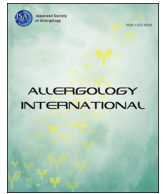




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Editorial

The start of a new era of biologics for treating allergic diseases

The 1966 discovery of IgE by Profs. Kimishige and Teruko Ishizaka was a breakthrough in our understanding of how allergic reactions occur at the molecular level. Since then, as the field of immunology has progressed, our understanding of the underlying mechanism of allergic reactions has been well advanced. In particular, an important milestone was reached in 1986 when Mosmann and Coffman proposed the Th1/Th2 paradigm,¹ which was the basis of the concept that type 2 inflammation is primarily responsible for allergic reactions. IL-4, IL-5, and IL-13 are signature cytokines of type 2 inflammation. In the 1990s, a controversy over which cytokine was dominant in the pathogenesis of mouse models of asthma led to the conclusion that each of these cytokines plays a role, particularly in the pathogenesis of asthma patients from different backgrounds. After 2000, several epithelial cytokines—IL-25, IL-33, and TSLP—were discovered,^{2–4} highlighting the importance of epithelial cells as the first line for allergic reactions. Subsequently, group 2 innate lymphoid cells (ILC2), discovered in 2010, provided us with the missing link between innate and acquired immunity in allergic reactions,^{5,6} shaping our present understanding of how allergic diseases arise.

IgE, the molecule with the longest history in the mechanism of allergic reactions, was targeted to develop the first biologic for allergic diseases. Omalizumab, anti-IgE Ab, was approved for asthma worldwide in 2002–2009. The application of omalizumab has since been expanded into chronic spontaneous urticaria (CSU) and Japanese cedar pollinosis. Then signature type 2 cytokines were targeted to develop molecularly targeted drugs for allergic diseases. Abs targeting IL-5 or anti-IL-5 receptor (IL-5R) — such as mepolizumab, reslizumab, and benralizumab — were approved for asthma in 2015–2018. Moreover, mepolizumab was approved for eosinophilic granulomatous with polyangiitis (EGPA) in 2017–2018. Dupilumab, anti-IL-4R Ab, blocking both IL-4 and IL-13 signals, was applied to atopic dermatitis (AD) in 2018, to asthma in 2019, and recently to chronic rhinosinusitis with nasal polyps (CRSwNP). However, this is just the start of a new era of biologics for treating allergic diseases. Clinical trials of biologics targeting epithelial cytokines such as TSLP and IL-33 for allergic diseases are now underway. Moreover, several chemokine/chemokine receptors are currently being examined for the development of biologics targeting these molecules. In the near future, more biologics for allergic diseases are certain to be added to the lineup.

We feature a set of review articles in this issue that includes four articles dealing with the biologics targeting IgE, IL-5/IL-5R, and IL-4R, all of which are already available for treating allergic diseases, and anti-TSLP Ab, which we can expect will soon appear on the

market. Many distinguished Japanese researchers, from basic to clinical science, and beyond specialties in allergic diseases, contributed to these articles.

Profs. Okayama, Matsumoto, Odajima, Hide, and Okubo summarize the roles of IgE in allergic conditions, about 10 years of experience of omalizumab for severe allergic asthma, and treatment of CSU and severe Japanese cedar pollinosis by omalizumab.⁷ Notably, omalizumab is useful in childhood as well as in adult asthma.

Profs. Nagase, Ueki, and Fujieda explain the roles of eosinophils in allergic diseases and application. They also describe the clinical trials of three IL-5/IL-5R antagonists—mepolizumab, reslizumab, and benralizumab—to asthma, EGPA, and CRSwNP.⁸ The success story of mepolizumab is a pioneering work of stratified medicine in allergic diseases. Moreover, it is interesting to know how different it is to target IL-5 versus IL-5R to deplete eosinophils.

Profs. Matsunaga, Kato, and Fujieda and I explain basic aspects of dupilumab regarding IL-4 and IL-13 signals and its application to allergic diseases.⁹ Dupilumab was the first biologic approved for AD and CRSwNP and is also approved for uncontrolled asthma. Many clinical trials are now underway for other allergic diseases in which the IL-4 and IL-13 signals are thought to play an important role.

Profs. Kabashima and Asano report the role of TSLP as a master regulator of type 2 inflammation and application of tezepelumab, anti-TSLP Ab, for AD and asthma.¹⁰ The phase 2 study for moderate to severe AD was completed with promising but not fully satisfactory results, and the phase 3 study for severe asthma is in progress. It is of note that in the phase 2 study for asthma patients, tezepelumab showed efficacy irrespective of type 2 or non-type 2 biomarkers of the patients.

Thus, an era when many biologics are available for allergic diseases is on the horizon. But we need to resolve several critical problems before we reach such an era. For example, using biomarkers, we need to stratify allergic patients based on endotypes to identify which allergic patients are responsive to which biologic. Moreover, a major challenge will be to develop new biologics for allergic patients who are resistant to available biologics, particularly for non-type 2 asthma patients. By resolving these problems, we can realize precision medicine for allergic diseases.

Conflict of interest

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