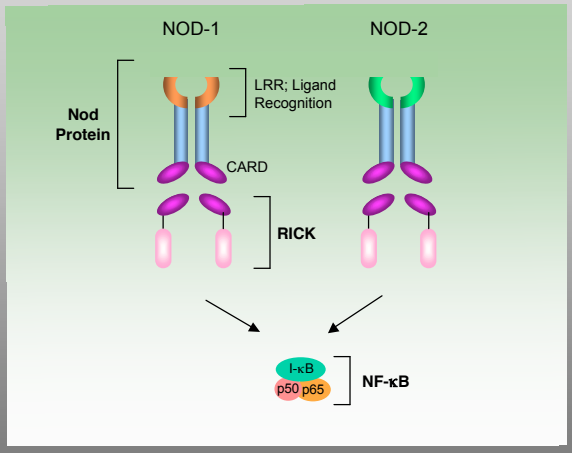
Newly Recognized Components of the Innate Immune System

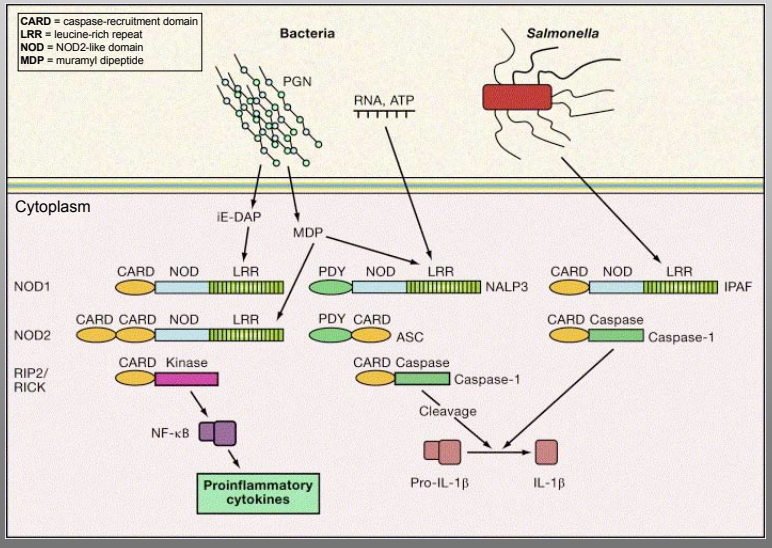
NOD Proteins: Intracellular Peptidoglycan Sensors



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

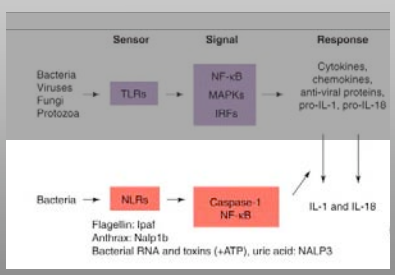
CARD, caspase-recruitment domain; **LRR**, leucine-rich repeat; **RICK**, a CARD-containing protein kinase

Cytosolic Bacterial Recognition Systems and "the Inflammasome"



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

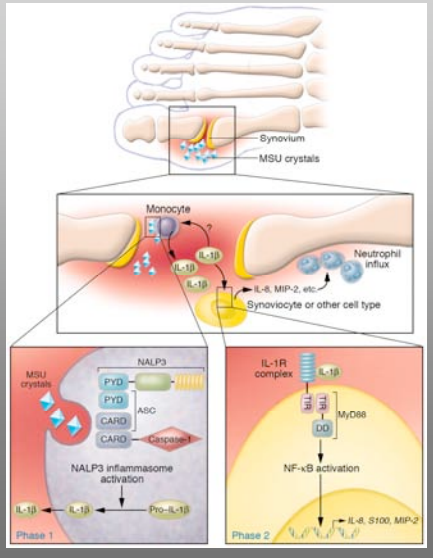
Nod-like Receptors (NLRs) Sense Microbial Products, Activate the "Inflammasome," and Trigger Maturation of IL-1



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

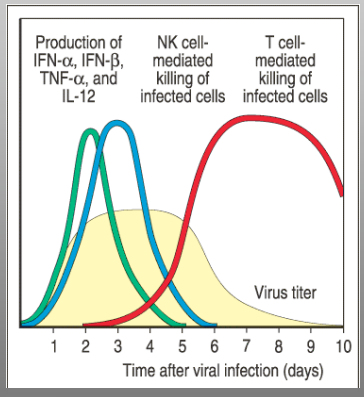
A Disease Associated with Activation of the Inflammasome

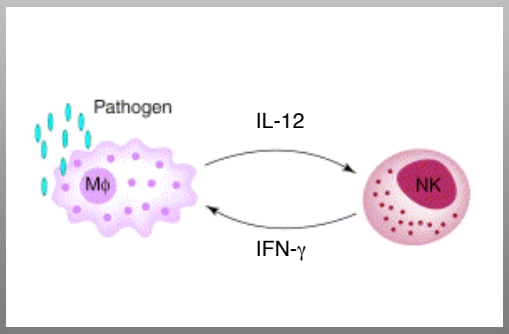
Pathogenesis of Gout Uncovered in 2006: Monosodium Urate Crystals Activate the Inflammasome



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

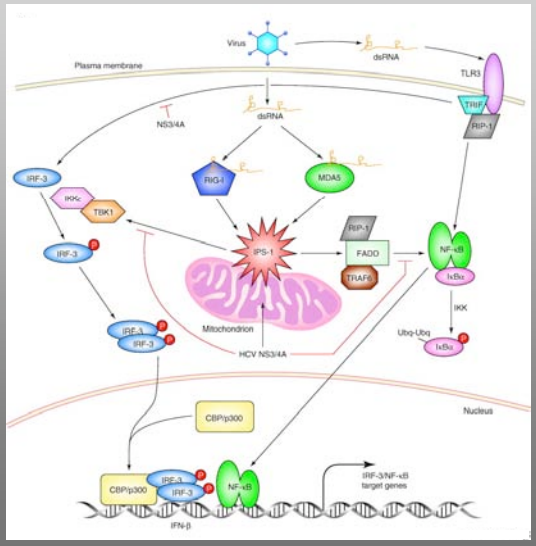
The Early Antiviral Response and the Innate Immune System





