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Innate immunity

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Lecture outline

- Components of innate immunity
- Recognition of microbes and dead cells
  - Toll Like Receptors
  - NOD Like Receptors/Inflammasome
- Inflammation
- Antiviral defense

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Innate Immune Responses

- The initial responses to:
  - 1. Microbes: essential early mechanisms to prevent, control, or eliminate infection;
  - 2. Injured tissues, dead cells: critical for repair and wound healing
- Limited types of defensive reactions:
  - Inflammation
  - Antiviral state
- Stimulate adaptive immunity
  - Innate immunity provides "danger signals"

Take home messages

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General features of innate immunity

- Phylogenetically ancient (evolved before adaptive immunity)
- Pre-existing (no prior immunization needed)
- Rapidly activated and/or recruited
- Resets to baseline (no memory)

Take home messages

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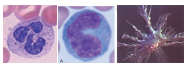
The components of the Innate Immune System-1

- Epithelial barriers
  - Defensins and cathelicidins (antibiotics)

- Phagocytes and other cells
  - Macrophages
  - Neutrophils
  - Dendritic cells



- Specialized lymphocytes
  - Innate lymphoid cells: Group 1 (IFN-γ+, includes NK cells); Group 2 (Th2 cytokines); Group 3 (Th17 cytokines)
  - NKT cells
  - B1 and Marginal Zone B cells

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The components of the Innate Immune System-2

- Plasma proteins
  - Complement
  - Pentraxins (C Reactive Protein, serum amyloid protein): coat microbes for phagocytosis
  - Collectins (e.g. Mannose Binding Lectin)

- Cytokines
  - Inflammatory (IL-1, TNF)
  - Chemokines (IL-8, MCP-1)
  - Anti-viral (type I interferons)

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Innate Immune System: What is recognized?

- Structures that are shared by various classes of microbes but are not present on host cells - Pathogen associated molecular patterns (PAMPs).
  - Innate immunity often targets microbial molecules that are essential for survival or infectivity of microbes (prevents escape mutants)
- Structures found in/on stressed, dying or dead host cells - Damage associated molecular patterns (DAMPs).

Take home messages

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Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	Unmethylated CpG repeats	Virus, bacteria
	Cyclic dinucleotides	Bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Glucans	Fungi

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Damage-Associated Molecular Patterns	
Stress-induced proteins	Heat shock proteins
	ATP
Crystals	Monosodium urate; cholesterol
Nuclear proteins	HMGB1

Cellular Pattern Recognition Receptors

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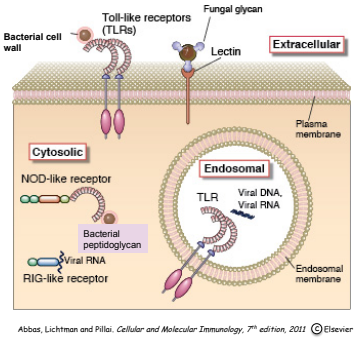

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Receptors are located such that they can sample all cellular compartments containing different types of pathogens

4 classes of receptors:
-TLRs: bacteria and viruses
-CLRs (C-type lectin receptors): fungi
-NLRs: bacteria and cell damage
-RLRs: viruses

Specificity of Receptors of Innate and Adaptive Immunity

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	INNATE	ADAPTIVE
Specificity: # of molecules recognized	~ 1,000	> 10^7
Types of receptors	< 100 TYPES; EACH TYPE INVARIANT	2 TYPES (Ig, TCR); MILLIONS OF VARIATIONS OF EACH TYPE
Distribution of receptors	NON-CLONAL	CLONAL

Toll-like Receptors (TLRs): specificity

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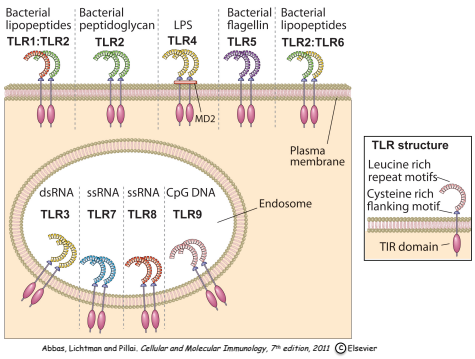

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Toll-like Receptors (TLRs): signaling

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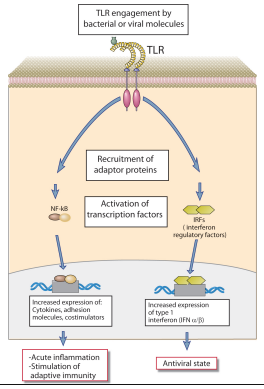

