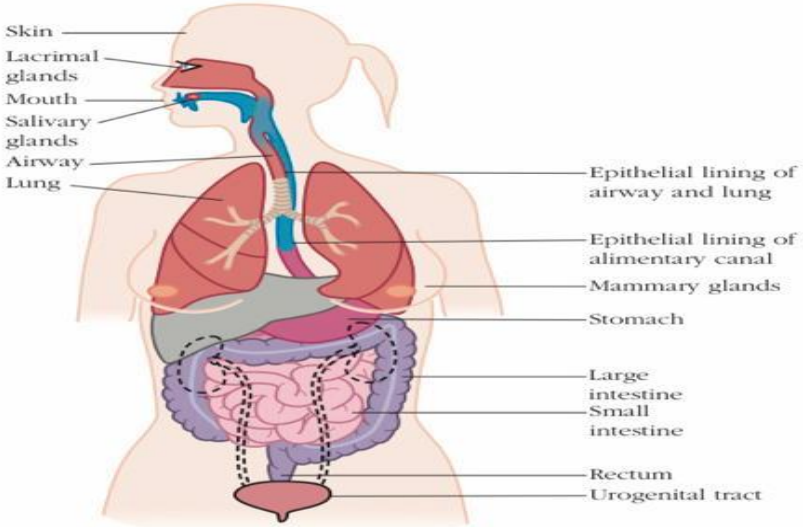
Innate VS Adaptive

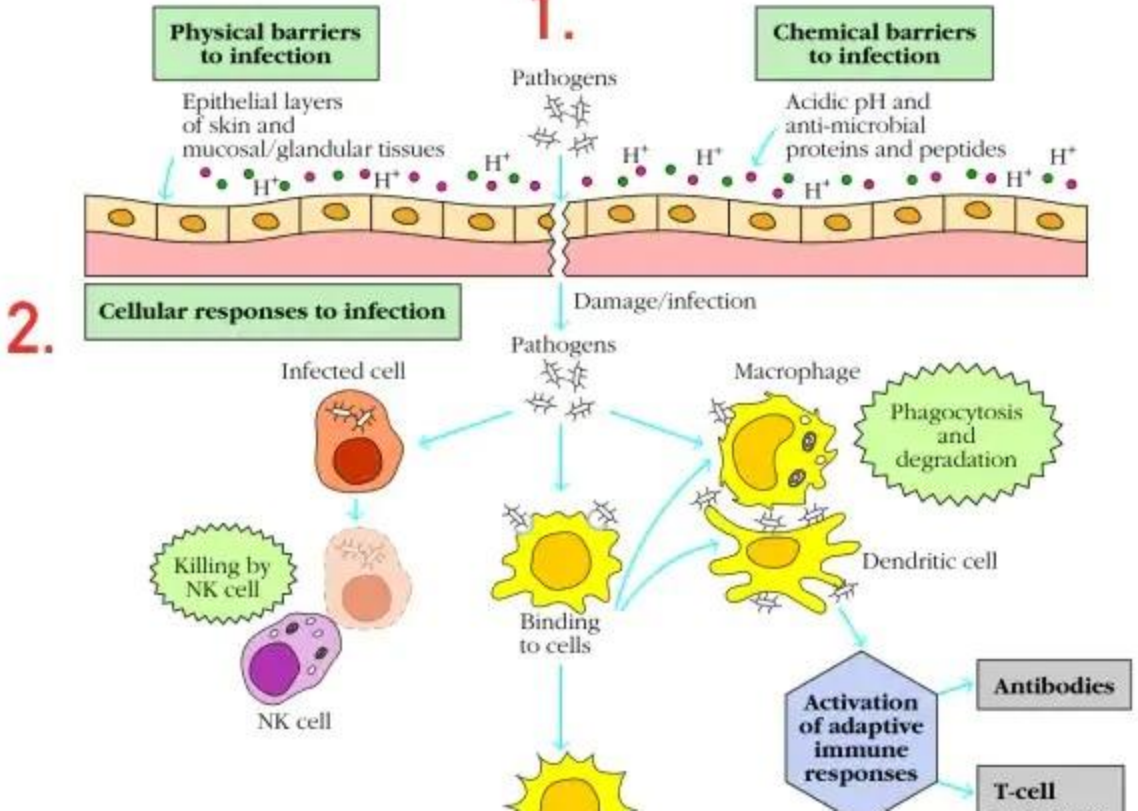
TABLE 5-1 Innate and adaptive immunity

Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Specific for molecules and molecular patterns associated with pathogens and molecules produced by dead/damaged cells	Highly specific; discriminates between even minor differences in molecular structure of microbial or nonmicrobial molecules
Diversity	A limited number of conserved, germ line–encoded receptors	Highly diverse; a very large number of receptors arising from genetic recombination of receptor genes in each individual
Memory responses	Some (observed in invertebrate innate responses and mouse/human NK cells)	Persistent memory, with faster response of greater magnitude on subsequent exposure
Self/nonself discrimination	Perfect; no microbe-specific self/nonself patterns in host	Very good; occasional failures of discrimination result in autoimmune disease

Organ or tissue	Innate mechanisms protecting skin/epithelium
Skin	Antimicrobial peptides, fatty acids in sebum
Mouth and upper alimentary canal	Enzymes, antimicrobial peptides, and sweeping of surface by directional flow of fluid toward stomach
Stomach	Low pH, digestive enzymes, antimicrobial peptides, fluid flow toward intestine
Small intestine	Digestive enzymes, antimicrobial peptides, fluid flow to large intestine
Large intestine	Normal intestinal flora compete with invading microbes, fluid/feces expelled from rectum
Airway and lungs	Cilia sweep mucus outward, coughing, sneezing expel mucus, macrophages in alveoli of lungs
Urogenital tract	Flushing by urine, aggregation by urinary mucins; low pH, anti-microbial peptides, proteins in vaginal secretions
Salivary, lacrimal, and mammary glands	Flushing by secretions; anti-microbial peptides and proteins in vaginal secretions



