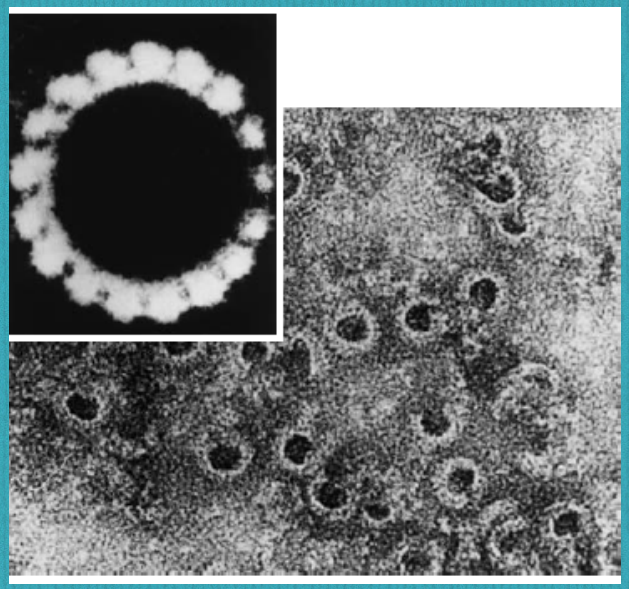
Curso de Ciencias Biologicas
Disciplina BMI-296 – Imunologia basica



Aula 3 – Imunidade inata

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Imunidade inata

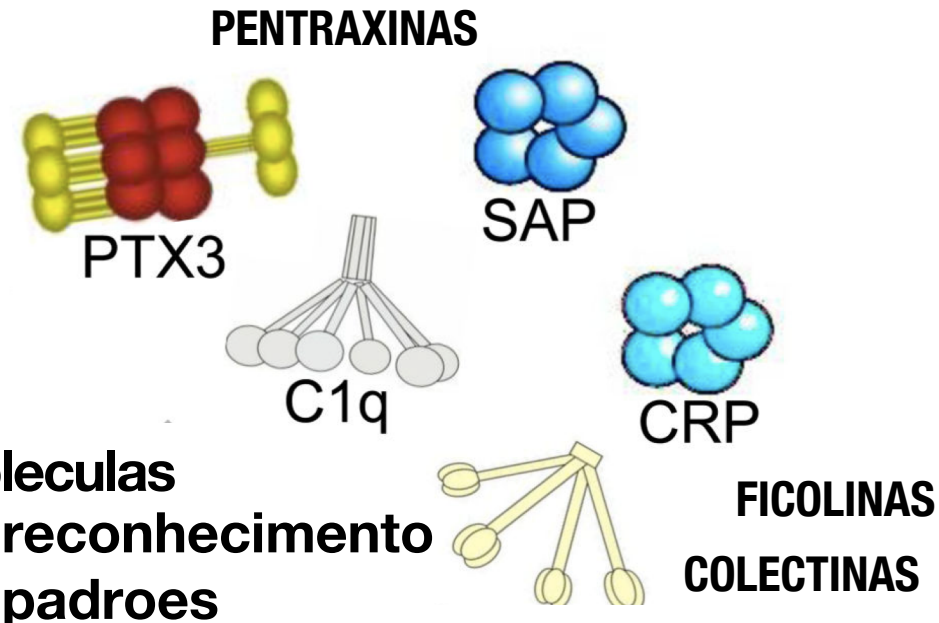
- pronta para atuar frente a um desafio
- “antiga” (plantas-invertebrados-vertebrados)

Barreiras anatômicas (físicas, químicas)

Resposta celular

Resposta humoral

Imunidade inata humoral



Moleculas de reconhecimento de padroes (PRMs)

Reconhecimento de patogeno/ celula danificada (circulante/tecidual)

- **Sistema complemento**
- Opsonizaçao (fagocitose)
- Aglutinaçao
- Neutralizaçao
- Prevençao expansao viral
- Cascadas proteicas (invertebrados)

Moleculas de reconhecimento de padroes (PRMs)

PRMs	Locus	PAMP/DAMP	Origem
Pentraxinas Short: SAP, CRP Long: PTX3	Plasma	Carboidratos, Fibras amiloide Material nuclear Proteinas da ME	Bacteria/Parasitas Celulas mortas/danificadas
Colectinas (MBL, SP-A/D)	Plasma (MBL) Alveolo (SPs)	Carboidratos (Man) Material nuclear	Bacteria/virus/fungo Celulas mortas
Ficolinas (Ficolina)	Plasma	Carboidratos (GlcNAc, SA)	Microbios Celulas mortas
Complemento (C1q, C3)	Plasma	Superficie microbiana	

Mannose-binding lectin (MBL)

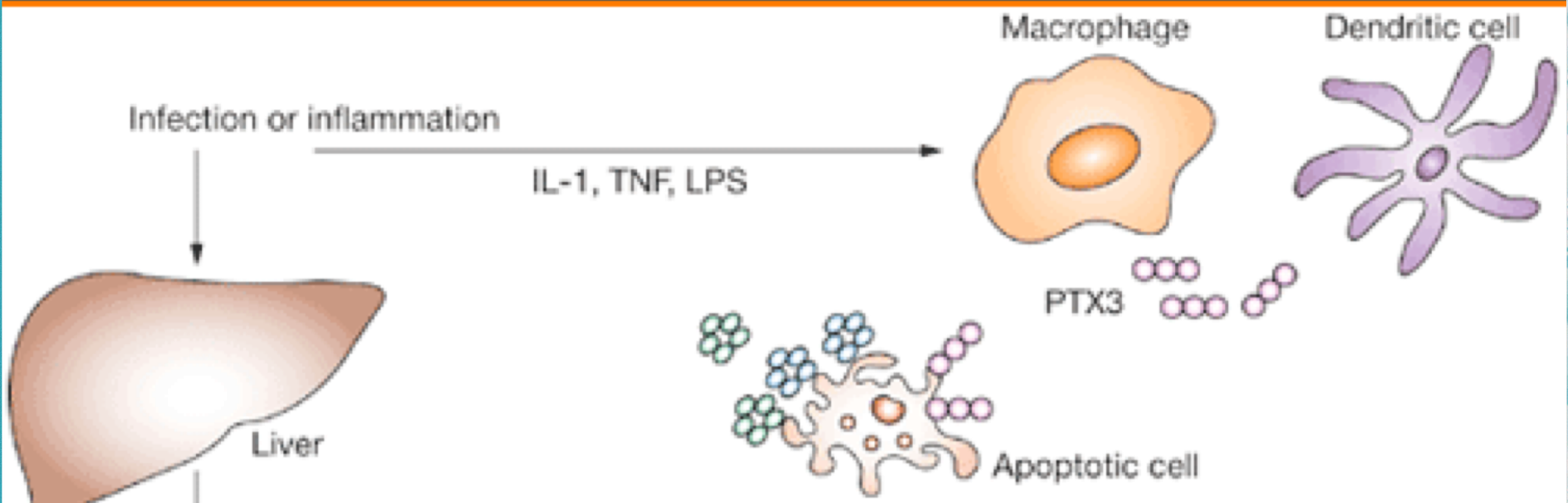
Table 1 Some clinically relevant microorganisms recognized by MBL

Bacteria	Viruses	Fungi	Protozoa
Staphylococcus aureus	HIV-1 and 2	*Aspergillus fumigatus*	*Plasmodium falciparum*
Streptococcus pneumoniae	Herpes simplex 2	*Candida albicans*	*Cryptosporidium parvum*
Streptococcus pyogenes	Influenza A	*Cryptococcus neoformans*	*Trypanosoma cruzi*
Enterococcus spp.	Hepatitis B virus	*Saccharomyces cerevisiae*	
Listeria monocytogenes	Hepatits C virus		
Haemophilus influenzae			
Neisseria meningitidis			
Neisseria gonorrhoeae			
Escherichia coli			
Klebsidla spp.			
Pseudomonas aeruginosa			
Salmondla montevideo			
Salmondla typhimurium			
H pylori			
Chlamydia trachomatis			
Chlamydia pneumonia			
Proprionibacterium acnes			
Mycobacterium avium			
Mycobacterium tuberculosis			
Mycobacterium leprae			
Leishmania chagasi			

Table 1

The endogenous ligands of MBL.

Endogenous ligands of MBL
Dying cells
Apoptosis
Necrosis
Ischemic tissues
Myocardial reperfusion injury
Renal reperfusion injury
Gastrointestinal reperfusion injury
Anoxic endothelia cells
Endothelial oxidative stress
Transformed cells
Colon adenocarcinoma
Colorectal carcinoma
Immunogloublins
Agalactosyl IgG
Dimeric/polymeric IgA
IgM
Nucleic acids
DNA
RNA
Phospholipids
Phosphatidylserine
Phosphatidylinositol
Phosphatidylcholine
Zinc metalloproteases
Meprin α and β



Ligands		
CRP	**SAP**	**PTX3**
C1q	C1q	C1q
Apoptotic cells	Apoptotic cells	Apoptotic cells
Histones	Histones	Histones
Pathogens	LPS and pathogens	Pathogens
Phosphatidyl choline	Phosphatidyl ethanolamine	Galactomannan
Fibronectin	Fibronecin	
Laminin	Laminin	
Chromatin	Chromatin	
snRNP	DNA	

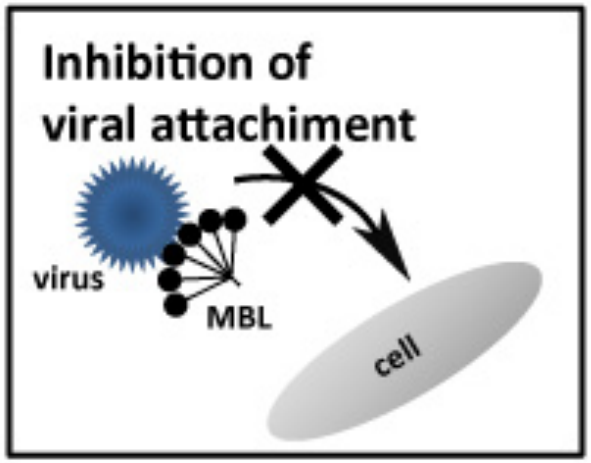
Moleculas de reconhecimento de padroes (PRMs)

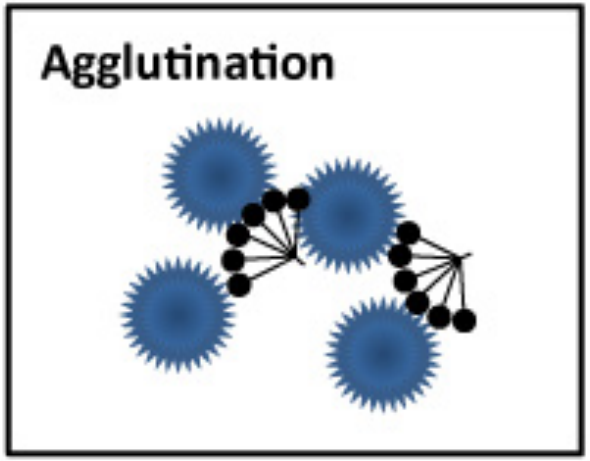
PRMs	Produçao	Orgao/celula
Pentraxinas **Short:** SAP, CRP **Long:** PTX3	**Infecçao/inflamaçao** IL-6 IL-1ß, TNF, TLR-agonists	Figado/hepatocitos PMN, Mø, DC
Colectinas (MBL, SP-A/D)	**Consitutiva** **Infecçao/inflamaçao** Citocinas proinflamatorias	Figado/hepatocitos Mø (?)
Ficolinas (Ficolina)	**Consitutiva** **Infecçao/inflamaçao** Citocinas proinflamatorias	
Complemento **(C1q, C3)**	**Consitutiva** **Infecçao/inflamaçao** Citocinas proinflamatorias	Figado/hepatocitos PMN, Mø, DC

