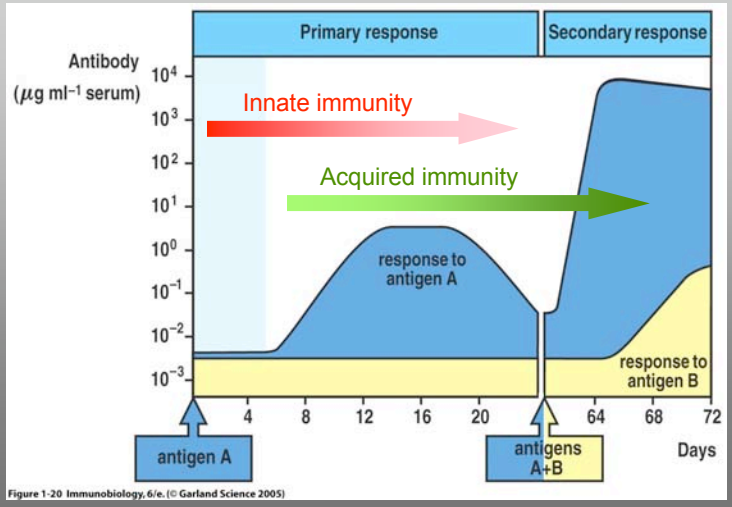
The Innate Immune Response to Infections

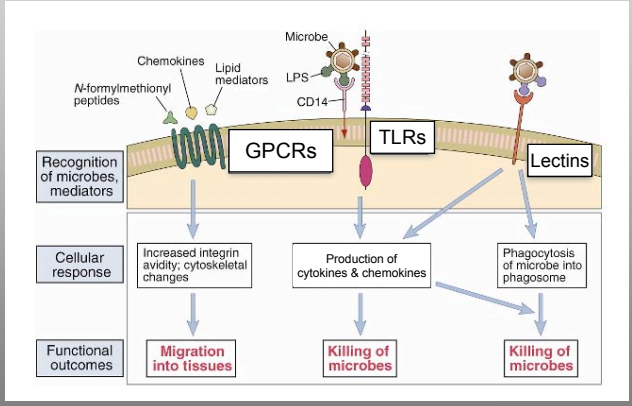
Distinctions Between Innate and Adaptive Immunity

	Innate immune system	Adaptive immune system
Receptors	Germline-encoded	Somatically engineered
Distribution	Non-clonal	Clonal
Kinetics	Rapid	Slow (requires clonal expansion)
Specificity	Recognizes non-self "pattern recognition"	Recognizes "altered self" Primary structure (TCR) Higher order structure (Immunoglobulin; BCR)
Effector Cells	All	Primarily lymphocytes, DCs, Mϕ

What Really Happens During the Lag Period Before the Acquired Immune Response?

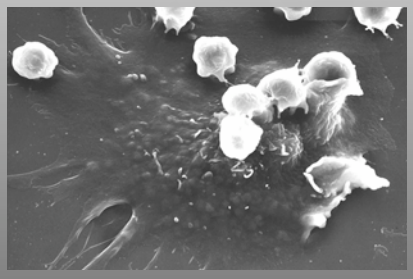


Receptors Important in Innate Immunity

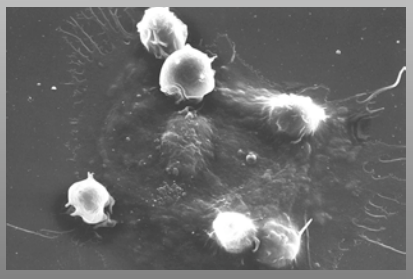


GPCR = G protein-coupled receptors
TLRs = Toll-like receptors
Lectin: A molecule that binds carbohydrates

Phagocytosis of IgG-coated Targets by Macrophages

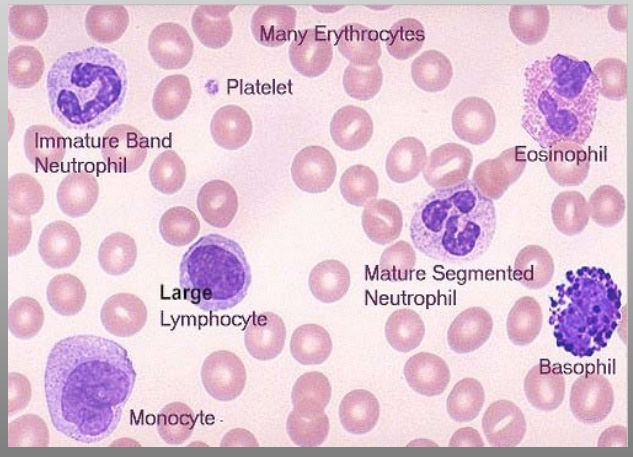


3 min



10 min

Most, but not all Leukocytes Can Perform Phagocytosis



Opsonic vs Non-opsonic Phagocytosis

• Non-opsonic phagocytosis is typically mediated by cell surface receptors on leukocytes that recognize repeating carbohydrate subunits (comprising “molecular patterns”) on microbes.

• Opsonic phagocytosis is typically mediated by deposition of proteins (e.g., antibodies) on microbes that target them for recognition by specific phagocytic receptors on leukocytes.

(<Latin *opsonare*, to buy provisions<Greek *opsonein*, condiment

"Opsonin is what you butter the disease germs with to make your white blood corpuscles eat them.”

