

Innate immunity: Sensing pathogens and danger

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FOCiS



Lecture outline

- Components of innate immunity
- Recognition of microbes and cell damage/stress
 - Toll Like Receptors
 - NOD Like Receptors/Inflammasome
- Role of innate immunity in inflammatory diseases

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”

General features of innate immunity

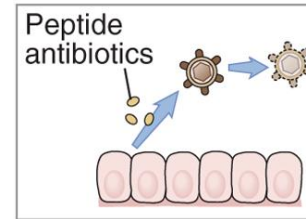
- Phylogenetically ancient (evolved before adaptive immunity)
- Functional even before exposure to microbes (no prior immunization needed)
- Resets to baseline (no or limited memory)

Components of the Innate Immune System

1. Cells

- **Epithelial barriers**

- Mechanical barrier
- Locally produced antibiotics



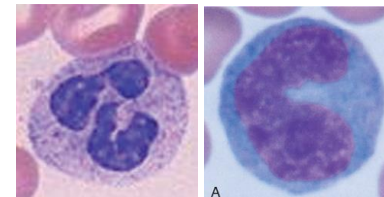
- **Sentinels**

- Dendritic cells



- **Phagocytes**

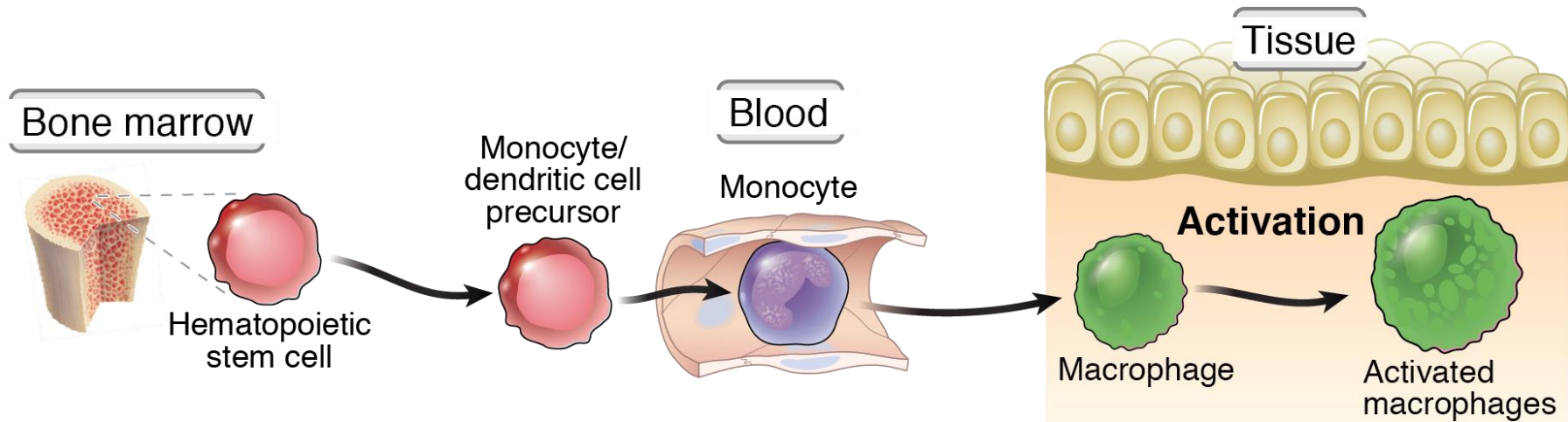
- Macrophages
- Neutrophils



- **Specialized lymphocytes**

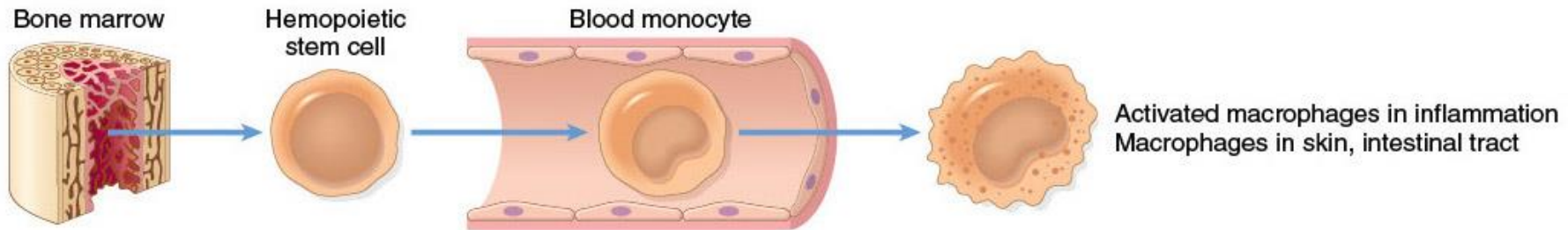
- Innate lymphoid cells: Cytokine producers

