

Patogênese Bacteriana – fatores de virulência

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Microbiologia Médica – Patrick Murray, Ken Rosenthal e Michael Pfaller, 6 ed. ou posterior

Mims – Microbiologia Médica – Goering, Dockrell, Zuckerman, Roitt, Chiodini, 5 ed ou posterior

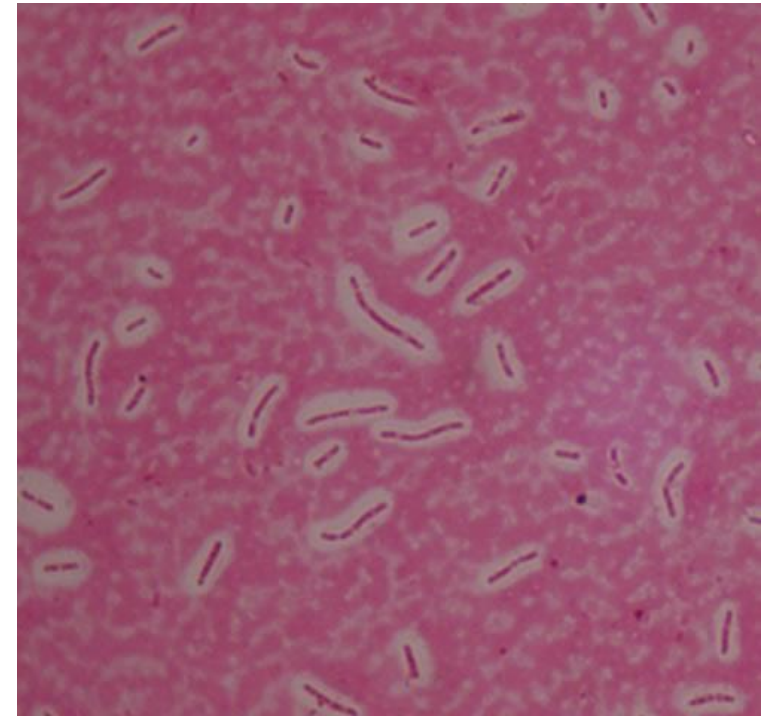
Fatores de virulência = fatores que aumentam a habilidade de uma bactéria em causar doença.

Podem estar relacionados com:

1. Estruturas de evasão
2. Liberação de toxinas
3. agentes estimuladores de resposta imune
4. Destruição direta dos tecidos
5. produtos do metabolismo e estruturas de captação de nutrientes

Uma doença infecciosa bacteriana é uma combinação entre o dano causado pela bactéria e das consequências das respostas inatas e imune à infecção

-Como as bactérias podem cruzar as barreiras do corpo?



-Qual o efeito disso para nossa saúde?



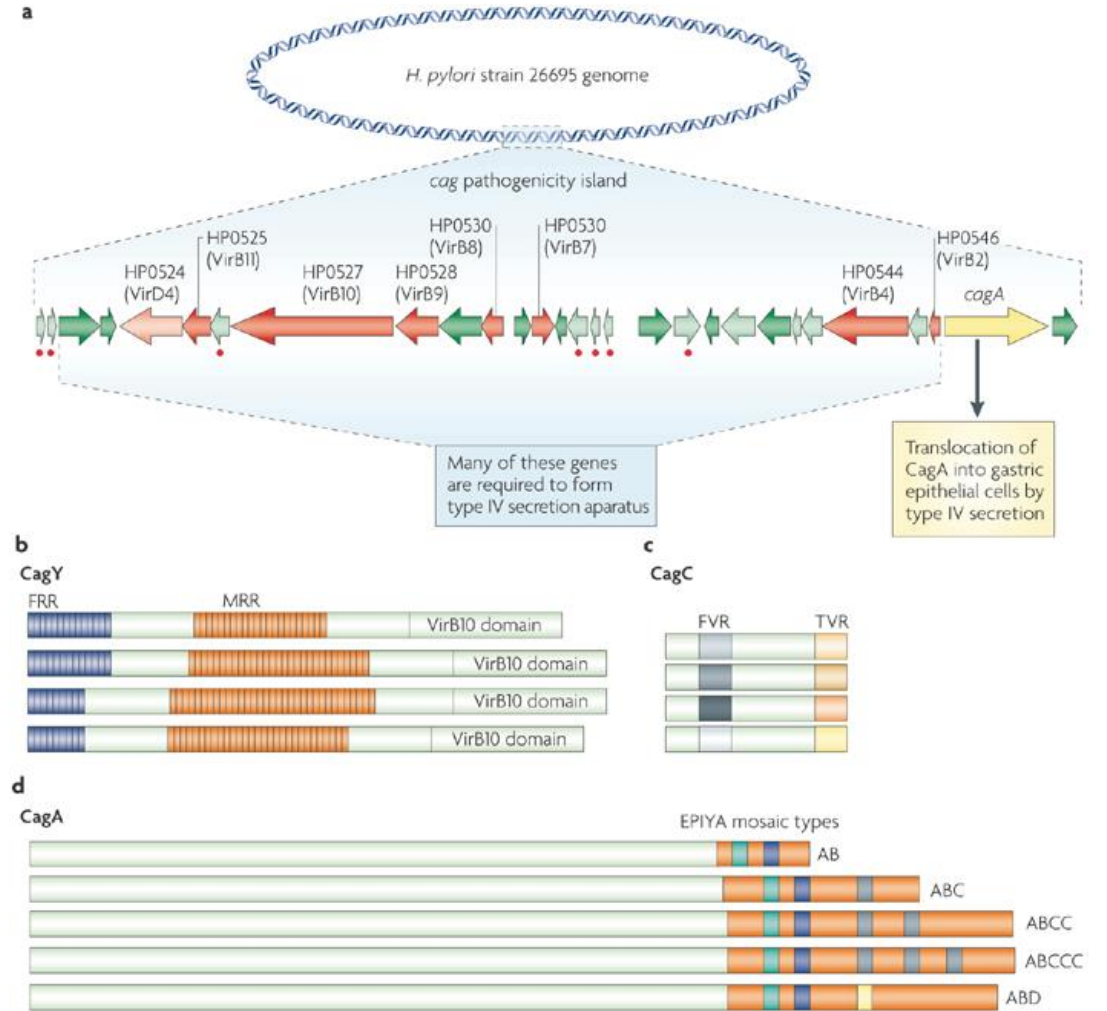
Ilhas de patogenicidade = regiões cromossômicas que contêm conjunto de genes que codificam diversos fatores de virulência



Geralmente é um transposon inserido no cromossomo ou um plasmídeo



Os genes são ativos por um determinado estímulo, como por exemplo pH



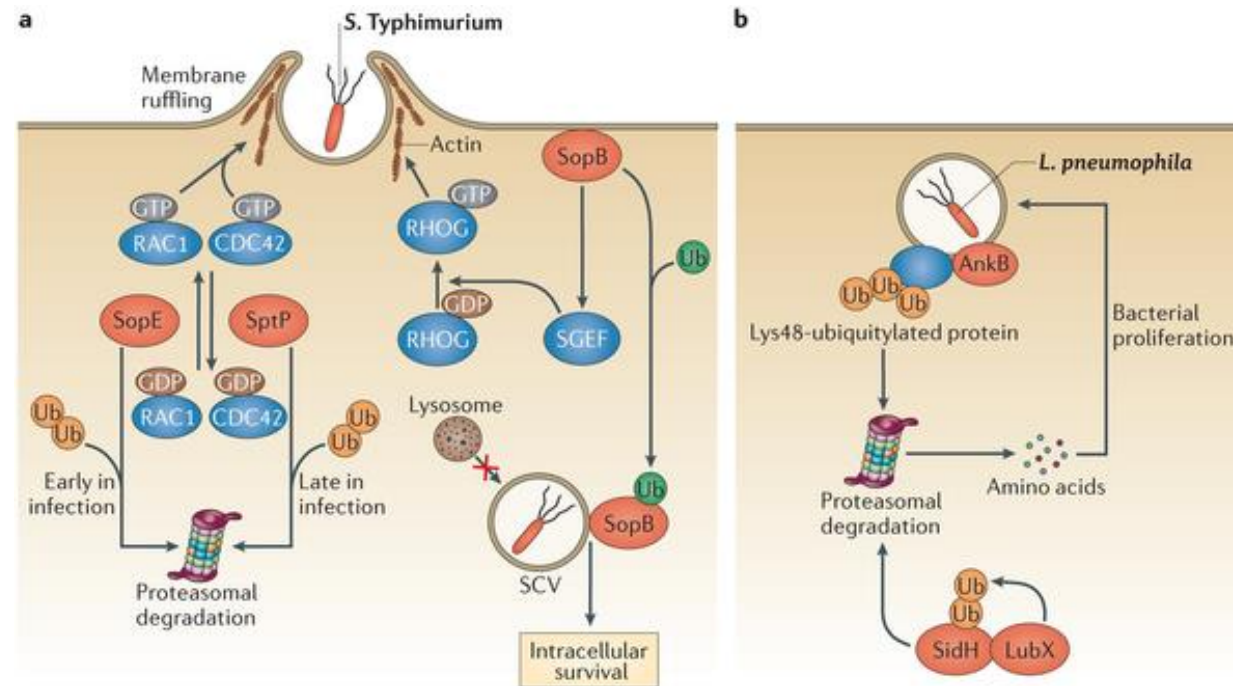
1. Mecanismos de evasão

Estratégias de evasão bacteriana das defesas naturais, não adaptativas

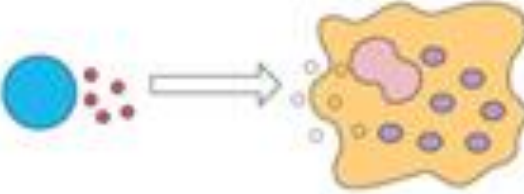
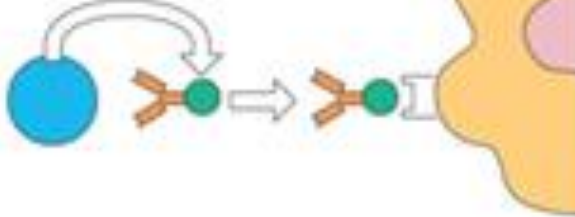



