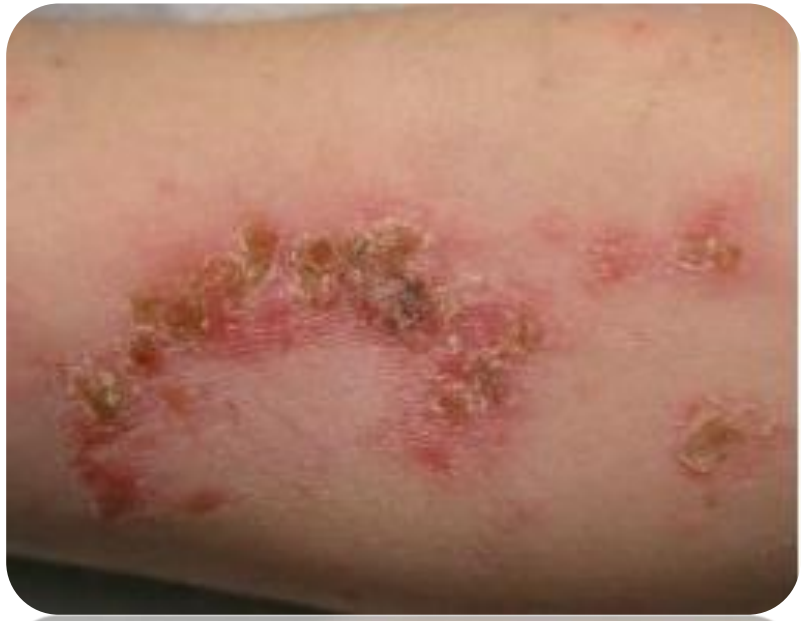
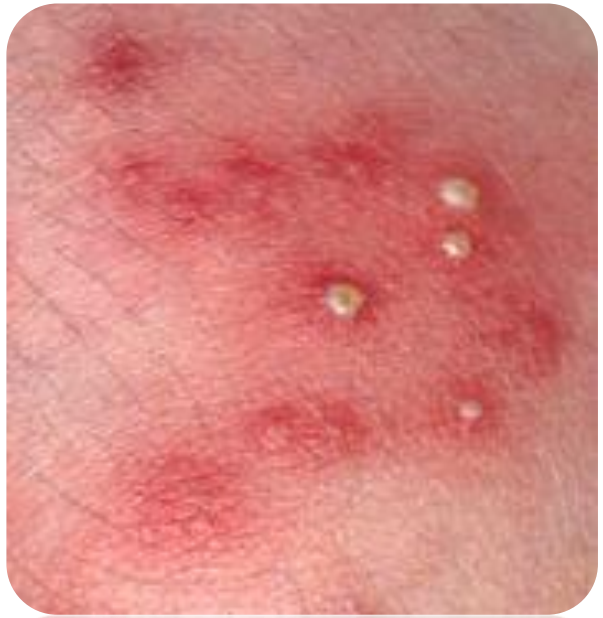
Imunidade Inata

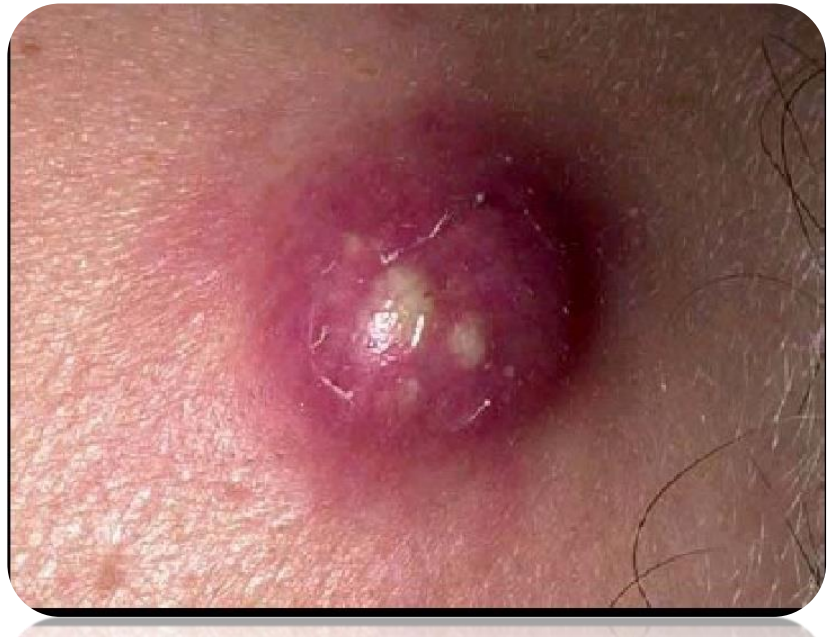
Prof. Jean Pierre



Impetigo



Foliculite



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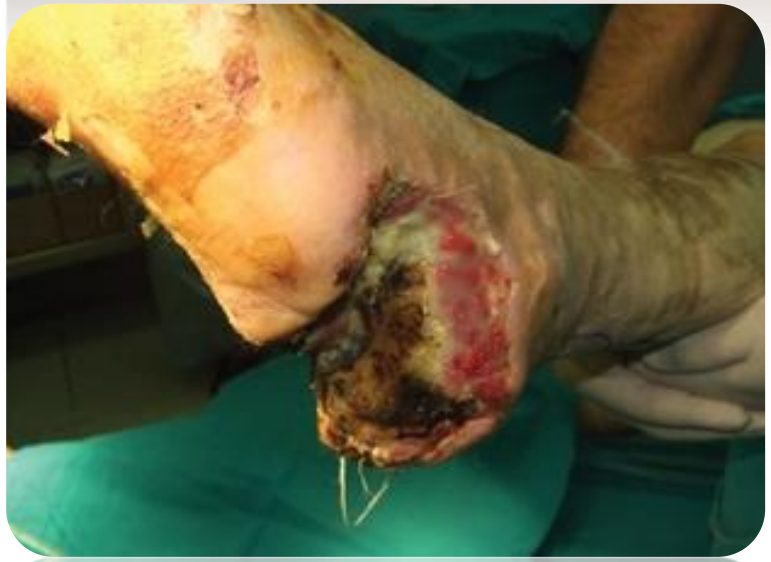
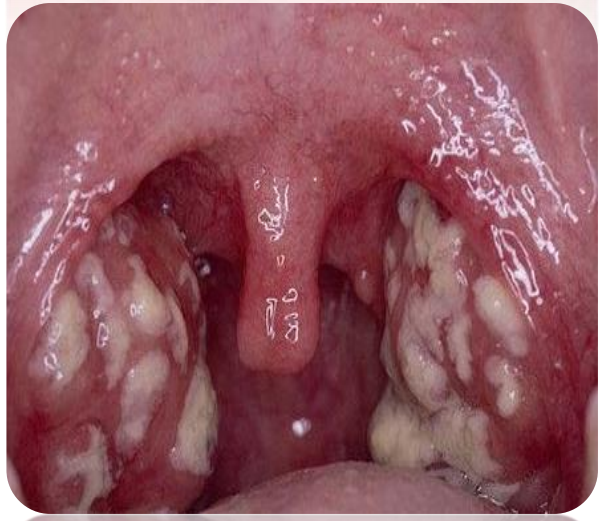
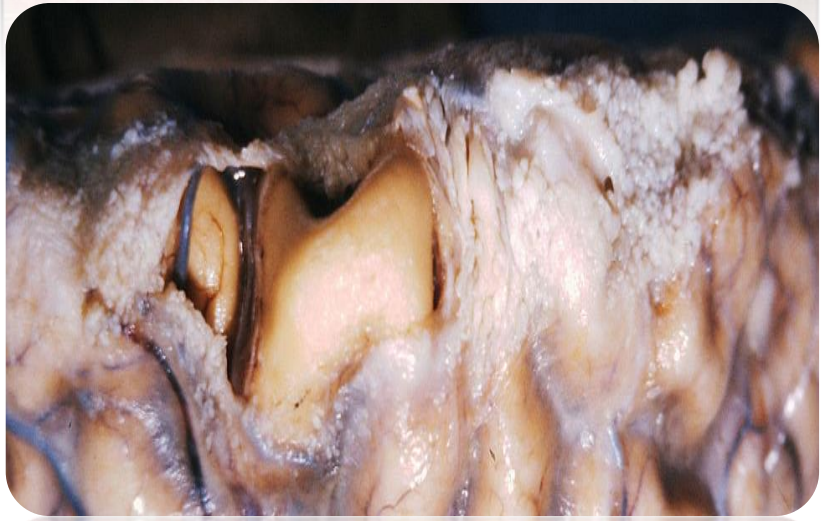


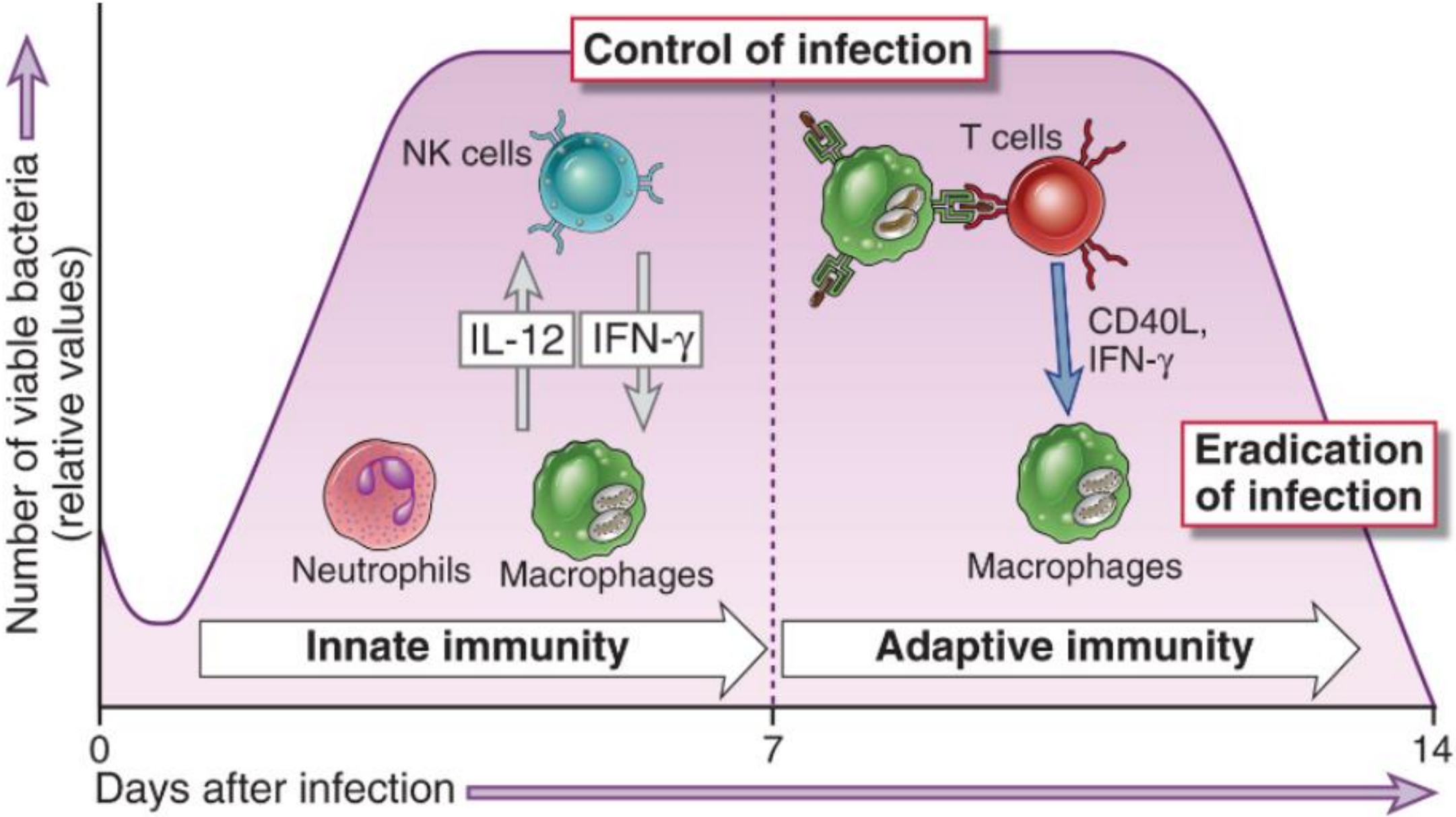
Osteomielite + pé-diabético



Amigdalite



Meningite


Control of infection
NK cells
T cells
IL-12
IFN-γ
CD40L,
IFN-γ
Neutrophils
Macrophages
Macrophages
Eradication
of infection
Innate immunity
Adaptive immunity
Number of viable bacteria
(relative values)
0
7
14
Days after infection

PAMPs vs DAMPs

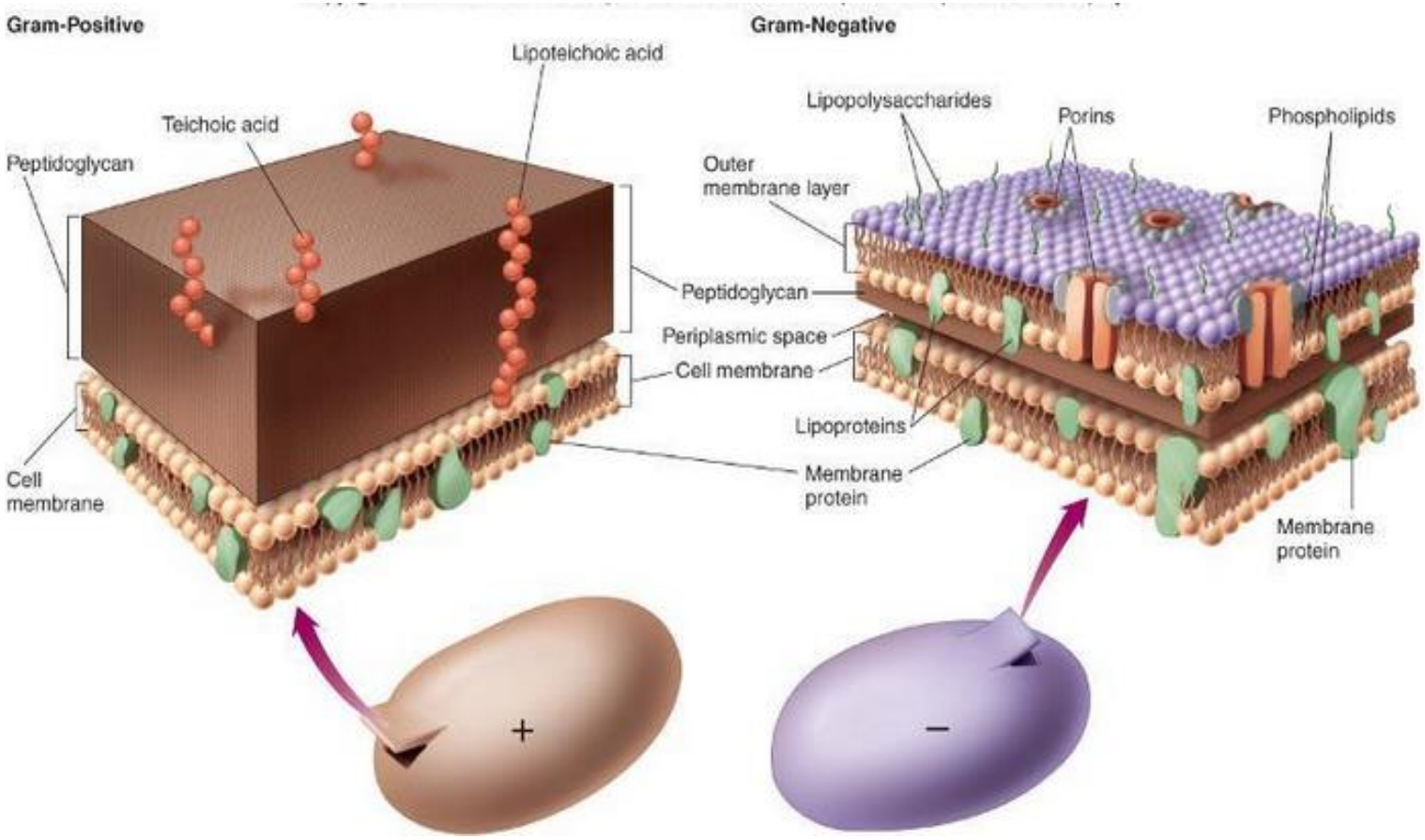
Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

CpG, cytidine-guanine dinucleotide; dsRNA, double-stranded RNA; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

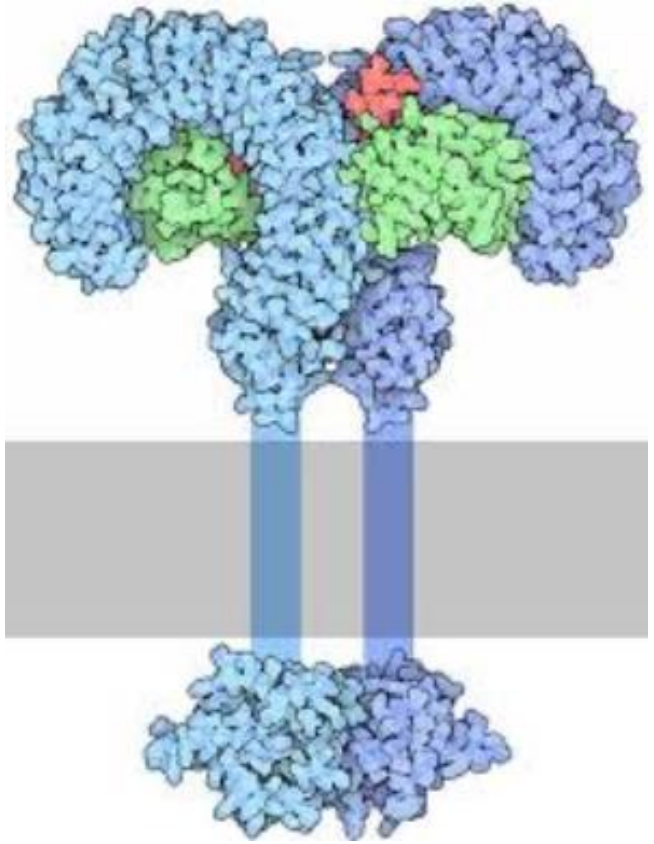
Staphylococcus aureus

Bactérias Gram (+) : Presença de Peptidoglicanos e Ac. Lipoteicóico.