Development of macrophages: the accepted view



Two pathways of macrophage development

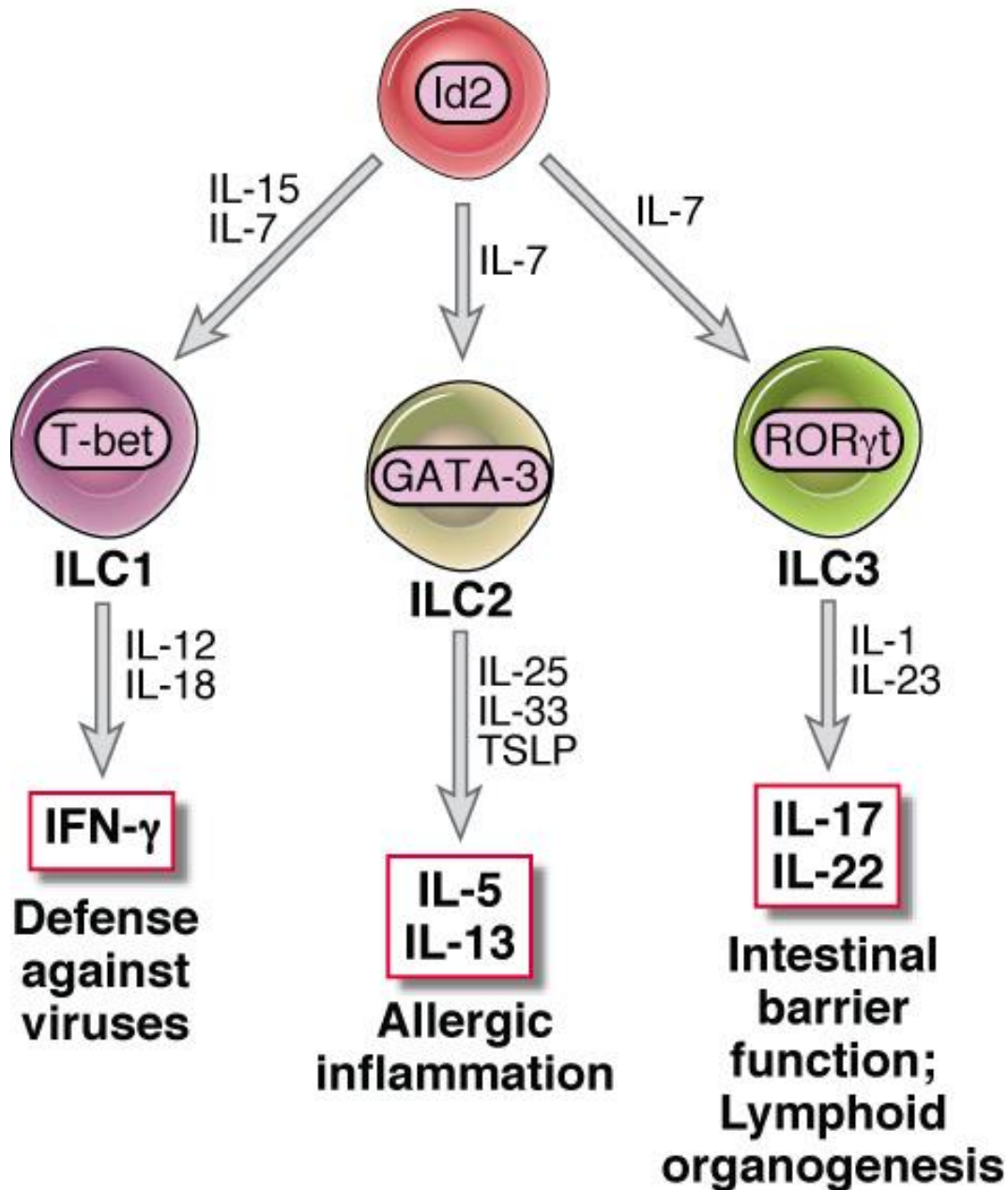
During inflammatory reactions



Tissue-resident macrophages



Innate lymphoid cells



ILCs make many of the same cytokines as T cells but lack TCRs (detected in RAG-/- mice)