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

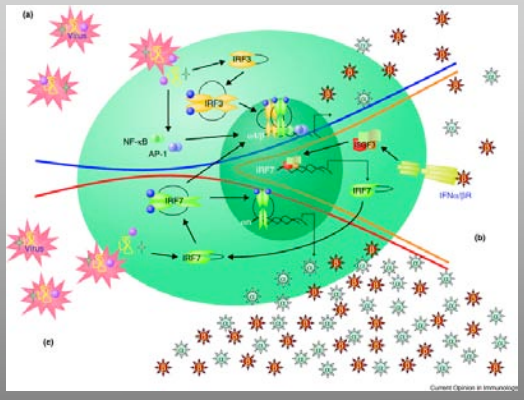


Double-stranded RNA products of virus infection bind to RIG-I or MDA5, which in turn bind to IPS-1 via CARD domain interactions. This complex then signals the activation of IKK-ε and TBK1 or other kinases to phosphorylate IRF-3, possibly through direct recruitment of signaling effectors, leading to IRF-3 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 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

The Antiviral Response: a Cascade of Transcriptional Events

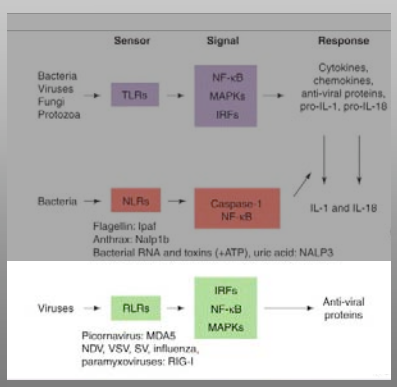


Some targets of IRFs

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

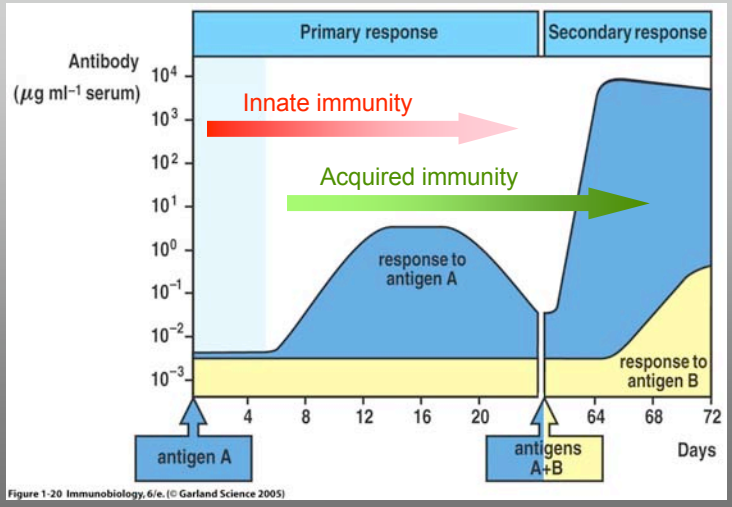
Multiphasic induction of murine type I IFN genes can be divided into three phases. (a) The immediate early phase. Virus infection stimulates a phosphorylation cascade, leading to the activation of at least three families of transcription factors, including NF-κB, AP-1 and IRF3. Activation of the IFN-α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

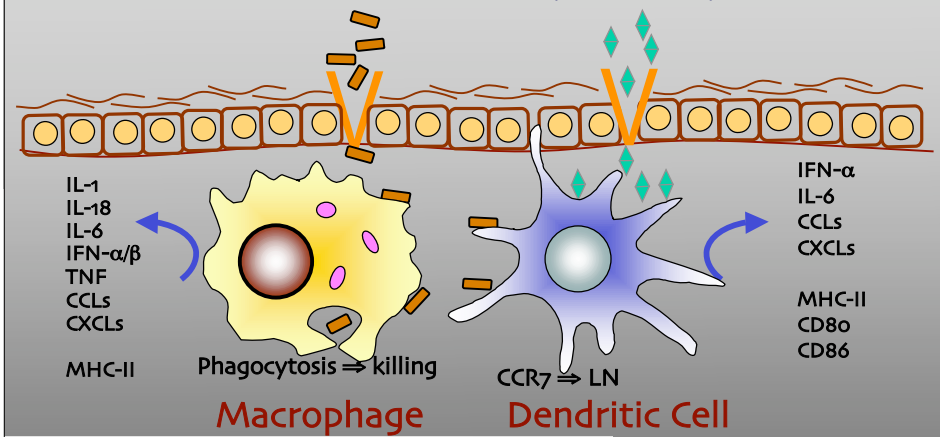


Adapted from: Creagh and O'Neill, *Trends Immunol.* 27:352, 2006

How does the Innate Response affect the Acquired Immune Response?

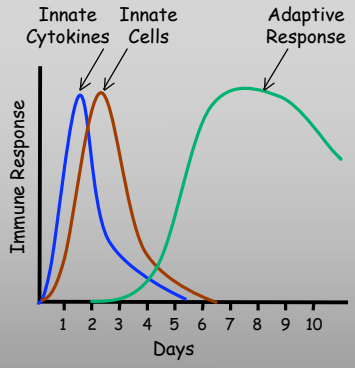


Cytokines and chemokines produced by innate cells influence the adaptive response



- Barrier
- Innate Receptors
- Cytokines
- Chemokines

Innate Vs. Adaptive Immunity



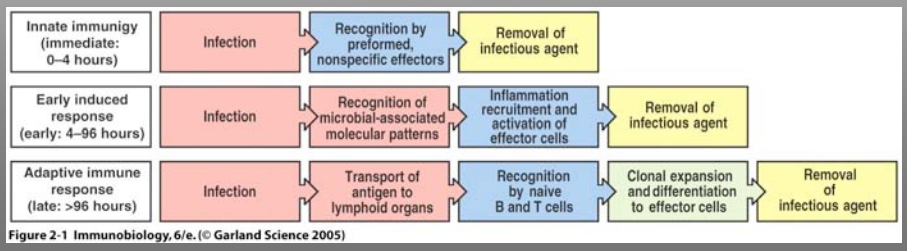
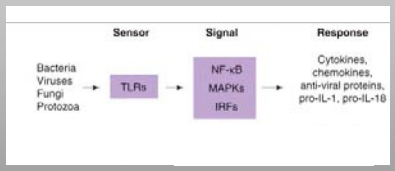