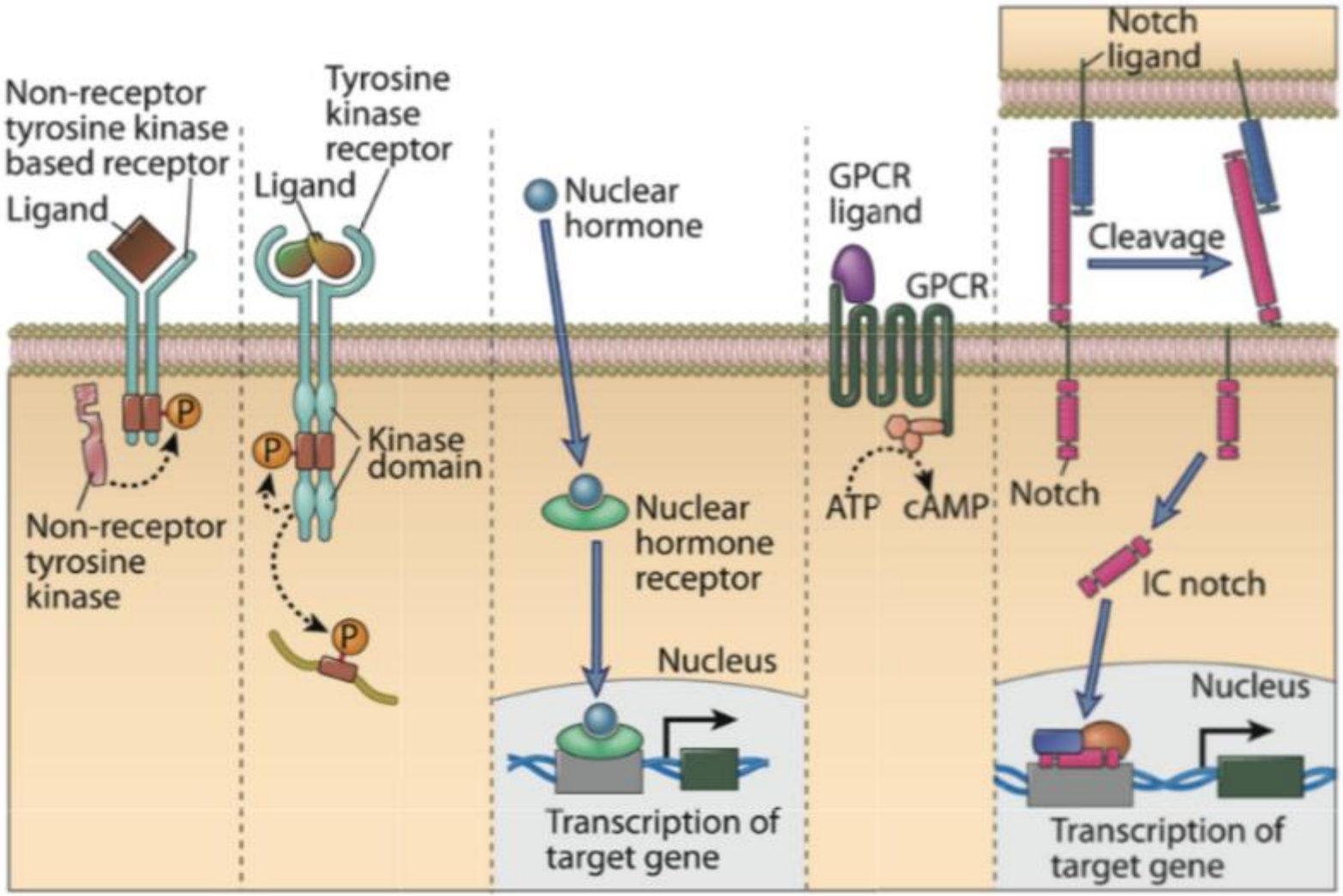
Ligantes de TLR-2: Dímeros com TLR-1 ou TLR-6

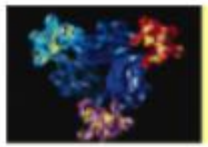


TLR-4



Types of Immune System Signaling Receptors





Specificity of Innate and Adaptive Immunity

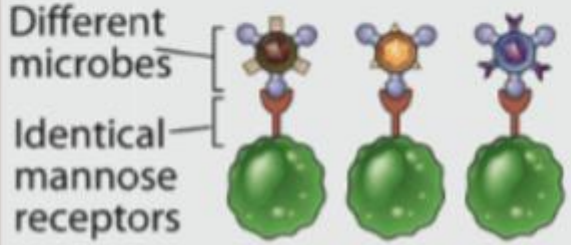
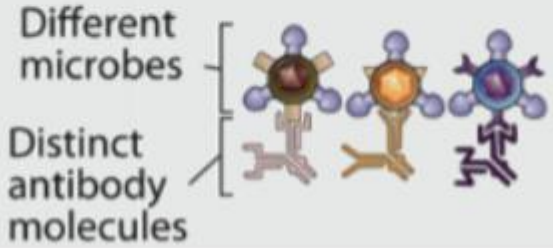
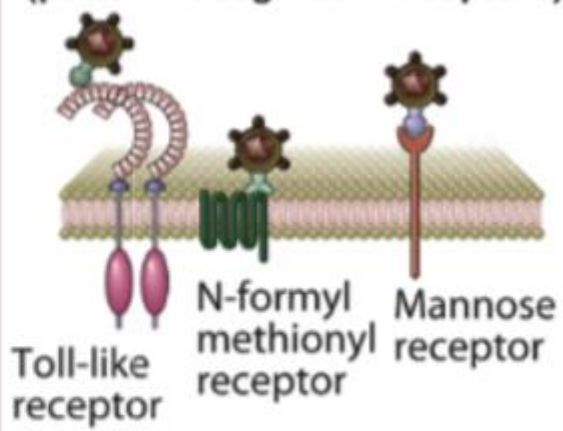
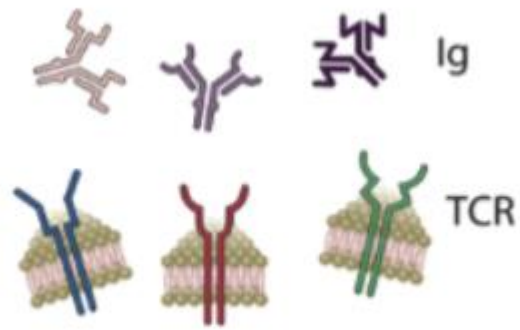
	Innate immunity	Adaptive immunity
Specificity	**For pathogen-associated molecular patterns (PAMPS)** 	**For structural details of any molecules (antigens)** 
Receptors	**Encoded in germline (pattern recognition receptors)** 	**Encoded by lymphocyte genes produced by somatic recombination** 
Distribution of receptors	**Non-clonal**	**Clonal**

Table 4-1

Cellular Location of Innate Immune Receptors

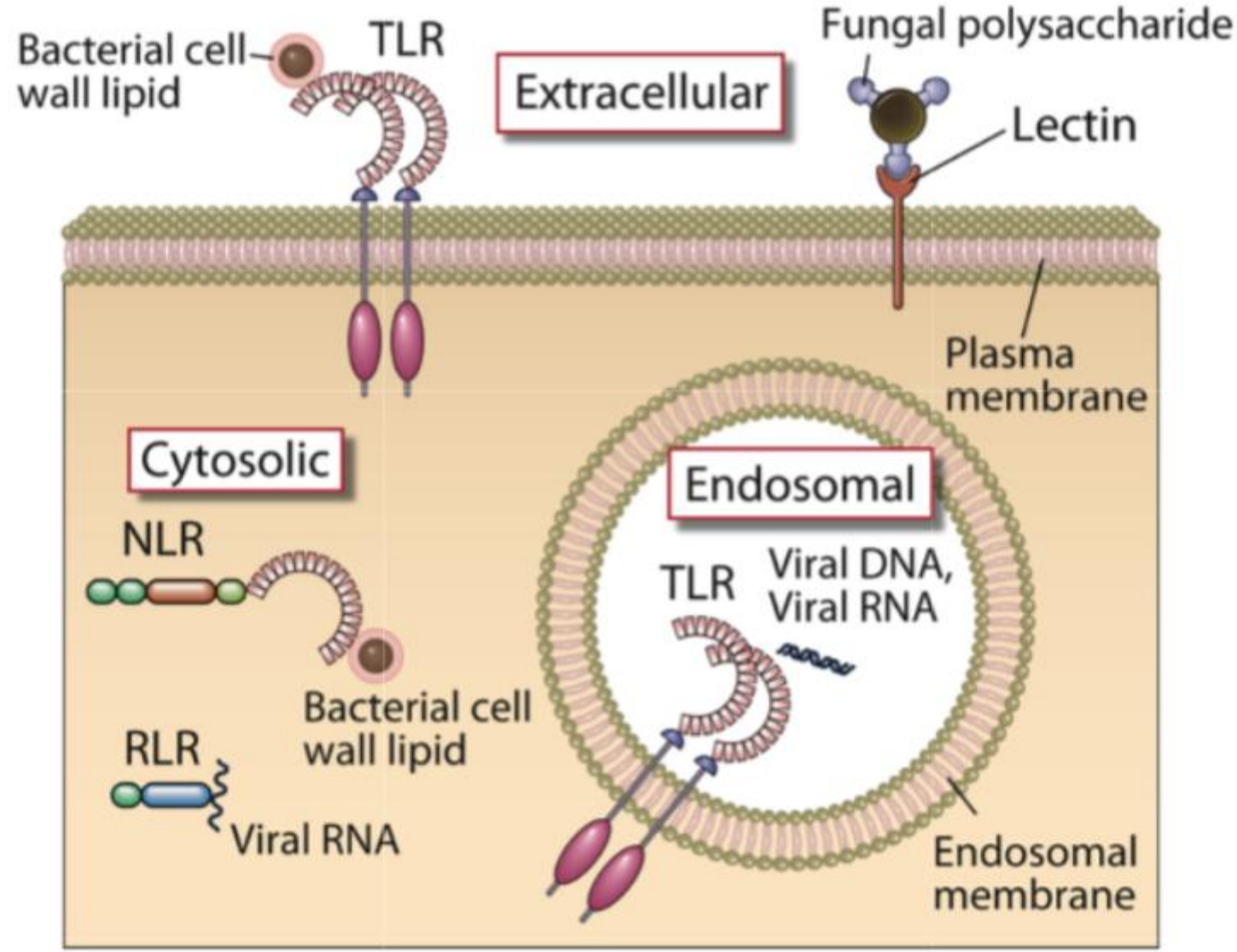
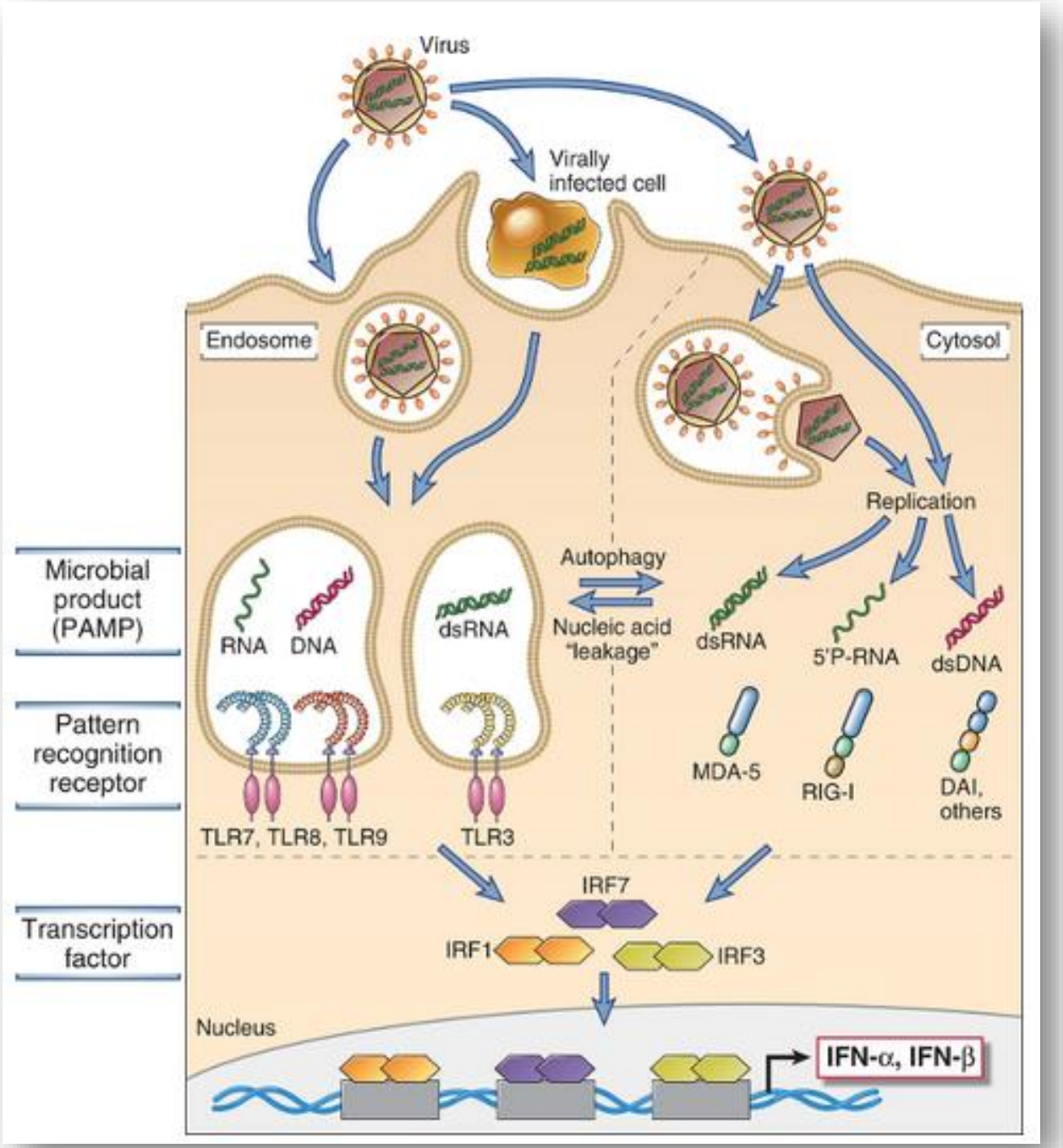
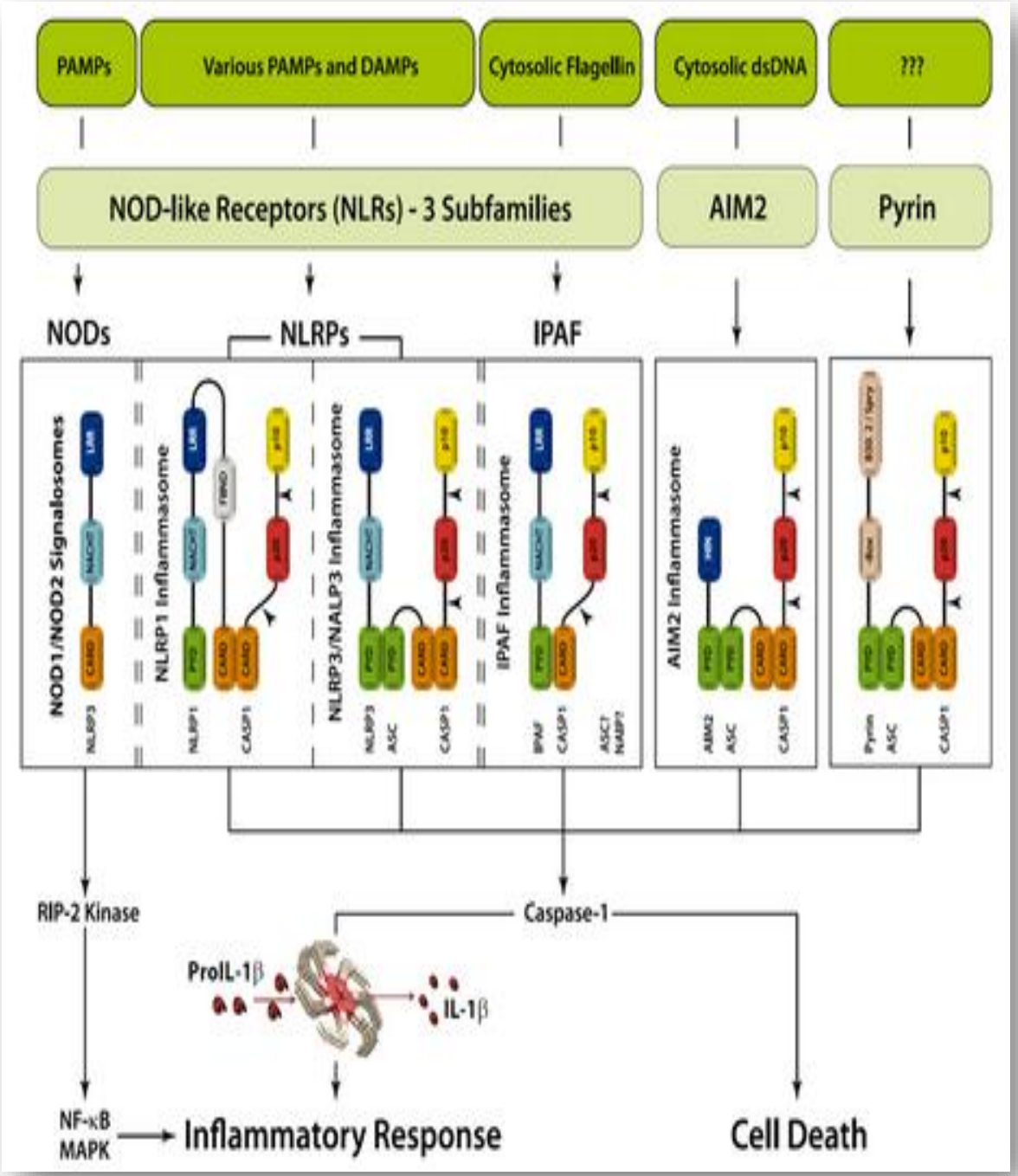
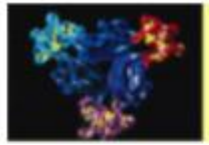


