Linking innate and adaptive immunity

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The evolution of mechanisms to fight pathogens in plants and animals is reflected in the complexity of the components of their so-called immune systems. Higher vertebrates have evolved two different ways to protect themselves against infectious pathogens [1]. The first is termed innate immunity and is mediated by non-clonally distributed receptors, which can also be found in plants with less complexity, while the second is termed adaptive immunity using clonally distributed receptors. It is thought that adaptive immunity is evolutionarily conserved and is present in organisms from early evolutionary periods, such as the amphioxus [2–4]. Because of the diversity of clonally distributed receptors, including T cell receptors and immunoglobulins, the adaptive immune system is capable of the precise recognition of almost all biological structures. In contrast, the innate immune system is mediated by pattern recognition receptors, such as Toll-like receptors (TLR), RIG-I like receptors (RLR), NOD-like receptors (NLR) and other newly-identified DNA sensors [5–10]. The primary defense against infection is mediated by innate immunity, which then paves the way for adaptive immunity, initiating a more powerful and complicated immune response to clear pathogens [1,11]. During this process, many receptors, coreceptors, signaling molecules and cytokines are involved in the regulation of the balance between innate and adaptive immunity to achieve homeostasis.

On the occasion of the 60th anniversary of *SCIENCE CHINA* journals, Chinese immunologists working inside and outside of China have jointly contributed to a special immunology issue containing six review articles [12–17], which provide an overview of the recent advances in immunology, highlighting the contributions of leading Chinese immunologists.

Prof. Cheng GenHong's group has reviewed the structural features and functional roles of TRAF family members as signaling molecules in innate immunity. Most TRAF proteins have two major subdomains, the C-terminal TRAF domain and the N-terminal RING domain. The C-terminal TRAF domains form a mushroom-shaped trimer, which is stabilized by coiled-coil interactions of elongated N-terminal α -helices [16]. Following the helix, the conserved C-terminal TRAF domain is folded as an eight-stranded structure formed by two layers of β -sheets. The TRAF trimer can interact with many linear sequence motifs from the intracellular domains of TNFR superfamily members and adaptor molecules involved in cell signaling [16]. The N-terminal RING domain contains ubiquitin ligase (E3), which functions with Ubc13/UevA, a ubiquitin-conjugating enzyme (E2) protein in the process of ubiquitination, to catalyze a unique lysine 63 (K63)-linked polyubiquitin chain formation, thus leading to IKK activation. These two structural modules determine the central role of TRAF proteins in inflammation and immunity, in the regulation of canonical and noncanonical NF- κ B pathways and in the production of type I interferons [16]. Despite tremendous progress, many aspects of canonical and noncanonical NF- κ B signaling and the production of type I interferons remain unclear. Further studies are required to elucidate the new functional roles of TRAF proteins in signaling pathways.

Prof. Liu Yang's group has reviewed how the pattern recognition receptors discriminate pathogen-associated molecular patterns (PAMPs) from danger-associated molecular patterns (DAMPs) [12]. This paradox was reconciled when they revealed a novel pathway mediated by CD24 and its receptor, Siglec G in mice or Siglec 10 in humans. This pathway represses host immune responses to DAMPs but not PAMPs, and thus initiates immunity against pathogens without significant immune-mediated self damage in case of tissue injuries.

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Prof. Liu YongJun's group has contributed to the discovery of plasmacytoid dendritic cells (pDCs), which not only play a crucial role in anti-viral innate immunity but are essential in linking the innate and adaptive immune systems [13]. pDCs display a plasma cell-like morphology, selectively express TLR7 and TLR9 in the endosomal compartments, and are characterized by rapidly secreting massive amounts of type I interferons during viral infection. Type I interferons produced by pDCs not only inhibit viral replication, but also contribute to the activation of NK cells, B cells, T cells and mature DCs. At a later stage of viral infection, pDCs differentiate to a unique type of mature DC, which directly regulate the functions of T cells, thus contributing to linkage of the innate and adaptive immune systems. The sustained activation of pDCs and the excessive expression of type I interferons from pDCs in response to TLR stimulation by sensing self nucleic acids, also function in the pathogenesis of autoimmune diseases. However, much remains to be investigated in order to enhance our understanding of pDC biology in antiviral immunity and autoimmunity, and to potentially allow us to harness pDCs to develop safe and effective immunotherapy for viral infectious diseases and autoimmune diseases.

