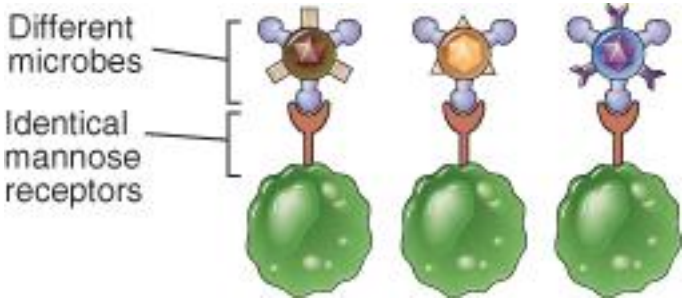
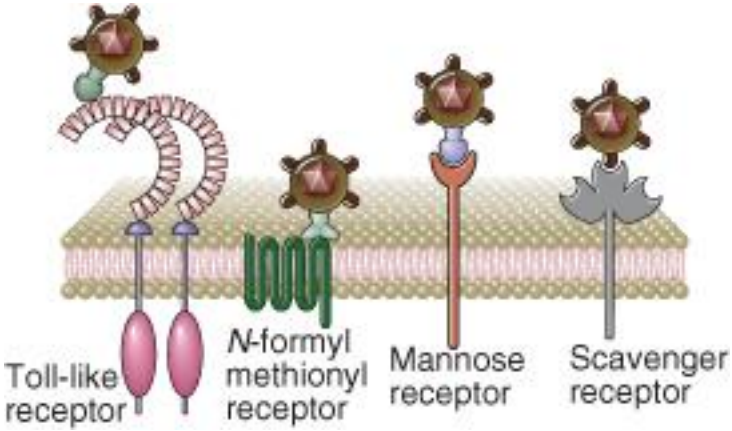
Principles of innate immunity (Abbas Chapter 4)

***Innate immunity** is the initial response to microbes that prevents, controls, or eliminates infection of the host by many microbes*

Principles of innate immunity (Abbas Chapter 4)





The innate IS recognizes pathogen-associated molecular patterns
PAMPs

with

pattern recognition receptors
PRRs

Receptors are non-clonal – identical receptors on all cells of the same lineage

Self /non-self discrimination – healthy host cells are not recognized or protected

Examples of PAMPs and DAMPs (Abbas Chapter 4)

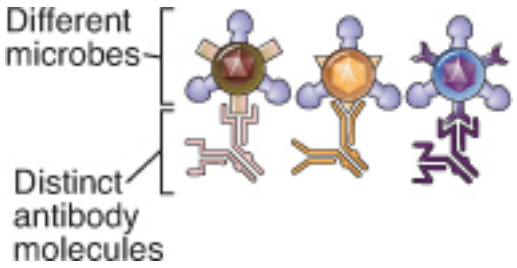
Pathogen-associated molecular patterns

Nucleic acids (ssRNA, dsRNA, CpG DNA) from viruses and bacteria
Proteins (pilin and flagellin) from bacteria
Cell wall lipids (LPS and lipoteichoic acid) from bacteria (gram-/+)
Carbohydrates (Mannan and dectin glucans) from fungi and bacteria

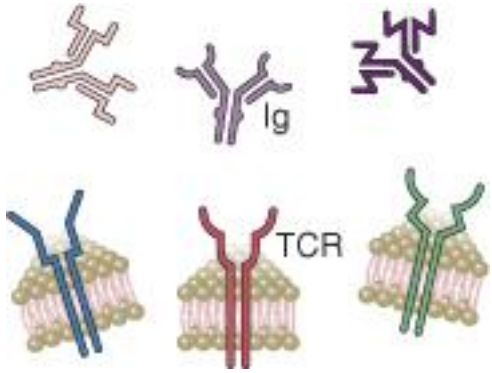
Damage-associated molecular patterns

Stress-induced proteins (heat shock proteins, HSPs)
Crystals (monosodium urate)
Nuclear proteins (high mobility group box 1, HMGB1)
Extracellular ATP

Principles of adapted immunity (Abbas Chapter 4)



Highly individualized response, able to „learn“ and to „optimize“, and to establish a memory



Antibodies and receptors are encoded by genes produced by somatic recombination of gene segments, resulting in high diversity

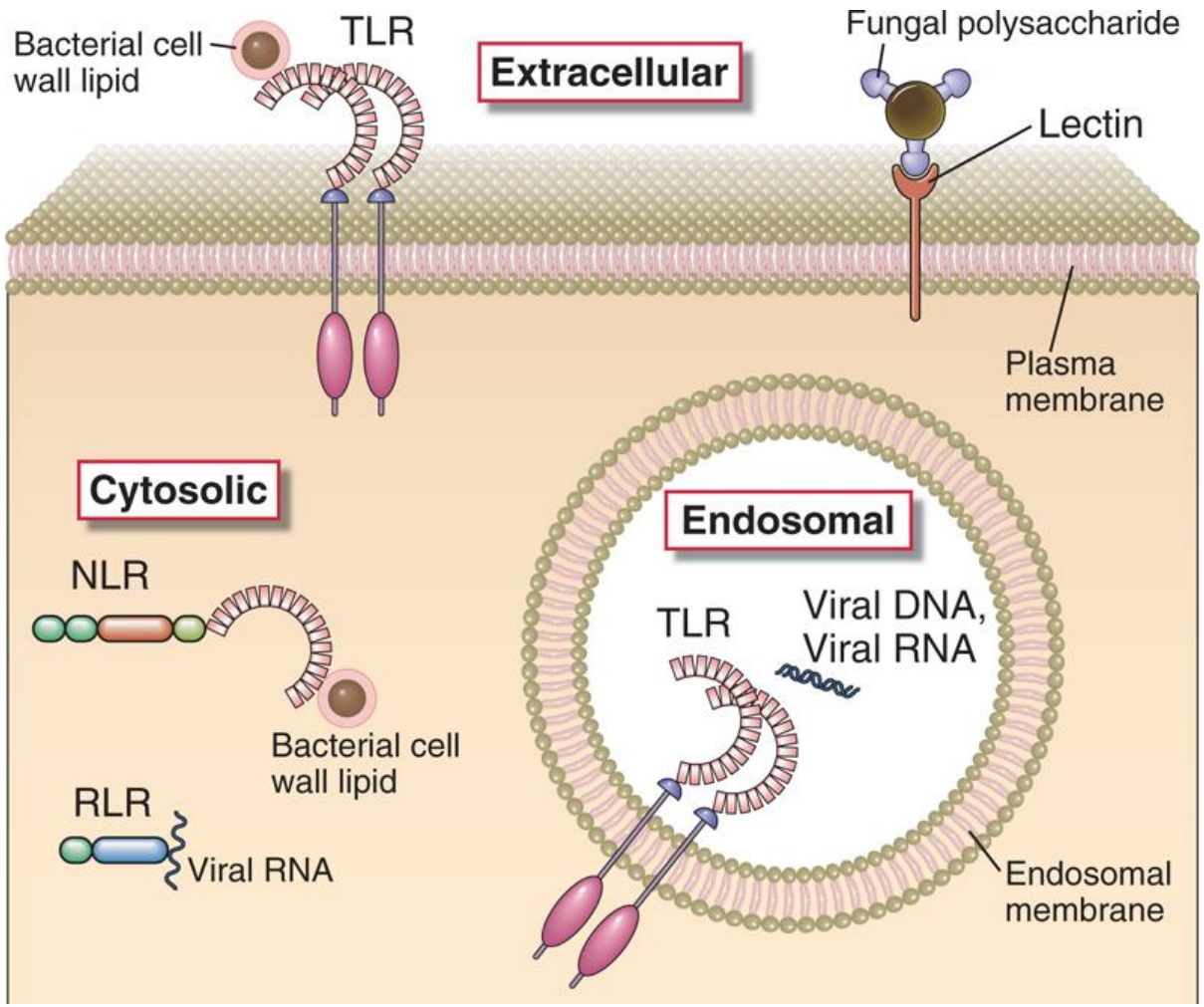
Receptors are clonal

lymphocytes with distinct specifities express different receptor

Self /non-self discrimination

is based on elimination or inactivation of self-reactive lymphocytes

Cellular localization of PRRs (Abbas Chapter 4)



