# Innate Immunity

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HARVARD MEDICAL SCHOOL

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# Lecture outline

- General features of innate immunity
- Components of the innate immune system
- Foreign and self molecules that stimulate innate immune responses
- Recognition molecules
  - TLRs, NLRs, Inflammasomes, RNA and DNA sensors
- Innate effector responses
  - Inflammation
  - Anti-viral state
- Innate immunity stimulation of adaptive immunity

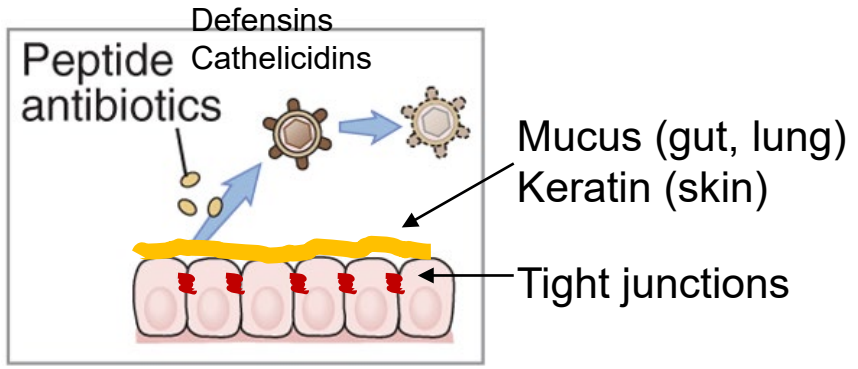
# General features of innate immunity

- Phylogenetically ancient (evolved before adaptive immunity)
- Functional even before exposure to microbes (no prior sensitization/immunization needed)
- First responders that eliminate some infections, or hold at bay other infections until adaptive immunity kicks in
- Limited types of induced responses:
  - Inflammation
  - Antiviral state
- Resets to baseline (limited memory)
  - Some evidence for macrophage and NK memory
- Stimulates adaptive immunity
  - Innate immunity provides “danger signals”

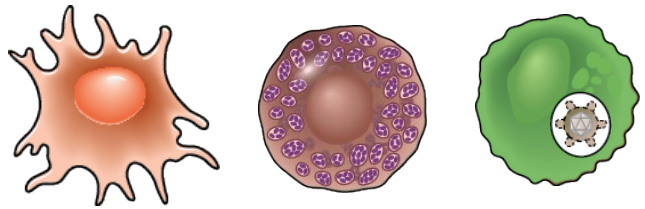
*Take home messages*

# Components of the Innate Immune System: Cells

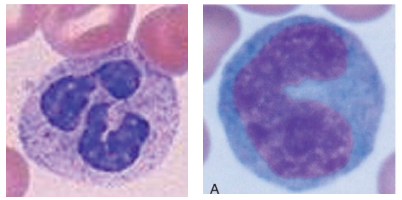
- **Epithelial barriers**
  - Mechanical barrier
  - Locally produced antibiotics




- **Sentinels**
  - Dendritic cells
  - Mast cells
  - Tissue resident macrophages

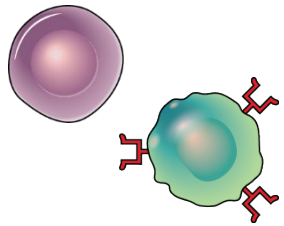


- **Recruited Phagocytes**
  - Macrophages
  - Neutrophils



Blood ⇩ Tissue

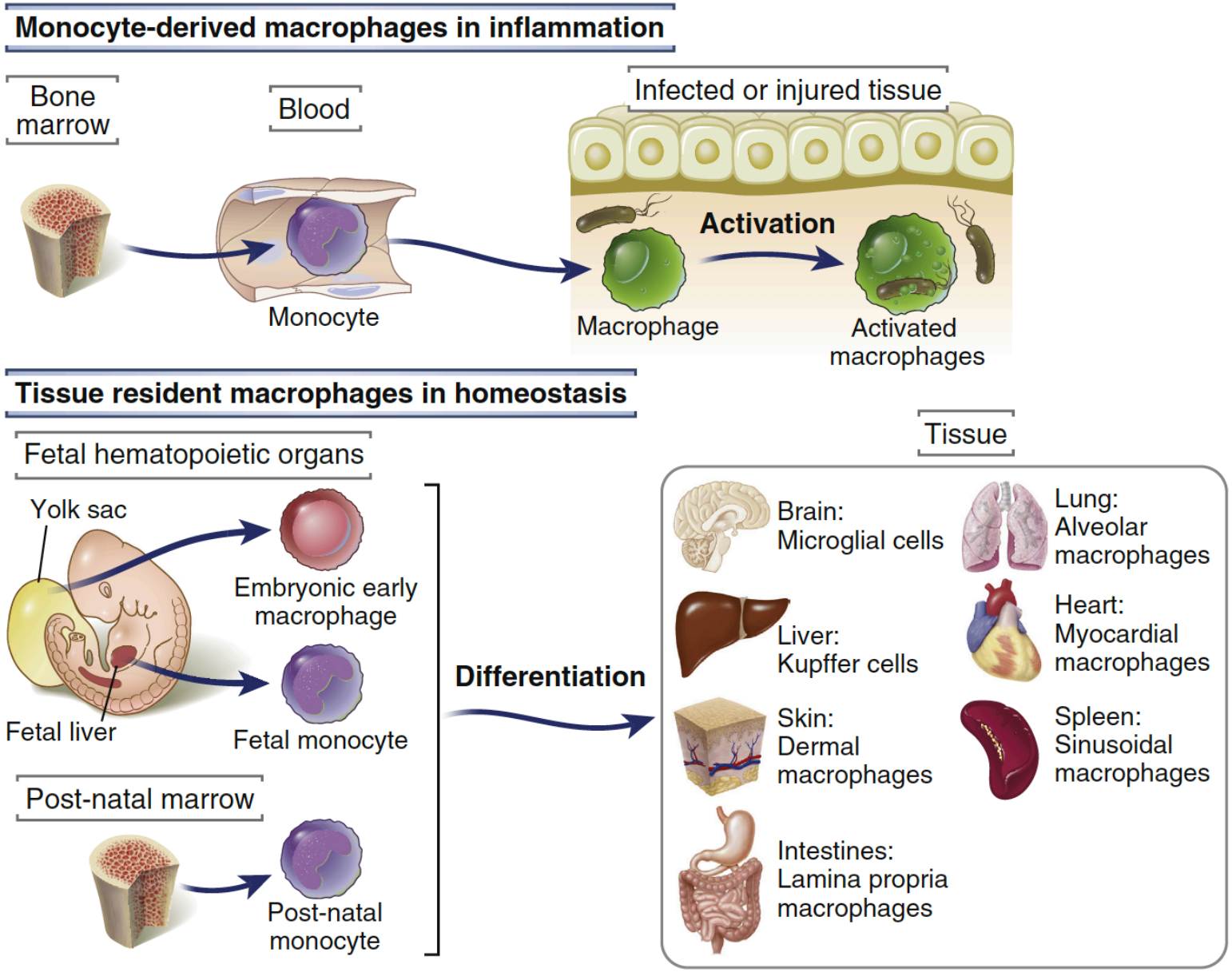
- **Specialized lymphocytes**
  - Innate lymphoid cells (ILCs): Cytokine producers
  - NK T cells, γδ T cells, MAIT cells



# Two Sources of Macrophages

**Recruited monocyte-derived macrophages:**
**Inflammation**

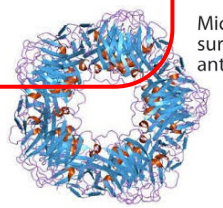
**Tissue resident macrophages:**
**Homeostasis**
**Sentinel role**

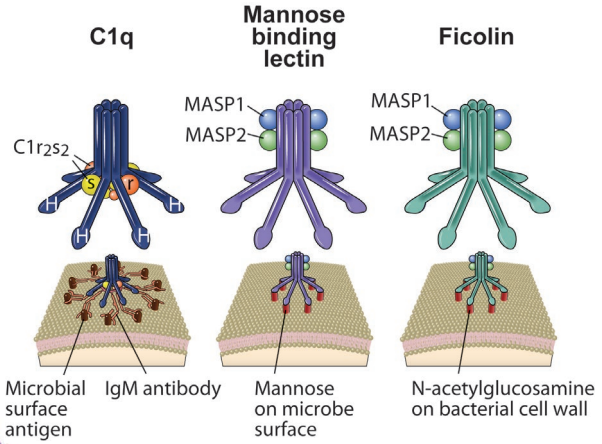


# Components of the Innate Immune System: Soluble proteins

- **Plasma proteins**
  - **Complement**
  - **Ficolins (lectins)**
  - **Collectins (Mannose Binding Lectin)**
  - **Pentraxins (C Reactive Protein, serum amyloid protein)**