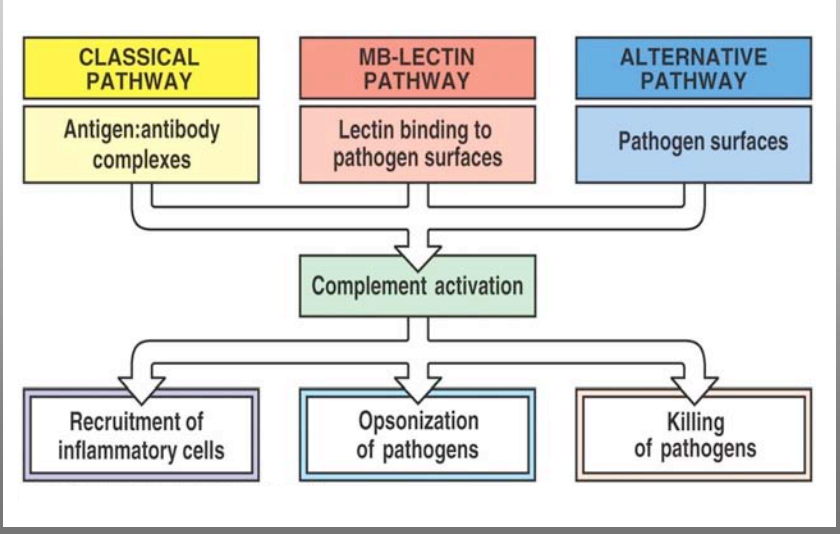
-G.B. Shaw, *The Doctor’s Dilemma*

The Biology of Complement

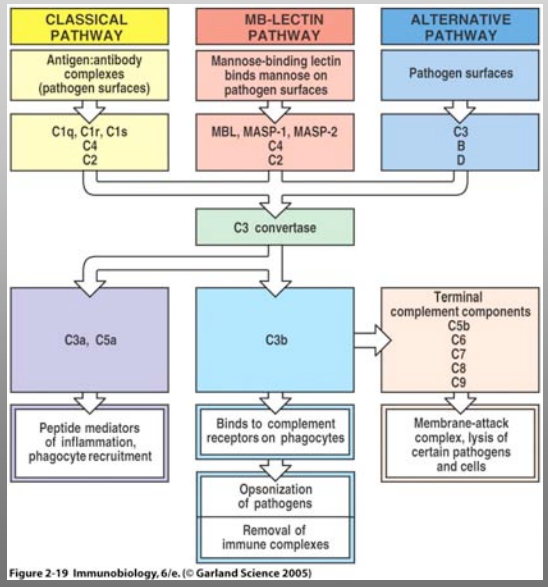
Recognized Functions of Complement

1. Host defense
2. Clearance of immune complexes
3. Disposal of apoptotic debris
4. Regulation of the immune response

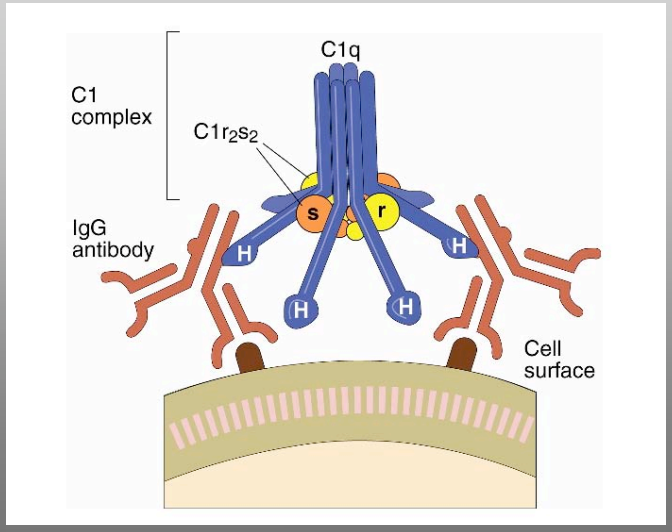
Complement Activation in Host Defense



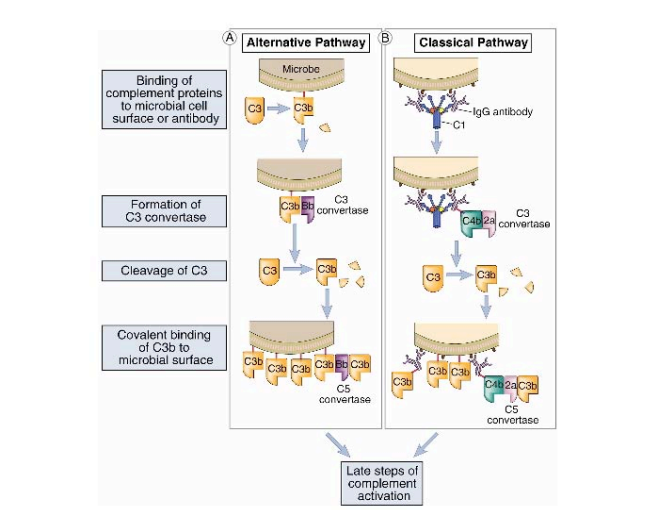
Components of Complement



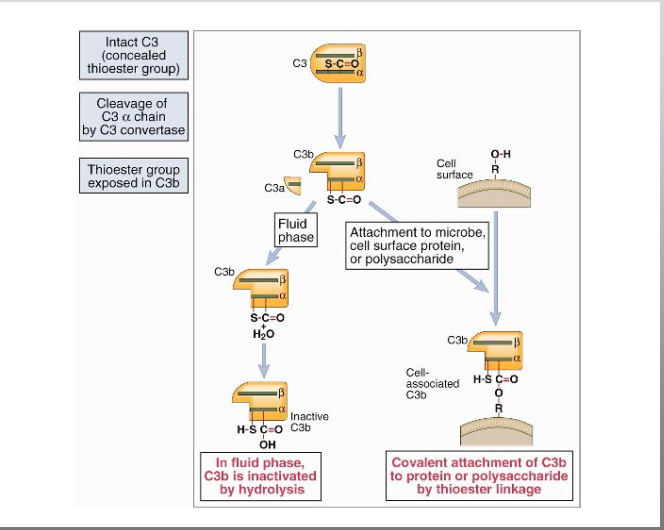
C1q, the Initiator of the Classical Pathway of Complement Activation



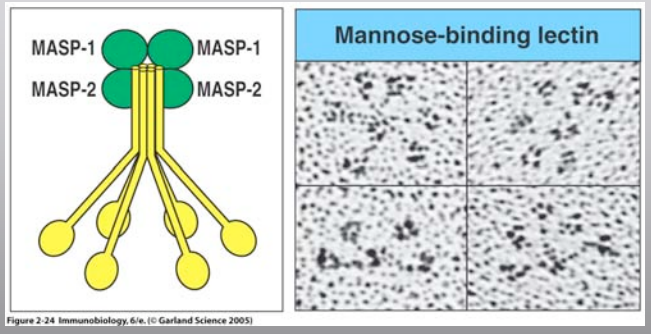
Formation of the C3 and C5 Convertases

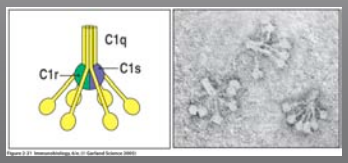


C3 Contains a Latent, Reactive Thioester Group



The Mannose-binding Lectin Resembles C1q

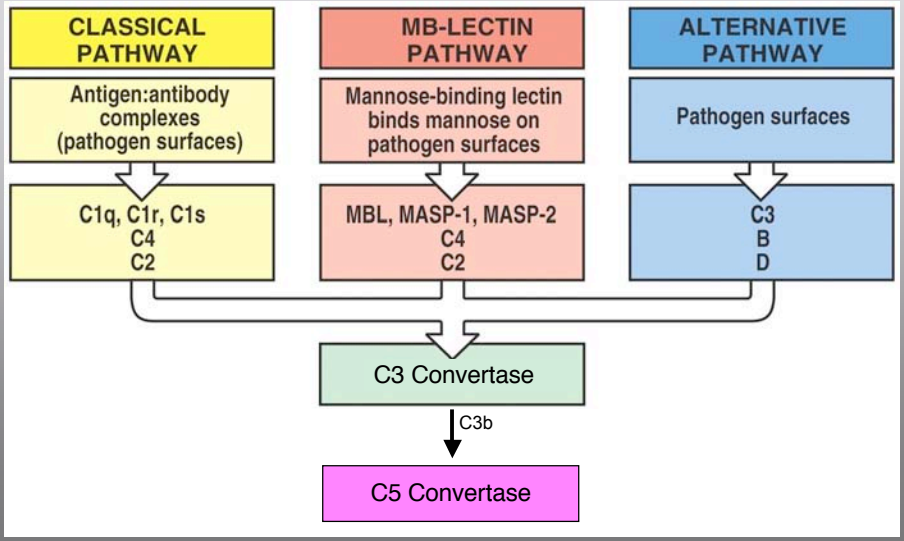




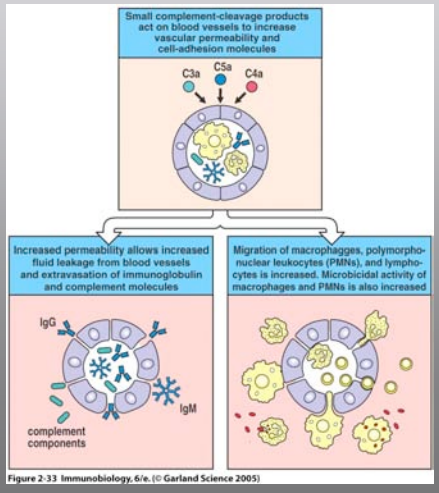
The Lectin Pathway and Other Activators of Complement in the Absence of Antibodies

- A lectin is a molecule that binds to carbohydrate structures
- A collectin (like C1q or Mannose Binding Lectin) is a lectin with collagen-like features
- MBL first binds to mannose on bacterial cell walls. It then binds serine proteases MASP-1, -2 or -3 (Mannose binding lectin Associated Serine Protease)
- MASPs can then activate C4 and C2, thus creating a C3 convertase without involving antibodies
- Deficiency in MBL is associated with increased susceptibility to bacterial infections
- It is simplistic to think of each "pathway" as acting in isolation. Thus, once the classical pathway has produced some C3b, these C3b molecules produce more C3b using the alternative pathway
- C-reactive protein (CRP) – An "acute phase" protein produced by the liver, binds to bacterial cell wall lipopolysaccharides. C1q then binds to CRP and thus activates complement without involving antibodies.