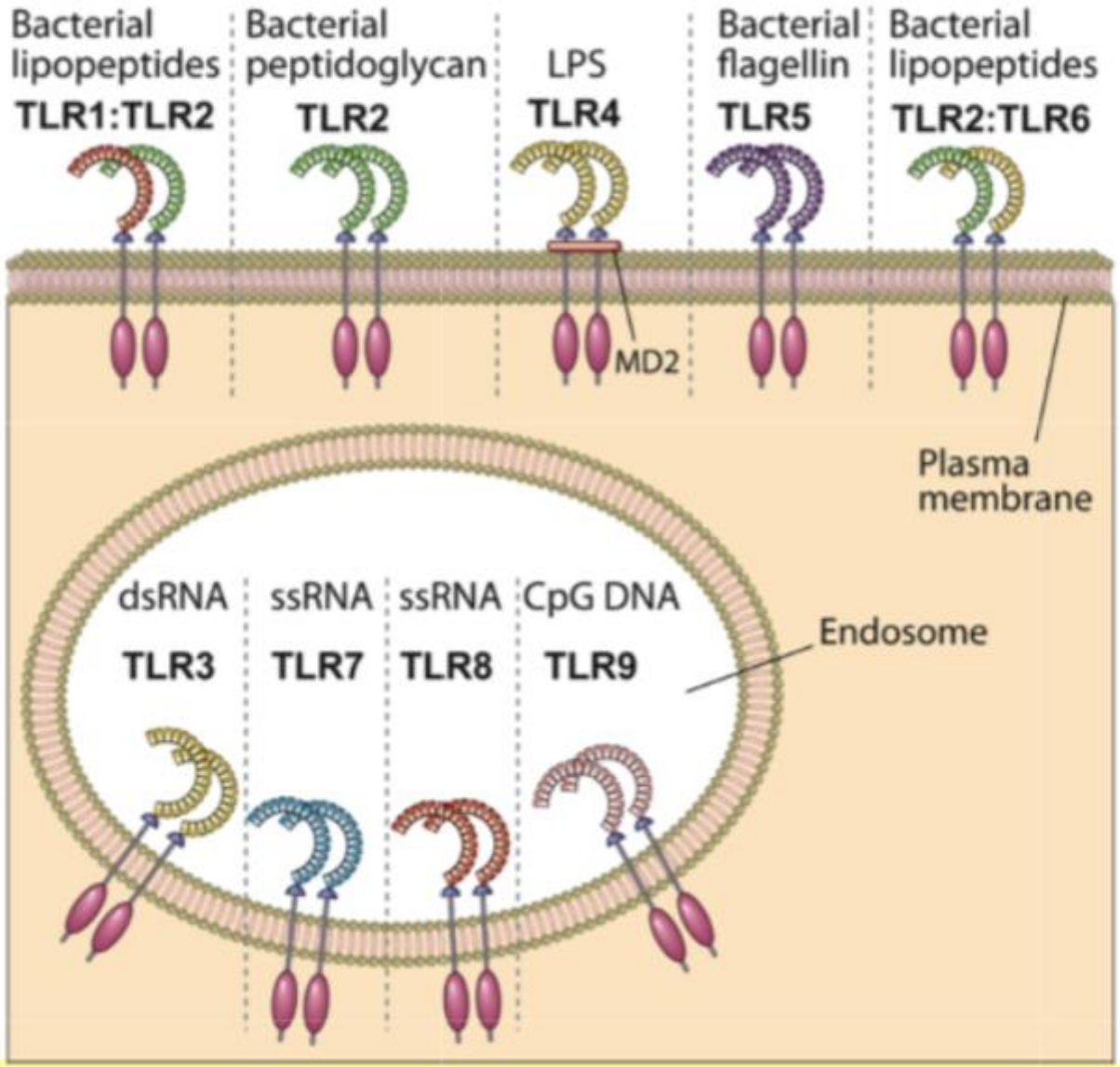
Fig. 4-1


Virus
Virally infected cell
Endosome
Cytosol
Replication
Microbial product (PAMP)
Pattern recognition receptor
Transcription factor
RNA
DNA
dsRNA
Autophagy
Nucleic acid "leakage"
dsRNA
5'P-RNA
dsDNA
MDA-5
RIG-I
DAI, others
TLR7, TLR8, TLR9
TLR3
IRF7
IRF1
IRF3
Nucleus
IFN-α, IFN-β


PAMPs
Various PAMPs and DAMPs
Cytosolic Flagellin
Cytosolic dsDNA
???
NOD-like Receptors (NLRs) - 3 Subfamilies
AIM2
Pyrin
NODs
NLRPs
IPAF
NOD1/NOD2 Signalosomes
NLRP1 Inflammasome
NLRP3/NALP3 Inflammasome
IPAF Inflammasome
AIM2 Inflammasome
RIP-2 Kinase
Caspase-1
ProIL-1β
IL-1β
NF-κB
MAPK
Inflammatory Response
Cell Death



Structure, Location, and Specificities of TLRs



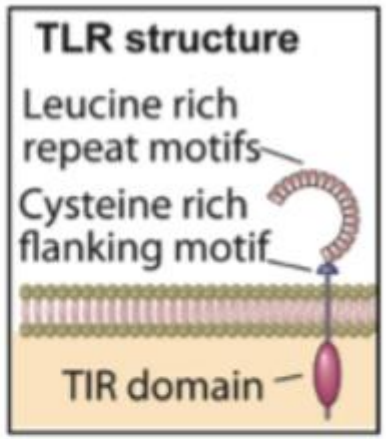
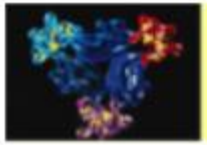


Fig. 4-2



Signaling functions of TLRs (1)

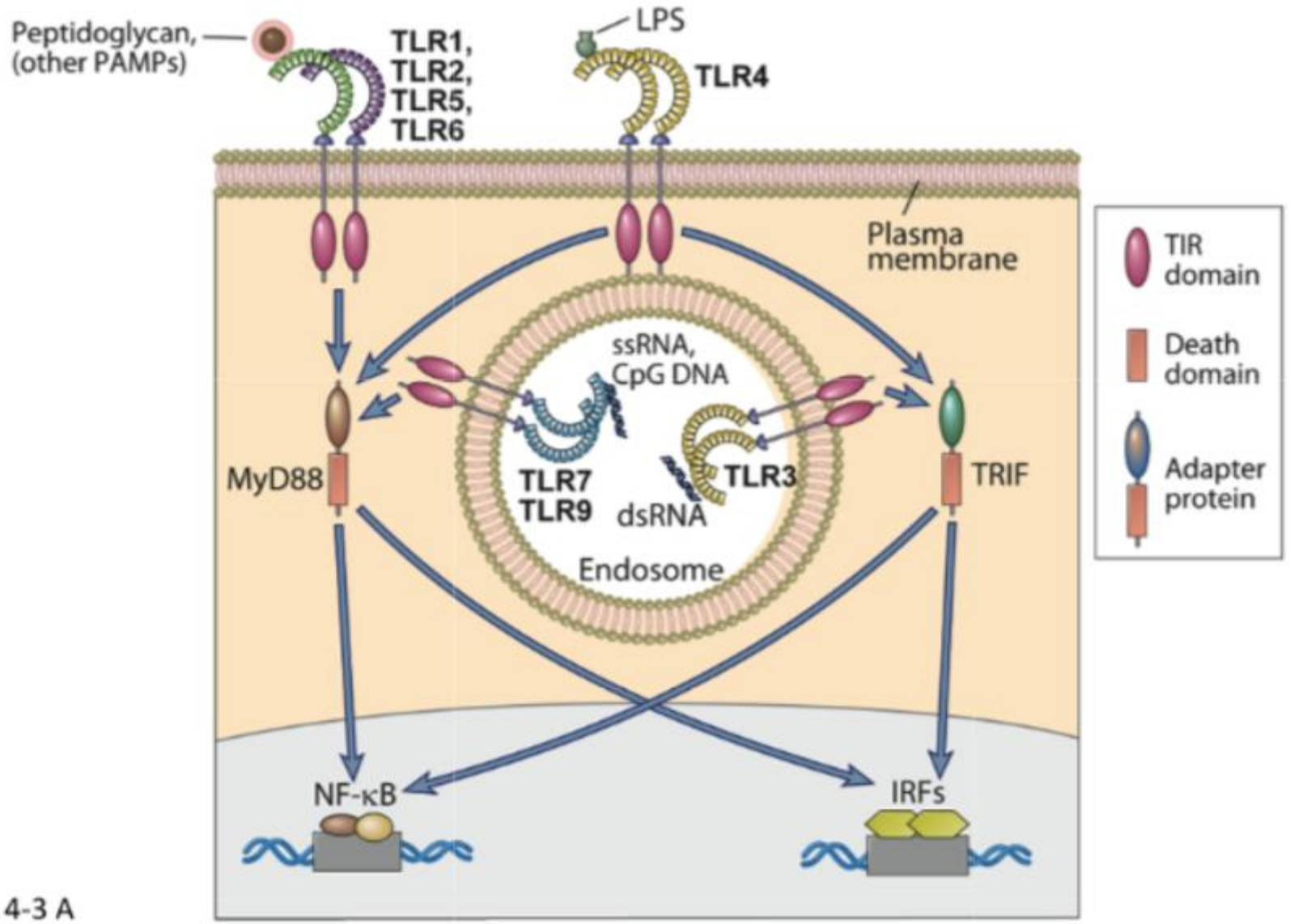
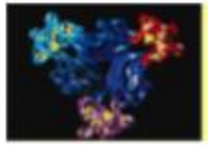
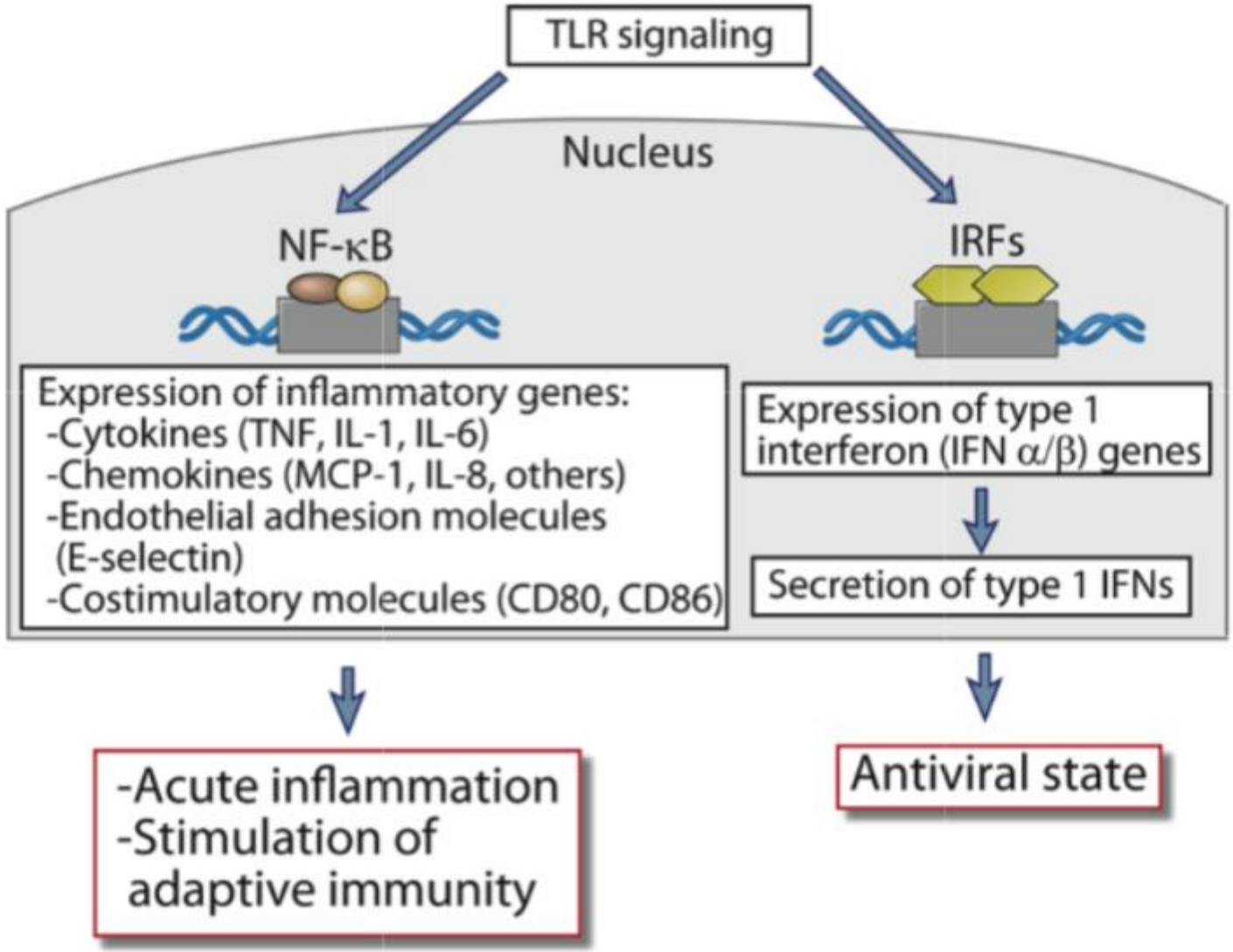


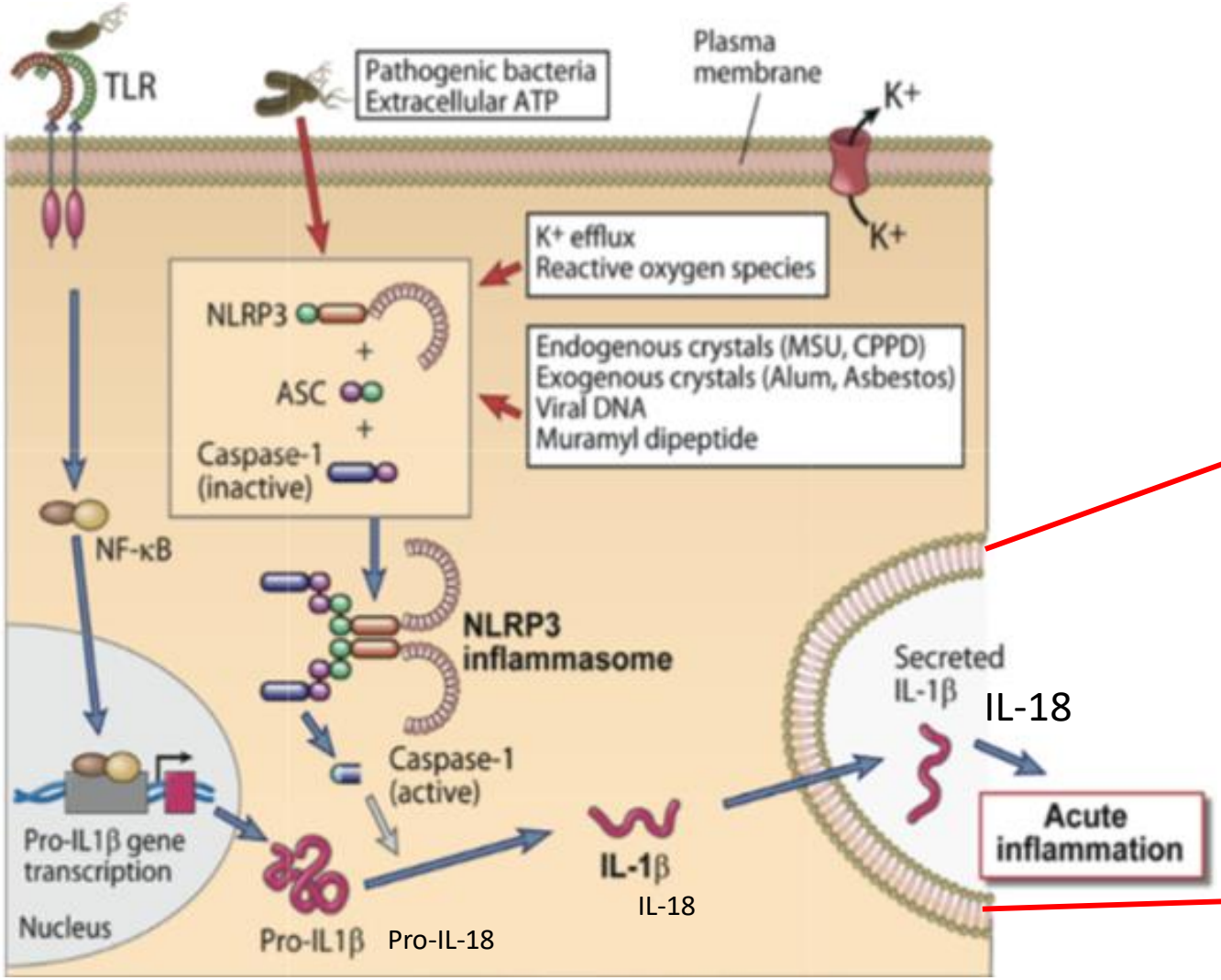
Fig. 4-3 A



Signaling functions of TLRs (2)



