Current reviews of allergy and clinical immunology

Series editor: Harold S. Nelson, MD

Innate immune responses to infection

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The human host survives many infectious challenges in the absence of preexisting specific (adaptive) immunity because of the existence of a separate set of protective mechanisms that do not depend on specific antigenic recognition. These antigen-independent mechanisms constitute innate immunity. Antimicrobial peptides are released at epithelial surfaces and disrupt the membranes of many microbial pathogens. Toll-like receptors on epithelial cells and leukocytes recognize a range of microbial molecular patterns and generate intracellular signals for activation of a range of host responses. Cytokines released from leukocytes and other cells exhibit a vast array of regulatory functions in both adaptive and innate immunity. Chemokines released from infected tissues recruit diverse populations of leukocytes that express distinct chemokine receptors. Natural killer cells recognize and bind virus-infected host cells and tumor cells and induce their apoptosis. Complement, through the alternative and mannose-binding lectin pathways, mediates antibody-independent opsonization, phagocyte recruitment, and microbial lysis. Phagocytes migrate from the microcirculation into infected tissue and ingest and kill invading microbes. These innate immune mechanisms and their interactions in defense against infection provide the host with the time needed to mobilize the more slowly developing mechanisms of adaptive immunity, which might protect against subsequent challenges. (J Allergy Clin Immunol 2005;116:241-9.)

Key words: *Innate immunity, antimicrobial peptides, Toll-like receptors, chemokines, natural killer cells, complement, phagocytes*

Abbreviations used

CXCL:	CXC ligand
HBD:	Human β-defensin
ICAM-1:	Intercellular adhesion molecule 1
LFA-1:	Lymphocyte function-associated antigen 1
MAC:	Membrane attack complex
Mac-1:	Macrophage antigen-1
MBL:	Mannan-binding lectin
NADPH:	Reduced nicotinamide adenine dinucleotide phosphate
NF:	Nuclear factor
NK:	Natural killer
PMN:	Polymorphonuclear leukocyte
TLR:	Toll-like receptor

It is traditional to organize host responses to infection into separate arms or compartments, such as complement, phagocytes, cytokines, cell-mediated immunity, and humoral immunity. A more current approach has been to consider 2 larger categories: *innate immunity*, incorporating the more rapid and phylogenetically primitive nonspecific responses to infection, such as surface defenses, cytokine elaboration, complement activation, and phagocytic responses,[1] and *adaptive immunity*, involving more slowly developing, long-lived, and highly evolved antigen-specific protective responses, such as antibody production and cell-mediated immunity, that exhibit extraordinarily diverse ranges of specificity.[2,3] However, the components of innate and adaptive immunity engage in a range of interactions that is remarkably diverse and complex. This review attempts to provide an overview of the main innate responses to infection that are available to the human host, including relevant examples of such interactions.

INNATE IMMUNITY

Epithelia, defensins, and other antimicrobial peptides

The epithelium of skin and mucosal tissue functions as a mechanical barrier to the invasion of microbial pathogens. In the last 2 decades, it has become clear that epithelial cells also are a major source of antimicrobial peptides that play important roles in local host defense.[4,5] Studies of their structure, sources, expression, and actions also have revealed an unexpected range of immunologic activities for these molecules, the functions of which once were considered mainly antimicrobial in nature.[4]

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Disclosure of potential conflict of interst: M. F. Tosi—none disclosed.

Received for publication May 17, 2005; accepted for publication May 18, 2005.

Available online July 5, 2005.

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0091-6749/$30.00

doi:10.1016/j.jaci.2005.05.036

Epithelial cells of mucous membranes of the airways and intestines, as well as keratinocytes, express the human β-defensins (HBD-1 through HBD-4). These small cationic peptides are similar to the α-defensins stored in the azurophilic granules of neutrophils, and they display antimicrobial activity against a broad range of bacteria, fungi, chlamydiae, and enveloped viruses.[4,5] Their production by epithelial cells might be constitutive, as for HBD-1, or inducible, as for HBD-2, HBD-3, and HBD-4. For example, recent evidence indicates that epithelial cells of the airway or intestine can produce HBD-2 in response to activation by bacterial products through toll-like receptors (TLRs) 2 or 4 (see below) on the epithelial cells.[6,7] Stimulation of epithelium by cytokines, including IL-1 or TNF-α, also can induce defensin production.[4] Defensins have been reported to exert their antimicrobial action either through the creation of membrane pores or through membrane disruption resulting from electrostatic interaction with the polar head groups of membrane lipids, with more evidence now favoring the latter mechanism.[4,8] Some microorganisms have evolved mechanisms for evading the action of defensins. For example, bacterial polysaccharide capsules might limit access of microbial peptides to the cell membrane,[9] and an exoprotein of *Staphylococcus aureus*, staphylokinase, neutralizes the microbicidal action of neutrophil α-defensins.[10]

