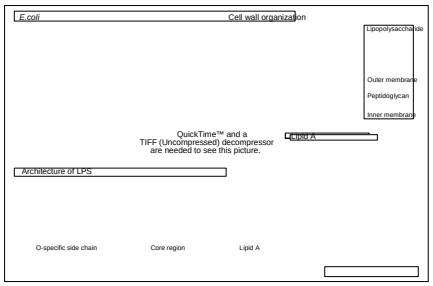
The Innate Immune Response is Conserved Throughout Evolution and is Triggered by Pattern Recognition

Innate Immune Receptors for PAMPs

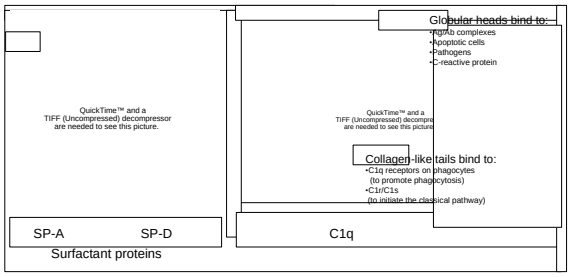
- Toll-like receptors (TLRs)
- Complement
- Collectins (e.g., Surfactant Protein-A)
- Scavenger receptors
- Pentraxins (e.g., CRP)
- Lectins (e.g., Dectin-1)
- CD14
- NOD-like receptors (NLRs)
- RIG-1-like receptors

Lipopolysaccharide = Lipid + Polysaccharide

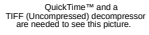


From: Beutler and Rietschel, *Nature Reviews Immunology* **3**; 169-176 (2003)

Collectins and Innate Immune Recognition

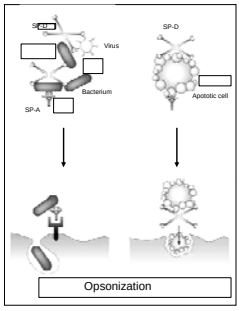


Diversity of "Pathogen-associated Molecular Patterns" (PAMPs)



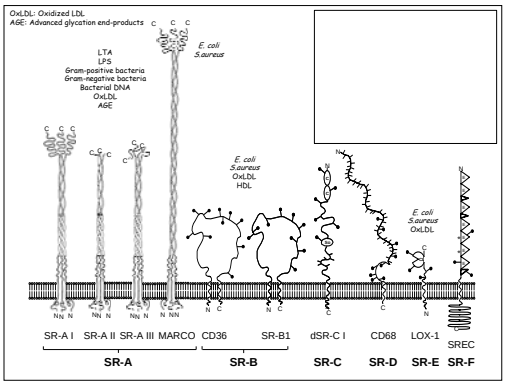
From: Akira et al., *Cell* 124:783, 2006

Collectins Can Serve as Opsonins

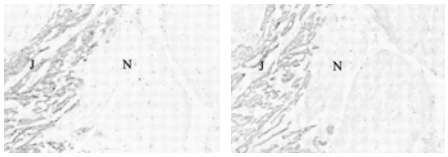


Modified from: Wright, *Nature Rev. Immunol.* **5**:58, 2005

The Scavenger Receptor Superfamily Recognizes PAMPs



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

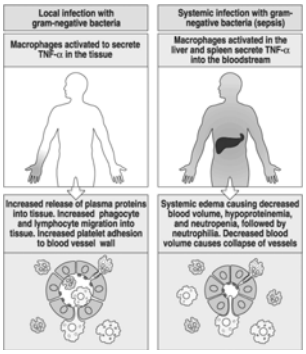


CRP C4d

J = jeopardized; N = normal

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

Innate Immune Receptors Also Trigger a Systemic Response to Infection

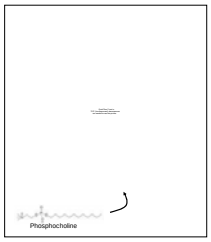


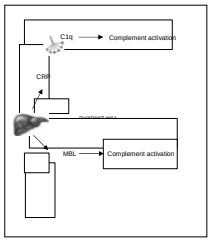
Treatment of Experimental Myocardial Infarction with a CRP-binding Analog of Phosphocholine Limits Infarct Size