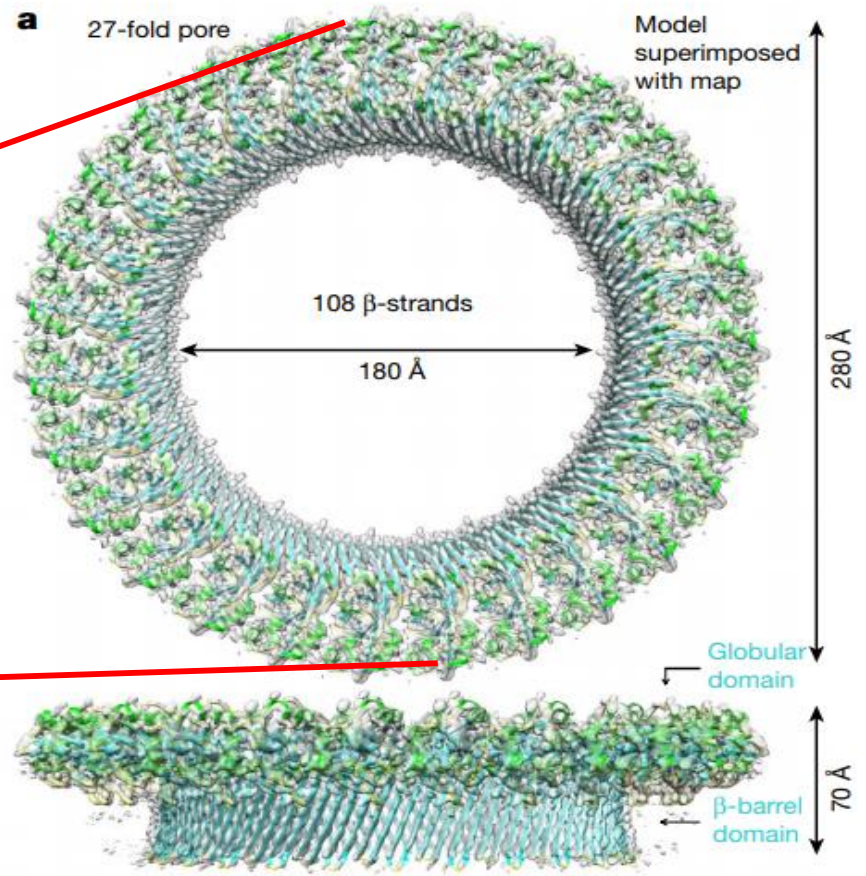
Inflamasoma, Gasdermina e Piroptose

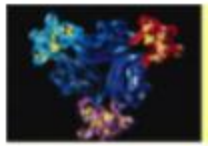


Cryo–EM structure of the gasdermin A3 membrane pore

Jianbin Ruan[1,2], Shiyu Xia[1,2], Xing Liu[1,3], Judy Lieberman[1,3] & Hao Wu[1,2]*

ten in mice, including three GSDMAs. GSDMs are cleaved by regulated processing that removes an inhibitory C-terminal fragment (GSDM-CT) to allow the N-terminal fragment (GSDM-NT) to bind to acidic lipids in the inner leaflet of mammalian cell membranes or on bacterial membranes to form pores. GSDMD is a substrate of inflam-

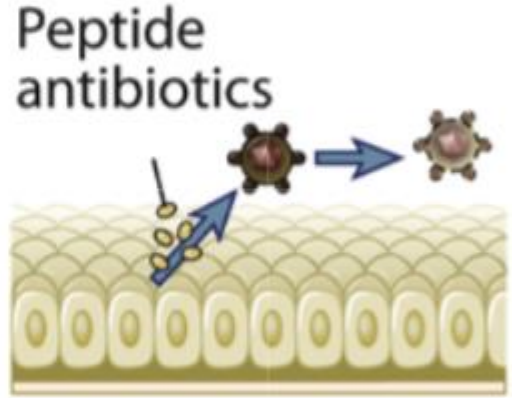




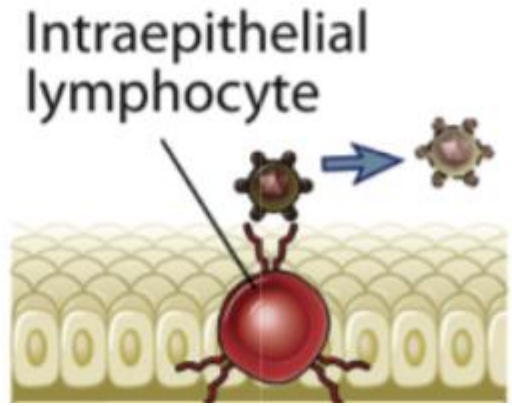
Epithelial Barriers

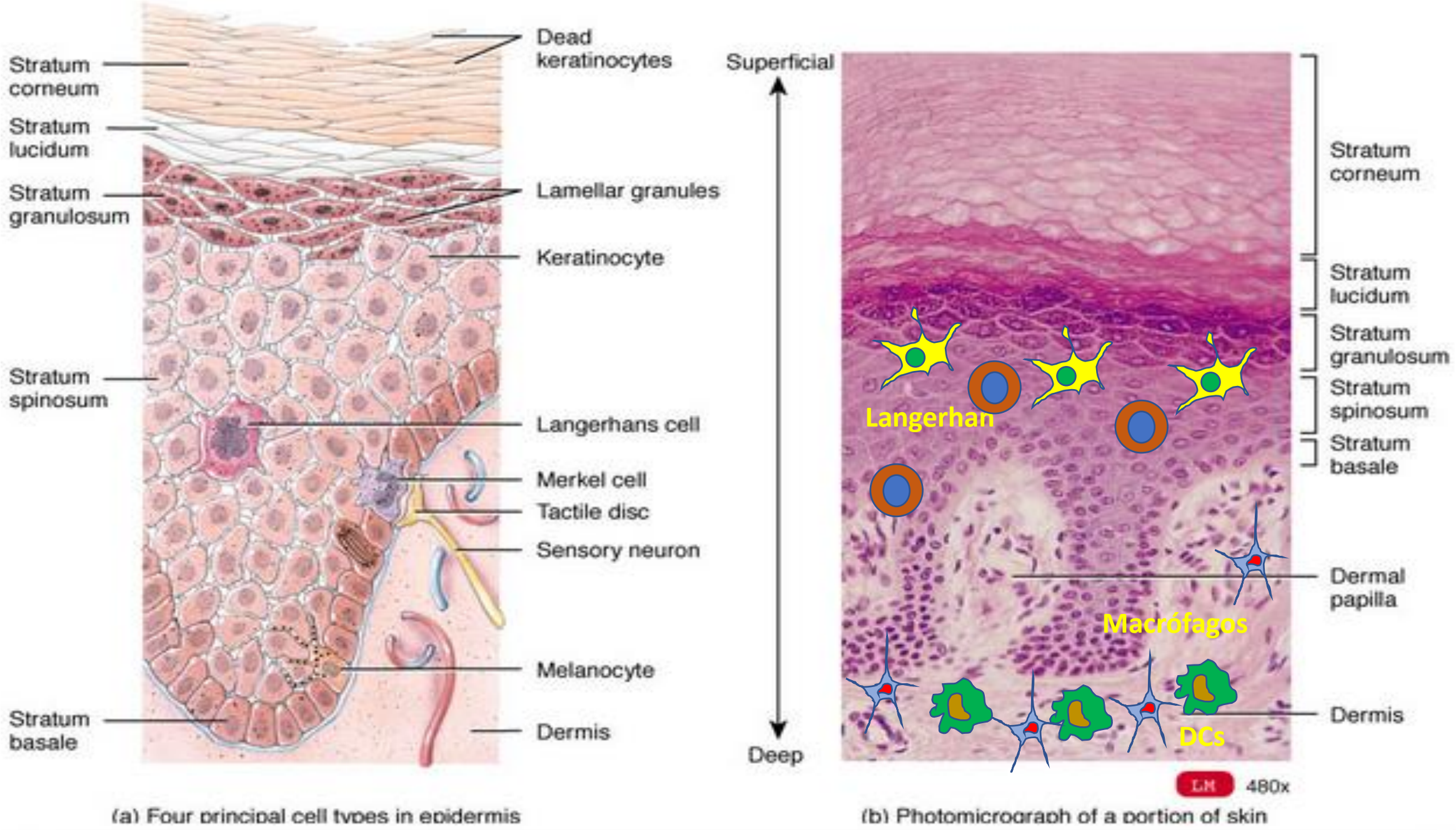
Physical barrier to infection

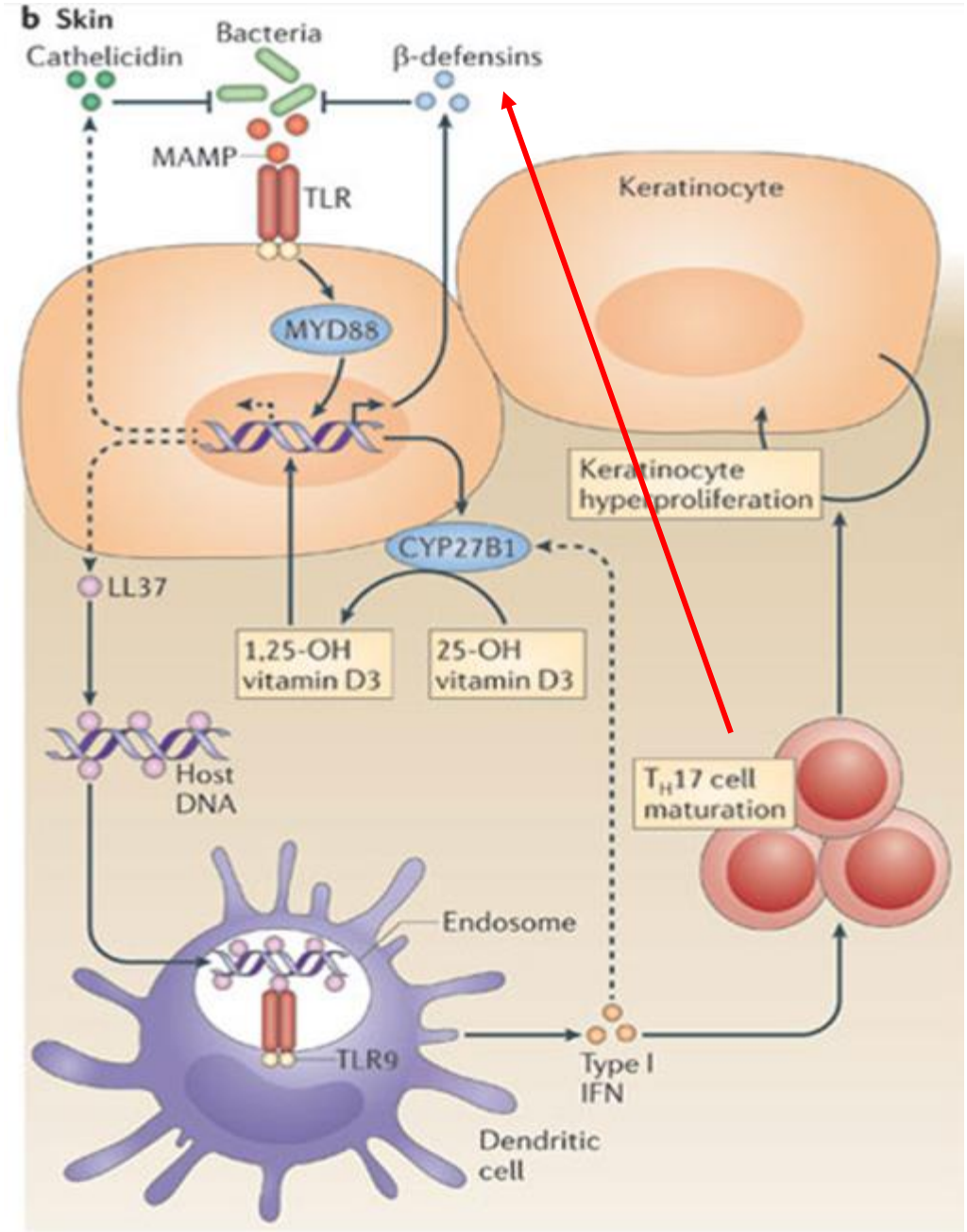
Killing of microbes by locally produced antibiotics, defensins, calthecidins



Killing of microbes and infected cells by intraepithelial lymphocytes

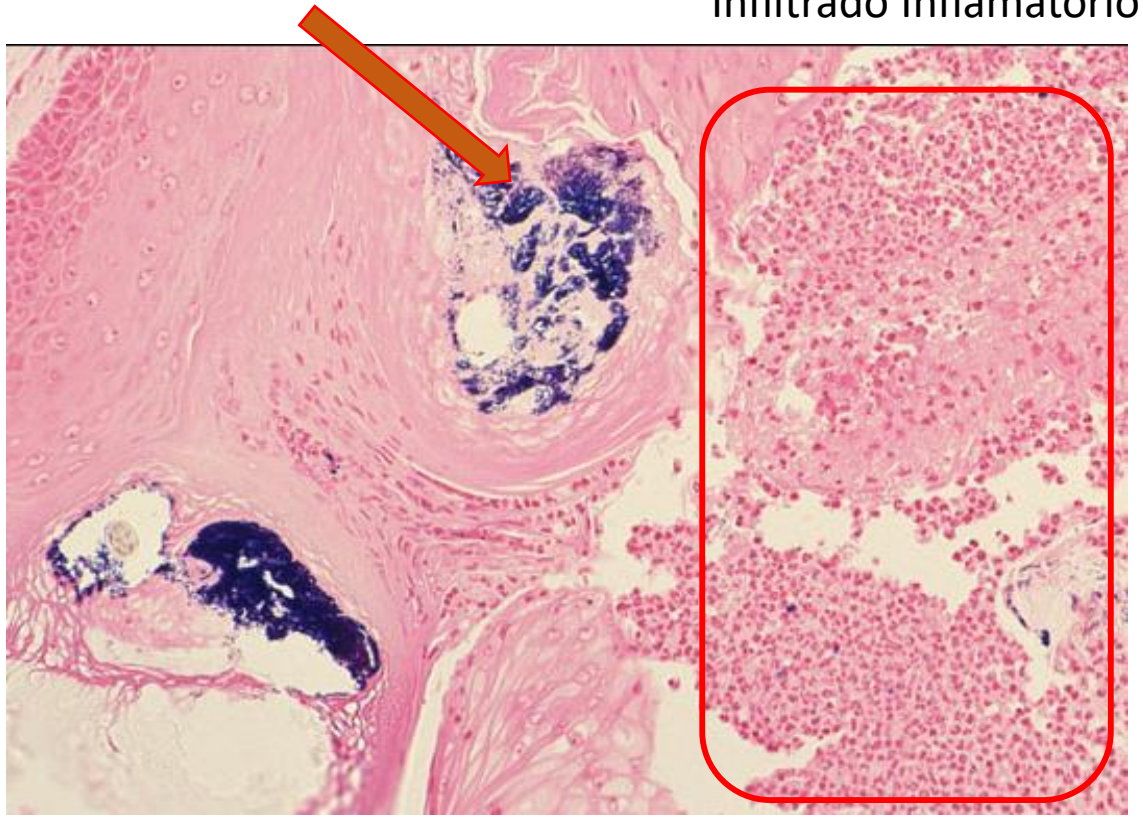


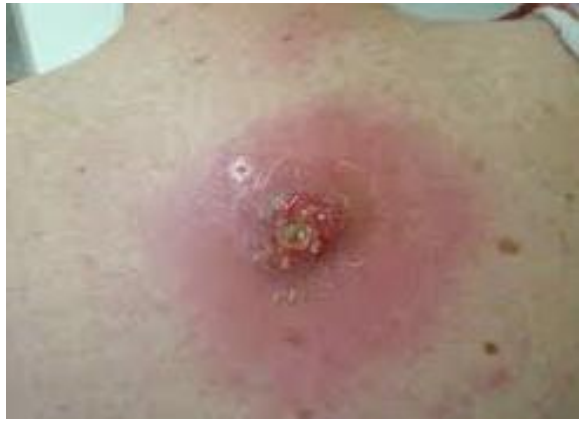

Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dead keratinocytes
Lamellar granules
Keratinocyte
Langerhans cell
Merkel cell
Tactile disc
Sensory neuron
Melanocyte
Dermis
(a) Four principal cell types in epidermis
Superficial
Deep
Langerhan
Macrófagos
DCs
Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermal papilla
Dermis
LM
480x
(b) Photomicrograph of a portion of skin