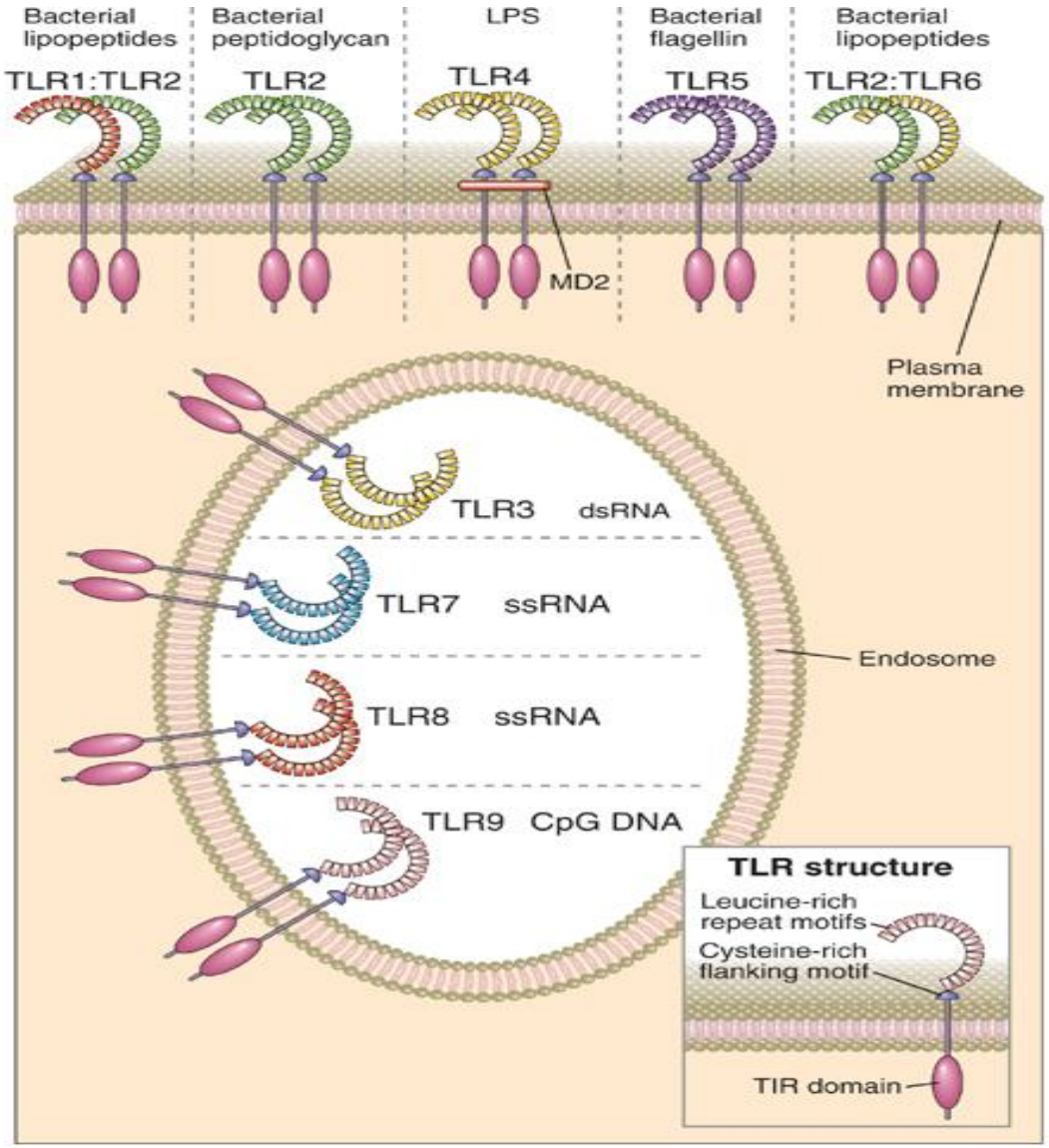
C-type Lectins: Mannose Receptors and Dectins (bind ß-glucans of fungi)

Scavenger Receptors: highly diverse group

N-formyl… Receptors recognize specific bacterial peptides

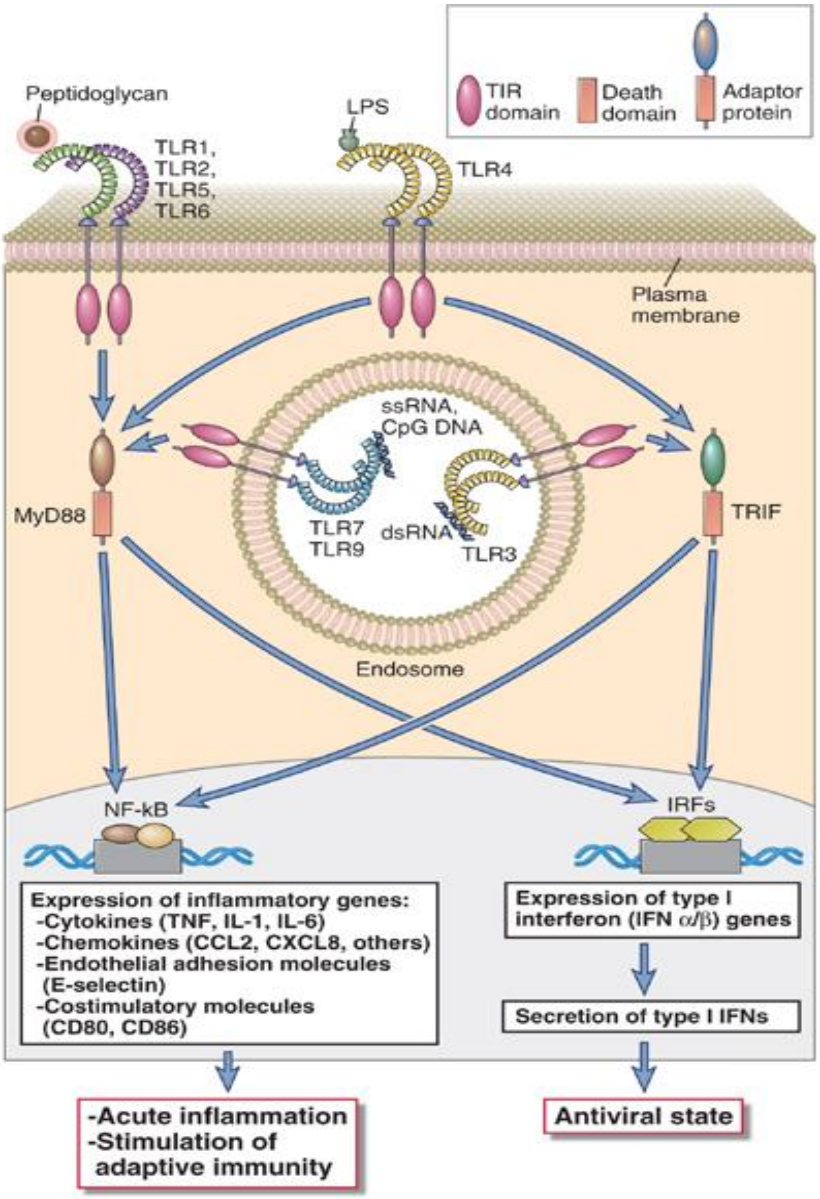
TLR=Toll-like receptor, NLR=Nod-like receptor, RLR=RIG-like receptor

Structure, location and specificity of TLRs (Abbas Chapter 4)