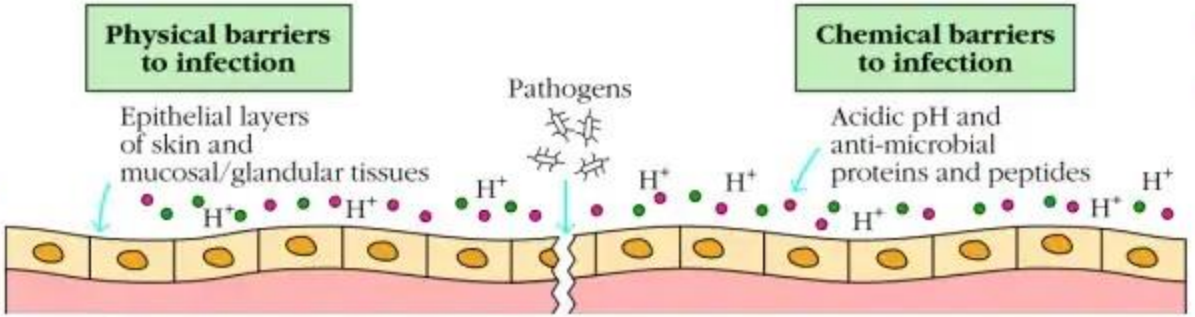
Component of innate immunity



1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines

1.) Anatomical barriers

- Skin
- Mucosal & Glandular tissues
- Mechanical :Cilia



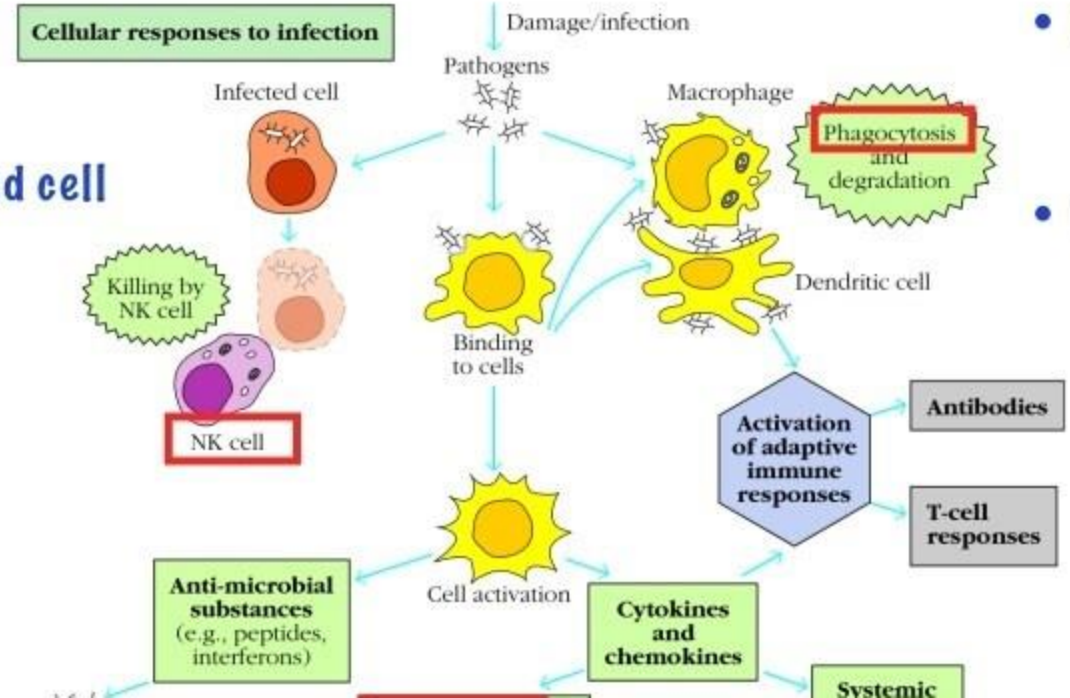
- Enzyme
- Antimicrob peptides (A
- pH

TABLE 5-2 Some human antimicrobial proteins and peptides at epithelial surfaces

Proteins and peptides*	Location	Antimicrobial activities
Lysozyme	Mucosal/glandular secretions (e.g., tears, saliva, respiratory tract)	Cleaves glycosidic bonds of peptidoglycans in cell walls of bacteria, leading to lysis
Lactoferrin	Mucosal/glandular secretions (e.g., milk, intestine mucus, nasal/respiratory and urogenital tracts)	Binds and sequesters iron, limiting growth of bacteria and fungi; disrupts microbial membranes; limits infectivity of some viruses
Secretory leukocyte protease inhibitor	Skin, mucosal/glandular secretions (e.g., intestines, respiratory, and urogenital tracts, milk)	Blocks epithelial infection by bacteria, fungi, viruses; antimicrobial
S100 proteins, e.g.: - psoriasin - calprotectin	Skin, mucosal/glandular secretions (e.g., tears, saliva/tongue, intestine, nasal/respiratory and urogenital tracts)	- Disrupts membranes, killing cells - Binds and sequesters divalent cations (e.g., manganese and zinc), limiting growth of bacteria and fungi
Defensins (α and β)	Skin, mucosal epithelia (e.g., mouth	Disrupt membranes of bacteria, fungi, protozoan

2.) Cellular Response (Recognized pathogen by receptors : PRRs)
3.) Soluble proteins

- NK cell
  - Viral infected cell
  - Malignancy



- Phagocytic cells
  - -Macrophage, Neutro
  - " Phagocytosis "
- Dendritic cell
  - >> Activated adaptiv immune response

Microbial pattern recognition by innate immunity

Cellular response

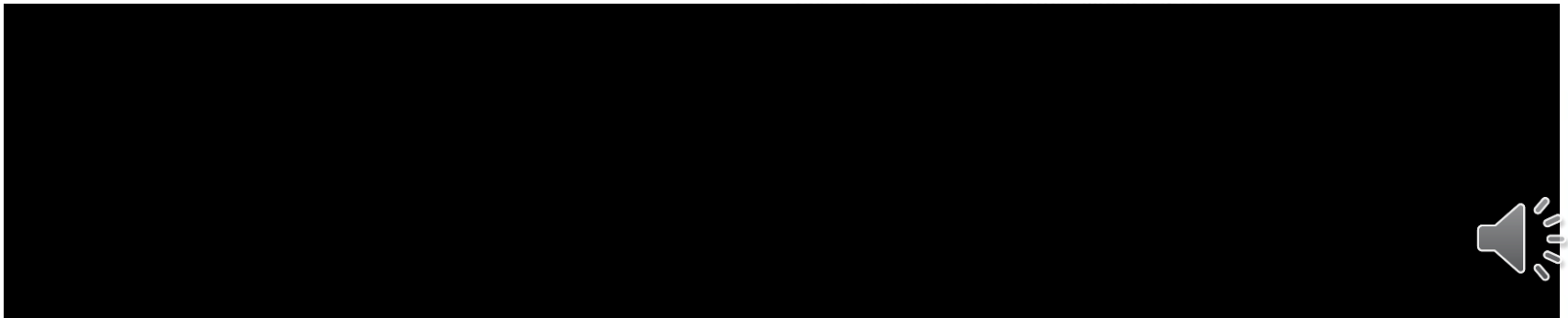
- Innate immune system recognizes
  - PAMPs (Pathogen-associated molecular pattern)
    : molecular structures of microbial pathogen that required for survival
  - DAMPs (Damage-associated molecular pattern)
    : result of cell damage by infections

PAMPs

1.) Produced only by microbes, not by their hosts

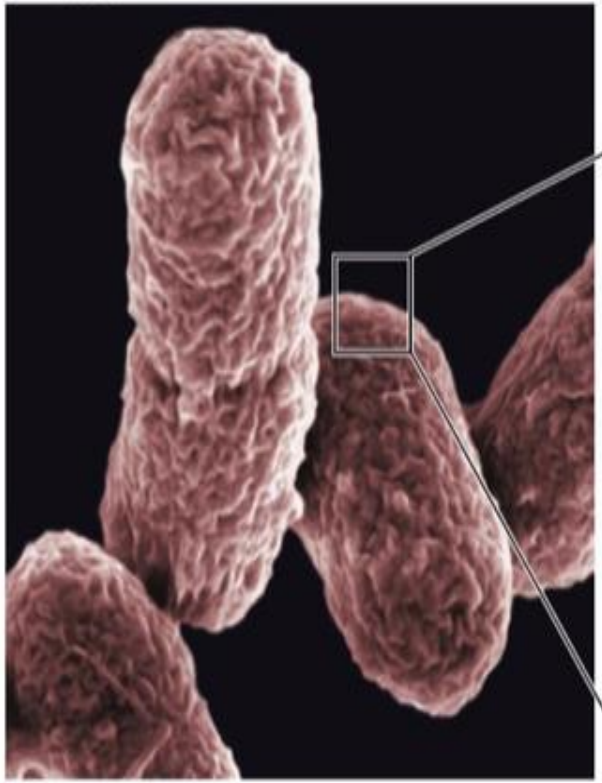
2.) PAMP structures are usually fundamental to the integrity, survival, and pathogenicity of the microorganisms

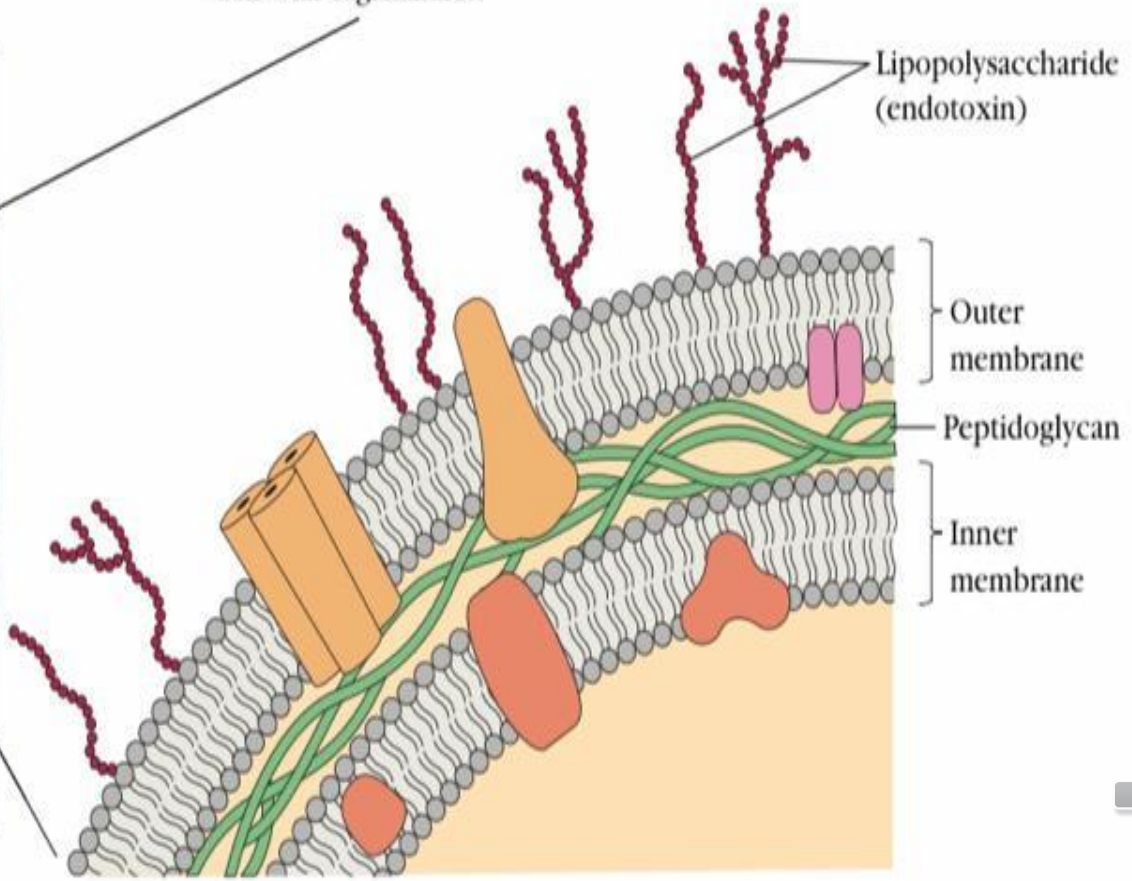
3.) Shared by entire classes of pathogens