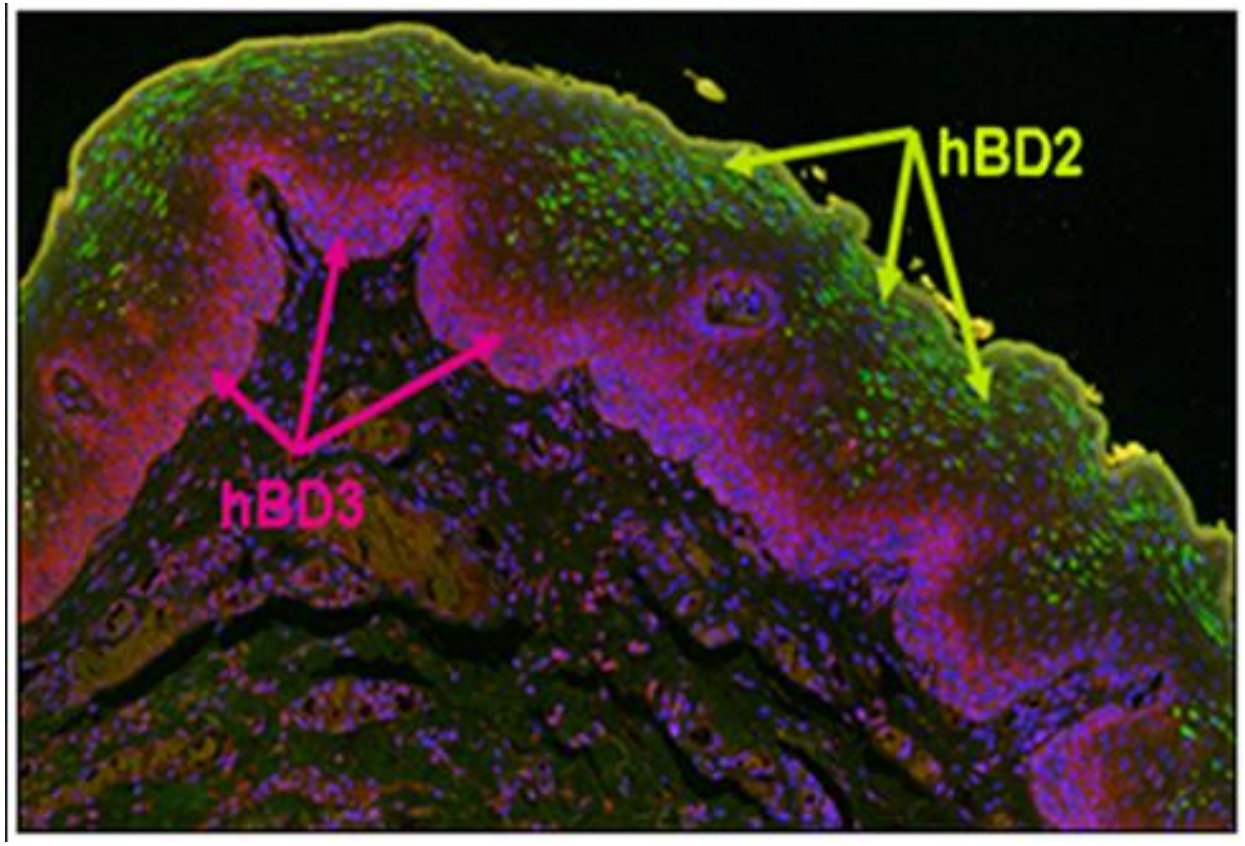
S aureus – Gram +

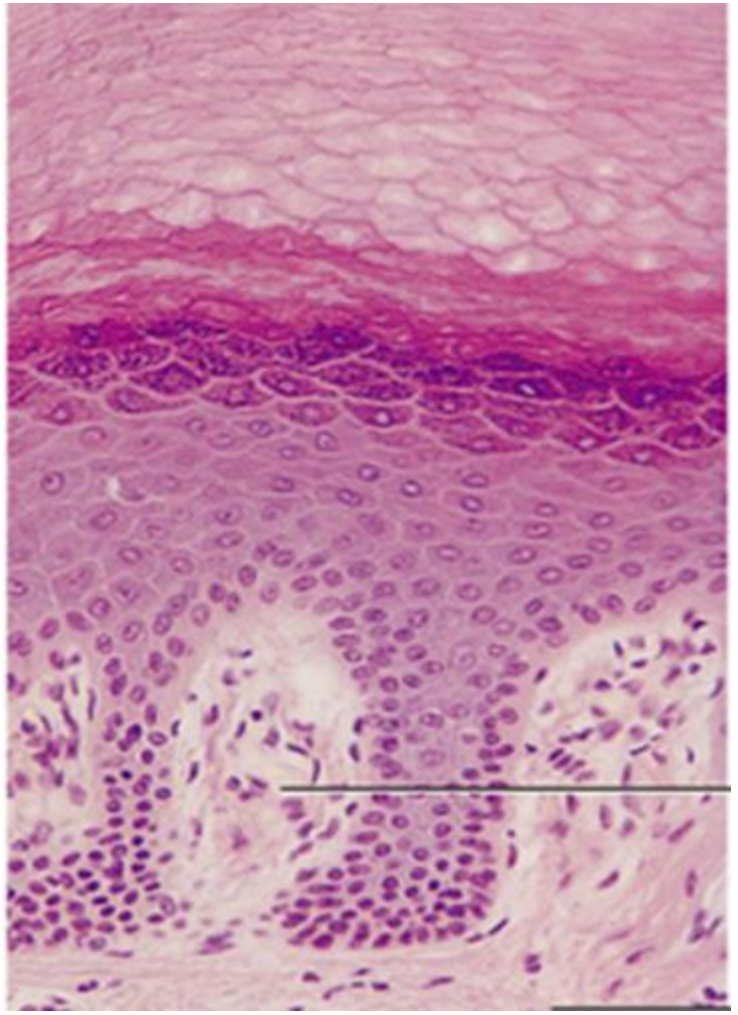
Infiltrado Inflamatório

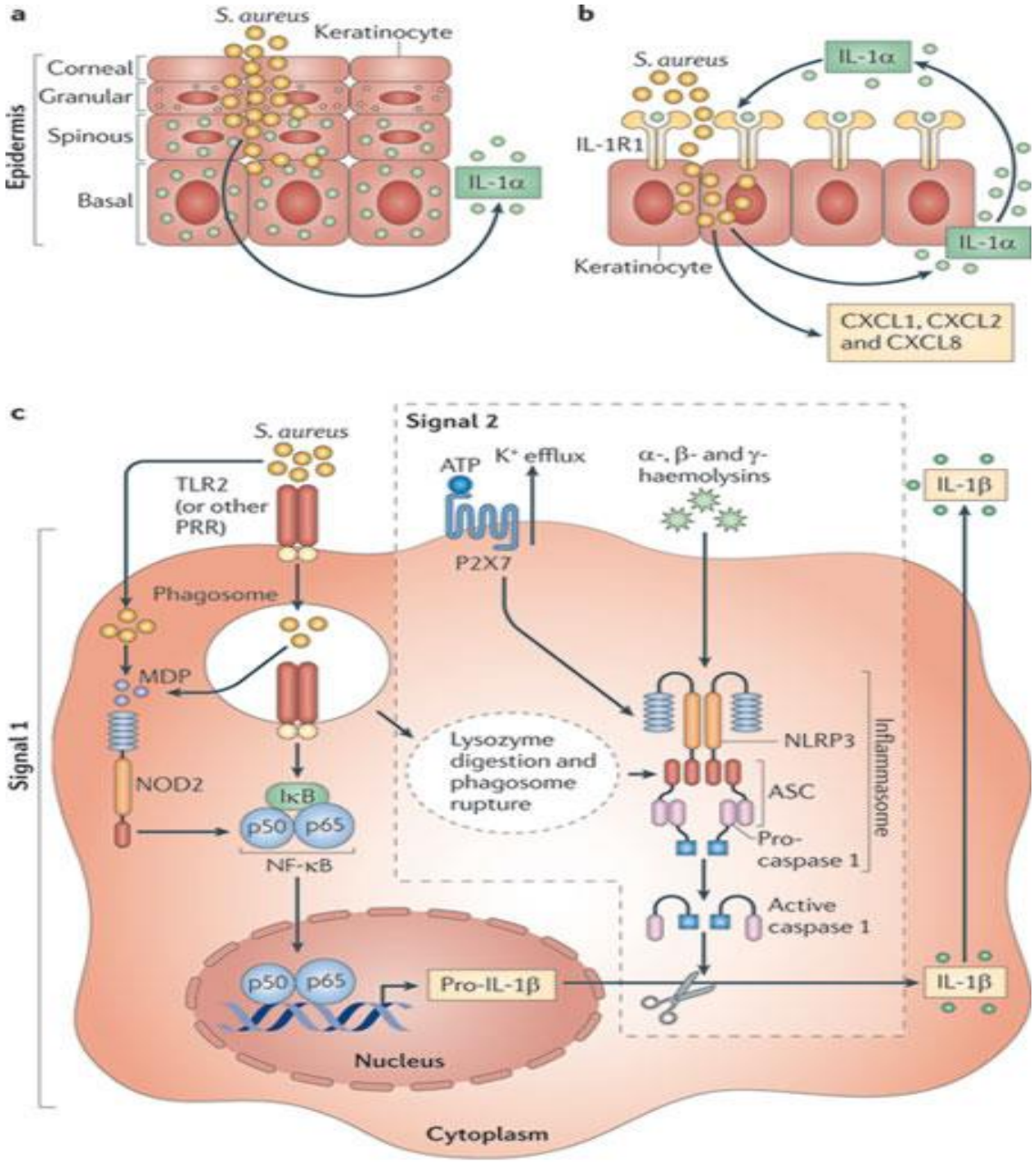




Human Beta-Defensina – hBD - Queratinócitos







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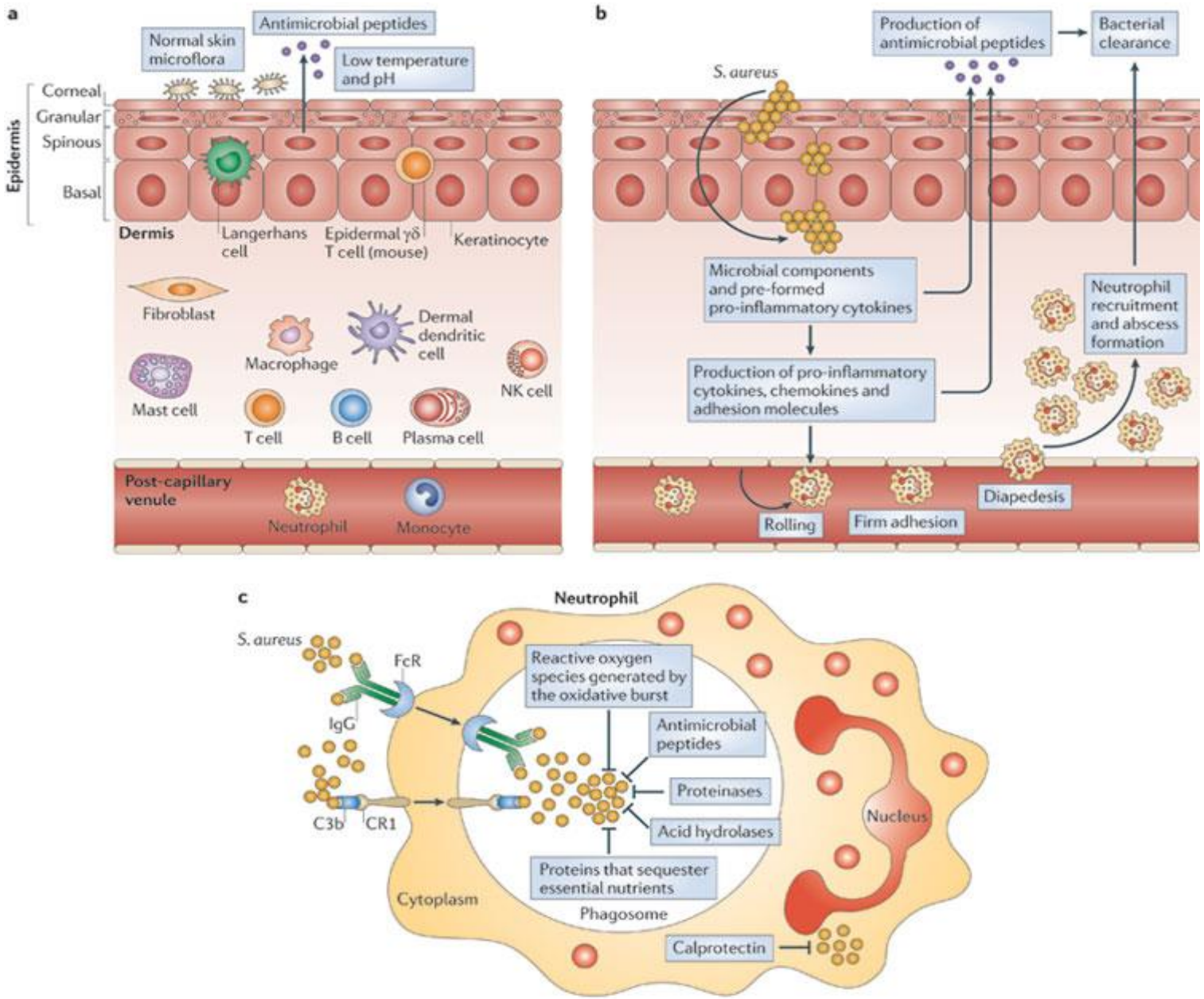

a
Normal skin microflora
Antimicrobial peptides
Low temperature and pH
Epidermis
Corneal
Granular
Spinous
Basal
Dermis
Langerhans cell
Epidermal γδ T cell (mouse)
Keratinocyte
Fibroblast
Macrophage
Dermal dendritic cell
NK cell
Mast cell
T cell
B cell
Plasma cell
Post-capillary venule
Neutrophil
Monocyte
b
Production of antimicrobial peptides
Bacterial clearance
S. aureus
Microbial components and pre-formed pro-inflammatory cytokines
Neutrophil recruitment and abscess formation
Production of pro-inflammatory cytokines, chemokines and adhesion molecules
Diapedesis
Rolling
Firm adhesion
c
Neutrophil
S. aureus
FcR
IgG
C3b
CR1
Reactive oxygen species generated by the oxidative burst
Antimicrobial peptides
Proteinases
Acid hydrolases
Proteins that sequester essential nutrients
Cytoplasm
Phagosome
Nucleus
Calprotectin

Phagocytosis and Killing of Microbes

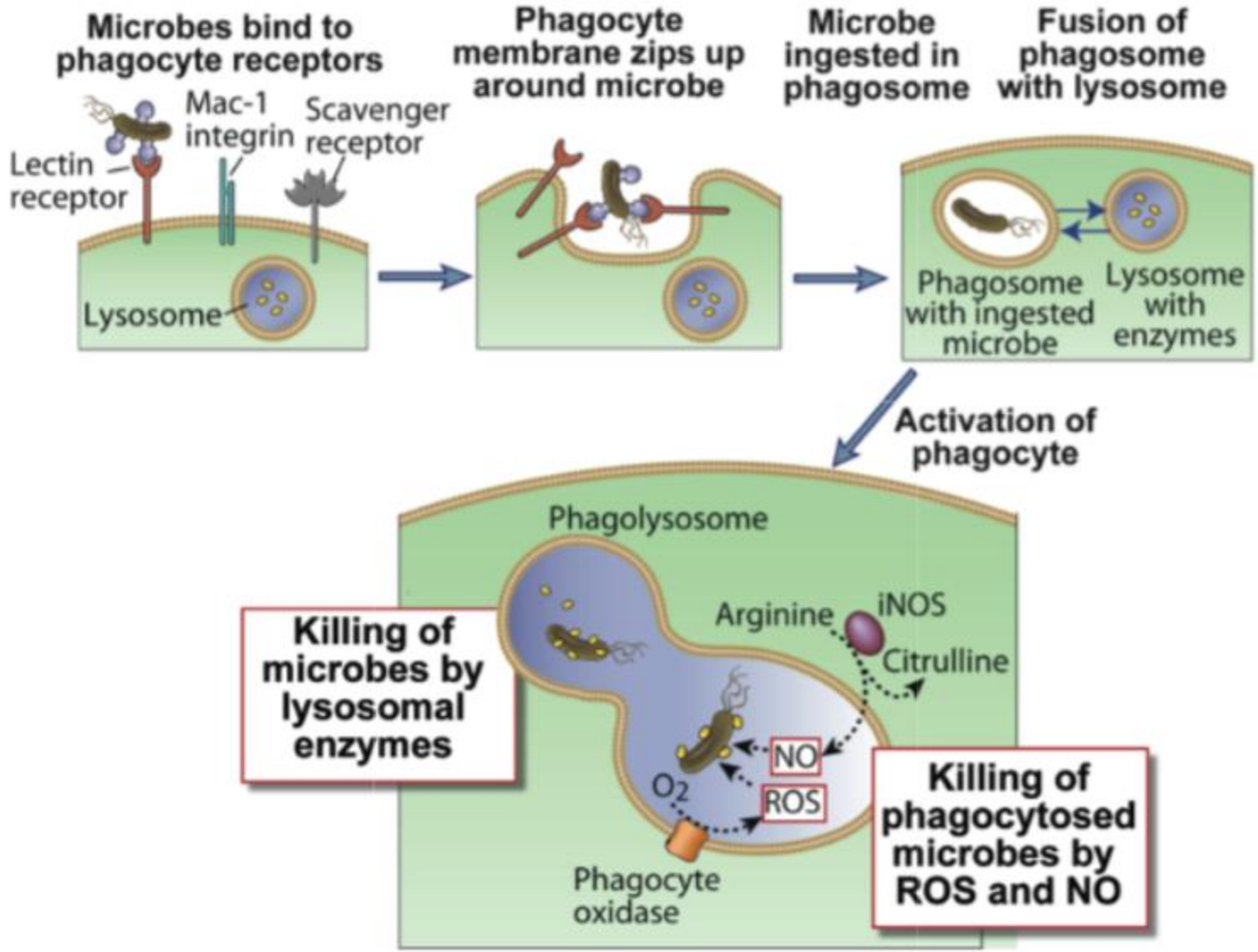
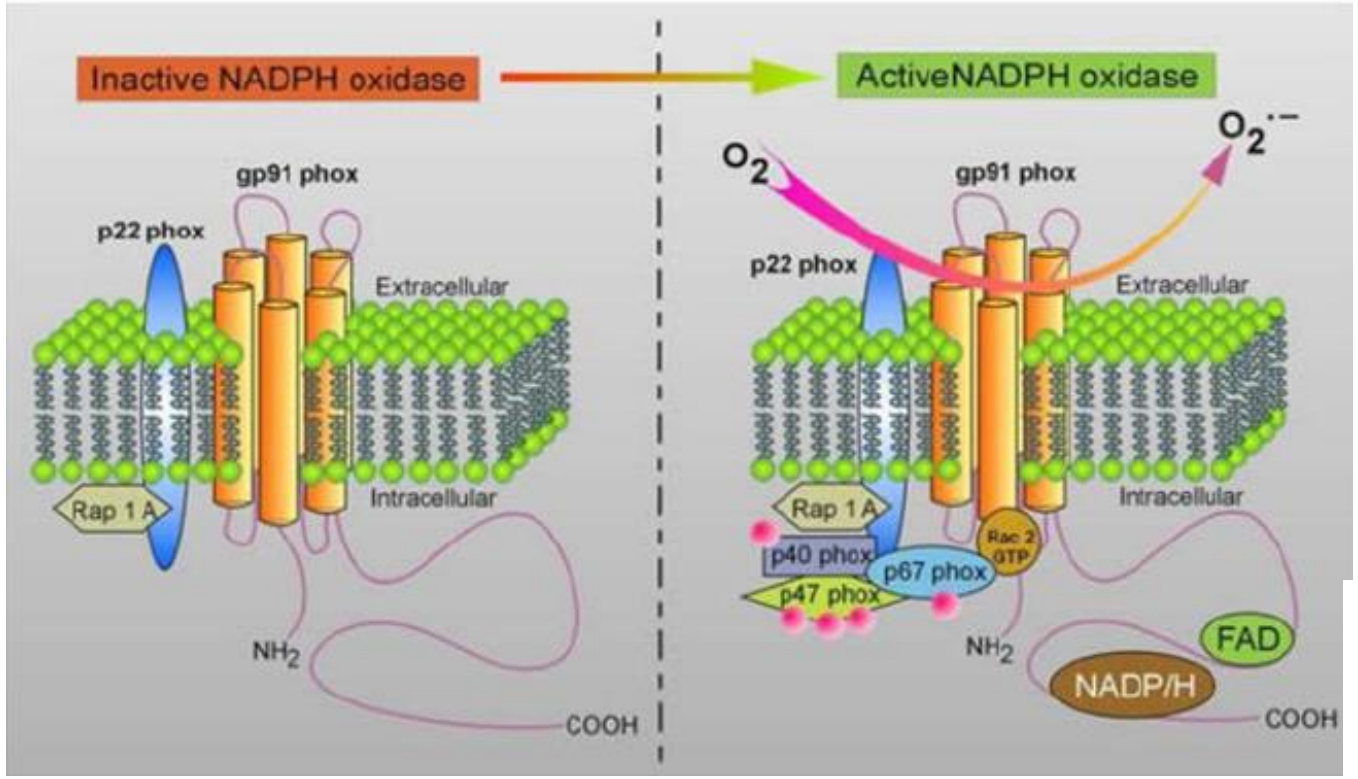
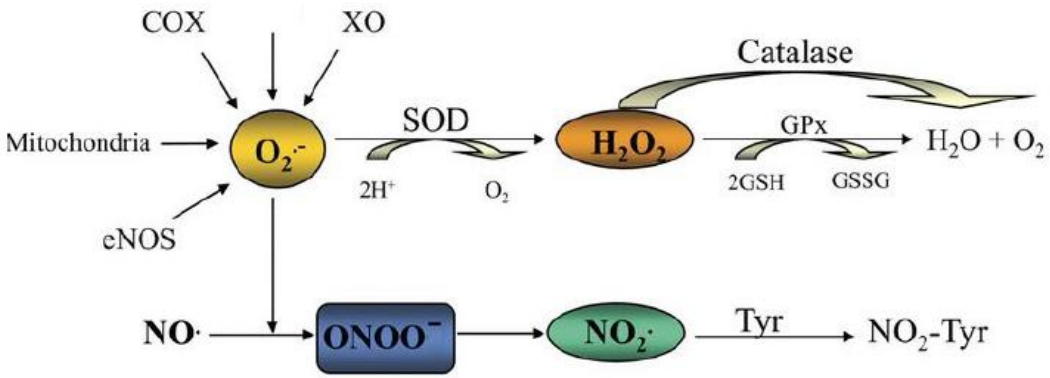


