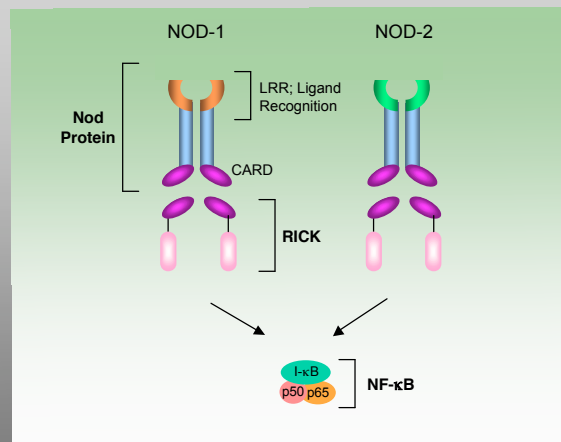


Newly Recognized Components of the Innate Immune System

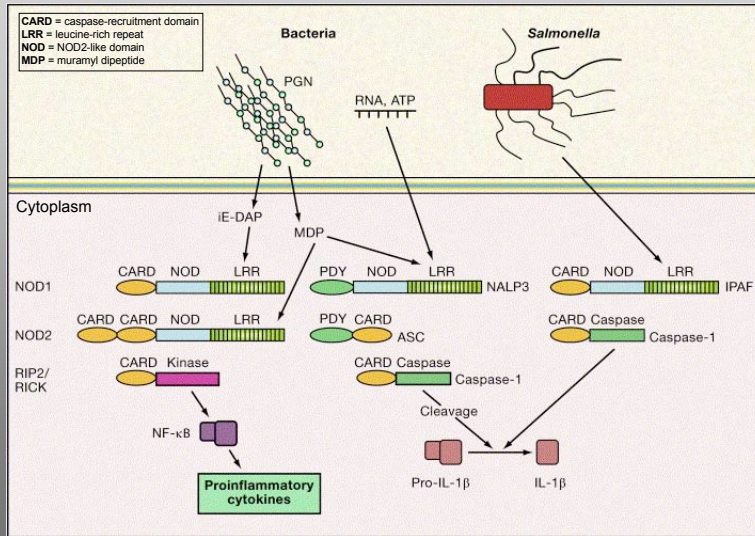
NOD Proteins: Intracellular Peptidoglycan Sensors



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

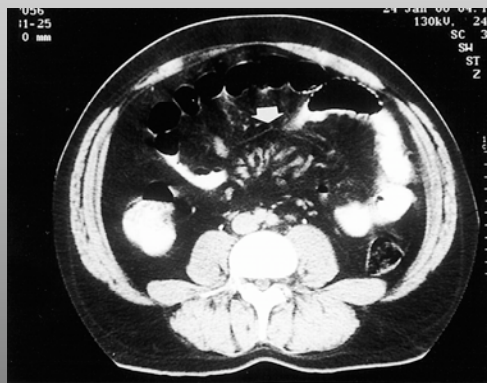
CARD, caspase-recruitment domain; **LRR**, leucine-rich repeat; **RICK**, a CARD-containing protein kinase

Cytosolic Bacterial Recognition Systems and "the Inflammasome"



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

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

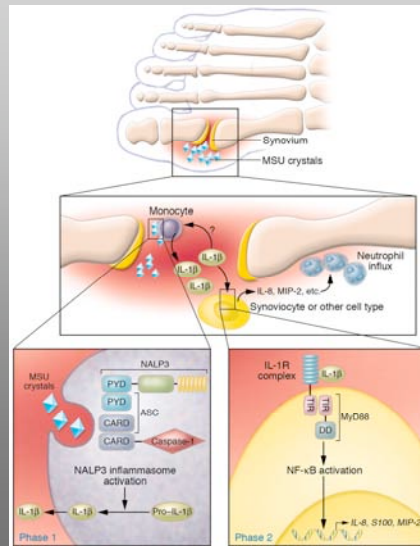


Contrast-enhanced abdominal CT from a 31 year-old patient with Familial Mediterranean Fever suffering an acute attack of abdominal pain, nausea, vomiting, and arthritis. Note mesenteric vessel with thickened mesenteric fold (*white arrow*). Histopathology demonstrated neutrophilic infiltrate and associated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

