# The Innate Immune Response to Infections

## Distinctions Between Innate and Adaptive Immunity

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<th>Innate immune system</th>
<th>Adaptive immune system</th>
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<td><strong>Receptors</strong></td>
<td>Germline-encoded</td>
<td>Somatically engineered</td>
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<td><strong>Distribution</strong></td>
<td>Non-clonal</td>
<td>Clonal</td>
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<td><strong>Kinetics</strong></td>
<td>Rapid</td>
<td>Slow (requires clonal expansion)</td>
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<td><strong>Specificity</strong></td>
<td>Recognizes non-self “pattern recognition”</td>
<td>Recognizes “altered self”</td>
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<td><strong>Effector Cells</strong></td>
<td>All</td>
<td>Primarily lymphocytes, DCs, Mφ</td>
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*Immunoglobulin; BCR*
What Really Happens During the Lag Period Before the Acquired Immune Response?

- Innate immunity
- Acquired immunity

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

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

- 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)
- MASP 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.
The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands

**All Roads Lead to Rome**

- **CLASSICAL PATHWAY**
  - Antigen:antibody complexes (pathogen surfaces)
  - C1q, C1r, C1s, C4, C2

- **MB-LECTIN PATHWAY**
  - Mannose-binding lectin binds mannose on pathogen surfaces
  - MBL, MASP-1, MASP-2
  - C4, C2

- **ALTERNATIVE PATHWAY**
  - Pathogen surfaces
  - C3, B, D

C3 Convertase → C3b

C5 Convertase

**C5a Increases Vascular Permeability and is a Potent Chemoattractant**

Small complement cleavage products act on local vessels to increase vascular permeability and adhesion molecule function

- Increased permeability allows increased fluid leakage from blood vessels and extravasation of immunoglobulins and complement components
- Redistribution of leukocytes, polymorphonuclear leukocytes (PMNs), and monocytes is increased. Microrheological activity of monocytes and PMNs is also increased

Diagram showing the effects of C5a on vascular permeability and leukocyte recruitment.
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
Post-phagocytic Events:
Phagosome-Lysosome Fusion

Phagocytosis of Bacteria
is Followed by Phagosome-Lysosome Fusion

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

What happens following pathogen ingestion?

Post-phagocytic Events
Post-phagocytic Events: “Phagosome-Oxidase Fusion”

Post-phagocytic Events: 
Generation of H$_2$O$_2$

Pathogen $\xrightarrow{2O_2} \text{NADPH oxidase} \xrightarrow{2O_2 + H^+} \text{Macrophage}$

Pathogen $\xrightarrow{2O_2} \text{NADPH oxidase} \xrightarrow{2O_2 + H^+} \text{Superoxide dismutase}$
Post-phagocytic Events:
Myeloperoxidase Activity

Reactive oxygen species: $O_2^-$, HOCl, $H_2O_2$, $O_3$

Post-phagocytic Events:
Peroxynitrite Production

Reactive oxygen species: $O_2^-$, HOCl, $H_2O_2$, $O_3$

Reactive nitrogen species: $ONOO^-$
Bacterial Virulence Factors Subvert Host Defenses

- Ingestion phase impaired (Yersinia)
- Phagosome maturation stalled (M. tuberculosis, Legionella)
- Resistance to lysosomal degradation (Salmonella)

- Modification of phagocytic receptors (P. aeruginosa)

- Escape from phagosome into cytosol (Listeria, Shigella)

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: Permeabilizes membranes
Phagocytosis: Not Just for Bugs

- 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.

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

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.

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

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

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

Globular heads bind to:
- Ag/Ab complexes
- Apoptotic cells
- Pathogens
- C-reactive protein

Collagen-like tails bind to:
- C1q receptors on phagocytes (to promote phagocytosis)
- C1r/C1s (to initiate the classical pathway)

Collectins Can Serve as Opsonins

The Scavenger Receptor Superfamily Recognizes PAMPs

Innate Immune Receptors Also Trigger a Systemic Response to Infection

Local infection with gram-negative bacteria
- Macrophages activated to secrete TNF-α in the tissue
- Increased release of plasma proteins and lymphocyte migration into tissue, increased platelet adhesion to blood vessel wall

Systemic infection with gram-negative bacteria (sepsis)
- Macrophages activated in the liver and spleen secrete TNF-α into the bloodstream
- Systemic edema causing decreased blood volume, hypotension, and neutropenia, followed by neutrophilia. Decreased blood volume causes collapse of vessels

OxLDL: Oxidized LDL
AGE: Advanced glycation end-products
History of Endotoxin Research

The post-microbial era began with the discoveries of Koch and Pasteur (1865). Four phases of discovery are depicted: the recognition that infection is "poisonous" (red); search for poisons culminating in the identification of endotoxin (green); the chemical and biological characterization of endotoxin (orange); the identification of the endotoxin receptor and its role in promoting the immune response (purple).

A Re-interpretation of the Endotoxin Research Timeline


Primitive Specificity in Target Recognition by the Innate Immune System
Ligand Specificity of TLRs

Specificity of TLR Transcriptional Programs

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

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

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