Fig. 4-12

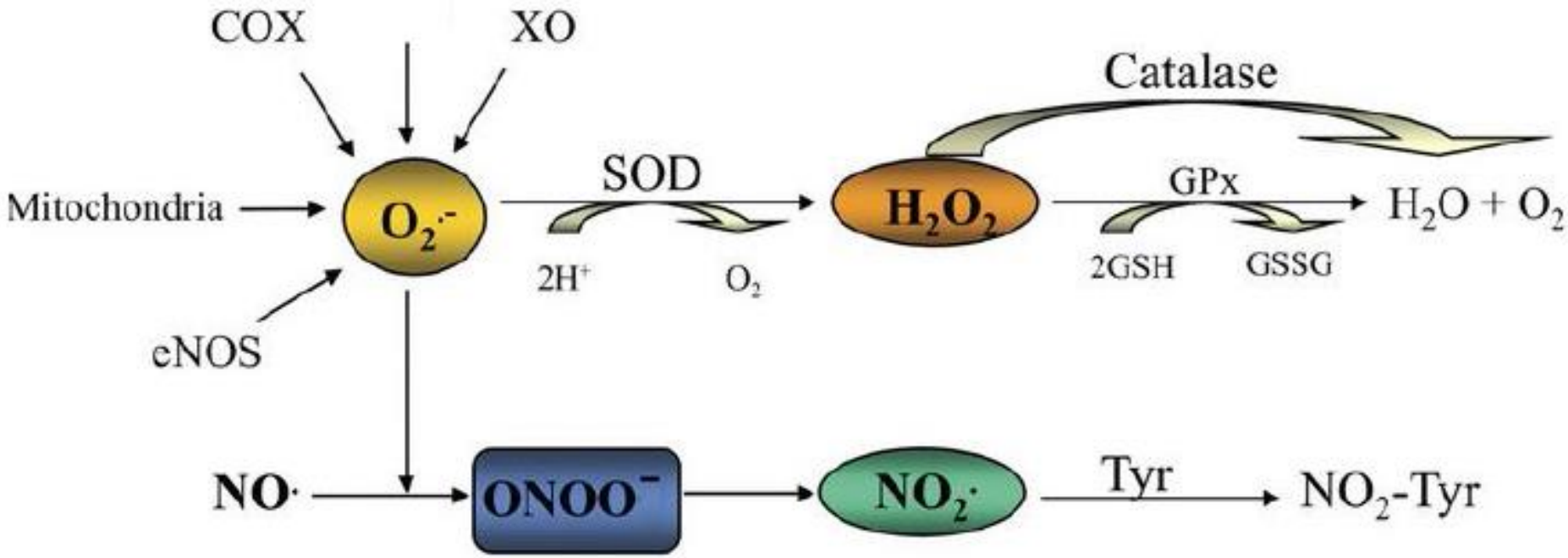


NADPH Oxidase



XO: xanthine oxidase
Nox: NADPH oxidase
$O_2^{\cdot-}$: superoxide anion
SOD: superoxide dismutase
H_2O_2: hydrogen peroxide
GPx: gluthatione peroxidase
GSH: reduced gluthatione
GSSG: oxidized gluthatione
NO·: nitric oxide
$ONOO^-$: peroxynitrite
$NO_2\cdot$: nitrogen dioxide
NO_2-Tyr: nitrotyrosine

NADPH Oxidase



XO: xanthine oxidase

SOD: superoxide dismutase

GSH: reduced gluthatione

$ONOO^-$: peroxynitrite

Nox: NADPH oxidase

H_2O_2: hydrogen peroxide

GSSG: oxidized gluthatione

NO_2·: nitrogen dioxide

$O_2^{\cdot-}$: superoxide anion

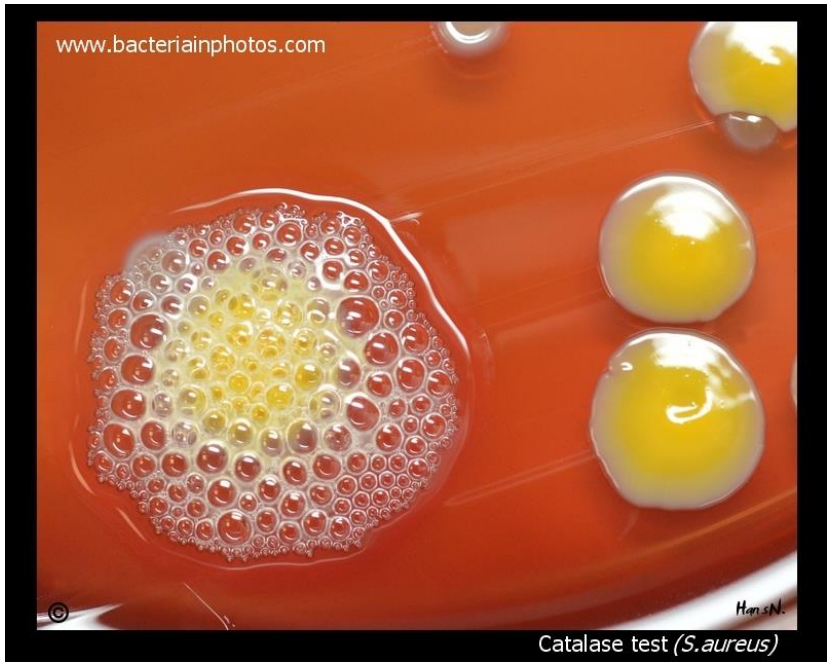
GPx: gluthatione peroxidase

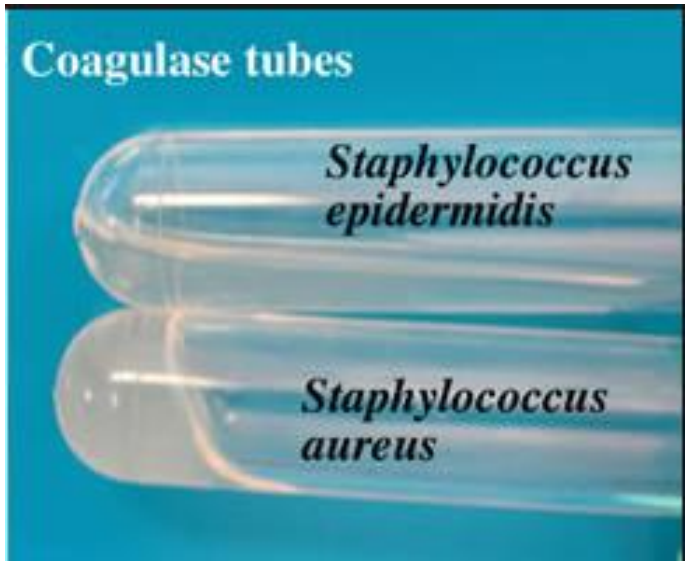
NO·: nitric oxide

NO_2-Tyr: nitrotyrosine

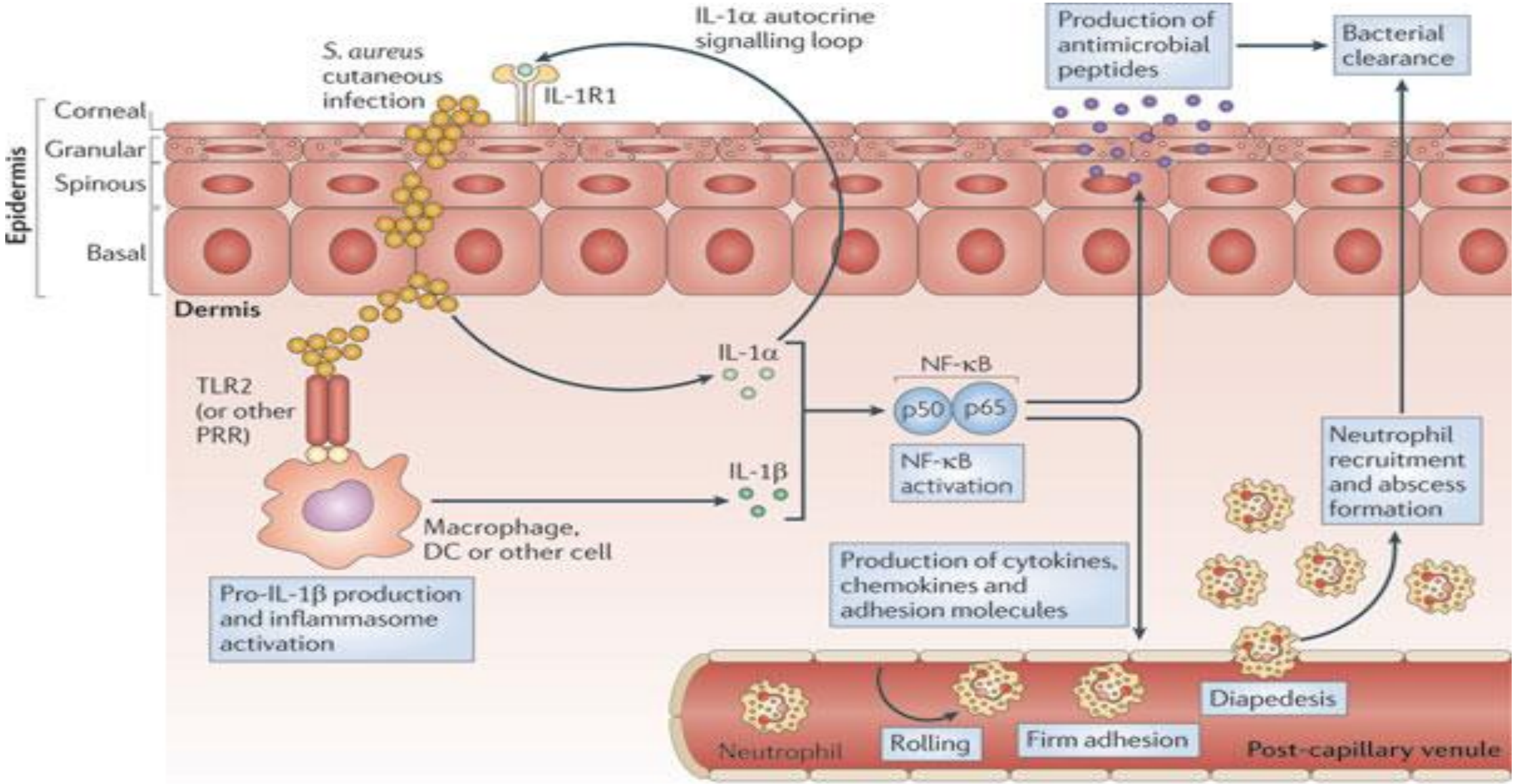
TABLE 15–2 Mechanisms of Immune Evasion by Bacteria

Mechanism of Immune Evasion	Examples
Extracellular bacteria	
Antigenic variation	*Neisseria gonorrhoeae, Escherichia coli, Salmonella typhimurium*
Inhibition of complement activation	Many bacteria
Resistance to phagocytosis	Pneumococcus
Scavenging of reactive oxygen species	Catalase-positive staphylococci
Intracellular bacteria	
Inhibition of phagolysosome formation	*Mycobacterium tuberculosis, Legionella pneumophila*
Inactivation of reactive oxygen and nitrogen species	*Mycobacterium leprae* (phenolic glycolipid)
Disruption of phagosome membrane, escape into cytoplasm	*Listeria monocytogenes* (hemolysin protein)





Fibrinogênio - fibrina



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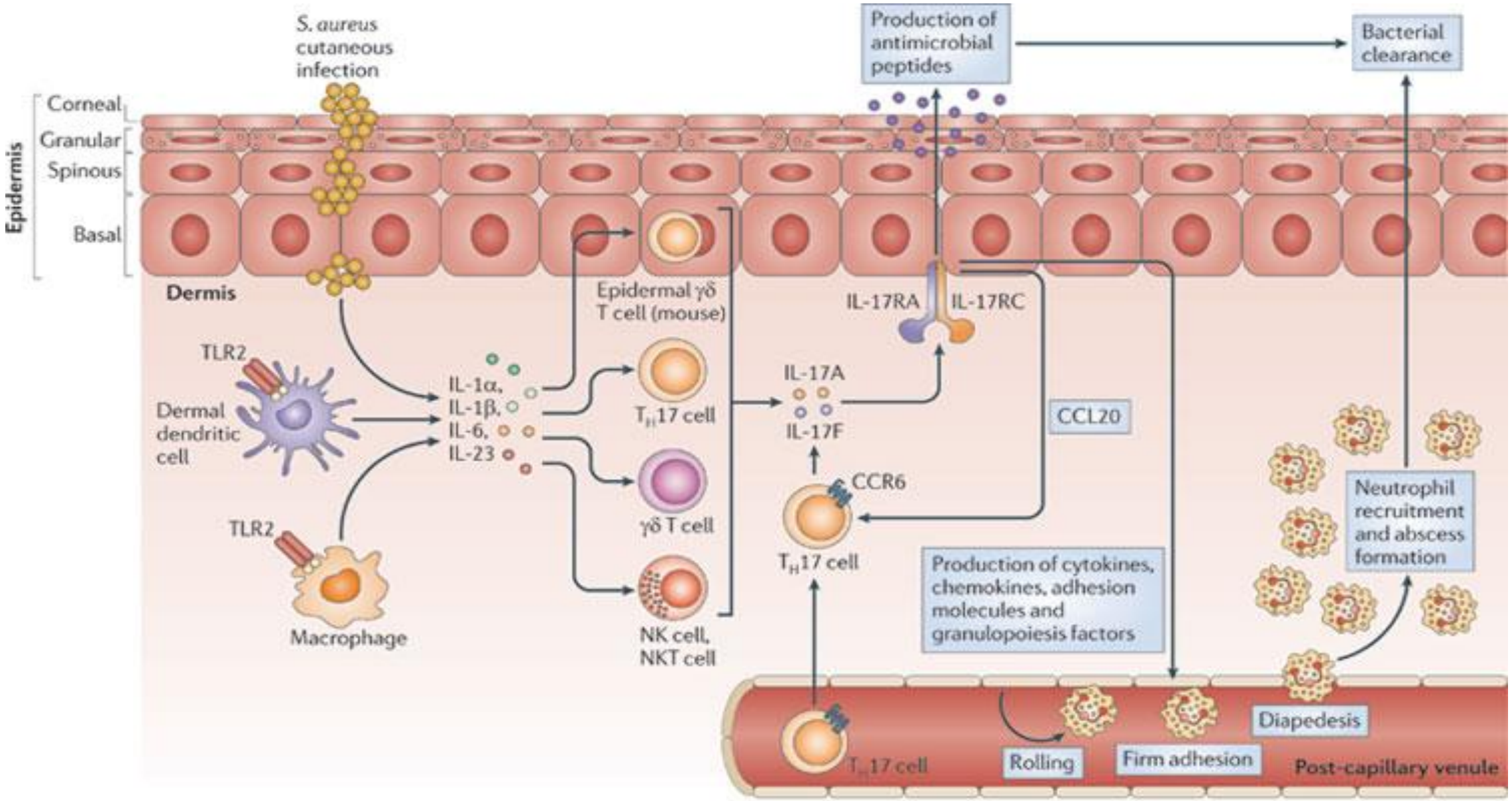
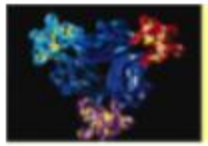

S. aureus cutaneous infection
Production of antimicrobial peptides
Bacterial clearance
Epidermis
Corneal
Granular
Spinous
Basal
Dermis
Epidermal γδ T cell (mouse)
IL-17RA
IL-17RC
TLR2
Dermal dendritic cell
IL-1α, IL-1β, IL-6, IL-23
TH17 cell
IL-17A
IL-17F
CCL20
γδ T cell
CCR6
TH17 cell
TLR2
Macrophage
NK cell, NKT cell
Production of cytokines, chemokines, adhesion molecules and granulopoiesis factors
Neutrophil recruitment and abscess formation
Diapedesis
TH17 cell
Rolling
Firm adhesion
Post-capillary venule



