue.^{8,9} EGID are chronic inflammatory disorders characterized by primary eosinophilic infiltration to the gastrointestinal (GI) tract without any overt cause. EGID are classified into eosinophilic esophagitis (EoE), characterized by eosinophilic infiltration limited to esophagus, and eosinophilic gastroenteritis (EGE), characterized by eosinophilic infiltration into any part of the GI tract. The exact etiology of EGID is unknown, although it is assumed that EGID has some allergic background. Moreover, in spite of the recently increased prevalence of EGID as well as other allergic diseases,^{10,11} we have only a little epidemiological information about EGID.

Ito *et al.* searched the literature related to EGID (687 records) using PubMed and compared Caucasian and Asian (South Korea, China, Taiwan, and Japan) cases in 121 studies fulfilling the eligibility criteria.⁸ They found that EoE was dominant in Caucasian cases, whereas EGE was dominant in Asian cases, particularly in adults. According to this different distribution, Caucasian cases showed more dysphagia and heartburn, whereas Asian cases showed more vomiting, abdominal pain, and diarrhea. Some factors such as genetic predisposition, diet habits, or *Helicobacter pylori* infection may have caused this difference. Although the exact connection between etiology and ethnic difference is unknown at this moment, this finding shows an important characteristic of EGID.

Shoda *et al.* assessed the gene profile expressions of esophageal biopsies from four Japanese adult EoE patients and compared them with the data from US patients with EoE to clarify ethnic differences with regard to EoE etiology.⁹ They found that several IL-13-inducible genes—cadherin-like 26, pro-melanin-concentrating hormone, eotaxin-3, arachidonate-15 lipoxigenase, periostin, and Charcot-Leyden Crystals—were significantly upregulated in EoE patients. These genes overlapped very well with the profiles from US patients, although the details of the ethnic

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distribution in US patients are unstated, suggesting that the pathogenic backgrounds EoE would be the same in Japan and Western countries. The mystery of how EGID occurs and why the distribution of EGID would differ in Western and Asian countries continues.

We offer our appreciation to all the authors for their contributions to the present issue of *Allergy International*.

Conflict of interest

The authors have no conflict of interest to declare.

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