Innate lymphoid cells

- ILCs respond not to antigens but to cytokines made by epithelial and other cells in response to cellular stress
- Difficult to study in humans; difficult to assess their contribution to immune responses even in normal mice

Components of the Innate Immune System

2. Plasma proteins

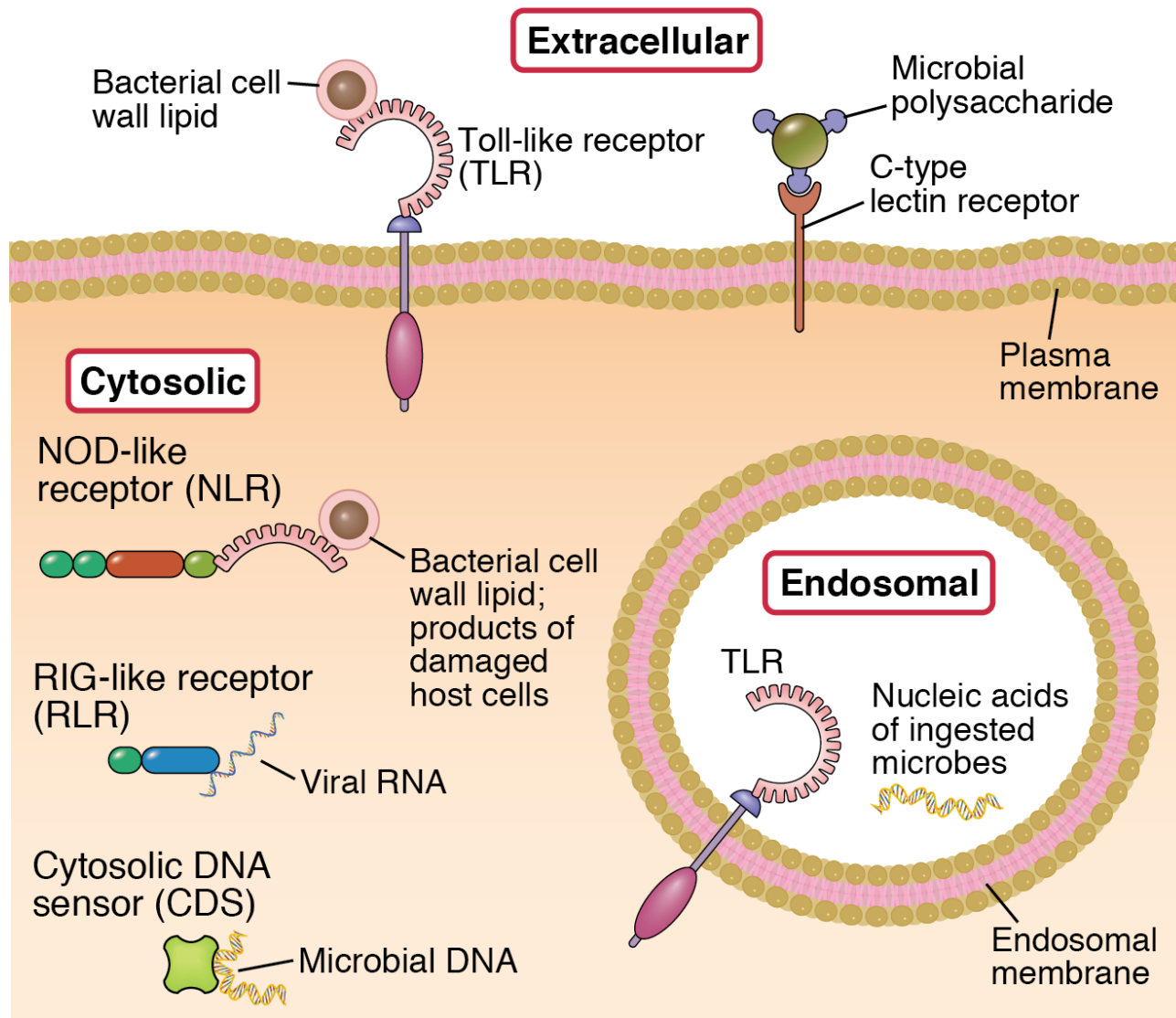
- **Complement**
 - Multiple functions
- **Pentraxins**: coat microbes for phagocytosis
 - C Reactive Protein, serum amyloid protein
- **Collectins**
 - Mannose Binding Lectin (activator of complement)