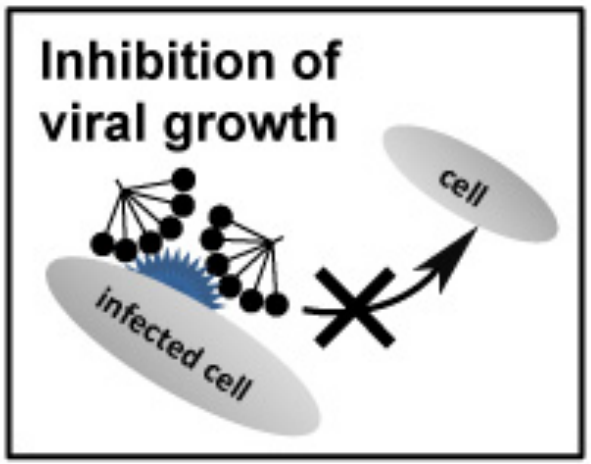
Acoes das PRMs

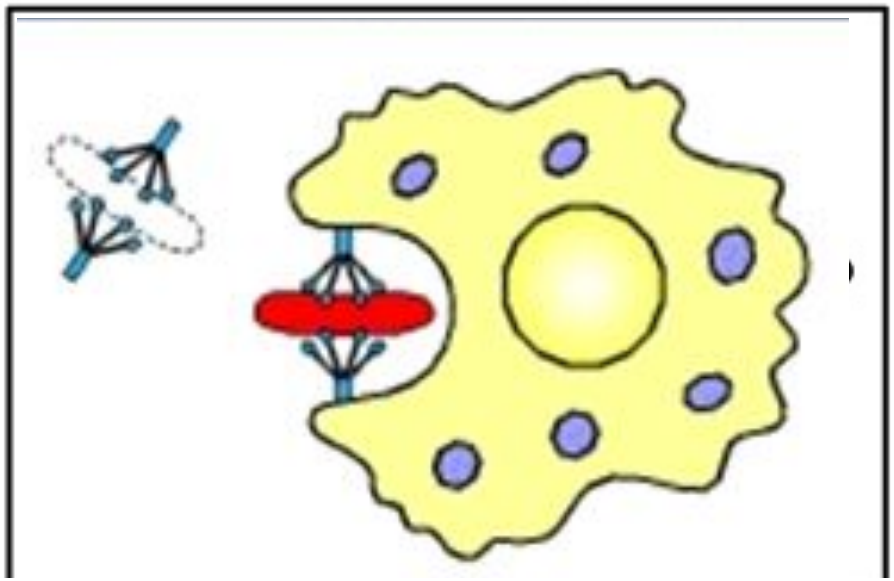
- Opsonizaçao (fagocitose)
- Aglutinaçao
- Neutralizaçao

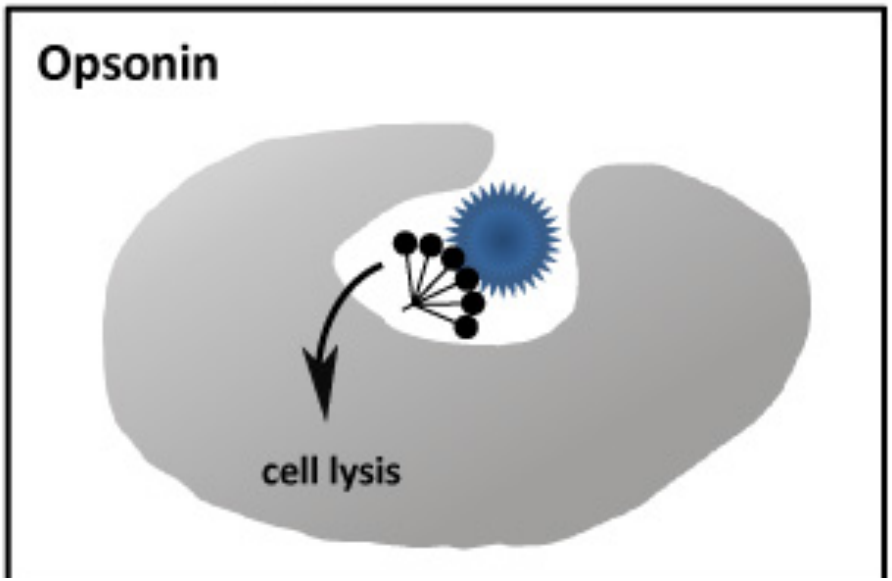
- Prevençao expansao viral
- Cascadas proteicas



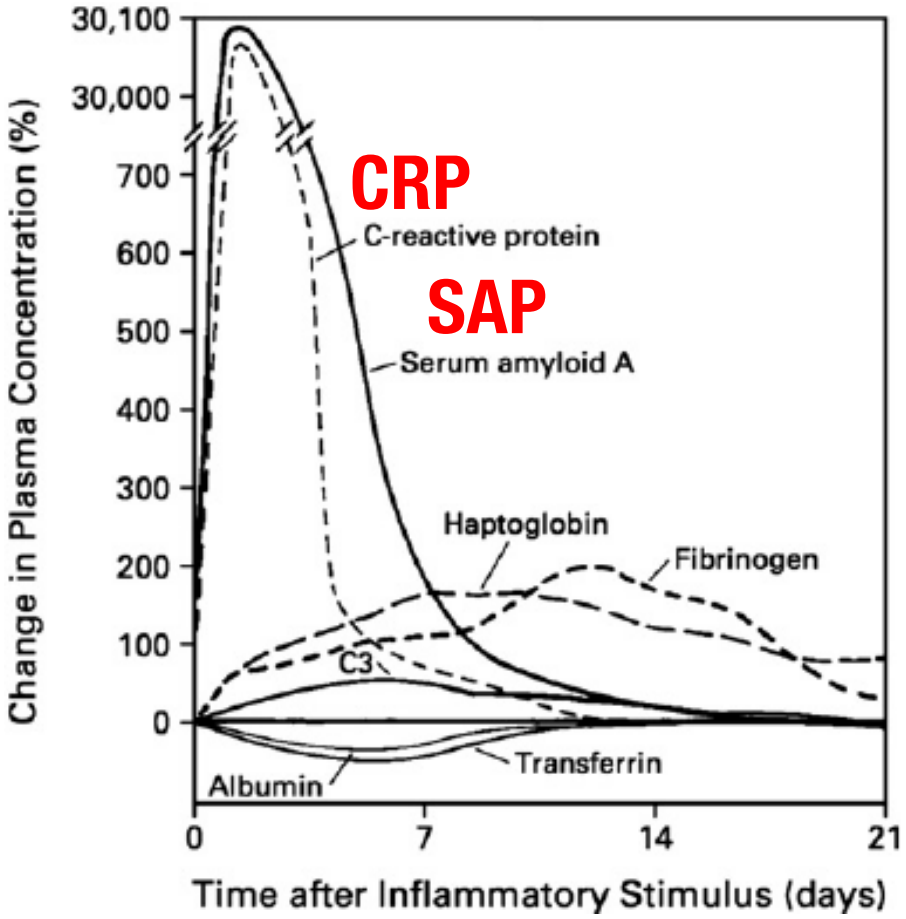








Moleculas da “fase aguda”

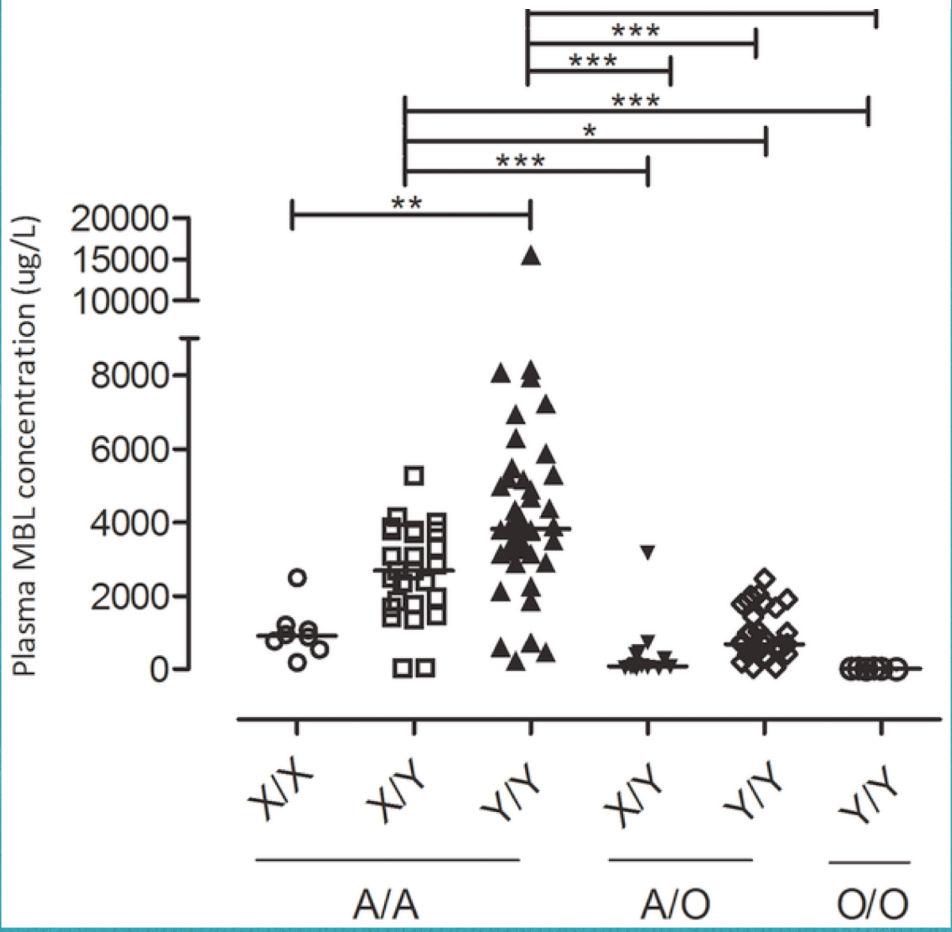


FILOGENIA DAS PRMs

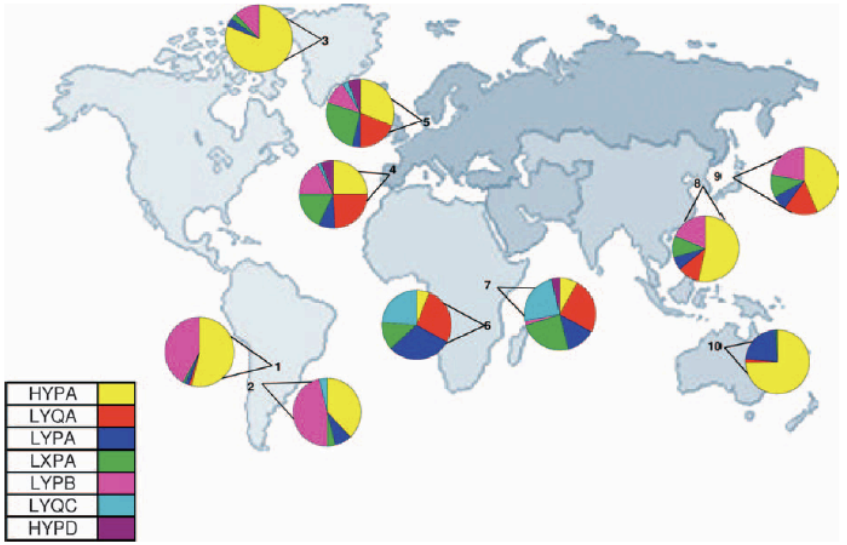
	sea urchin	amphioxus	urochordates	fish	human
collectin	1 collectin	66 collectins	9 collectins	4 collectins CL-P1 CL-K1 CL-L1(except for zebrafish) MBL	6 collectins CL-P1 CL-K1 CL-L1 MBL SP-A SP-D
C1q	4 C1q-like	50 C1q- like	2 C1q-like	1 C1q	1 C1q

MBL: protege mesmo?