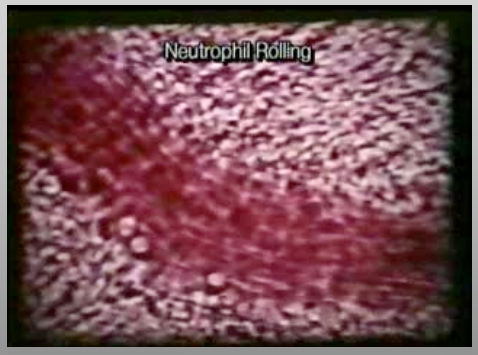
Figure 2-1 Immunobiology, 6/e. (© Garland Science 2005)

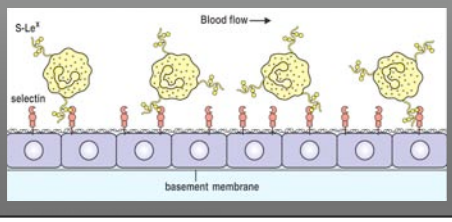
TLRs Sense Microbial Pathogens and Trigger Expression of Pro-inflammatory Cytokines and Chemokines



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

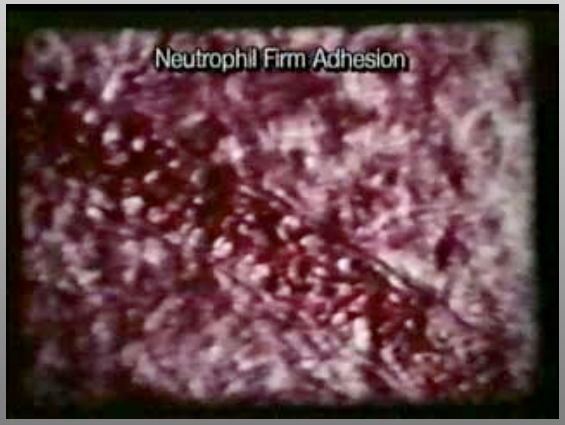
Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia

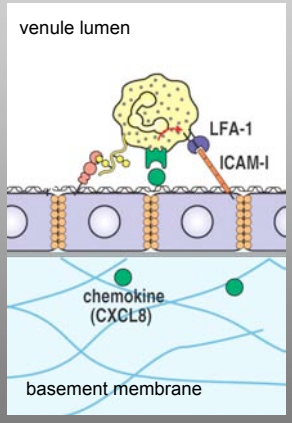




Movie, courtesy T. Springer

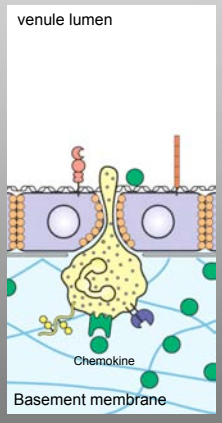
Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins





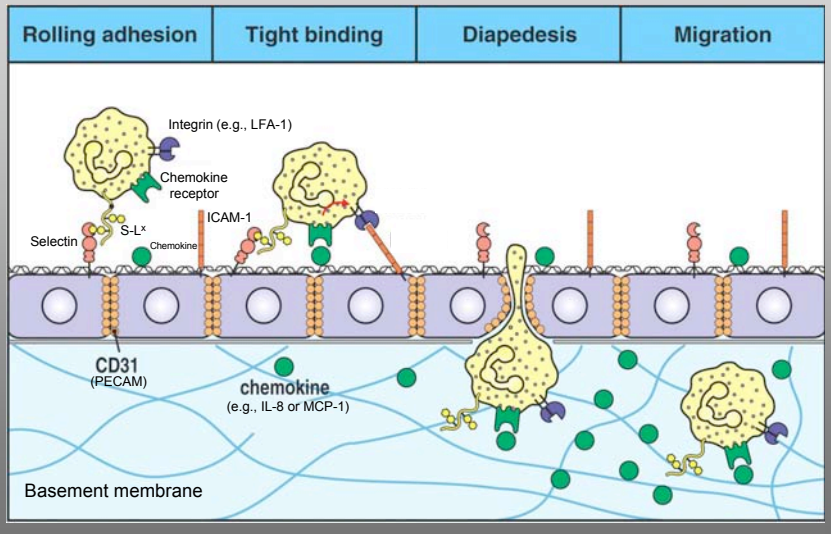
Movie, courtesy T. Springer

Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue



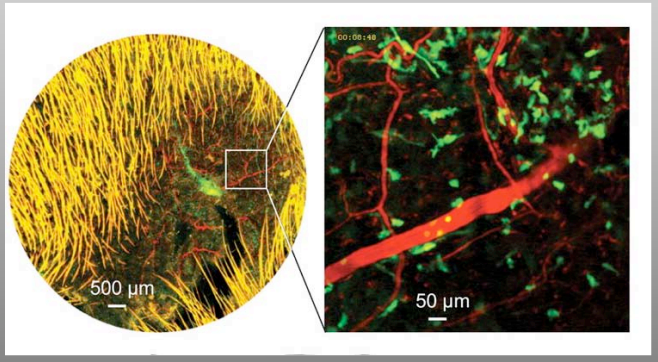
Movie, courtesy T. Springer

Leukocyte Migration, Start to Finish



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

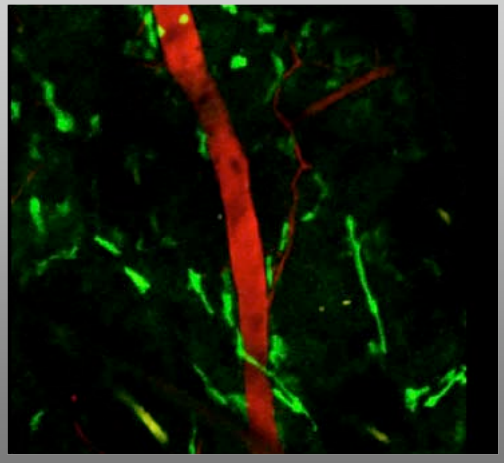
Intravital Imaging of a Subset of Mouse Monocytes in Dermal Blood Vessels



CX_3CR1-expressing cells express GFP in reporter mice, and dermal blood vessels are labeled with rhodamine-conjugated dextran.

