Published in final edited form as:

Curr Opin Immunol. 2008 February ; 20(1): 1–2. doi:10.1016/j.coi.2008.01.004.

Innate Immunity to Pathogens

Wayne M. Yokoyama¹ and Marco Colonna²

¹Howard Hughes Medical Institute, Division of Rheumatology, Department of Medicine, Campus Box 8045, Washington University School of Medicine, 600 South Euclid Avenue, St. Louis, MO 63110

²Department of Pathology and Immunology, Campus Box 8118, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110

The innate immune system is responsible for early detection and response to pathogens that then modulate subsequent immune responses [1]. A characteristic of innate immunity is the recognition of pathogen associated molecular patterns (PAMPs) by germline-encoded receptors such as the Toll-like receptors (TLRs) [2]. A wealth of information is now available on TLRs but more recent studies, as reviewed in this issue, indicate that the NLRs (nucleotide-binding domain, leucine-rich repeat) proteins and cytoplasmic viral RNA sensors also provide major PAMP recognition functions. Another hallmark of innate immunity is the phylogenetic conservation of molecules and pathways [3], as illustrated by the NLR and the resistance (R) proteins in plants, plant resistance receptors that also indicate the importance of innate immunity. Pathogen encoded immune evasion of innate immune components and primary immunodeficiencies in humans also provide evidence for the significance of innate immunity in host defense against pathogens. In this issue, these concepts are reviewed, particularly as related to innate immunity to pathogens, and emerging new concepts are described as we learn more about innate immunity.

Ye and Ting [4] review emerging information on the role of the NLR family of molecules in host defense. NLR proteins comprise part of a macromolecular complex, termed the inflammasome, that can activate caspase-1 and IL-1 processing. Inflammasomes can differ according to the NLR component which themselves differ by their domain content and sequence. Data continue to emerge indicating that the different NLR proteins have distinct functional roles, such as response to different pathogens, and involvement in different diseases including gout, pseudogout, and distinct autoinflammatory disorders. The NLR proteins are generally related to the R proteins in plants, also discussed by Zipfel [5] who reviews emerging information on other plant recognition and immune strategies as well. The emerging data indicate that plants and animals use innate immune receptors to recognize similar bacterial products, such as flagellin (a ligand for plant leucine-rich repeat receptor-like kinase and mammalian TLR5), suggesting evolutionary conservation for functional recognition of specific pathogen components.

Corresponding author: Wayne M. Yokoyama, Email: yokoyama@im.wustl.edu.

Wayne M. Yokoyama, M.D. is an Investigator of the Howard Hughes Medical Institute and Levin Professor of Medicine and Professor of Pathology and Immunology at Washington University. His laboratory studies natural killer cell recognition and development, and innate immunity to viruses.

Marco Colonna, M.D. is Professor of Pathology and Immunology at Washington University. His laboratory studies murine and human innate immunity, focusing on natural killer and dendritic cell receptors and functions.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Takeuchi and Akira [6] discuss recent developments in the study of the cytoplasmic viral RNA sensors, retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5). Recent studies indicate that they have overlapping specificities for different RNA viruses, and use a novel adapter to signal host responses, such as type I interferon and pro-inflammatory cytokine production. These insights may provide targets to exploit in therapies for influenza and emerging pathogens, such as West Nile virus.

Innate immunity often involves cellular processes that are not restricted to innate immunity. Lee and Iwasaki [7] discuss the role of autophagy in host responses to viruses. Initially described as a response to starvation, autophagy is now known to play a major role in many different cellular processes and has been implicated in several diseases. As reviewed by Lee and Iwasaki, recent data suggest that autophagy is a host response to limit viral replication, such as by engulfment and destruction of viruses, and the autophagy pathway is implicated in antigen processing and presentation. Interestingly, the autophagy pathway intersects with the pathways stimulated by pathogen sensors, such as TLR and RIG-I/MDA-5, discussed by Takeuchi and Akira [6]. On the other hand, several viruses hijack the autophagocytic process for replication, such as using the pathway as a niche for replication or for nonlytic viral release. Moreover, viruses encode mechanisms to evade autophagy, supporting their significance in host responses to infection.

Viruses also encode molecules to evade natural killer (NK) cells, cementing the importance of NK cells in control of viral infections, as reviewed by Jonjic et al [8]. Recent studies indicate that viruses block the function of NK cells by targeting different receptors and pathways. Perhaps the most significant is the NKG2D receptor because a single virus, like murine cytomegalovirus, uses multiple open reading frames to block NKG2D whereas other viruses utilize fundamentally different strategies to inhibit NKG2D function. Thus, viruses provide clues to vital host innate immune responses.

Finally, the significance of innate immunity to control of infections is perhaps best illustrated by the susceptibility of hosts with genetic mutations in critical innate system components [9]. As discussed by Bustamante et al [10], this is especially challenging to ascertain in human patients. Moreover, primary immunodeficiencies in humans are difficult to strictly classify as being innate or adaptive immune defects because of pleiotrophic effects. However, insight is provided as to the medical and biological significance of various “innate” immune components and pathways by studies of inborn errors of NK- κ B, TLR and IL-1, TLR3, type I IFNs, IFN γ , IL-12, IL-23, and IL-6. In many cases, it is surprising that the patients do not appear to suffer from a more severe phenotype, and frequently they have difficulty with only one or a restricted set of microbes.

Therefore, the field of innate immunity has been enriched by the description of new receptors and sensors, and new pathways. There is much more to learn since many molecules are still orphan receptors or sensors. Moreover, the biological significance of these molecules and pathways is just beginning to be explored. Meanwhile, clues to some of the most important come from studies of pathogen evasion strategies and insight from human patients. We hope that you will be similarly enriched by the concepts raised in the reviews in this issue, and thank the authors for their perceptive contributions.

References

1. Kaufmann, SHE.; Medzhitov, R.; Gordon, S. The Innate Immune Response to Infection. Philadelphia, PA: American Society for Microbiology Press; 2004.
2. Medzhitov R, Janeway CA Jr. Innate immunity: the virtues of a nonclonal system of recognition. *Cell* 1997;91:295–298. [PubMed: 9363937]

3. Hoffmann JA. The immune response of *Drosophila*. *Nature* 2003;426:33–38. [PubMed: 14603309]
4. Ye Z, Ting JP-Y. NLR, the nucleotide-binding domain leucine rich repeat containing gene family. *Current Opinion in Immunology* 2008;20in press
5. Zipfel C. Pattern-recognition receptors in plant innate immunity. *Current Opinion in Immunology* 2008;20in press
6. Takeuchi O, Akira S. MDA5/RIG-I and virus recognition. *Current Opinion in Immunology* 2008;20in press
7. Lee HK, Iwasaki A. Autophagy and antiviral immunity. *Current Opinion in Immunology* 2008;20in press
8. Jonjic S, Babic M, Polic B, Krmpotic A. Immune evasion of natural killer cells by viruses. *Current Opinion in Immunology* 2008;20in press
9. Beutler B, Jiang Z, Georgel P, Crozat K, Croker B, Rutschmann S, Du X, Hoebe K. Genetic analysis of host resistance: Toll-like receptor signaling and immunity at large. *Annu Rev Immunol* 2006;24:353–389. [PubMed: 16551253]
10. Bustamante J, Boisson-Dupuis S, Jouanguy E, Picard C, Puel A, Abel L, Casanova J-L. Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. *Current Opinion in Immunology* 2008;20in press