TIR = Toll/interleukin1 receptor

Innate Immunity (Abbas Chapter 4)



Adaptors:

TRIF=TIR-domain-containing adapter-inducing interferon-β

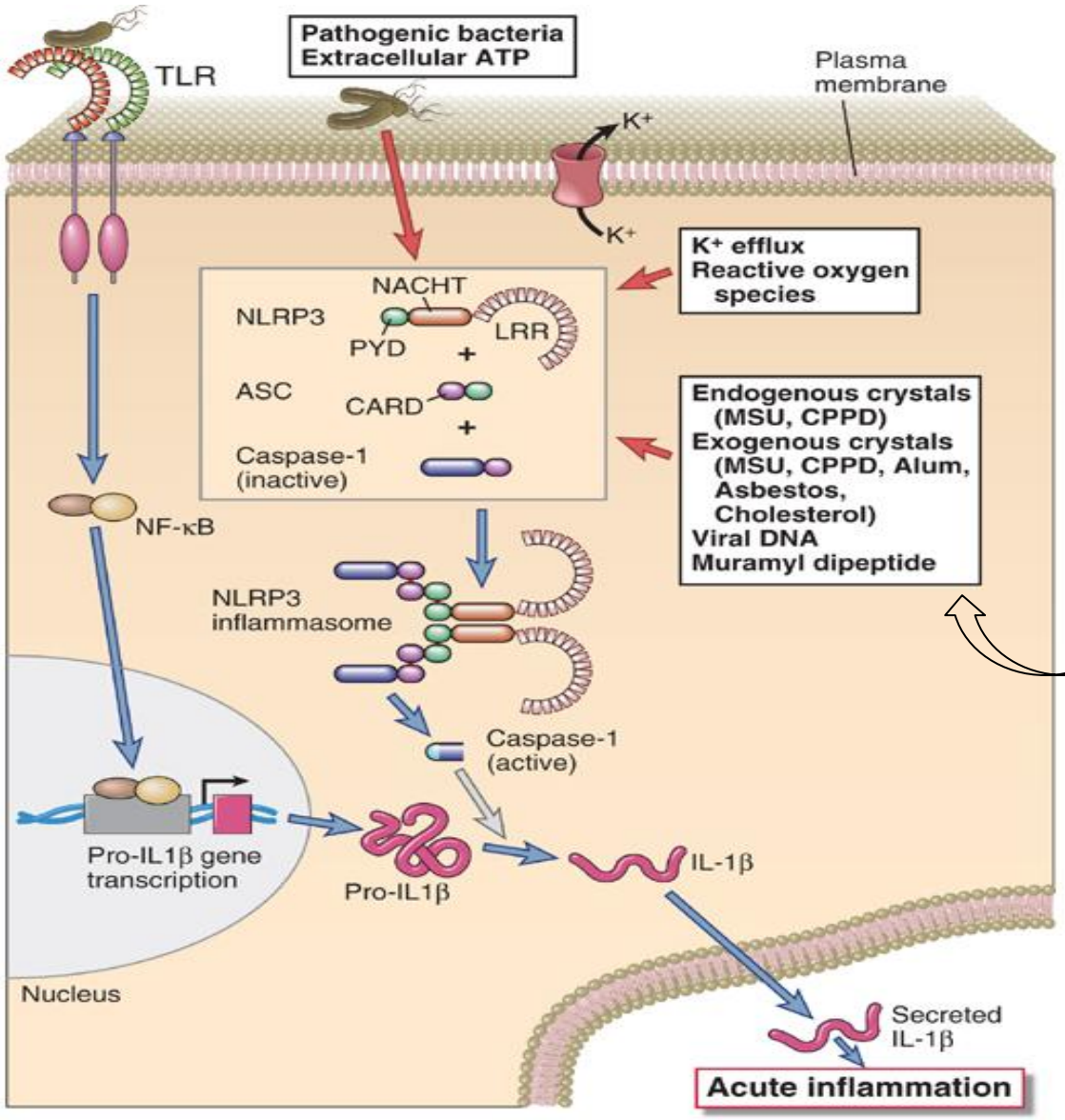
MyD88=Myeloid differentiation primary response gene

Transcription factors:

IRF=interferon regulatory factor

NF-kappaB=nuclear factor kB

The inflammasome (Abbas Chapter 4)

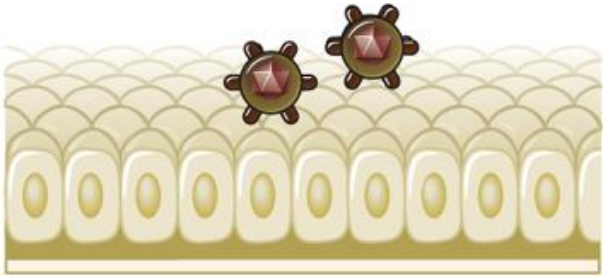


MSU=monosodium urate
CPPD=calcium pyrophosphate dihydrate

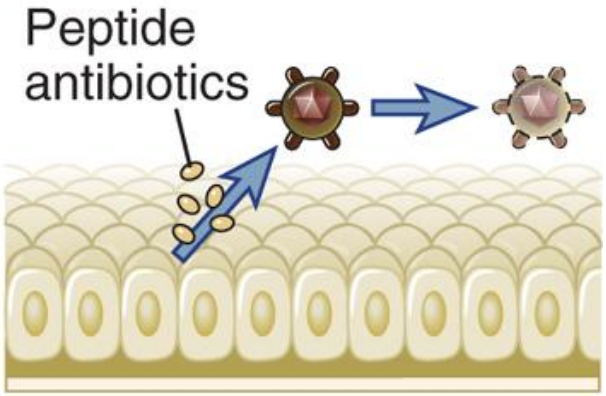
extracellular ATP from dead cells

Epithelial barriers (Abbas Chapter 4)