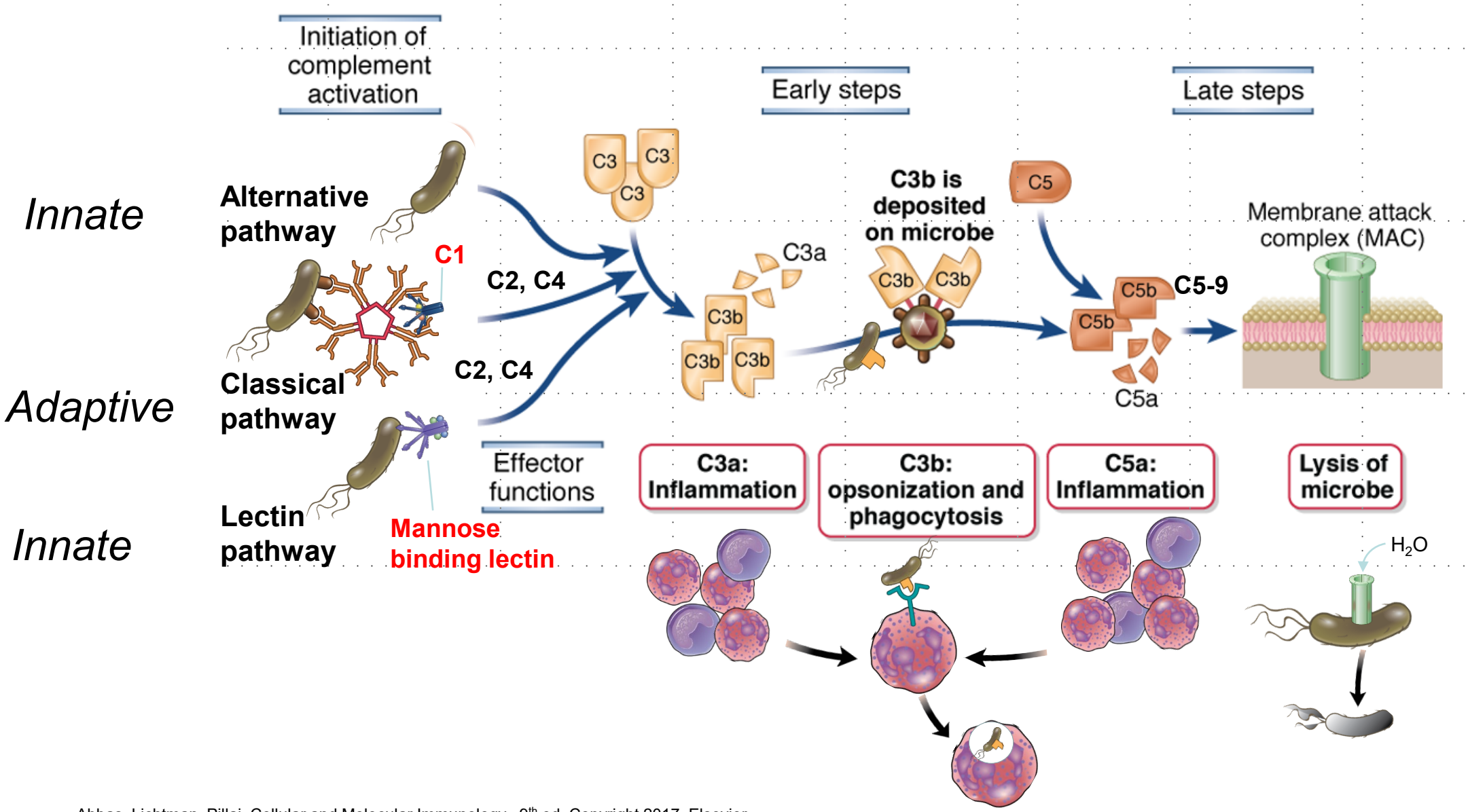
Work in part through complement






- **Cytokines**
  - **Inflammatory (IL-1, TNF, IL-6, IL-12)**
  - **Chemokines (CXCL8, CCL2, many others)**
  - **Anti-viral (Type 1 interferons: IFN $\alpha$, IFN $\beta$)**

# Complement Pathways

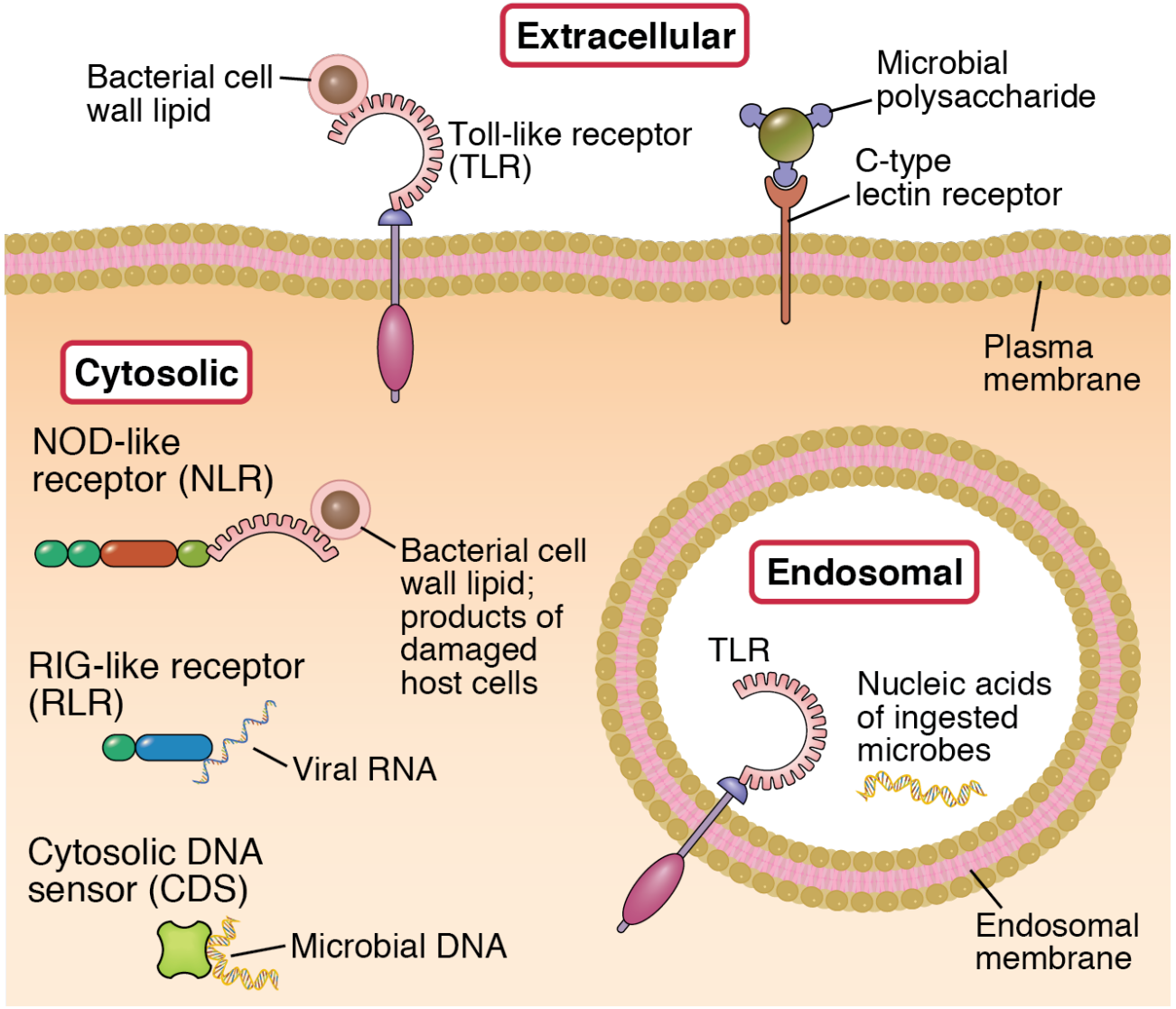


# Innate Immune System:
## What is recognized?

- **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

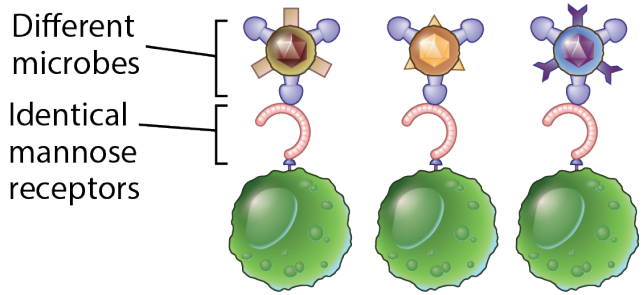
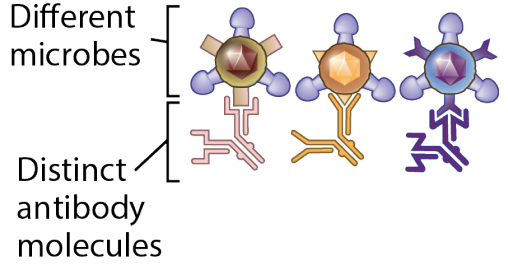
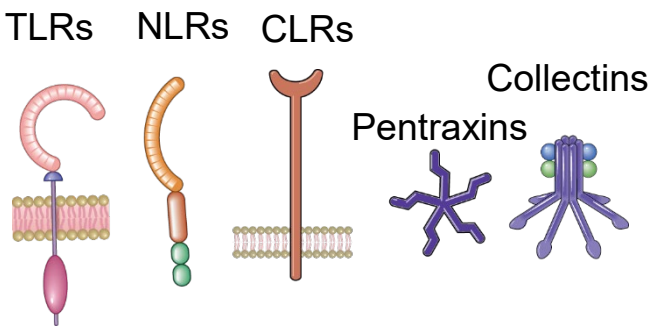
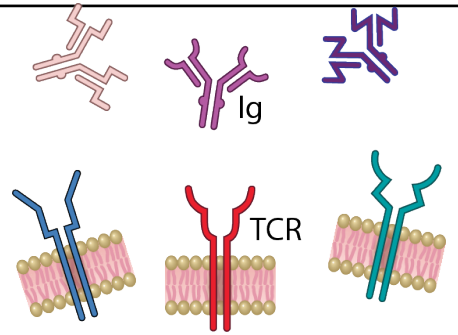