MBL2 SNPs e niveis de MBL



Distribuiçao mundial dos SNPs



Deficiencia de MBL:
25% populaçao mundial
↑ infecçoes respiratorias (pneumococco)
↓ TB

Sistema complemento

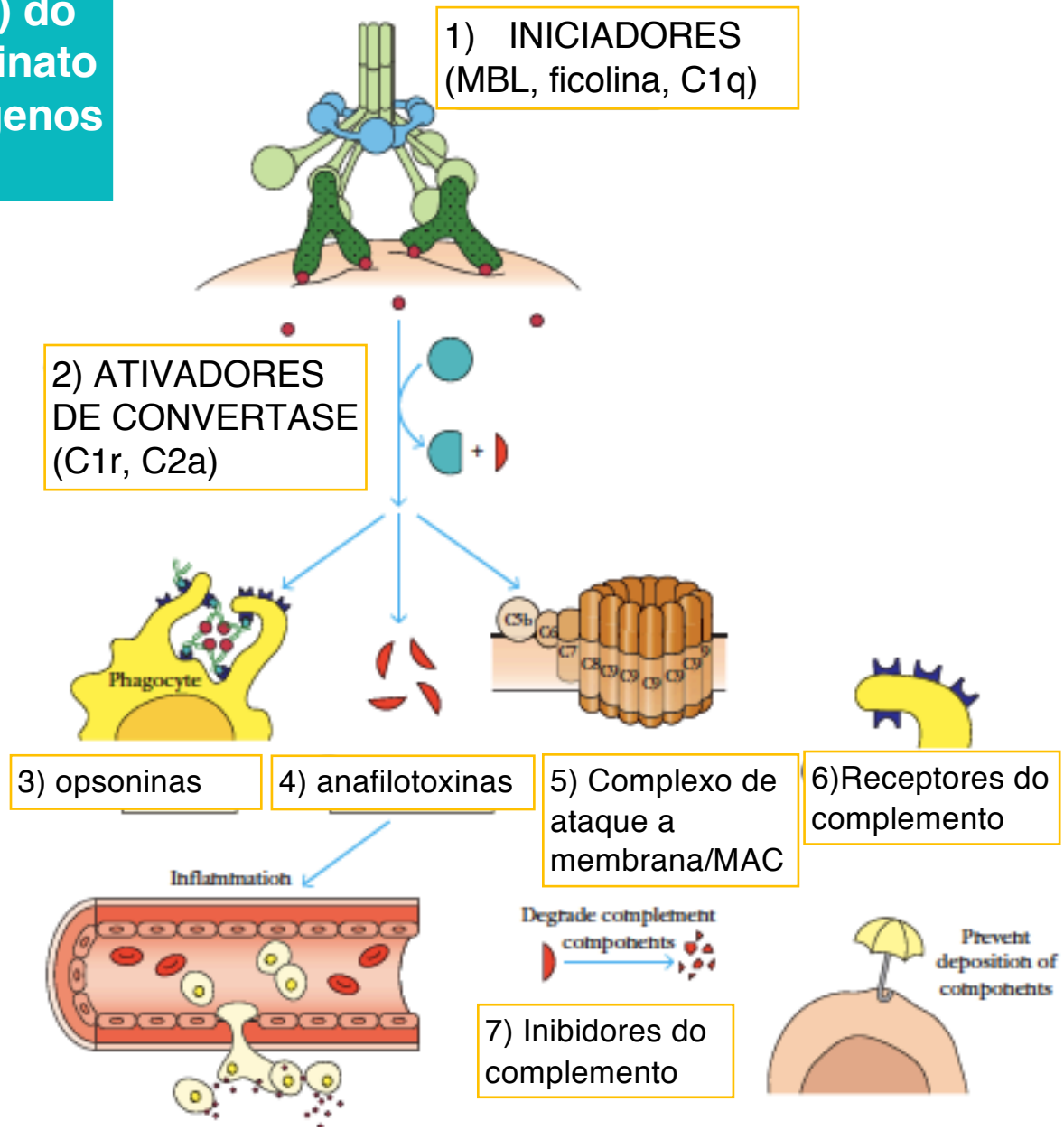
Conjunto de proteinas (C1-C9) do soro que cooperam com o S.I. inato e adquirido para eliminar patogenos sanguineos e teciduais

- interagem entre elas atraves de cascadas cataliticas

- produzidas pelo **figado** ou por outra celulas (mono/Mø, celulas epiteliais, fibroblastos)

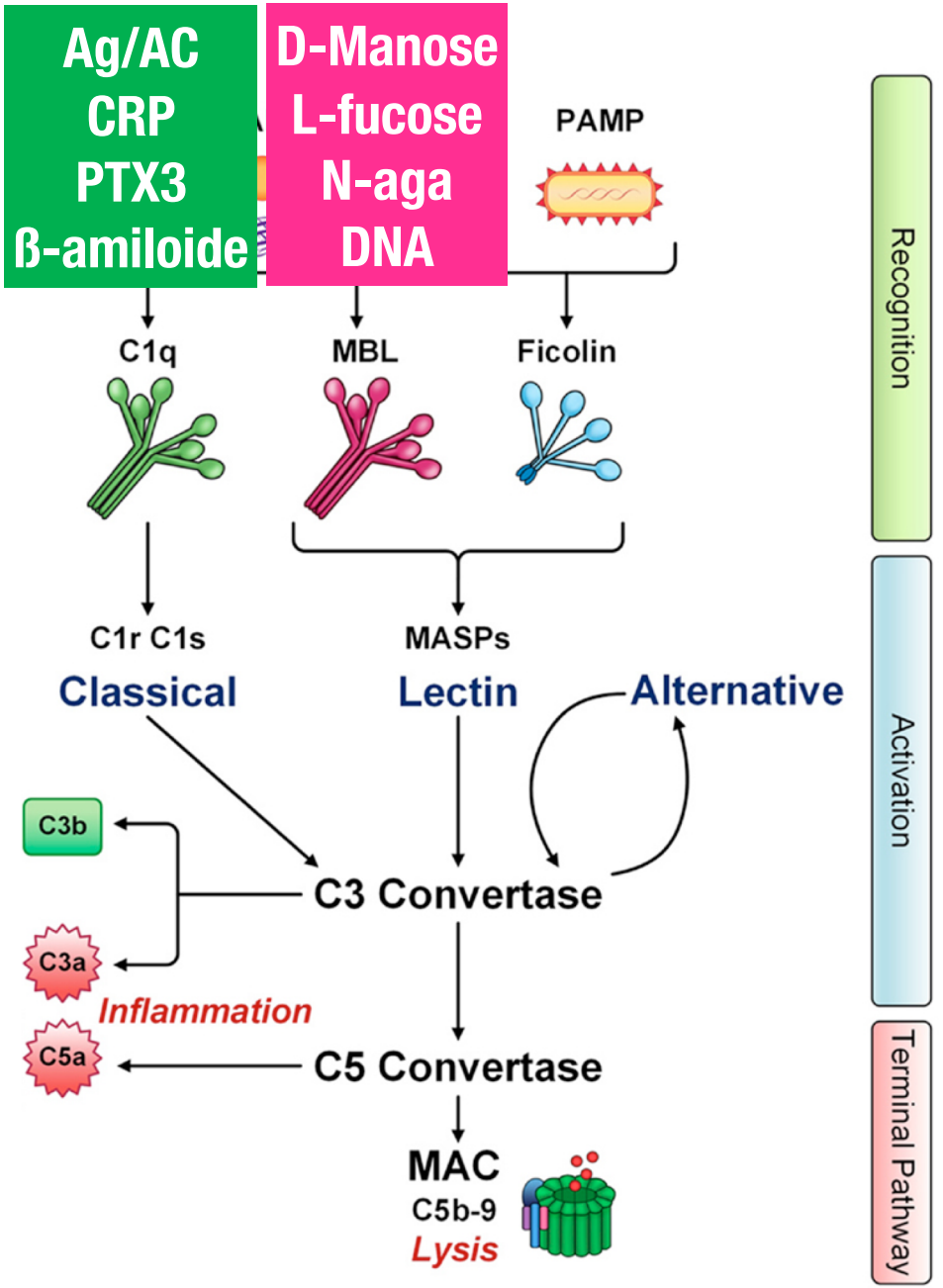
- pertencem a 7 categorias funcionais

Sistema evolutivamente antigo!



Sistema complemento

- ✓ A cascada de ativaçao começa com *reconhecimento* (*inato ou adquirido*)
- ✓ 3 vias de ativaçao (classica, lectinica, alternativa)
- ✓ As 3 vias convergem na **ATIVACAO da C3 CONVERTASE** (C3→C3a + C3b → ↑**C3b**)
- ✓ C3b atua como opsonina, e ativa **C5 CONVERTASE** (C5→C5a + C5b)
- ✓ **Formaçao do MAC** (**C6-C9**): poro no rivestimento do patogeno/celula danificada
- ✓ Alguns "pedaços" atuam como opsoninas (C3b) ou mediadores inflamatorios (anafilotoxinas: C3a, C5a)

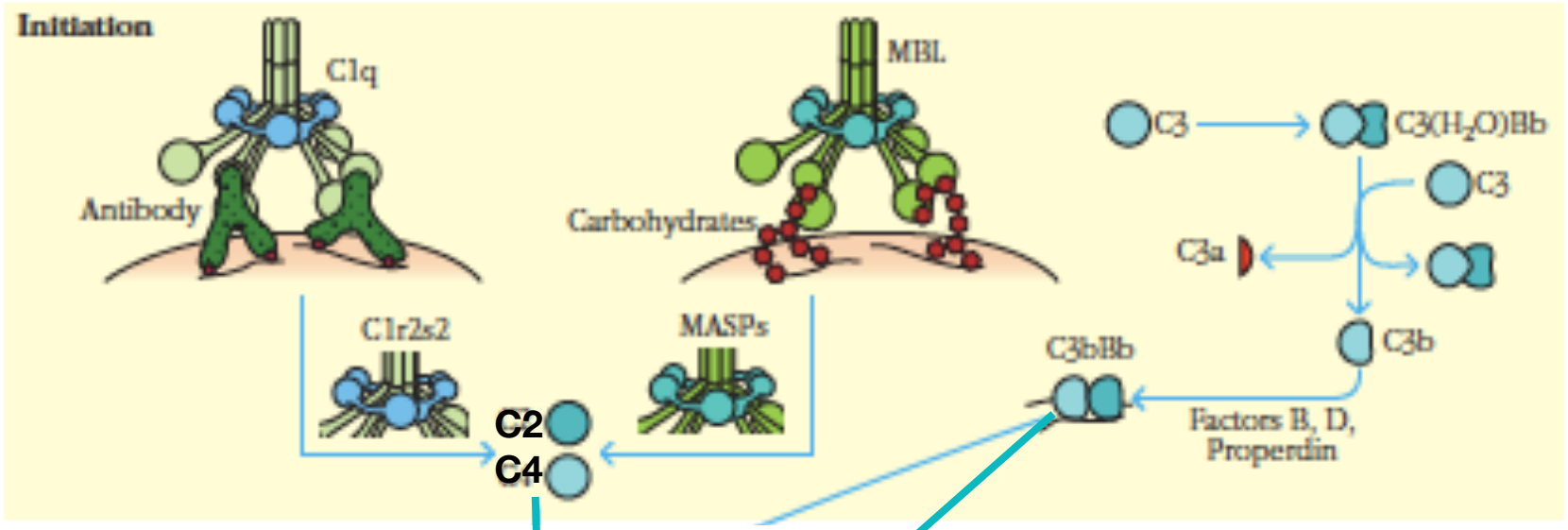


Sistema complemento

Via classica
Complexos Ag-AC /C1q

Via lectinica
PAMPs ou DAMPs /Lectinas

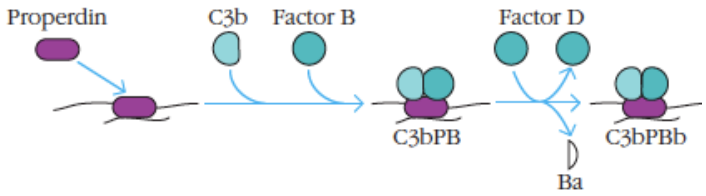
Via alternativa
Hidrolisi espontanea do C3 (C3 convertase solúvel, vida curta)