Another Disease Associated with Activation of the Inflammasome

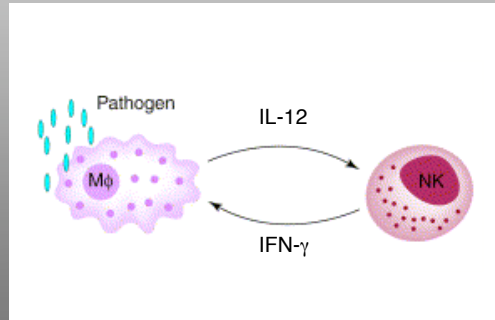
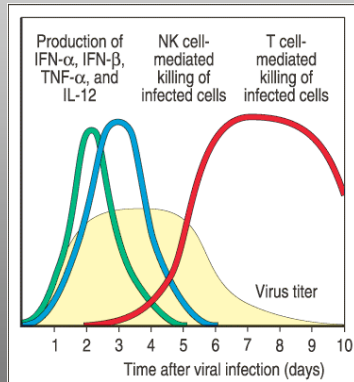


Pathogenesis of Gout Uncovered in 2006: Monosodium Urate Crystals Activate the Inflammasome



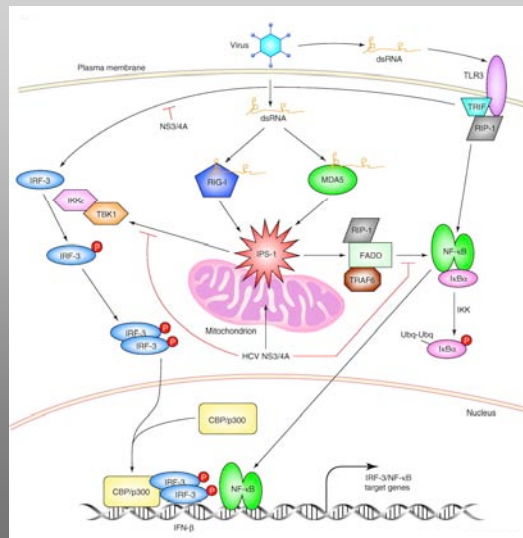
From: Martinon and Glimcher *J. Clin. Invest.* 116:2073, 2006

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

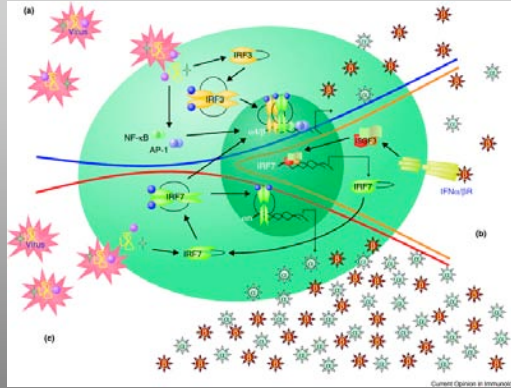


Double-stranded RNA products of virus infection bind to RIG-I or MDA5, which in turn bind to IPS-1 via CARD domain interactions. This complex then signals the activation of IKK- ϵ and TBK1 or other kinases to phosphorylate IRF-3, possibly through direct recruitment of signaling effectors, leading to 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 I κ B, the inhibitor of NF- κ B. Phosphorylated I κ B is then ubiquitinated and targeted to the proteasome for degradation, releasing the active NF- κ B complex to translocate to the nucleus. During virus infection, dsRNA products can signal through TLR3 to activate IRF-3 and NF- κ B 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-1, MDA5) and plasma membrane-associated dsRNA receptors (TLR3) cooperate to activate IRF- and NF- κ B-dependent gene expression.