***All cellular compartments and all microbe types are covered***

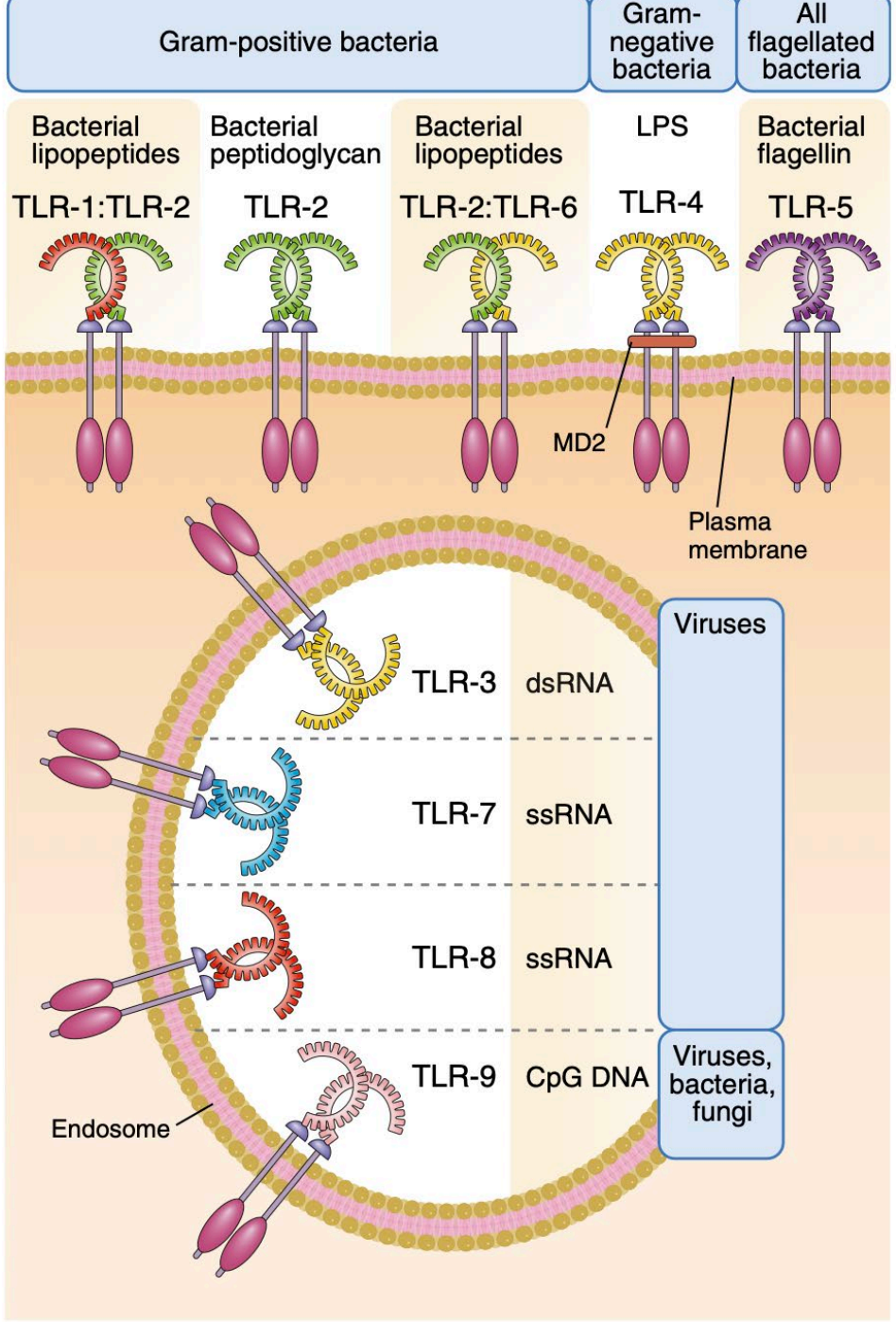
***5 major classes***

- ***TLRs: Toll like receptors***
- ***CLRs: C-type lectin receptors***
- ***NLRs: NOD-like receptors***
- ***RLRs: RIG like receptors***
- ***CDSs: Cytosolic DNA sensors***

# Innate vs Adaptive Immune Recognition

| | | |
|---|---|---|
| **Structures recognized** | ~1,000<br>  <br> | $>10^7$<br>  <br> |
| **Receptors** |  <br><br>~100 types;<br>Limited variation of each type |  <br><br>Two types;<br>Millions of variations of each type |
| **Distribution of receptors on cells** | Non-clonal | Clonal |

# Toll-like Receptors: Specificity Location

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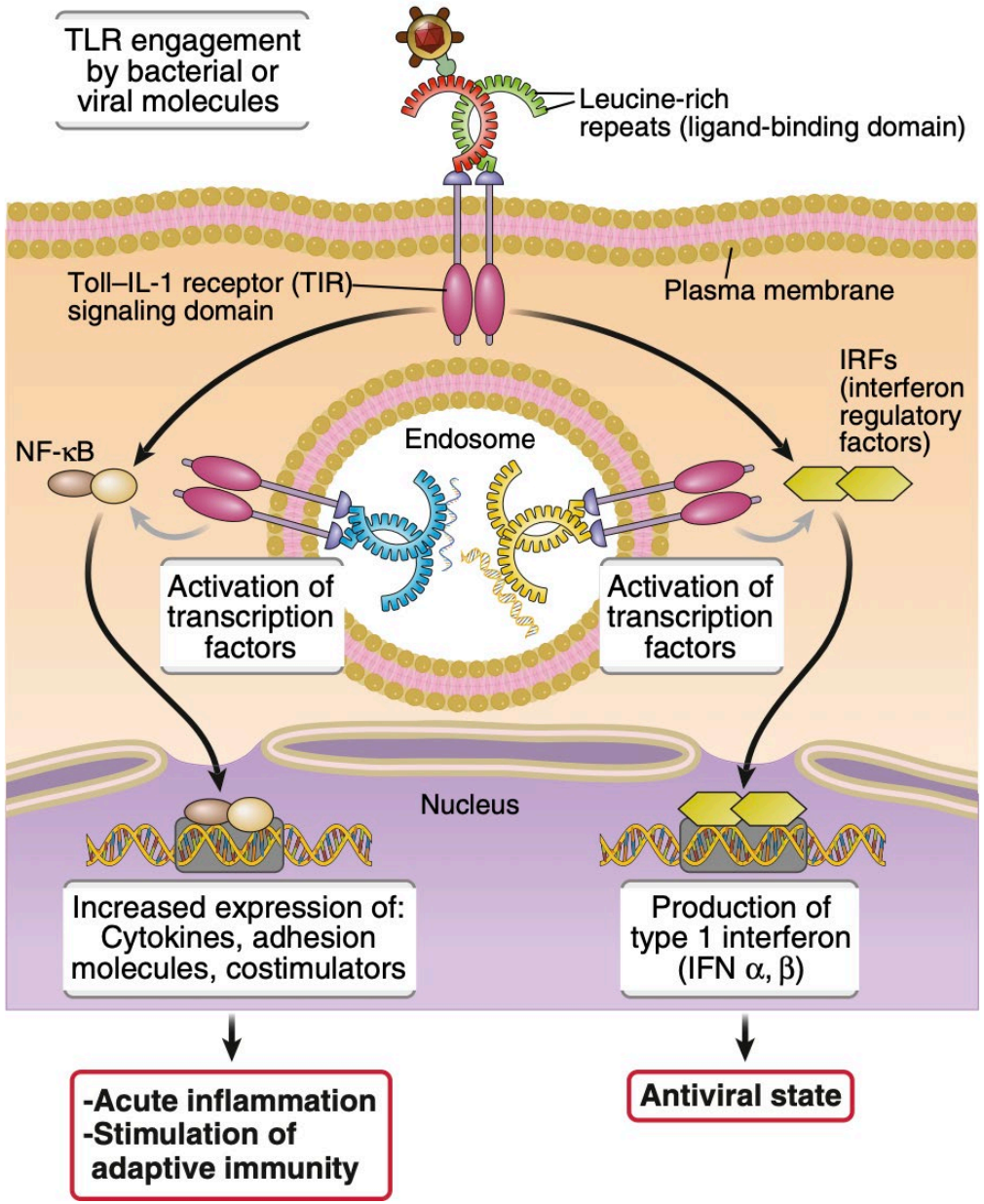
# Toll-like Receptor signaling




