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

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

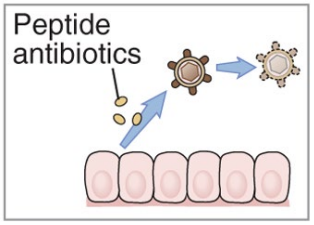
- Stimulate adaptive immunity
  - Innate immunity provides "danger signals"

General features of innate immunity

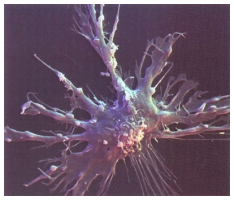
- **Phylogenetically ancient** (evolved before adaptive immunity)
- **Functional even before exposure to microbes** (no prior immunization needed)
- **Resets to baseline** (no or limited memory)

Cells of the Innate Immune System (the Cellular Arm of Innate Immunity)

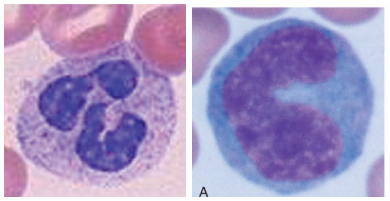
- **Epithelial barriers**
  - Mechanical barrier
  - Locally produced antibiotics



- **Sentinels**
  - Dendritic cells



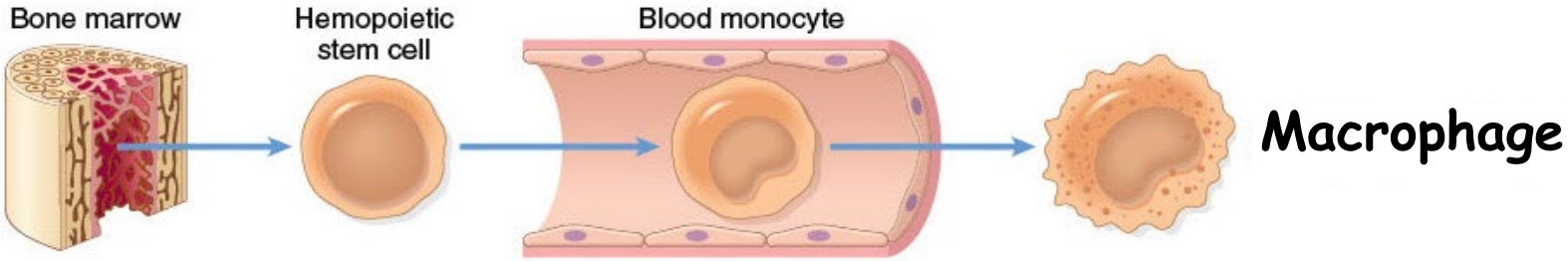
- **Phagocytes**
  - Macrophages
  - Neutrophils