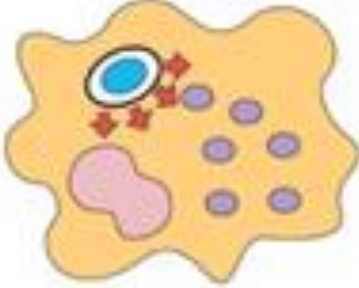
- Matar os fagócitos ou sobreviver à fagocitose
 - Interferir na ação ciliar
 - Interferir na ativação do complemento
 - Evitar o reconhecimento do sistema imune
- Clivagem do peróxido de hidrogênio e peptídeos antimicrobianos

Alteração do citoesqueleto

Produção de proteínas chamadas de invasinas. Ex. *Salmonella typhimurium*



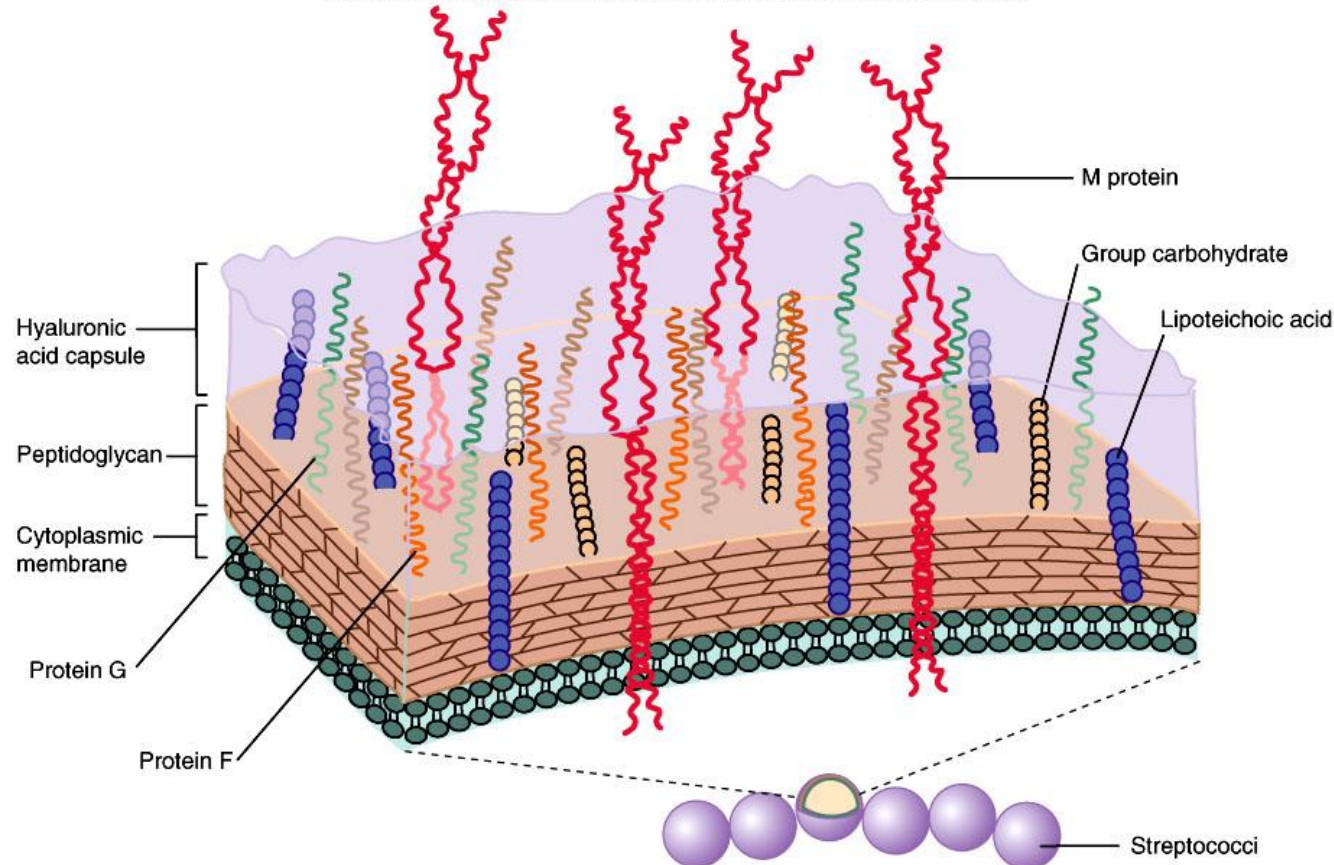
Como evitar a fagocitose?