NF-κB induced expression of proinflammatory genes:
- Cytokines (TNF, IL-1, IL-6, IFN α)
- Chemokines
- Endothelial adhesion molecules

***Acute inflammation***

IRF7/3 induced expression of Type 1 interferon genes
- IFN-α
- IFN-β

***Anti-viral state***

NF-κB induced expression of costimulatory molecules
- CD80
- CD86

***Stimulation of T cells / adaptive immunity***

# Toll-like Receptors (TLRs): Clinical Relevance

- **Excessive/systemic TLR signaling underlies pathophysiology of sepsis (LPS/TLR4; Peptidoglycan/TLR2)**
- **TLR signaling in B cells promotes auto-antibody production**
- **Gain of function MyD88 mutations drive B cell lymphomas**
- **TLR ligands, such as CpG nucleotides, are potentially useful adjuvants to enhance effectiveness of vaccines**

# NOD-like receptors (NLRs)*

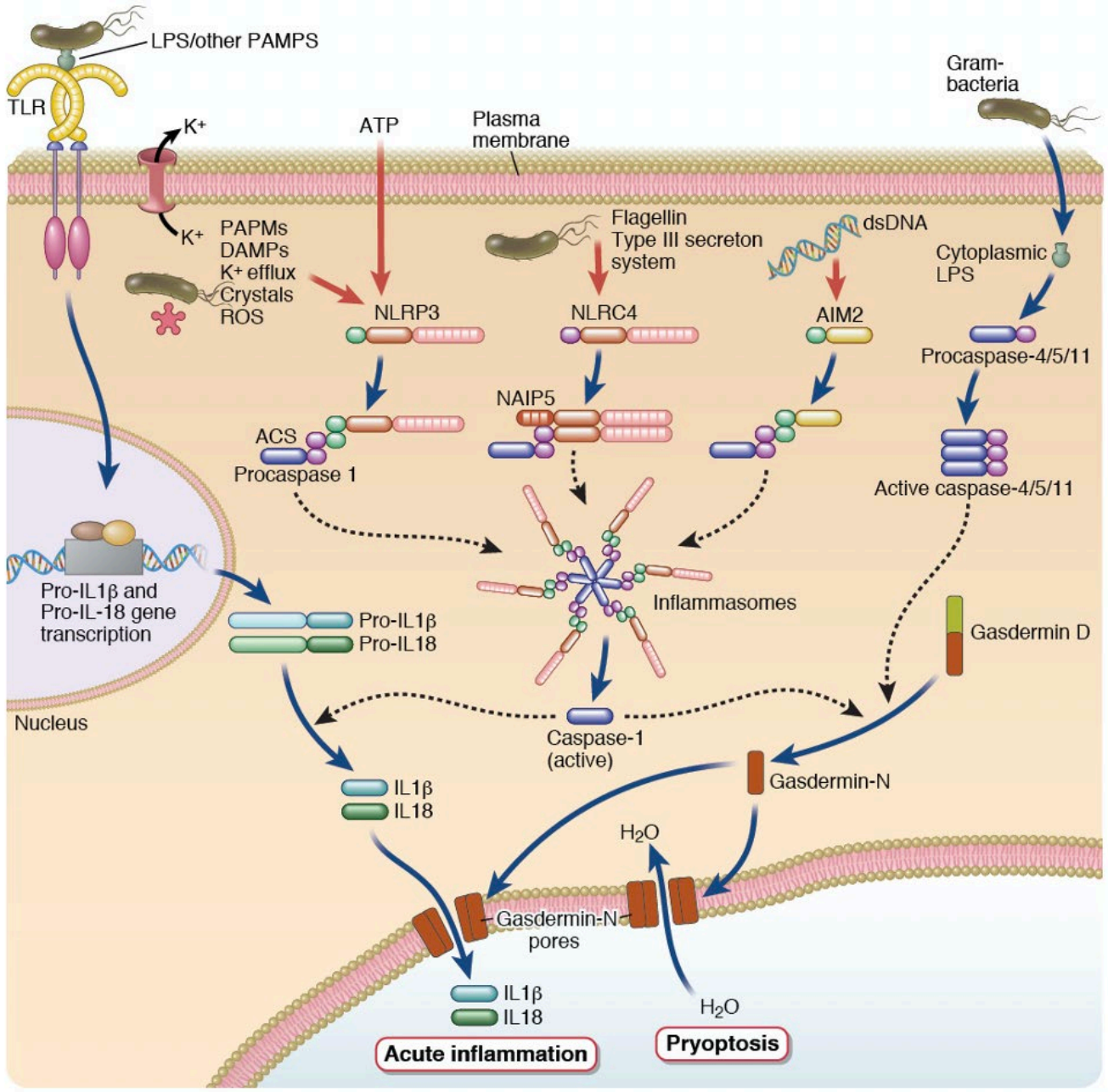
- **A family of >20 cytosolic proteins, best known:**

- **NOD1 and NOD2**
  - **Recognize derivatives of bacterial peptidoglycan ** ; Activate NF-kB 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; **DAP , Diaminopimelic acid; MDP, muramyl dipeptide; ***n.b. not all inflammasomes use NLRPs

# Inflammasomes




**Main components:**
Sensor
Adaptor
Caspase 1

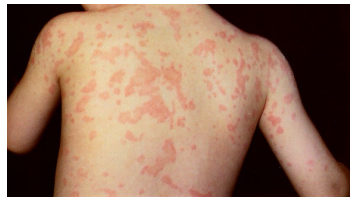
**Main functions:**
Caspase-1 mediated processing and release of Interleukin-1 ( IL-1)

Pyroptosis: Gasdermin D-mediated inflammatory cell death

**Triggers:**
Diverse PAMPs, DAMPs, changes in cells caused by microbes

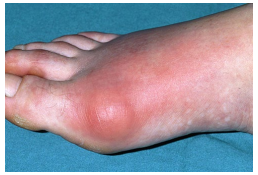
# Inflammasomes/IL-1 in rare and common inflammatory diseases

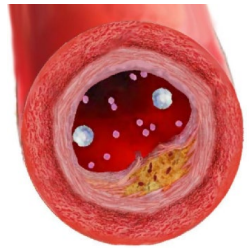
- **Gain of function mutations in inflammasome components cause rare inherited "auto-inflammatory" syndromes**
  - **Constitutive activation and uncontrolled IL-1 production**
  - **IL-1 antagonists are very effective treatments for these disorders.**



**Rare**

- **Gout, pseudogout: Deposition of crystals (e.g. urate) → IL-1-mediated acute inflammation**
- **Deposition of cholesterol crystals → role of inflammation in atherosclerosis ( ? basis of clonal hematopoiesis association with CVD)**
- **Others**





**Common**

# DNA sensing:
# the cGAS STING pathway

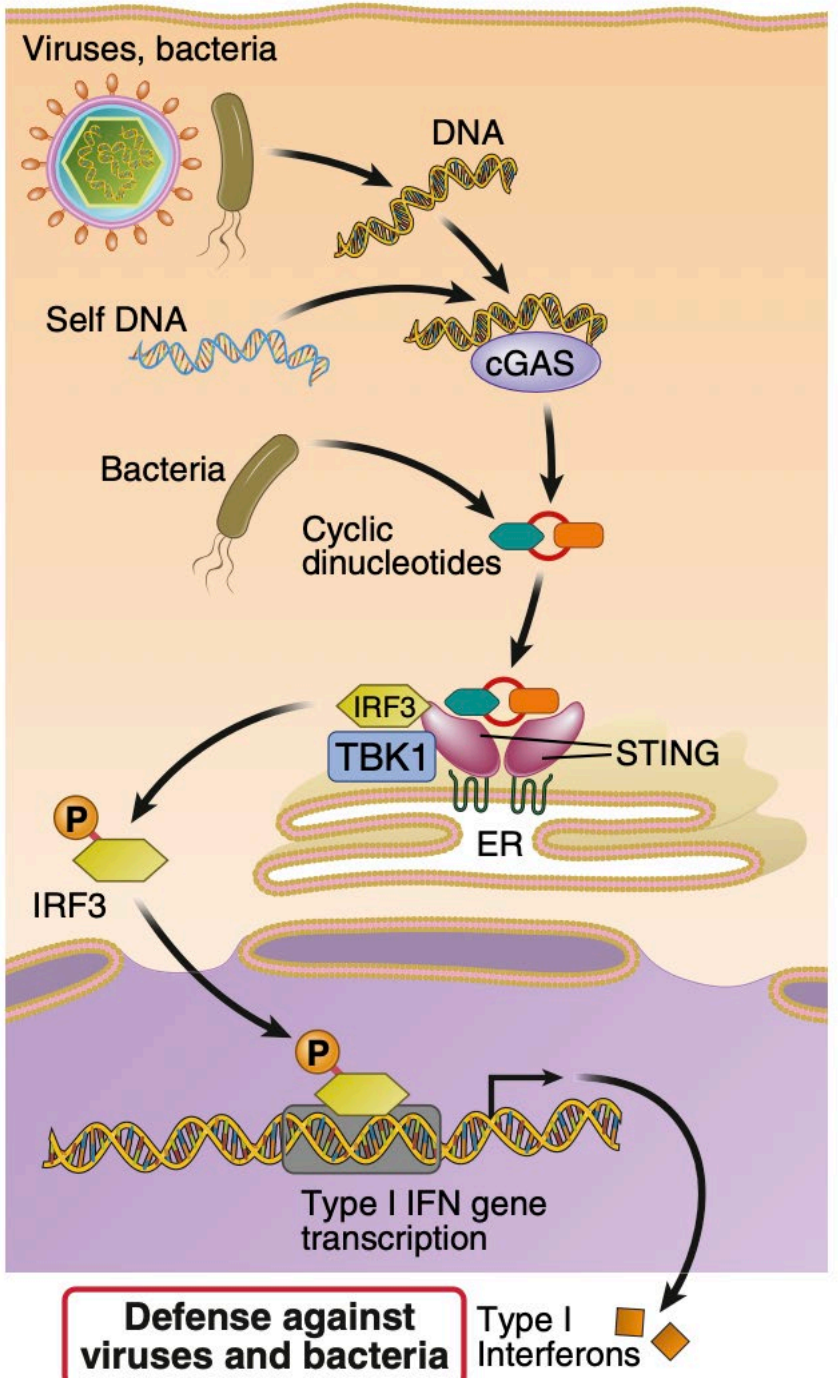
***There are many DNA sensors in the cytosol of cells.****

