How do primitive metazoans survive without an acquired immune system?

How important is innate immunity for higher metazoans?

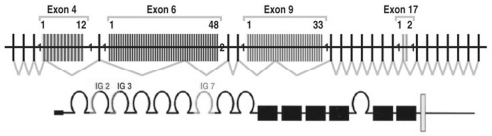
Mechanisms of Generating Immunological Diversity in Primitive Metazoans

Taxonomic group	Genetic variability (polymorphism+polyclonism)	Somatic variability			
		Alternative splicing	Mutation, conversion	Rearrangement	Combinatorial association of peptides
Nematodes	Lectins				
Mollusks	Fibrinogen-related proteins (immunoglobulin SF), lectins (s)	Fibrinogen-related proteins (immunoglobulin SF)	Fibrinogen-related proteins (immunoglobulin SF)		
Arthropods	**Thioester-containing proteins, peptidoglycan binding proteins (s), Gram-negative binding protein, lectins (s), Toll-like receptor (leucine-rich repeat)**	**Dscam (immunoglobulin SF) (s),** peptidoglycan binding proteins (s)			
Echinoderms	Scavenger receptor cysteine rich (s), 185/333	Scavenger receptor cysteine rich (s), 185/333			
Prochordates	**Variable region-containing chitin binding protein (immunoglobulin SF),** lectins (s), Toll-like receptors (leucine-rich repeat)				
Agnathans	Agnathan paired receptors resembling Ag receptors (immunoglobulin SF), variable lymphocyte receptor (leucine-rich repeat)		Variable lymphocyte receptor?	Variable lymphocyte receptor	
Gnathostomes	Many immunoglobulin SF multigene families (s), Toll-like receptor (leucine-rich repeat), lectins (s), peptidoglycan binding proteins (s), **complement,** major histocompatibility complex class I and II	Immunoglobulin SF families (s)	Immunoglobulin (s)	Immunoglobulin (s), T cell receptor	Immunoglobulin (s), T cell receptor, Toll-like receptors (leucine-rich repeat), major histocompatibility complex class I and II

Red, membrane-associated; **Black**, soluble

From: Du Pasquier *Science* 309:1826, 2005

Dscam, a Secreted Opsonic Protein with Extensive Alternative Splicing in *Drosophila*

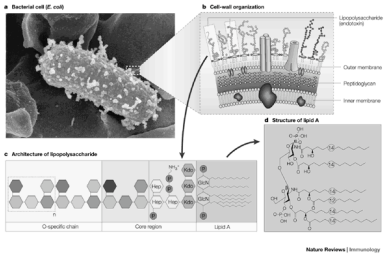


From: Watson et al., *Science* 309:1874, 2005

The Innate Immune Response to Bacterial and Fungal Infections

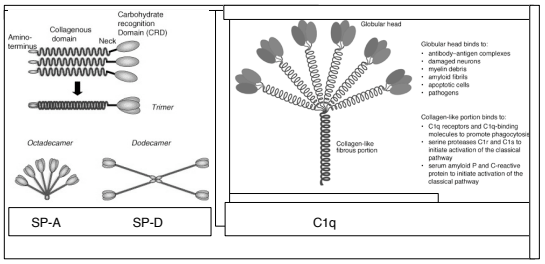
The Innate Immune Response is Conserved Throughout Evolution and is Triggered by Pattern Recognition

Lipopolysaccharide is Composed of Lipid and Polysaccharide

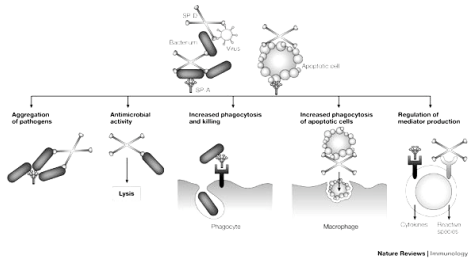


From: Beutler and Rietschel, *Nature Reviews Immunology* **3;** 169-176 (2003)