C4b2a

C3 CONVERTASE

C3bBb



C3 → C3b + C3a

C5 CONVERTASE

C4b2aC3b

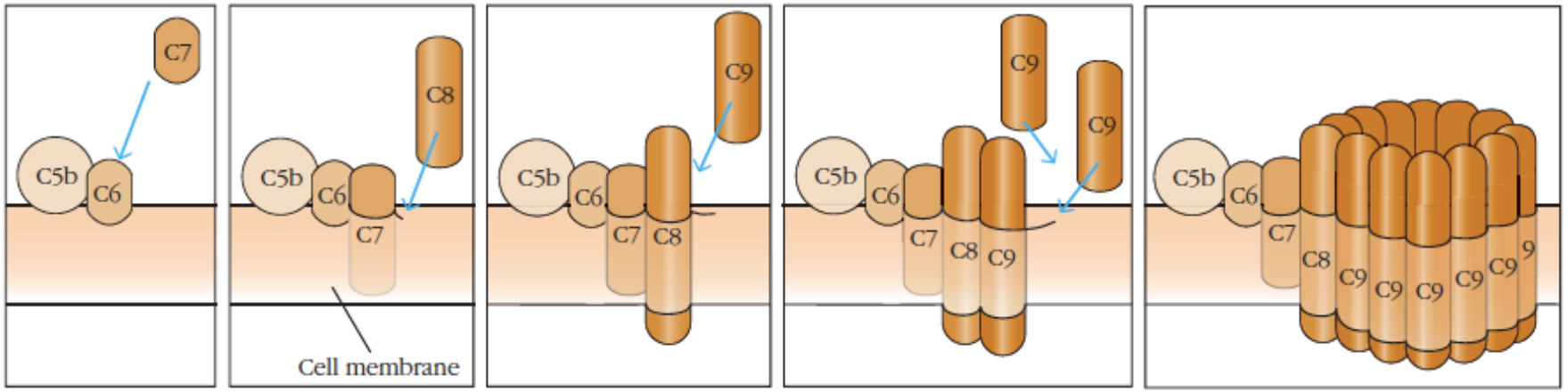
C5 → C5b + C5a

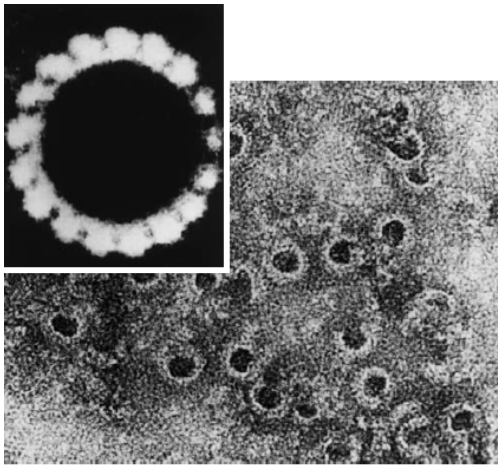
C5b → **C6, C7, C8, C9**

Sistema complemento

FUNCOES

1) FORMACAO DO MAC/PORO → LISE MEMBRANAS

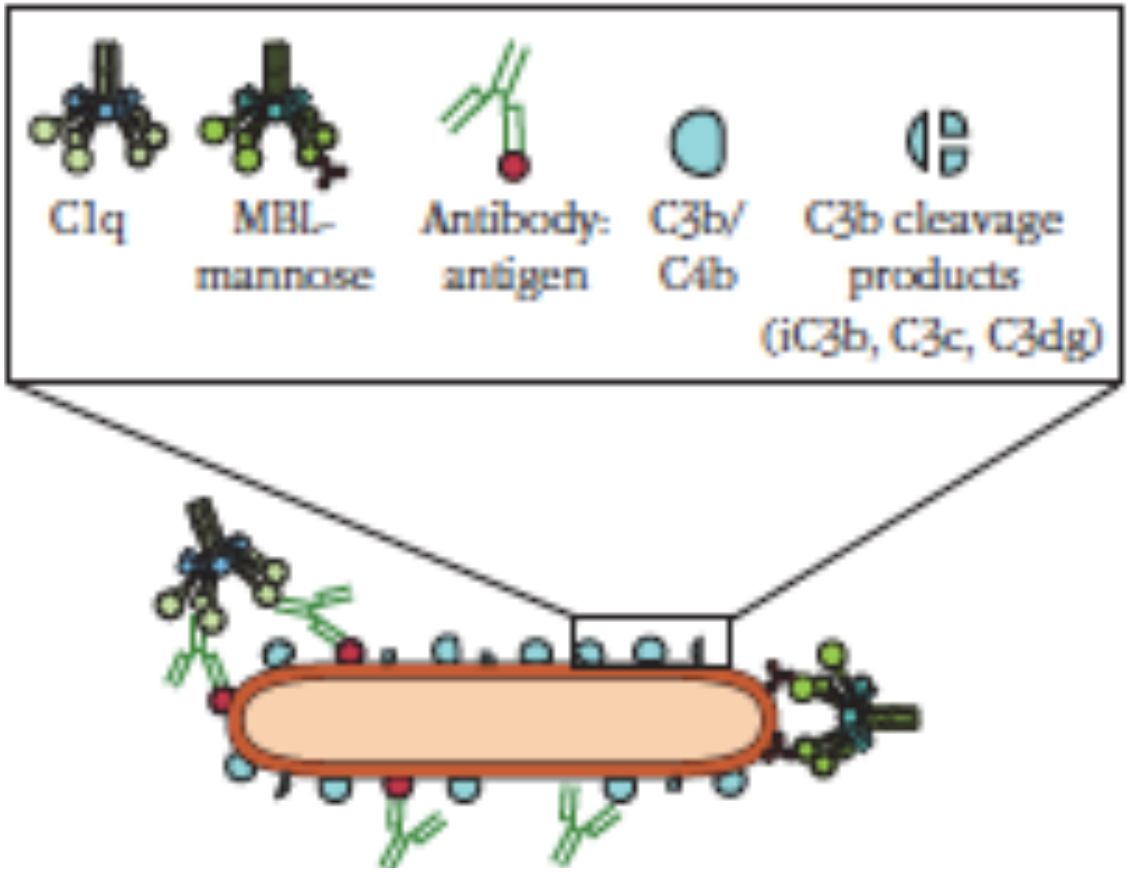




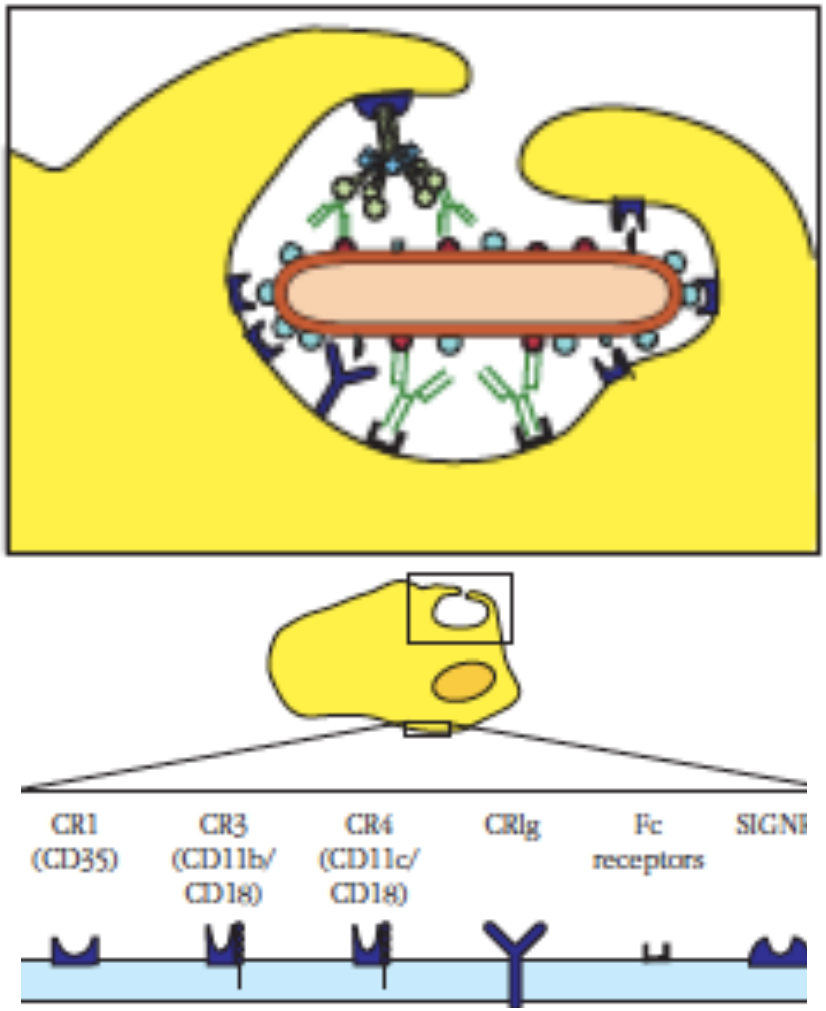
Sistema complemento

FUNCOES

2) OPSONIZACAO→ FAGOCITOSE



Fagocitose de patognos mediada por complemento



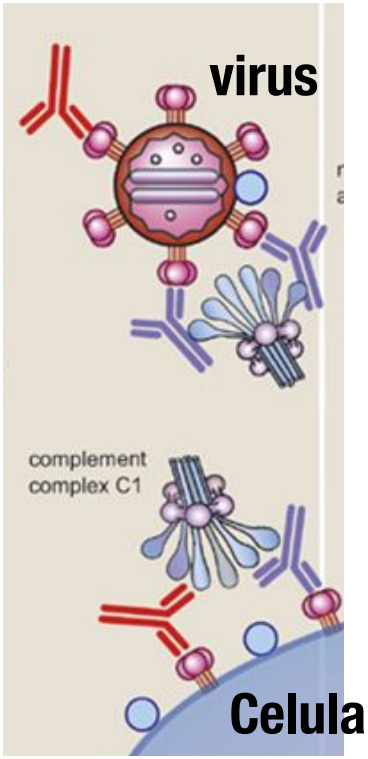
Sistema complemento

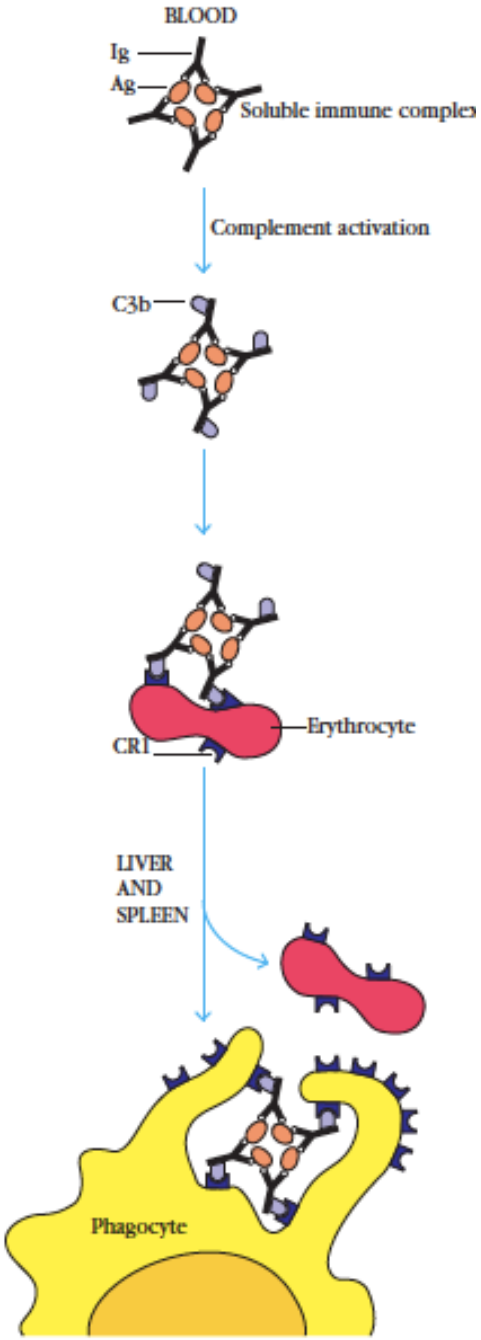
FUNCOES

2) OPSONIZACAO

→ REMOCAO DE IMUNOCOMPLEXOS

→ NEUTRALIZACAO/FAGOCITOSE VIRUS

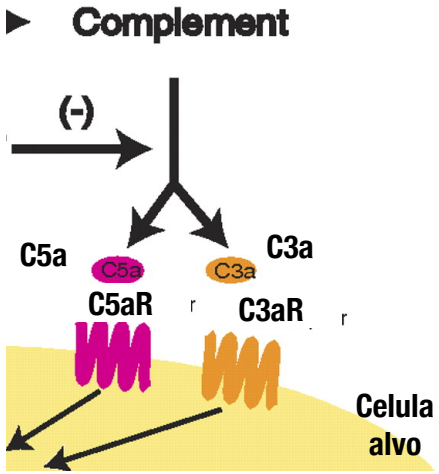




Sistema complemento

FUNCOES

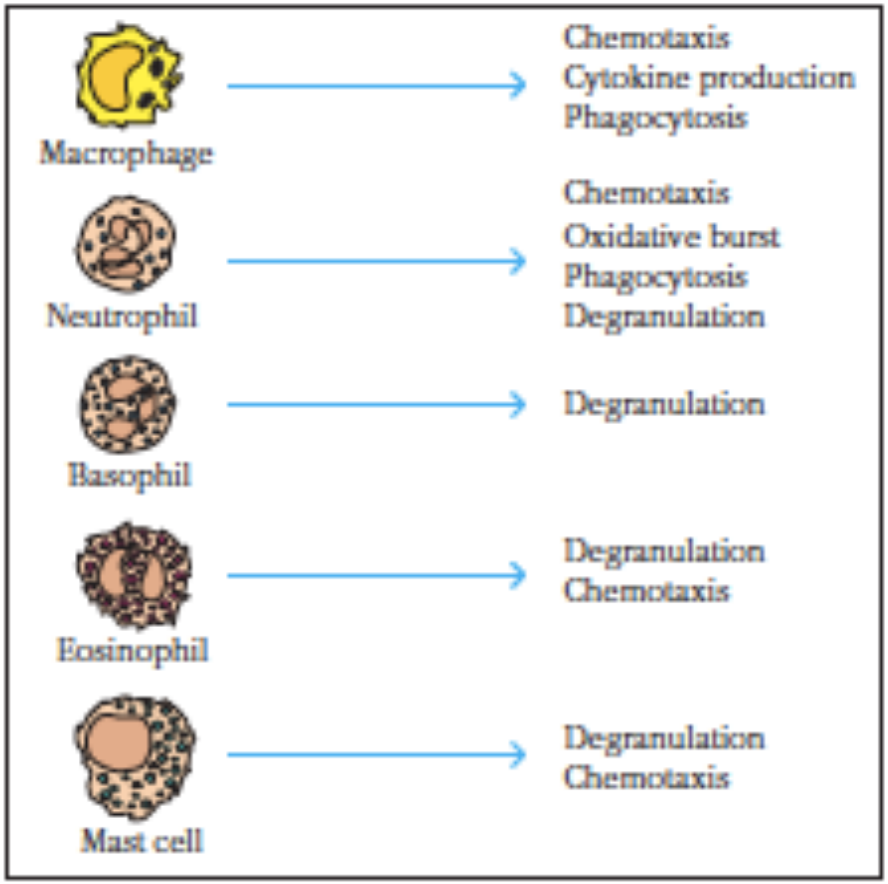
3) PROMOCAO DA INFLAMACAO
→ ATIVACAO CELULAS ALVO
→ QUIMIOTAXIA LEUCOCITOS



Celulas imunes

Celulas endoteliais e epiteliais

Plaquetas



Sistema complemento

REGULACAO

PASSIVA
- ***Instabilidade***
- ***≠ carboidrados***

ATIVA
- ***inibidores***

Protein	Fluid phase or membrane	Pathway affected	Function
C1 inhibitor (C1INH) serpins	Fluid phase	Classical and lectin	Induces dissociation and inhibition of $C1r_2s_2$ from C1q; serine protease inhibitor
Decay Accelerating Factor (DAF) CD55	Membrane bound	Classical, alternative, and lectin	Accelerates dissociation of C4b2a and C3bBb C3 convertases