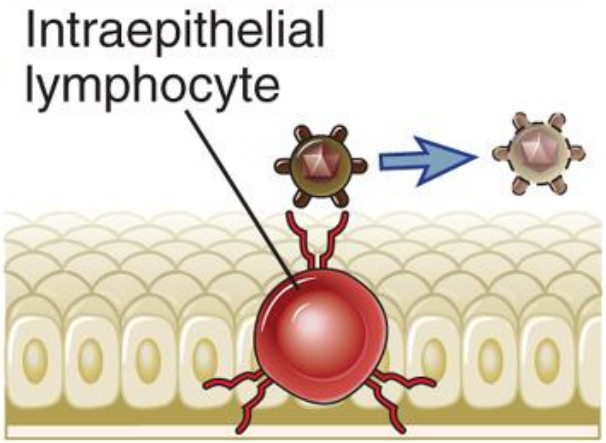
Physical barrier to infection



Killing of microbes by locally produced antibiotics, defensins, calthelicidins



Killing of microbes and infected cells by intraepithelial lymphocytes



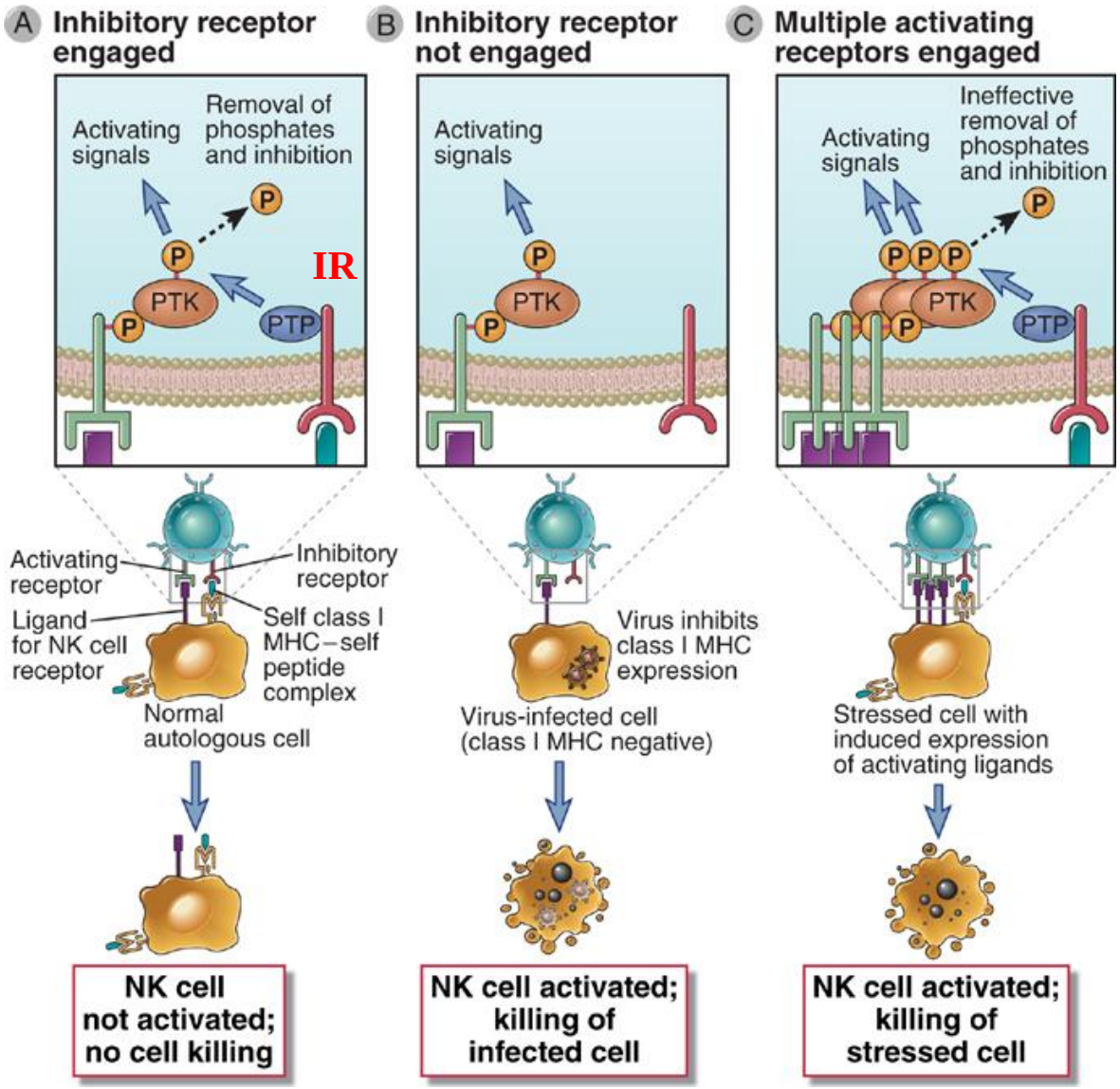
Defensins:
29-34 aa-long peptides
Cathelicidins:
polypeptide from a 18kD precursor

made by epithelial cells, neutrophils, NKs, CTLs, paneth cells …

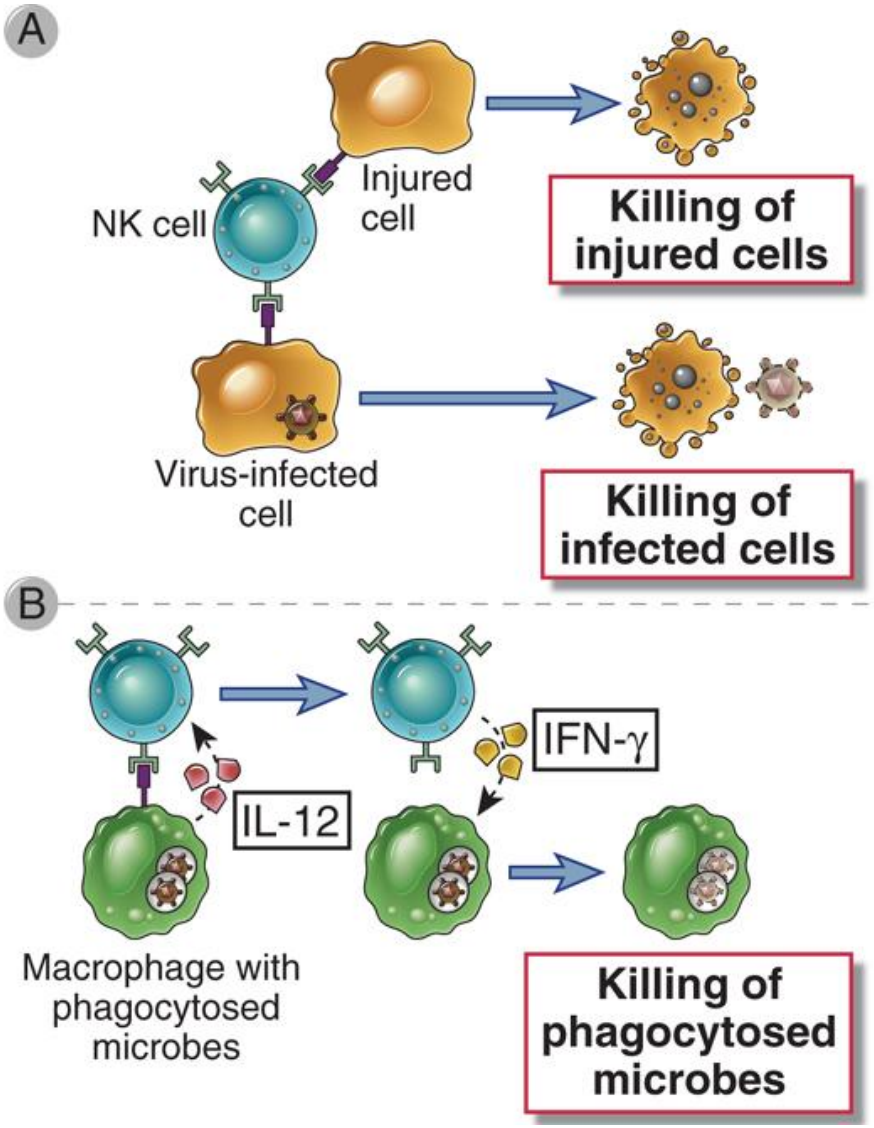
can permeabilize bacterial membranes

IE lymphocytes:
alpha/beta and gamma/delta TcR positive cells
low diversity
specific for bacterial proteins
activate phagocytes
kill infected cells

Natural killer cells (Abbas Chapter 4)



Functions of NKs (Abbas Chapter 4)



SOLUBLE RECOGNITION AND EFFECTOR MOLECULES OF INNATE IMMUNITY (Abbas Chapter 4)

These molecules provide early defense against pathogens that are present outside host cells at some part of their life cycle

By binding to microbes, they act as opsonins

After binding to microbes, soluble mediators of innate immunity promote inflammatory responses

The complement system (Abbas Chapter 4)

Example for one general principle of complement:

Complement component C3 is „always“ present and is constitutively activated at low levels (recognizes e.g. LPS)

