Beyond Th2, more than ILC2

In Allergology International (AI) Vol. 66, Issue 3, we offer a set of review articles entitled “Beyond Th2, more than ILC2” as well as original articles and letters to the editor. We believe that this issue will be of great help in understanding how several newly emerging cells shape type 2 inflammation.

We can say that the discovery of IgE by Ishizaka in 1966 opened the door to molecular research in allergy. The explosive development of molecular biology and immunology, beginning in the 1970s, has expanded our understanding of the underlying mechanisms of allergic inflammation. The biggest breakthrough in this field would be the Th1/Th2 paradigm proposed by Mosmann and Coffman in 1986.1 This theory proposed that there exist Th1 cells and Th2 cells in helper T cells and that these cells show different cytokine production profiles and play different pathophysiological roles. Then based on this theory, it became widely accepted in the 1990s that Th2 cells play a crucial role in the pathogenesis of allergic diseases. Moreover, this knowledge has now led to the development of novel agents against allergic diseases targeting signature type 2 cytokines—IL-4, IL-5, and IL-13—produced by Th2 cells. The development of immunology after 2000 has furthermore shaped the details of type 2 inflammation, originally thought to be caused by Th2 cells. The discovery of innate lymphoid cells (ILCs) is one of the most important successes, and right now ILC2 is receiving great attention as the cells that initiate type 2 inflammation.2 However, ILC2s are not the only newly emerging cells that have appeared to be involved in type 2 inflammation. This review series highlights several such cells under investigation by expert researchers.

Prof. Nakayama’s group first introduces memory-type pathogenic Th2 (Tpath2) cells.3 Tpath2 cells are phenotypically and functionally distinct from the usual Th2 cells and produce a large amount of IL-5. Since these cells survive and continue to function at the infiltrated sites, they are important in chronic inflammation. Next, Prof. Kubo explains follicular helper (Tfh1) cells.4 Tfh1 cells are a subset of CD4+ helper T cells and play a critical role in antibody maturation in germinal center. IgG and IgG1 antibody responses, important events in type 2 inflammation, are mainly controlled by IL-4–secreting Tfh1 cells, not by Th2 cells. Then Prof. Karasuyama’s group discusses the roles of basophils in allergic inflammation.5 Basophils have long been neglected in immunological studies as only minor relatives of mast cells. However, it has recently turned out that basophils play non-redundant roles in both IgE-dependent and -independent allergic inflammation. It is of note that basophils supply large amounts of IL-4 in response to various stimuli. Lastly, Prof. Nakajima’s group introduces alternatively activated macrophages (M2 macrophages).5 Currently, macrophages are divided into classically activated macrophages (M1 macrophages) and M2 macrophages. M2 macrophages are differentiated by IL-4 or IL-13, signature type 2 cytokines. It is generally accepted that M2 macrophages suppress type 1 inflammation and accelerate tissue repair, phagocytosis, angiogenesis, and fibrosis. However, recent findings indicate that M2 macrophages possess remarkable plasticity and may exacerbate inflammation by producing pro-inflammatory cytokines such as IL-1β, IL-6, and TNFz like M1 macrophages. This review series will help you to understand the latest concepts supporting the roles of these cells play in allergic inflammation.

Prof. Furue et al. contribute an excellent review article about atopic dermatitis (AD).7 This article underscores the importance of the TSLP/Th2/T22 pathway in the underlying immune responses in AD. TSLP release is triggered by activation of ORAI1, a calcium channel in keratinocytes, leading to initiation of Th2 and T22 responses. This article then explains that IgE autoreacting to membrane or intracellular proteins of keratinocytes may precipitate the chronicity of AD. The authors lastly introduce new strategies and therapies in treating AD, including the agents targeting IL-4/IL-13 and IL-31, a downstream molecule of type 2 inflammation important for itching.8

A lot of attention has been paid to biomarkers in treating asthma. Nagasaki et al. contribute an interesting and timely review article about fraction of exhaled nitric oxide (FeNO) and periostin, both of which are now widely accepted as biomarkers reflecting type 2/eosinophilic asthma.9–13 In this article, they briefly summarize the strengths and weaknesses of these two biomarkers individually, and then they show the results of taking a combinational approach with these biomarkers. They found that patients with both high FeNO (≥25 ppb) and periostin (≥95 ng/mL) showed high frequency of asthma exacerbation compared to patients with high levels of each biomarker alone, reflecting severe type 2/eosinophilic airway inflammation. They also analyzed the genotypes correlated with FeNO and periostin levels. Such a multiple-marker approach would be useful in the future for realizing precision medicine to select therapeutic agents for asthma.

The mammalian circadian clock system, consisting of the central oscillator located in the suprachiasmatic nucleus of the hypothalamus and the peripheral oscillator in virtually all cell types, drives daily oscillations of behavior and physiology such as sleep-wake cycles and hormonal secretion and may be linked to temporal variations of allergic symptoms. Kawauchi et al. in this issue show how
the IL-33 responses in mast cells are regulated by the circadian clock system. They found that CLOCK, a transcriptional factor correlating with the circadian clock in peripheral cells, regulates expression of ST2, the receptor molecule of IL-33, causing a time-of-day-dependent variation in IL-33 responses in mast cells. The authors’ group has previously shown that IgE-mediated mast cell responses such as degranulation exhibit a time-of-day-dependent variation in which CLOCK regulates the expression of the β subunit of high-affinity IgE receptor (FceRIβ). These findings together could clarify the underlying mechanism of how circadian rhythm affects the symptoms of allergic patients.

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

Conflict of interest
The author has no conflict of interest to declare.

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