Innate immunity: Sensing pathogens and danger

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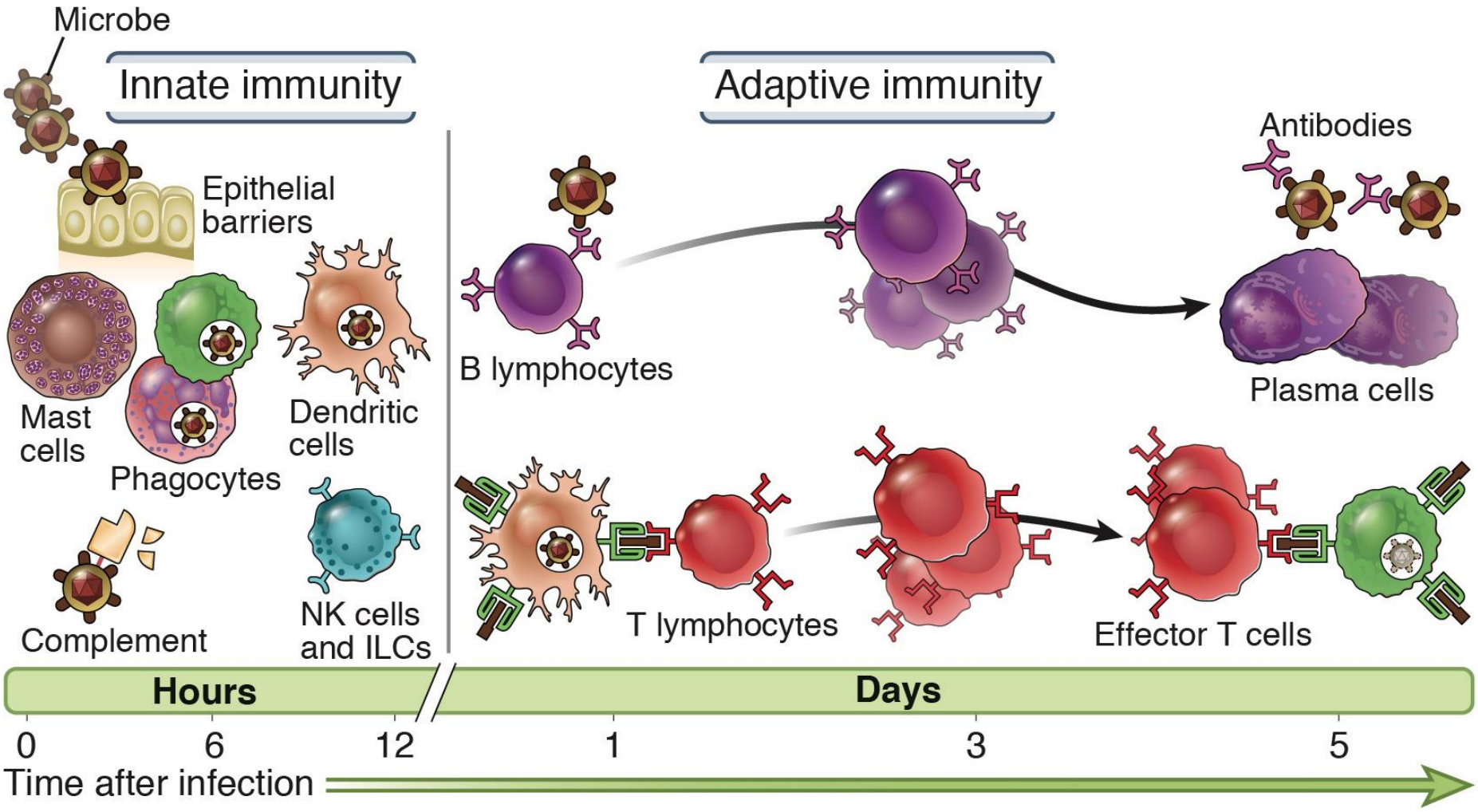
FOCiS

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 autoimmune diseases

Innate and adaptive immunity



Abbas, Lichtman and Pillai. *Basic Immunology*, 5th edition, 2016, Elsevier

Innate immunity: ***always present (ready to attack); many pathogenic microbes have evolved to resist innate immunity***

Adaptive immunity: ***stimulated by exposure to microbe; more potent***

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

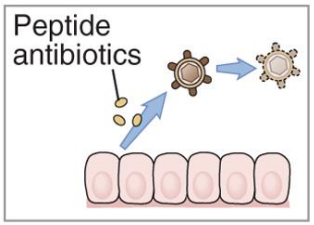
- Stimulate adaptive immunity
  - Innate immunity provides "danger signals"

