The Innate Immune Response is Conserved Throughout Evolution and is Triggered by Pattern Recognition

Lipopolysaccharide = Lipid + Polysaccharide


Diversity of "Pathogen-associated Molecular Patterns" (PAMPs)

From: Akira et al., Cell 124:783, 2006

Innate Immune Receptors for PAMPs

- Toll-like receptors (TLRs)
- Complement
- Collectins (e.g., Surfactant Protein-A)
- Scavenger receptors
- Pentraxins (e.g., CRP)
- Lectins (e.g., Dectin-1)
- CD14
- NOD-like receptors (NLRs)
- RIG-1-like receptors

Collectins and Innate Immune Recognition


Collectins Can Serve as Opsonins

The Scavenger Receptor Superfamily Recognizes PAMPs

Innate Immune Receptors Also Trigger a Systemic Response to Infection

Innate Immune Functions of C Reactive Protein (CRP), an Acute Phase Protein Synthesized by Hepatocytes

CRP acts as a bridge between phosphocholine on bacterial targets and C1q

Adapted from: Black et al., J. Biol. Chem. 47:48487, 2004

Co-localization of CRP and Activated Complement in Infarcted Human Myocardium

J = jeopardized; N = normal

From: Nijmeijer et al., Am. J. Pathol. 163:269, 2003

Treatment of Experimental Myocardial Infarction with a CRP-binding Analog of Phosphocholine Limits Infarct Size


History of Endotoxin Research


The post-microbial era began with the discoveries of Koch and Pasteur (1865). Four phases of discovery are depicted: the recognition that infection is poisonous (red); search for poisons culminating in the identification of endotoxin (green); the chemical and biological characterization of endotoxin (orange); the identification of the endotoxin receptor and its role in promoting the immune response (purple).
A Re-interpretation of the Endotoxin Research Timeline

- Discovery of the NF-κB signaling pathway by Toll in Drosophila by Hoffman and colleagues
- Molecular basis of adjuvant discovered by Medzhitov and Janeway
- "Infectious-non-self" model of immunity described by Janeway
- Use of adjuvant to stimulate the immune response
- Endotoxin = LPS
- TNF mediates septic shock
- TLR2 is the receptor for PG
- LPS = TLR4
- Primary structure of LPS reported
- C3H/HeJ mutation reported

Primitive Specificity in Target Recognition by the Innate Immune System

Recruitment of TLR2 to Yeast Phagosomes

From: Underhill et al., Nature 401:811, 1999

Ligand Specificity of TLRs

Specificity of TLR Transcriptional Programs


TLR Signaling: Two Major Pathways

Cartoon of major signal transduction pathways following engagement of TLRs. TLR4 is the major sensor of LPS, TLR3 recognizes dsRNA and is important in the anti-viral response. The NF-κB pathway leading to production of most pro-inflammatory proteins, and one that activates the IRF pathway leading to production of Type I IFNs (i.e., IFN-α/β) is particularly prominent in a minor subset of dendritic cells (called "plasmacytoid DCs") that are the major source of these IFNs in response to viral infections.

Do not memorize this cascade but rather appreciate that it consists of two parallel pathways, one that activates NF-κB, leading to production of most pro-inflammatory proteins, and one that activates the IRF pathway leading to production of Type I IFNs.

From: Moynagh, Trends Immunol. 26:469, 2005

TLRs Sense Microbial Pathogens and Trigger Expression of Pro-inflammatory Cytokines and Chemokines

Adapted from: Creagh and O'Neill, Trends Immunol. 27:352, 2006

Newly Recognized Components of the Innate Immune System

NOD Proteins: Intracellular Peptidoglycan Sensors

Polymorphisms in Nod-2 are associated with up to 30-40% of cases of Crohn's disease (an inflammatory bowel disease)

CARD: caspase-recruitment domain; LRR, leucine-rich repeat; RICK, a CARD-containing protein kinase


Cytosolic Bacterial Recognition Systems and "the Inflammasome"

From: Akira et al., Cell 124:783, 2006
Contrast-enhanced abdominal CT from a 31-year-old patient with Familial Mediterranean Fever suffering an acute attack of abdominal pain, nausea, vomiting, and arthritis. Note mesenteric vessel with thickened mesenteric fold (white arrow). Histopathology demonstrated neutrophilic infiltrate and associated vasculitis. Treatment with an IL-1 receptor antagonist (Anakinra) resulted in prompt cessation of symptoms.