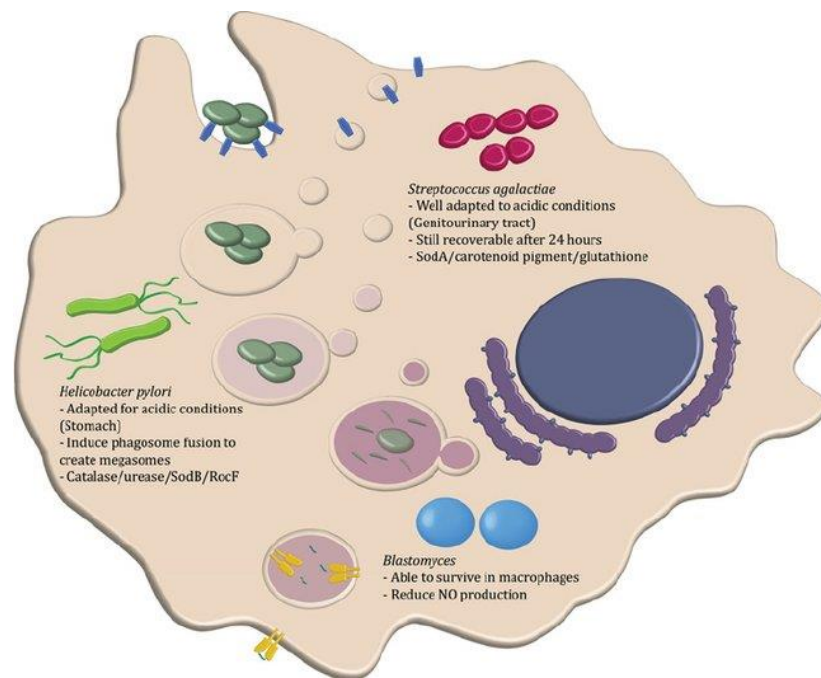
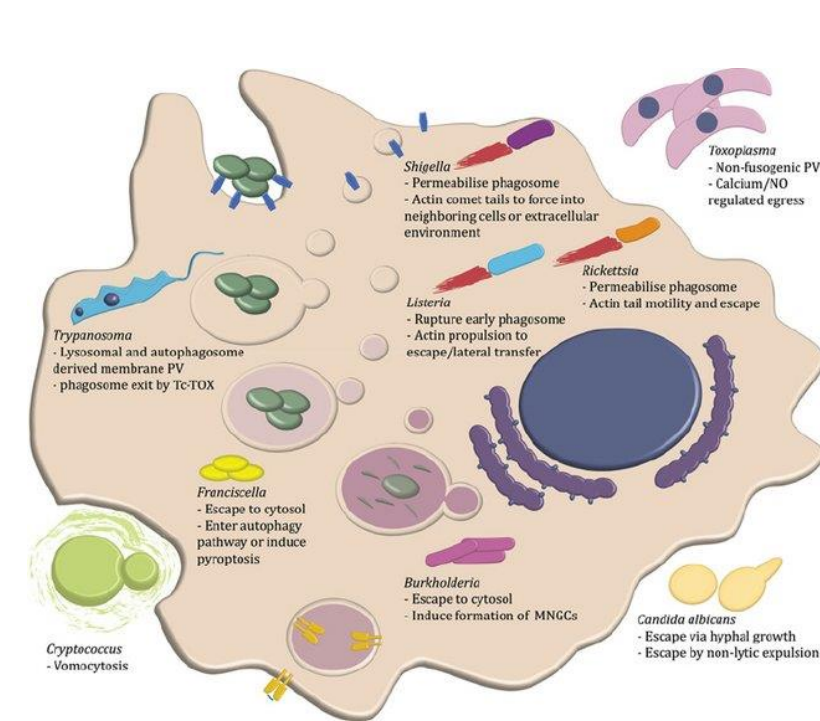
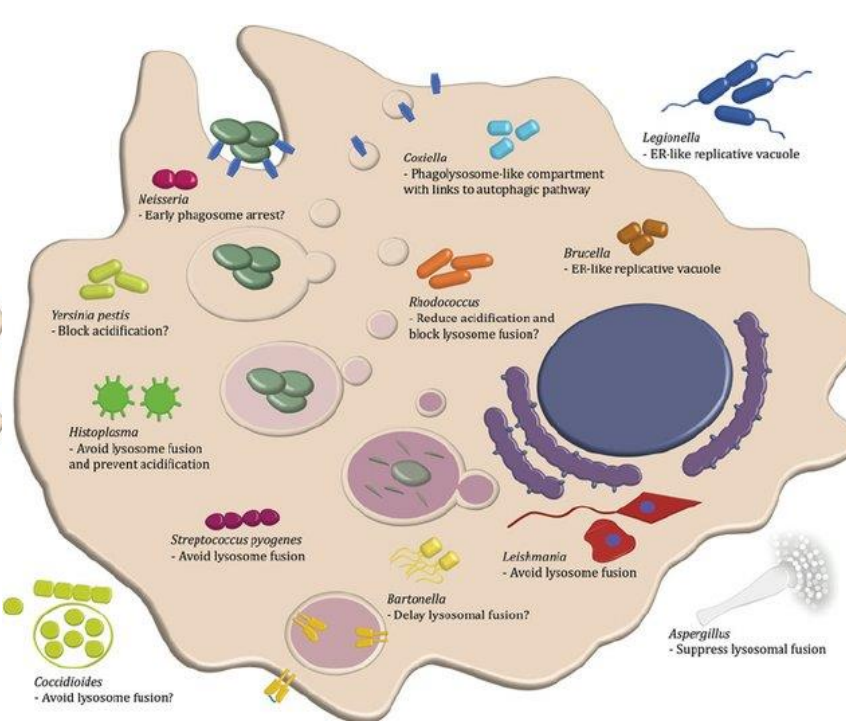
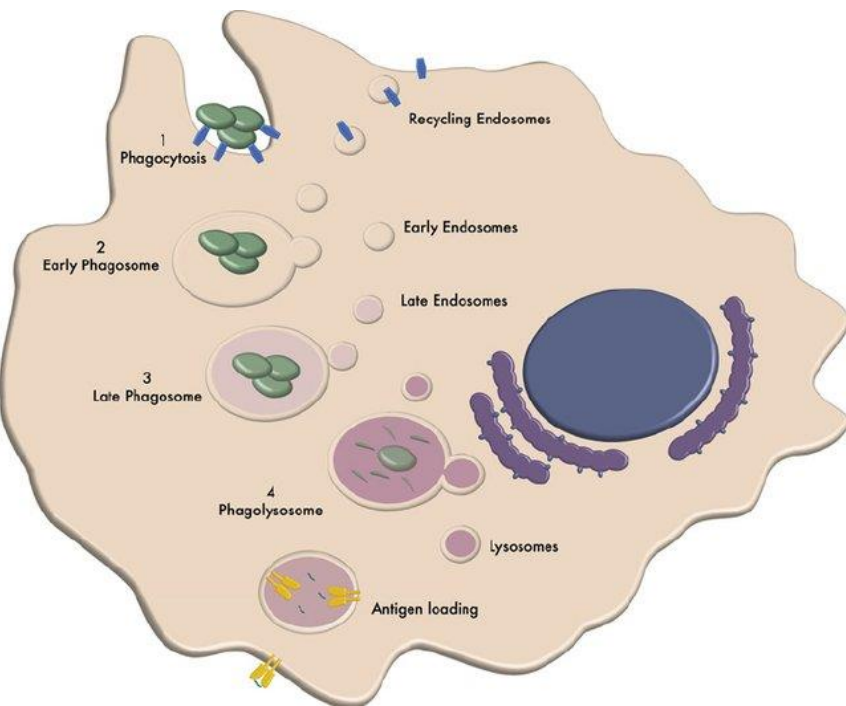
toxin release	opsonization prevented	contact with phagocyte prevented
 <p data-bbox="402 591 912 733">organism releases toxin, e.g. staphylococci, streptococci, amoebae</p> <p data-bbox="774 591 912 691">phagocyte killed by toxin</p>	 <p data-bbox="970 591 1600 733">organism (e.g. staphylococci) produces a protein (e.g. protein A) which prevents interaction between opsonizing antibody and phagocyte, so preventing phagocytosis</p>	 <p data-bbox="1633 591 2160 733">organism possesses a capsule which prevents contact with the phagocyte, e.g. <i>Streptococcus pneumoniae</i>, haemophilus, <i>Bacillus anthracis</i></p>
phagolysosome fusion inhibited	escape into the cytoplasm	resistance to killing
 <p data-bbox="402 1219 912 1362">fusion of phagosome and lysosome inhibited by organism, e.g. <i>Mycobacterium tuberculosis</i>, toxoplasma, chlamydia</p>	 <p data-bbox="970 1219 1600 1362">organism escapes from the phagolysosome into the cytoplasm and replicates within the phagocyte, e.g. <i>Listeria</i>, leishmania, <i>T. cruzi</i>. Even <i>M. tuberculosis</i> may do this!</p>	 <p data-bbox="1633 1219 2160 1390">organism resists killing by producing antioxidants, e.g. by catalase in staphylococci, or by scavenging free radicals, e.g. by phenolic glycolipid of <i>M. leprae</i></p>

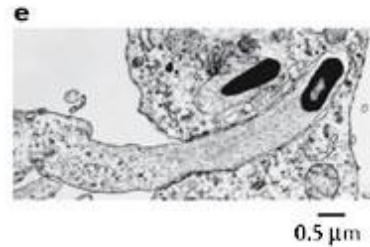
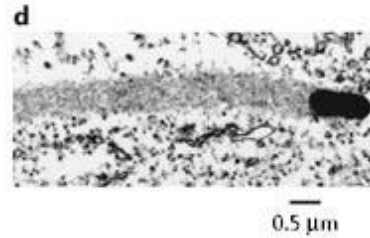
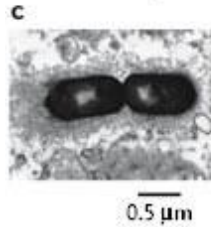
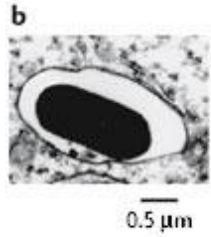
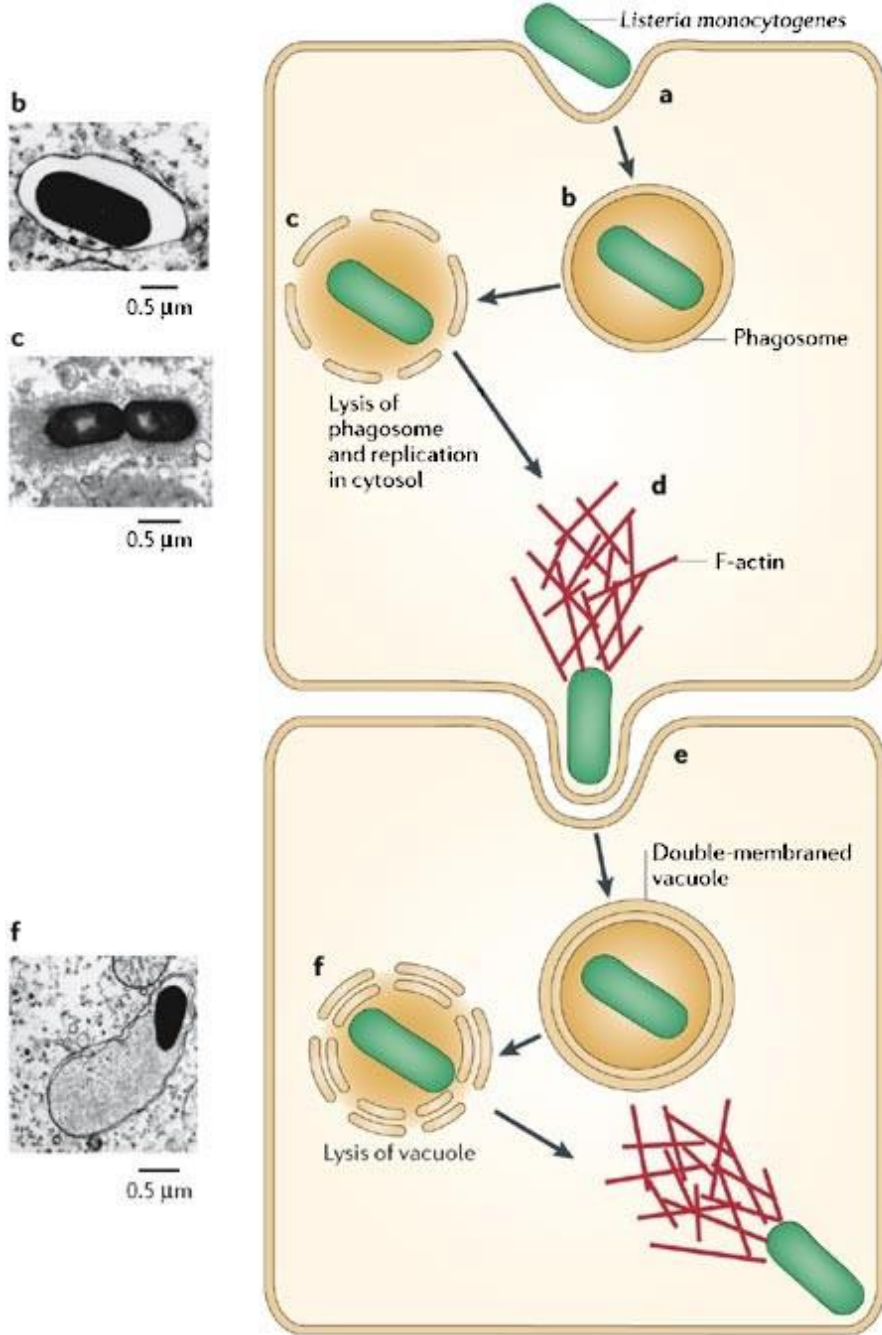
Componentes da parede celular que auxiliam na adesão e invasão