***cGAS is a major sensor***

***STING mediates the function of most of these DNA sensors***

***Main signaling function of STING is IRF3-dependent type 1 interferon anti-viral response***

***STING pathway may also be activated by damaged tumor DNA-***
***? role in tumor immunity***




* cGAS, DDX41, DAI, RNA polymerase III, IFI16

*cGAS,* cyclic GMP-AMP synthase

# RNA sensing: Rig-like Receptors (RLRs)

***The two main RLRs are RIG-I and MDA5***

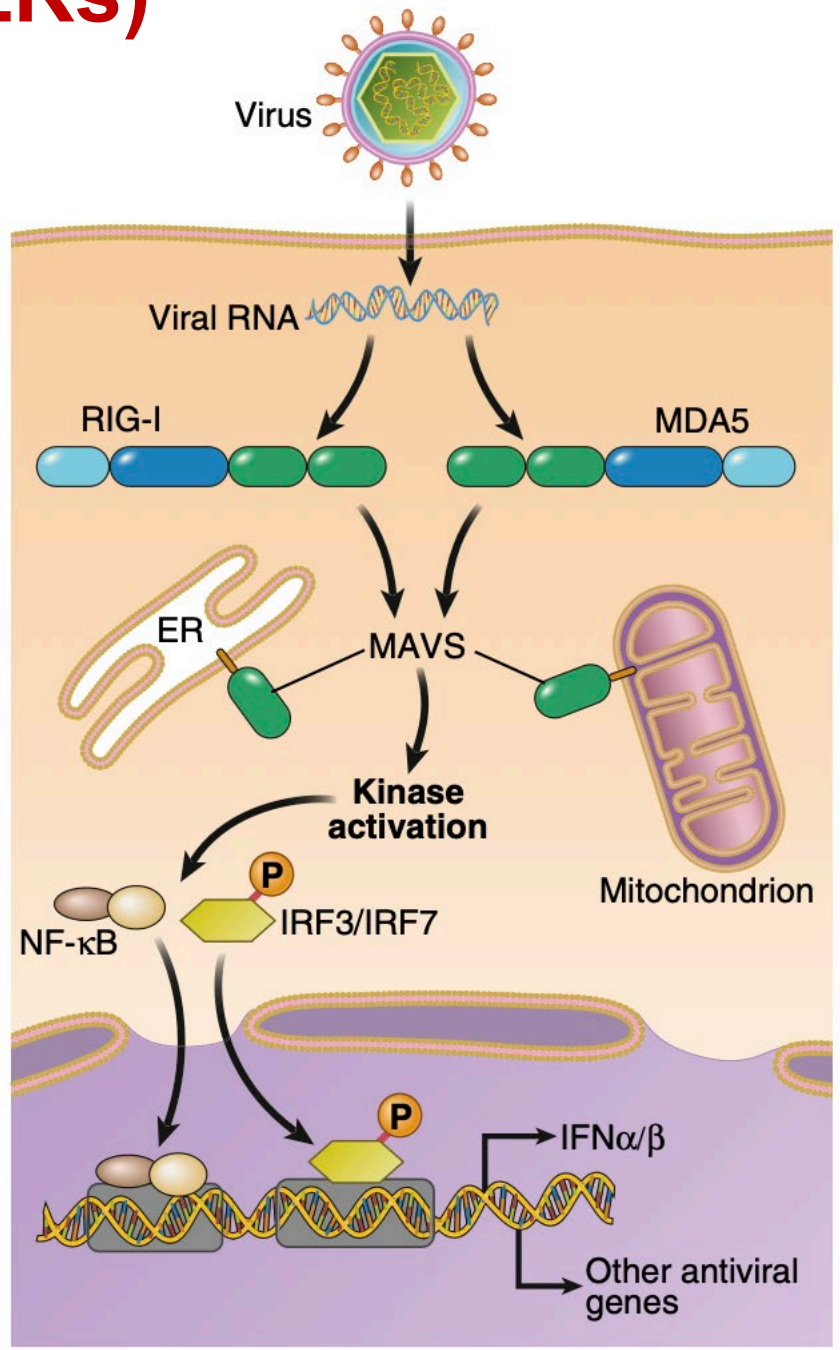
***Recognize cytosolic viral RNA and trigger a signaling pathway that leads to the activation of IRFs that stimulate type I interferons***

***RLRs interact with a mitochondrial membrane protein mitochondrial antiviral- signaling (MAVS)***

Features of Viral RNA ditected

**RIG-1**
-short ds RNA
-5’ triphosphate or diphosphate
-absence of 2′-O-methylation of the 5′ end of nucleotides
-blunt-ended base pairing

**MDA5**
long dsRNA >300 bp



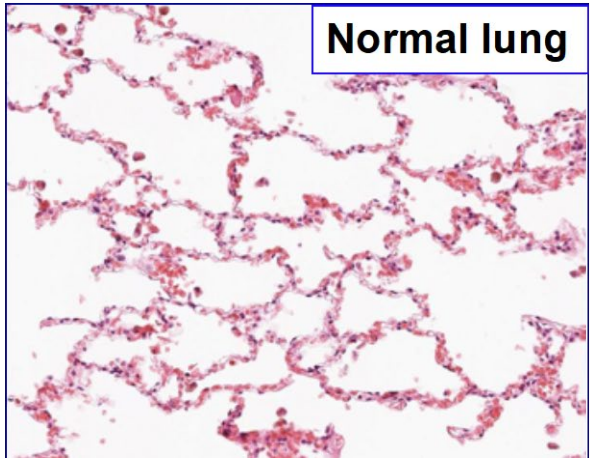
# The major reactions and functions of innate immunity

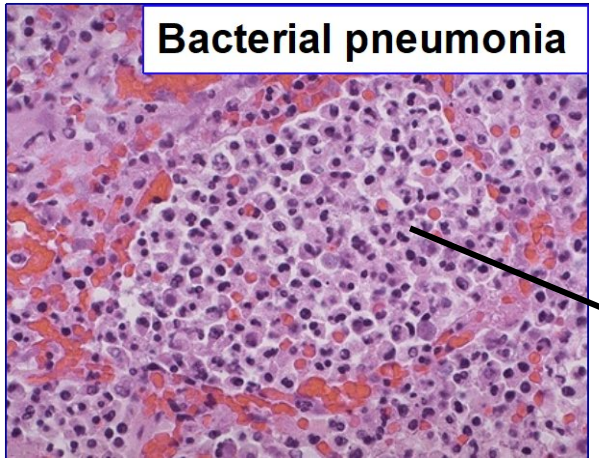
- **Induction of inflammation: killing of microbes, removal of dead cells, foreign bodies**
- **Induction of the anti-viral state: inhibition of viral replication**
- **Stimulation of the adaptive immune response**