General features of innate immunity

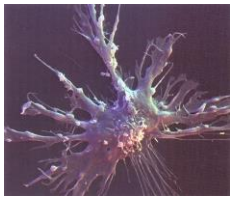
- **Phylogenetically ancient** (evolved before adaptive immunity)
- **Functional even before exposure to microbes** (no prior immunization needed)
- **Resets to baseline** (no or limited memory)

Components of the Innate Immune System
1. Cells

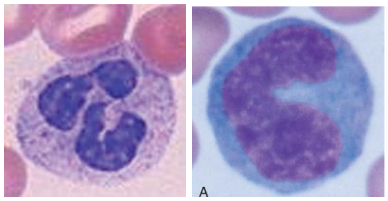
- **Epithelial barriers**
  - Mechanical barrier
  - Locally produced antibiotics



- **Sentinels**
  - Dendritic cells

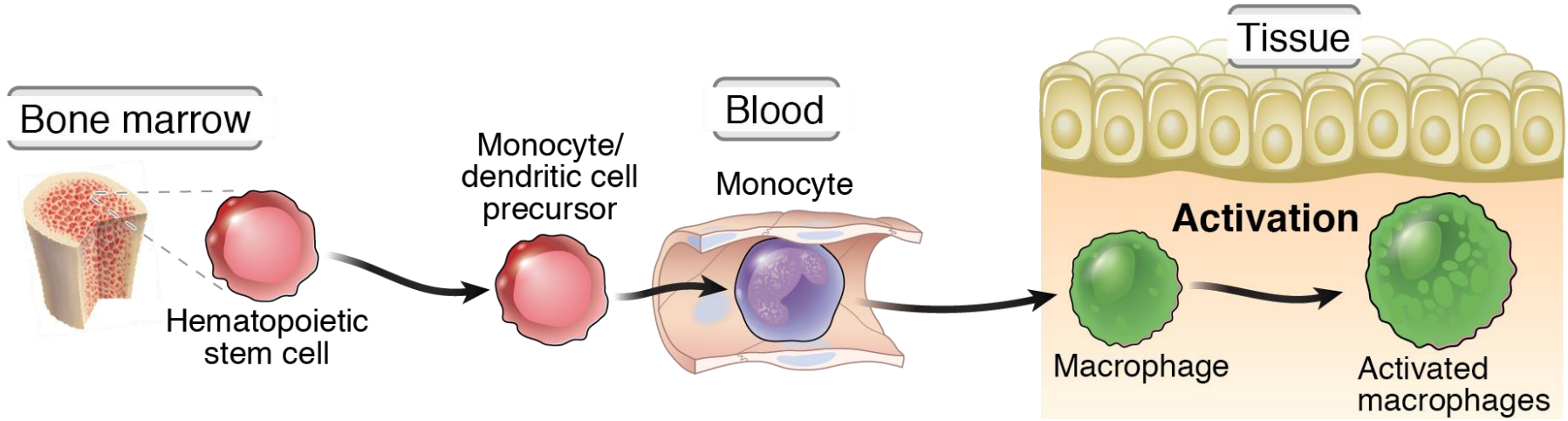


- **Phagocytes**
  - Macrophages
  - Neutrophils



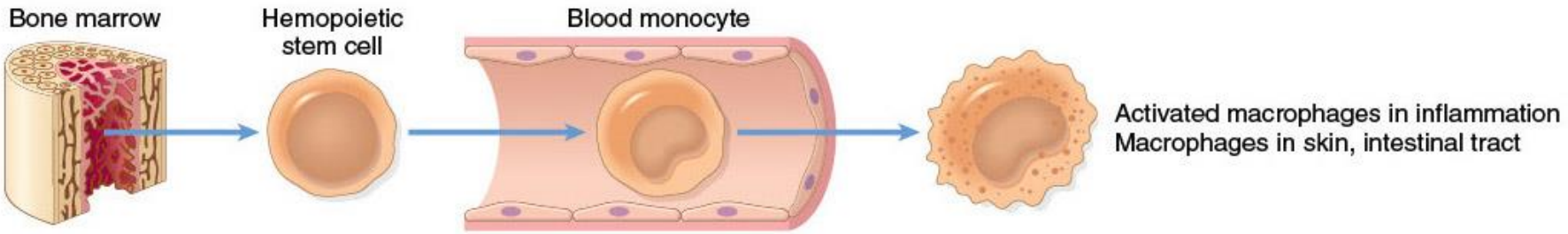
- **Specialized lymphocytes**
  - Innate lymphoid cells: Cytokine producers