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

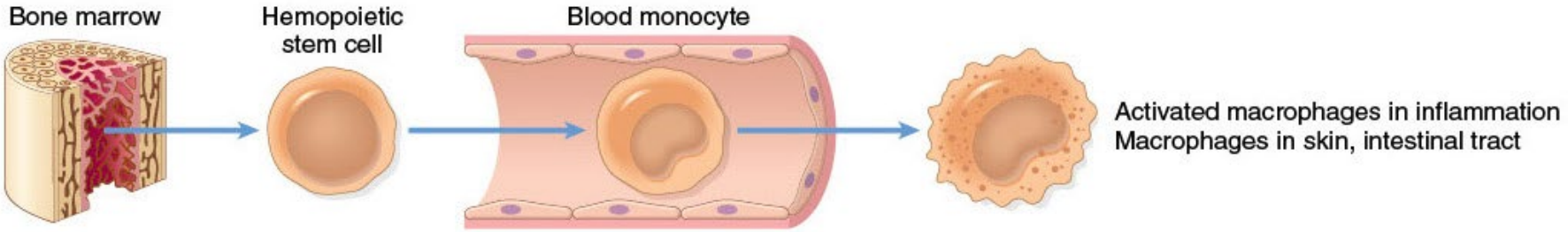
Macrophage development

The traditional view



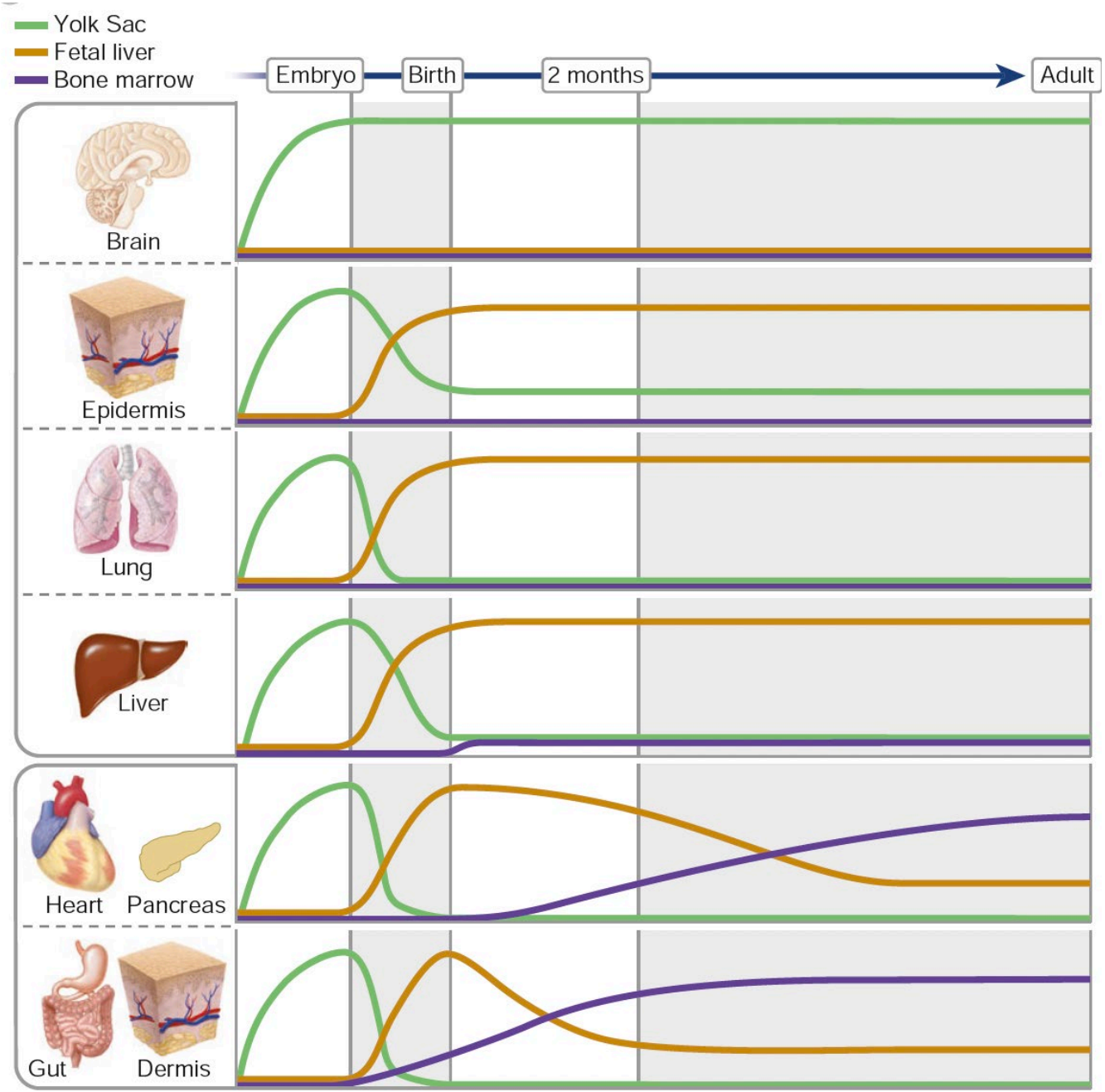
Two pathways of macrophage development

During inflammatory reactions



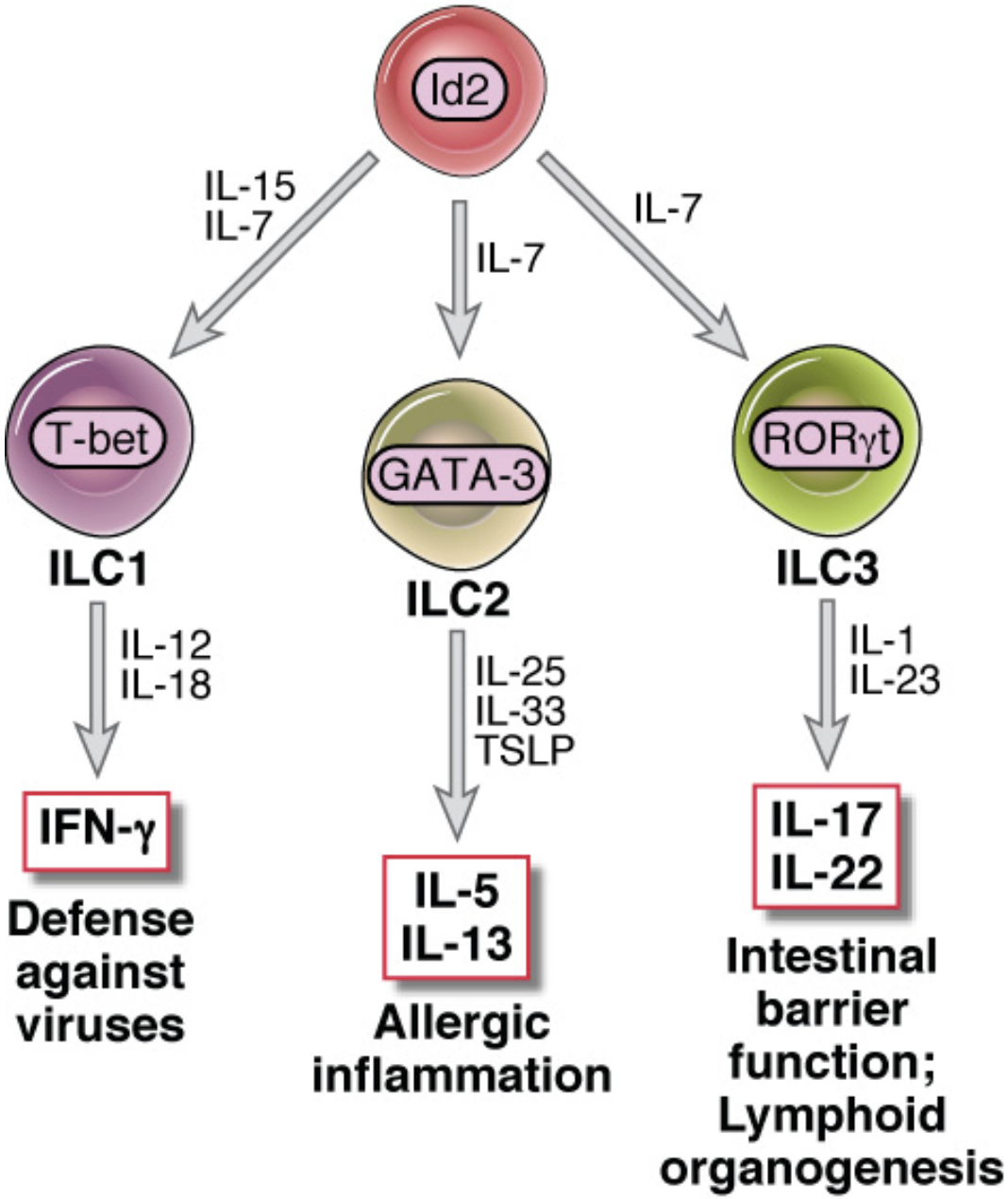
Tissue-resident macrophages

Origin of tissue-resident macrophages



F. Ginhoux

Innate lymphoid cells



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

May contribute to early cytokine responses to microbes and tissue damage

Most often studied in T-deficient (e.g. RAG-ko) mice; unclear contribution in intact mice; difficult to study in humans (lack of markers, location in tissues)

Natural killer cells

- Ability to kill cells depends on:
  - Expression of activating ligands (often on infected and tumor cells)
  - Loss of inhibitory self ligands (MHC-I)
- How important is NK memory?
- Functions:
  - Killing of virus-infected cells
  - Killing of tumors?