- Proteínas ou outras substâncias químicas: **proteína M** em *Streptococcus pyogenes* – impedem a ação da fagocitose destruindo Convertase C3 produzida pelos glóbulos brancos. Assim como as **proteínas L** auxiliam no adesão.

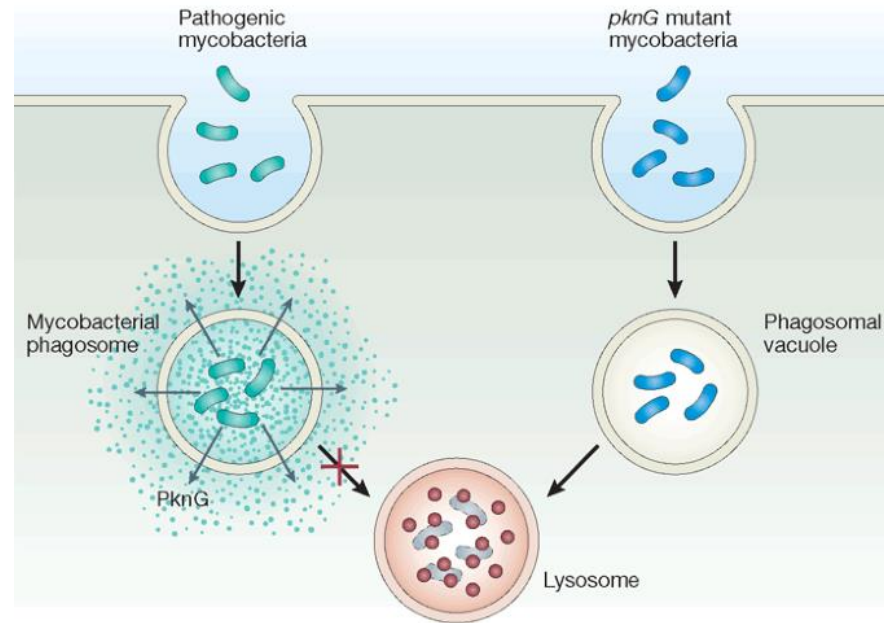
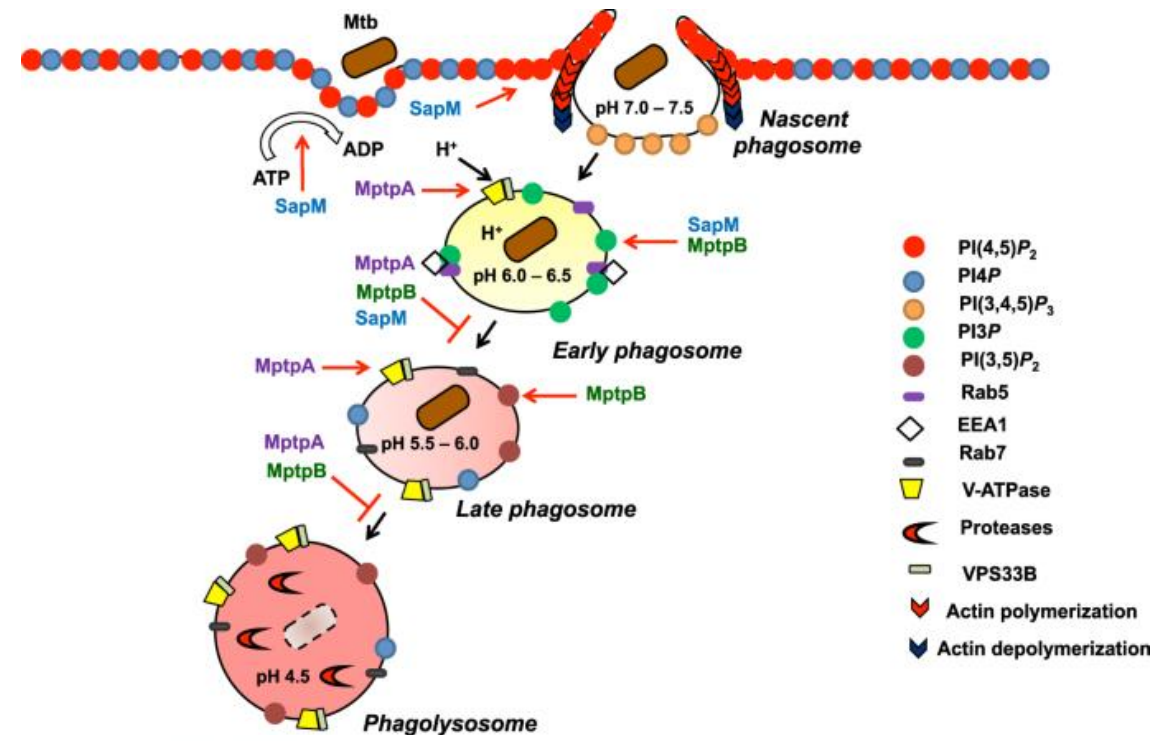
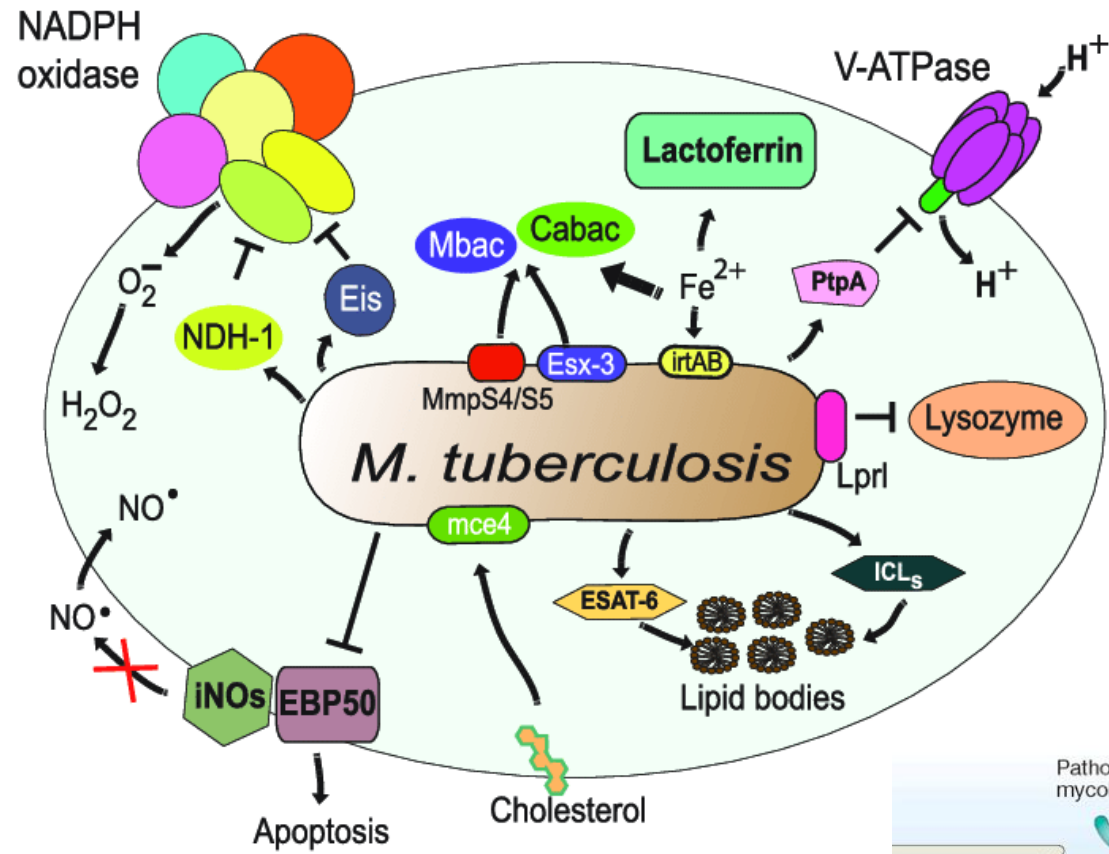
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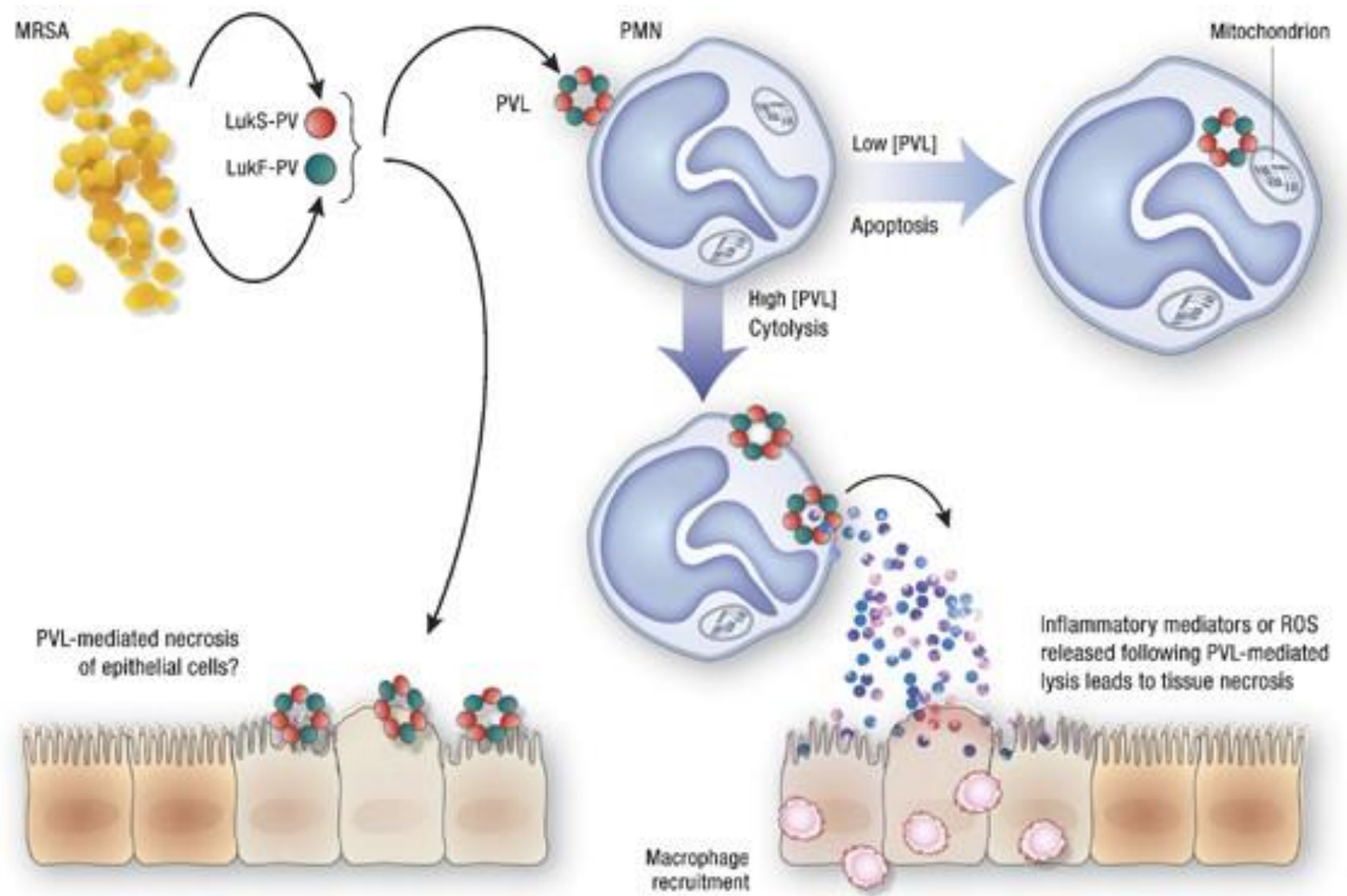