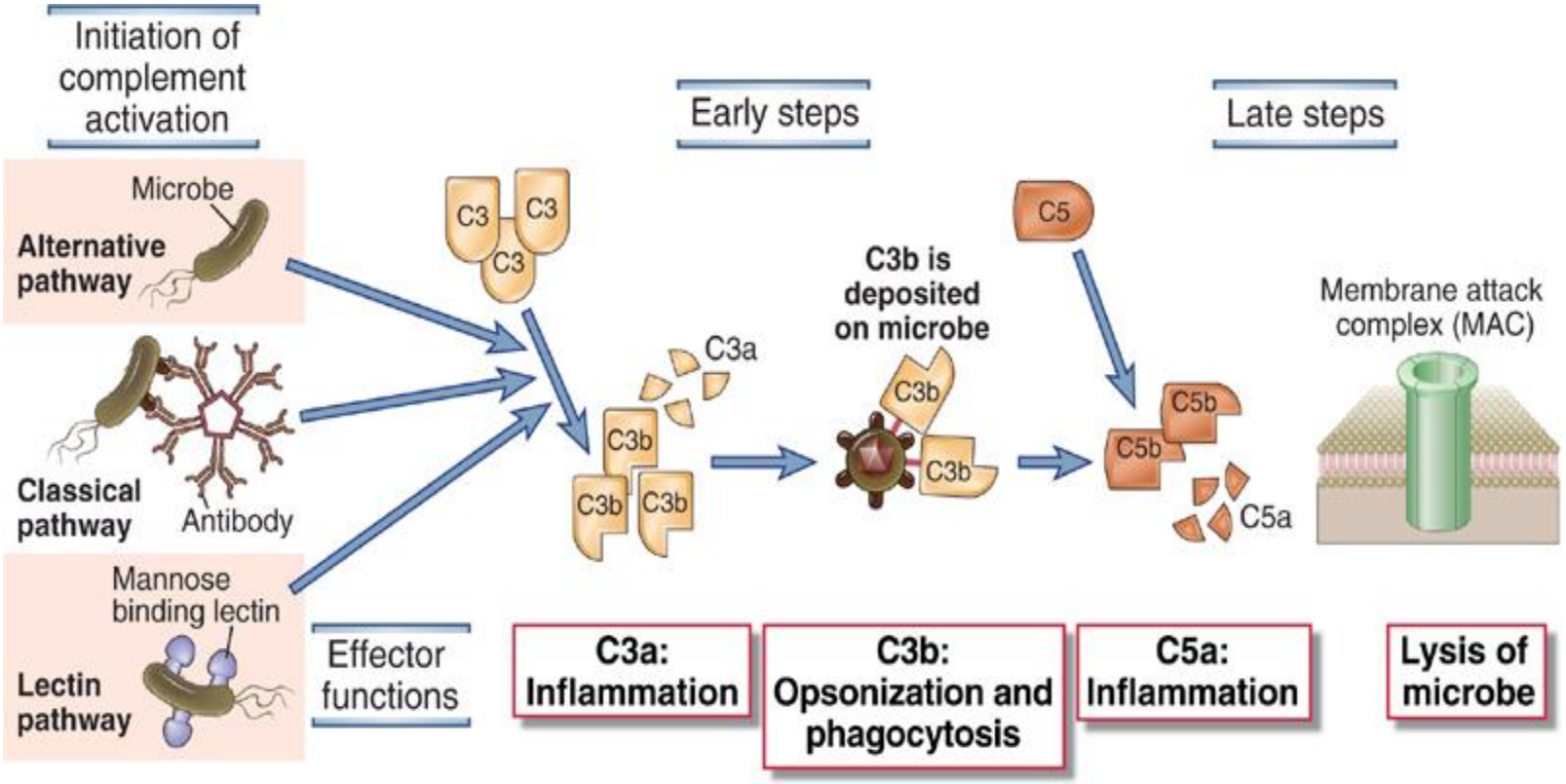
activated C3 binds to all cell surfaces

however

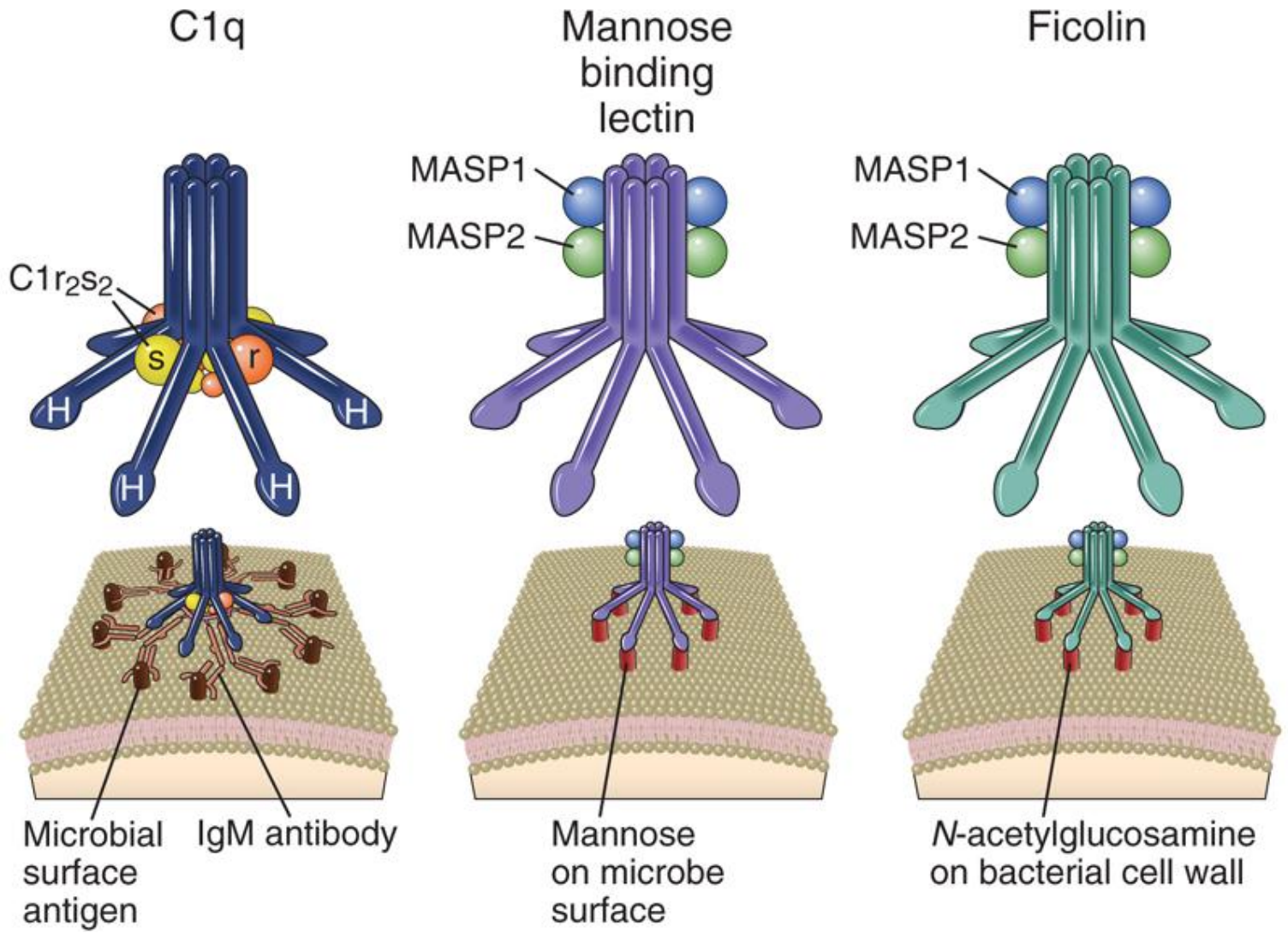
„self“ cells inhibit binding, microbes do not

activation is amplified on microbial surfaces

The complement system (Abbas Chapter 4)