Several immunoregulatory properties of defensins and related peptides, distinct from their antimicrobial actions, have been documented.[4] Several such peptides have been shown to facilitate posttranslational processing of IL-1β.[11] Some of the β-defensins have been shown to function as chemoattractants for neutrophils, memory T cells, and immature dendritic cells by binding to the chemokine receptor CCR-6.[5,12,13] Separately, HBD-2 has been shown to activate immature dendritic cells through a mechanism that requires TLR4.[14] The activation of immature dendritic cells by these mechanisms also promotes their maturation. The β-defensins also act as a chemoattractant for mast cells through an undefined mechanism and can induce mast cell degranulation.[15] HBD-2 and several other antimicrobial peptides can interfere with binding between bacterial LPS and LPS-binding protein.[16]

Additional antimicrobial peptides of epithelial cells include lysozyme and cathelicidin. Lysozyme, an antimicrobial peptide also found in neutrophil granules, attacks the peptidoglycan cell walls of bacteria and can be released from cells through mechanisms that involve TLR activation.[17] Cathelicidin, or LL37, like lysozyme, is released from both neutrophils and epithelial cells. It exhibits broad antimicrobial activity and can inhibit lentiviral replication.[5,18] Cathelicidin also exhibits chemotactic activity for neutrophils, monocytes, and T lymphocytes. This activity is mediated by a formyl peptide receptor-like molecule, FPRL1, rather than the chemokine receptor CCR6 bound by β-defensins.[19]

The release of defensins in response to activation of TLRs and the many actions of these peptides, including their direct antimicrobial activities, their chemoattractant actions for a wide range of immune cells, and their activation of dendritic cell maturation, already suggest a highly complex and regulatory role in the development of host defense and immunity. Recent genomic evidence for the possible existence of as many as 25 additional human defensins that have not yet been characterized suggests that current knowledge describes but a small sample of the overall contribution of these peptides to immune responses.[20]

TLRs

Mononuclear phagocytes, including circulating monocytes and tissue macrophages, other phagocytic cells, and many epithelial cells, express a family of receptors that is highly homologous to the *Drosophila* receptor called Toll.[6,7,21] These receptors mediate a phylogenetically primitive, nonclonal mechanism of pathogen recognition based on binding not to specific antigens but to structurally conserved pathogen-associated molecular patterns.[21-23] There are at least 10 human TLRs with a range of microbial ligands, such as gram-negative bacterial LPS, bacterial lipoproteins, lipoteichoic acids of gram-positive bacteria, bacterial cell-wall peptidoglycans, cell-wall components of yeast and mycobacteria, unmethylated CpG dinucleotide motifs in bacterial DNA, and viral RNA.[22-24] Gram-positive cell-wall components bind mainly to TLR2, and TLR2 also can bind components of herpes simplex virus.[22-25] Gram-negative LPS activates TLR4 indirectly by first binding to LPS-binding protein, which binds in turn to CD14 at the cell surface. The bound CD14 has no transmembrane domain but associates directly with an extracellular domain of TLR4.[23,24] TLR5 has been identified as the receptor for bacterial flagellin, TLR9 recognizes CpG motifs of bacterial DNA, and TLR3 has been shown to bind synthetic and viral double-stranded RNA.[26-28]

Signalling through TLRs occurs through a well-described pathway in which receptor binding generates a signal through an adaptor molecule, MyD88, that leads to intracellular association with IL-1 receptor-associated kinase. In turn, this leads to activation of TNF receptor–associated factor 6, which results in nuclear translocation of nuclear factor κB (NF-κB).[23,24] NF-κB is an important transcription factor that activates the promoters of the genes for a broad range of cytokines and other proinflammatory products, such as TNF-α, IL-1, IL-6, and IL-8. This signalling pathway, on the basis of studies with TLR4, is similar but not identical to the signalling pathways activated by other TLRs.[24] The activation of cytokine production by TLRs plays an important role in recruiting other components of innate host defense against bacterial pathogens. However, with large-scale cytokine release, the deleterious effects of sepsis or other forms of the systemic inflammatory response syndrome demonstrate that these pathways have both beneficial and potentially harmful effects for the host.[24] Genetic polymorphisms in TLRs might play a role in determining the balance of these effects in certain individuals responding to the challenge of systemic infection.[24,29,30]