*Take home messages*

# 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

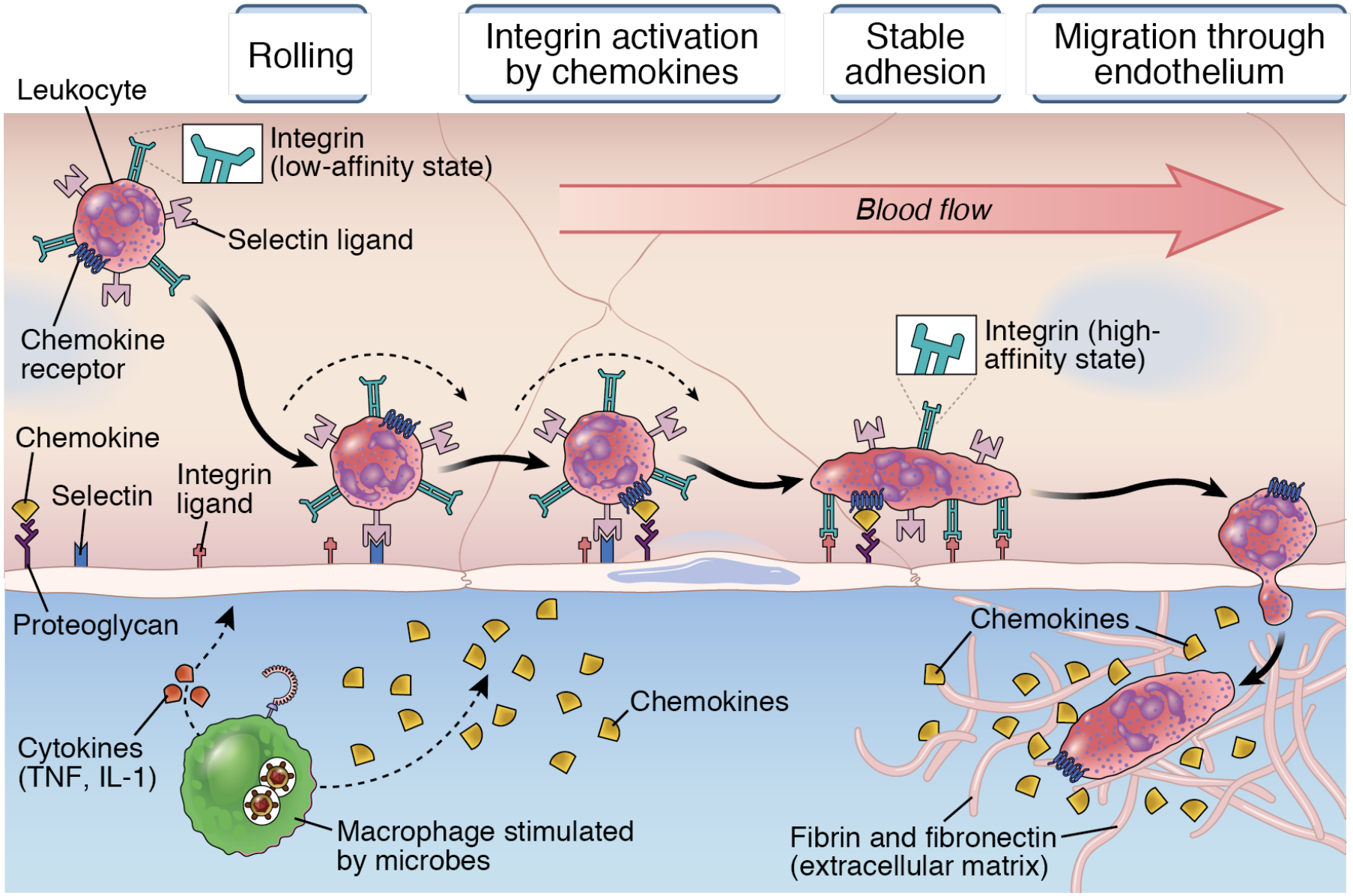



*Acute Inflammation:*
*An innate immune response to infection (or sterile injury)*

*PMNs*
*Monocyte-macrophages,*
*Plasma proteins*
*Fluid*

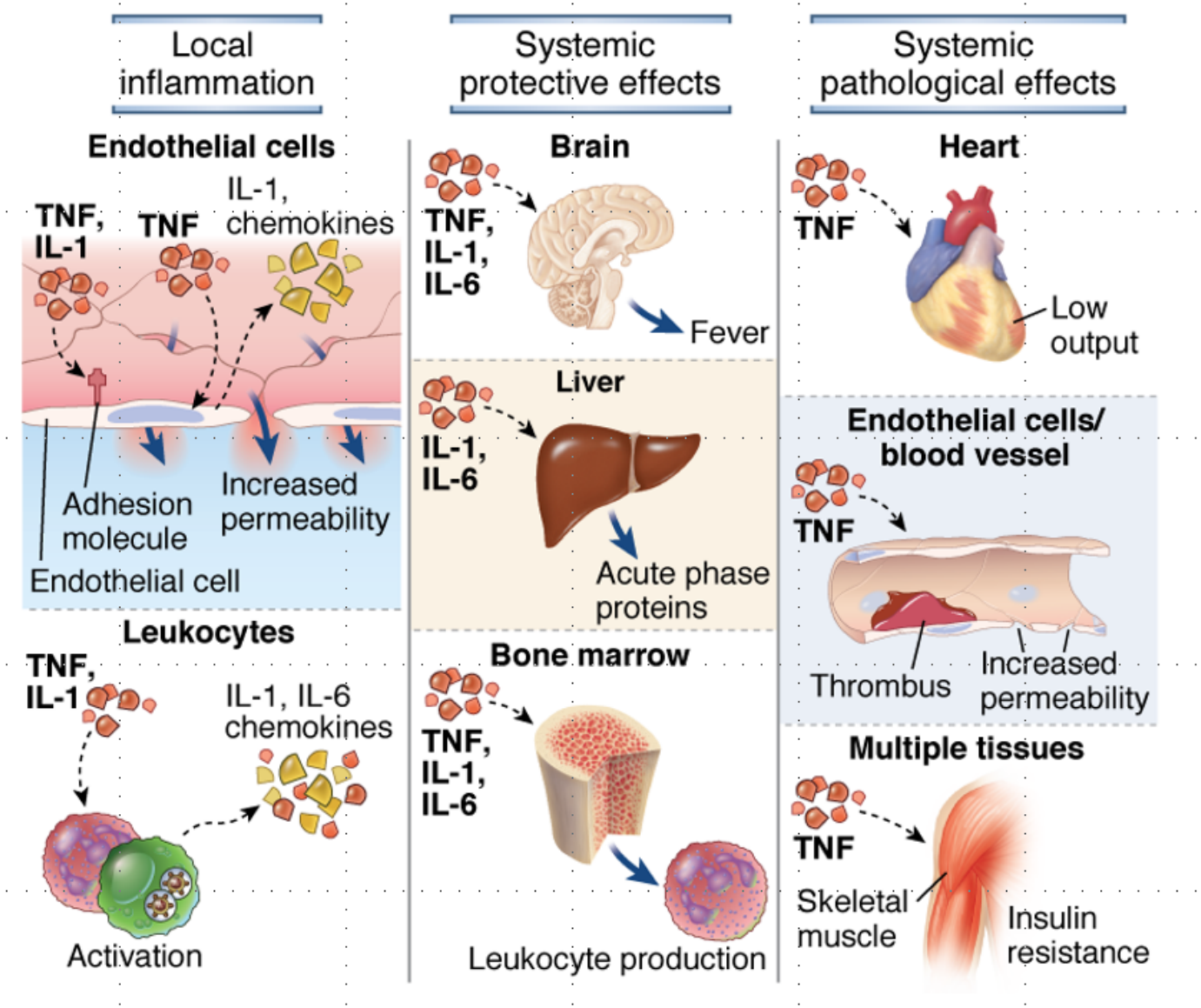
# Leukocyte migration from blood into tissues



# Molecular basis of leukocyte migration through endothelium

- **Selectins**: low-affinity binding of leukocytes to endothelium (slows down flowing cells)
- **Chemokines**: activation of integrins to high affinity state (and chemokinesis of leukocytes in tissues to site of infection or tissue damage)
- **Integrins**: firm adhesion/arrest of leukocytes on endothelium

# Actions of Cytokines in Inflammation



# Excess Innate Cytokine Syndromes

- **Pathologically abundant innate cytokine production (TNF, IL-1, IL-6) leading to systemic inflammation with organ damage, caogulopathy, and shock occurs, in various clinical syndromes, e.g.:**
  - **Macrophage activation syndrome: JRA**
  - **Cytokine release syndrome: Adoptive T cell therapy for cancers**
  - **Cytokine storm: SARS CoV2**
  - **Hemophagocytosis and lymphohistiocytosis (HLH): Perforin deficiency**
  - **Septic shock: infections**
  - **Toxic shock syndrome (TSS): bacterial infections**

- **In some cases excess T cell activation with IFNγ leads to excess macrophage activation which leads to excess IL-1, TNF, IL-6**