Development of macrophages: the accepted view



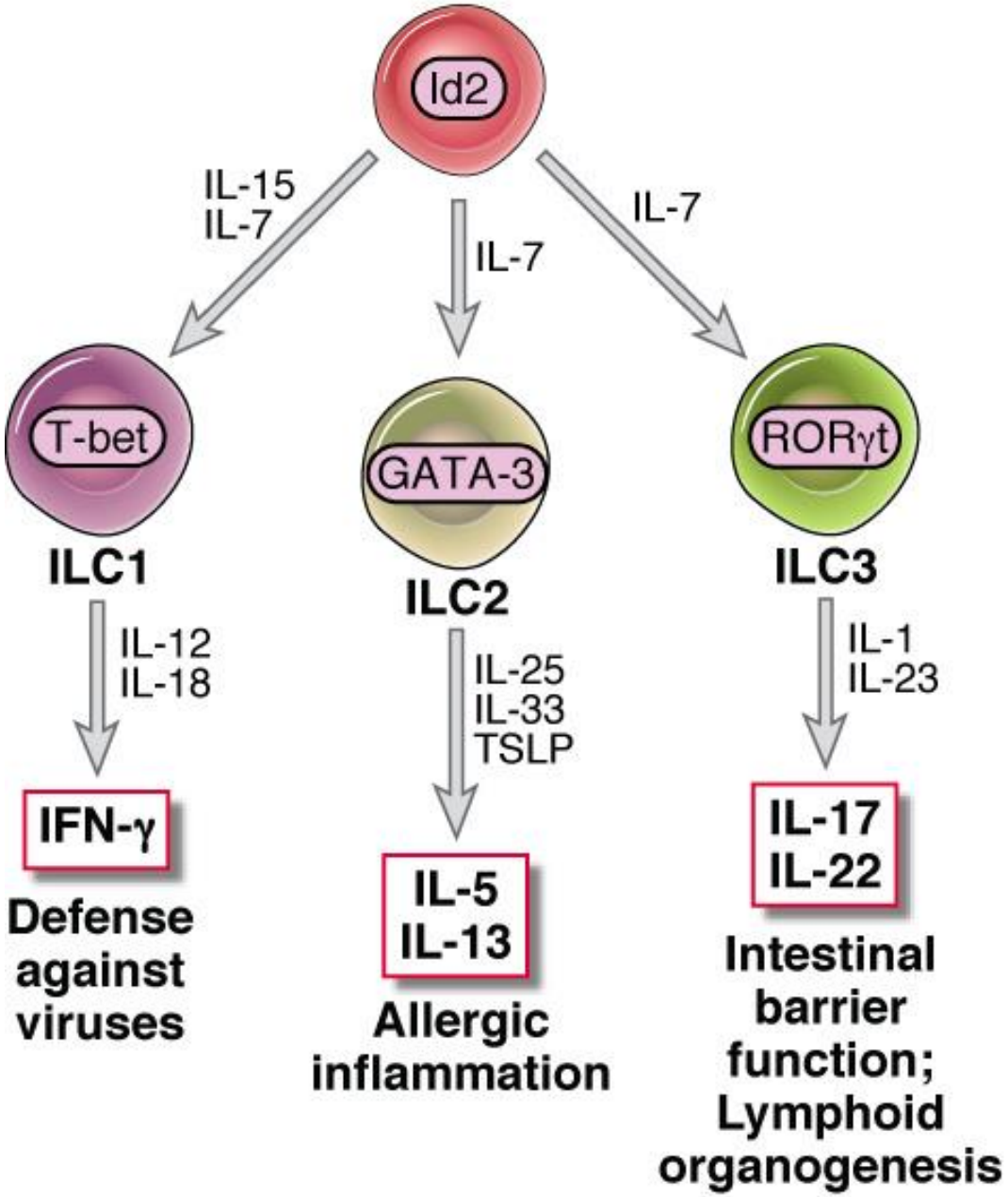
Two pathways of macrophage development

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

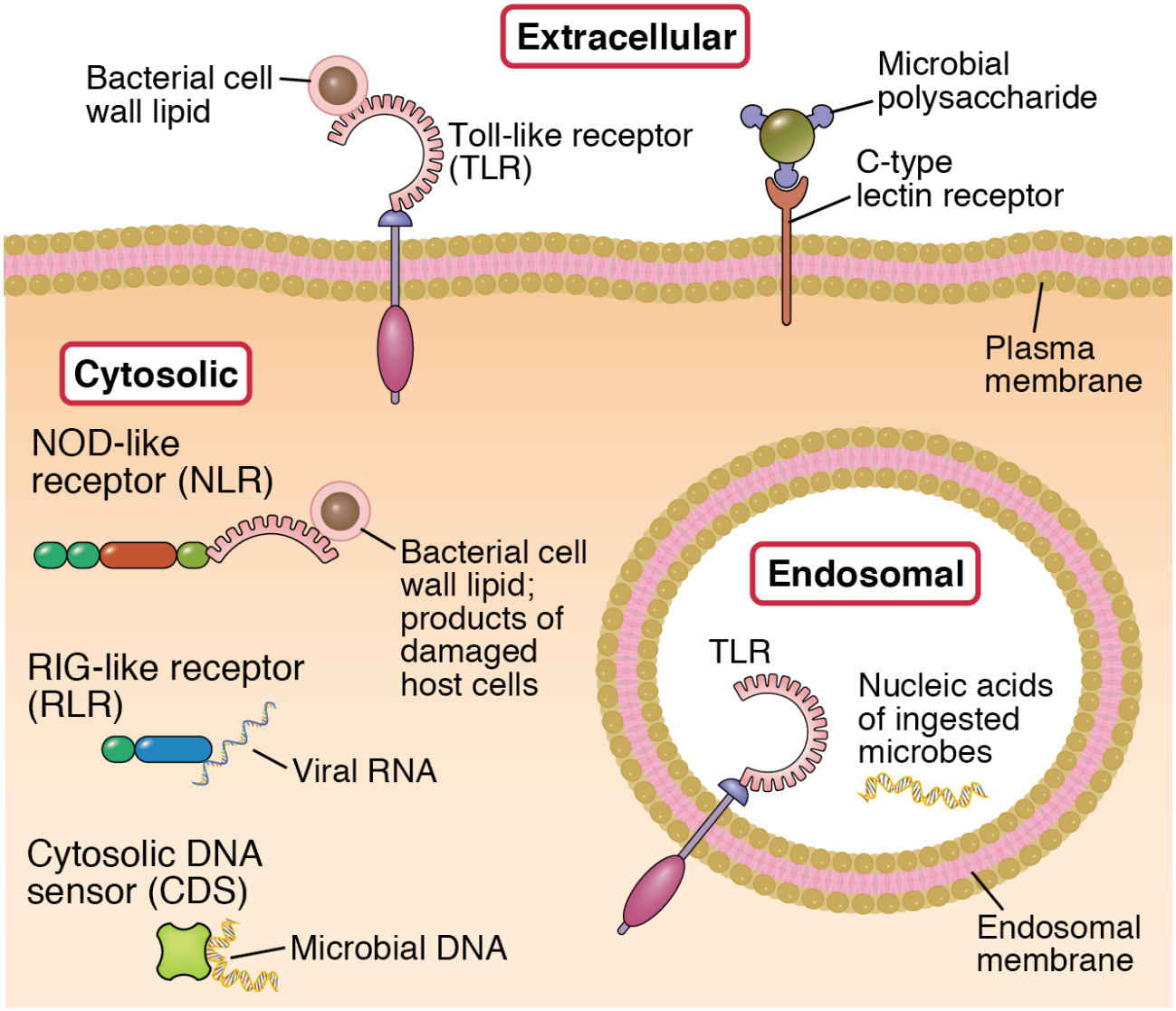
- **Complement**
  - Multiple functions
- **Pentraxins**: coat microbes for phagocytosis
  - C Reactive Protein, serum amyloid protein
- **Collectins**
  - Mannose Binding Lectin (activator of complement)