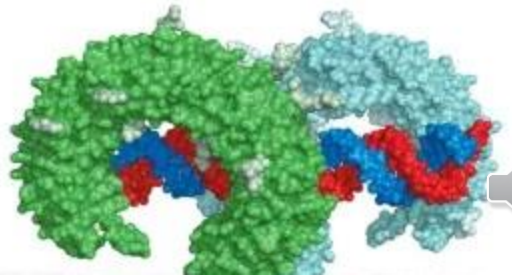
(a) Gram negative bacteria

E. coli





Toll-like receptors (TLRs)



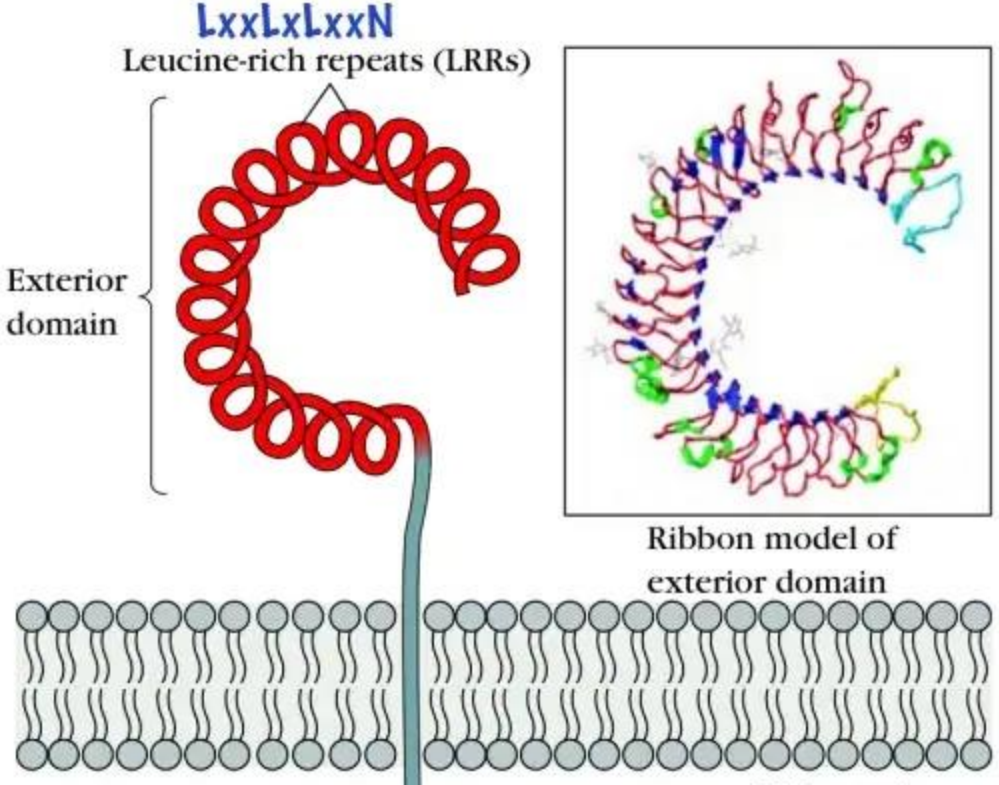
- Germany, 1980
- Drosophila fruit fly embryos
- " Toll " = Weird
- Regulation of embryonic developm
- Cytoplasmic domain of Toll prot.
  : homologous to IL-1 in vertebrate
  " Toll-like receptors (TLRs) "

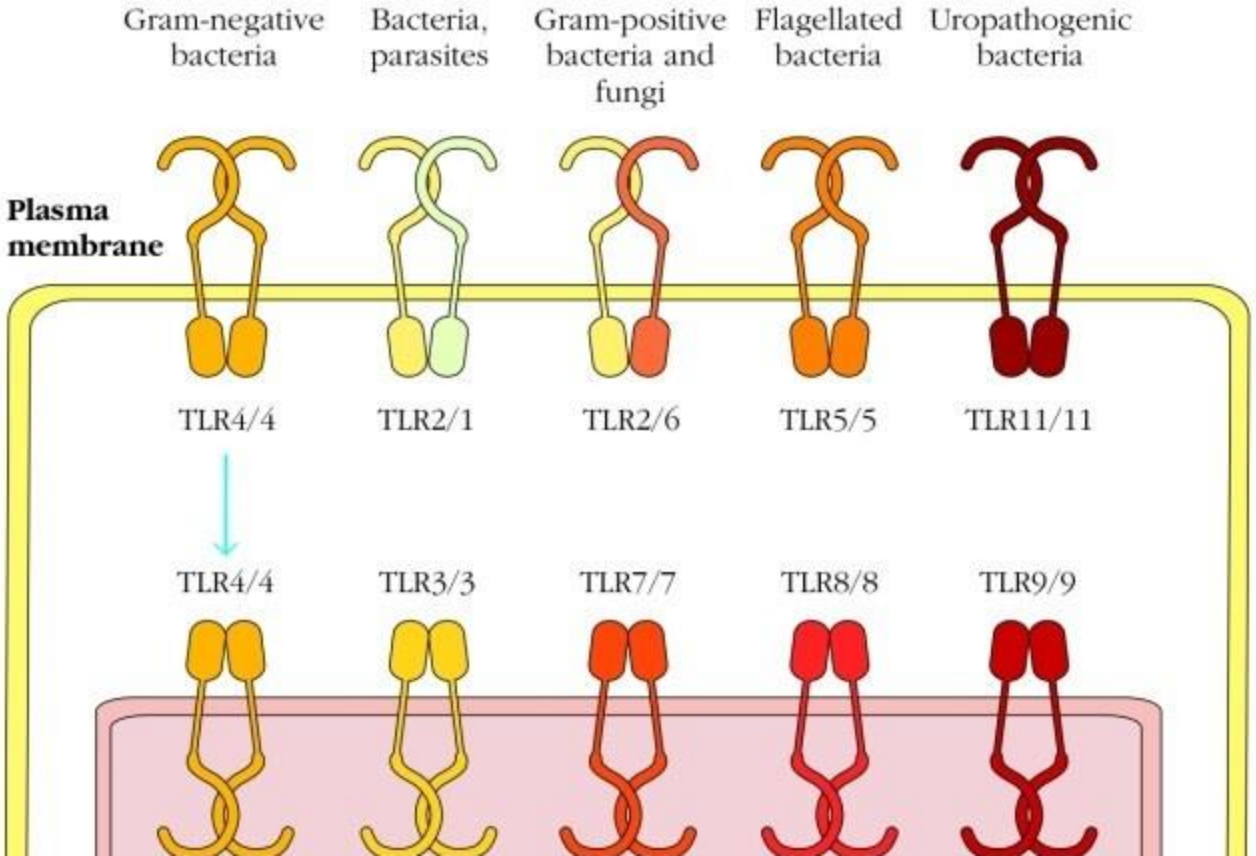
TABLE 5-4 TLRs and their microbial ligands

TLRs*	Ligands	Microbes
TLR1	Triacyl lipopeptides	Mycobacteria and Gram-negative bacteria
TLR2	Peptidoglycans GPI-linked proteins Lipoproteins Zymosan Phosphatidlyserine	Gram-positive bacteria Trypanosomes Mycobacteria and other bacteria Yeasts and other fungi Schistosomes
TLR3	Double-stranded RNA (dsRNA)	Viruses
TLR4	LPS F-protein Mannans	Gram-negative bacteria Respiratory syncytial virus (RSV) Fungi
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopolypeptides Zymosan	Mycobacteria and Gram-positive bacteria Yeasts and other fungi
TLR7	Single-stranded RNA (ssRNA)	Viruses
TLR8	Single-stranded RNA (ssRNA)	Viruses
TLR9	CpG unmethylated dinucleotides Dinucleotides Herpes virus components Hemozoin	Bacterial DNA Some herpesviruses Malaria parasite heme byproduct
TLR10	Unknown	Unknown
TLR11	Unknown Profilin	Uropathogenic bacteria Toxoplasma
TLR12	Unknown	Unknown
TLR13	Unknown	Vesicular stomatitis virus