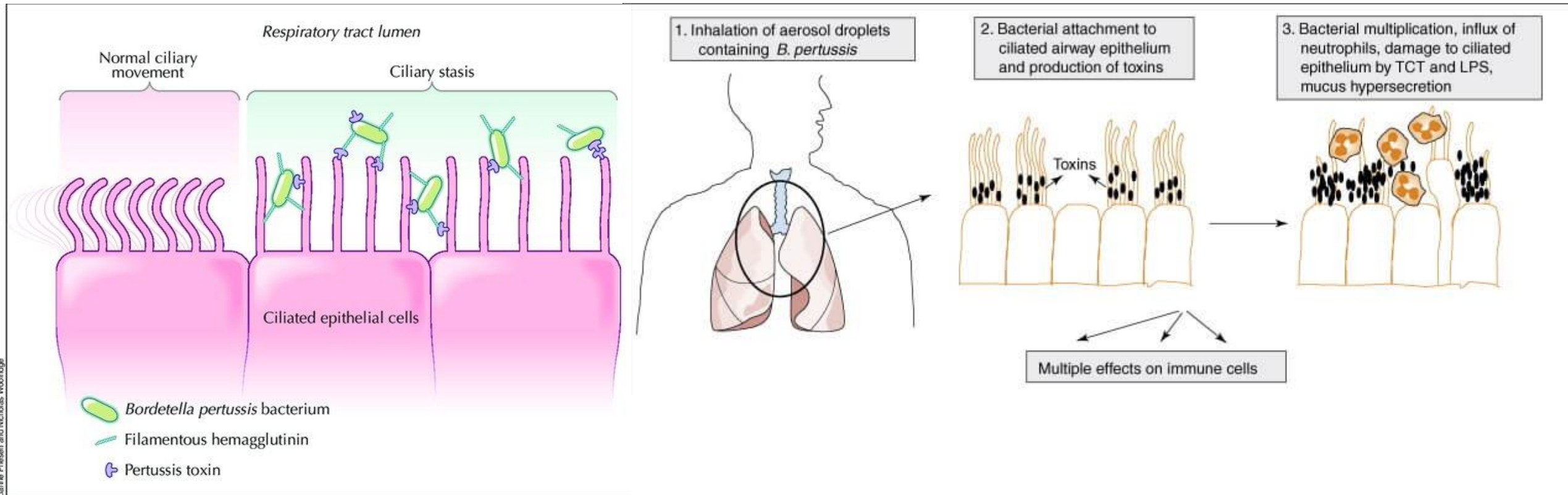


<https://youtu.be/4JWpG8XPku4>





Interferência na ação ciliar por *Bordetella*



Interferência na ativação do complemento

1 – presença de cápsula previne a ativação;