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



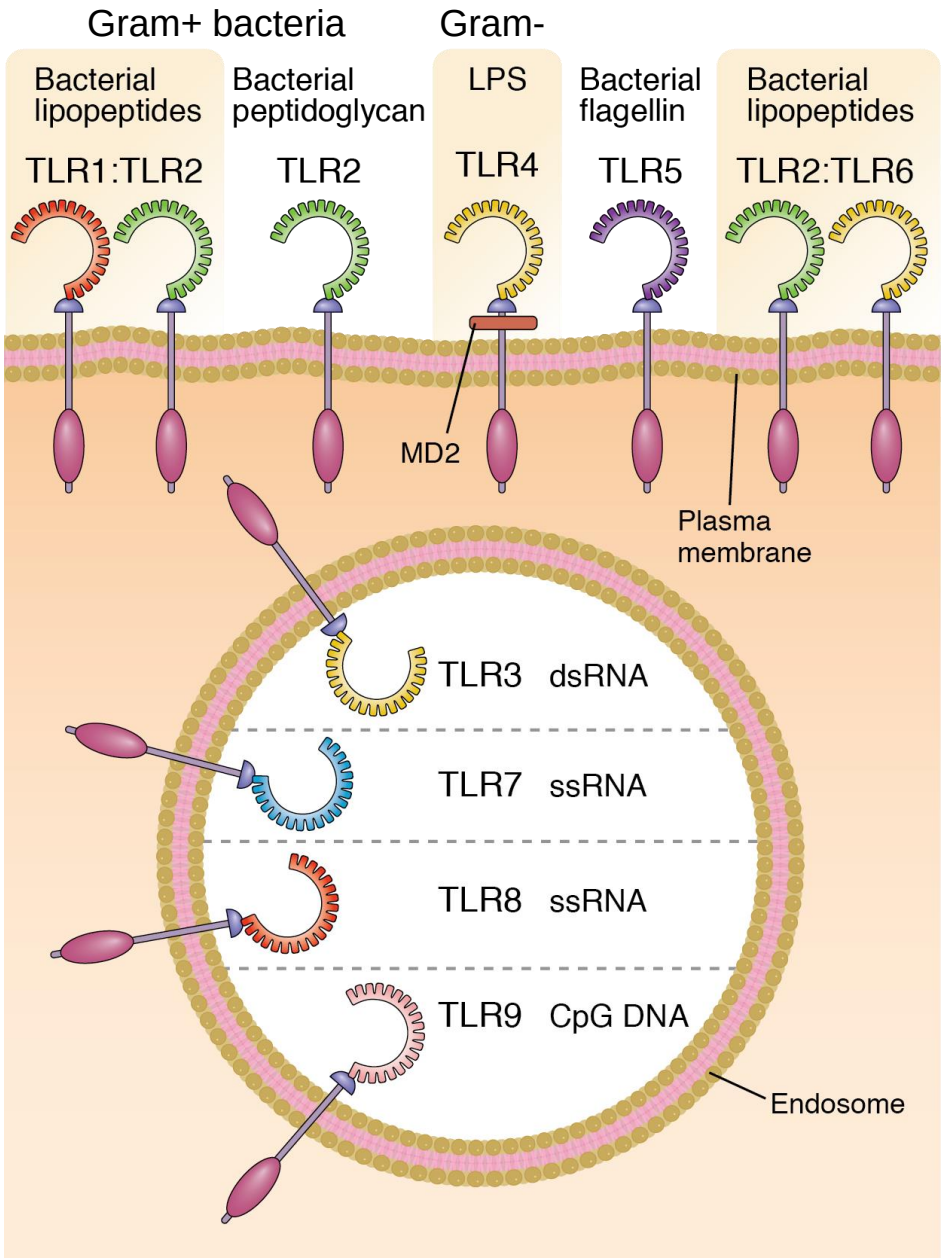
Receptors are located such that they can sample all cellular compartments containing different types of pathogens

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)

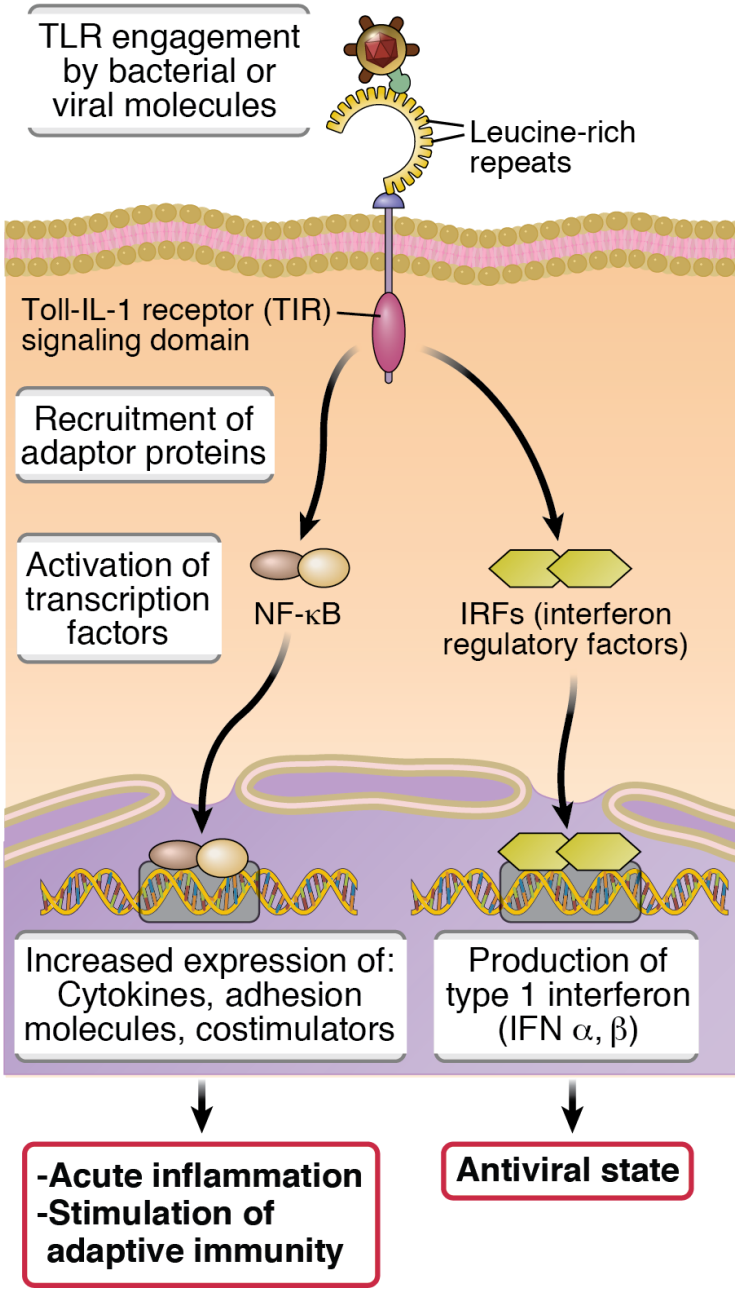
Specificity of Receptors of Innate and Adaptive Immunity