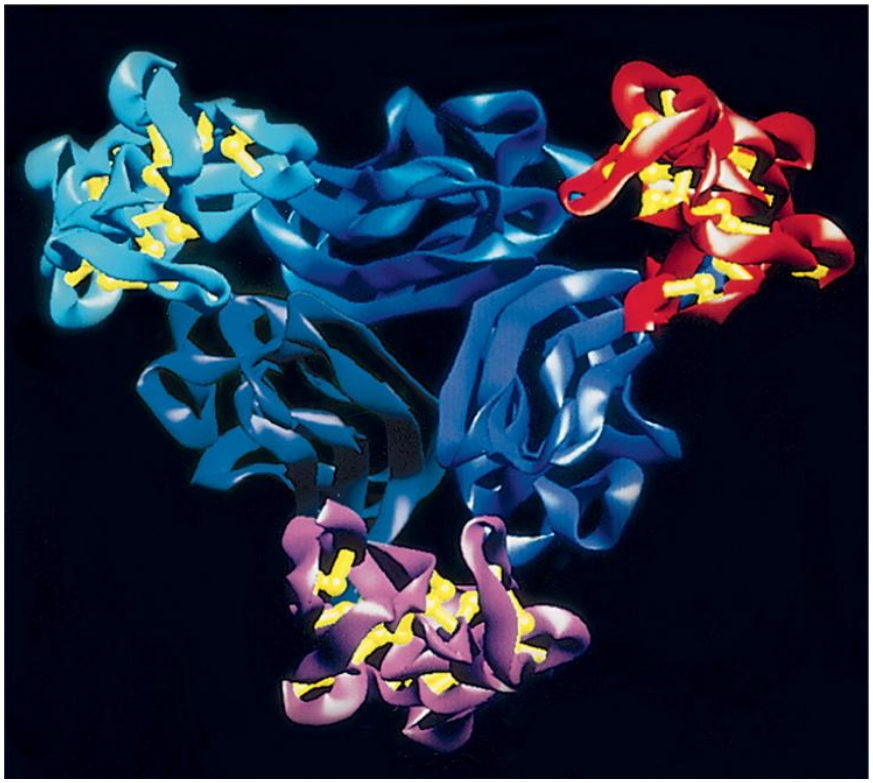
C1, mannose-binding lectin, and ficolin (Abbas Chapter 4)



The inflammatory response (Abbas Chapter 4)

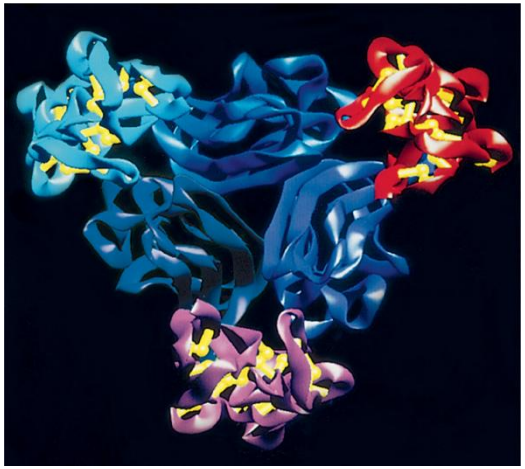
The major way by which the innate immune system deals with infections and tissue injury is to stimulate acute inflammation, which is the accumulation of leukocytes, plasma proteins, and fluid derived from the blood at an extravascular tissue site of infection or injury

TNF – the major pro-inflammatory cytokine (Abbas Chapter 4)



Structure of the TNF receptor with bound lymphotoxin. The ribbon structure depicts a top view of a complex of three TNF receptors (TNF-RI) and one molecule of the bound cytokine, revealed by x-ray crystallography. Lymphotoxin is a homotrimer in which the three subunits are colored dark blue. The lymphotoxin homotrimer forms an inverted three-sided pyramid with its base at the top and its apex at the bottom. Three TNF-RI molecules, colored magenta, cyan, and red, bind one homotrimer of lymphotoxin, with each receptor molecule interacting with two different lymphotoxin monomers in the homotrimer complex. Disulfide bonds in the receptor are colored yellow. TNF is homologous to lymphotoxin (TNF-ß) and presumably binds to its receptors in the same way

TNF – the major pro-inflammatory cytokine (Abbas Chapter 4)



TNF alpha is mainly produced by macrophages and activates pro-inflammatory transcription factors (e.g. NF kappa B and AP-1)

Interleukin 1, another pro-inflammatory cytokine

IL-1 is produced by activated macrophages, neutrophils, epithelial cells and endothelial cells

The NLRP3 inflammasome activates pro-IL-1ß, IL-1 is released when cells are killed by pathogens

Interleukin 6, another pro-inflammatory cytokine

IL-6 is made by various cells in response to PAMPs

IL-6 has both, local and systemic effects

(inflammatory mediators from the liver, stimulation of neutrophils in the bone marrow, differentiation of Th17 cells)

Recruitment of Leukocytes to Sites of Infection

Both TNF and IL-1 induce postcapillary venule endothelial cells to express E-selectin and to increase their expression of ICAM-1 and VCAM-1, the ligands for leukocyte integrins

TNF and IL-1 also stimulate various cells to secrete chemokines, such as CXCL1 and CCL2, that bind to receptors on neutrophils and monocytes, and stimulate directional movement of leukocytes

Other Cytokines Produced During Innate Immune Responses

***IL-12** is secreted by dendritic cells and macrophages and stimulates **IFN-γ** production by NK cells and T cells, and promotes differentiation of Th1 cells*

IL-18** enhances the functions of NK cells, similar to **IL-12

IL-15** is a cytokine that serves important growthstimulating and survival functions for both NK cells and T cells, similar to **IL-2

Systemic and Pathologic Consequences of the Acute Inflammatory Responses

***TNF*, *IL-1*, and *IL-6* all act on the hypothalamus to induce an increase in body temperature (fever), and these cytokines are therefore called *endogenous pyrogens* (LPS=exogeneous pyrogen)**

***IL-1*, *TNF*, and *IL-6* induce hepatocytes to express *acute-phase reactants*, including *CRP*, *SAP* (serum amyloid P), and *fibrinogen*, which are secreted into the blood**

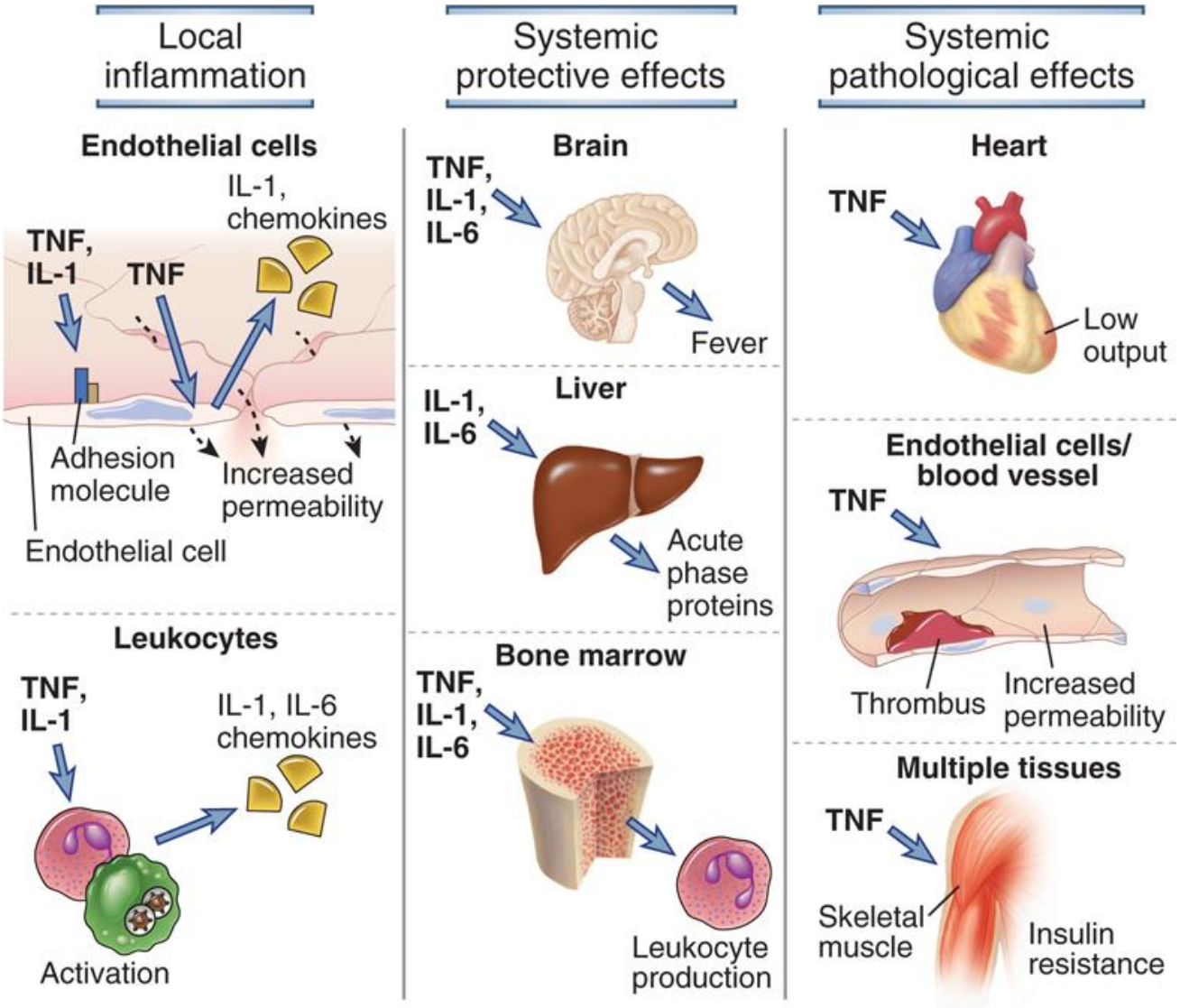
In severe infections, *TNF* may be produced in large amounts and causes systemic clinical and pathologic abnormalities