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

The Antiviral Response: a Cascade of Transcriptional Events

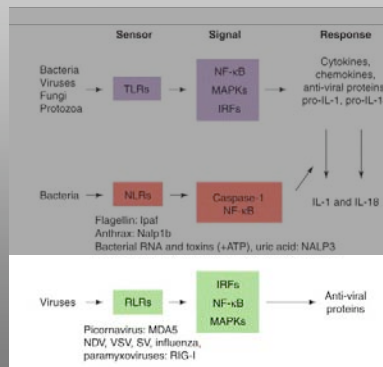


Some targets of IRFs

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

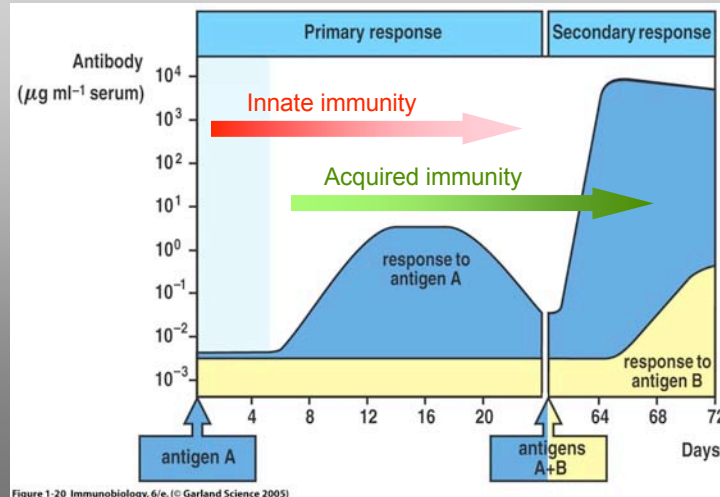
Multiphasic induction of murine type I IFN genes can be divided into three phases. (a) The immediate early phase. Virus infection stimulates a phosphorylation cascade, leading to the activation of at least three families of transcription factors, including NF- κ B, AP-1 and IRF3. Activation of the IFN- 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

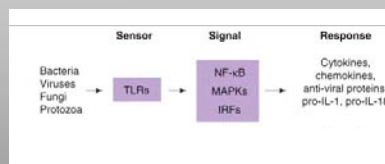


Adapted from: Creagh and O'Neill, *Trends Immunol.* 27:352, 2006

How does the Innate Response affect the Acquired Immune Response?

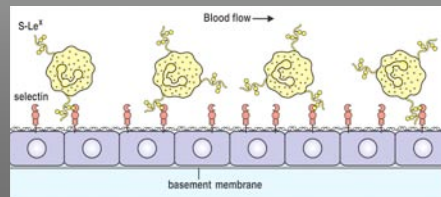
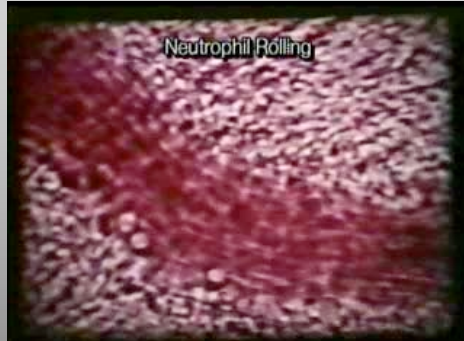


TLRs Sense Microbial Pathogens and Trigger Expression of Pro-inflammatory Cytokines and Chemokines



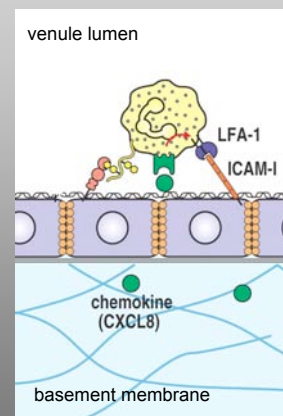
Adapted from: Creagh and O'Neill, *Trends Immunol.* 27:352, 2006

Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia



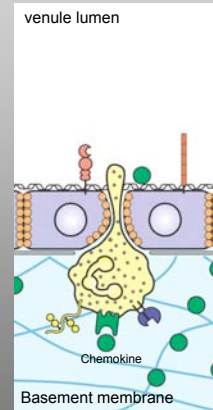
Movie, courtesy T. Springer

Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins



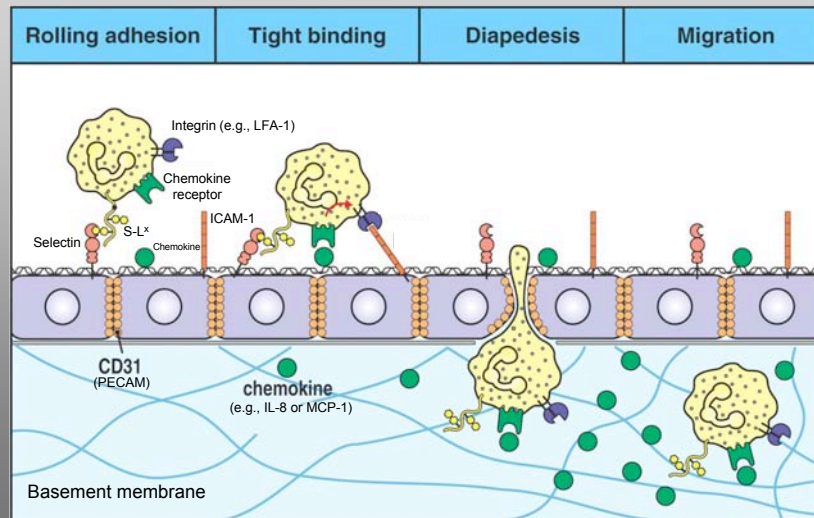
Movie, courtesy T. Springer

Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue



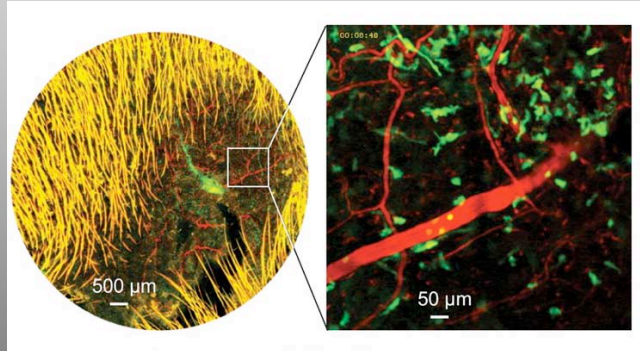
Movie, courtesy T. Springer

Leukocyte Migration, Start to Finish



Modified from: Parham, *The Immune System, 2nd ed.* (Garland: New York), 2005

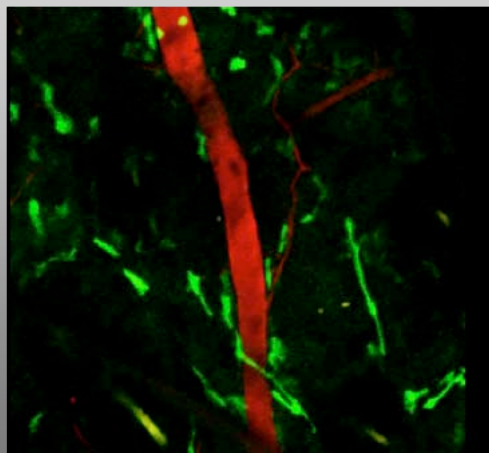
Intravital Imaging of a Subset of Mouse Monocytes in Dermal Blood Vessels



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

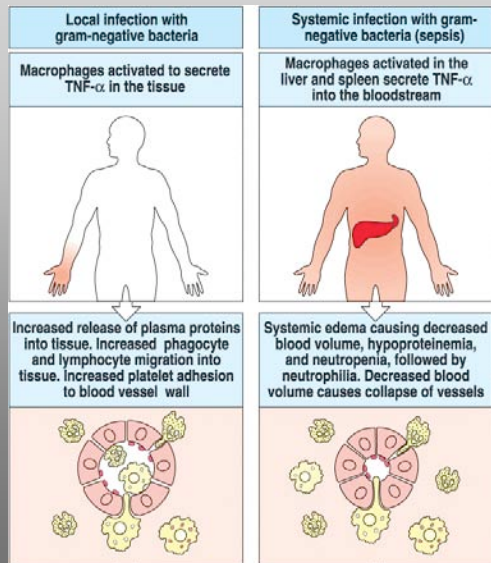
From: Auffray et al., *Science* 317:666, 2007