Structure of TLRs

- Transmembrane
  - LLR domain
  - TIR domain





Plasma membrane
1/2, 2/6, 4, 5, 11

Endosomes/ Lysosom

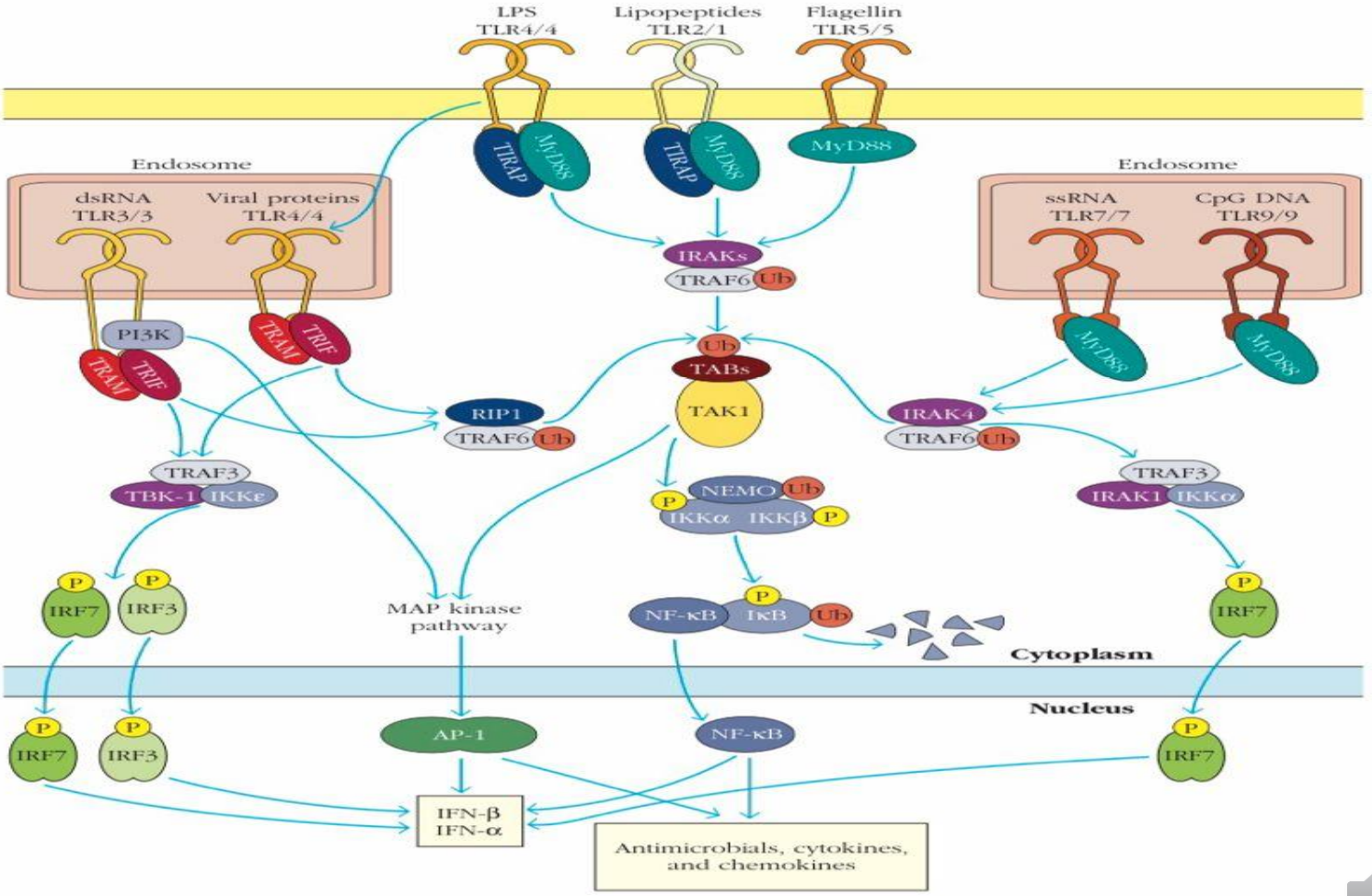


FIGURE 5-13 TLR signaling pathways. Signaling pathways activated by the TIRAP and MyD88 receptor-binding adapt

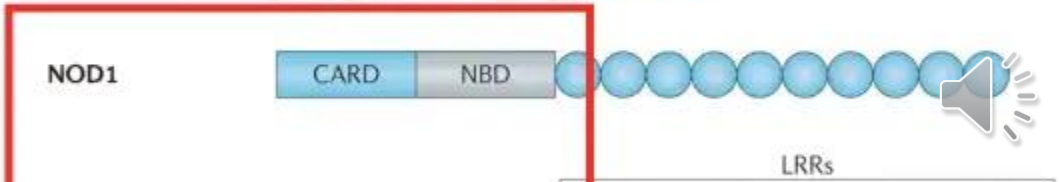
Nucleotide-binding oligomerization domain-like receptors (NLRs)

NOD-Like Receptors (NLRs)

- Cytosolic PRRs
- Recognized - PAMPs & DAMPs
  - Stress/ Damage signal
- Similar to the TLRs : linked to signal transduction
- NLR family : 23 Members

NOD

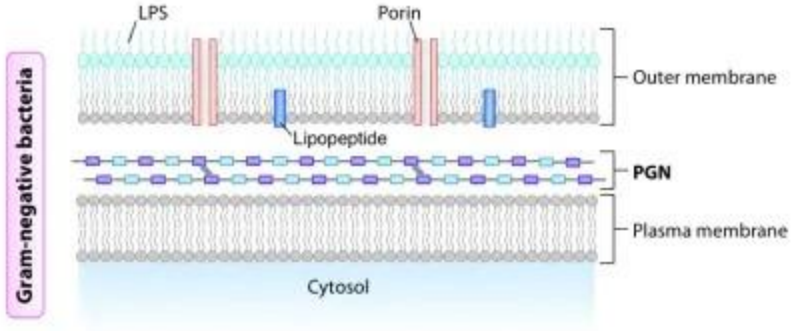
- Member of CARD domain containing NOD family
- NLRC subfamily
- Expressed on several cell types
  : Mucosal epithelial cells, Phagocytes
- Response to bacterial cell wall peptidoglycans
- 2 Groups
  - NOD 1 (CARD4)

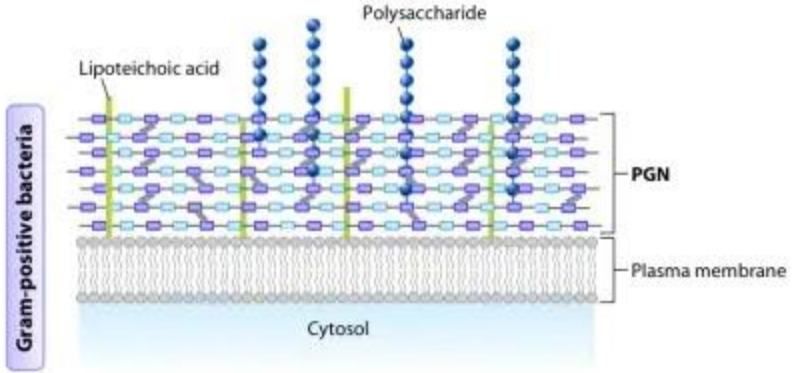


NOD Response to

bacterial cell wall peptidoglycans

- NOD 1 : iE-DAP
- NOD 2 : MDP





NOD 1

- Recognizes Diaminopimelic acid (DAP) derived mainly from gram-negative bac. peptidoglycans

NOD 2

- Recognizes Muramyl dipeptide (MDP) derived both gram-negative & gram-positive bac. peptidoglycans
- Highly expressed in intestinal Peneth cells