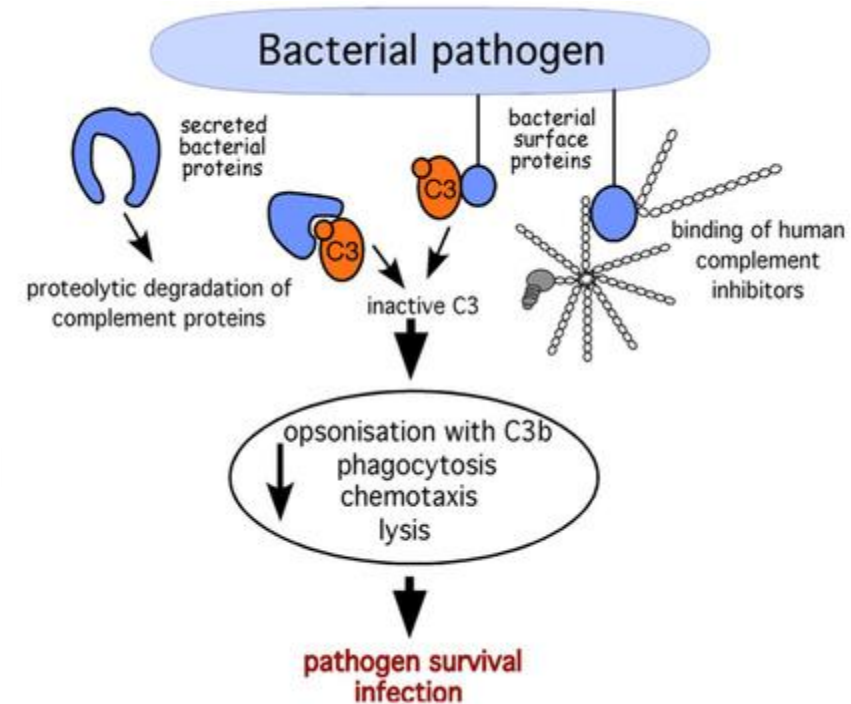
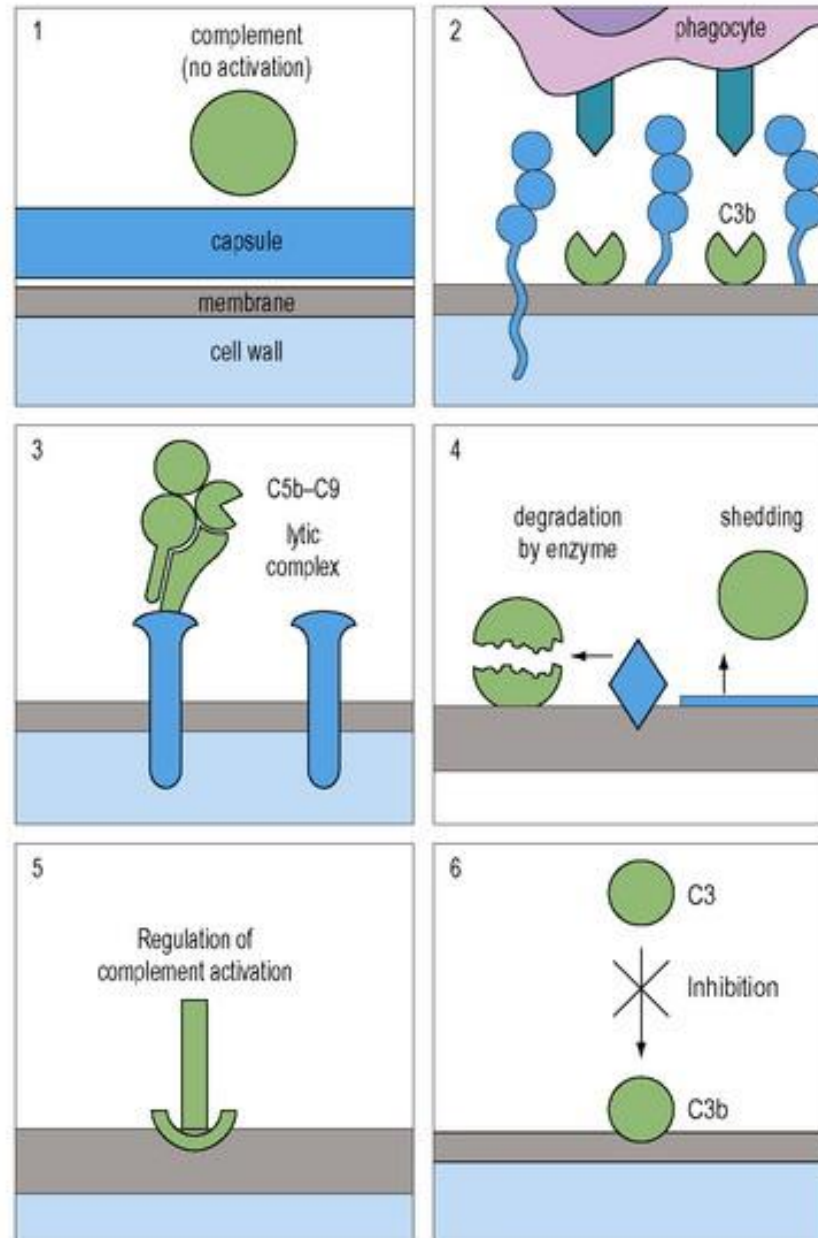
2 – configuração da superfície bacteriana evitando que receptores celulares não tenham acesso a C3b;

3- estruturas superficiais podem ser expressas e divergem da anexação do complexo lítico da membrana celular

4- proteases ligadas a membrana degradam o complemento

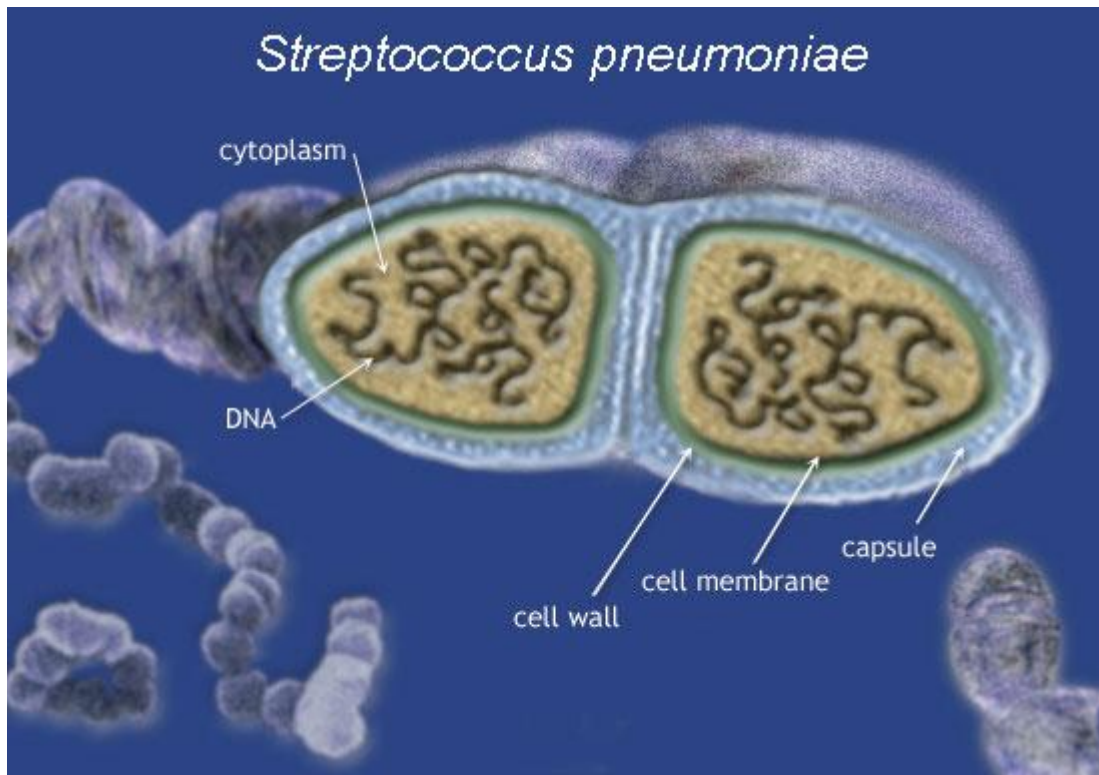
5- a superfície bacteriana pode apresentar inibidores da ativação do complemento

6- inibidores diretos das convertases C3 e C5 bloqueando a ativação do complemento