CR1 (CD35)	Membrane bound	Classical, alternative, and lectin	Blocks formation of, or accelerates dissociation of, the C3 convertases C4b2a and C3bBb by binding C4b or C3b Cofactor for factor I in C3b and C4b degradation on host cell surface
C4BP	Soluble	Classical and lectin	Blocks formation of, or accelerates dissociation of, C4b2a C3 convertase Cofactor for factor I in C4b degradation
Factor H	Soluble	Alternative	Blocks formation of, or accelerates dissociation of, C3bBb C3 convertase Cofactor for factor I in C3b degradation
Factor I	Soluble	Classical, alternative, and lectin	Serine protease: cleaves C4b and C3b using cofactors shown in Figure 6-16
Membrane cofactor of proteolysis, MCP (CD46)	Membrane bound Celulas hospedeiro	Classical, alternative, and lectin	Cofactor for factor I in degradation of C3b and C4b
S protein or Vitronectin	Soluble	All pathways	Binds soluble C5b67 and prevents insertion into host cell membrane
Protectin (CD59)	Membrane bound	All pathways	Binds C5b678 on host cells, blocking binding of C9 and the formation of the MAC complex
Carboxypeptidases N, B, and R	Soluble	Anaphylatoxins produced by all pathways	Cleave and inactivate the anaphylatoxins C3a and C5a

Inibiçao do C3b/MASP

Degradaçao da C3 convertase

Degradaçao de C3b e C4b

Inibiçao do MAC

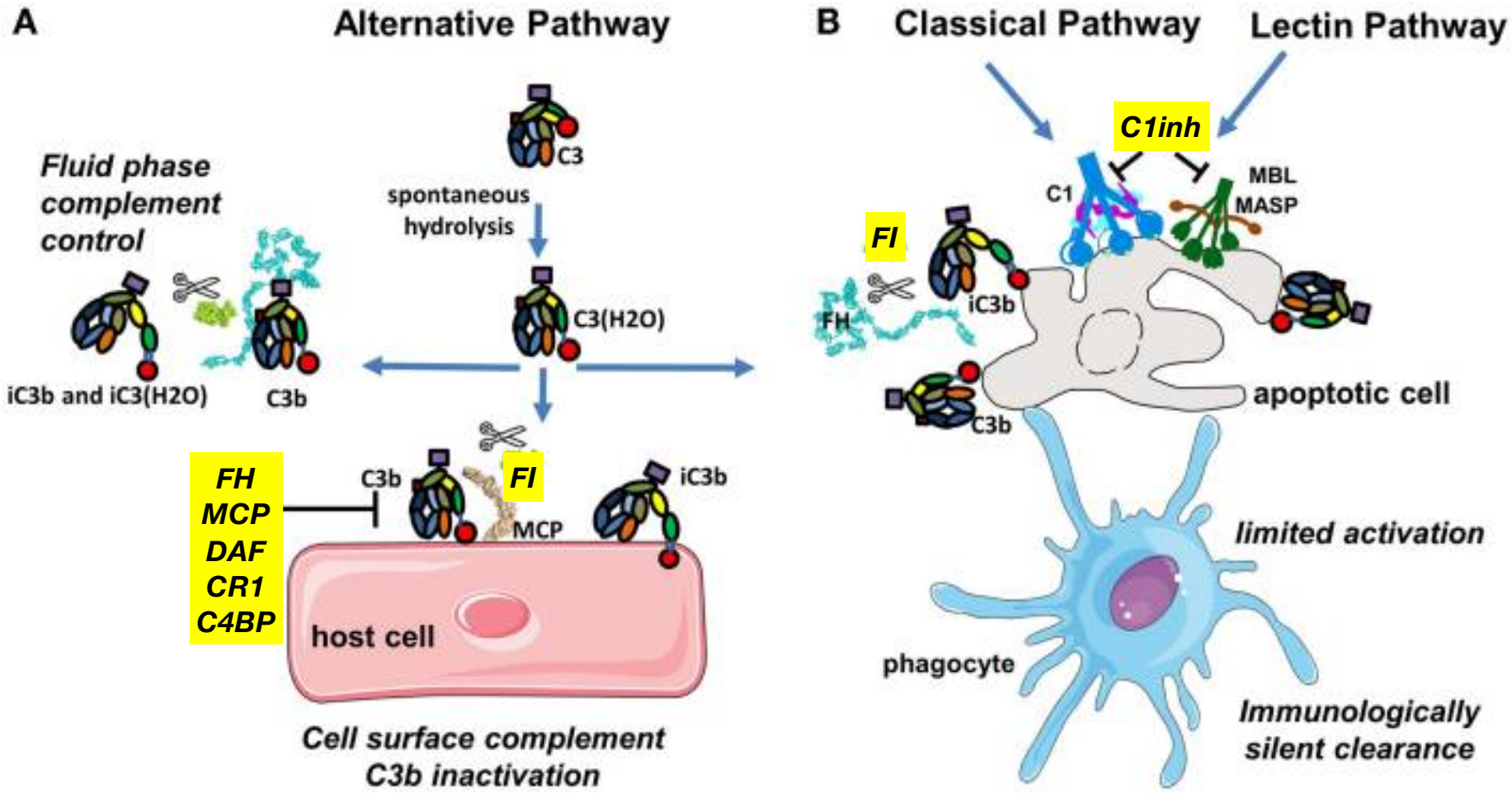
Inativaçao das anafilatoxinas

Sistema complemento

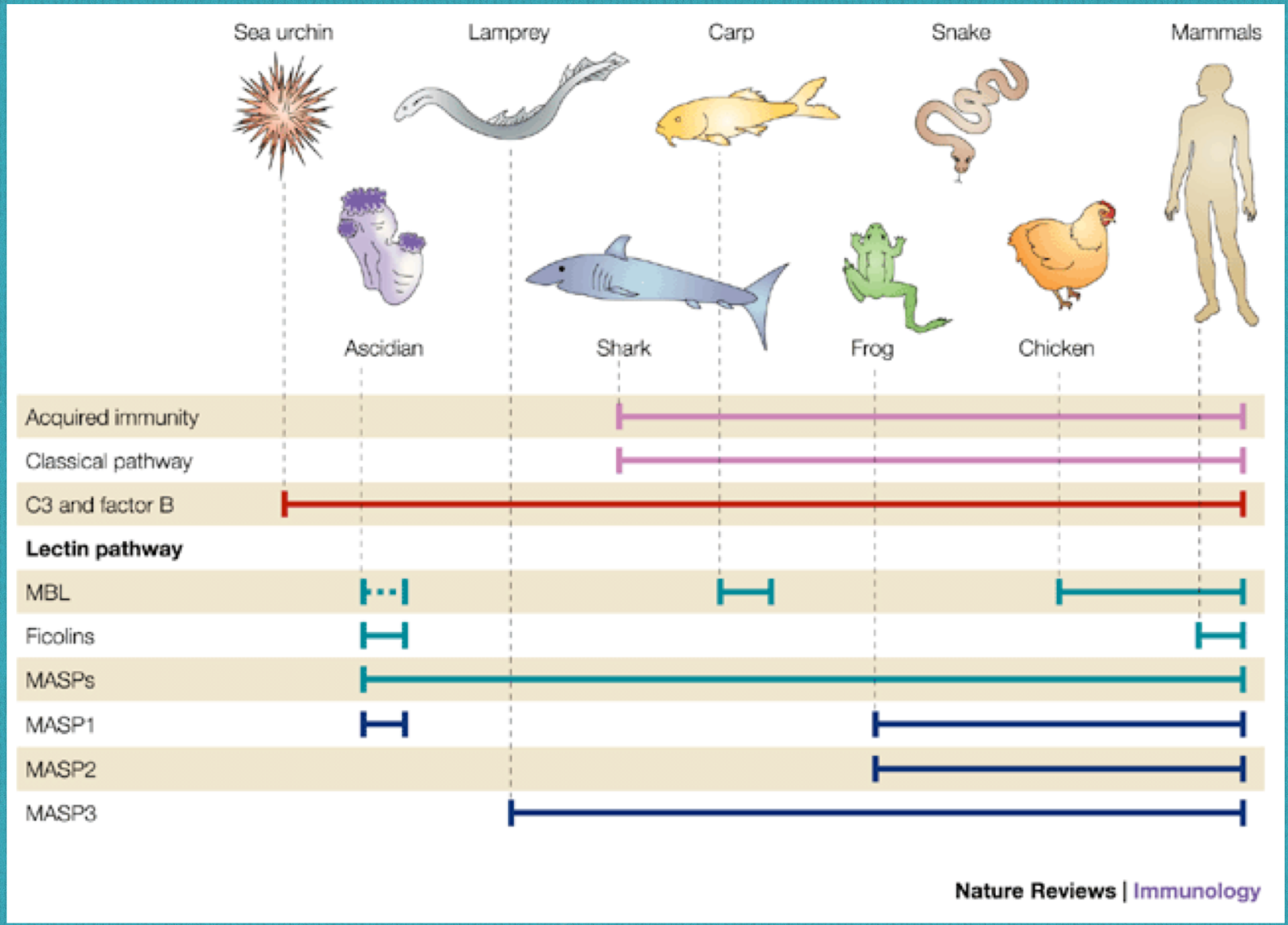
Funçao fisiologica do complemento

Complemento não ataca celulas do hospedeiro

Eliminaçao silenciosa das celulas apoptoticas (tmb linfocitos)