Collectins and Innate Immune Recognition

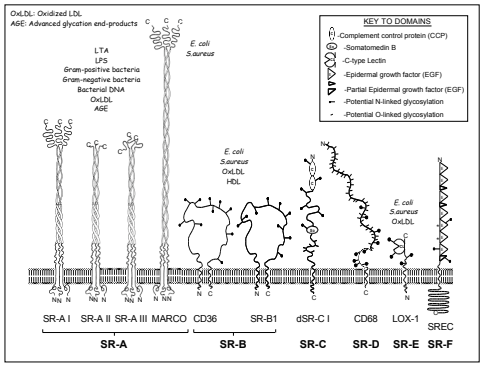


Some Functions of Collectins

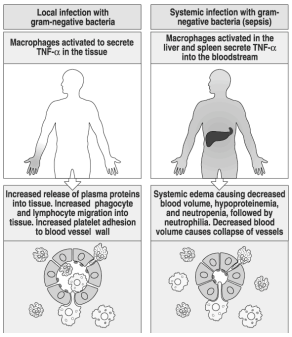


From: Wright, *Nature Rev. Immunol.* **5**:58, 2005

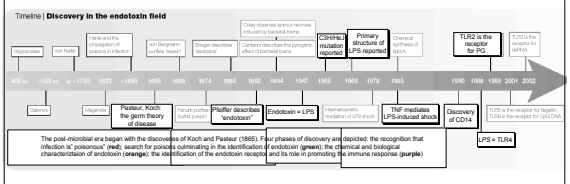
The Scavenger Receptor Superfamily



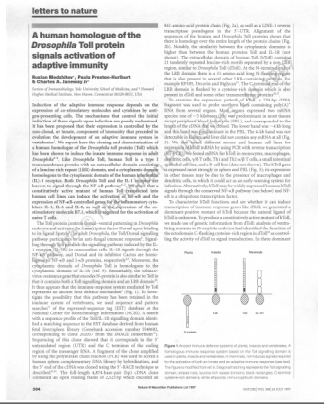
Receptors Important in The Systemic Response to Infection



History of Endotoxin Research



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

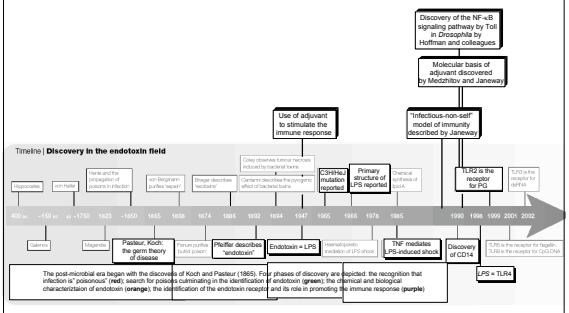


letters to nature

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

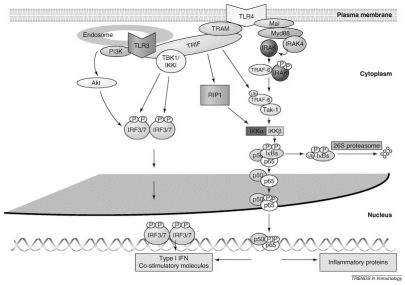
Nature 388, 394–397 (1997)

A Re-interpretation of the Endotoxin Research Timeline



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

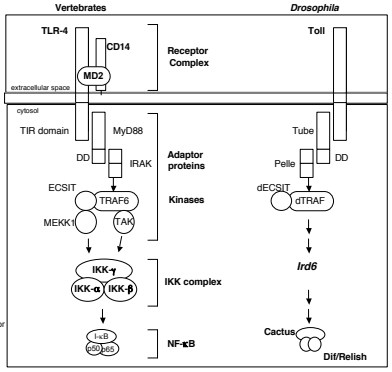
TLR Signaling: Not So Simple



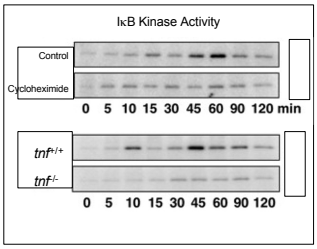
Cartoon of major signal transduction pathways following engagement of TLRs. TLR4 is the major sensor of LPS. TLR3 recognizes dsRNA and is important in the anti-viral response. The IRF pathway leading to production of Type I IFNs (i.e., IFN-α/β) is particularly prominent in a minor subset of dendritic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

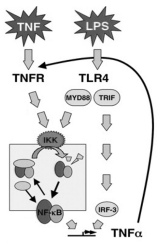
From: Moynagh, *Trends Immunol.* 26:469, 2005

Selected Pro-inflammatory TLR Signaling Components



Positive Feedback Loops in Innate Immunity



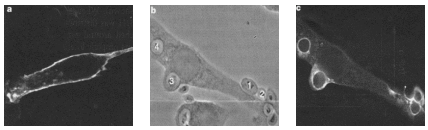


The existence of multiple, overlapping positive feedback loops helps explain why targeting any one pro-inflammatory mediator is typically ineffective in the treatment of severe, systemic inflammation (e.g., during Gram-negative septicemia).