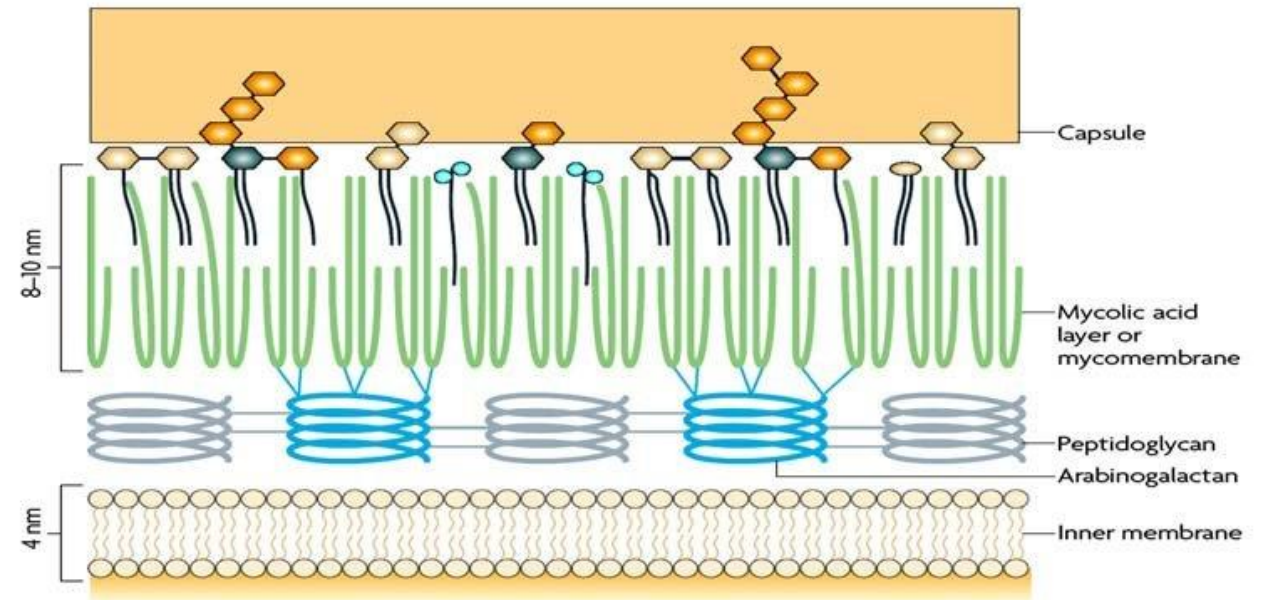


Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

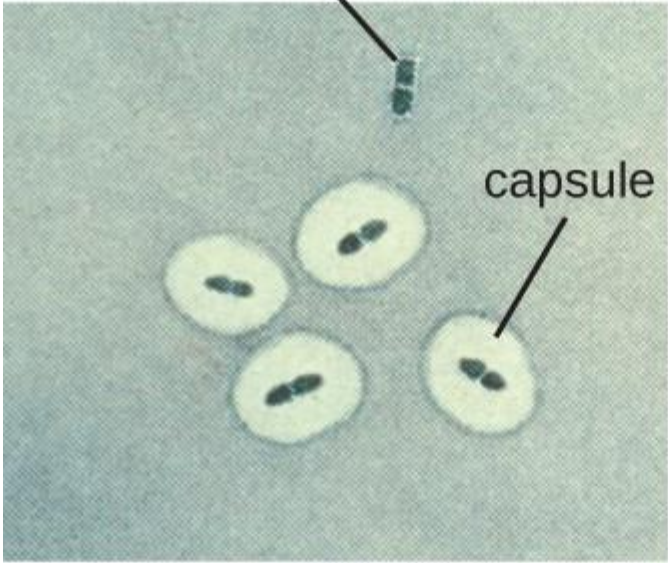
- Cápsula = impede a fagocitose



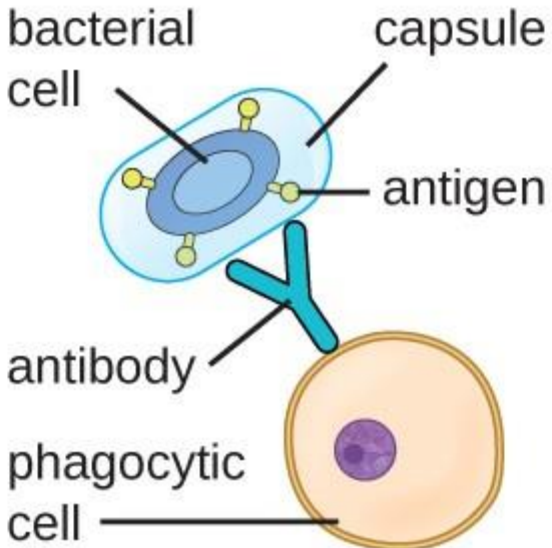
Parede celular micobacterina



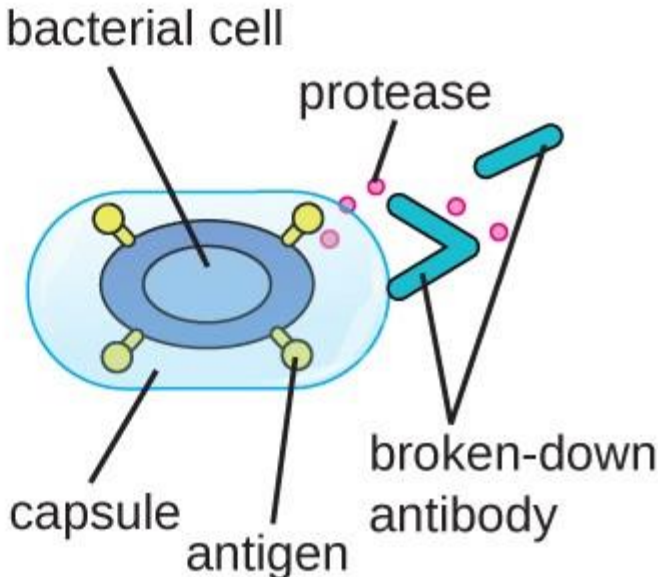
nonencapsulated bacteria



(a)



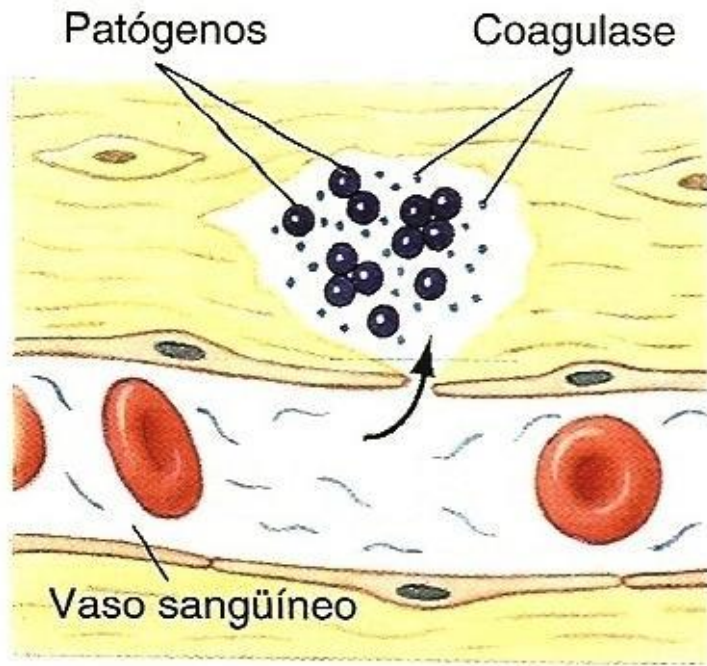
(b)



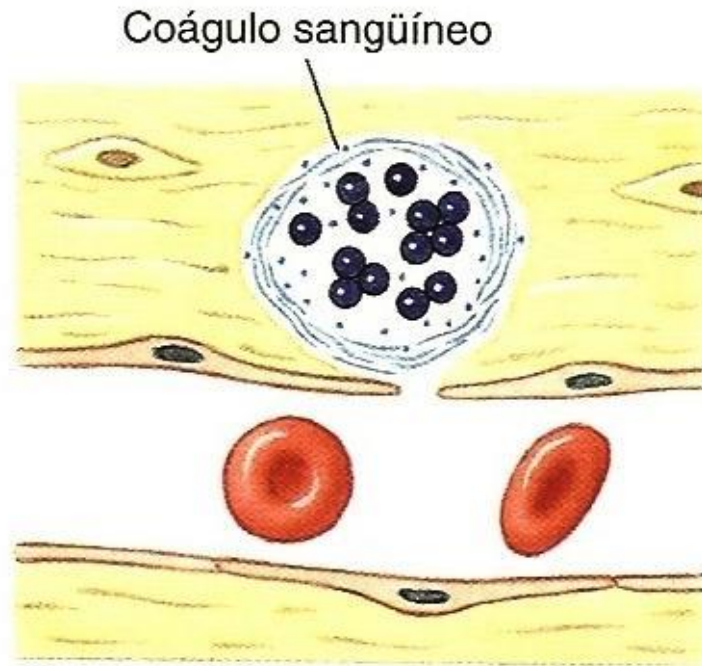
(c)

Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

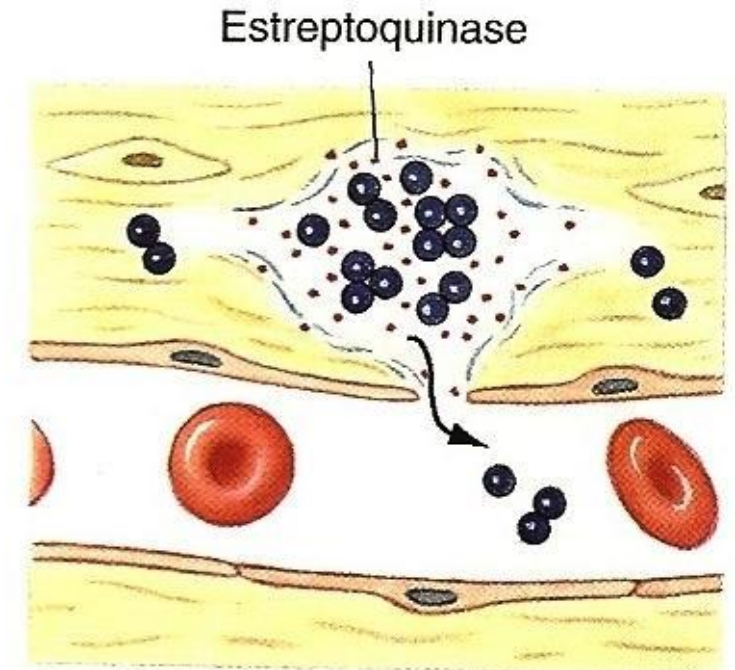
Presença de coagulase – *Staphylococcus aureus*



