

## Some research advances of immune mechanism during infection in China

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Newly emerging and reemerging infectious diseases continue to pose a substantial threat throughout the world. Understanding the immune mechanism during infection contributes not only to discoveries in science but also to advances in health care. Chinese researchers have made tremendous efforts to decipher the underlying mechanism of how pathogens elicit and evade immune responses and the immune homeostasis during infection. Here, we review new findings in Chinese studies concerning immune response to pathogens, immunoregulation and pathogen evasion, which offer us new insight into the trend in infectious immunology in China.

### Response to pathogens

The immune response triggered by microbial pathogens achieves appropriate effector function from diverse pathways to protect the host against destructive invasion. However, most of the underlying mechanism remains unclear.

The first defense employed by the innate immune response is to recognize molecular patterns expressed by invading pathogens via pattern recognition receptors (PRRs). Proteins on pathogens which are involved in driving host immune response are defined. The surface glycoprotein hemagglutinin (HA), the most important protein in molecular epidemiology and pathogenesis of influenza viruses, is characterized in the swine-origin influenza virus A

(H1N1)-2009 [1]. Tp0751 recombinant protein from *T. pallidum* is found to induce the production of proinflammatory cytokines and the ensuing immune responses [2]. The PRRs may locate either on the membrane surface e.g. Toll-like receptors (TLRs) or inside the cytoplasm e.g. Nod-like receptors (NLRs). NLRs assemble into multimolecular machines termed inflammasomes to detect intracellular pathogens [3]. Inflammasomes drive inflammatory processes through promoting the maturation of inflammatory cytokines such as interleukin (IL)-1 $\beta$  and IL-18 [4–7]. Alternatively, the recognition of lipopolysaccharide (LPS) is mainly mediated by TLR4/myeloid differentiation protein-2 (MD-2) heterodimers. During this process, residues Glu24-Met41 in the N terminal of TLR4 are involved in TLR4 binding to MD-2 and LPS-stimulated TLR4 aggregation [8]. Signaling pathways initiated by ligand binding to TLRs activate NF- $\kappa$ B, Mitogen-activated protein kinase (MAPK), and interferon (IFN), during in which the tumor necrosis factor (TNF) receptor-associated factor (TRAF) family is shown to participate [9–11]. These responses triggered by PRRs recognizing pathogens culminate activation of antimicrobial killing mechanisms and secretion of cytokines and chemokines. For example, production of broad-spectrum antimicrobial peptides is a common innate immunity defense mechanism against infection. As potentially great alternatives to current antibiotics, antimicrobial peptides have been studied in most researches [12–17]. Chen and colleagues have first isolated antibacterial peptides from the ovine reproductive tract [18]. Two novel temporins, one of important families of antimicrobial peptides from Litho-

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bates catesbeianus, have been molecular cloned [19]. The antimicrobial mechanism of these peptides has been investigated. Due to the critical role of type I IFNs in innate antiviral response, their production and downstream signaling cascades are often the hot topics under intensive investigation. Plasmacytoid dendritic cells (pDCs), which sense viral nucleic acids within the endosomal compartments through their TLR7 and TLR9, are professional type I IFN-producing cells. These IFNs not only directly inhibit viral replication but also play an essential role in linking the innate and adaptive immune system [20]. The Mx GTPase pathway is one of the most powerful antiviral mechanisms induced by IFNs. Belonging to the dynamin superfamily of large GTPases, Mx proteins have direct antiviral activity by interfering with viral genome replication [21–23]. Sun and colleagues have well reviewed recent findings in the structural and functional studies of Mx protein, which are significant for prophylaxis and control of the emerging and re-emerging viruses [24].

## Immunoregulation

Although these responses are physiologically designed for the defense against pathogens, their inappropriate or poorly restricted activation drives inflammatory disorders and causes host pathology. Thus, not only pathogen-associated molecular pattern recognition but also inflammatory process are normally under stringent regulation. A novel pathway mediated by CD24 and its receptor is essential in self-nonself discrimination in pattern recognition, enabling to initiate immunity against pathogens without significant immune-mediated self-destruction in case of tissue injuries [25]. Recent studies have revealed that conventional T cells dampen the innate immune response during the early phases of infection, and effector and memory T cells dampen the hyperactive inflammasome during late phase of primary responses or on secondary challenges, regulating host immunity appropriately [26]. In addition, regulators, such as soluble TLRs, growth arrest-specific gene 6 (Gas6), suppressor of tumorigenicity (ST2) and so on, act at multiple levels within TLR signaling transduction [27,28]. As a transcriptional factor significantly involved in inflammation, Kruppel-like factor 4 (KLF4) inhibits LPS-induced IL-6 release and thus limits potentially harmful immunopathological consequences [29]. Some mechanisms are employed by negative regulators to ensure the appropriate modulation of immune response [30–32].

## Pathogen evasion

In opposition to host protective strategy, some pathogens may be able to evade and subvert immune responses. Programmed death 1 (PD-1), a negative regulator for activation,

expansion and acquisition of effector functions of T cells, is well involved in pathogen evasion strategies [33,34]. Although extensive studies have been performed on function of PD-1, as so far regulation mechanism of PD-1 expression has not been reported. Zheng and colleagues have identified and characterized the promoter and upstream regulation region of mouse PD-1, providing important clues for the PD-1 gene transcriptional regulation [35]. In addition, papain-like proteases (PLPs), produced by coronavirus such as SARS and NL63, attenuate the innate response against virus through their IFN antagonism activities. As deubiquitinating enzymes, PLPs block polyI:C-induced activation of Interferon regulatory factor 3 (IRF3) and NF- $\kappa$ B, thus reducing IFN induction. Meanwhile, PLPs deactivate ERIS, an endoplasmic reticulum IFN stimulator, by inhibiting the ERIS dimerization [36–41]. Another mechanism involved in pathogen evasion is induced by IbeT, an *E. coli* K1 pathogenicity island gene. It has been shown that IbeT contributes to escape from the lysosomes into the cytoplasm for replication after *E. coli* K1 invasion into human brain microvascular endothelial cells [42,43].

These studies have evaluated immune mechanisms involved in infection in cutting-edged aspects, which will not only help us better understand the process of infection but also lay a foundation for developing novel therapies for infectious diseases.

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