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Recent Progresses in Immunology in Japan

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The immune system consists of two types; one is acquired immunity, in which the role of lymphocytes predominates, and the other is innate immunity, in which macrophages and dendritic cells play a key role. Modern immunology began with the invention of smallpox vaccine by Jenner and the discovery of antibodies by Shibasaburo Kitasato and Paul Ehrlich. Since then, research efforts have focused on studies on lymphocytes, namely acquired immunity, such as B cells, the antibody-producing cells, and T cells that control immune responses including antibody production. In the field of acquired immunity, studies on the specific mechanisms of pathogen recognition—for example, those involving antibodies and T-cell receptors—have received a great deal of attention. On the other hand, much has remained unclear in the field of specific pathogen-recognition mechanisms in innate immunity, and even the existence of such mechanisms had been denied by some researchers. However, various pathogen sensors have been found to date, demonstrating that specific mechanisms for recognizing pathogens are also functioning in innate immunity. This paper introduces recent advances in immunology, including the study of pathogen sensors, with the contribution of Japanese researchers highlighted.

It has long been known that components of pathogens robustly activate the immune system. The activated cells are mostly macrophages rather than lymphocytes. Along with advances in the study of pathogen components that activate the immune system, bacterial components such as endotoxin (lipopolysaccharide, LPS) and lipopeptide were identified. Kusumoto of Osaka University and Iwanaga of Kyushu University contributed greatly to the analysis of lipid A, the active moiety of LPS. Tokunaga of the National Institute of Health and others clarified that nucleic acids like DNA and RNA also are able to activate the immune system.

Nevertheless, sensors for these pathogen components had long been unknown, until Toll-like receptors (TLR) were found to be functioning as pathogen sensors in humans, following the rediscovery of *Drosophila* Toll as a pathogen sensor. TLR1 through TLR10 function in humans, and of those, TLR4 mediates LPS actions. It was reported by Miyake and Kimoto of Saga Medical School and others that MD-2 associated with TLR4 binds to LPS. Akira of Osaka University and others succeeded in producing a catalogue of knockout mice that lack TLR and downstream signaling molecules, thereby making a worldwide contribution to the analysis of TLR function. It is particularly noteworthy that they reported for the first time ever that TLR9 and TLR7 respond to DNA and RNA, respectively.

Following TLRs, various pathogen sensors localized in the cytoplasm became evident one after another—namely, Nod-like receptors and RIG-I-like receptors. In particular, the RIG-I-like receptor, an RNA sensor playing an important role in the defense mechanism against viral infection, was found by Fujita of the Tokyo Metropolitan Institute of Medical Science (currently of Kyoto University) and others. So, the pathogen recognition mechanisms in the innate immune system have been clarified in succession over the past few decades, providing new and better understanding of the importance of innate immunity in the immune system.

In addition to innate immunity, considerable progress has been made in the study of T-cell

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functions recently—another field in immunology to which Japanese researchers have contributed significantly. Regulatory T cells (Tregs) that suppress immune response were discovered by Sakaguchi of Kyoto University and others. Tregs were found to be deeply involved in pathologic conditions such as autoimmune disease, and intense research in this area is underway throughout the world. In addition to Tregs, Th17 cells that take part in the pathology of autoimmune disease and inflammatory bowel diseases were discovered. Identification of Th17 brought substantial progress in our understanding of immune response and autoimmune disease, which previously had been explained only in terms of Th1 and Th2 cells. Th17 cells were so named because they produce cytokine IL-17. The importance of Th17 was first demonstrated by Iwakura of the University of Tokyo who produced IL-17 knockout mice.

Interestingly, it has been found that Tregs and Th17 cells are present in large quantities in the mucosal immune tissue of the intestine. In particular, it has become apparent that the development of Th17 cells in the intestine is dependent on intestinal bacterial flora, and Honda and Takeda of Osaka University and others revealed that ATP plays an important role in this process. So, the elucidation of the state of equilibrium between the intestinal bacterial flora and the mucosal immune system is progressing at the molecular level, providing a far better understanding of the interaction between the two.

Th2 cells, which are believed to be deeply involved in the pathogenesis and pathologic conditions of allergy and atopy, were discovered at the same time as Th1 cells. However, much of the differentiation process of Th2 cells remained unclear. It was then found that basophils present antigen to T cells and that induce their differentiation to Th2 cells by producing cytokine IL-4. This discovery was made by Yoshimoto and Nakanishi of Hyogo College of Medicine and others, at the same time as the researchers in Europe and North America. This added a new aspect in the study of the regulatory mechanism of acquired immunity by innate immune system cells, where differentiation of Th1 cells had been considered the prototype.

Although studies of basophils were delayed due to their marked scarcity in peripheral blood, basophils have recently been attracting the attention of researchers throughout the world. In this area, studies by Karasuyama of Tokyo Medical and Dental University and others who clarified the importance of basophils in allergic inflammation have made much contribution, as well as studies by Yoshimoto, Nakanishi, and others.

In conclusion, immunology research in Japan has been making continuous progresses toward our better understanding of the molecular mechanisms underlying a variety of diseases. Such progresses have enabled us to develop novel, therapeutic interventions for the diseases with which we have long been afflicted.