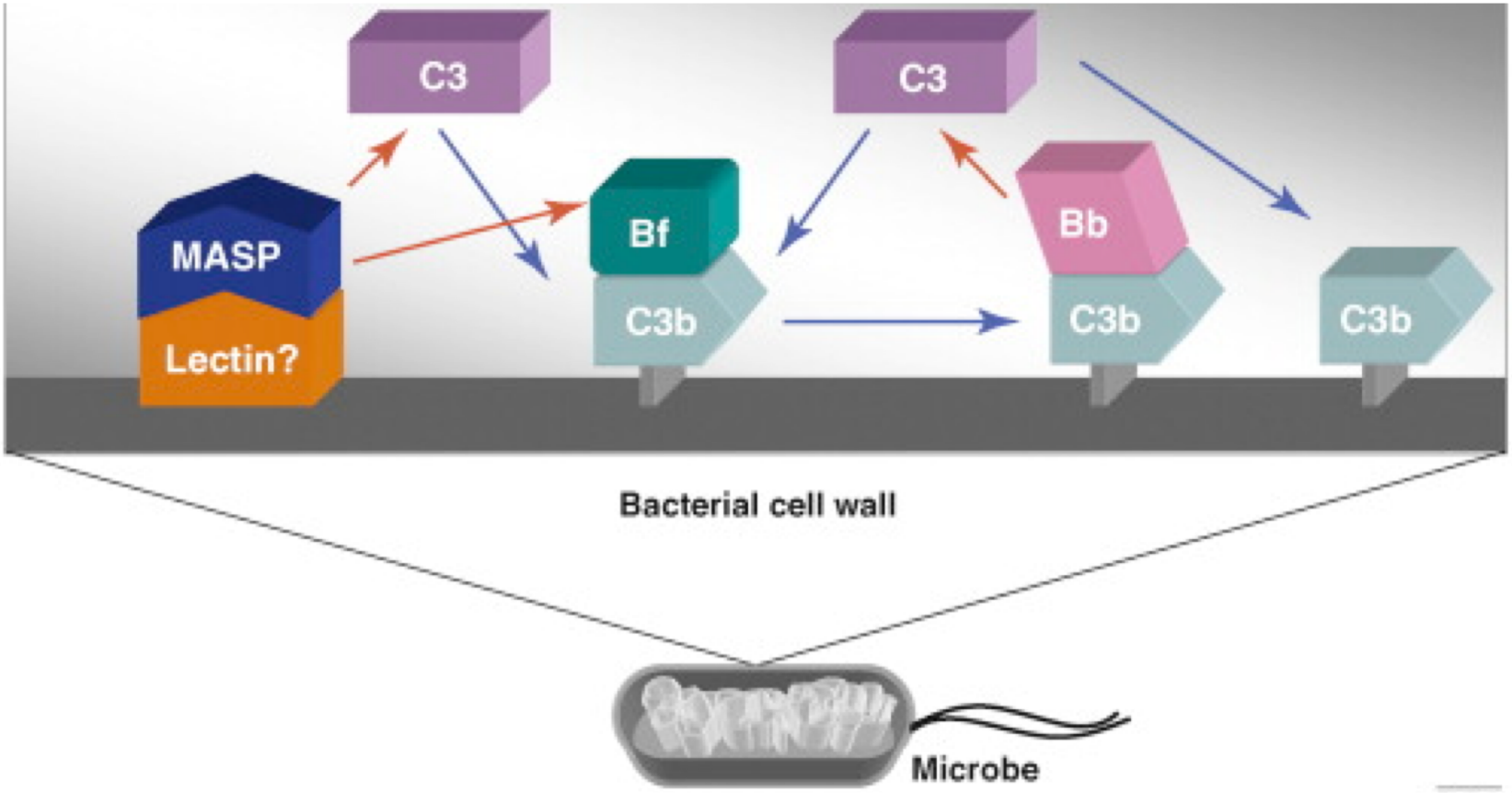


FILOGENIA DO COMPLEMENTO



Sistema complemento

The hypothetical proto-complement system



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complemento: protege mesmo?

ADVANCES

Staphylococcus aureus Employs Diverse Methods to Evade Destruction by the Complement System

Staphylococcus aureus has developed an impressive variety of mechanisms that inhibit both the classical and the alternative pathways of complement activation.

S. aureus is an encapsulated, Gram-positive bacterial strain. The capsular polysaccharide itself provides the bacterium with some mechanical inhibition of opsonization (1 in Figure 1). Although complement factors can assemble on the cell-wall surface underneath the capsule, most are then inaccessible to the complement receptors on phagocyte surfaces. However, if the C3 convertases C4b2a and C3bBb do succeed in assembling at the bacterial surface, they are then bound by a small, 9.8 kDa protein called *Staphylococcus* Complement Inhibitor (SCIN). Blockage of further convertase activity prevents amplification of

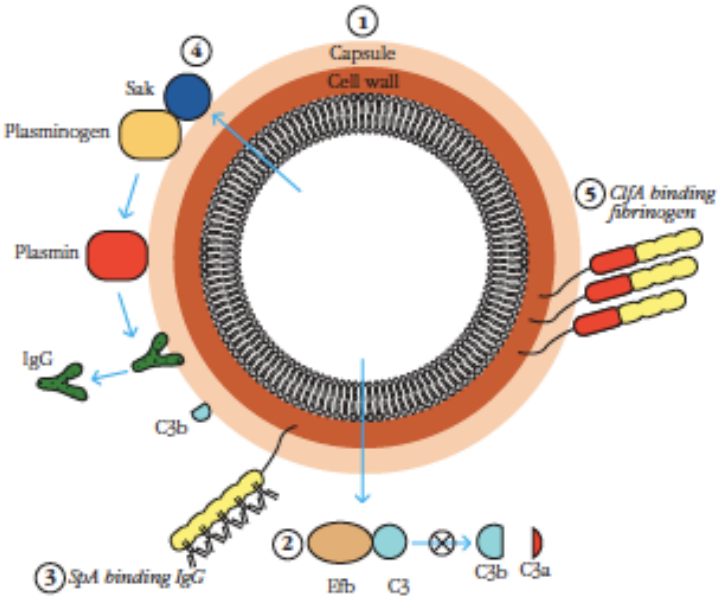
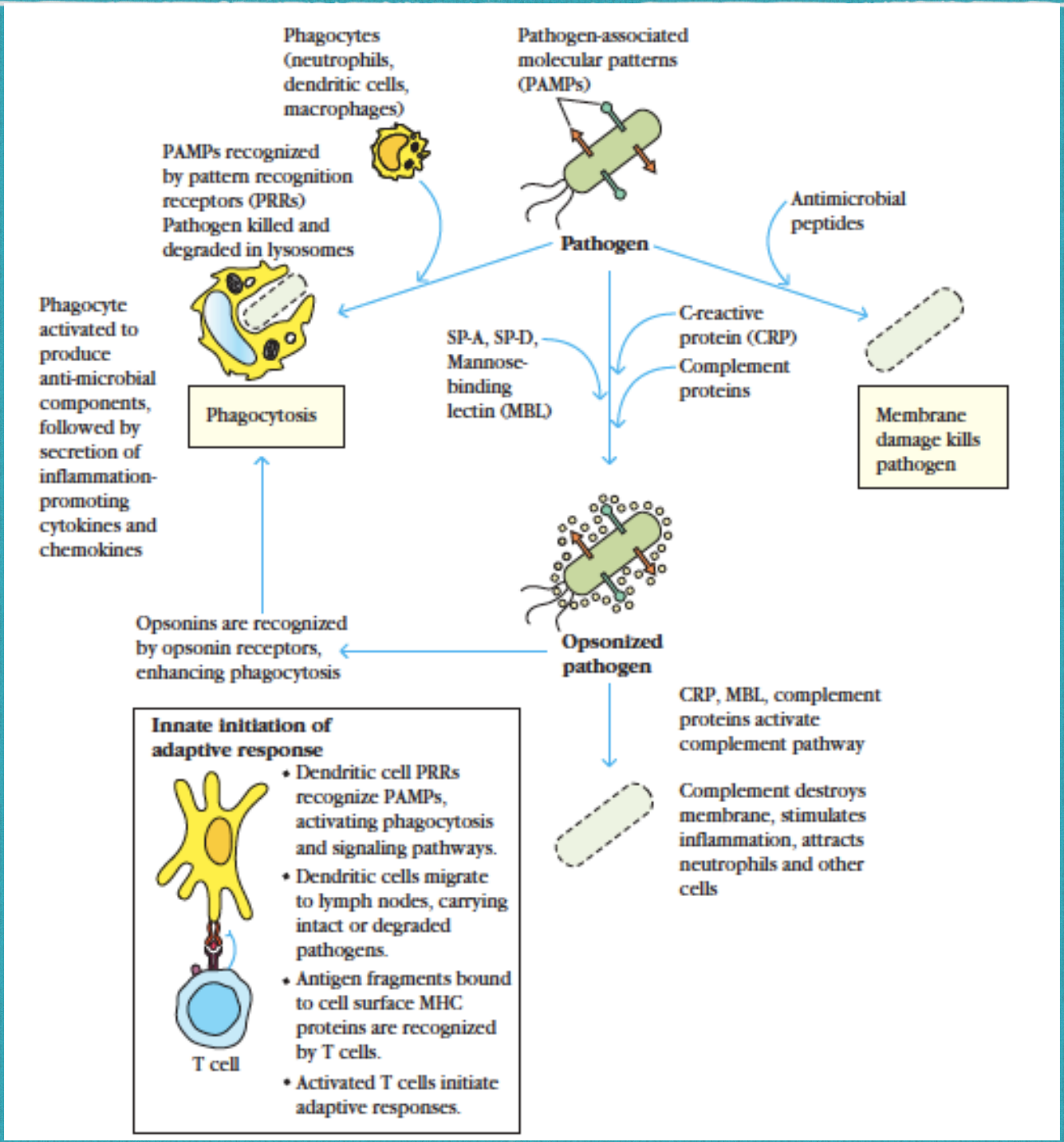
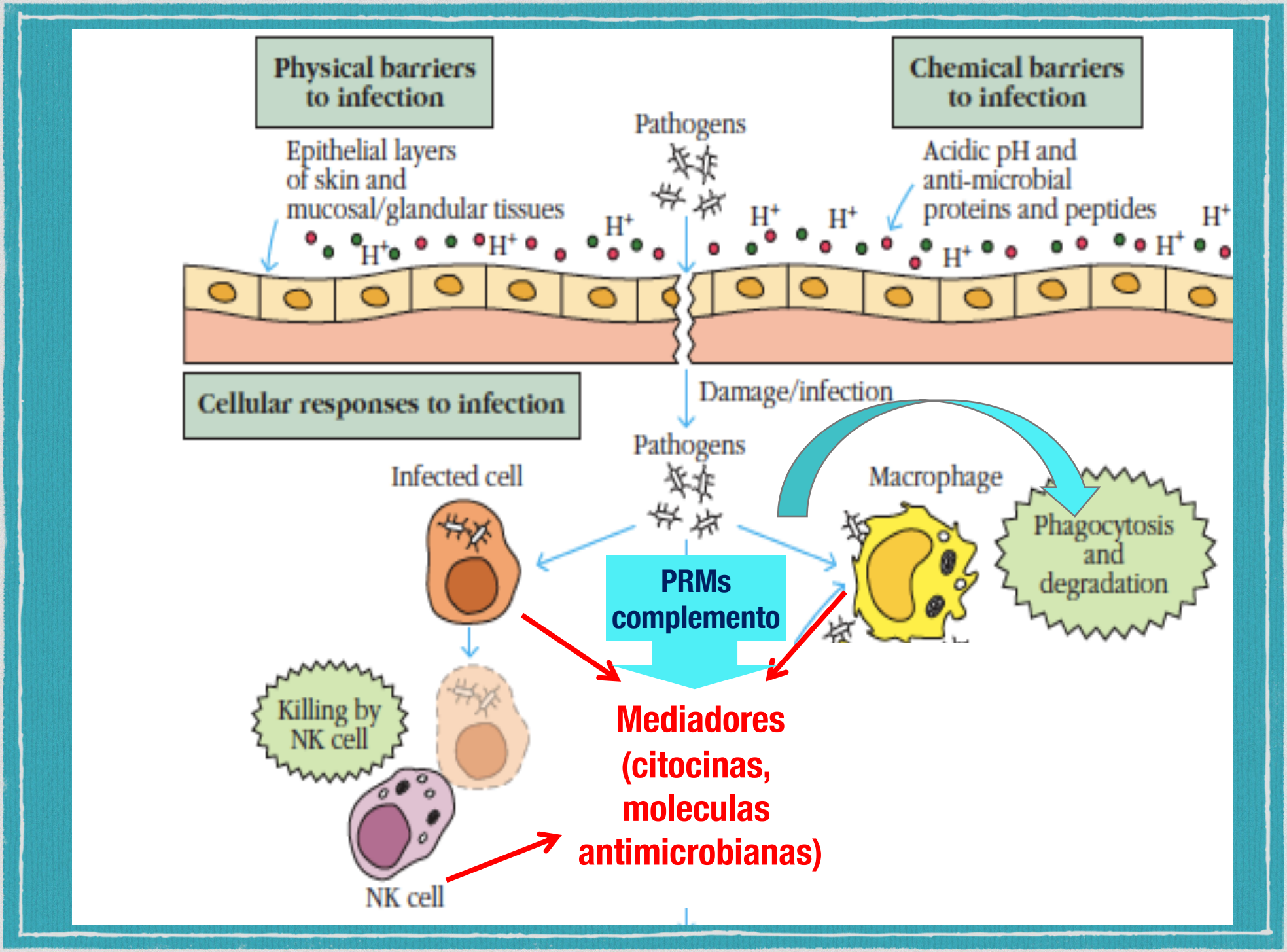


