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Editorial

Immunological memory and allergic diseases

Immunological memory refers to the ability of the immune system to respond more rapidly and effectively to pathogens/antigens/stimuli that have been encountered previously. Research on immunological memory got its start in relation to the immune response to viral infections, i.e., type 1 immunity,¹ and this continues to be the main focus during the current SARS-CoV-2 pandemic.^{2,3} However, immunological memory is also critically involved in the pathophysiology of allergic diseases, since allergic symptoms are induced upon each successive exposure to the eliciting allergen. Following the discovery of IgE by Profs. Kimishige and Teruko Ishizaka in 1966, research on immunological memory's role in allergic diseases, i.e., type 2 immunity, has seen much progress. In this issue, we feature a set of review articles on immunological memory written by three outstanding research groups who have made key discoveries on the roles of B cells, T cells and innate lymphoid cells (ILCs).

B cells are one of the key cell types that play a central role in immunological memory. In the case of viral infections (type 1 immunity), the generation of long-lived plasma cells that produce high-affinity antigen-specific IgG and long-lived memory B cells is the main immunological memory mechanism that provides life-long protection against offending pathogens.⁴ However, in the case of allergic diseases, the mechanisms underlying immunological memory have only recently come to be better understood.

Haniuda and Kitamura⁵ focused on the differences in the characteristics of IgE production and IgE's affinity and specificity between physiological conditions—such as immune responses to parasite infections, bee sting venom, etc.—and allergic diseases. In physiological conditions, IgE production is transient, and the serum IgE level does not persist for a long time, partly because of the short half-life of the IgE. In addition, the IgE produced in this setting is antigen-nonspecific or has extremely low affinity. On the other hand, in allergic diseases the serum IgE persists even in the absence of re-exposure to the eliciting allergen, and the IgE is antigen-specific and functional. Based on these facts, they explain the underlying mechanisms of IgE production in allergic diseases and point out issues that need further investigation.⁵

T cells are another key cell type involved in immunological memory. Recent progress in this area includes discovery of heterogeneity of memory T cells. New technologies such as lineage tracing

and single-cell RNA-sequencing enable determination of the localization, dynamics and characteristics of specific cell types at the single-cell level. As a result, it is becoming clear that memory T cells are heterogeneous in terms of localization and function. Hirahara, Aoki and Nakayama⁶ summarize the current knowledge regarding a novel memory T-cell subset, i.e., pathogenic Th2 cells (Tpath2), which is more highly functional. They also discuss the heterogeneity of Tpath2, including IL-5-producing Tpath2 and amphiregulin-producing Tpath2, and explain their functional differences.

Immunological memory was considered to be an exclusive hallmark of the adaptive immune system. However, a growing body of literature shows that the innate immune system is also able to enhance its response to earlier insults, which was proven by protection against re-infection of invertebrates lacking an adaptive immune system. This memory-like property of the innate immune system is now referred to as “trained immunity”. Ebihara *et al.*⁷ summarize the current knowledge regarding trained immunity of group 2 innate lymphoid cells (ILC2s) and its epigenetic regulation. They also propose a new facet of trained immunity of ILC2s, that is, that they become immune suppressive or less functional, similar to the concept of T-cell exhaustion.

Our understanding of immunological memory continues to evolve and is undoubtedly not yet fully understood. We hope that further clarification of the immunological memory of B cells, T cells and ILCs will lead to development of new preventive and therapeutic strategies for allergic diseases.

Conflict of interest

The author has no conflict of interest to declare.

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