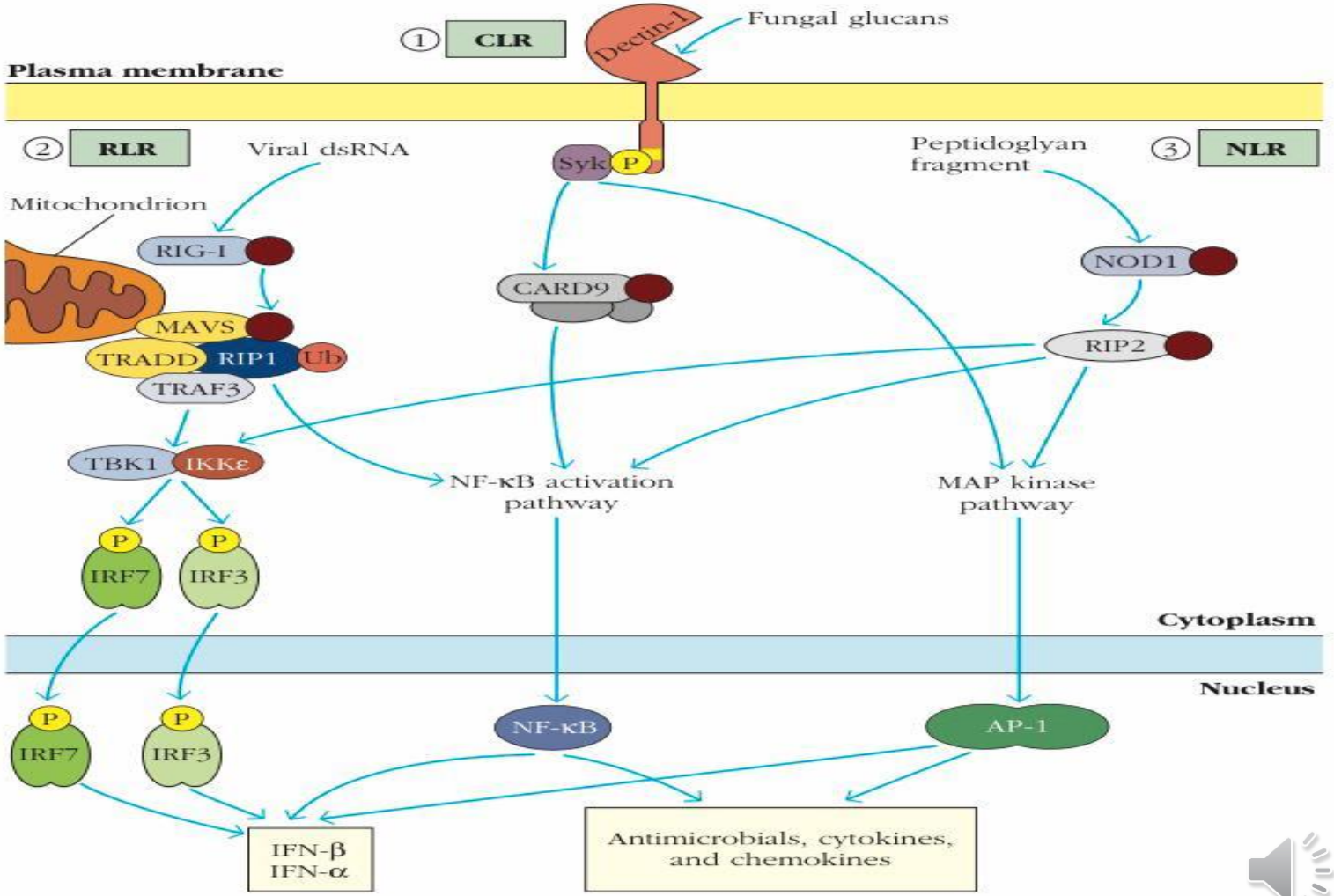


FIGURE 5-14 **CLR, RLR, and NLR signaling pathways.** are shown. CARD domains are shown in brown

Inflammasome

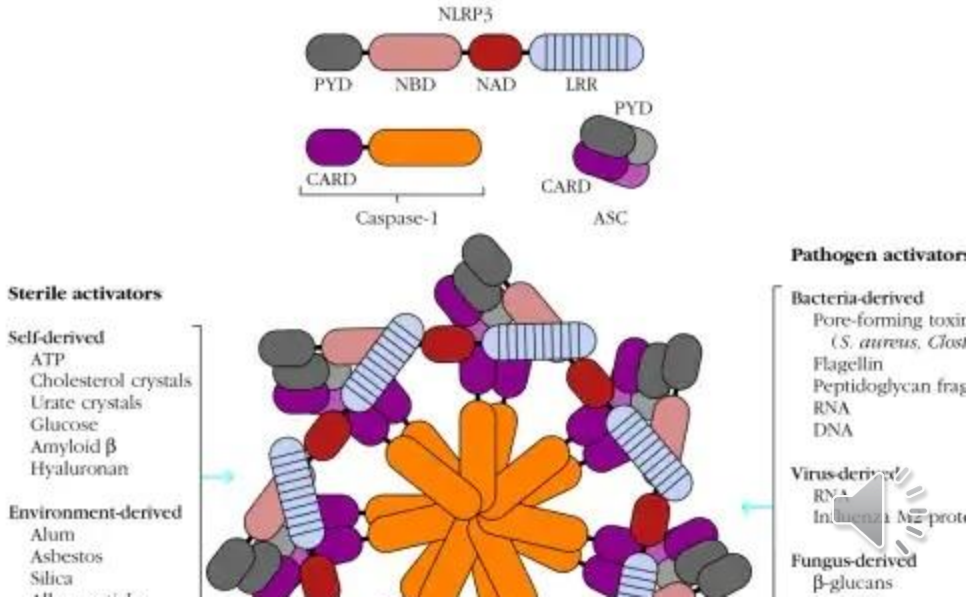
- Large protein complex that activates caspase-1 to generate I
- Containing

1.) NLR subfamily

- NLRP 1
- NLRP 3
- NLRC 4/ IPAF

2.) Non-NLR/ Adaptor protein

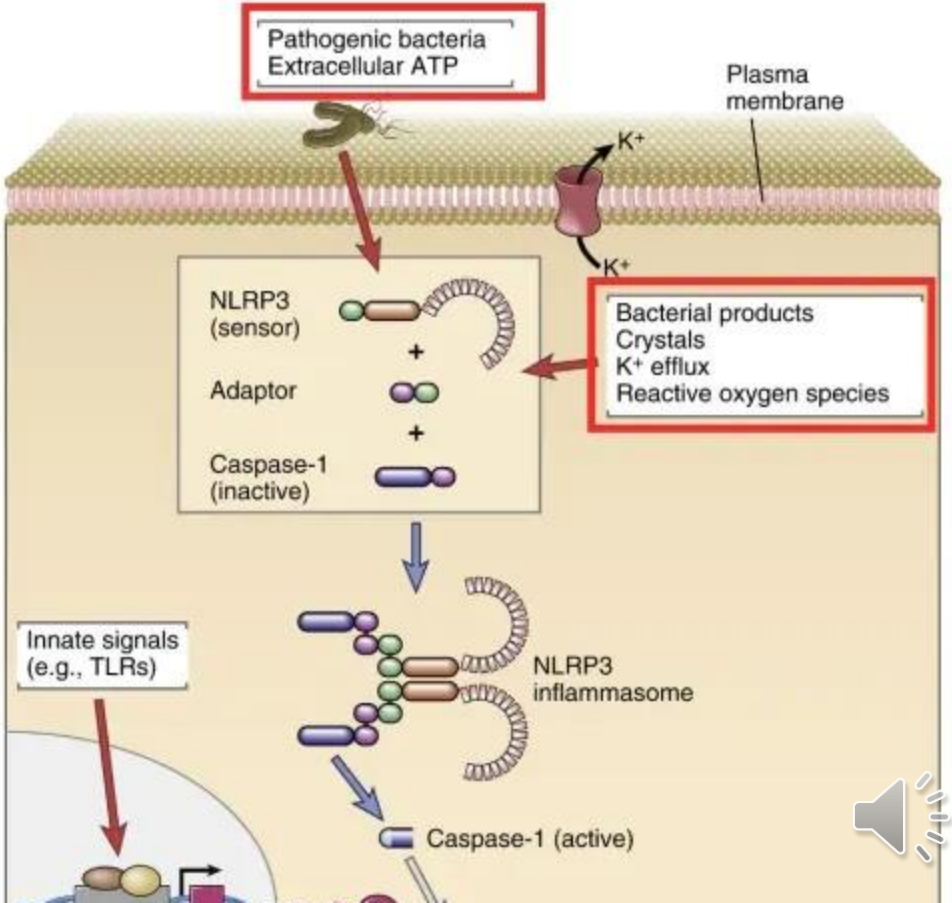
Ex. ASC, AIM2



NLRP3 Inflammasome

- Monocyte
- Macrophage
- Neutrophils
- DC
- Lymphocyte

Variety stimuli activated Inflammasome

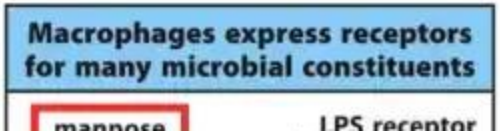


C-Type Lectin Receptors (CLRs)