FIGURE 1
Mechanisms by which *S. aureus* avoids opsonophagocytosis. (1) The capsular polysaccharides denies access of neutrophils to opsonized bacteria. (2) The extracellular fibrinogen binding protein (Efb) binds C3, preventing it from reaching the cell surface and inhibiting further activation of the complement cascade. (3) Protein A (SpA) binds IgG in a conformation that does not permit Fc receptor binding. (4) Staphylokinase (Sak), secreted by the bacterium, activates plasminogen, a protease capable of cleaving and inactivating IgG and C3b. (5) Clumping factor A binds factor I and localizes it to the microbial surface, where it cleaves and inactivates any C3b that binds there. *[Adapted from Foster, T. J., 2005. Immune evasion by Staphylococci. Nature Reviews Microbiology 3: 948–958, Figure 3.]*

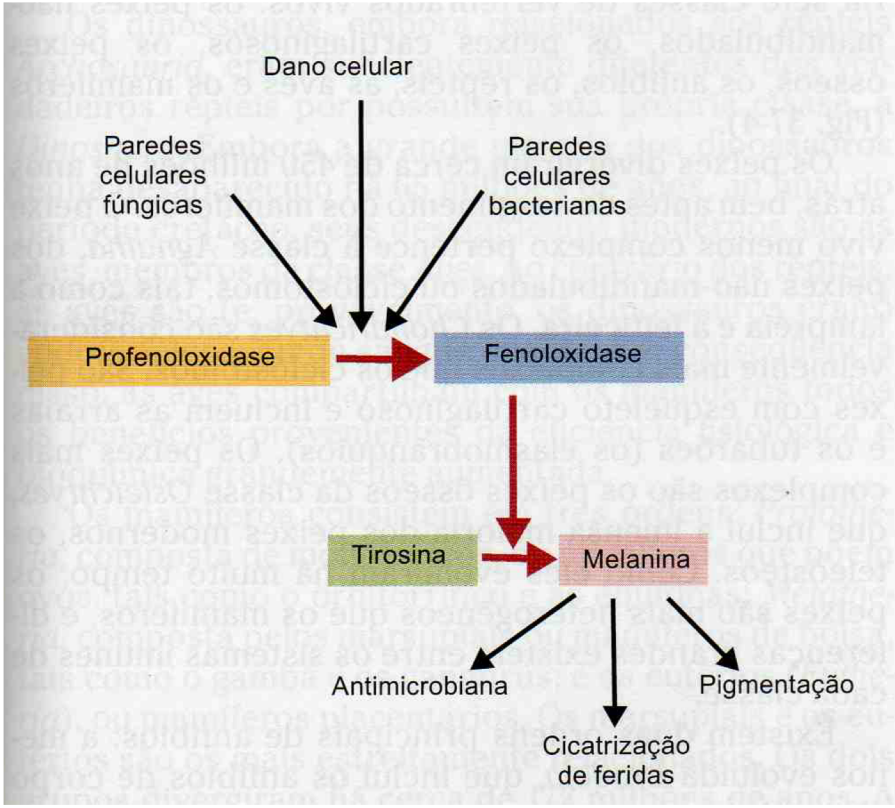

Phagocytes (neutrophils, dendritic cells, macrophages)
Pathogen-associated molecular patterns (PAMPs)
PAMPs recognized by pattern recognition receptors (PRRs)
Pathogen killed and degraded in lysosomes
Antimicrobial peptides
Pathogen
Phagocyte activated to produce anti-microbial components, followed by secretion of inflammation-promoting cytokines and chemokines
Phagocytosis
SP-A, SP-D, Mannose-binding lectin (MBL)
C-reactive protein (CRP)
Complement proteins
Membrane damage kills pathogen
Opsonized pathogen
Opsonins are recognized by opsonin receptors, enhancing phagocytosis
CRP, MBL, complement proteins activate complement pathway
Complement destroys membrane, stimulates inflammation, attracts neutrophils and other cells
Innate initiation of adaptive response
• 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.
T cell

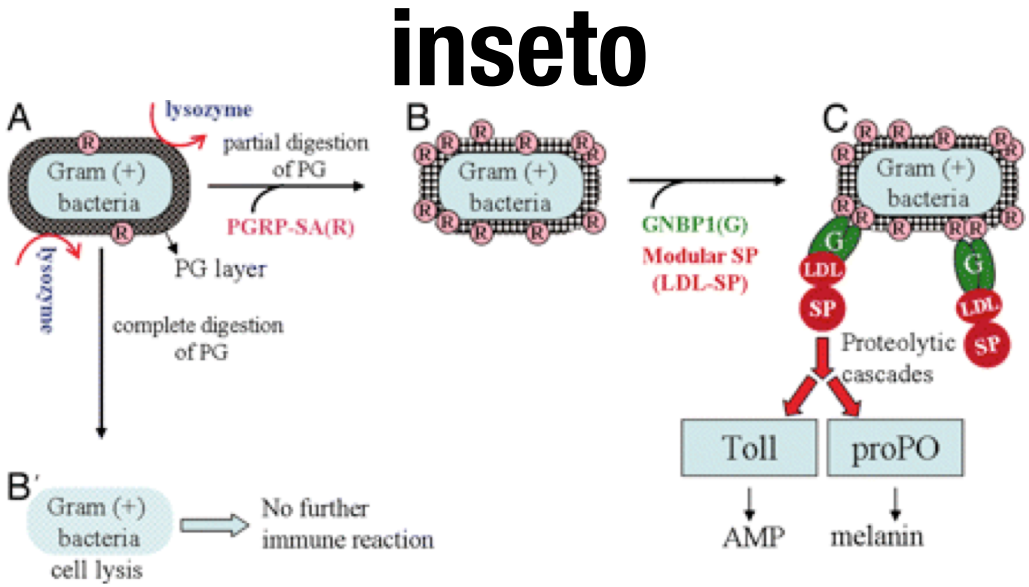

Physical barriers to infection
Chemical barriers to infection
Pathogens
Epithelial layers of skin and mucosal/glandular tissues
Acidic pH and anti-microbial proteins and peptides
H+
Cellular responses to infection
Damage/infection
Pathogens
Infected cell
Macrophage
Phagocytosis and degradation
PRMs complemento
Killing by NK cell
Mediadores (citocinas, moleculas antimicrobianas)
NK cell

Cascadas antimicrobianas

- Sistema do complemento
- Via da profenoloxidase (invertebrados)
- Via da coagulaçao (invertebrados)

Via da profenoloxidase

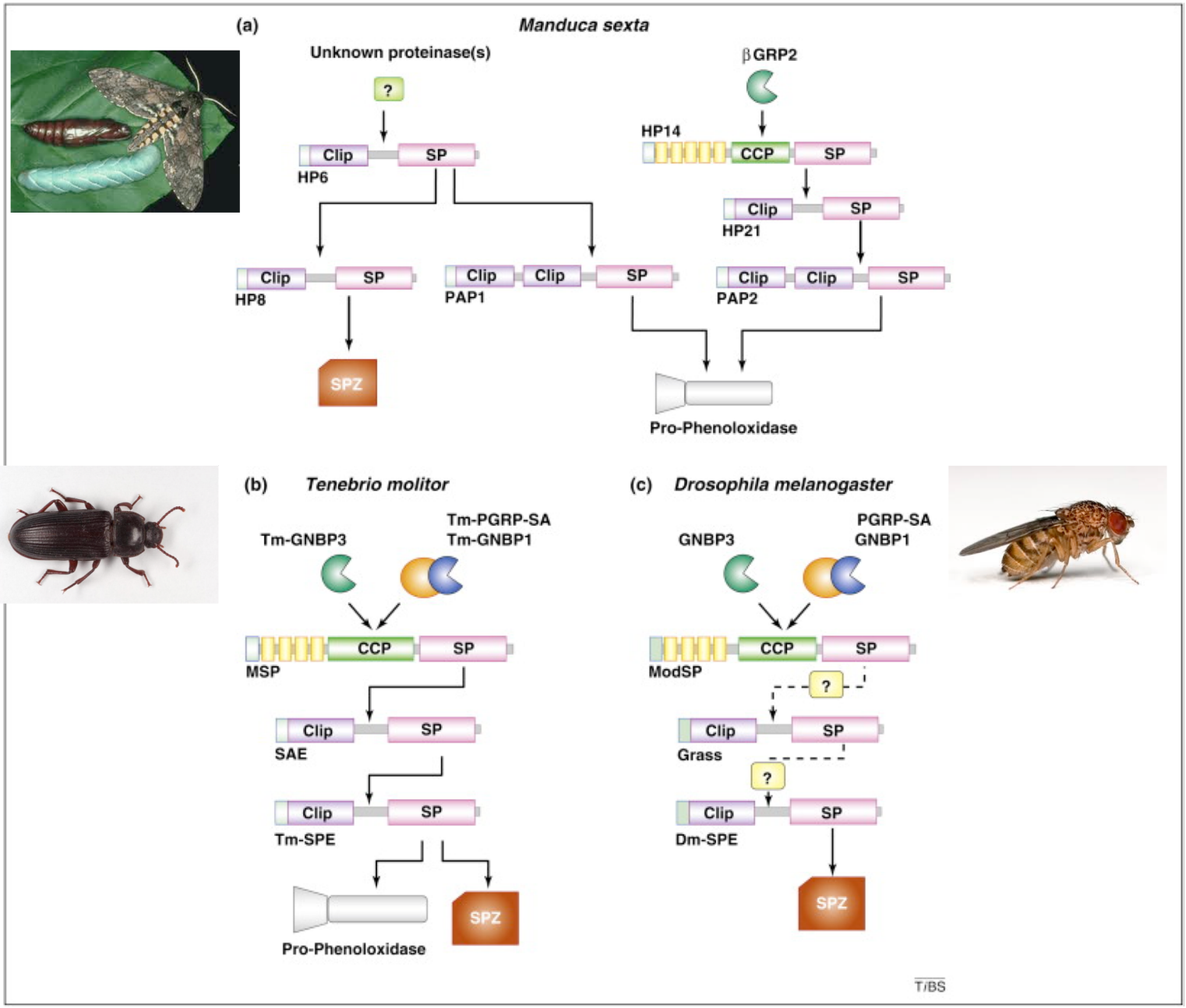




Maior sistema de defesa dos invertebrados è a melanizaçao dos patogenso e dos tecidos danificados

- **pode inibir o crescimento do parassita**
- **Induz junto com a ativaçao de PPO varias reaçoes imunes como a produçao de fatores anti-microbianos, citotoxicos, de osponizaçao etc**

Via da profenoloxidase



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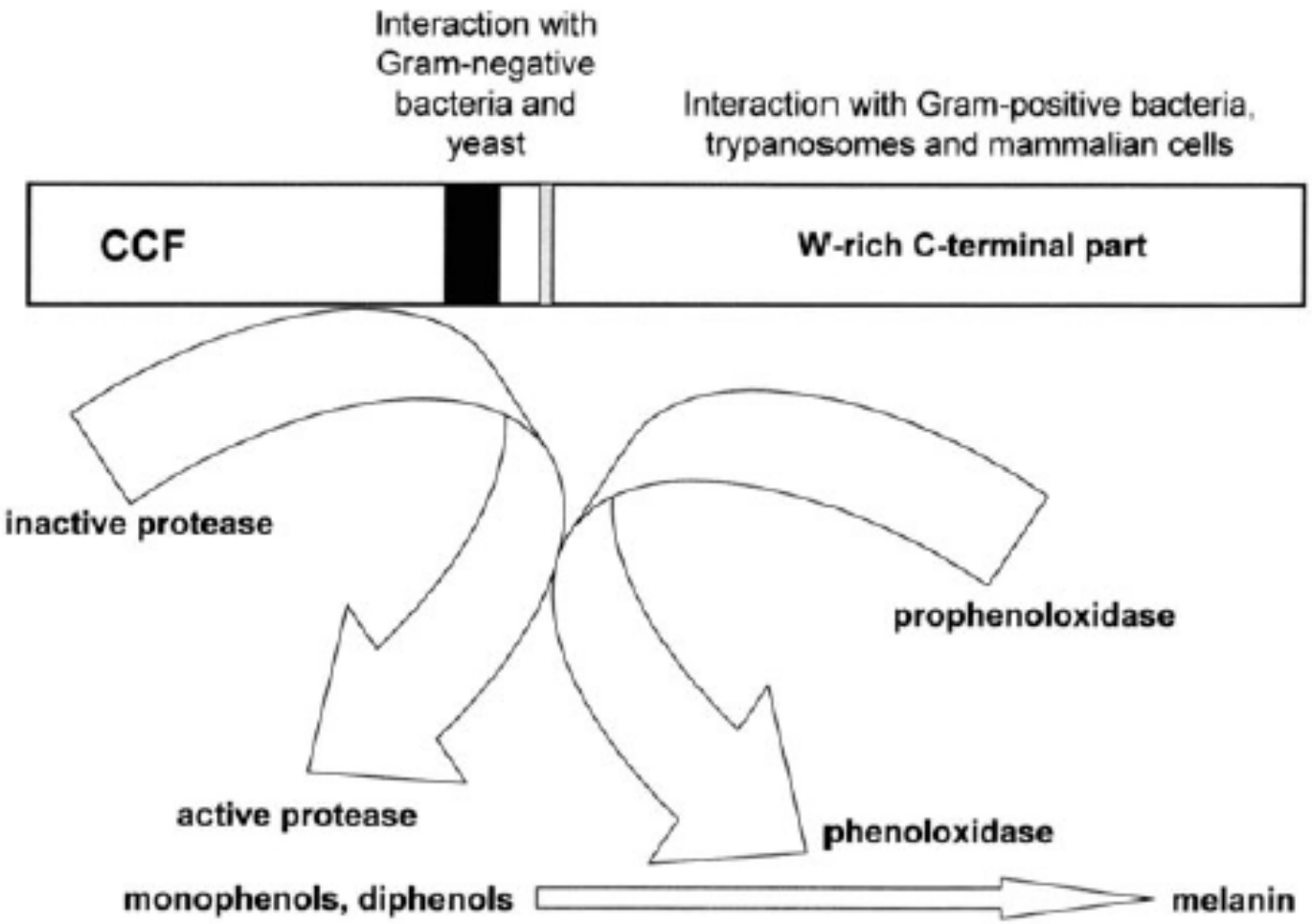
Via da profenoloxidase

