Since their discovery by Paul Ehrlich in 1879, eosinophils have been regarded as a central player in the pathogenesis of allergic diseases such as atopic dermatitis, bronchial asthma, and allergic rhinoconjunctivitis. Eosinophils have a thousand disguises — including beneficial, detrimental, regulatory, hemostatic, and complementary effects — on inflammation and immunity. The present issue of Allergology International features four outstanding reviews presenting new insights into the eosinophil world in allergic diseases.

Eosinophils are basically defined morphologically like other immune cells such as lymphocytes and dendritic cells. Lymphocytes are classified into several subpopulations such as T cells, B cells, and innate lymphoid cells (ILCs) by cell surface markers and genes. Similar attempts have been made to determine whether eosinophils have subtypes associated with diverse functions. Traditionally, there are two types of eosinophils based on density, called normodense and hypodense, of which the latter show higher cytotoxic abilities. In the present issue, Aoki and Hirahara et al. and Kanda et al. review the modern classification of eosinophil subtypes, including resident and inducible eosinophils, in steady-state and pathological conditions, respectively. In addition, Kanda et al. suggest that morphology-based normodense and hypodense eosinophils are nearly the same as surface phenotype-based resident and inducible eosinophils, respectively. Of note, resident eosinophils express genes implicated in the negative regulation of immune responses, suggesting that this subtype is involved in the regulation and homeostasis of immune responses and subsequent tissue inflammation.

Fibrosis is the major hallmark of tissue remodeling, resulting from abnormal repair. Although eosinophils are involved in tissue repair and regeneration by secreting IL-4, chronic activation of eosinophil plays a role in tissue fibrosis. Aoki and Hirahara et al., based on their outstanding findings, review how eosinophils promote airway fibrosis. They clearly show that memory-type pathogenic Th2 cells expressing ST2, the receptor for IL-33, release amphiregulin in response to IL-33. Amphiregulin binds to epidermal growth factor receptor (EGFR) on eosinophils, leading to the secretion of osteopontin, an extracellular matrix protein associated with tissue fibrosis.

Eosinophil extracellular cell death (EEToSis) is one of the hottest topics in the field of eosinophil research. EEToSis is the active non-apoptotic cell death of eosinophils, which releases DNA fibers. Patients with eosinophilic chronic rhinosinusitis (ECRS), the typical type 2 inflammation in the upper airway, show very viscous and sticky nasal discharge that resembles the mucus plugs observed in bronchial asthma of the lower airway. Every researcher handling DNA, e.g., for gene analysis, knows well that DNA is very sticky. After the discovery of EEToSis, we can imagine why patients with ECRS have such sticky nasal discharge. In the present issue, Fukuchi and Ueki et al. demonstrate how to detect EEToSis and extracellular traps using shear stress and bacteria-sized microbeads, and we can see that extracellularly spread DNA traps the microbeads like a “spider web.” They also include a unique cartoon of their own creation, called “EOSMAN,” which illustrates the fate of eosinophils. Readers will feel their love for eosinophils.

There is no doubt that the major histological characteristic of eosinophils is the presence of acidophilic cytoplasmic granules. In this issue, Gigon and Simon et al. review the current understanding of the mechanisms of toxicity of eosinophil granule proteins together with neutrophil granule proteins. Using as an example primary granule proteins, they discuss the Charcot-Lyden crystal (CLC) protein, also known as galectin-10. Although CLC was identified in 1853, earlier than the discovery of eosinophils, the precise characterization of CLC has not been fully understood. However, attention has been focused again on CLC protein/galectin-10 because CLC is formed during the process of EEToSis. In addition, CLC protein/galectin-10 itself can promote type 2 inflammation.
We hope that the present reviews will enable our readers to understand current insights into eosinophils in allergic diseases.

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