Genetic evidence for the importance of TLRs

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- Mutations in signaling adaptor protein MyD88 (for all TLRs except TLR3): invasive bacterial infections
  - Mouse knockouts are susceptible to diverse infections: different extent of redundancy or differences due to experimental challenge
- Mutations affecting TLR3 and signaling molecules: herpes virus encephalitis
- Mutations in IRAK, NF-κB pathway: more complex, diverse infections

Toll-like Receptors (TLRs): Clinical Relevance

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- Excessive/systemic TLR signaling underlies pathophysiology of sepsis (LPS/TLR4)
- TLR signaling in B cells promotes auto-antibody production
- TLR ligands, such as CpG nucleotides, are potentially useful adjuvants to enhance effectiveness of vaccines

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NOD*-like receptors (NLRs)

- A family of more than 20 different cytosolic proteins, best studied are two types…
- NOD1 and NOD2
  - Bind peptidoglycan components of bacterial cell walls
  - Form signaling complexes that activate NF-κB and induce expression of inflammatory genes
- NLRPs
  - Pyrin-domain containing NLRs
  - Respond to diverse cytoplasmic PAMPs and DAMPs
  - Form signaling complexes called inflammasomes, which generate active forms of the inflammatory cytokines IL-1 and IL-18

*NOD=nucleotide oligomerization domain

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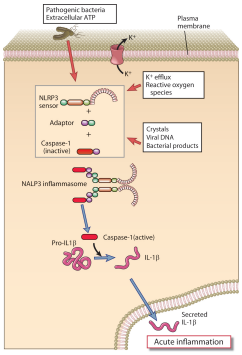
Activation of inflammasome by microbial products and/or host-derived molecules



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Physiologic functions of the inflammasome

- To sense and eliminate necrotic cells (caused by microbes, other insults) and foreign bodies
  - Reactions: Inflammation and repair
- Mutations in components of inflammasomes are the cause of rare inherited "auto-inflammatory" syndromes characterized by periodic fever, skin rashes, and amyloidosis
  - These are gain-of-function mutations that lead to constitutive activation and uncontrolled IL-1 production
  - IL-1 antagonists are very effective treatments for these disorders.

Take home messages

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Inflammasome activation in common inflammatory diseases

- Gout, pseudogout: Recognize crystals (e.g. urate) and induce IL-1-mediated acute inflammation
- Metabolic syndrome: Recognize lipids and free fatty acids → IL-1 production in obesity → insulin resistance → type 2 diabetes?
- Recognize cholesterol crystals → role of inflammation in atherosclerosis?
- Reaction to abnormal protein deposits: Alzheimer disease? Other disorders?

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The major reactions and functions of innate immunity

- Induction of inflammation: removal of microbes, dead cells, foreign bodies
- Induction of the anti-viral state: inhibition of viral replication
- Stimulation of the adaptive immune response

Take home messages

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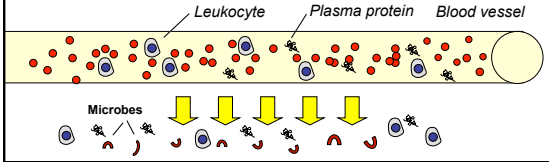
What is Inflammation ?

- A response to infection and/or injury of vascularized tissues whereby…
- Blood-derived fluid, proteins, and leukocytes accumulate, which…
- Kill and remove offending agent (e.g. microbes), remove dead cells, and repair damage



Induction of the anti-viral state

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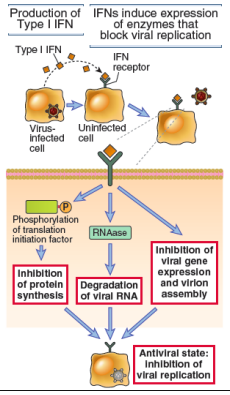

The innate immune system provides second signals required for lymphocyte activation

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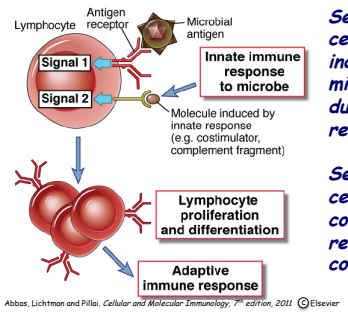

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Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

Second signals for B cells: products of complement activation recognized by B cell complement receptors

Take home messages