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

CARD = caspase-recruitment domain
LRR = leucine-rich repeat
NOD = NOD2-like domain
MDP = muramyl dipeptide

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

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.
Another Disease Associated with Activation of the Inflammasome

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

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 IKKε 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 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.

N.B.: Do not memorize this cartoon, but appreciate how cytosolic dsRNA receptors (RIG-I, MDA5) and plasma membrane-associated dsRNA receptors (TLR3) cooperate to activate IFN- and NF-κB-dependent gene expression.

From: Johnson and Gale, Trends Immunol. 27:1, 2006
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 stimulates a phosphorylation cascade, leading to the activation of at least three families of transcription factors, including NF-κB, AP-1 and IRFs. Activation of the IFN-α promoter requires all three transcription factors. (b) IRF7 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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
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<tbody>
<tr>
<td>p21</td>
<td>Cell cycle arrest</td>
</tr>
<tr>
<td>IL-15</td>
<td>NK cell maturation</td>
</tr>
<tr>
<td>FasL</td>
<td>Cell death</td>
</tr>
<tr>
<td>IL-12</td>
<td>Th1 immune response</td>
</tr>
</tbody>
</table>

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

Adapted from: Creagh and O’Neill, Trends Immunol. 27:352, 2006
How does the Innate Response affect the Acquired Immune Response?

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

Adapted from: Creagh and O’Neill, Trends Immunol. 27:352, 2006
Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia

Movie, courtesy T. Springer

Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins

Movie, courtesy T. Springer
Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue

Leukocyte Migration, Start to Finish

<table>
<thead>
<tr>
<th>Rolling adhesion</th>
<th>Tight binding</th>
<th>Diapedesis</th>
<th>Migration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrin (e.g., LFA-1)</td>
<td>Chemokine receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selectin</td>
<td></td>
<td></td>
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<tr>
<td>CD31 (PECAM)</td>
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Intravital Imaging of a Subset of Mouse Monocytes in Dermal Blood Vessels

CX3CR1-expressing cells express GFP in reporter mice, and dermal blood vessels are labeled with rhodamine-conjugated dextran.


A Subset of Monocytes "Patrol" the Vasculature, Primed for Diapedesis

Innate Immune Receptors Also Trigger a Systemic Response to Infection

Ligand Specificity of TLRs

<table>
<thead>
<tr>
<th>Ligand</th>
<th>TLRs</th>
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<tbody>
<tr>
<td>Lipoprotein</td>
<td>TLR6 or TLR1</td>
</tr>
<tr>
<td>Peptidoglycan</td>
<td>TLR2 or TLR1</td>
</tr>
<tr>
<td>Flagellin</td>
<td>TLR2</td>
</tr>
<tr>
<td>Imidazoquinolines</td>
<td>TLR4</td>
</tr>
<tr>
<td>LPS</td>
<td>TLR1</td>
</tr>
<tr>
<td>dsRNA</td>
<td>TLR1</td>
</tr>
</tbody>
</table>

- Adaptor proteins, kinases
- NF-κB
- Inflammatory cytokines
Specificity of TLR Transcriptional Programs


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

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

<table>
<thead>
<tr>
<th>Principal Function</th>
<th>Immature dendritic cell</th>
<th>Mature dendritic cell</th>
</tr>
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<tbody>
<tr>
<td>Antigen capture</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Antigen presentation</td>
<td>-- or low</td>
<td>++</td>
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The (Primary) Acquired Immune Response is Initiated by Innate Immune Recognition
Chemokines Direct Trafficking of Immune Cells


Science is like looking through a keyhole: The closer you get to the keyhole, the more you see of the room on the other side.

-George Wald
1967 Nobel Laureate in Medicine