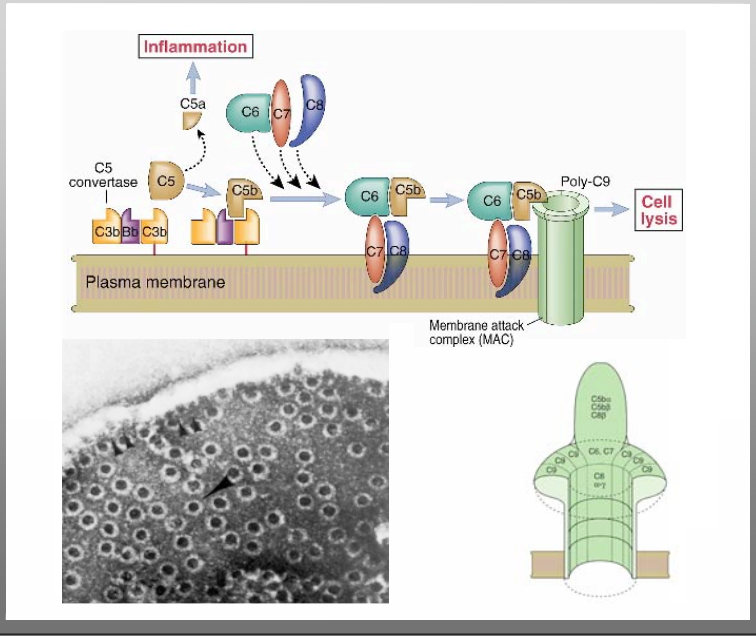
All Roads Lead to Rome



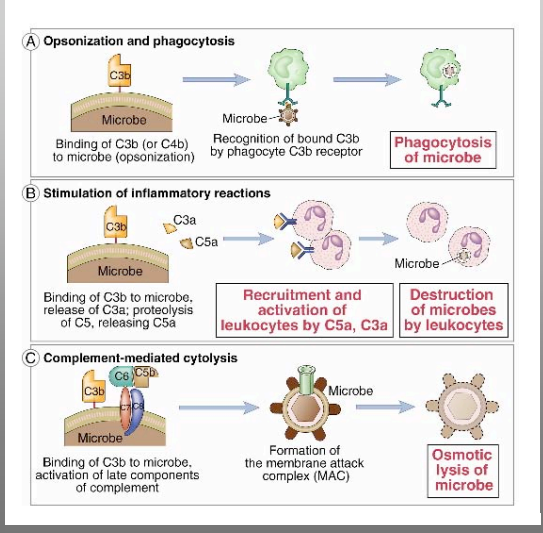
C5a Increases Vascular Permeability and is a Potent Chemoattractant



Big MAC Attack



Summary: Three Major Functions of Complement in Host Defense



Summary: Complement

1. Complement is an ancient system of host defense that has well-defined functions in host defense: it opsonizes microbes (C3b, C3bi), stimulates inflammation (C3a, C4a, C5a), and mediates lysis of pathogens by the membrane attack complex (C5-9).
2. Additional functions of complement include clearance of immune complexes and apoptotic debris. These functions have major implications for the emergence of autoimmunity.
3. Among the known inherited complement deficiencies include Leukocyte Adhesion Deficiency (LAD) and complement component deficiencies; these are associated with frequent infections and, in the latter case, autoimmunity.

Metchnikoff is the First to Describe a Role for Phagocytosis in Immunity

Elie Metchnikoff, 1845-1916

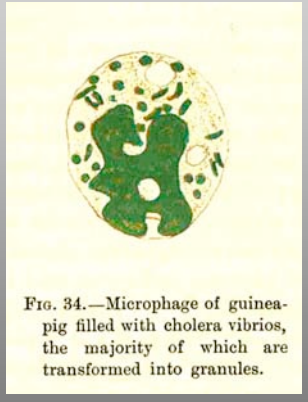
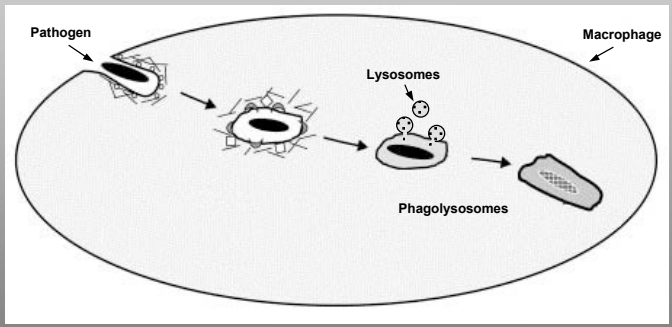


FIG. 34.—Microphage of guinea-pig filled with cholera vibrios, the majority of which are transformed into granules.

Phagosome-Lysosome Fusion?