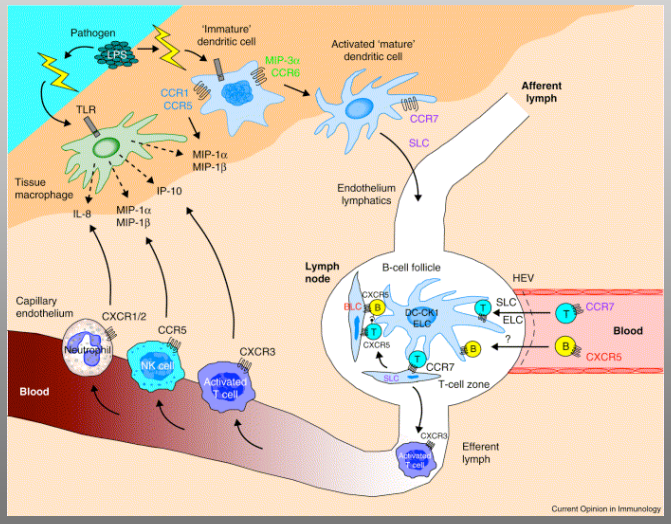
From: Auffray et al., *Science* 317:666, 2007

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



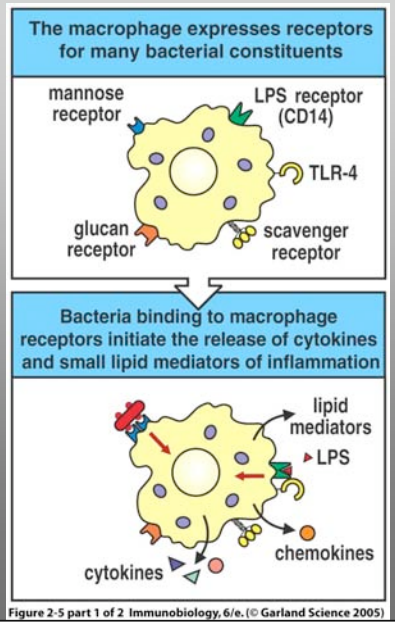
From: Auffray et al., *Science* 317:666, 2007