Soluble Molecules of the Innate Immune System (the Humoral Arm): Plasma proteins

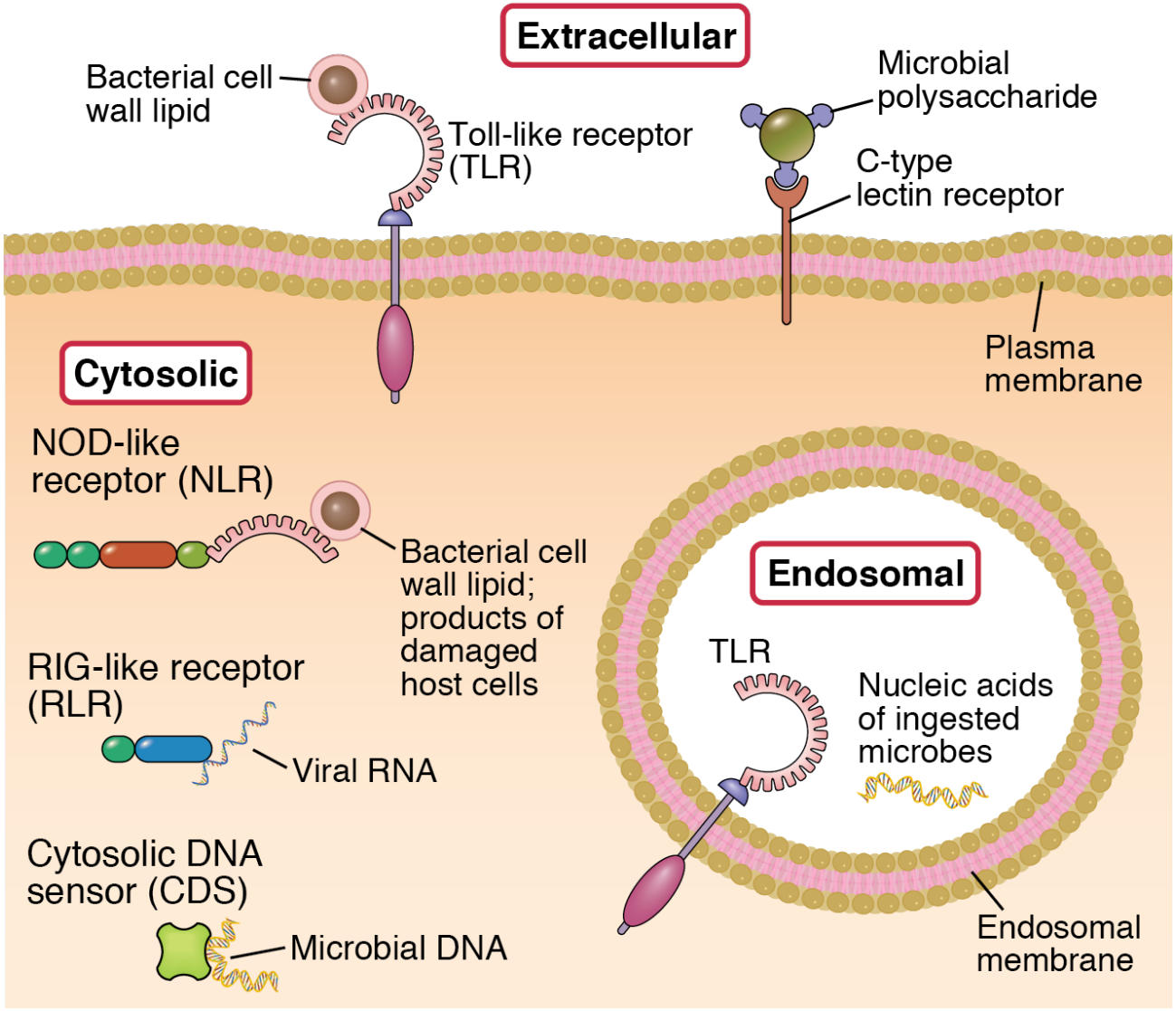
- **Complement**
  - Multiple functions
- **Pentraxins**: coat microbes for phagocytosis
  - C Reactive Protein, serum amyloid protein
- **Collectins**
  - Mannose Binding Lectin (activator of complement)