Post-phagocytic Events: Phagosome-Lysosome Fusion



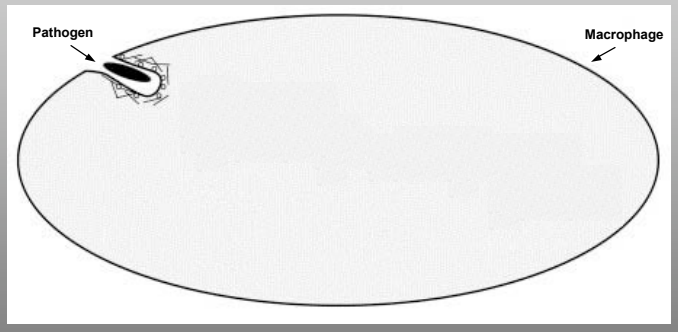
Phagocytosis of Bacteria is Followed by Phagosome-Lysosome Fusion

0-3 min | 1-5 min | 30 min-hrs

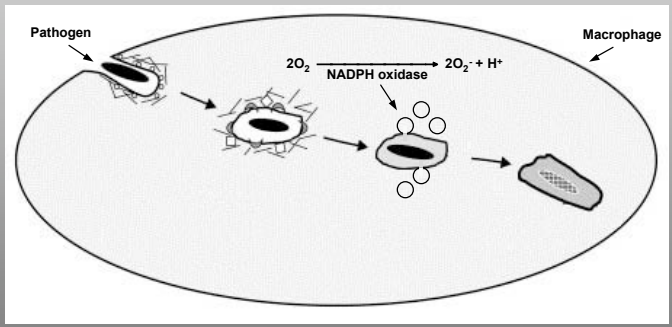
From: Allen et al., *J. Exp. Med.* 191:115, 2000

What happens following pathogen ingestion?

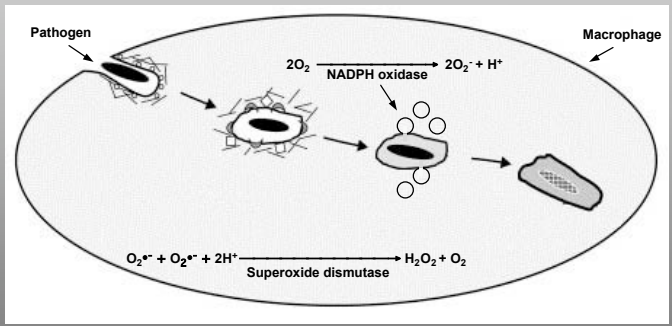
Post-phagocytic Events



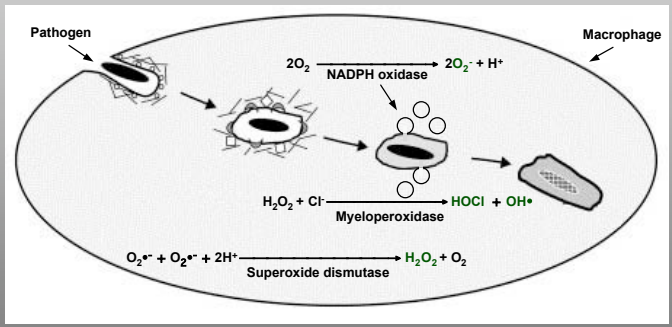
Post-phagocytic Events: "Phagosome-Oxidase Fusion"



Post-phagocytic Events: Generation of H_2O_2

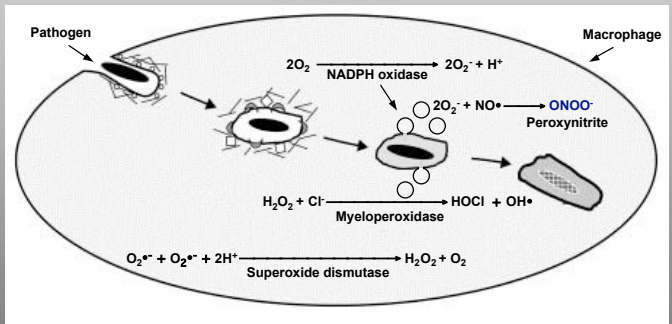


Post-phagocytic Events: Myeloperoxidase Activity



Reactive oxygen species: $O_2^{-}\bullet$, HOCl, H_2O_2, O_3

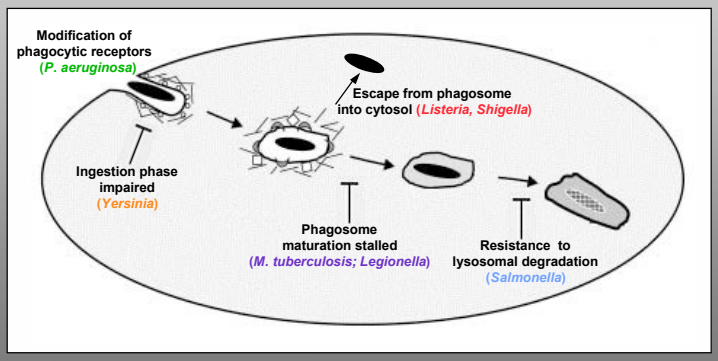
Post-phagocytic Events: Peroxynitrite Production



Reactive oxygen species: $O_2^{-}\bullet$, HOCl, H_2O_2, O_3

Reactive nitrogen species: $ONOO^-$

Bacterial Virulence Factors Subvert Host Defenses

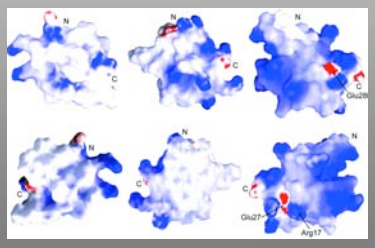


Non-oxidative Killing Mechanisms of Phagocytes

- Principally proteins within granules that are released upon cell stimulation
- These proteins include lysozyme, lactoferrin, proteases, defensins and other cationic proteins