Chemokines Direct Trafficking of Immune Cells

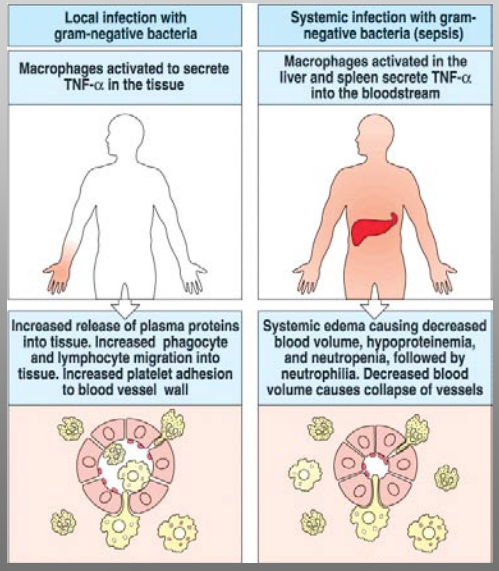


From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

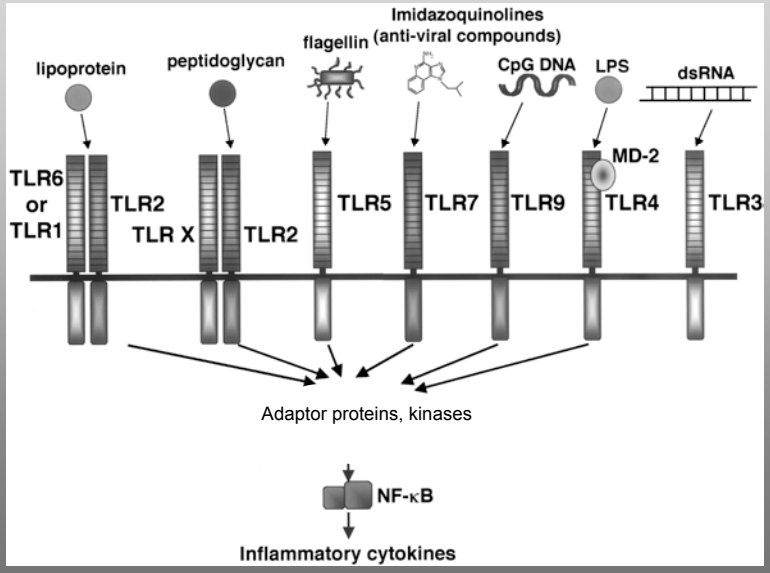
PRRs detect the infection



Innate Immune Receptors Also Trigger a Systemic Response to Infection



Ligand Specificity of TLRs



Cytokines and Chemokines recruit WBCs

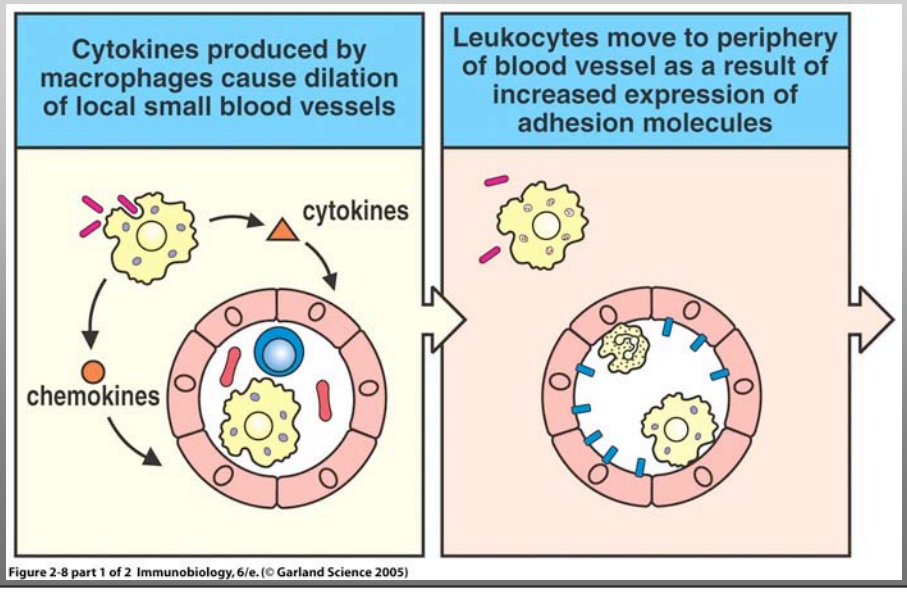


Figure 2-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Cytokines & Chemokines direct the growing immune response

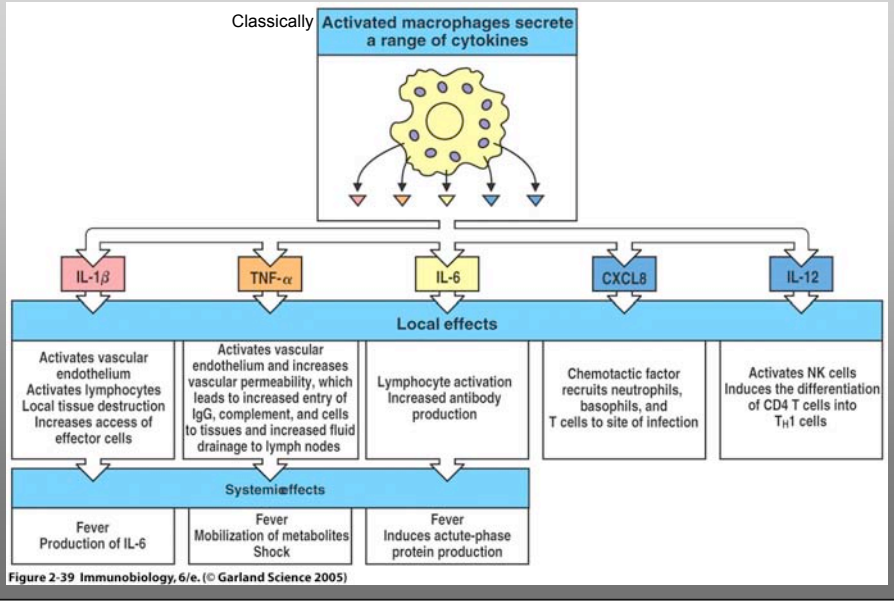
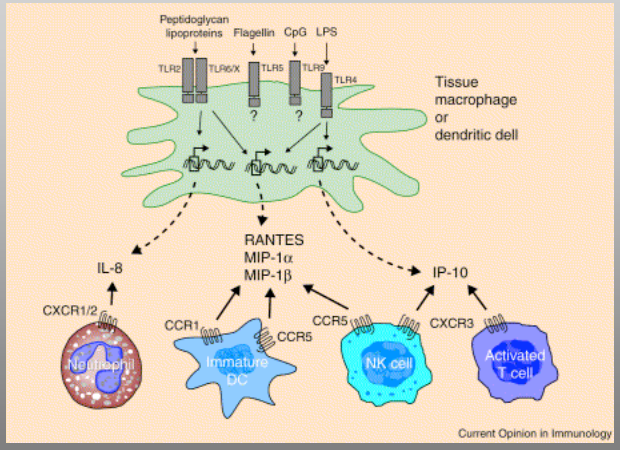


Figure 2-39 Immunobiology, 6/e. (© Garland Science 2005)

Specificity of TLR Transcriptional Programs



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

What do cytokines, chemokines and growth factors do?

They direct the development, maturation, localization, interactions, activation and life span of immune cells (they also regulate activity of non-immune cells).

Thus, they play an essential role in regulating both innate and adaptive immunity, serving as a critical interface between these two limbs of the immune system.

Dendritic Cells pick up antigen, get activated and migrate to lymph nodes

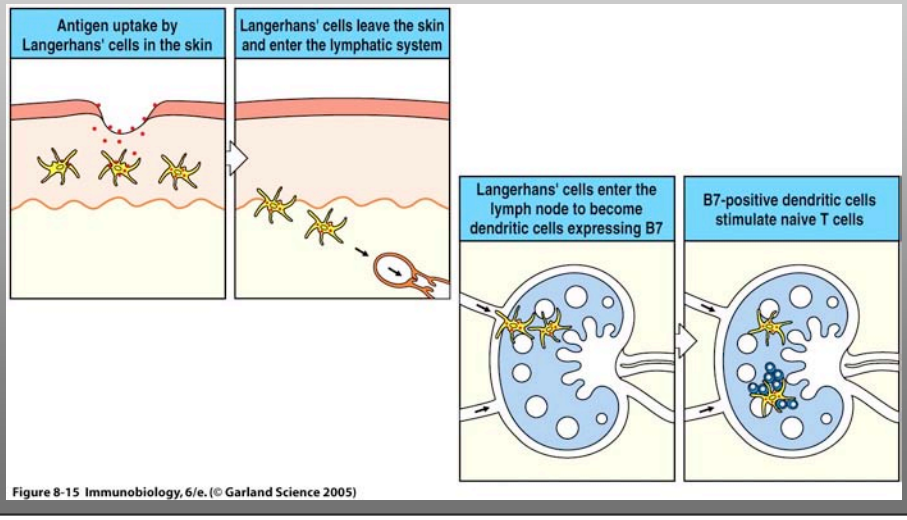


Figure 8-15 Immunobiology, 6/e. (© Garland Science 2005)