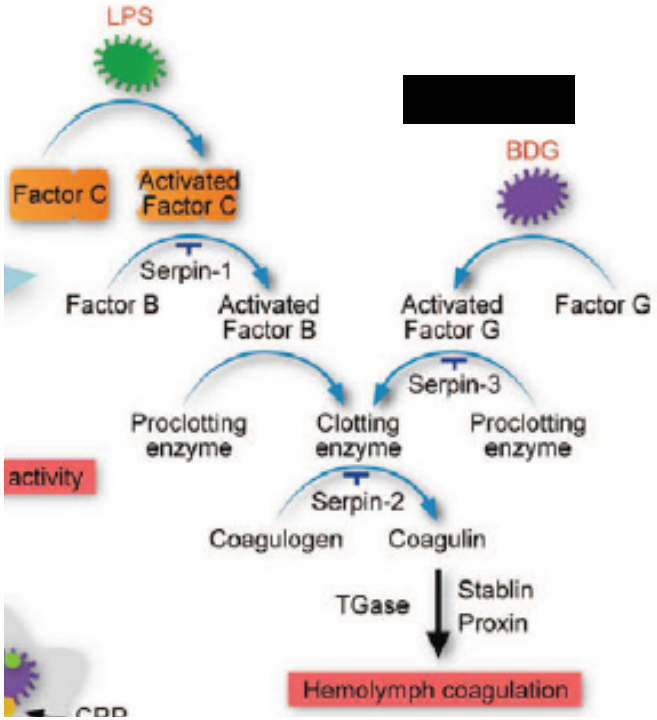
Anellidi PRM



Invertebrate immuniity, Soderhall

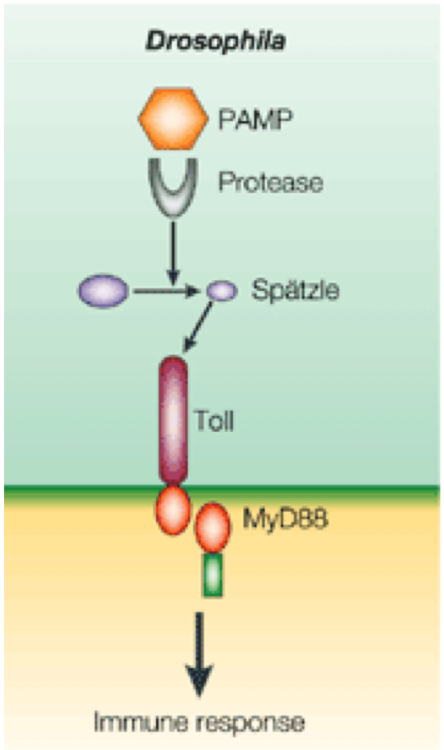
Cascada enzimaticas

PRM ativa a coagulaçao

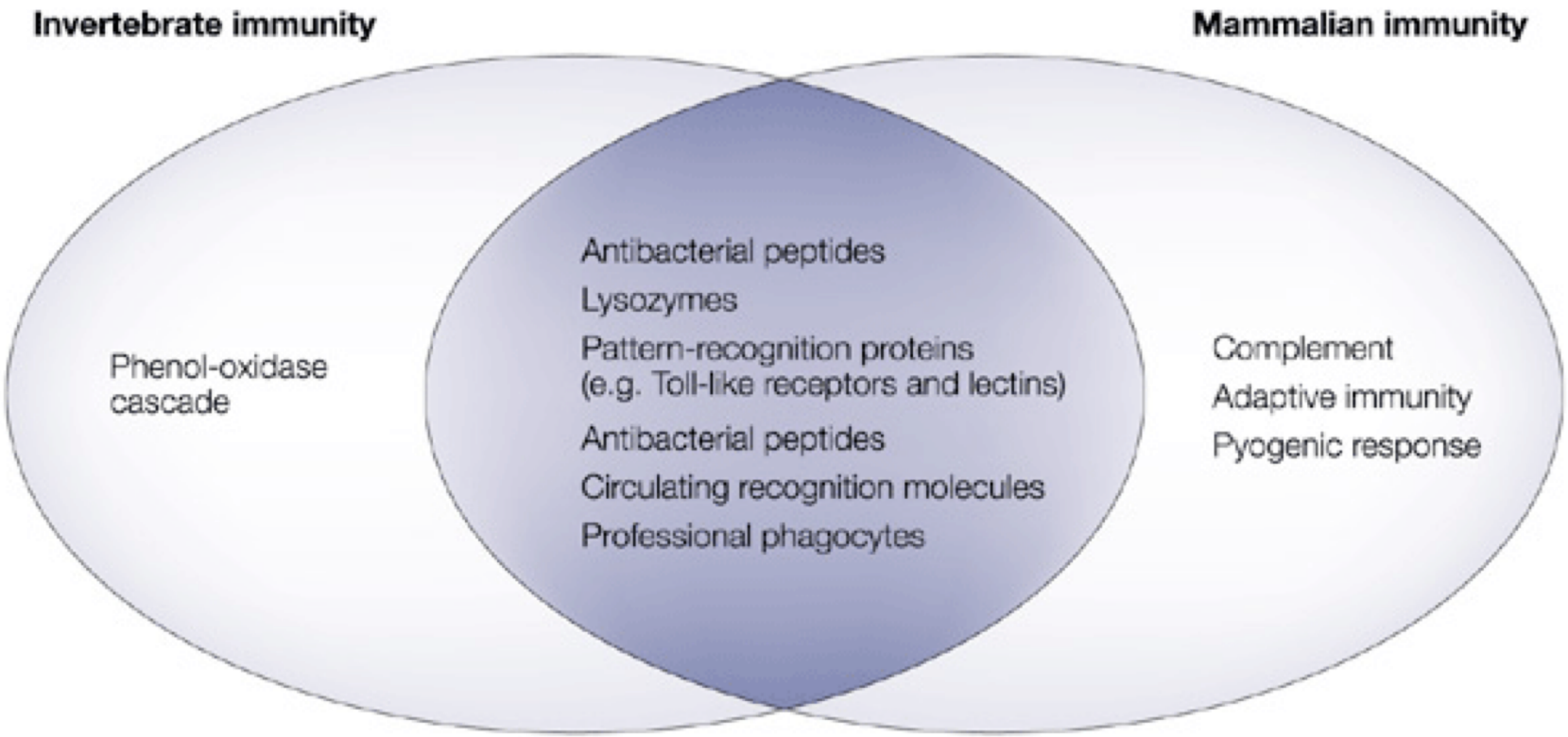


Invertebrate immuniity, Soderhall

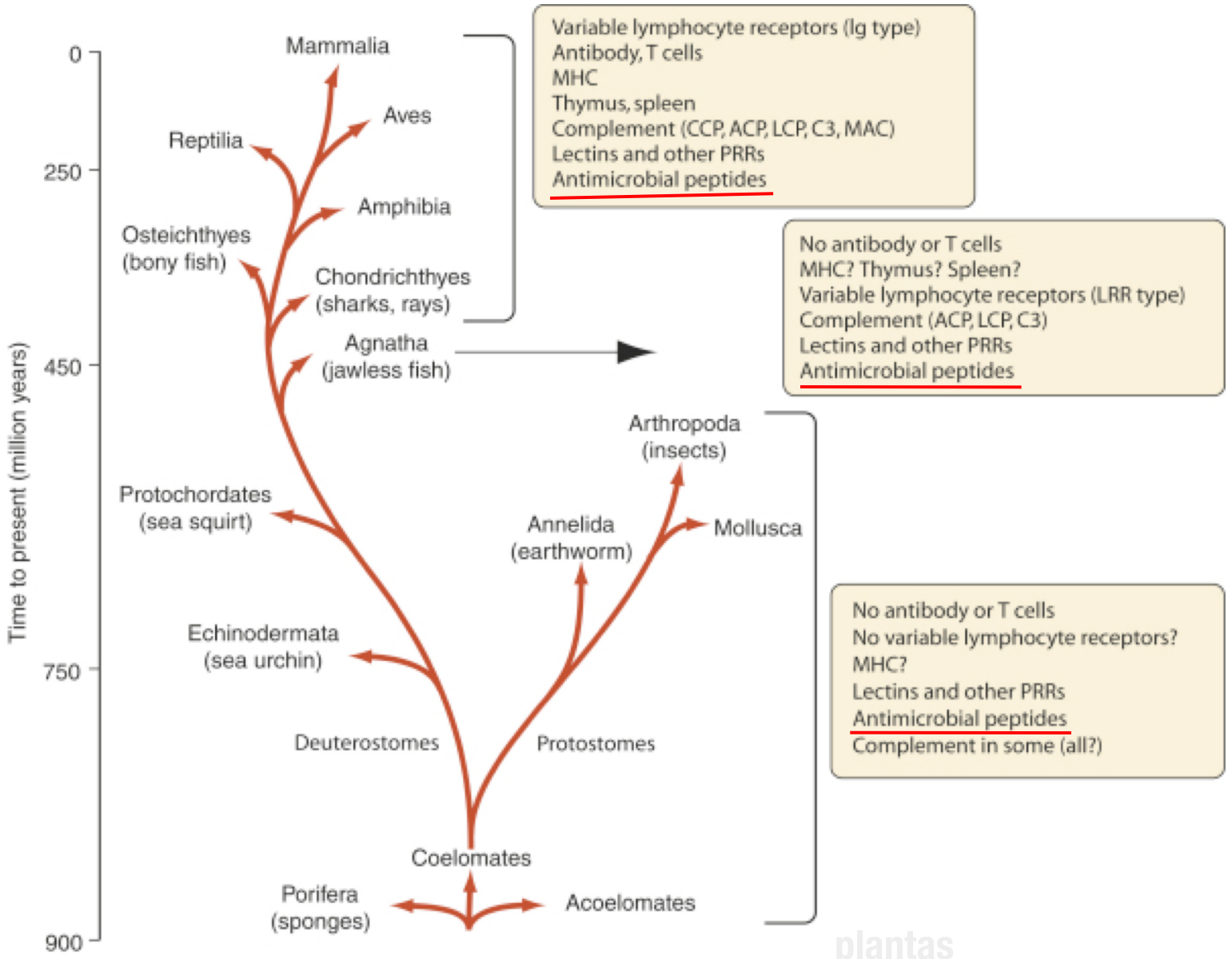
PRM ativa um ligando para PRRs



Imunidade


Invertebrate immunity
Mammalian immunity
Phenol-oxidase cascade
Antibacterial peptides
Lysozymes
Pattern-recognition proteins (e.g. Toll-like receptors and lectins)
Antibacterial peptides
Circulating recognition molecules
Professional phagocytes
Complement
Adaptive immunity
Pyogenic response
Nature Reviews | Microbiology

Imunidade



plantas