Lysozyme

Disrupts peptidoglycan

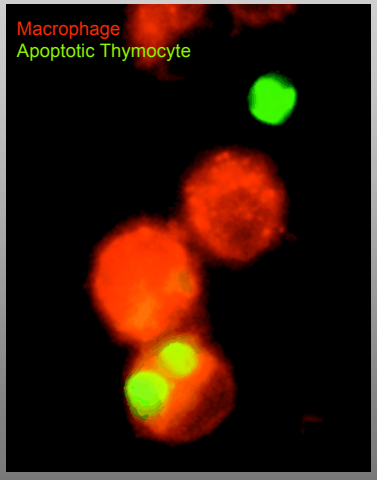


HBD1 HBD2 HBD3

Permeablizes membranes

Phagocytosis: Not Just for Bugs

Phagocytosis is the Principal Mechanism of Disposal of Apoptotic Corpses



- Phagocytosis is the means of disposal of apoptotic corpses, and occurs continuously during the lifetime of an individual.
- In this setting, phagocytosis is not accompanied by inflammation, but rather leads to an "anti-inflammatory" signal (the production of TGF-β).
- As apoptotic corpses contain many potential self antigens, the lack of an appropriate anti-inflammatory signal has the potential to trigger autoimmunity.

From: Jennings et al., *Am. J. Resp. Cell Mol. Biol.* 32:108, 2005

Immunological Consequences of Phagocytosis

Clearance of pathogens

Death of pathogenic microbe
Resolution of infection

Persistence of pathogenic microbe
Failure of resolution of infection

Clearance of apoptotic corpses

Suppression of inflammation
Tolerance

Inappropriate inflammation
Break in tolerance

Summary

1. Phagocytosis is a component of innate and aquired immunity. It is the principal means of destroying pathogenic bacteria and fungi. Phagocytosis initiates the process of antigen presentation.

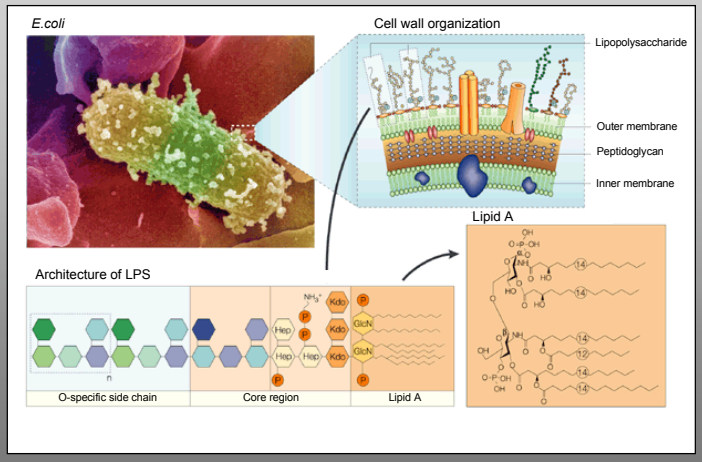
2. Many phagocytic receptors recognize a diverse array of microbial pathogens. Some pathogens (e.g., *S. pneumoniae*) require opsonization by antibodies and complement for their clearance. However, bugs fight back.

3. Phagocytic leukocytes employ oxidative and non-oxidative means of killing. The NADPH oxidase generates reactive oxidants, such as superoxide anion and hypochlorous acid (bleach).

4. Phagocytosis is an essential component of development and tissue remodelling. Ingestion of apoptotic bodies is immunologically "silent" and is normally accompanied by a suppression of inflammation. Failure of this mechanism may result in autoimmunity.

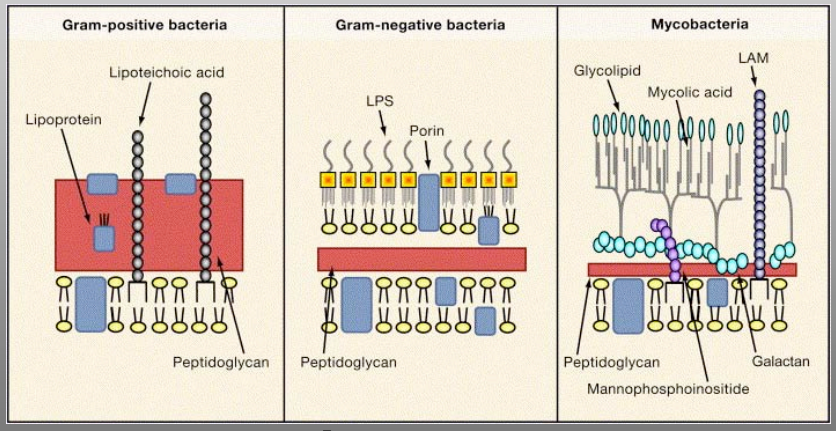
The Innate Immune Response is Conserved Throughout Evolution and is Triggered by Pattern Recognition