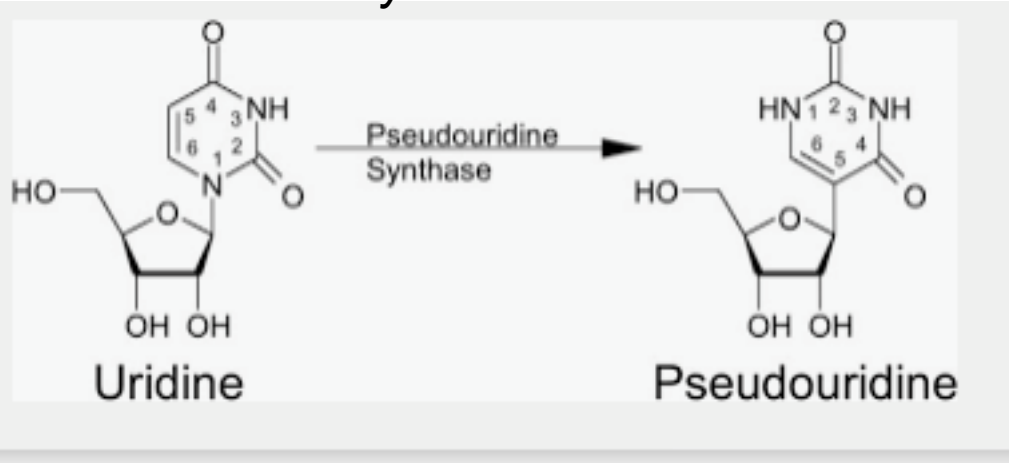
- **Cytokine antagonists ( e.g. mAbs specific for IL-1, IL-6R, TNF, IFN-γ) may be effective in some cases .**

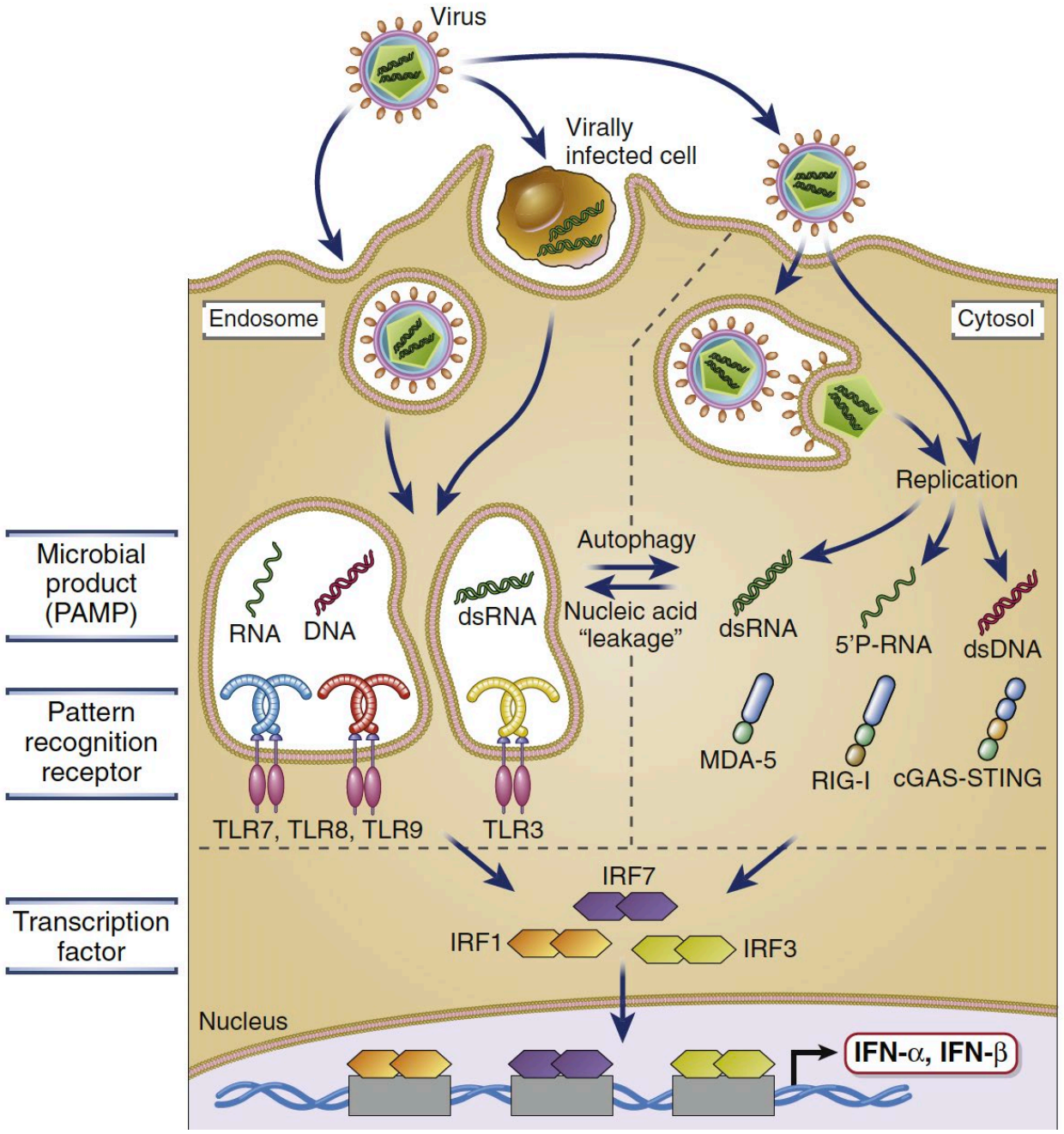
# Induction of the Anti-Viral State:

# Type 1 interferon production

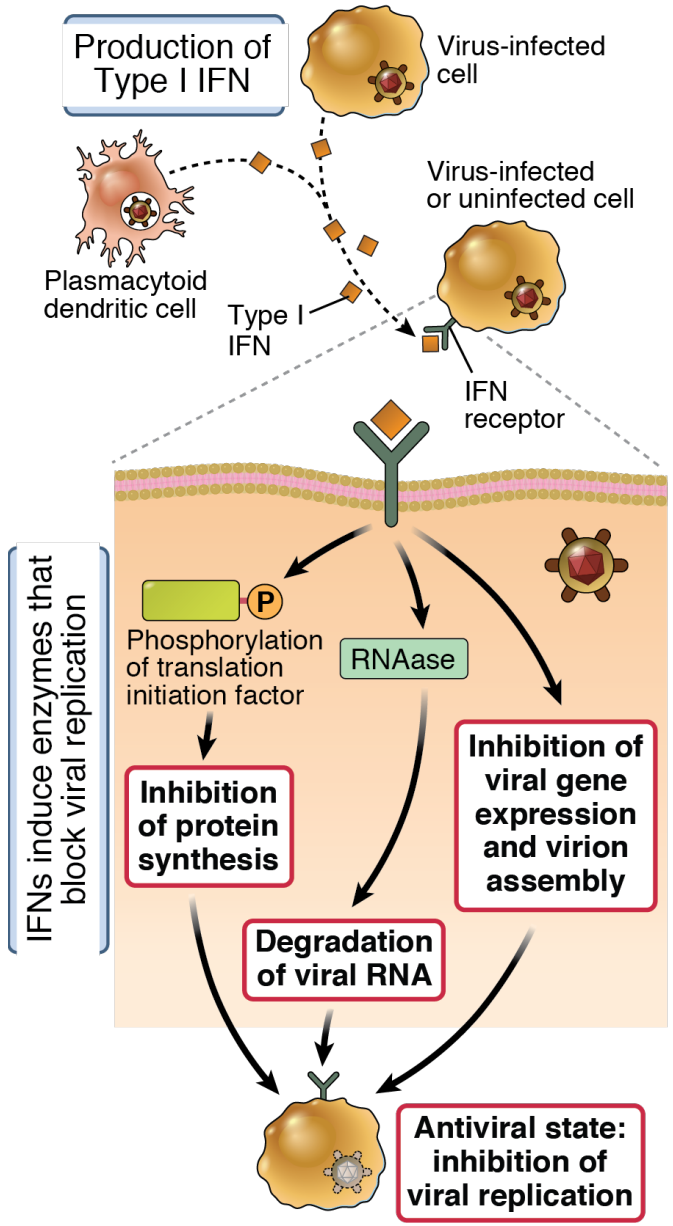
- *Many pathways induce IRFs*
- *IRFs promote Typ1 IFN transcription*

*The key to RNA vaccines*



# Induction of the anti-viral state: Functions of Type I IFNs




- *Activate transcription of several genes that confer on cells a resistance to viral infection*
- *Sequestration of lymphocytes in lymph nodes, maximizing opportunity for encounter with microbial antigens*
- *Increase cytotoxicity of NK cells and CD8+ CTLs*
- *Promote the differentiation of naive T cells to the Th1 subset of helper T cells.*
- *Upregulate class I MHC expression increasing CTL recognition of virally infected cells*

# Importance of Type I IFN Responses: Lessons from COVD19 Patients

**Inborn errors of type I IFN immunity in patients with life-threatening COVID-19**

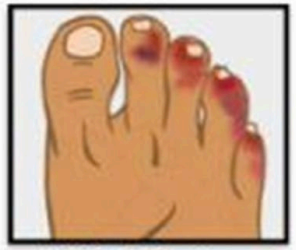
Q. Zhang *et al.*, *Science*
10.1126/science.abd4570 (2020).

**Auto-antibodies against type I IFNs in patients with life-threatening COVID-19**

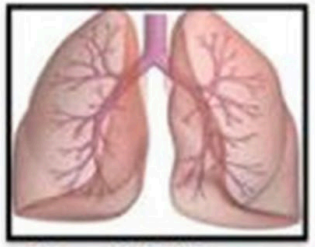
P. Bastard *et al.*, *Science*
10.1126/science.abd4585 (2020).