Effector Functions of Macrophages

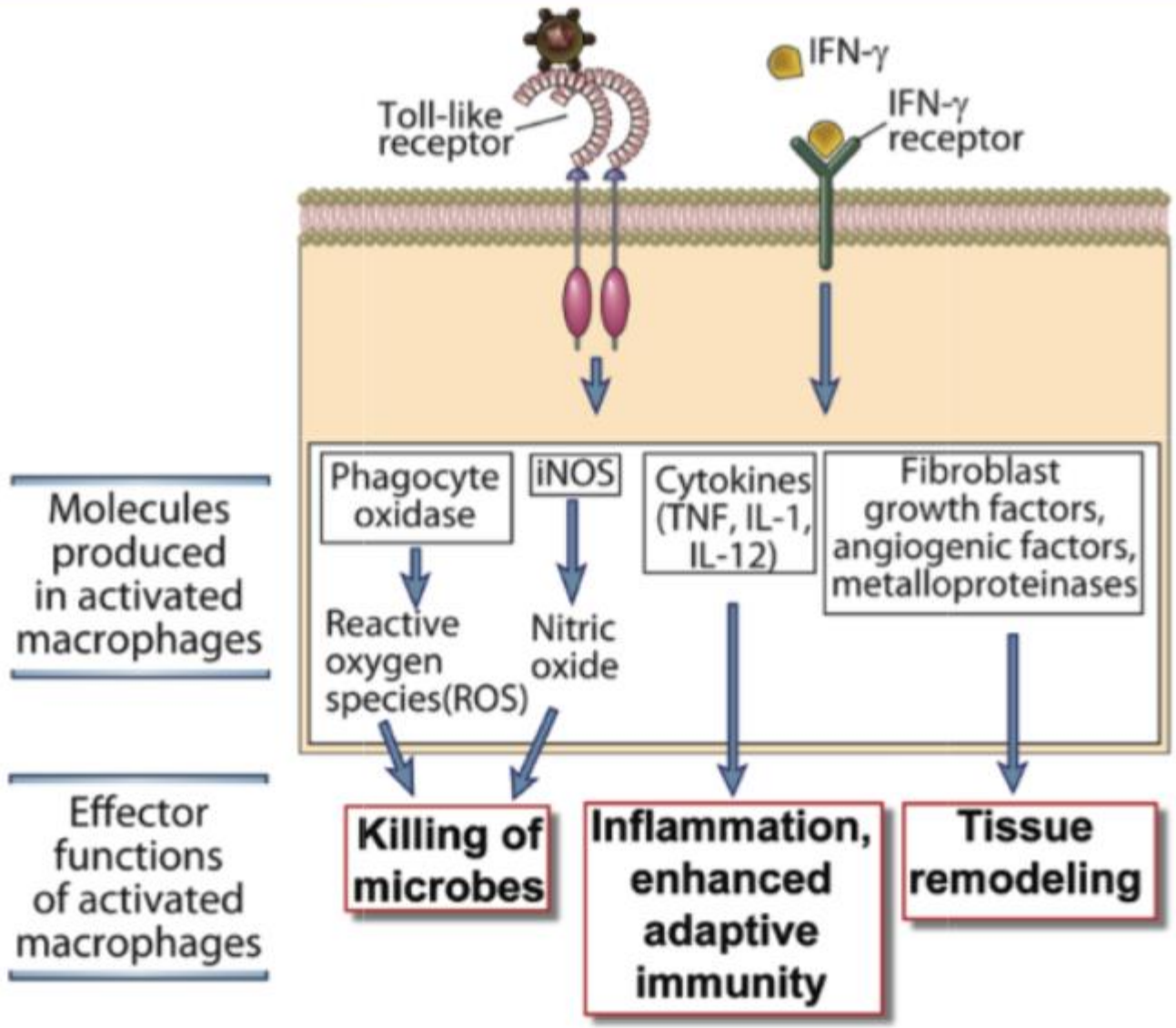
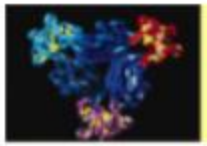


Fig. 4-13



Biologic Actions of Type I Interferons (2)

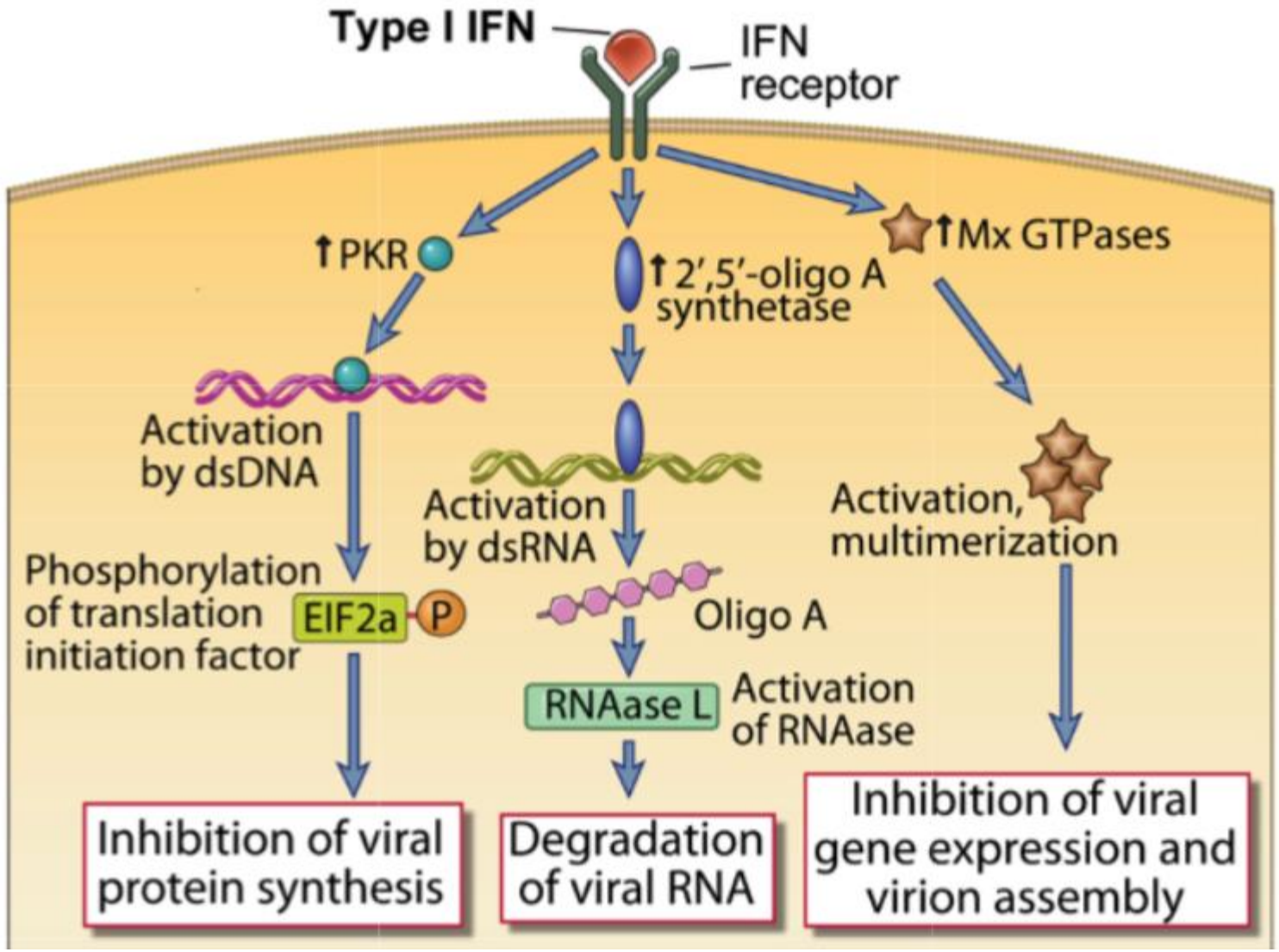
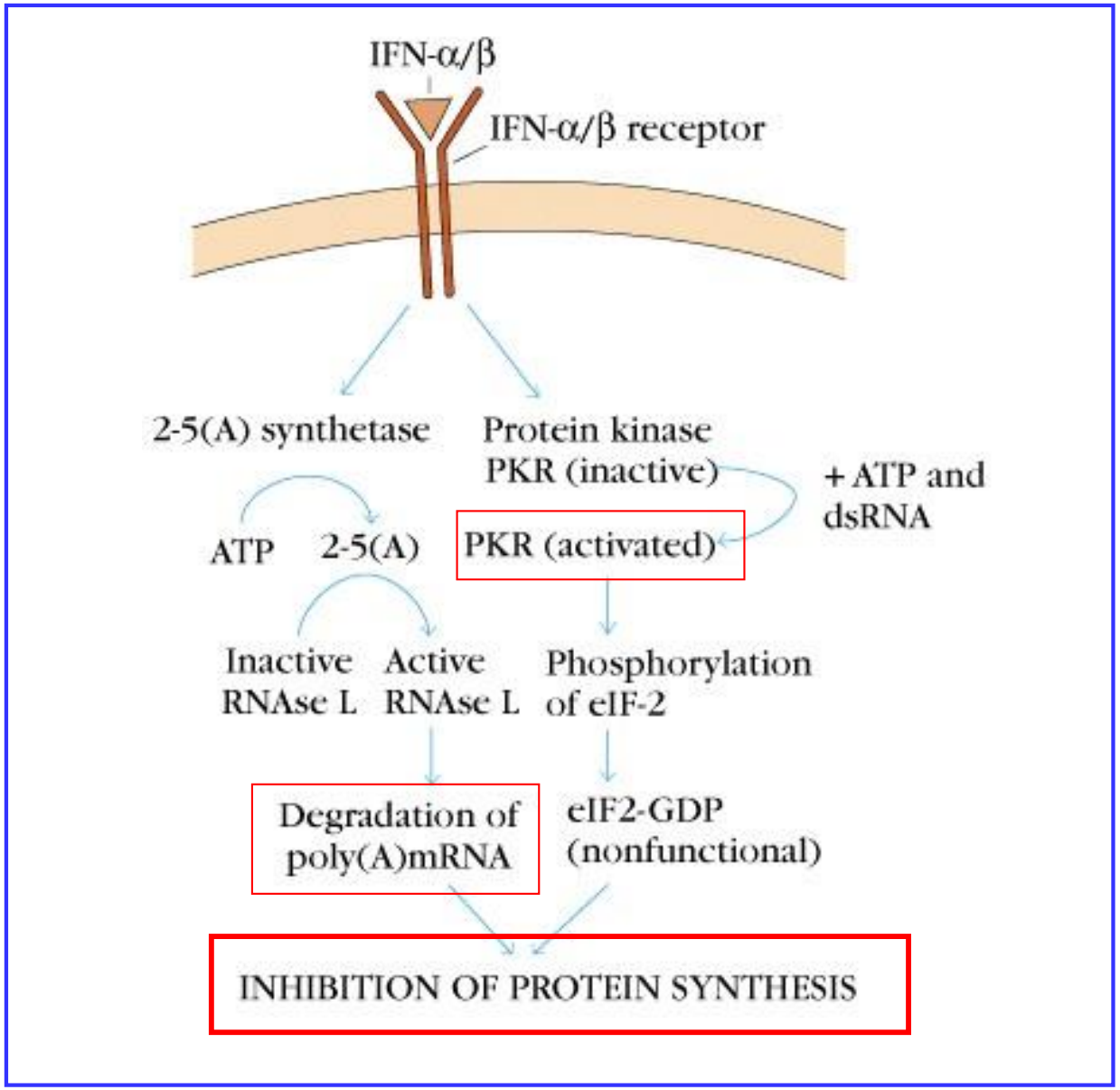
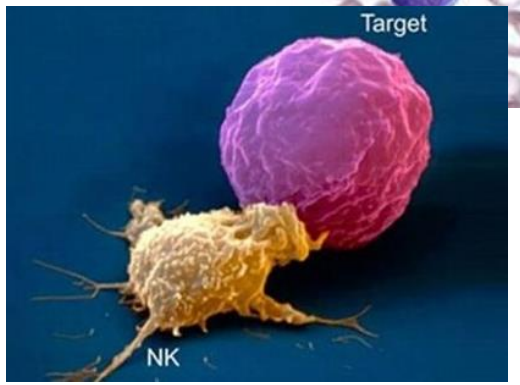


Fig. 4-15

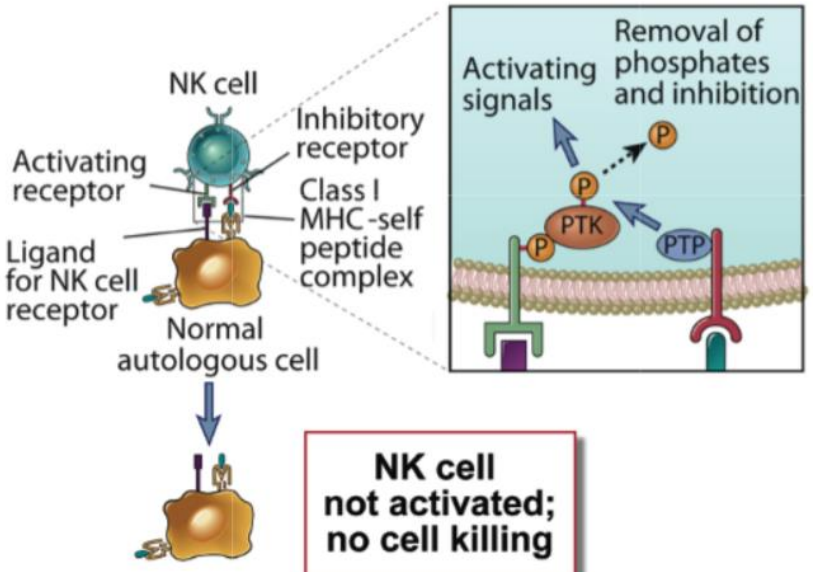
Ação antiviral do IFNα/β



Natural Killer Cells



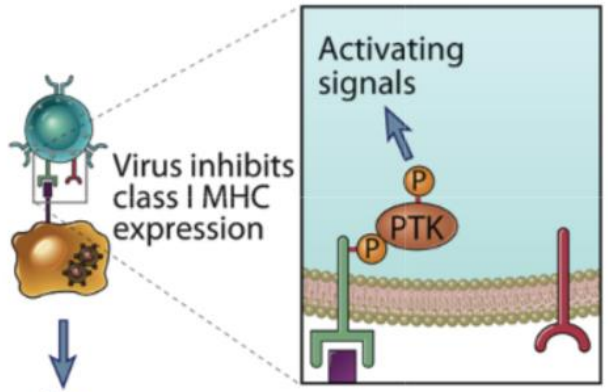
Inhibitory receptor engaged



NK cell not activated; no cell killing

ALIVE

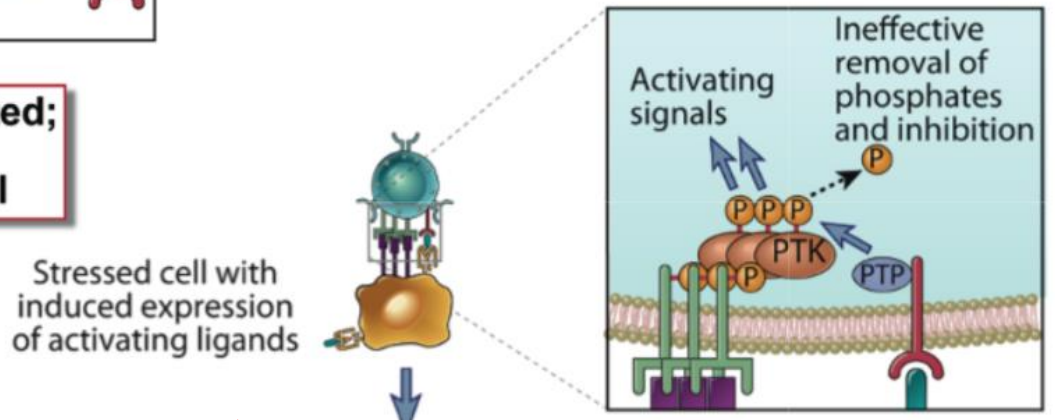
Inhibitory receptor not engaged



NK cell activated; killing of infected cell

DEAD

Multiple activating receptors engaged



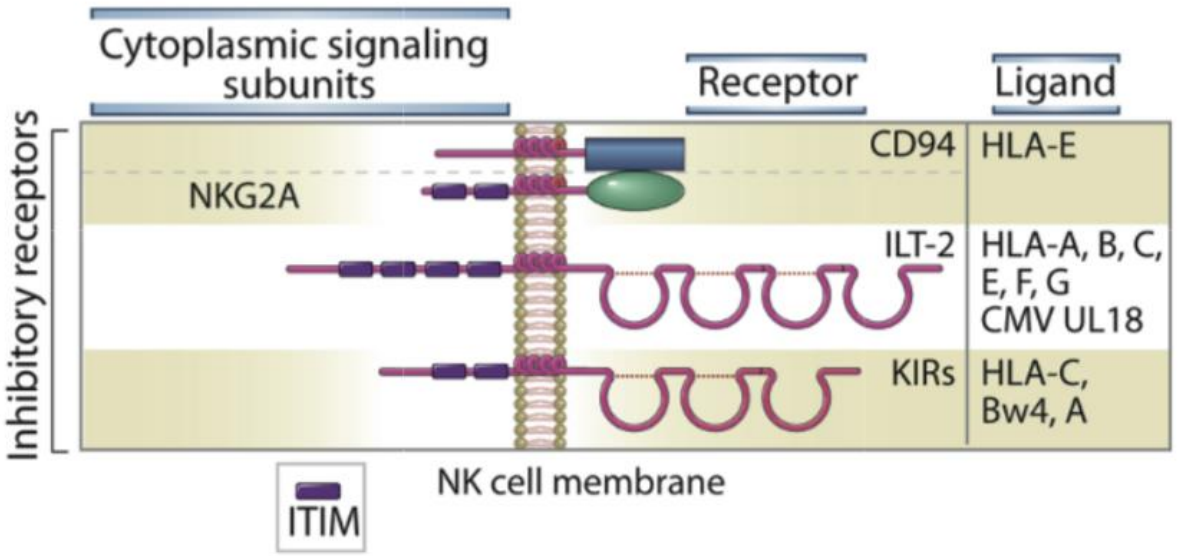
DEAD

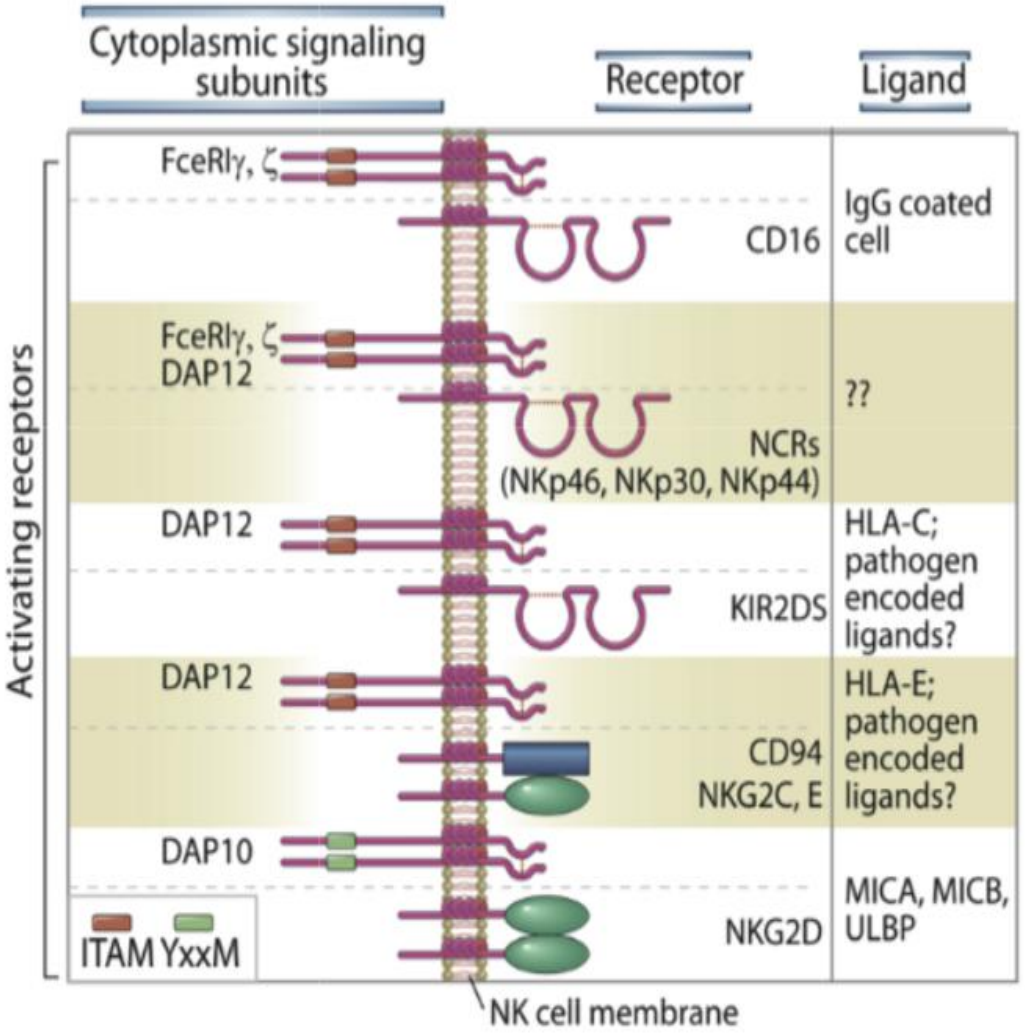
NK cell activated; killing of stressed cell

