

## Editorial

In general, there are two types of immune systems: innate immunity and acquired immunity. The innate immune system provides the first line of defense against many common microorganisms including bacteria and virus. This primitive immune system provides broad but relatively non-specific host defense that lacks the properties of antigenic specificity and immunological memory. In contrast, the acquired immune system is more sophisticated and is mediated by T and B cells, both of which generate their own receptors and specificities through DNA rearrangement, and is observed only in highly organized organisms. This highly sophisticated system has received much more attention and been studied more extensively in the past than the innate immune system. However, innate immunity is very important because of the following two reasons: 1) only innate immunity can respond to infections early on because it takes three to seven days before the initial adaptive immune response takes effect; and 2) recent studies have revealed that the innate immune response is vital to the activation of acquired immunity. For example, innate immune signaling such as Toll-like receptor (TLR) mediated signaling influences T cell activation and differentiation through dendritic cells (DCs) (Scheme 1). DCs are the most important antigen-presenting cells and are involved in the activation of naïve T cells. Upon infection, DCs recognize invariant molecular structures called pathogen-associated molecular patterns (PAMPs) that are expressed by many pathogens but not by hosts. TLRs in DCs recognize PAMPs. Upon PAMP stimulation, TLRs mostly form homodimers, resulting in a conformational change in their cytoplasmic TLR/IL-1R/plant R (TIR) domain and the subsequent recruitment of an adaptor protein, MyD88. MyD88 associates with TLRs via the TIR domain. MyD88 then recruits downstream IL-1 receptor associated kinase-4 (IRAK-4) via its death domain (DD). Four IRAKs have been identified so far, namely, IRAK-1, IRAK-2, IRAK-M and IRAK-4. Of these, IRAK-4 is the most indispensable to TLR signaling according to knockout mouse studies. The TNF receptor associated factor 6 (TRAF6) is activated, which in turn activates such nuclear transcription factors as NF- $\kappa$ B and AP-1 through the IKK complex and JNK, respectively. NF- $\kappa$ B and AP-1 finally induce the activation of immune response genes, resulting in the production of inflammatory cytokines. These cytokines are involved in the differentiation of naïve T cells. On the other hand, TLR signaling also induces the expression of MHC and costimulatory molecules on the surface of DCs in order to induce clonal expansion and differentiation of the recipient naïve T cells. Naïve T cells finally differentiate into Th1 and Th2 cells that influence macrophage activation and Ag-specific B cell activation, respectively. These T cell responses are classified under the acquired immune system. Scheme 1 shows an example of how the innate immune system is linked to acquired immunity. Recently, it has been recognized that innate immunity is a fundamental and critical system for triggering acquired immunity.

Dr. Takeda has summarized TLRs that are specific for innate immune responses, and has discussed adaptor molecules that can bind to TLRs. Our group has summarized IL-1 receptor associated kinases (IRAKs), which are the regulatory kinases of innate immune signaling. We have also discussed how IRAKs, in particular IRAK-4, effect acquired immunity and human disease. On the other hand, Dr. Li has summarized signal transduction in innate immunity by concentrating on a critical TLR negative regulator, SIGIRR. Dr. Fujita's group has given us a more detailed scheme of innate immune signaling by paying attention to the IRF family. Dr. Cheng's group has introduced Rip2, a kinase crucial to both innate and acquired immunity. Dr. Inohara's group has introduced Nod proteins, which are important for innate immunity and apoptosis. Dr. Shibuya's group has summarized DNAM-1, a leukocyte adhesion molecule considered to be a two-sword fencer in innate and adaptive immunity. Dr. Taniguchi's group has summarized NKT cells, which are bridging cells between innate and acquired immunity.

The objectives of this review are to: 1) summarize most recent knowledge of innate immunity; and 2) present lines of evidence indicating that innate immunity is indispensable to acquired immunity. This new concept of the innate immune system poses a challenge to the current views on pathogenesis and the treatment of infectious diseases, immune diseases, allergenic diseases, and cancers.

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