*These two studies indicated that impaired Type 1 interferon responses increase risk for severe SARS CoV-2 infection*

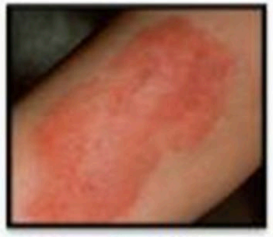
# Type I interferonopathies:
# Genetic diseases with dysregulated type 1 IFN responses



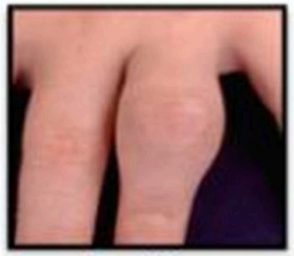
Chiblain lesions
Necrotizing vasculitis



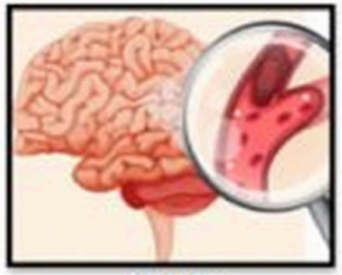
Interstitial lung disease



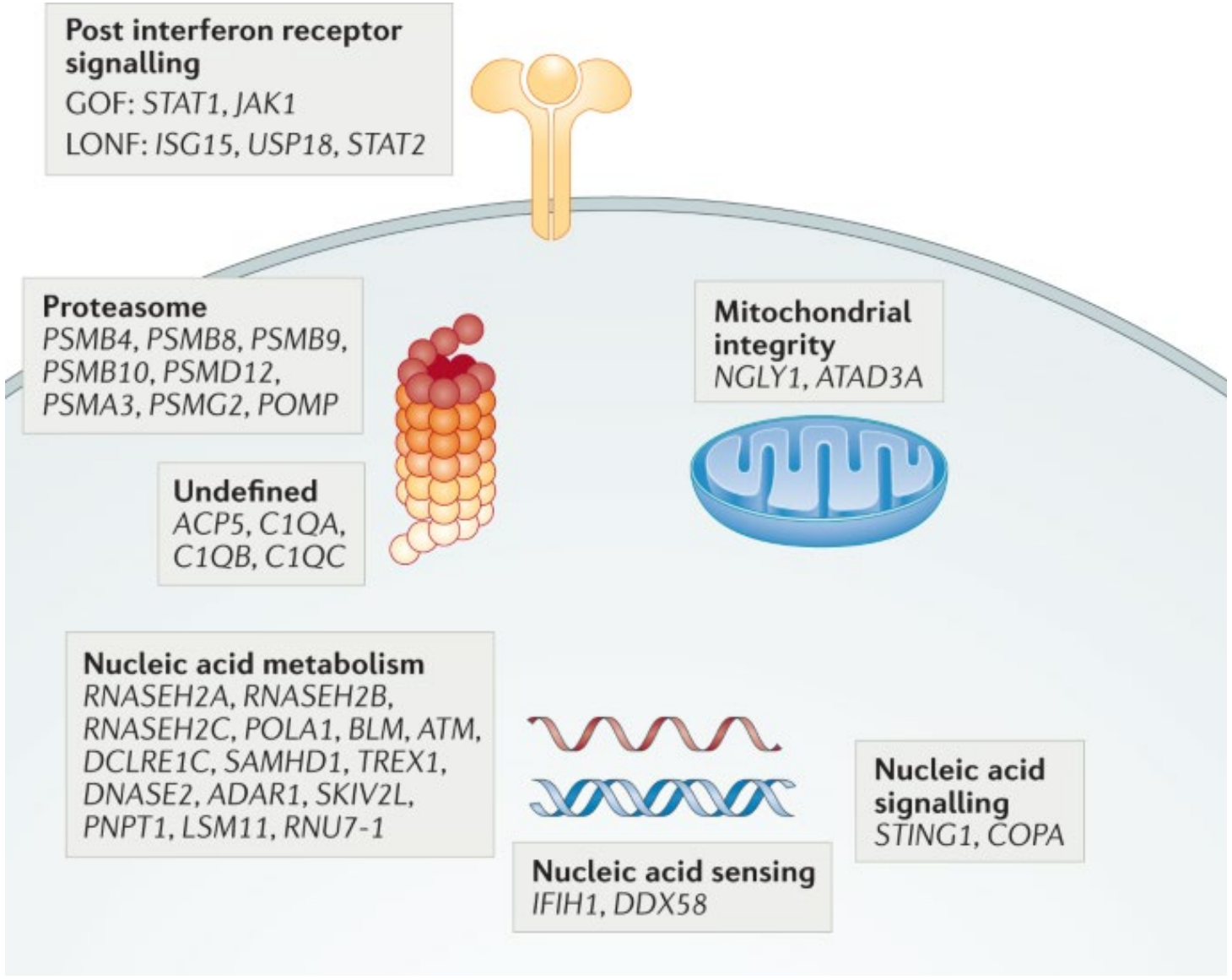
Panniculitis lipodystrophy



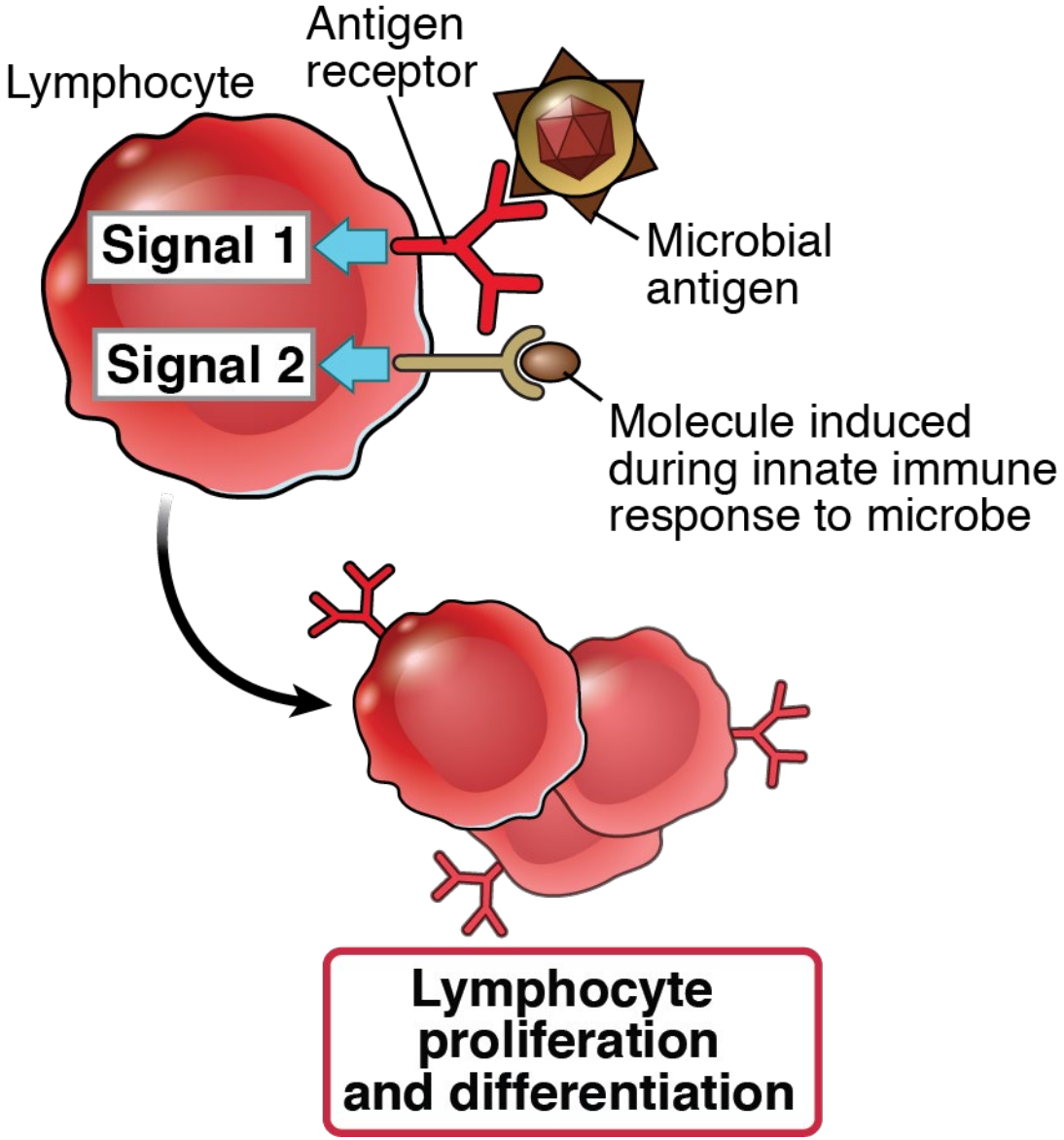
Familiar Polyarthritis JIA–like



Early thrombotic events



# 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***

*Take home messages*