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

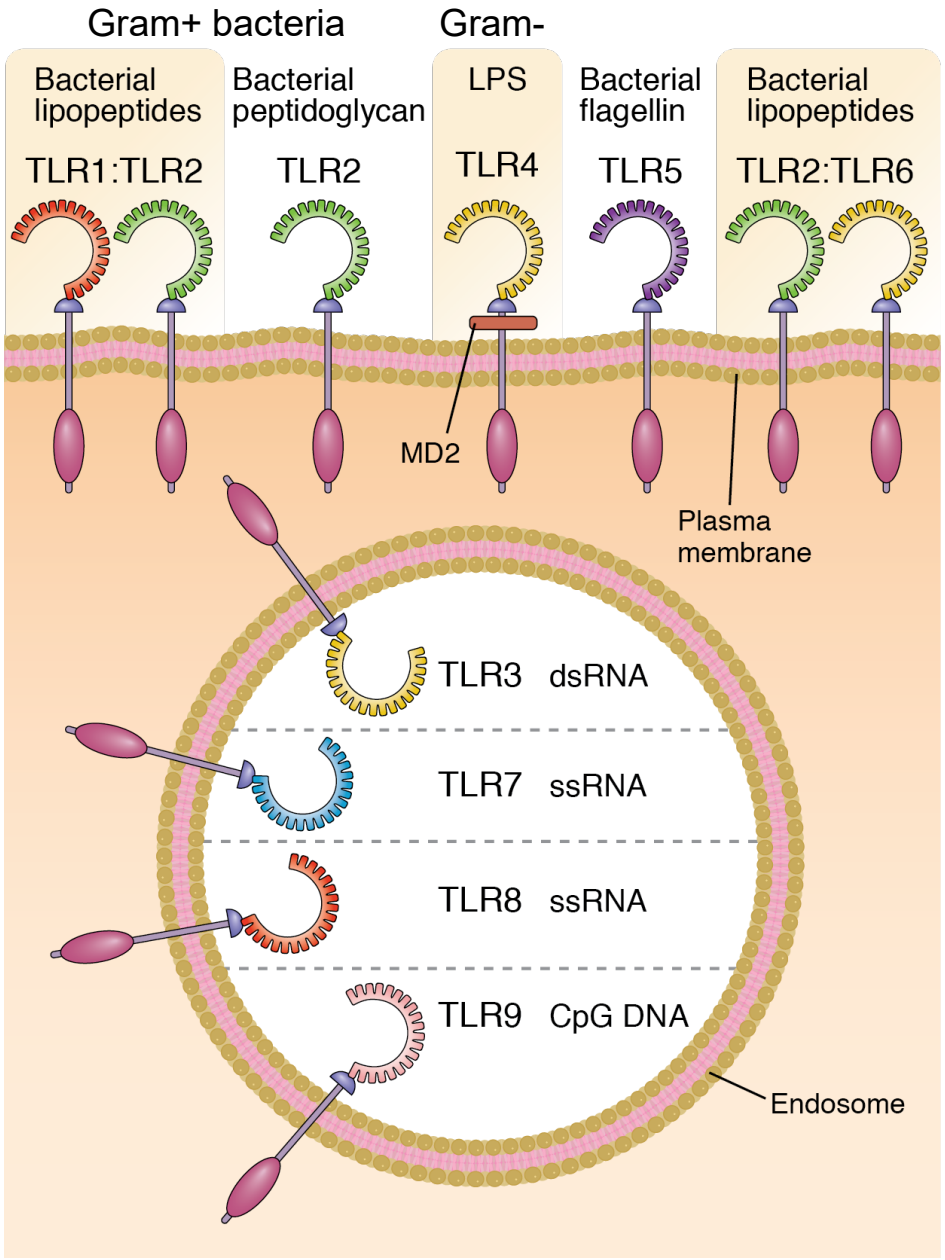


Receptors are located such that they can sample all cellular compartments containing different types of pathogens

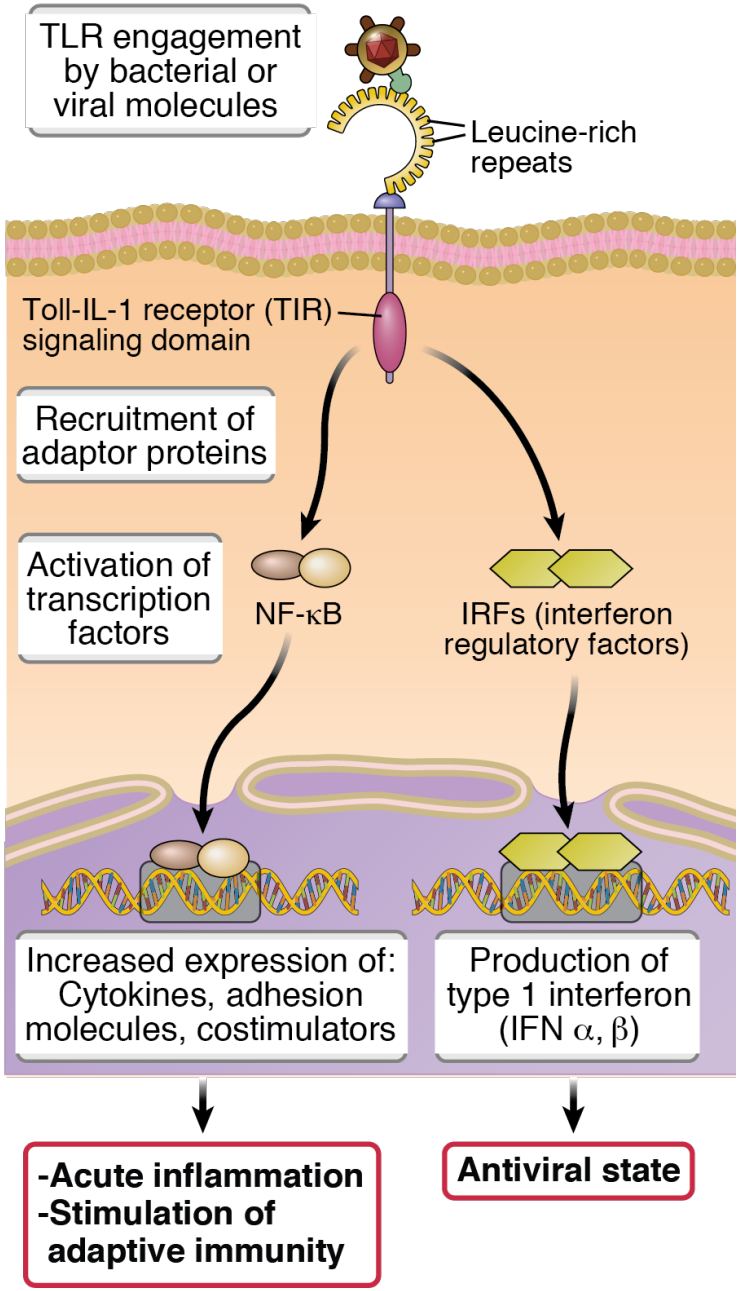
Receptors of Innate and Adaptive Immunity