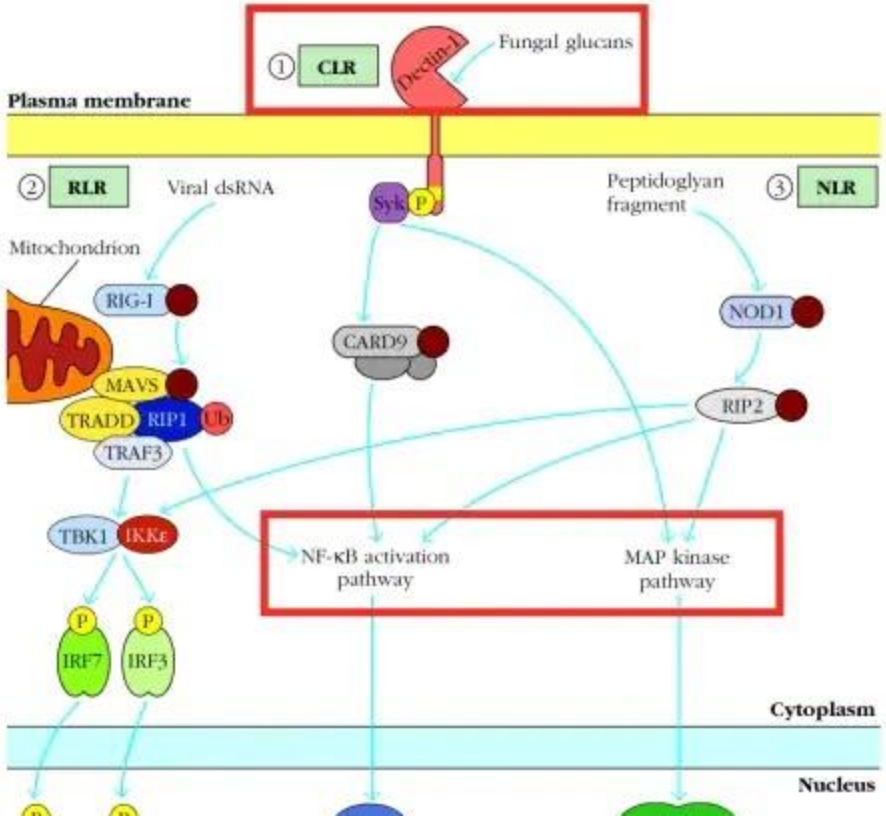
- CLRs functions : Variety function
  - Signaling
  - Phagocytosis

TABLE 5-3 Human receptors that trigger phagocytosis

Receptor type on phagocytes	Examples	Ligands
Pattern recognition receptors		**Microbial ligands (found on microbes)**
C-type lectin receptors (CLRs)	Mannose receptor	Mannans (bacteria, fungi, parasites)
	Dectin 1	β-glucans (fungi, some bacteria)
	DC-SIGN	Mannans (bacteria, fungi, parasites)



CLRs signaling pathways



RIG-Like Receptors (RLRs)

- Soluble PRRs
- Sensors of viral infection ex. Influenza, Measles
- Recognize the RNA viruses in the cytoplasm of infected cells

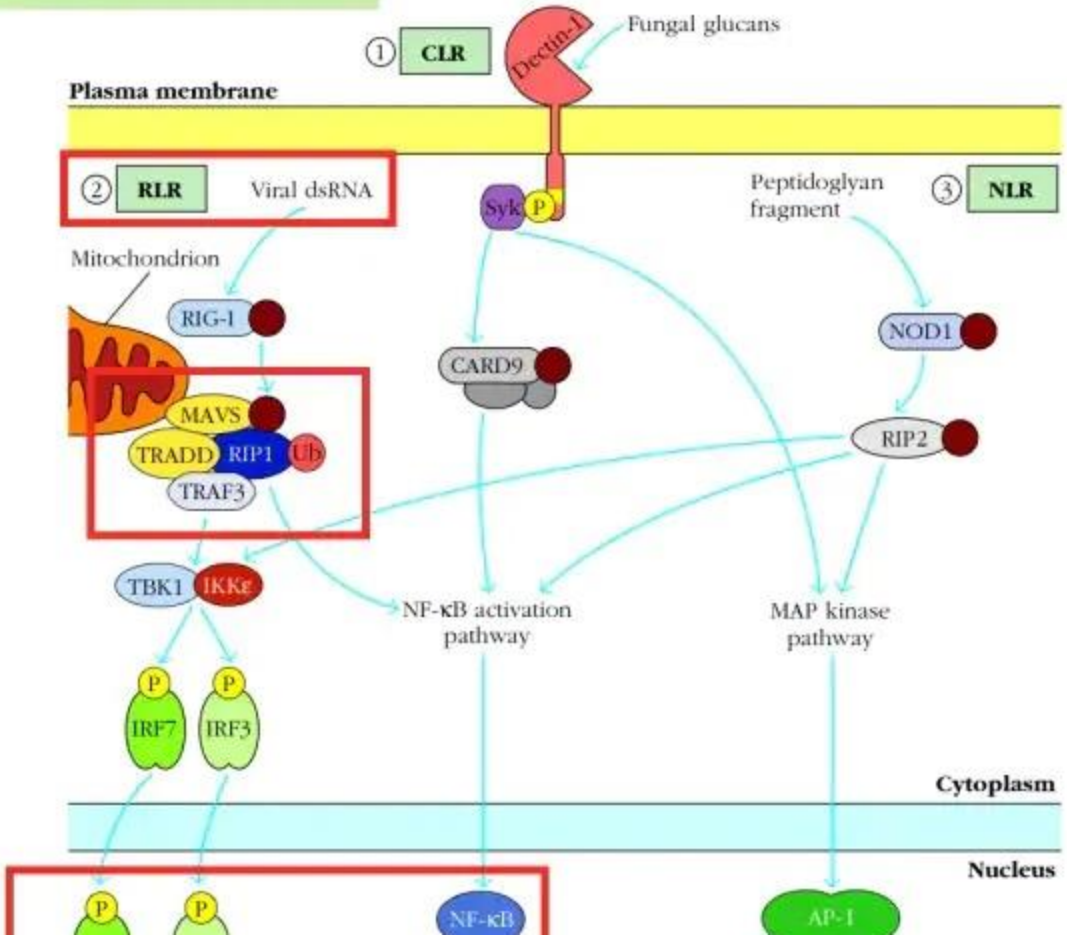
  –> induce inflammatory cytokines and type I interferons
- 3 Members : CARD-containing RNA helicase

  1.) RIG-I

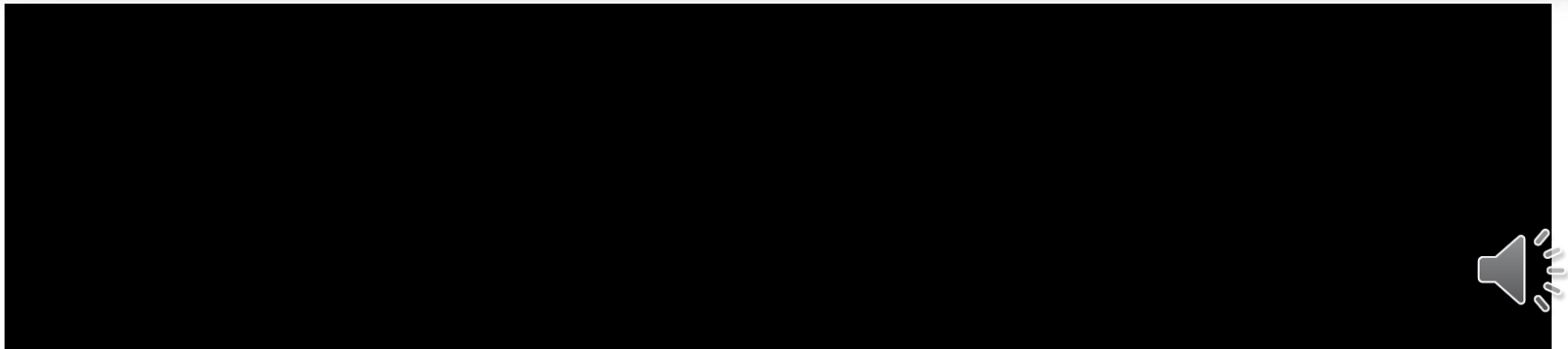
  2.) MDA5

  3.) LGP2

Signaling of RLRs



Phagocytosis



- Macrophage, Neutrophil, DC : Tissue
- Monocyte : Blood

1.) Direct : PRRs rec.