- TNF inhibits myocardial contractility and vascular smooth muscle tone, resulting in a marked fall in blood pressure, or shock
- TNF causes intravascular thrombosis, mainly as a result of loss of the normal anticoagulant properties of the endothelium
- Prolonged production of TNF causes wasting of muscle and fat cells, called cachexia

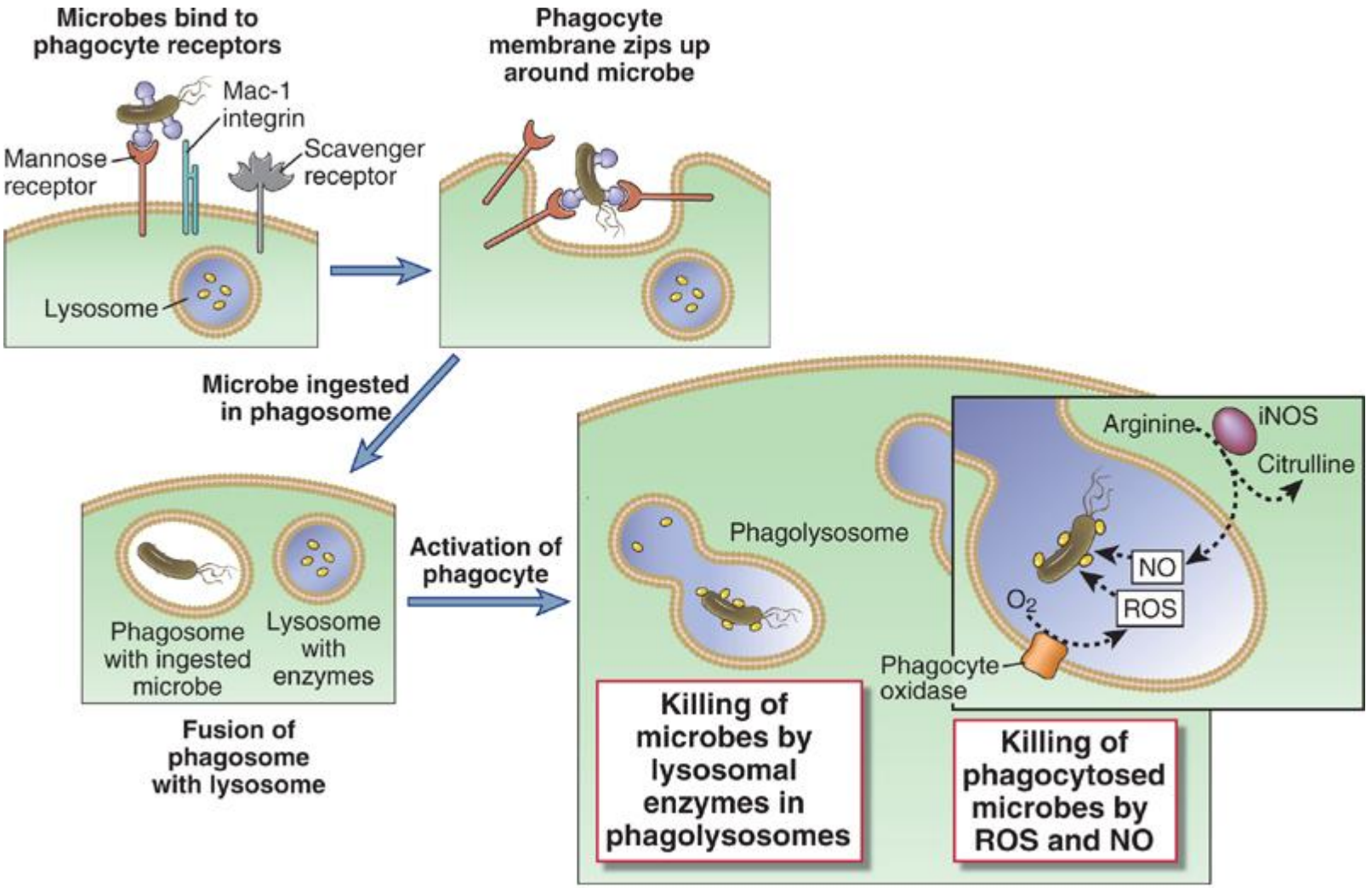
Septic Shock

A complication of severe bacterial sepsis is a syndrome called **septic shock**, which may be caused by LPS released from gram-negative bacteria (in which case it is called endotoxin shock) or lipoteichoic acid from grampositive bacteria. Septic shock is characterized by vascular collapse, disseminated intravascular coagulation, and metabolic disturbances. This syndrome is due to LPS- or lipoteichoic acid-induced TLR signaling leading to the production of TNF and other cytokines, including IL-12, IFN-γ, and IL-1