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

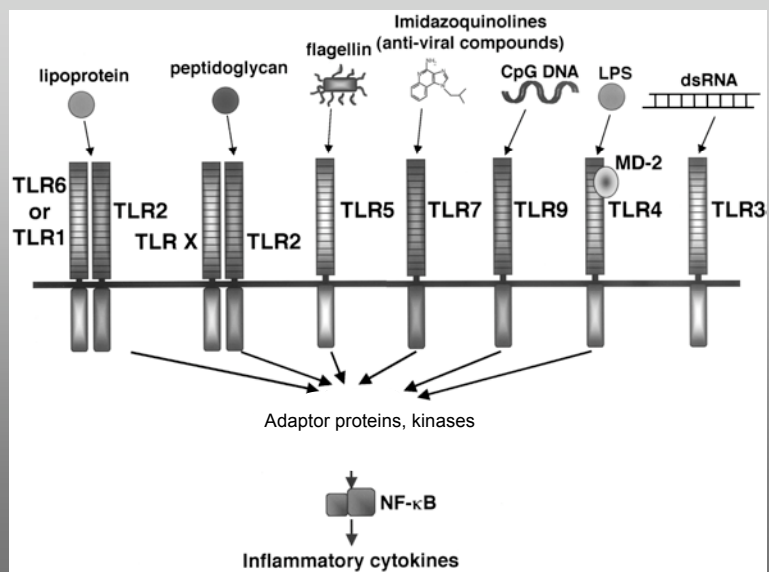


From: Auffray et al., *Science* 317:666, 2007

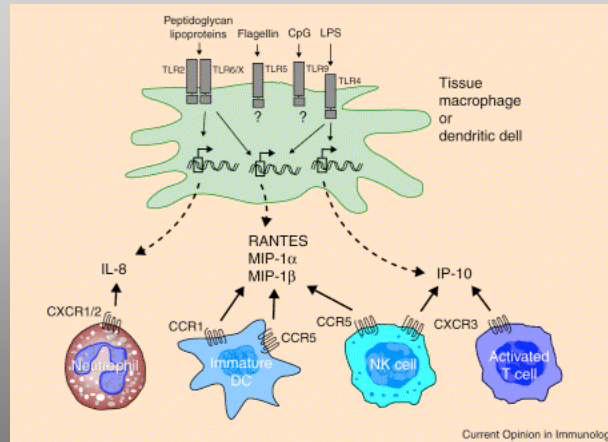
Innate Immune Receptors Also Trigger a Systemic Response to Infection



Ligand Specificity of TLRs

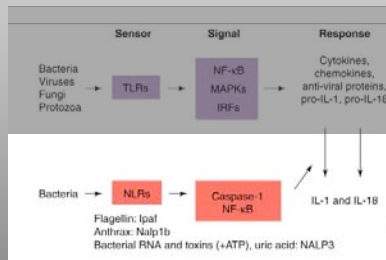


Specificity of TLR Transcriptional Programs



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

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

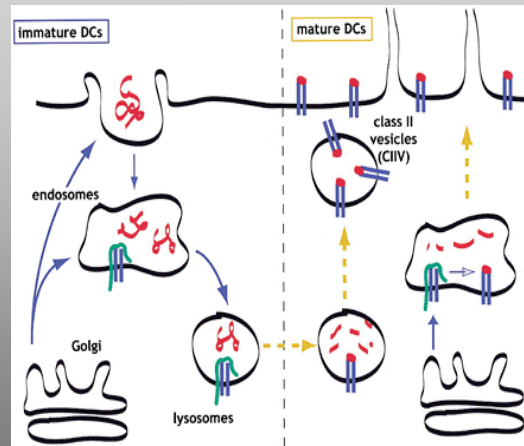


Adapted from: Creagh and O'Neill, *Trends Immunol.* 27:352, 2006

The Dendritic Cell and Development of The Primary Immune Response:

