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Mast Cells in Allergic Diseases

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Mast cells were named after the Greek word ‘mastos’, which means breast, in 1878 by Paul Ehrlich because he believed that the intracellular granules contained nutrients. The discovery of IgE and its association with mast cell histamine release provided the initial understanding of the role of mast cells in asthma and acute allergic reactions. Thus, the cross-linking of high-affinity IgE receptors on mast cells was regarded as the essential mechanism involved in allergic diseases and was the major target for the therapeutic development of drugs. After the 1980s, allergic inflammation characterized by eosinophil recruitment into tissues was found to be essential in asthma pathology. Then, inhaled corticosteroids, which prevent eosinophilic inflammation but not mast cell degranulation, were widely recognized as the first-line therapy for asthma. The role of mast cells was thus considered relevant only for the early asthmatic response to allergen challenge, but less involved in asthmatic reactions found in patients having chronic symptoms.

Recently, the difference between asthma and eosinophilic bronchitis lacking airway hyperresponsiveness and airflow obstruction was found to be infiltration of airway smooth muscle by mast cells [1]. Mast cells produce a variety of lipid mediators, chemokines, cytokines, and enzymes that may interact with airway smooth muscle cells and cause hyperreactivity to constrictive stimuli and proliferation.

More recently, Oguma et al. [2] have described an exemplary investigation of the prostaglandin D₂ (PGD₂) receptor gene (PTGDR) as a candidate for a role in the susceptibility to asthma in young adults. PGD₂ is almost exclusively produced by activated mast cells but not other cell types and can evoke airway
hypersensitivity and the chemotaxis of T cells, eosinophils and basophils through interaction with two different receptors: one is prostanoid DP receptor (translated from \textit{PTGDR}) and the other is chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2).

Cytokines generated by both resident and freshly recruited cells are responsible for the initiation and coordination of many local processes, including allergic inflammation and tissue remodeling. In IgE-dependent allergic inflammation it would be logical to expect that the mast cell would generate a spectrum of cytokines directed at initiating and maintaining allergic inflammation. Indeed, human mast cells were found to generate multiple cytokines and chemokines, which activate a variety of cell types including T cells and eosinophils.

Mast cells are now recognized as tissue-dwelling effector cells that play multiple roles not only in immediate-type allergic reaction but also in innate immunity, inflammation, angiogenesis, and tissue remodeling. In this book, we have focused on the roles of mast cells in allergic diseases and discuss the future direction of discovering drugs. Another implication of this book is to understand mast cells at the system level. System biology is a research category to understand biology at the system level by examining the structure and dynamics of cellular and organismal functions, rather than the characteristics of isolated parts of a cell or organism [3]. Understanding the properties of systems may have an impact on the future of medicine. The most feasible application of systems biology research is to create a detailed model of cell regulation, focused on particular signal-transduction cascades. It is expected to provide system-level insights into mechanism-based drug discoveries. Such models may help to identify feedback mechanisms that offset the effects of drugs and predict systemic side effects.

\textit{Hirohisa Saito, Tokyo}

\textbf{References}