Homage to Mechnikov – the phagocytic system: past and present

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More than 100 years ago, the Russian scientist Ilya Ilyich Mechnikov (1845–1916) first proposed that our cells eliminate foreign pathogens such as bacteria by engulfing and destroying them, thereby protecting our body from infectious diseases. Legend has it that the idea hit him while at the beach during summer vacation. It is said that he was watching a starfish (which looks like macrophage cell, does not it?) as it internalized a rose thorn stuck in its body. It is a nice story, but I am not sure about its veracity (Fig. 1).

This system, called the “phagocytic system,” is now known to be involved in the elimination of not only foreign pathogens but also self-pathogens, including dead cells, cancer cells, unfolded proteins, advanced glycation end products, and damage-associated molecular patterns (DAMPs). As all of these can be thought of as “buds of disease,” the phagocytic system plays a crucial role in the prevention of multiple diseases and maintaining the body’s homeostasis. In addition, accumulating evidence has demonstrated that along with professional phagocytes like macrophages, other various epithelial cells in different organs also can act as phagocytic cells (i.e., non-professional phagocytes). Non-professional phagocytes express various types of scavenger receptors on their cell surfaces on demand, and thus help contribute to the removal of self-pathogens. As we can see, the concept of the phagocytic system initially proposed by Mechnikov has been expanding broadly, and its importance in disease regulation has been recognized more and more profoundly as our understanding of immunology and medical science has progressed.

The phagocytic system is necessarily quite strong as it is the first-line defense against both external (infectious) and

internal diseases. In addition, the clinical application of harnessing and using the phagocytic system would be a major paradigm shift for disease therapy, as it would be the first direct use of our intrinsic and fundamental defense mechanism as a human-created therapy. To date, however, this goal has not been achieved. This may be because the cell types and associated mechanisms responsible for phagocytosis appear to vary in different situations and places, and therefore are not fully understood. Another, even more critical reason might be that appropriate drug targets for utilizing the phagocytic system clinically have not been identified. Thus, the aims of this issue are to provide an overview of the most recent understanding of the molecular, cellular, and in vivo biology regarding pathogen removal achieved by professional and non-professional phagocytes in various diseases, and to help with identifying promising drug targets.

Within this issue, eight contributors cover a number of diverse situations involving the types of phagocytes that contribute to the clearance of pathogens in different diseases. These are largely classified into three topic categories: (i) pathogen removal by professional phagocytes, (ii) non-professional phagocytes in the context of disease regulation, and (iii) regulation of states in the survival, activation, and mobility of phagocytes. The first category (i) includes three articles by Tsuyama et al. [7], Chen et al. [3] and Werfel and Cook [8]. Tsuyama et al. [7] dissect the paradoxical roles of microglia cells and infiltrating myeloid cells. After ischemic events, these cells play both detrimental and beneficial roles during progressive and repair processes. In the article, the authors clearly show that these cells not only sustain post-ischemic inflammation but also have a repair function that works through the removal of DAMPs and dead cell debris. They also put the spotlight on the key molecule MafB, which has the potential to be an excellent therapeutic target for post-ischemic recovery.

In the next article, Chen describes the pathogenesis of an autoimmune kidney disease, IgA nephropathy (IgAN), which is the most common cause of primary chronic glomerulonephritis. One of the most important histologic

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Fig. 1 Today, the concept of the phagocytic system initially proposed by Mechnikov more than 100 years ago has greatly expanded, and its importance in the regulation of multiple diseases is widely recognized

characteristics broadly observed in the kidney of IgAN patients is the depositing of polymeric IgA1. These deposits form immune-complexes together with variable IgM and IgG, as well as complement 3, in the glomerular mesangial region. Chen shows how lesional phagocytes attempt to remove the harmful immune-complex in the mesangial region in order to prevent the progression of inflammation. The author also explains how such a phagocytic system could be therapeutically applied to the disease, which currently has no effective clinical therapy.

In the third article in category (i), Cook presents an overview of efferocytosis. Efferocytosis is an extraordinary system in which phagocytes precisely identify and engulf neighboring apoptotic cells. In addition to the molecular mechanism of efferocytosis, Cook describes in detail the involvement of efferocytosis in the tumor "wound healing" process, and discusses the possibility of targeting efferocytosis in existing tumor treatments.

In category (ii), on the other hand, two articles by Günther and Seyfert [5] and Arai [1] present the pivotal roles which non-professional phagocytes play in disease regulation. Among these, epithelial cells are the major cell type in epithelial tissues, which cover most surfaces of the body, thereby serving as the first line of defense against various types of pathogens. Günther explains the diverse types and mechanisms of phagocytosis employed by epithelial cells to protect our body from pathogens through orchestrating the innate immune responses.

In the next article under category (ii), Arai focuses on injured renal proximal tubular epithelial cells and highlights their increased phagocytic ability during acute kidney injury (AKI). Although such cells usually behave as the luminal coating cells of renal tubules and are mainly responsible for the re-absorption of nutrients, when an AKI occurs, they actively contribute to phagocytosis. By expressing the scavenger receptor kidney injury molecule 1 on their luminal cell surface, epithelial cells contribute to the clearance of lumen-obstructing dead cell debris. Arai also describes a circulating protein, apoptosis inhibitor of macrophage, as an indispensable matching element for phagocytic epithelial cells and dead cell debris. These two articles may suggest that epithelial cells can not only serve as a substitute for professional phagocytes such as macrophages, but also exhibit their own novel phagocytic mechanisms and independent functionality.

Lastly, in category (iii), three contributors describe new aspects of regulating the phagocytic system. In the first of these, Bose Dasgupta [2] Pieters introduce a smart strategy handled by a microbe, such as by mycobacterium tuberculosis. They focus on a unique molecule, coronin-1, which is now known to play beneficial roles in a wide variety of immune functions. The authors show that the endocytosed microbe hijacks coronin-1 to survive within phagocytes. So, their idea is that regulating coronin-1, which leads to the parasitic microbe being digested in a lysosome, might be a new therapeutic strategy for microbial infection.

The second contributor in category (iii), Ginton et al. [4] demonstrates that phagocytes, including monocyte-derived macrophages as well as innate dendritic cells, contribute not only to phagocytosis but also to cross-talk with T, B, and fibroblast cells. This appears to be a critical issue in the pathogenesis and repair process of cardiac allograft vasculopathy.

In the final article in category (iii), Mylvaganam et al. [6] provides an interesting take on the modification of phagocyte activation states. The article focuses on the targeting of the cellular cytoskeleton and the exoskeleton created by the pericellular coat, as well as their association with the transmembrane proteins known as “pickets.” These three articles help to greatly expand the concept of phagocytes and the phagocytic system.

Glancing through the entire issue, readers can now see that we may have already found hopeful candidates for new drug targets, which may open a much needed path toward the therapeutic application of the phagocytic system (i.e., Mechnikov-based drug development). The editor thanks the authors for their incredibly valuable contributions and hopes that readers will appreciate the timely topics presented in this issue.

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