Fosfatases Vs Quinases

Sobrevivência

Morte



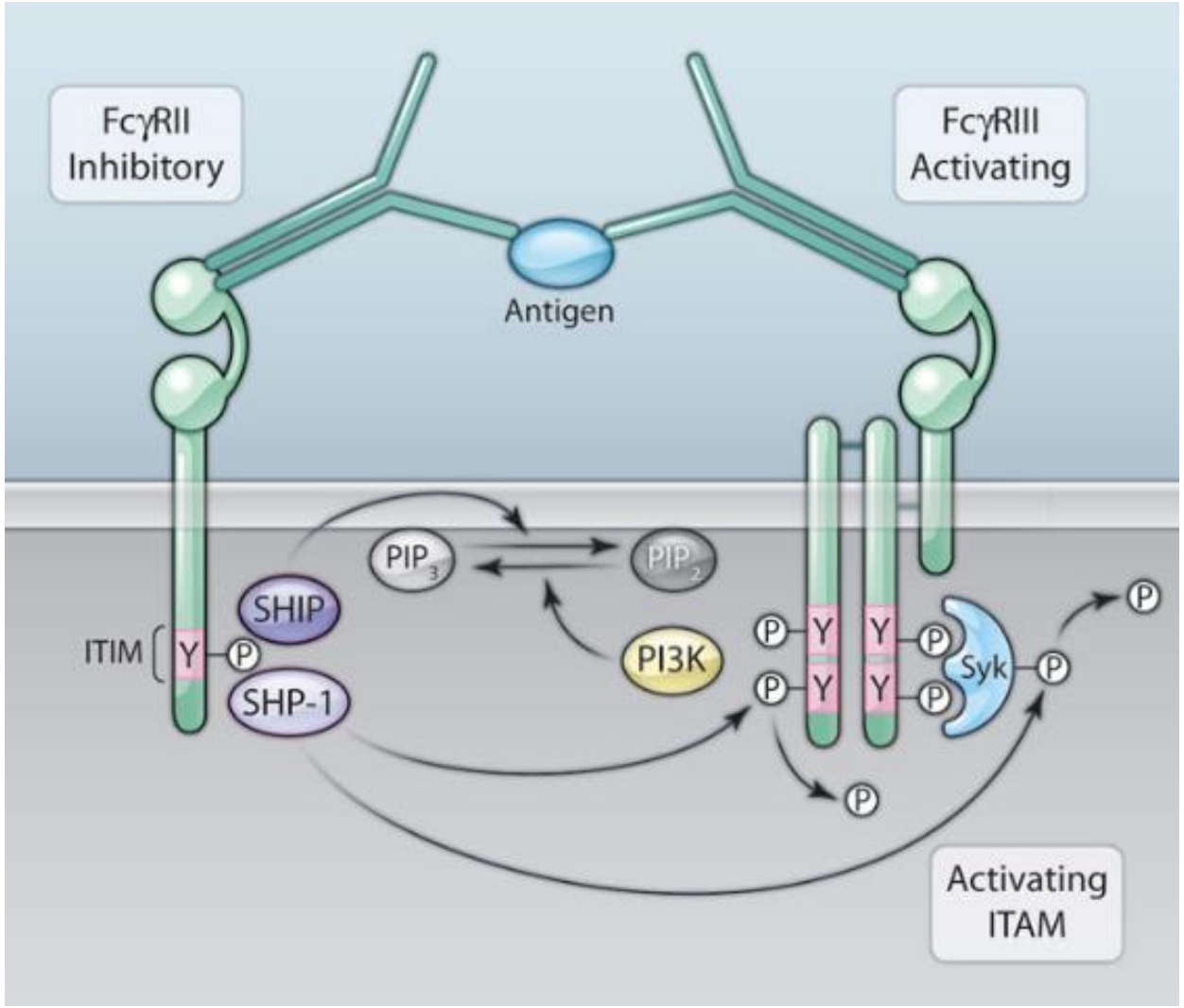


NKS – importantes contra infecções virais e tumores

Immunereceptor Tyrosine Inhibitory Motif (ITIMs)
Vs.
Immunereceptor Tyrosine Activation Motif (ITAMs)

SHP-1 and SHP-2

Fosfatases



Syk Lck Fyn

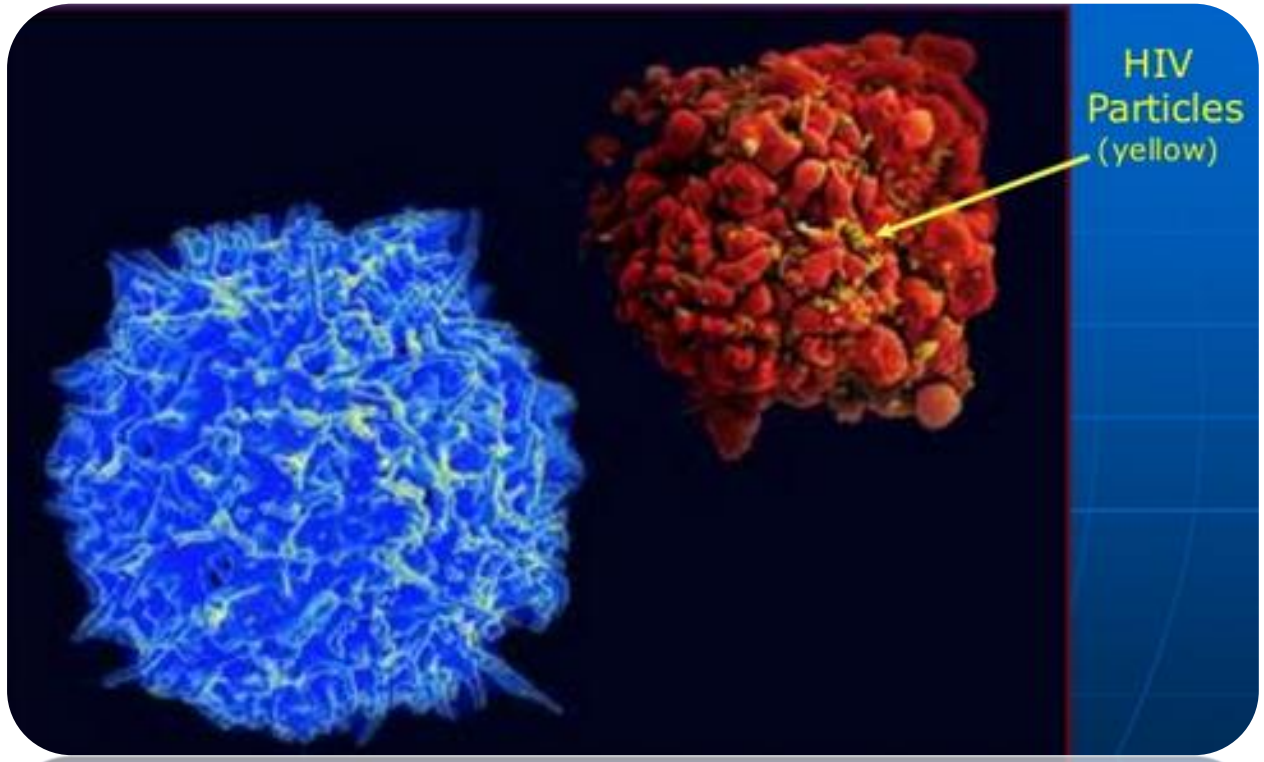
Quinases

Intracellular Bacteria		
Mycobacteria	Tuberculosis, leprosy	Macrophage activation resulting in granulomatous inflammation and tissue destruction
Listeria monocytogenes	Listeriosis	Listeriolysin damages cell membranes
Legionella pneumophila	Legionnaires' disease	Cytotoxin lyses cells and causes lung injury and inflammation
Fungi		
Candida albicans	Candidiasis	Unknown; binds complement proteins
Aspergillus fumigatus	Aspergillosis	Invasion and thrombosis of blood vessels causing ischemic necrosis and cell injury
Histoplasma capsulatum	Histoplasmosis	Lung infection caused by granulomatous inflammation
Viruses		
Polio	Poliomyelitis	Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)
Influenza	Influenza pneumonia	Inhibits host cell protein synthesis (tropism for peripheral nerves)
Rabies	Rabies encephalitis	Inhibits host cell protein synthesis (tropism for ciliated peripheral nerves)
Herpes simplex	Various herpes infections (skin, systemic)	Inhibits host cell protein synthesis; functional impairment of immune cells
Hepatitis B	Viral hepatitis	Host CTL response to infected hepatocytes
Epstein-Barr virus	Infectious mononucleosis; B cell proliferation, lymphomas	Acute infection: cell lysis (tropism for B lymphocytes) Latent infection: stimulates B cell proliferation
Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Multiple: killing of $CD4^+$ T cells, functional impairment of immune cells (see Chapter 20)

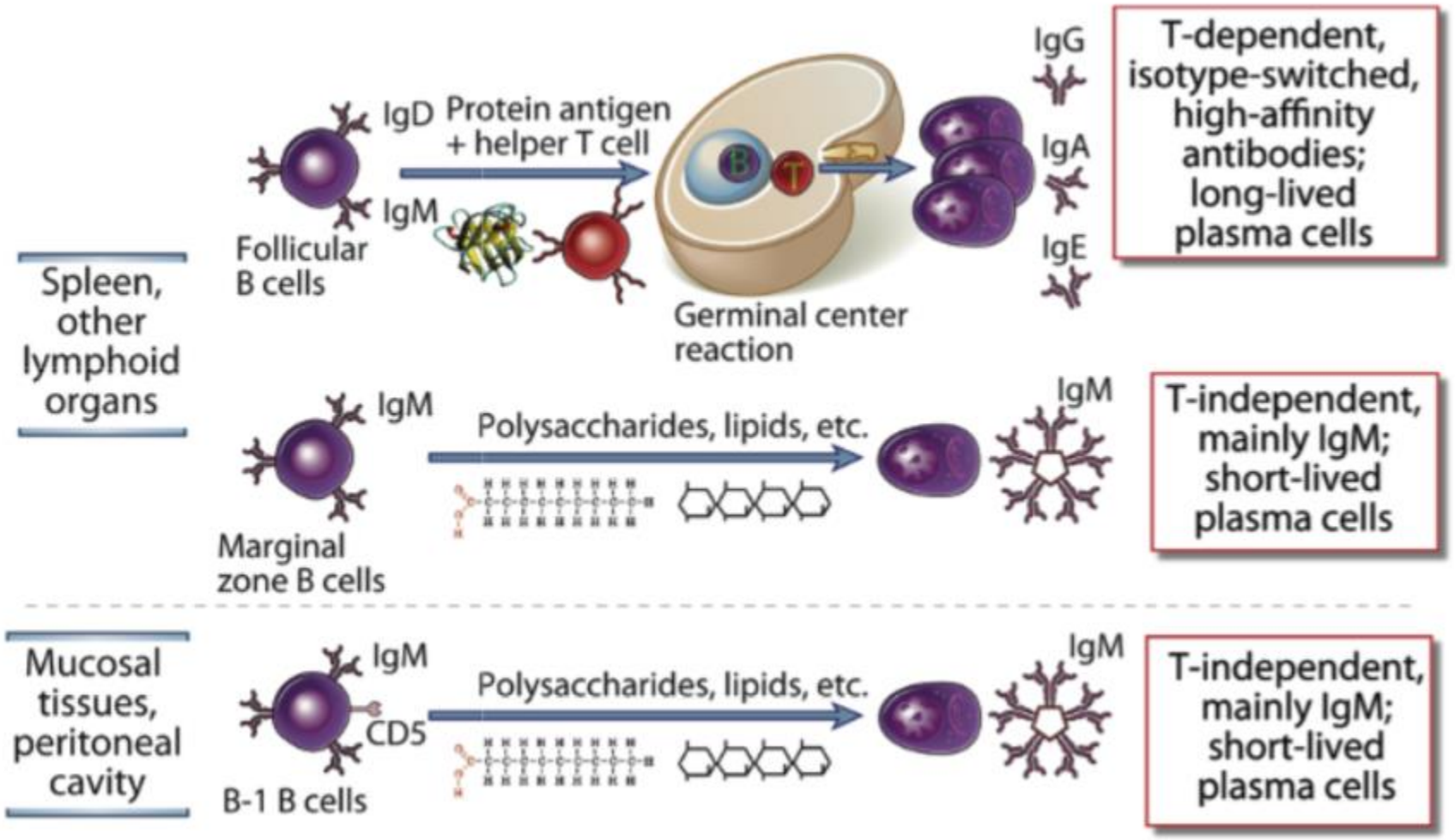
TABLE 15–3 Mechanisms of Immune Evasion by Viruses

Mechanism of Immune Evasion	Examples
Antigenic variation	Influenza, rhinovirus, HIV
Inhibition of antigen processing	
Blockade of TAP transporter	Herpes simplex
Removal of class I molecules from the ER	Cytomegalovirus
Production of cytokine receptor homologues	Vaccinia, poxviruses (IL-1, IFN-γ) Cytomegalovirus (chemokine)
Production of immunosuppressive cytokine	Epstein-Barr (IL-10)
Infection and death or functional impairment of immune cells	HIV

Representative examples of different mechanisms used by viruses to resist host immunity are listed. ER, endoplasmic reticulum; HIV, human immunodeficiency virus; TAP, transporter associated with antigen processing.



Anticorpos Naturais e Linfócitos B1



Imunógenos X Antígenos

IMUNÓGENO → **ANTÍGENO**

IMUNÓGENO ← ! → **ANTÍGENO**

HAPTENO +

PROTEÍNA CARREADORA →

Anticorpos:

Anti-hapteno

Anti-proteína

Anti-hapteno/proteína

Características do Reconhecimento Antigênico

Característica	Célula B	Célula T
Interação com o Ag	Direta	Indireta
Ligação ao Ag solúvel	Sim	Não
Necessidade de apresentação	Não	Sim
Natureza química do Ag	Proteínas, Lipídios, Polissacarídeos	Proteínas
Propriedades dos epítopos	Acessível, hidrofílico, estrutura conformacional	Denaturado, linear, comjugado à proteínas apresentadoras

Imunogeneicidade Proteica

Fatores que influenciam na imunogeneicidade:

Parâmetro	Aumenta	Diminui
Tamanho	Grande	Pequeno (MW <2500)
Dose	Intermediária	Alta ou baixa
Via de administração	Subcutânea > intraperitoneal > Intravenosa > oral	
Composição	Complexa	Simples
Forma	Particulado	Solúvel
	Denaturado	Integro
Similaridade ao próprio	Muito diferente	Pouco diferente
Adjuvantes	Liberação lenta	Liberação rápida
	Substâncias de patógenos	
Interação com proteínas apresentadoras de Ag	Eficiente	Pouco eficiente

Adjuvantes

Adjuvante	Composição	Mecanismo
IFA	Emulsão Óléo-Água	Liberação lenta do Ag
CFA	Emulsão Óleo-Água + M.t.	Liberação lenta + ativação M0
FA + MDP	Emulsão + muramildipeptídio	Liberação lenta + ativação M0
Hidróxido de Alumínio	Gel de $Al(OH)_3$	Liberação lenta + > fagocitose NLRP3
Hidróxido de Alumínio + *Bordetella pertussis*	$Al(OH)_3$ + *B. pertussis* morta	= $Al(OH)_3$ + ativação M0
ISCOMs (Complexos Imunoestimulatórios)	Matriz de Quil A + proteínas virais	Liberação do Ag no citoplasma (ativação de células T $CD8^+$)

Sensibilização (1ª Imunização) → **Resposta secundária (1º desafio Ag) Resposta terciária (2o desafio Ag) Etc...** → **Hiperimunização (Várias doses Ag)**