Basic function of the immune response

Protect against a "limitless" number of pathogens and toxins (viruses, bacteria, protozoans)

Avoid injuring the host
Basic function of the immune response

Protect against a "limitless" number of pathogens and toxins (viruses, bacteria, protozoans)

Avoid injuring the host

Distinguish "self" from "non-self"

Is the immune response complicated? Yes, but…

Not any more complicated than anything else

Understandable in cellular terms

Profoundly important to a wealth of important human disorders: infectious disease, arthritis, Crohns disease, asthma, autoimmunity, cancer…

The immune response consists of two interconnected “arms”:

Innate immunity

detects molecular components shared by all pathogens

Adaptive immunity

molecular components ("antigens") specific to individual pathogens
Elie Metchnikoff: Inflammation is protective process of immunity, not tissue destruction.

Microorganisms are killed, ingested, and degraded - and inflammation is enhanced.

Cytotoxic agents: $\text{H}_2\text{O}_2, \text{O}_2^-$
Degrades bacterial cell walls: lysozyme
Degradates everything: lysosomal enzymes
Promotes inflammation: cytokines (IL-1, interferons)
Why do phagocytes respond to microorganisms?:
The role of "Toll"-like receptors

"Toll" was first identified as a gene essential for fly embryonic development
“Toll” receptor-deficient adult flies develop fungal infections.
12 different Toll-like receptors (TLRs) serve as the innate immune system's "sensor".

Intracellular signaling pathways are induced by TLRs.

Activated phagocytes -- neutrophils, macrophages -- chase down, eat, and kill microorganisms.

QuickTime™ and a Sorenson Video 3 decompressor are needed to see this picture.
Activated phagocytes (neutrophils, macrophages) chase down, eat, and kill microorganisms

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Actin polymerization drives phagocytosis

Incoming phagosomes fuse with degradative lysosomes

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Innate immunity (Metchnikoff, 1908):

- shared pathogen-derived components recognized by TLRs and related receptors
- phagocytes (macrophages, neutrophils) mediate protection by activating cytotoxic mechanisms

Paul Ehrlich (1908): "adaptive immunity"

- immunized individuals make protective antibodies in blood
Paul Ehrlich (1908): "adaptive immunity"

- Immunized individuals make protective antibodies in blood
- Antibodies see antigens specific to individual pathogen types
- Antigen-specific lymphocytes make antibodies and kill infected target cells
Immunoglobulin Fc receptors trigger killing and ingestion by macrophages

H$_2$O$_2$ phagocytosis
B-lymphocytes generate antigen-specific antibodies: humoral immunity

B-cells make antibody molecules against specific antigens

- Immunoglobulin (Ig) gene rearrangement
- Somatic hypermutation

B-lymphocytes make the best antibodies when "helped" by T-lymphocytes
B-lymphocytes make the best antibodies when “helped” by T-lymphocytes

T-lymphocytes recognize antigen fragments directly: help B cells, kill targets

T-cell antigen receptor = TCR

Diversity generator: TCR gene rearrangement

Peptides on MHC class I molecules are derived from intracellular antigens: eg, virus-infected cells
Cytotoxic T cells release granules that induce target cell killing

- Perforins
- Fas/Fas ligand
- Lytic enzymes

**CD8+ cytotoxic T cell**

**Virus-infected target cells**

**CTL granules**

**CTL**

**Target**

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The immunological synapse

T cell activation requires TCR (tyrosine kinase) stimulation + "costimulatory receptors" + cytokines

Ira Mellman, September 2008

The American Society for Cell Biology 14

Cell Biology of the Immune Response, Part I

Innate immunity (Metchnikoff, 1908):
- direct cellular response to pathogens
- detects shared microbial ‘patterns’
- not ‘antigen-specific’

Adaptive immunity (Ehrlich, 1908):
- specific antibodies
- variable antigens
- stimulation of T- and B-lymphocytes
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Dendritic cells: the missing link