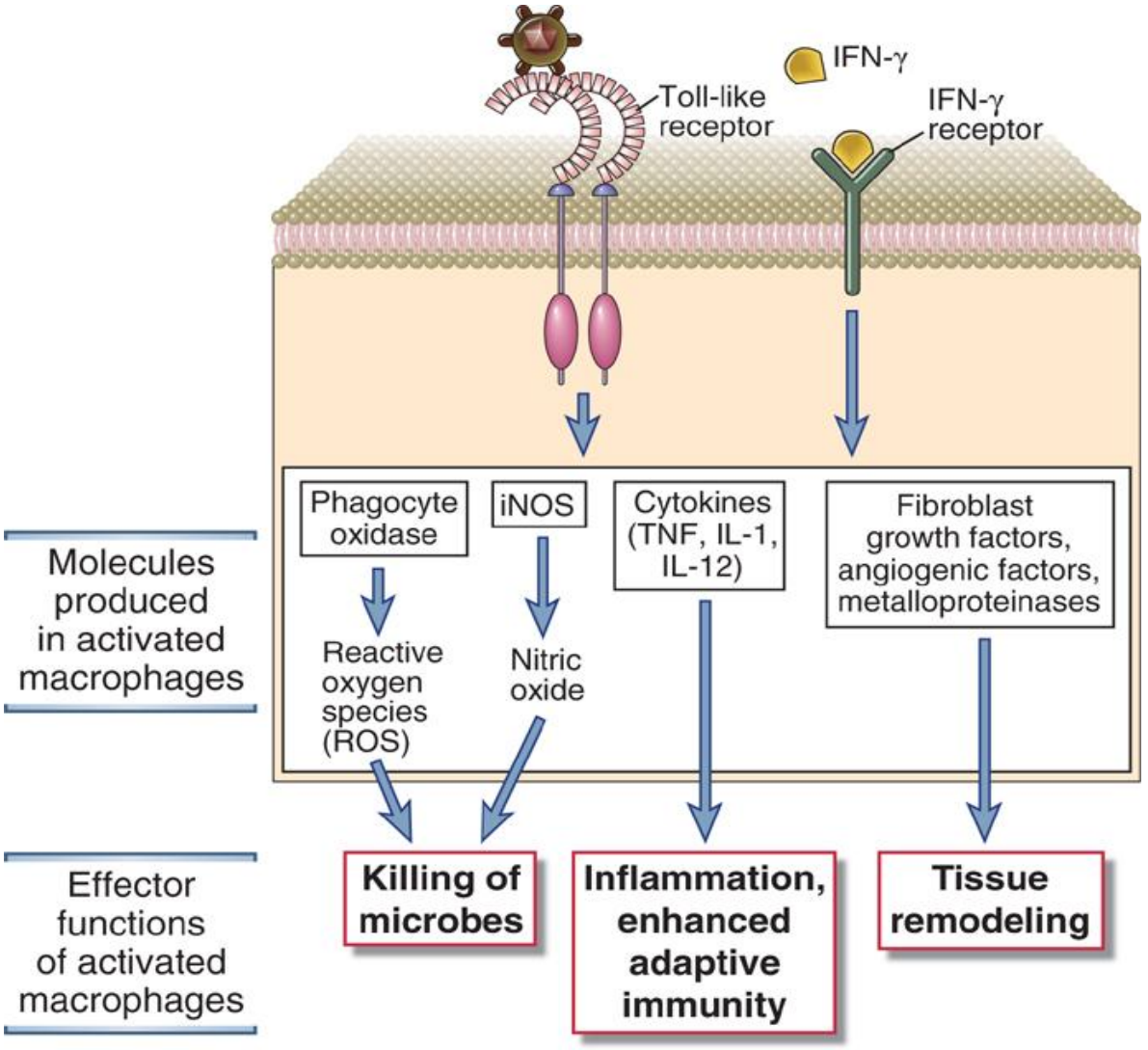
Actions of cytokines in inflammation (Abbas Chapter 4)



Phagocytosis and destruction of microbes (Abbas Chapter 4)



Effector functions of macrophages (Abbas Chapter 4)



Antiviral Responses (Abbas Chapter 4)

Type I interferons are a large family of structurally related cytokines that mediate the early response to viral infections

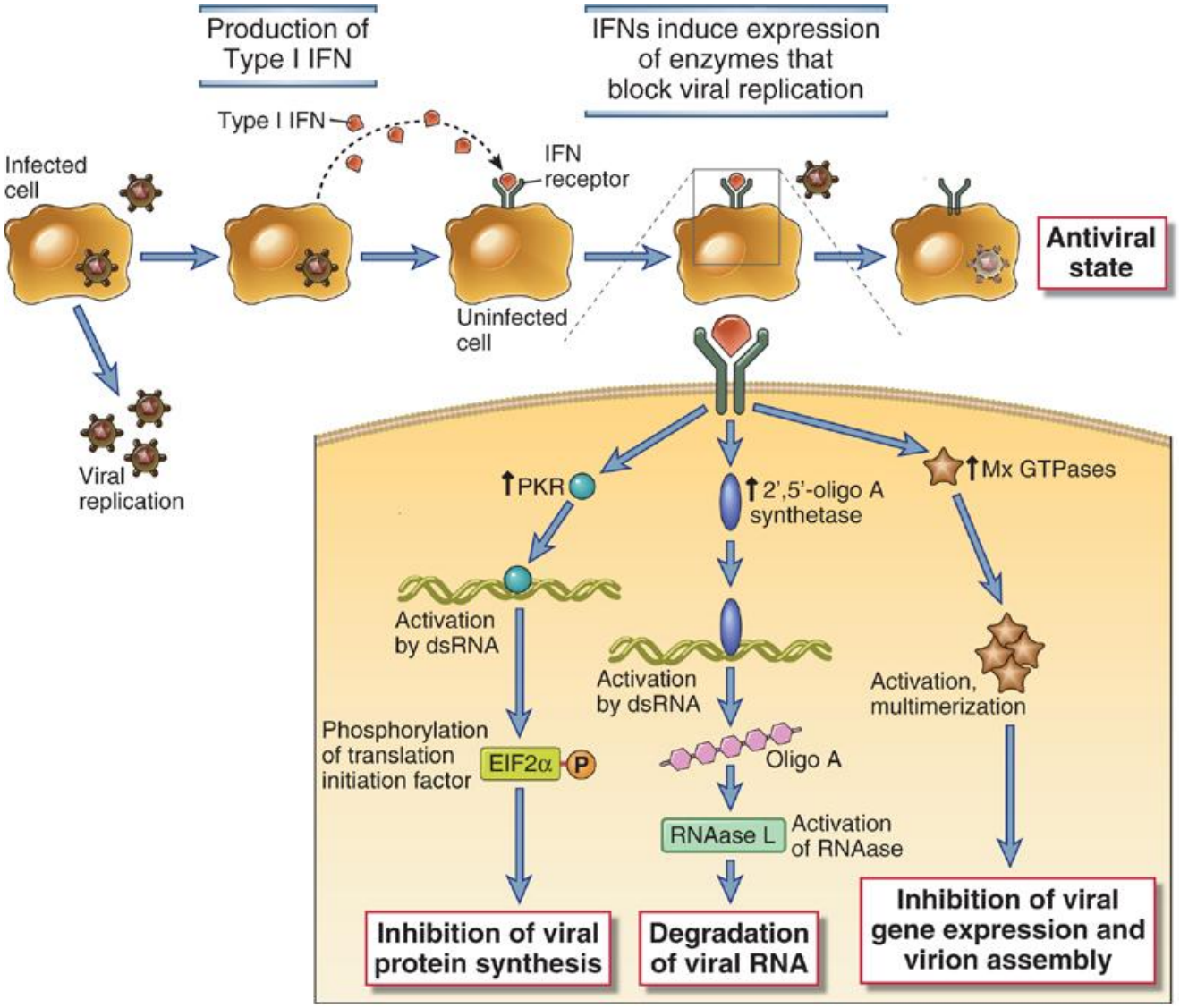
Type I interferons, signaling through the type I interferon receptor, activate transcription of several genes that confer a resistance to viral infection, called an antiviral state

Type I interferons cause sequestration of lymphocytes in lymph nodes, thus maximizing the opportunity for encounter with microbial antigens

Type I interferons increase the cytotoxicity of NK cells and CD8+ CTLs and promote the differentiation of naive T cells to the TH1 subset of helper T cells

Type I interferons upregulate expression of class I MHC molecules and thereby increase the probability that virally infected cells will be recognized and killed by CD8+ CTLs

Biological actions of type I interferons (Abbas Chapter 4)



FEEDBACK MECHANISMS THAT REGULATE INNATE IMMUNITY

The magnitude and duration of innate immune responses are regulated by a variety of feedback inhibition mechanisms that limit potential damage to tissues

IL-10 is a cytokine that inhibits macrophages and dendritic cells (typical feedback mechanisms)

Competitive IL-1 receptor antagonist (biologically inactive IL-1 homolog) represents another feedback loop

Autophagy regulates secretion of inflammatory cytokines (degradation of self-organelles and proteins in lysosomes)

Negative regulatory signaling pathways block activation, such as suppressors of cytokine signaling (SOCS) proteins, which inhibit JAK-STAT signaling.


SCENE
TAKE
2
DAY