Lipopolysaccharide = Lipid + Polysaccharide



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

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

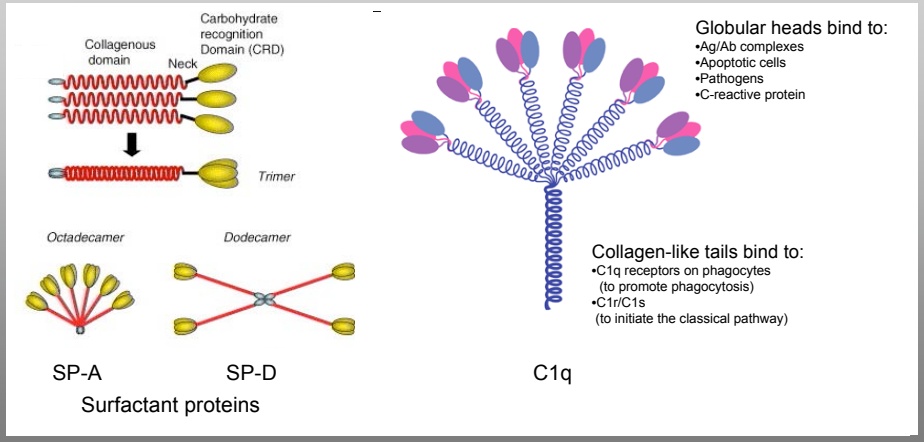


From: Akira et al., *Cell* 124:783, 2006

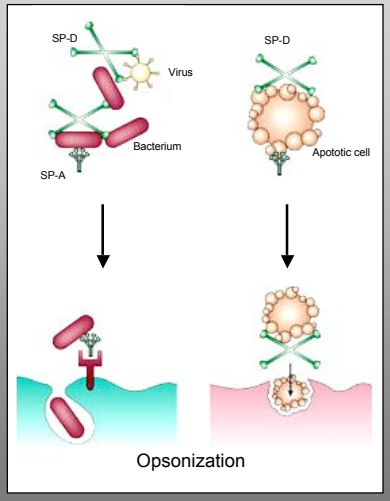
Innate Immune Receptors for PAMPs

- 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

Collectins and Innate Immune Recognition

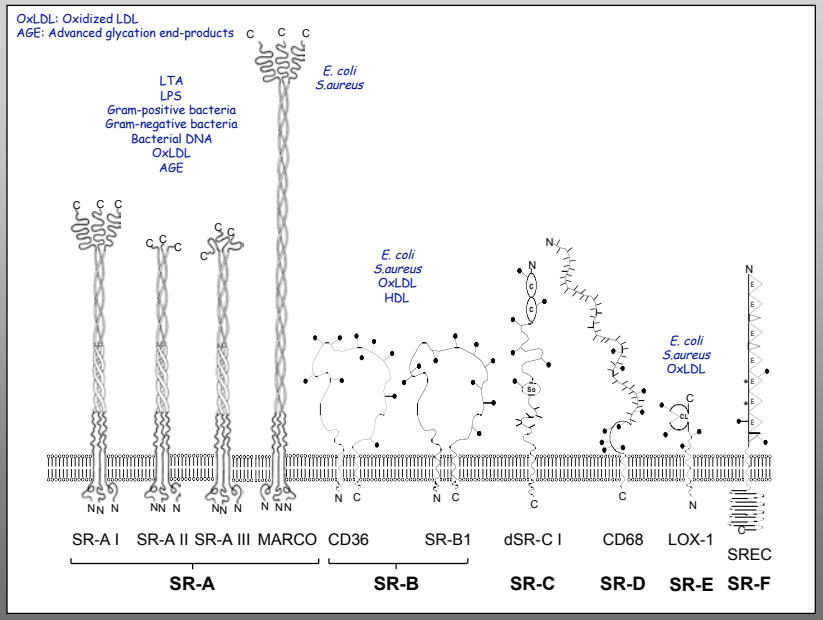


Collectins Can Serve as Opsonins

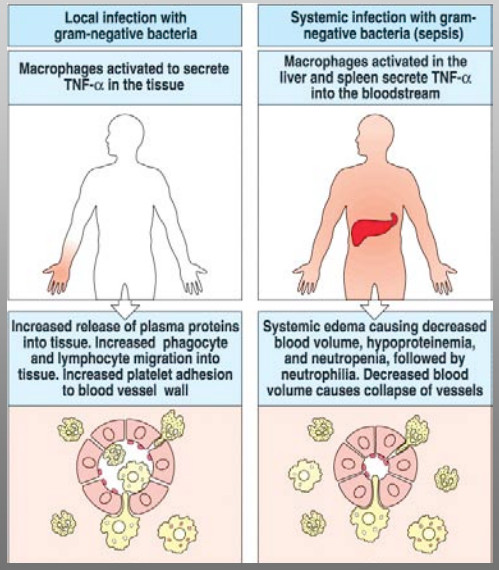


Modified from: Wright, *Nature Rev. Immunol.* **5**:58, 2005

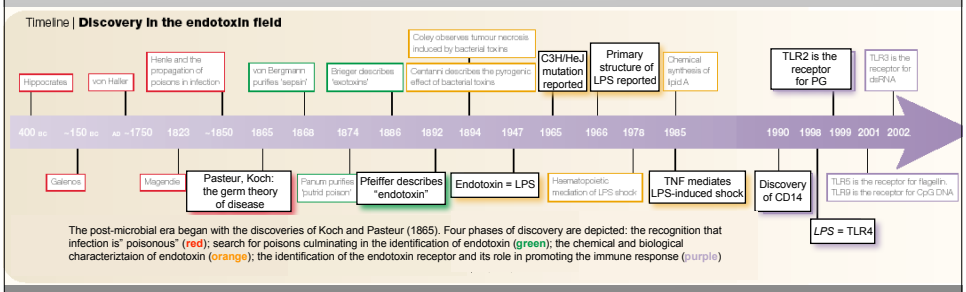
The Scavenger Receptor Superfamily Recognizes PAMPs