	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



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)

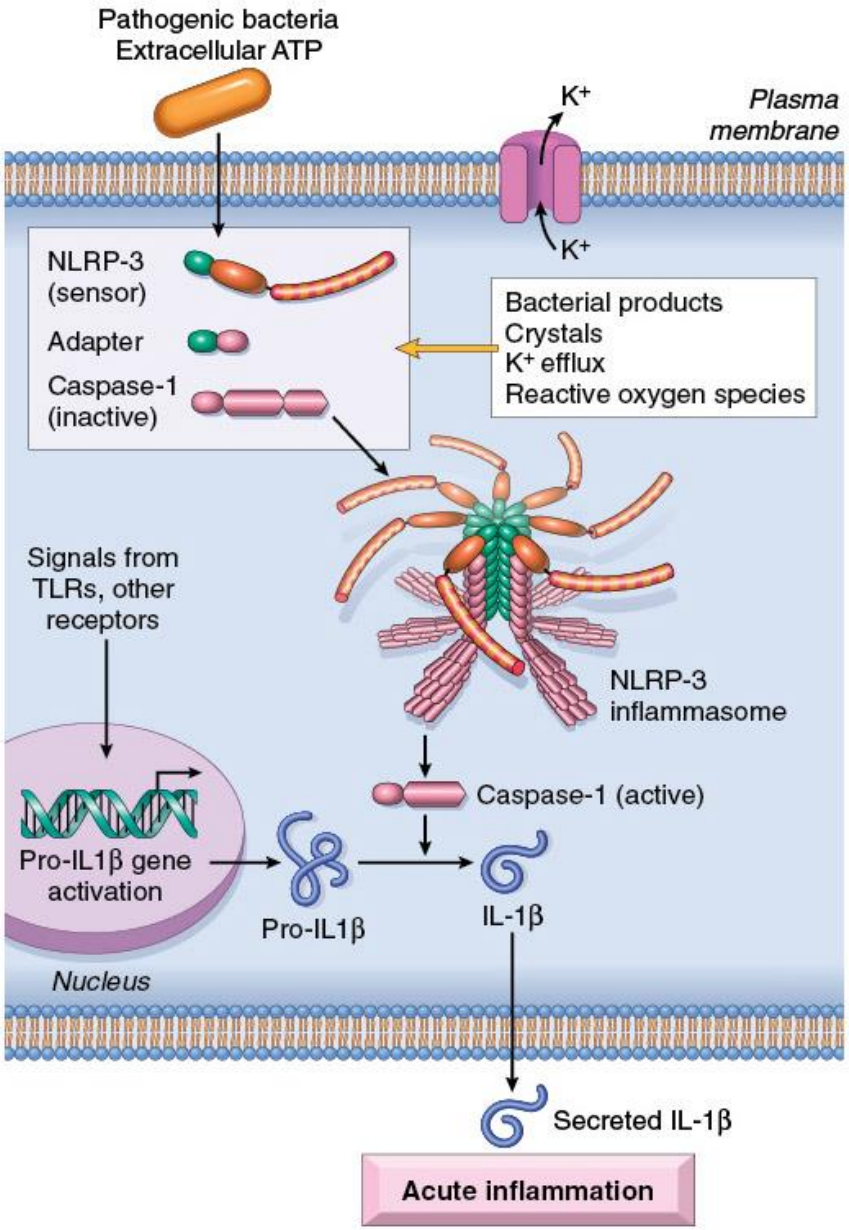
- A family of >20 cytosolic proteins, best known:

- NOD1 and NOD2
  - Bind bacterial peptides
  - Activate NF-κB 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 = nucelotide oligomerization domain