	INNATE	ADAPTIVE
Microbial molecules recognized	~1,000; essential for microbes	>10^7; non-essential
Types of receptors	~100 types, each invariant	2 types (Ig, TCR); millions of variations
Genes encoding receptors	Germline, in all cells; non-clonal	Somatic recombination in B and T cells; clonal distribution

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)

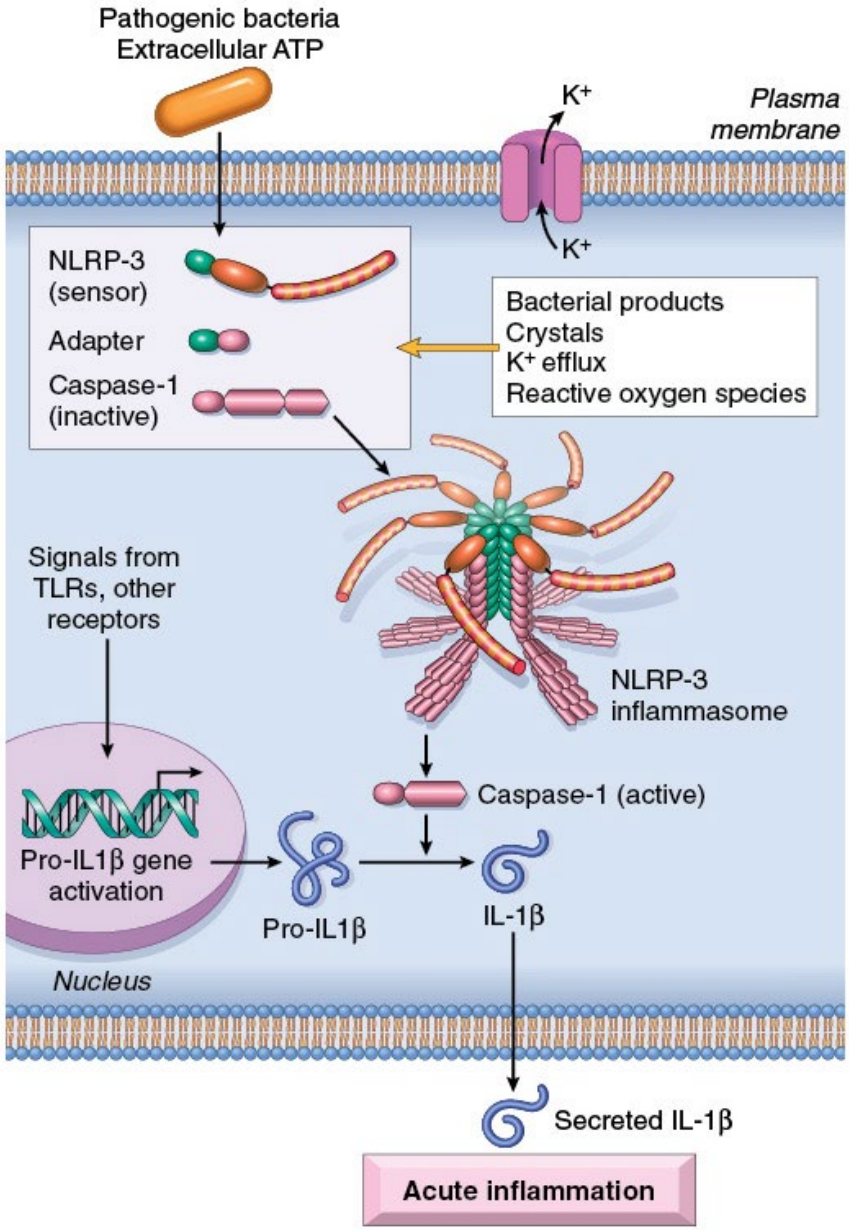
- A family of >20 cytosolic proteins, best known:

- 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



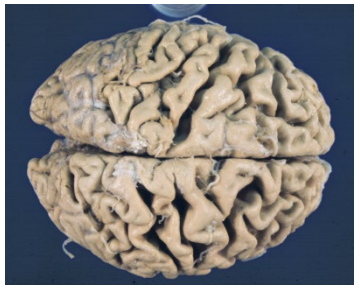
Signaling involves prion-like propagation of adaptor protein (ASC), forming filaments

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
  - Most are gain-of-function mutations that lead to constitutive activation and uncontrolled IL-1 production
  - How do we treat these disorders?

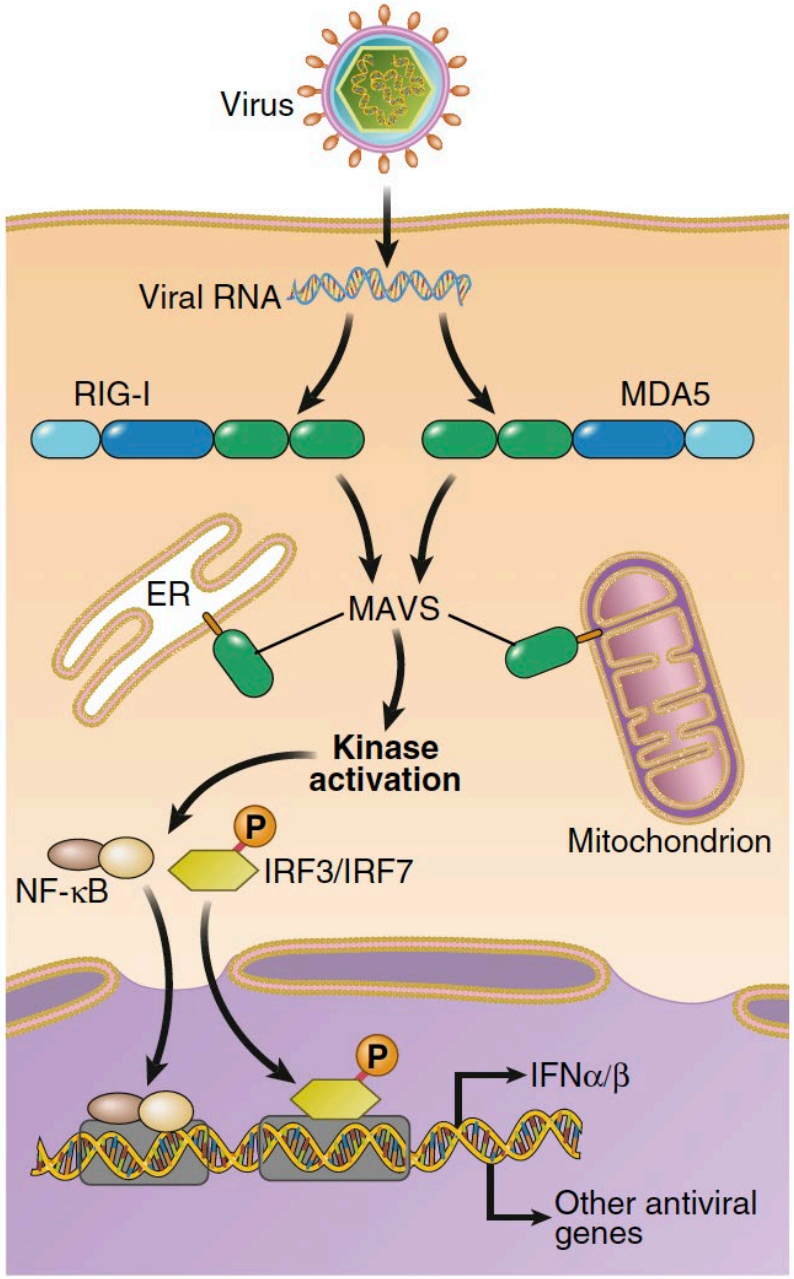
Inflammasome activation in common inflammatory diseases