Morphology of dendritic cells in different compartments

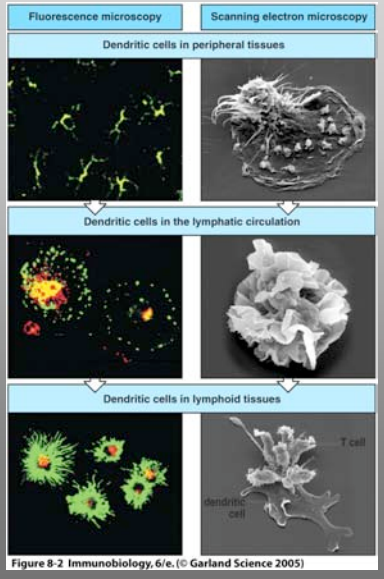


Figure 8-2 Immunobiology, 6/e. (© Garland Science 2005)

The three major kinds of APC's

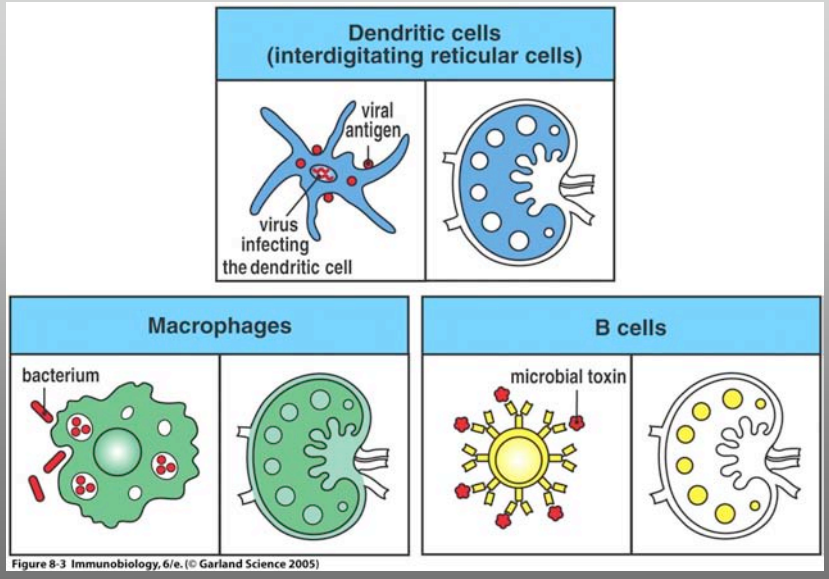


Figure 8-3 Immunobiology, 6/e. (© Garland Science 2005)

Properties of the different APC's

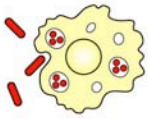
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutiveby mature, nonphagocyticlymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellularand extracellularpathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Figure 8-18 Immunobiology, 6/e. (© Garland Science 2005)

Naïve CD4 cells kiss APCs to sample them for right antigen ($1<10^4$-10^6)

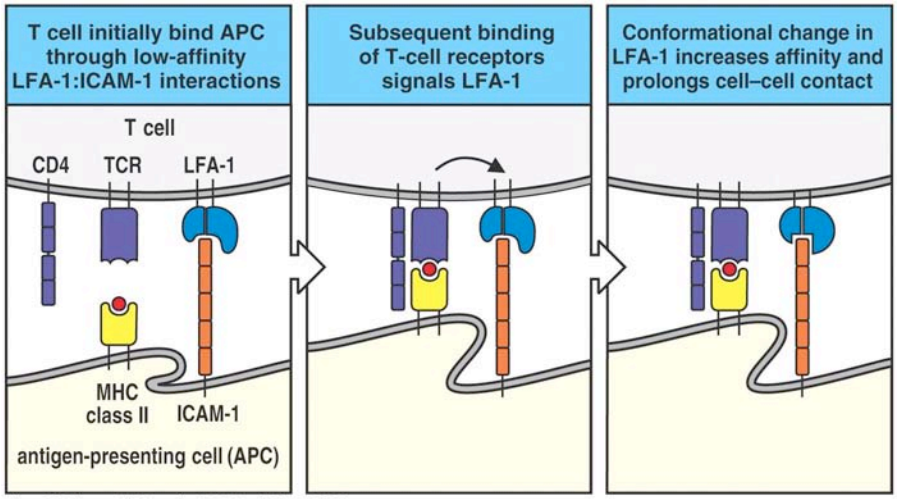


Figure 8-9 Immunobiology, 6/e. (© Garland Science 2005)

Different adhesion molecules involved in T-cell-APC interactions

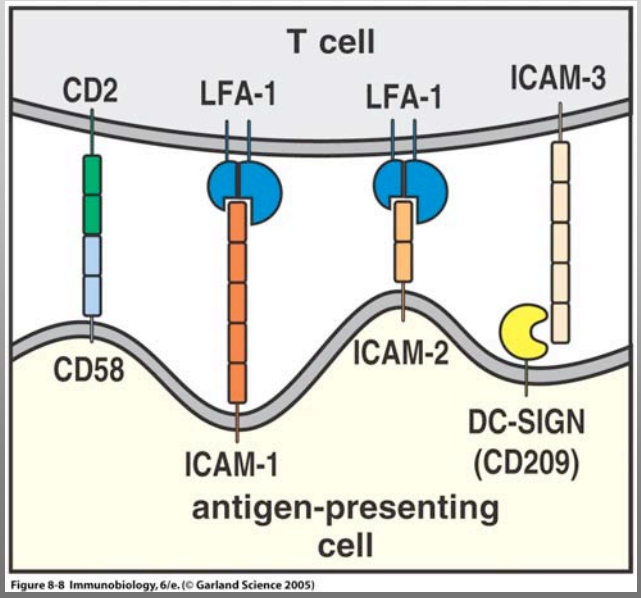


Figure 8-8 Immunobiology, 6/e. (© Garland Science 2005)

Signal #1 (TCR) and Signal #2 (co-receptors) direct activation of naïve T-cells.