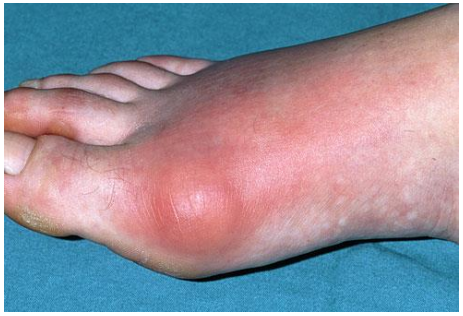
Activation of inflammasome by microbial products and/or host-derived molecules

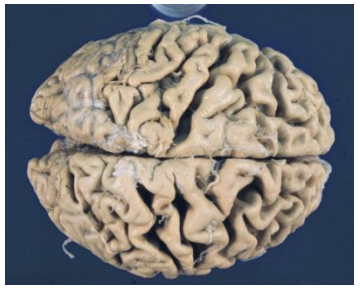


Physiologic functions of the inflammasome

- To sense and eliminate necrotic cells (caused by microbes, other insults) and foreign bodies
  - Reactions: Inflammation
- 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.

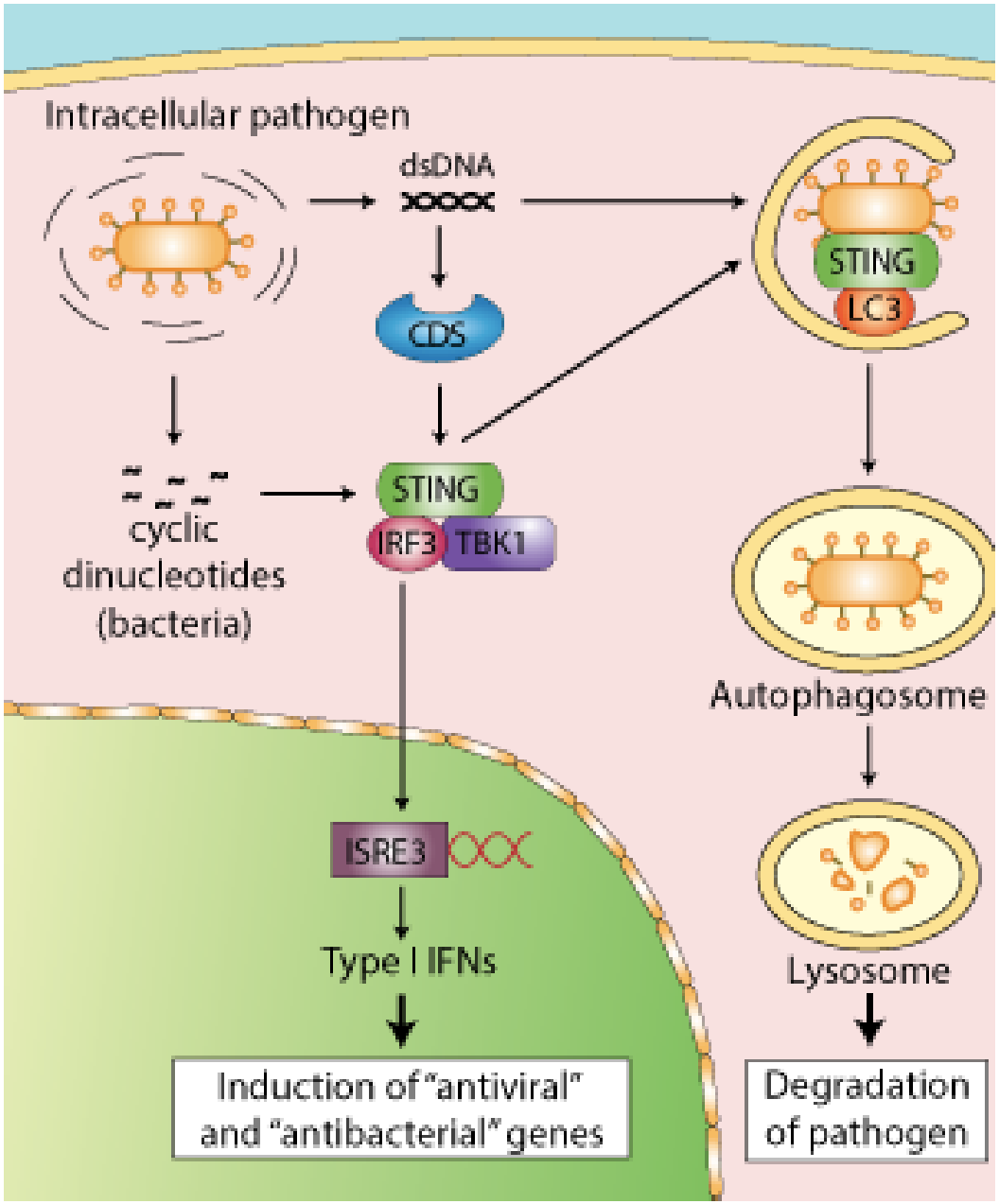
Inflammasome activation in common inflammatory diseases



