International Reviews of Immunology, 32:113–115, 2013

ISSN: 0883-0185 print / 1563-5244 online
DOI: 10.3109/08830185.2013.775803

informa
healthcare

EDITORIAL

Innate Immune Recognition Mechanisms and Translational Opportunities

Himanshu Kumar, PhD[1,2,*] and Adrian Bot, MD, PhD[3]

[1]Laboratory of Immunology, Department of Biological Sciences, Indian Institute of Science Education and Research (IISER), Bhopal, India; [2]Laboratory of Host Defense, WPI, Immunology Frontier Research Center, Osaka University, Japan; [3]Kite Pharma, Inc., Los Angeles, CA 90124, USA

Innate immune sensors are a family of receptors which play a pivotal role in immune surveillance in various cellular compartments, recognizing numerous motifs derived from pathogens or associated with altered self molecules. Sensing of pathogenic components of self or nonself origin leads to a variety of integrated responses such as induction of proinflammatory and antiviral cytokines and lipid mediators, as well as upregulation of costimulatory molecules on a variety of cells. Furthermore, these sensors play a crucial role in cell survival, autophagy and pluripotency, and therefore, they are essential for the maintenance of cellular metabolic homeostasis. Finally, these sensors also play a substantial role in elicitation of specific immune responses, deploying and regulating the development of appropriate adaptive immunity against pathogens. This issue focuses on the biology of innate immune sensors, particularly Toll-like receptors and C-type lectin receptors, mutations in such sensors and/or their signaling components associated with disorders and the role of innate immune sensors in the mechanism of response to particulate vaccine adjuvants.

Keywords immunogenetics, immunotherapies, innate immunity, pathogen-associated molecular patterns (PAMPs), pattern recognition receptors (PRRs)

Perception of microbial intruders, nonself entities and damaged tissues (altered self) induces immediate activation of a range of protective responses (immune defense program), a hallmark of primitive and higher metazoans, including mammals. In higher metazoans, the innate immunity is the first line of defense and it is primarily mediated by various kinds of natural barriers including physical, chemical and enzymatic barriers. These innate immune barriers are specialized in humoral and cellular arms of response, to protect the host against a vast and diversified range of microbes and their products. The humoral effectors of innate immunity consist of families of soluble proteins such as complement and acute-phase response proteins, which not only are important for the initial neutralization or elimination of microbes, but also alert the host's immunity through the recruitment of a variety of cells at the site of infection or tissue injury. The cellular arm consists of "nonprofessional" somatic cells

Accepted 9 February 2013.
Himanshu Kumar is the Guest Editor and Section Editor of International Reviews of Immunology.
Adrian Bot is Editor in Chief of International Reviews of Immunology.
Address correspondence to Himanshu Kumar, Laboratory of Immunology, Department of Biological Sciences, Indian Institute of Science Education and Research (IISER) Bhopal, Indore By-pass Road, Bhauri, Bhopal - 462030, Madhya Pradesh, India. E-mail: hkumar@iiserb.ac.in

such as epithelial cells and "professional" immune cells such as various types of tissue phagocytic cells and dendritic cells. These cells mediate immune defense via sensing biochemical signatures [also known as pathogen-associated molecular patterns (PAMPs)] of microbes or components of damaged or "stressed" cells [also known as danger-associated molecular patterns (DAMPs)] by families of receptors [also known as pattern recognition receptors (PRRs)] located strategically in different cellular compartments such as plasma membrane, endosomes and within the cytoplasm. The PRRs are germ-line encoded and consist of several families such as Toll-like receptors (TLRs), Nod-like receptor (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs). Sensing of PAMPs and DAMPs by PRRs initiates a specific cascade of intracellular signaling which activates in turn an immune defense program tailored to specific stimuli and consisting in a range of transcription factors leading to expression of effector molecules such as proinflammatory cytokines, chemokines, type I interferons and costimulatory molecules. Additionally, this inflammatory response is also associated with the synthesis of lipid mediators (prostaglandins). Collectively, these responses are aimed to restrict the multiplication and invasion and subsequently to eliminate microbial pathogens from the host through initiation of microbe-specific adaptive immunity mediated by B and T cells.

In addition to their participation to host defense against microbial pathogens, in certain conditions, innate immune sensors could participate to or amplify certain types of inflammation that favor tumor progression.

In this issue, we cover PAMPs and DAMPs sensed by TLRs, CLRs, other receptors and signaling pathways, as well as several translational opportunities afforded by these sensors, including development of novel vaccine adjuvants for infectious diseases and cancer. We also discuss the impact of mutation(s) in sensors/signal transducers, on immune defense in humans, as depicted in Figure 1.

The first discovered innate immune sensors were TLRs. In the first review of this issue, Drs. Miwa Sasai and Masahiro Yamamoto provide an in-depth state of the art description of the TLR biology. The authors describe the PAMPs sensed by different TLR family members, the structural basis of recognition and the downstream signaling pathways, together with their regulation.

In the second review, Drs. Anthony Plato, Janet A. Willment and Gordon D. Brown discuss the Dectin-1 cluster and the CLRs in general, which play a pivotal role in the clearance of microbes through phagocytosis, induction of inflammatory responses and activation of adaptive immunity. Additionally, the authors highlight the importance of CLRs in the maintenance of tissue homeostasis through the initiation of a variety of physiological processes such as the removal of apoptotic cells or cell debris. The authors also highlight the importance of the CLR family members in the maintenance of the circulatory system and the overall physiology.