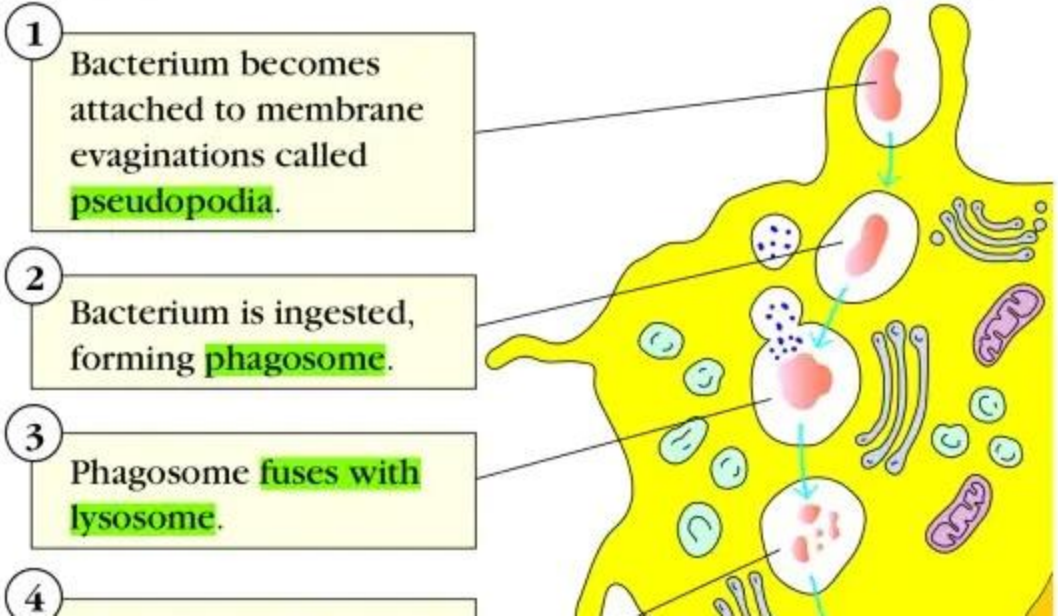


TABLE 5-3 Human receptors that trigger phagocytosis

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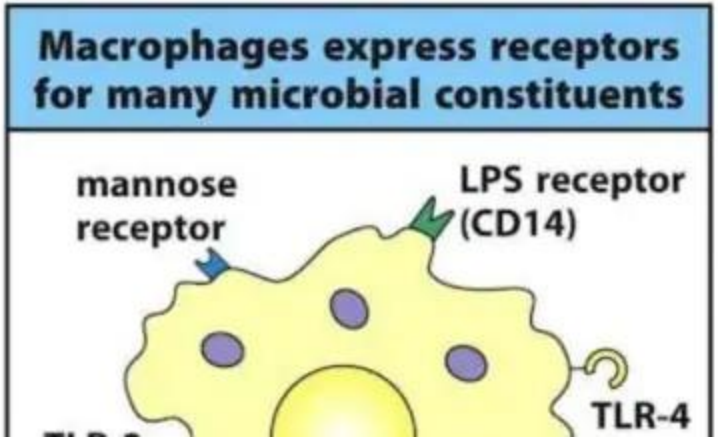
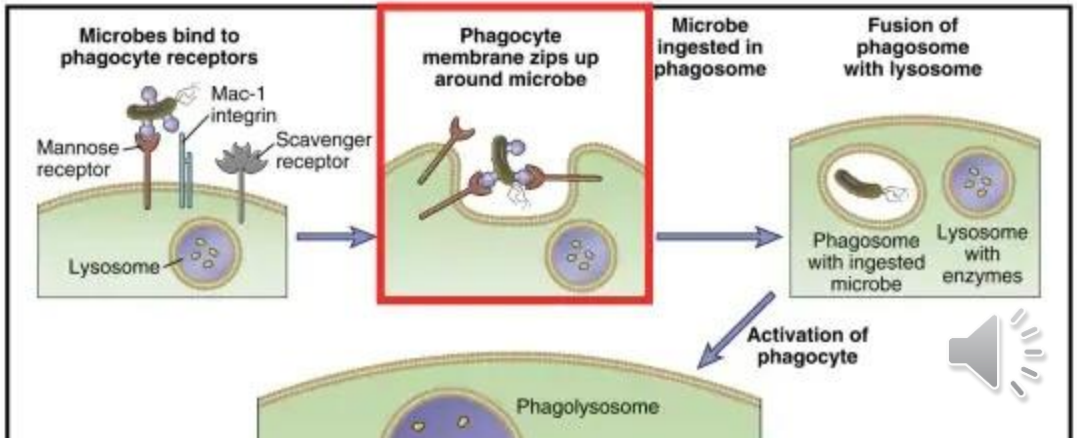
C-type lectin receptors (CLRs)	Mannose receptor	Mannans (bacteria, fungi, parasites)
	Dectin 1	β-glucans (fungi, some bacteria)
	DC-SIGN	Mannans (bacteria, fungi, parasites)
Scavenger receptors	SR-A	Lipopolysaccharide (LPS), lipoteichoic acid (LTA) (bacteria)
	SR-B	LTA, lipopeptides, diacylglycerides (bacteria), β-glucans (fungi)



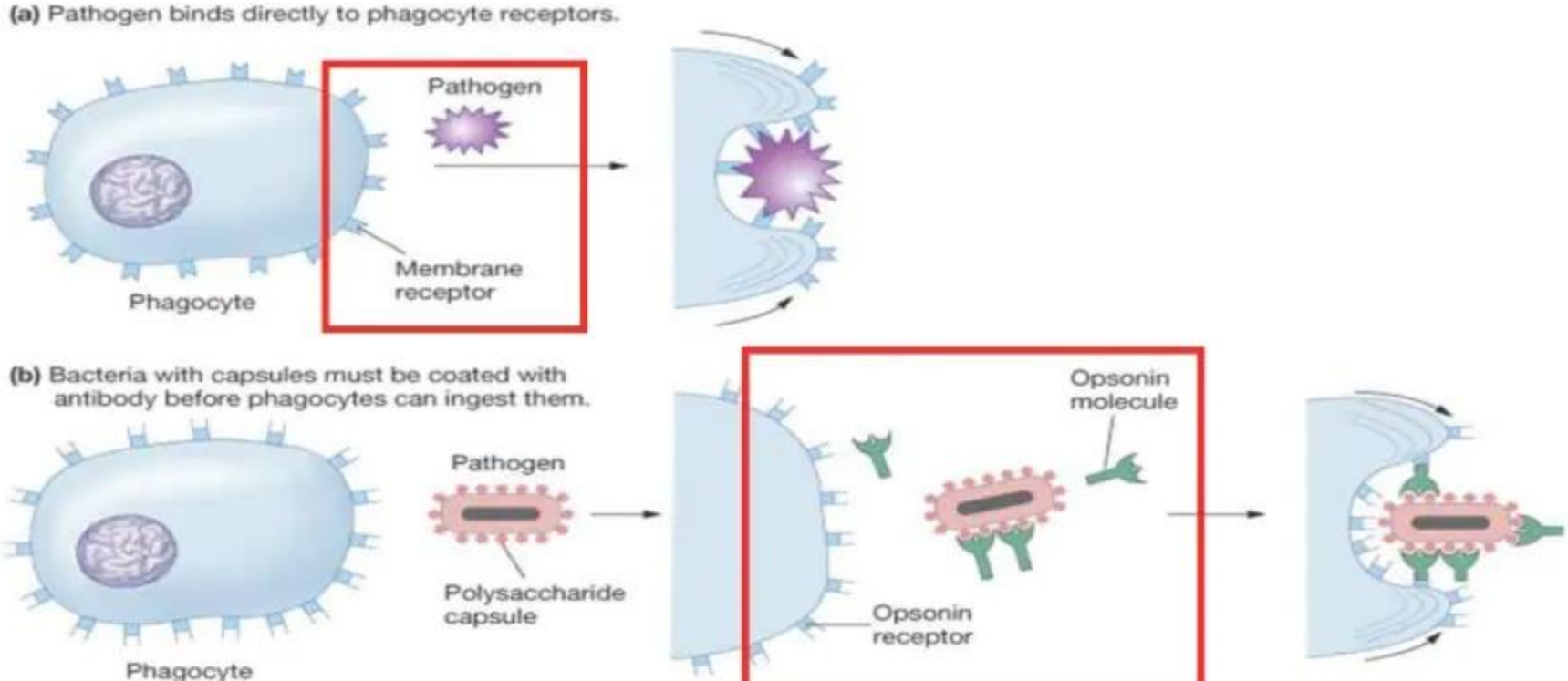


2.) Indirect : Opsonin rec.