Wisdom Through Maturity

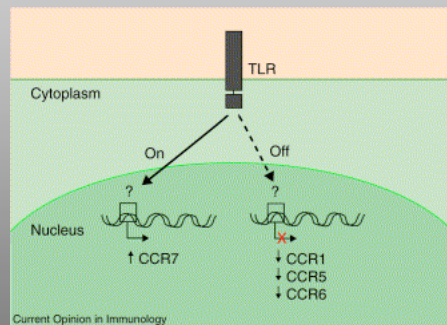
Dendritic Cell Maturation



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

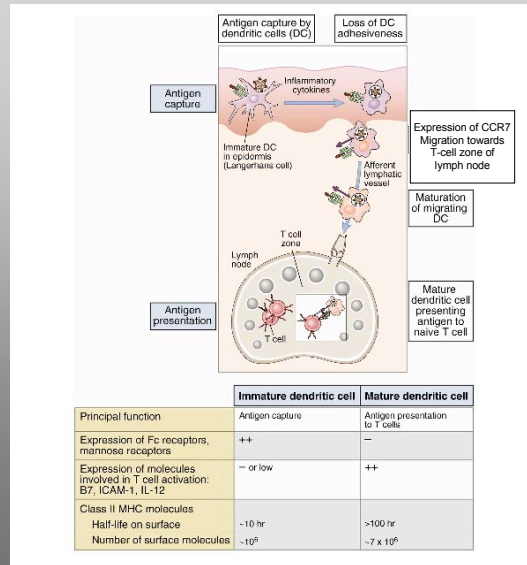
Question: What Triggers Maturation of DCs?

The Innate Immune Response Orchestrates DC Trafficking to Secondary Lymphoid Organs

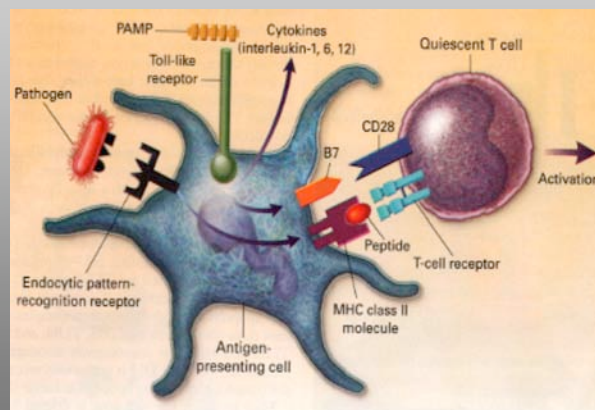


From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

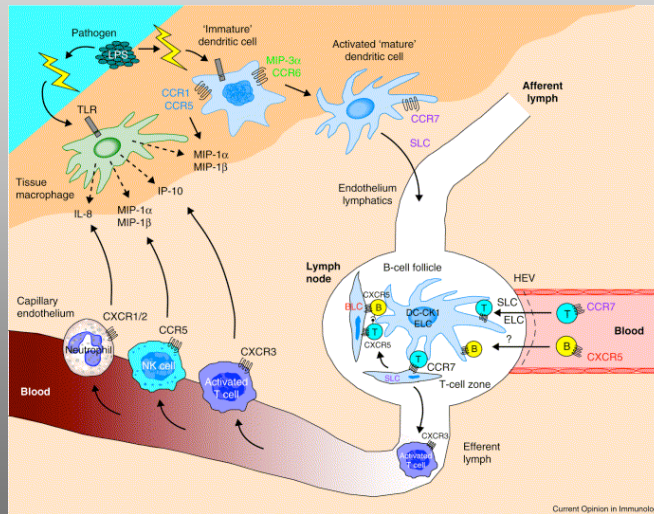
Functional Differences Between Immature and Mature DCs



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



Chemokines Direct Trafficking of Immune Cells



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

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