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 produced in damaged or necrotic host cells - **Damage associated molecular patterns (DAMPs)**.

Cellular Pattern Recognition Receptors



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

4 major classes of receptors:

- TLRs: bacteria and viruses*
- CLRs (C-type lectin receptors): fungi*
- NLRs: bacteria and cell damage*
- RLRs: viruses*
- (CDS: DNA sensors)*

Specificity of Receptors of Innate and Adaptive Immunity

INNATE

ADAPTIVE

Specificity:
of
molecules
recognized

~1,000

$>10^7$

Types of
receptors

<100 types,
each invariant

2 types (Ig,
TCR), millions
of variations of
each

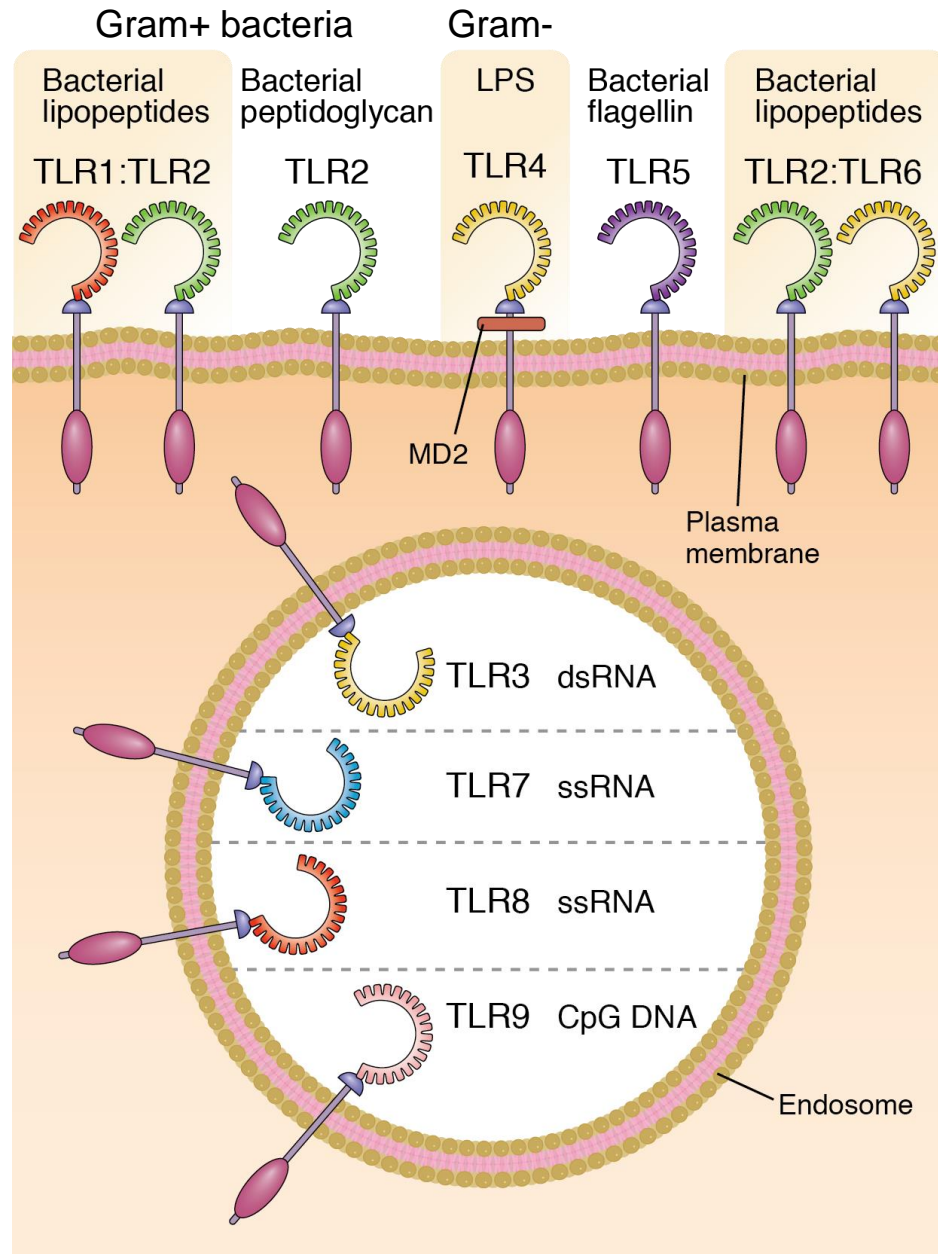
Distribution
of receptors

Non-clonal

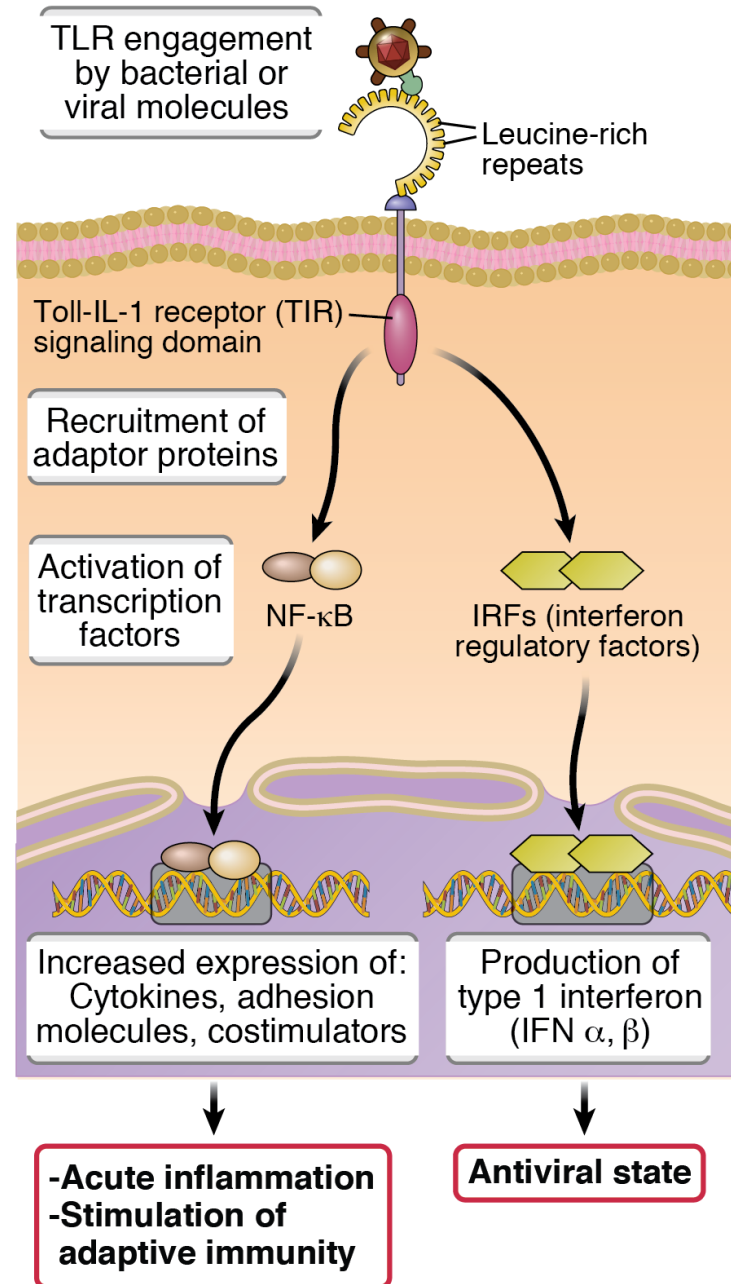
Clonal

Toll-like Receptors (TLRs): specificity

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Toll-like Receptors (TLRs): signaling