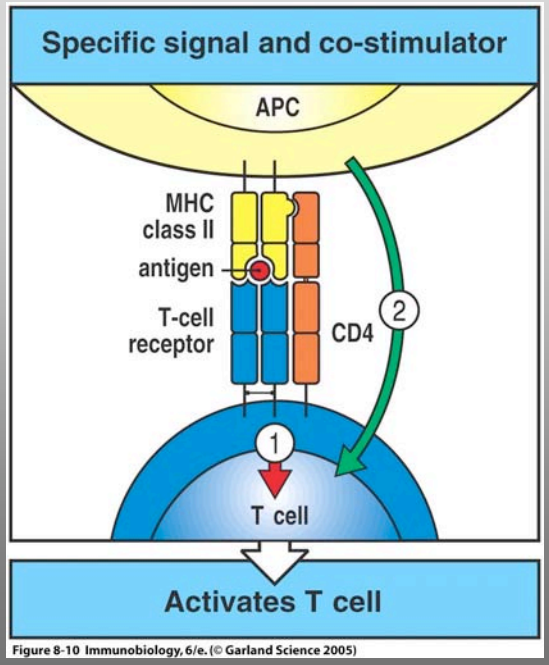


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

Co-stimulatory signals help prevent recognition of self-antigens

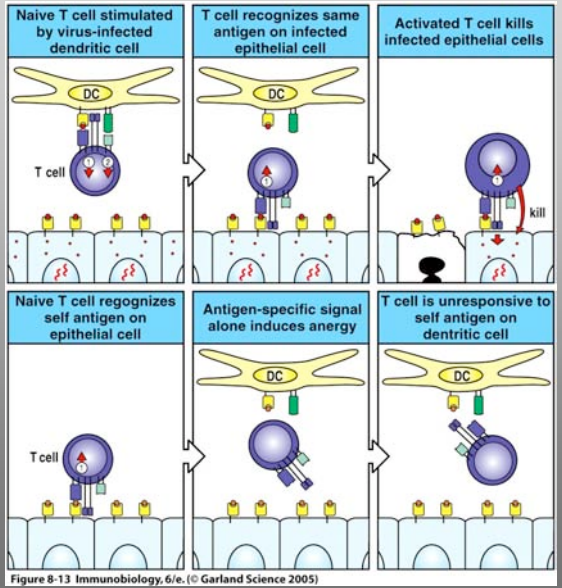


Figure 8-13 Immunobiology, 6/e. (© Garland Science 2005)

Activation without co-stimulatory signal leads to anergy

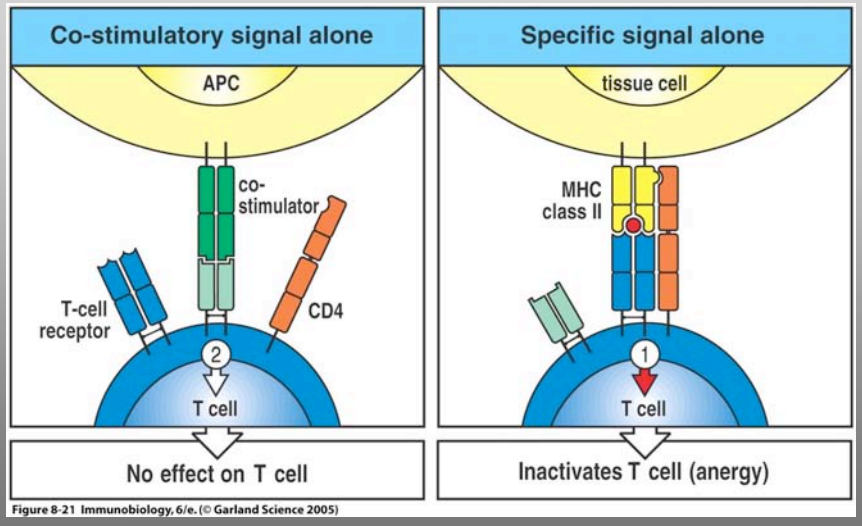
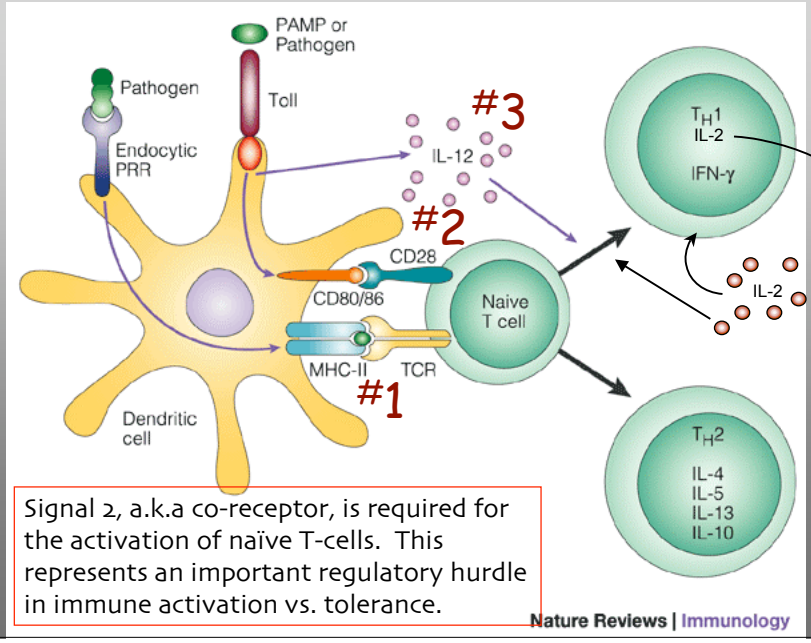