Prof. Chen LiePing's group has reviewed the structural basis of various costimulatory and coinhibitory molecules in T cell activation, especially investigating the functions of the B7/CD28 family in the regulation of adaptive immunity [15]. The molecular structures of costimulatory or coinhibitory complexes have revealed invaluable mechanistic insights underlying costimulatory or coinhibitory receptor/ligand specificity, affinity and oligomeric state, providing the basis for better manipulation of these signaling pathways. For example, Abatacept, a drug formed from CTLA-4-immunoglobulin (Ig) fusion proteins that target the B7/CTLA-4 pathway, was approved to treat rheumatoid arthritis by the US Food and Drug Agency (FDA) in 2006 and by the European Medicines Agency in 2007. Furthermore, using structural information from B7/CTLA-4 interactions, mutagenesis was introduced to CTLA-4 Ig to increase its affinity for B7 molecules. A CTLA-4 Ig variant, LEA29Y (Belatacept) was then developed to treat graft rejection. Thus, a greater structural understanding of these costimulatory or coinhibitory events will provide the basis for studying the biological functions of signaling pathways and encouraging their application for therapy, including PD1 and its ligands PDL1/2 or ILT proteins [18,19].

Prof. Fu YangXin's group has reviewed the role of the adaptive immune system in the negative regulation of innate immune responses [14]. Normally, pro- and anti-inflammatory mediators maintain the homeostasis during inflammatory responses. However, the presence of anti-inflammatory mediators may not always be sufficient to prevent the initiation of deleterious inflammation. Thus, the inflammatory response must be actively terminated because a failure to do so may result in 'bystander' injury to tissues as

seen in arthritis or hepatitis. The underlying mechanisms that control excessive acute inflammatory responses are still elusive. Although current opinion holds that T cells activate innate cells to clear pathogens, recent studies have revealed that adaptive immune system cells can actively dampen initial innate immune responses. This was demonstrated in a mouse model where sufficient numbers of T cells were required to control inflammation in neonatal mice challenged with LPS or virus infection. The neonatal mice had approximately 50-fold fewer T cells than adult mice, and died of an uncontrolled proinflammatory innate immune response. Furthermore, recent findings suggest that T cells dampen innate immune responses through the inhibition of NLRP1 and NLRP3 inflammasomes.

Prof. Su LiShan's group has reviewed the history and establishment of new humanized mice, an animal model for studying human immunology and human diseases *in vivo* [17]. They proposed the criteria for establishing a robust animal model for "hypothesis-testing/mechanistic" research in human immunology and immunopathology. It is described as follows: "First, it has well-studied hemato-lymphoid organs and target cells similar to those of humans. Second, the human pathogens establish infection and lead to relevant diseases. Third, it is genetically inbred and can be manipulated via genetic, immunological and pharmacological means." [17]. Recent progress in the development of humanized mouse models has focused on using immunodeficient mice that carry a defective *gammaC* gene, which are then reconstituted with human CD34⁺ hematopoietic stem cells to form a functional human immune system in the central and peripheral lymphoid organs. Such human-mouse chimeric models will greatly contribute to the study of human immunology, human-tropic pathogens and human stem cell biology *in vivo*.

These reviews contribute to our current understanding of innate immunity and adaptive immunity. In the early days of immunology research, the Nobel Prize for Physiology or Medicine in 1908 was awarded to Paul Ehrlich and Ilya Metchnikoff and revealed two divergent views of how the body protects itself against foreign invaders, by introducing the concepts of adaptive and innate immunity. After that, the two strands of immunity were always considered largely separate. In 1989, at the opening of the Cold Spring Harbor Symposium on Quantitative Biology, Charles Janeway proposed a revolutionary concept that adaptive immunity is initiated by pattern recognition of innate immunity. Great theories need to be tested and confirmed by experimental data. The recent 2011 Nobel Prize for Physiology or Medicine honored three remarkable scientists and recognized their efforts to unite the disparate strands of immunology by the merging of innate and adaptive immune systems into a coherent system. The new Nobel Laureates Jules Hoffmann and Bruce Beutler discovered the molecular mechanisms that control the activation of innate immunity and the late Ralph Steinman discovered the myeloid dendritic cell

(mDC) and its role in adaptive immunity. In the future, our immunologists will focus on bridging innate and adaptive immunity, to explore the fascinating and complicated immune system. More importantly they hope to identify the origin and evolution of adaptive immunity from lower vertebrates, such as the living fossil amphioxus.

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