Understanding the innate immune sensors and the associated signaling is essential for immunobiologists, but this knowledge cannot be translated to man unless we characterize their specific role in human diseases. In the third review, Drs. Julien Pothlichet and Lluis Quintana-Murci highlight the pathological significance of mutations in various innate immune receptors/signal transducers and their association with infectious diseases (bacterial, viral, fungal and parasitic diseases), noninfectious diseases (autoimmune disorders) and cancer. The authors showcase the interesting association between such gene defects and noninfectious diseases and cancer, respectively, suggesting that environmental factors, in direct interplay with genetic mutations and pathogens, predispose individuals to autoimmunity or cancer through impacting the innate immunity.

In the last review of this special issue, Drs. Etsushi Kuroda, Cevayir Coban and Ken J. Ishii discuss the innate immune response to particulate materials and crystals ranging

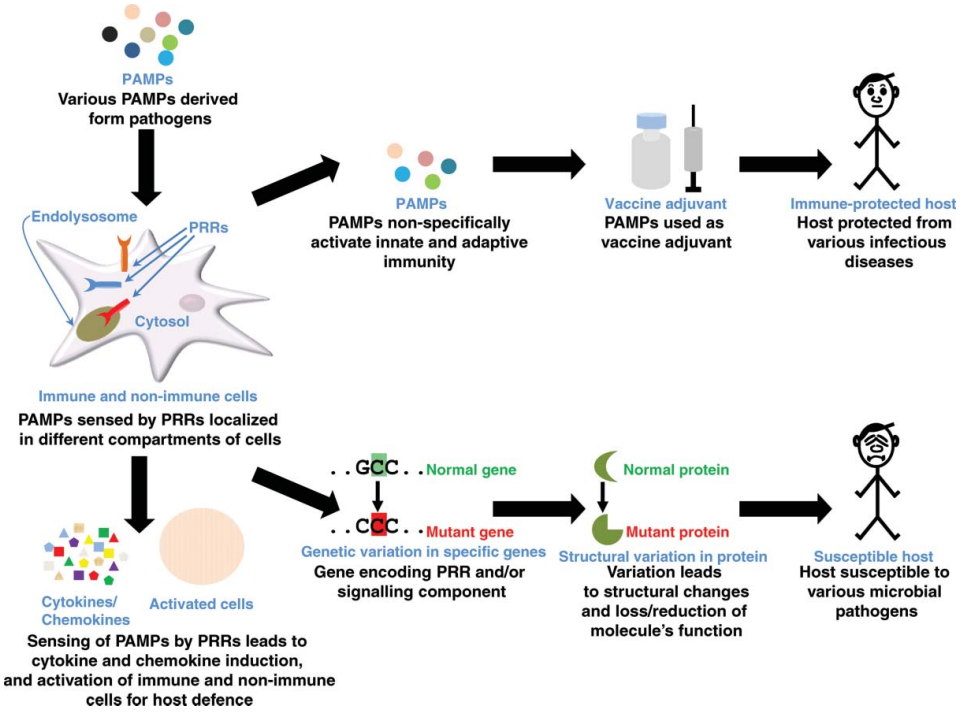

FIGURE 1 *Immunobiology of microbial sensing, impact of genetic defects of innate immune receptors and translational applications*: Signature molecules of microbial pathogens, also known as pathogen-associated molecular patterns (PAMPs) are sensed by a family of host innate sensors known as pattern recognition receptors (PRRs). The PRRs are localized at the cell surface (TLR1/2, TLR2/6, TLR4, TLR5 and various CLR members), in the endolysosomes (TLR3, TLR7, TLR8 and TLR9) or cytoplasm (members of RLR, NLR and DNA sensors). Sensing of PAMPs by PRRs activates signaling cascades consisting of adaptors, kinases and transcription factors, to induce an array of proinflammatory cytokines, lipid mediators, chemokines and type I interferons. Additionally, this also activates different cells through expression of various surface molecules leading to a stronger activation of innate immunity. Finally, altogether, these events initiate pathogen-specific adaptive immunity that also requires antigen recognition by B- and T-cell antigen receptors. The PAMPs are strong stimulators of innate immunity and could be used as adjuvants (components of vaccines) as such or in the form of agonistic molecules (analogues), for the development of prophylactic or therapeutic vaccines against infectious diseases and cancer. Hosts harboring genetic variations in PRRs, within downstream components of signaling cascade, and/or regulatory molecules, show disregulation of PRR-mediated signaling and impaired immunity. Therefore, these individuals show susceptibility to microbial pathogens.

up to a diameter of 2.5 micrometer, with specific reference to the adjuvant "alum" (a crystalline aluminum salt adjuvant used in human vaccine formulations). The review also focuses upon the relationship between particle size and the immune response. The authors emphasize that further research is needed for understanding the mechanism of action of various existing adjuvants, to fully tap into the translational potential of this field and to discover new vaccine adjuvants or immune modulators for infectious diseases, allergy or cancer.

In the upcoming issues of the *International Reviews of Immunology*, we will cover a range of topics such as immunodeficiencies, lymphocyte signaling, Th17 cells and microbial immunopathology.