Genetic evidence for the importance of TLRs

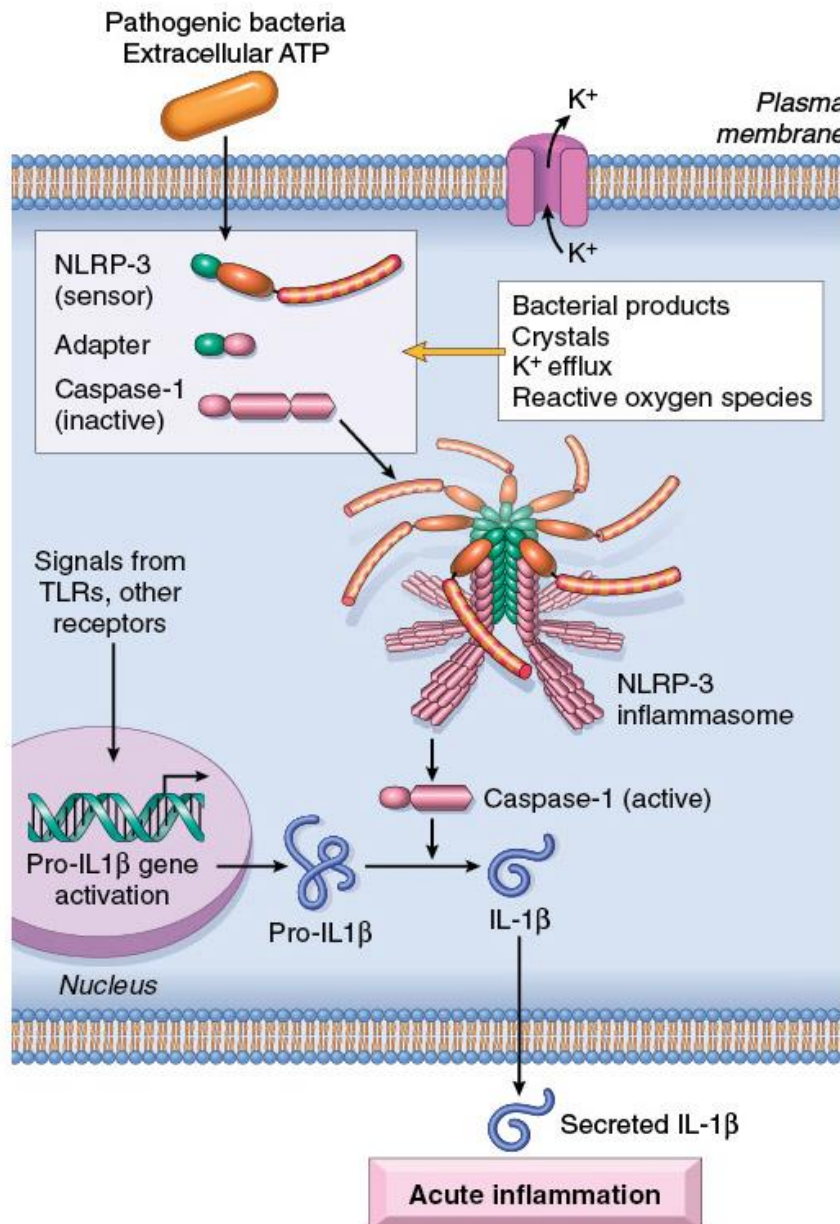
- Mutations in signaling adaptor protein MyD88 (for all TLRs except TLR3): invasive bacterial infections, mainly pneumonia
- Mutations affecting TLR3 and signaling molecules: herpes virus encephalitis

NOD-like receptors (NLRs)

- A family of >20 cytosolic proteins, best known:
- NOD1 and NOD2
 - Bind bacterial peptides
 - Activate NF- κ B and trigger inflammation
- NLRPs
 - NLRs that contain “pyrin” domains
 - Sense diverse DAMPs and PAMPs
 - Form signaling complex called the **inflammasome**, which leads to the production of IL-1 and inflammation

NOD = nucleotide oligomerization domain

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



Signaling involves prion-like propagation of adaptor protein (ASC), forming filaments