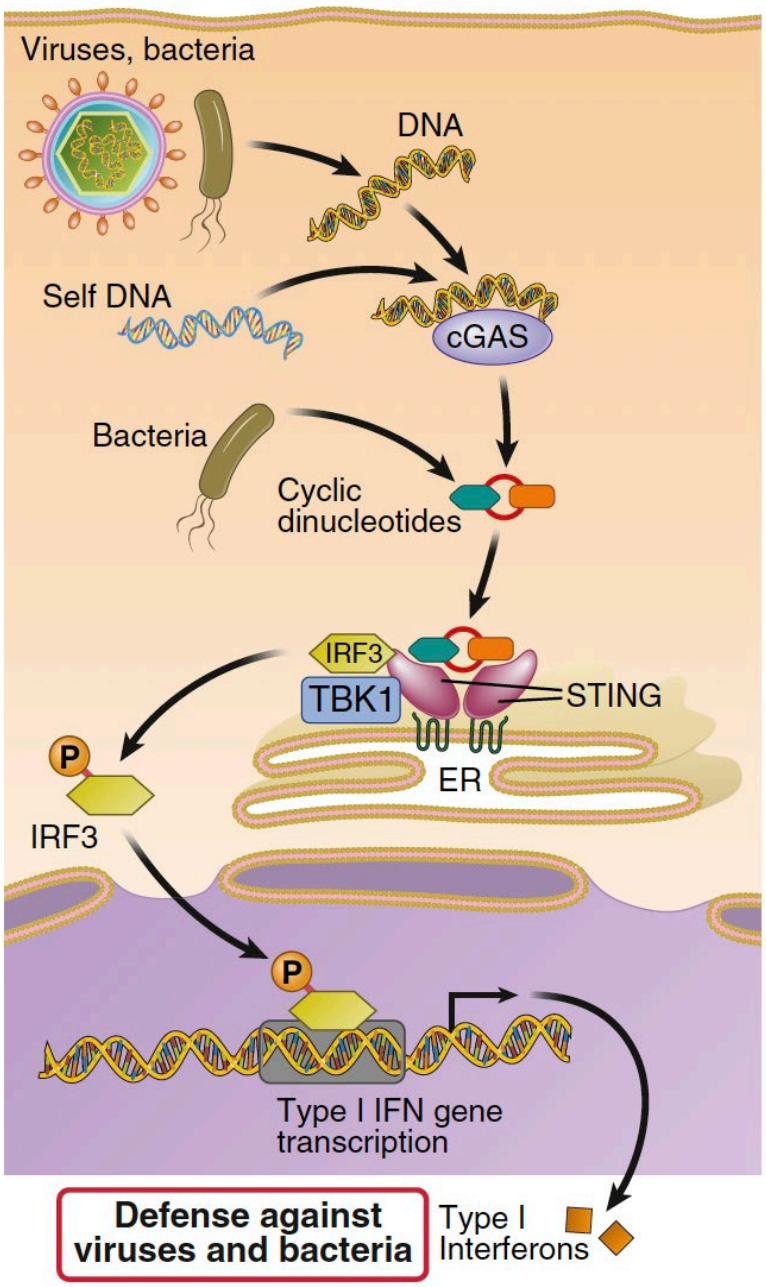
- Gout, pseudogout: Deposition of crystals (e.g. urate) → IL-1-mediated acute inflammation
- Obesity-associated metabolic syndrome: Deposition of lipids and free fatty acids → IL-1 production → insulin resistance → type 2 diabetes?
- Deposition of cholesterol crystals → role of inflammation in atherosclerosis?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

Cytosolic RNA sensing



Defects in type I IFN production or activity are associated with severe COVID

Cytosolic DNA sensing: the STING



Spontaneous activation of this pathway causes systemic inflammatory diseases grouped under interferonopathies

The major reactions and functions of innate immunity

- Induction of inflammation: removal of microbes, dead cells, foreign bodies
  - Cytokines
  - TLR-mediated leukocyte activation

- Inhibition of viral replication
  - Type I IFNs
  - (NK cells kill virus-infected cells)

- Stimulation of the adaptive immune response
  - Costimulators, cytokines