From Werner et al., *Science* 309:1826, 2005

Primitive Specificity in Target Recognition by the Innate Immune System

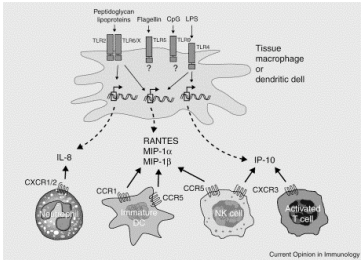
Recruitment of TLR2 to Yeast Phagosomes



TLR2 **Phase Contrast** **TLR2**

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

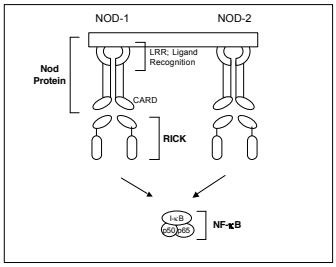
Specificity of TLR Transcriptional Programs



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

Newer Innate Immune Proteins

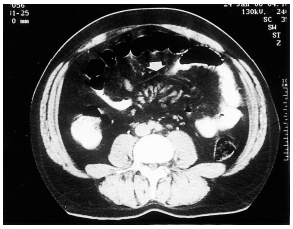
NOD Proteins: Intracellular Peptidoglycan Sensors



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

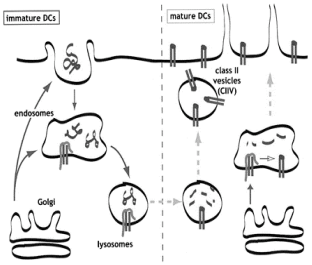
Mutations in Pyrin, Another CARD-containing Innate Immune-like Protein, is Responsible for Familial Mediterranean Fever



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.

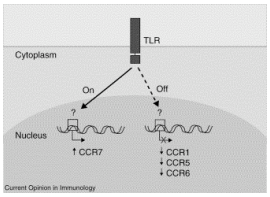
The Dendritic Cell and Development of The Primary Immune Response

Dendritic Cell Maturation



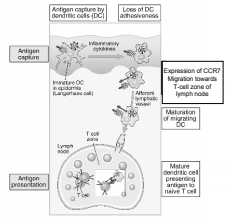
From: Mellman & Steinman, *Cell* 106:255, 2001

The Innate Immune Response Orchestrates DC Trafficking to Secondary Lymphoid Organs



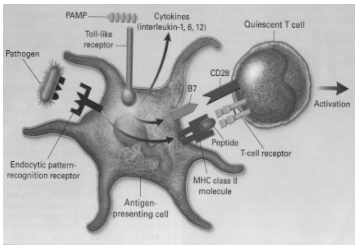
From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Functional Differences Between Immature and Mature DCs

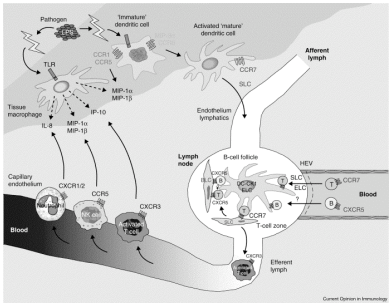


	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	–
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	– or low	++
Class II MHC molecules		
Half-life on surface	~10 hr	>100 hr
Number of surface molecules	~10^6	~2×10^6

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

The Early Antiviral Response: Cytokines of the Innate Immune System

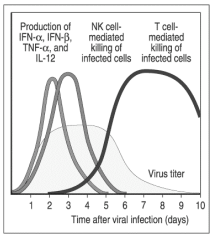
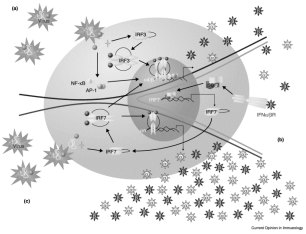


Fig 2.41 © 2001 Garland Science

The Antiviral Response: a Cascade of Transcriptional Events

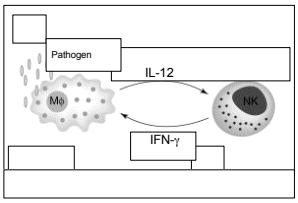


Some targets of IRFs

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.

NK Cells are an Important Early Source of IFN-γ



Modified from: Cooper et al., *Trends Immunol.* 22:633, 2001

Summary

1. Innate immunity is conserved throughout evolution and is triggered by recognition of repetitive 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 (AGEs) 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. Via engagement of a series of adaptor proteins and kinases, it triggers activation of NF-κB (leading to production of TNF-α, for example) and the IRF pathway (and production of IFN-α/β).

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.

6. NK cells, a component of innate immunity, especially to viruses, represent an early source of IFN-γ which serves to stimulate macrophages in inflammatory sites.