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

From: Kitsis and Jialal, *New Engl. J. Med.* 355:513, 2006

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

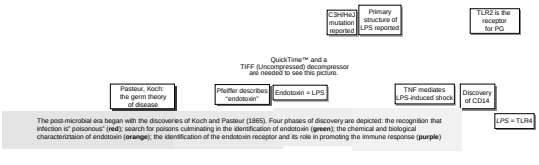




CRP acts as a bridge between phosphocholine on bacterial targets and C1q

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

History of Endotoxin Research



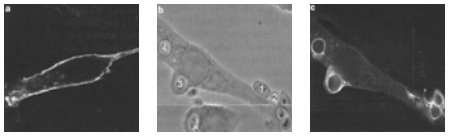
Modified from: Beutler and Rietschel, *Nature Reviews Immunology* **3**; 169-176 (2003)

Primitive Specificity in Target Recognition by the Innate Immune System


letters to nature

A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity

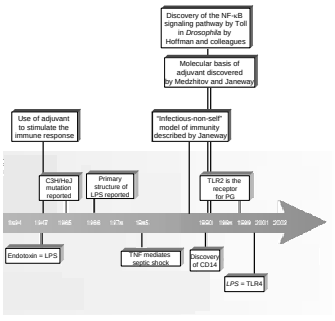
Recruitment of TLR2 to Yeast Phagosomes



TLR2 | Phase Contrast | TLR2

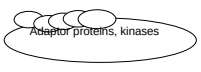
From: Underhill et al., *Nature* 401:811, 1999

A Re-interpretation of the Endotoxin Research Timeline

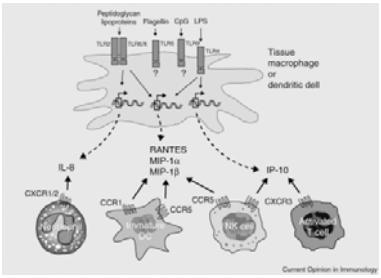


Modified from: Beutler and Rietschel, *Nature Reviews Immunology* **3**; 169-176 (2003)

Ligand Specificity of TLRs



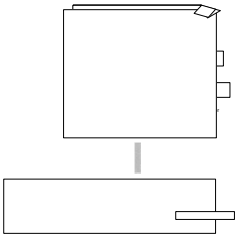
Specificity of TLR Transcriptional Programs



From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Newly Recognized Components of the Innate Immune System

TLR Signaling: Two Major Pathways

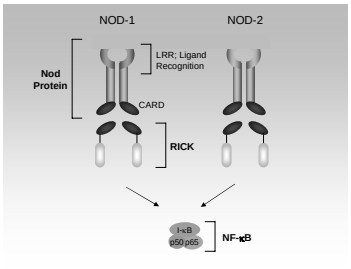


Cartoon of major signal transduction pathways following engagement of TLRs. **TLR4** is the major sensor of LPS. **TLR3** recognizes dsRNA and is important in the anti-viral response. The **IRF** pathway leading to production of **Type I IFNs** (i.e., IFN-α/β) is particularly prominent in a minor subset 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

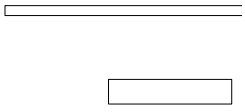
NOD Proteins: Intracellular Peptidoglycan Sensors



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

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



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

Cytosolic Bacterial Recognition Systems and "the Inflammasome"

CARD = caspase-recruitment domain
LRR = leucine-rich repeat
NOD = NOC0-like domain
MDP = muramyl dipeptide

Cytoplasm

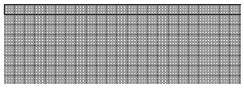
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

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

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.