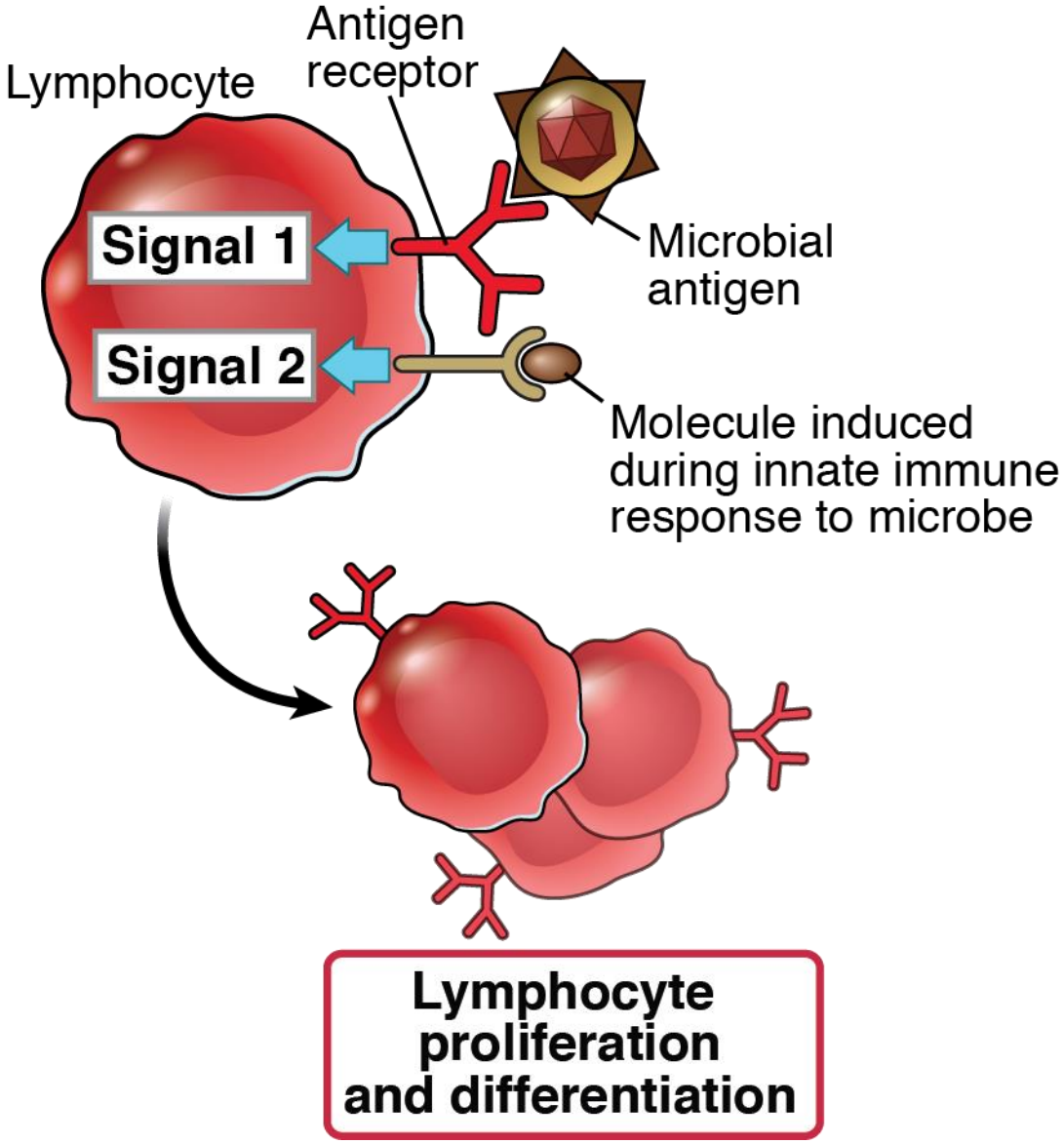



- Gout, pseudogout: Deposition of crystals (e.g. urate) → IL-1-mediated acute inflammation
- Obesity-associated metabolic syndrome: Deposition of lipids and free fatty acids → IL-1 production → insulin resistance → type 2 diabetes?
- Deposition of cholesterol crystals → role of inflammation in atherosclerosis?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

DNA sensing: the STING pathway



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