Physiologic functions of the inflammasome

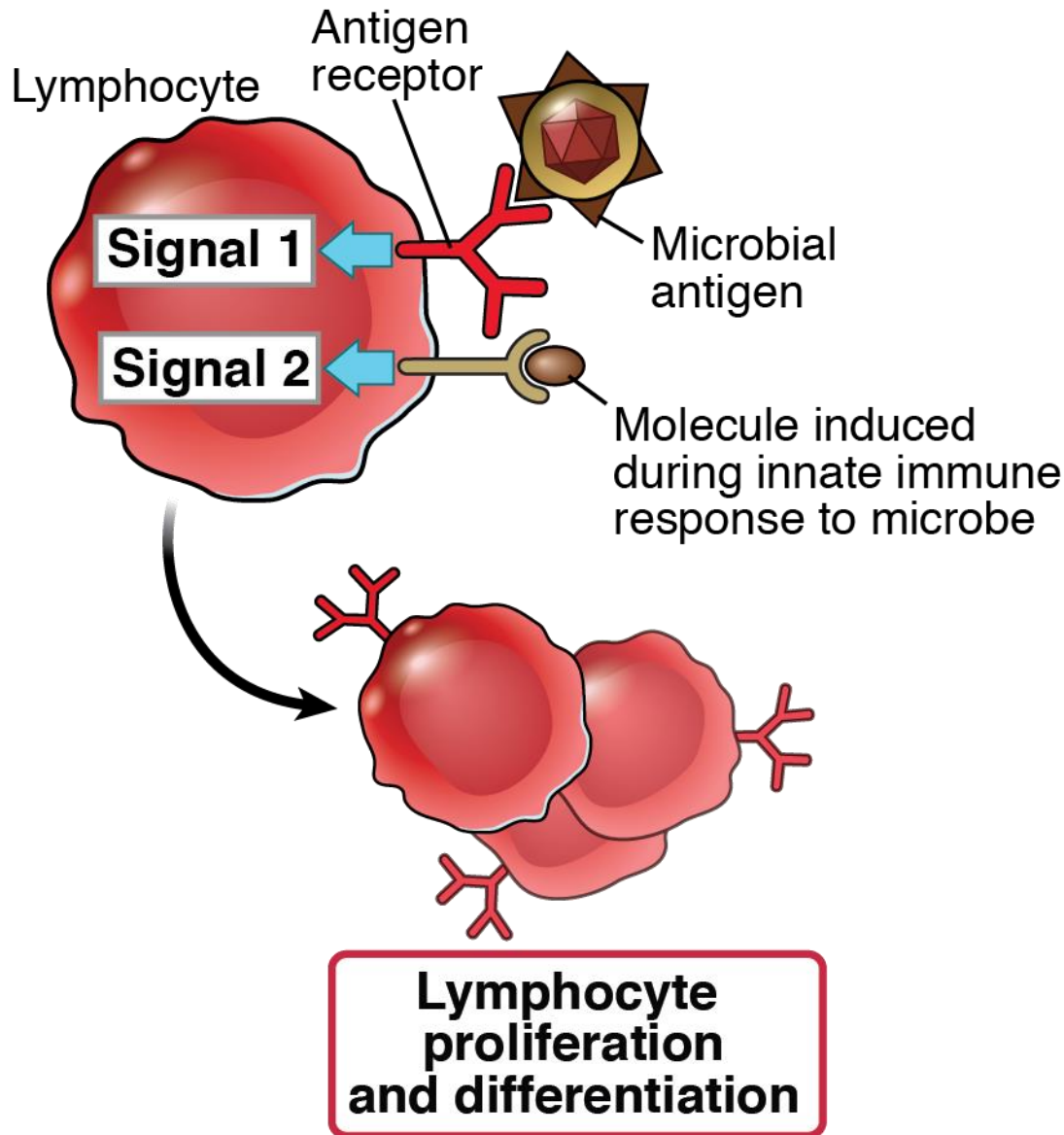
- To sense and eliminate necrotic cells (caused by microbes, other insults) and foreign bodies
 - Reactions: Inflammation
- Gain of function mutations in components of inflammasomes are the cause of rare inherited “auto-inflammatory” syndromes characterized by periodic fever, skin rashes, and amyloidosis
 - Therapy for these disorders?

Inflammasome activation in common inflammatory diseases



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

The innate immune system provides second signals required for lymphocyte activation



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

Role of innate immunity in autoimmune diseases

- Innate immune reactions to microbes or damaged host cells may initiate adaptive responses to self antigens
 - Role of type I IFN in SLE?
- TLR7/TLR9 responses to nucleic acids promote anti-RNA/DNA antibody responses in SLE