Mutations in Pyrin, Another CARD-containing Innate Immune-like Protein, is Responsible for Familial Mediterranean Fever

Another Disease Associated with Activation of the Inflammasome

Pathogenesis of Gout Uncovered in 2006: Monosodium Urate Crystals Activate the Inflammasome

Nod-like Receptors (NLRs) Sense Microbial Products, Activate the "Inflammasome," and Trigger Maturation of IL-1

The Dendritic Cell and Development of The Primary Immune Response: Wisdom Through Maturity

Dendritic Cell Maturation


From: Mellman & Steinman, Cell 106:255, 2001
Question: What Triggers Maturation of DCs?

The Innate Immune Response Orchestrates DC Trafficking to Secondary Lymphoid Organs


Functional Differences Between Immature and Mature DCs

The (Primary) Acquired Immune Response is Initiated by Innate Immune Recognition


Chemokines Direct Trafficking of Immune Cells

The Early Antiviral Response and the Innate Immune System


NK cells are a major source of a rapidly mobilizable pool of pro-inflammatory cytokines
Innate Immune Receptors for dsRNA Cooperate to Initiate the Immune Response to RNA Viruses

Double-stranded RNA products of virus infection bind to RIG-I or MDA5, which in turn bind to IPS-1 via CARD domain interactions. This complex then signals the activation of IKK-ε and TBK1 or other kinases to phosphorylate IRF-3, possibly through direct recruitment of signaling effectors, leading to IRF-3 dimerization, nuclear translocation and assembly onto the IFN-β enhancer. IPS-1 might also signal the activation of the IKK complex via direct binding of the IKK components or through recruitment of RIP-1, FADD and/or TRAF6, causing the phosphorylation of IκB, the inhibitor of NF-κB. Phosphorylated IκB is then ubiquitinated and targeted to the proteosome for degradation, releasing the active NF-κB complex to translocate to the nucleus. During virus infection, dsRNA products can signal through TLR3 to activate IRF-3 and NF-κB by the actions of the TRIF adaptor protein and RIP-1, respectively.

RIG-1-like Receptors (RLRs) Sense Viral Products, Activate the IRF Pathway, and Trigger Production of Antiviral Proteins

The Antiviral Response: a Cascade of Transcriptional Events

Multiphasic induction of murine type I IFN genes can be divided into three phases. (a) The immediate early phase. Virus infection initiates a phosphorylation cascade, leading to the activation of at least three families of transcription factors, including NF-κB, AP-1 and IRF7. Activation of the IRF7—promoter requires all three transcription factors. (b) IFN induction phase. Secretion of early IFN produces an autocrine response through stimulation of the JAK-STAT pathway. Among the pathway’s target genes is IRF7, itself. (c) Delayed early (amplification) phase. Many members of the IFN-α gene family possess promoter binding sites for activated IRF7 and become transcriptionally active.

Summary

1. Innate immunity is conserved throughout evolution and is triggered by recognition of “pathogen-associated molecular patterns” (e.g., LPS) by “pattern recognition receptors.”

3. Collectins (e.g., SP-A, C1q, MBP) recognize carbohydrates on pathogen surfaces and perform multiple anti-microbial functions (e.g., opsonization). Collectins are essential for innate immunity, but also help clear apoptotic debris.

5. Members of the Scavenger Receptor superfamily recognize bacteria as well as glucose-modified proteins and oxidized lipoproteins. They are implicated in the response to infection as well as atherosclerosis and other degenerative diseases.

7. TLR4 is the major LPS receptor in mammalian cells. TLR4 triggers activation of NF-κB (leading to production of TNF-α, for example). Other TLRs recognize additional microbial products. NOD-like receptors are intracellular sensors of bacterial products that activate the “inflammasome,” triggering caspase-dependent maturation of IL-1.

5. Dendritic cells undergo a maturation program: immature DCs, which traffic to the periphery, capture antigen, and mature DCs, which traffic to the lymph node, present antigen. Innate immune stimuli trigger DC maturation, which upregulates co-stimulatory molecules and facilitates antigen presentation. Thus, the innate immune response ushers in the acquired immune response.

6. NK cells, a component of innate immunity, especially to viruses, represent an early source of IFN-γ and serve to stimulate macrophages and DCs in inflammatory sites. Additional components of the antiviral response include intracellular dsRNA sensors (RLRs like RIG-1) that activate the IRF pathway to signal antiviral gene expression.