" Opsonization " (to make it tasty)

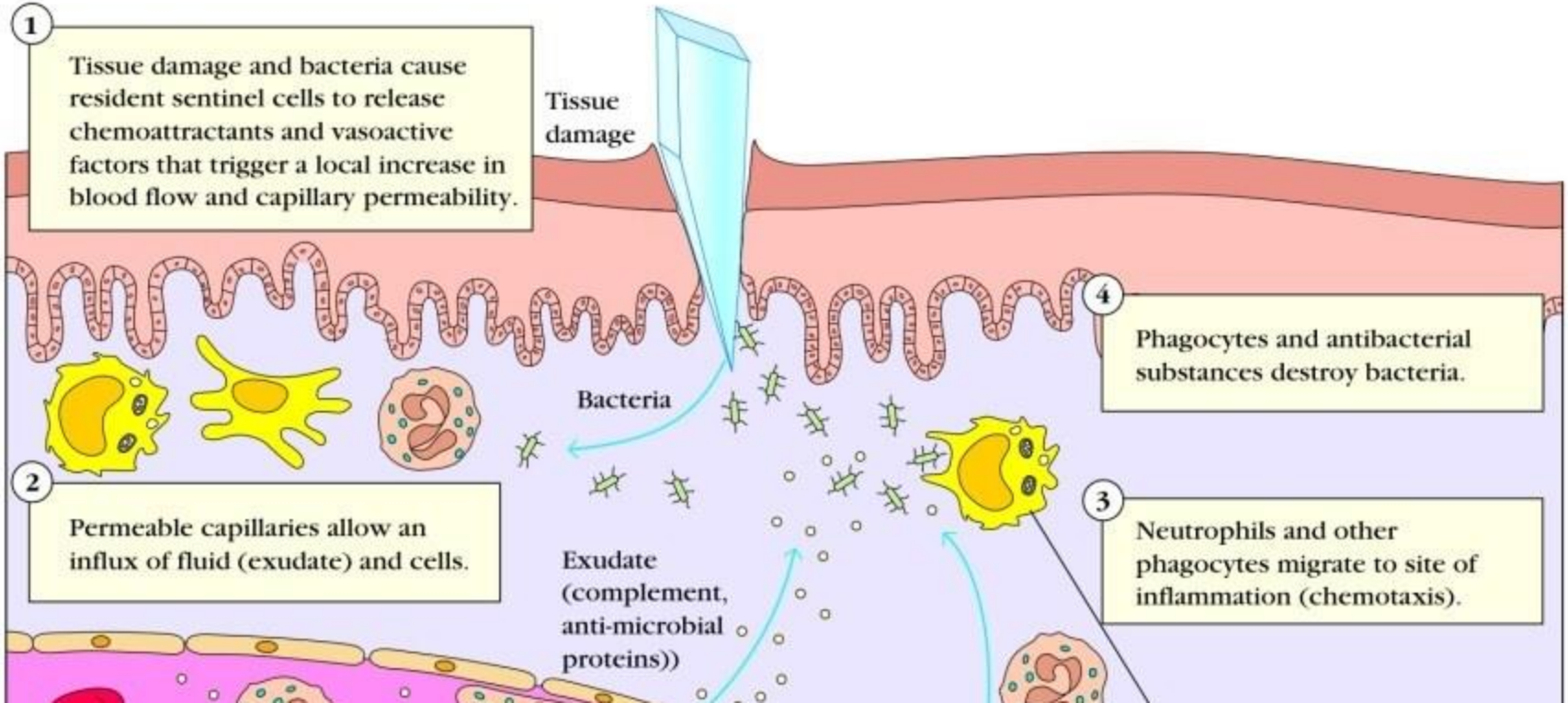
- recognition of soluble proteins that have bound to microbial surfaces
- Soluble prot. = Opsonin

Opsonin receptors		Microbe-binding opsonins (soluble; bind to microbes)
Collagen-domain receptor	CD91/calreticulin	Collectins SP-A, SP-D, MBL; L-ficolin; C1q
Complement receptors	CR1, CR3, CR4, CRIg, C1qRp	Complement components and fragments*
Immunoglobulin Fc receptors	FcαR	Specific IgA antibodies bound to antigen#
	FcγRs	Specific IgG antibodies bound to antigen;# C-reactive protein

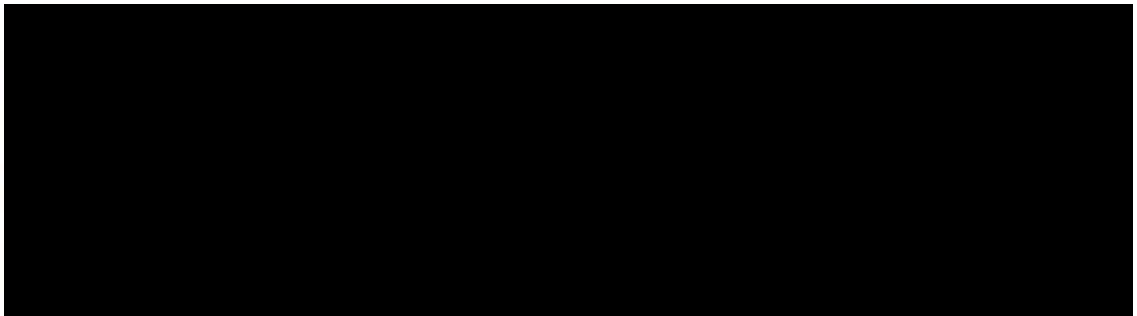

(a) Pathogen binds directly to phagocyte receptors.
Pathogen
Membrane receptor
Phagocyte
(b) Bacteria with capsules must be coated with antibody before phagocytes can ingest them.
Pathogen
Polysaccharide capsule
Phagocyte
Opsonin molecule
Opsonin receptor

Inflammatory response

Acute Phase : Local inflammatory response



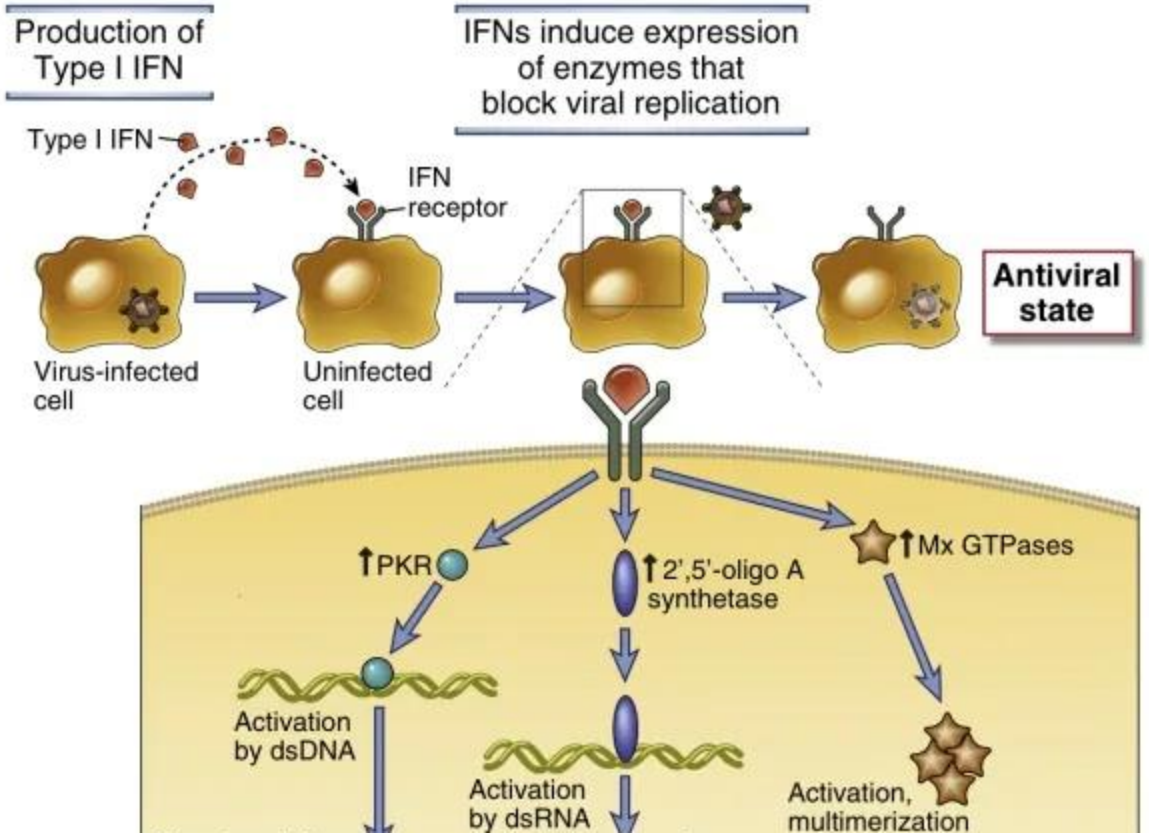
- Phase
  - Acute : Local inflammation followed by healing
  - Chronic : Long- term, not resolved
- Hallmarks of a localized inflammatory response
  : Redness, Swelling, Warm, Pain
  - Vasodilatation >> Warm, Redness
  - Increased Vascular permeability >> Swelling



Acute Phase Response proteins (APRs)

- Normally found in blood at low concentrations
- Secreted from hepatocyte of liver following stimulation by proinflammatory cytokines (TNF-alpha, IL-1, IL-6)
- Function as "opsonin"
- Ex. - C-reactive protein (CRP)
  - Mannose-binding lectin (MBL)

Action of Type 1 interferons



Innate initiation of adaptive response

T cell

- Dendritic cell PRRs recognize PAMPs, activating phagocytosis and signaling pathways.
- Dendritic cells migrate to lymph nodes, carrying intact or degraded pathogens.
- Antigen fragments bound to cell surface MHC proteins are recognized by T cells.
- Activated T cells initiate adaptive responses.

References

1.Kindt, Richard A. Goldsby, Barbara 2018

2.Jawetz Melnick&Adelbergs Medical Microbiology 26/E