Innate Immune Receptors Also Trigger a Systemic Response to Infection

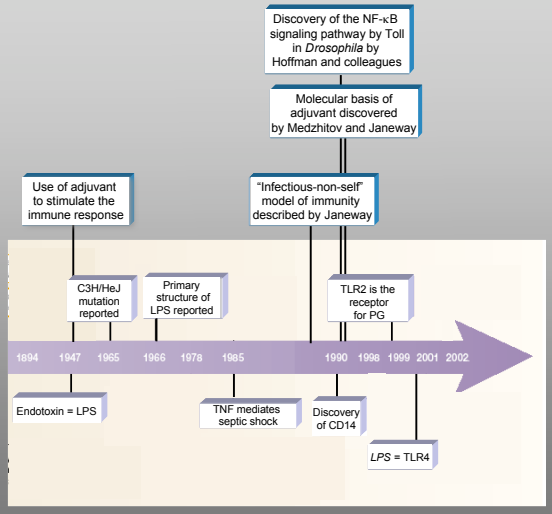


History of Endotoxin Research



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

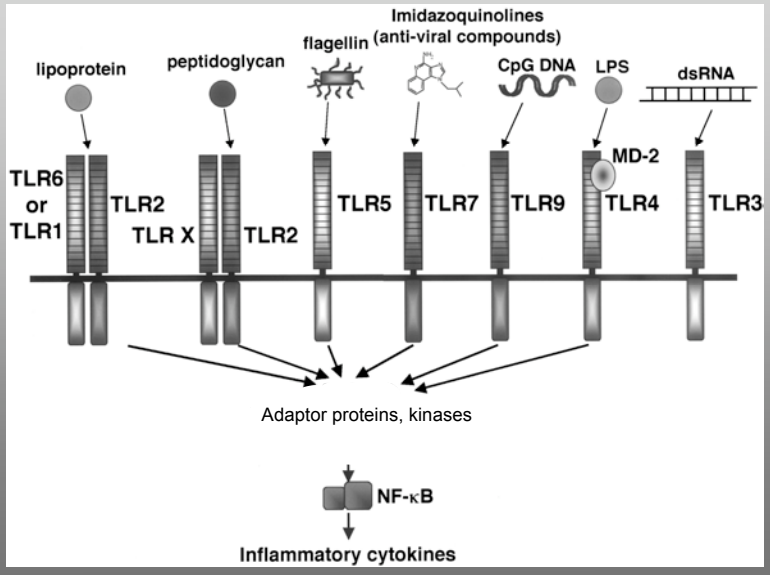
A Re-interpretation of the Endotoxin Research Timeline



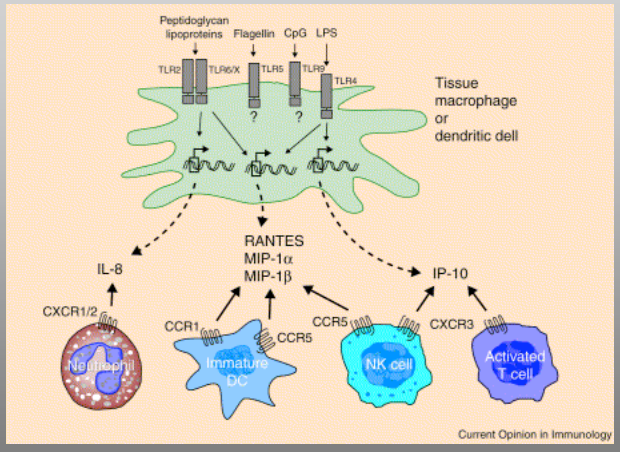
Modified from: Beutler and Rietschel, *Nature Reviews Immunology* **3**; 169-176 (2003)

Primitive Specificity in Target Recognition by the Innate Immune System

Ligand Specificity of TLRs

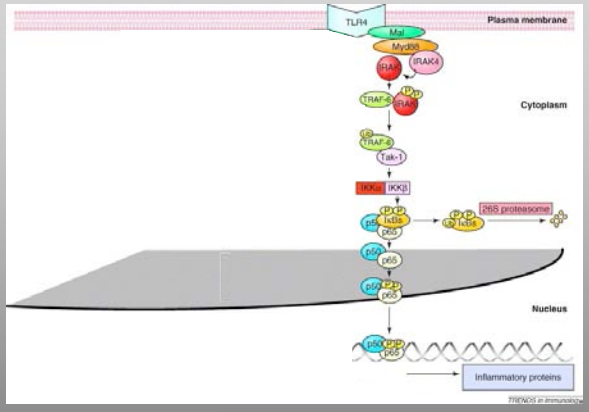


Specificity of TLR Transcriptional Programs



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

TLR Signaling: Two Major Pathways

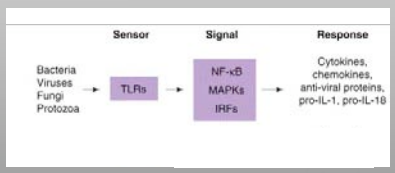


Cartoon of major signal transduction pathways following engagement of TLRs. **TLR4** is the major sensor of LPS. **TLR3** recognizes dsRNA and is important in the anti-viral response. The **IRF** pathway leading to production of **Type I IFNs** (i.e., IFN-α/β) is particularly prominent in a minor subset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

Do <u>not</u> 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

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



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