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

Another Disease Associated with Activation of the Inflammasome

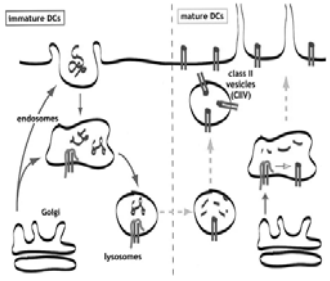
The Dendritic Cell and Development of The Primary Immune Response:

Wisdom Through Maturity

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

From: Martinon and Glimcher J. *Clin. Invest.* 116:2073, 2006

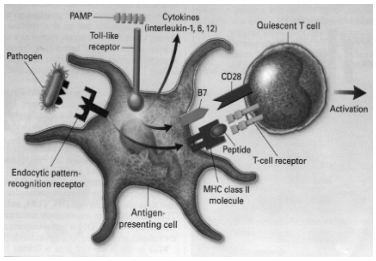
Dendritic Cell Maturation



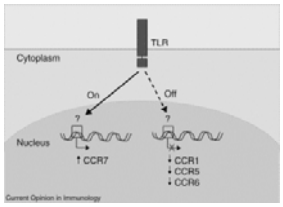
From: Mellman & Steinman, *Cell* 106:255, 2001

Question: What Triggers Maturation of DCs?

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

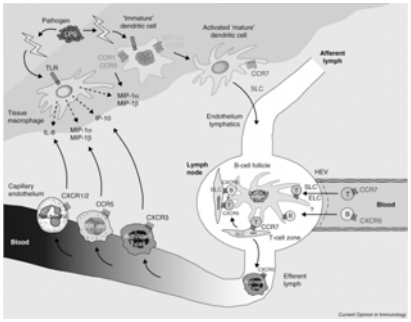


The Innate Immune Response Orchestrates DC Trafficking to Secondary Lymphoid Organs



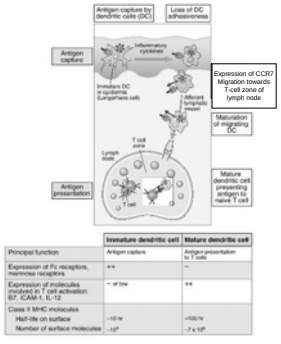
From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Chemokines Direct Trafficking of Immune Cells

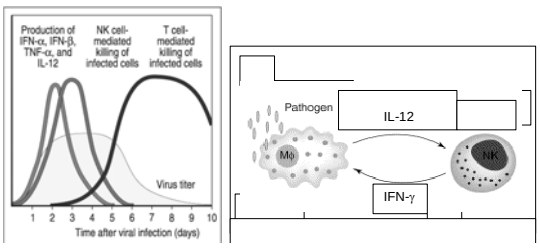


From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Functional Differences Between Immature and Mature DCs



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 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.

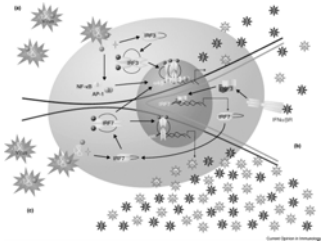
N.B.: Do <u>not</u> memorize this cartoon, but appreciate how cytosolic dsRNA receptors (RIG-1, MDA5) and plasma membrane-associated dsRNA receptors (TLR3) cooperate to activate IRF- and NF-κB-dependent gene expression.

From: Johnson and Gale, *Trends Immunol.* 27:1, 2006

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."
2. 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.
3. 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.
4. 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 (NLRs) 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 (RIG-like proteins) that activate the IRF pathway to signal antiviral gene expression.

The Antiviral Response: a Cascade of Transcriptional Events

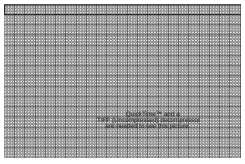


Some targets of IRFs

Gene	Function
p21	Cell cycle arrest
IL-15	NK cell maturation
FasL	Cell death
IL-12	Th1 immune response

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 IRF3. 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.

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