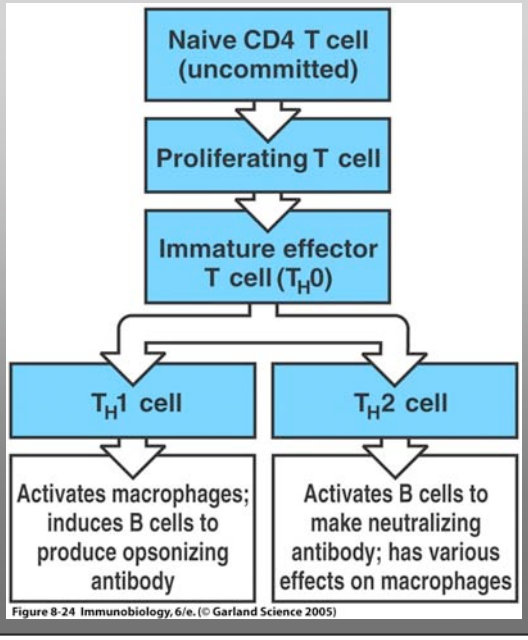
Figure 8-21 Immunobiology, 6/e. (© Garland Science 2005)

Cytokines direct Th1-Th2 polarization



Signal 2, a.k.a co-receptor, is required for the activation of naïve T-cells. This represents an important regulatory hurdle in immune activation vs. tolerance.

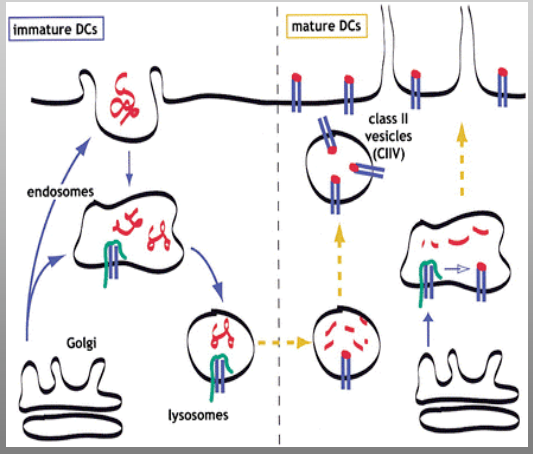
Different functional properties of Th1 and Th2 cells



The Dendritic Cell and Development of The Primary Immune Response:

Wisdom Through Maturity

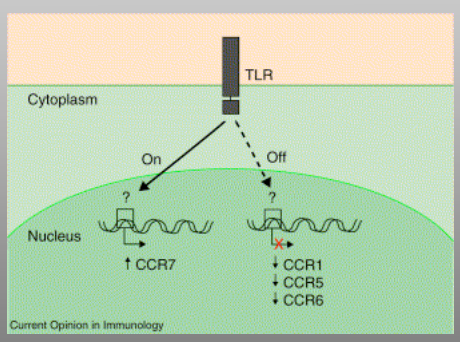
Dendritic Cell Maturation



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

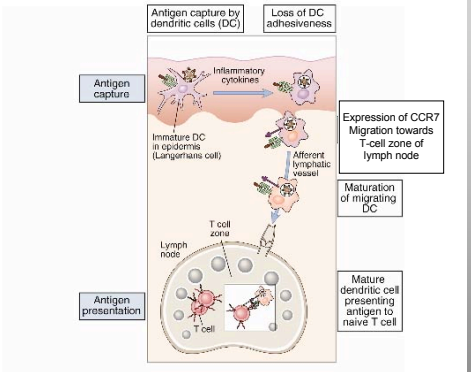
Question: What Triggers Maturation of DCs?

The Innate Immune Response Orchestrates DC Trafficking to Secondary Lymphoid Organs



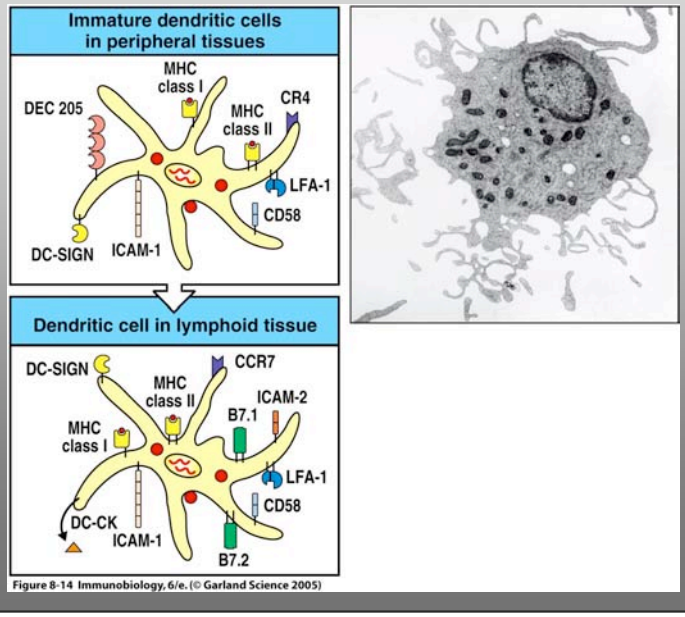
From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Functional Differences Between Immature and Mature DCs

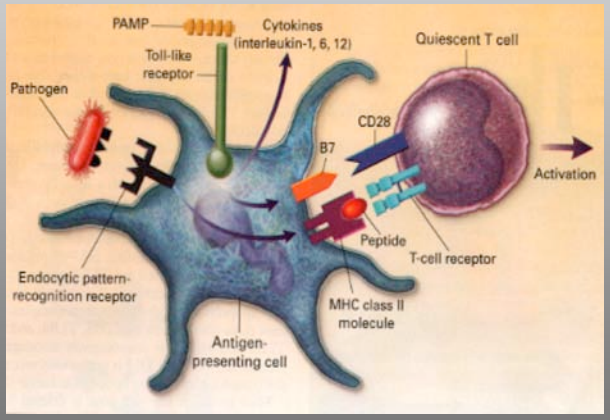


	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	–
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	– or low	++
Class II MHC molecules		
Half-life on surface	~10 hr	>100 hr
Number of surface molecules	~10^6	~7×10^6

Maturation of dendritic cells involves expression of specific genes



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



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