1. Patógenos produzem coagulase



2. Forma-se um coágulo sangüíneo ao redor dos patógenos

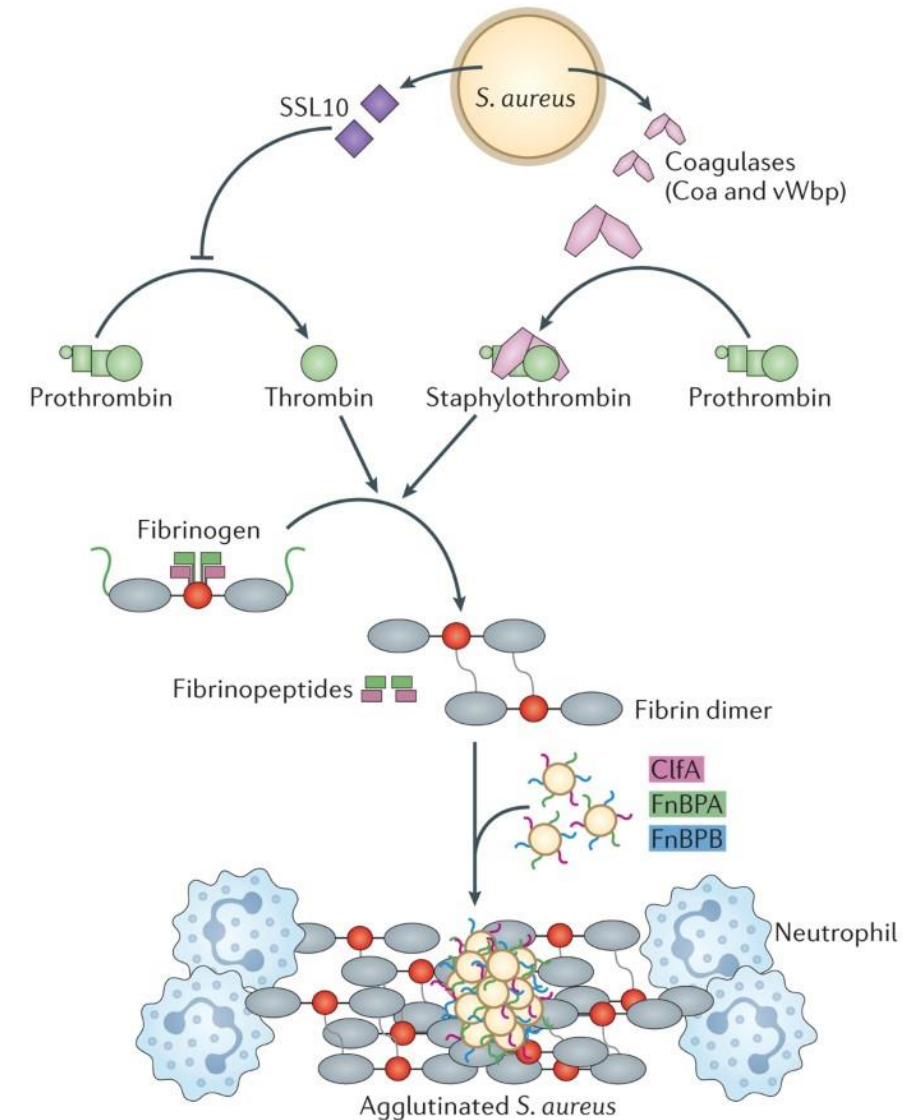
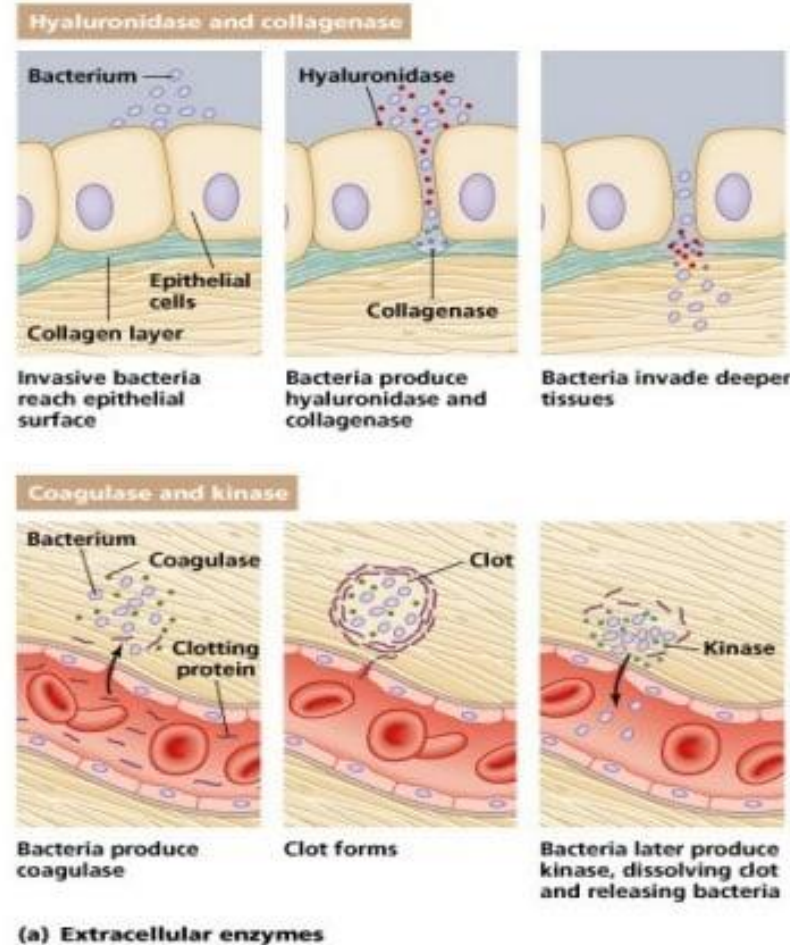


3. Patógenos produzem estreptoquinase, ocorrendo a dissolução do coágulo e liberando as bactérias

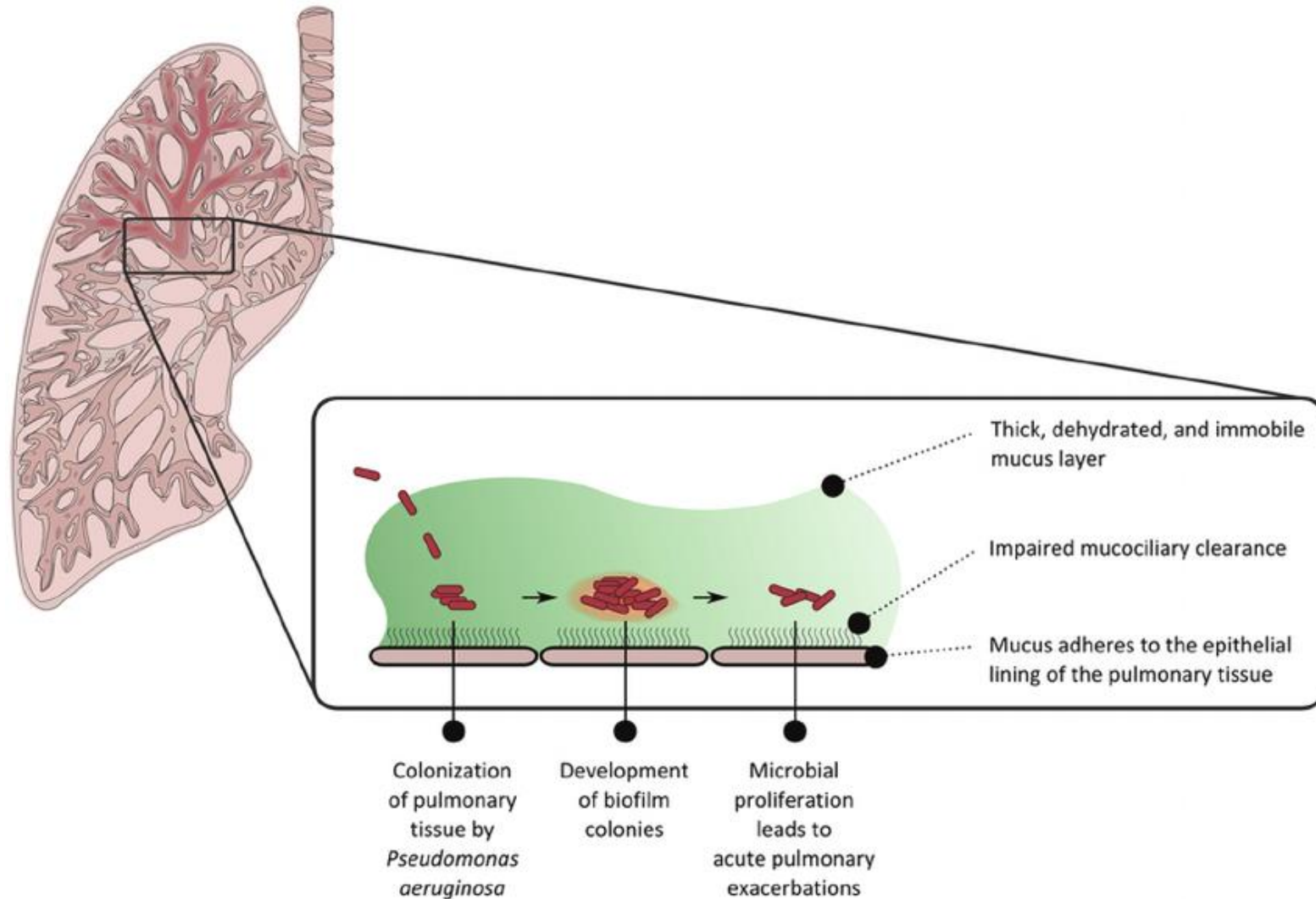
Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

Invasiveness

- Hyaluronidase
- Coagulase
- Streptokinase (dissolves Clots)

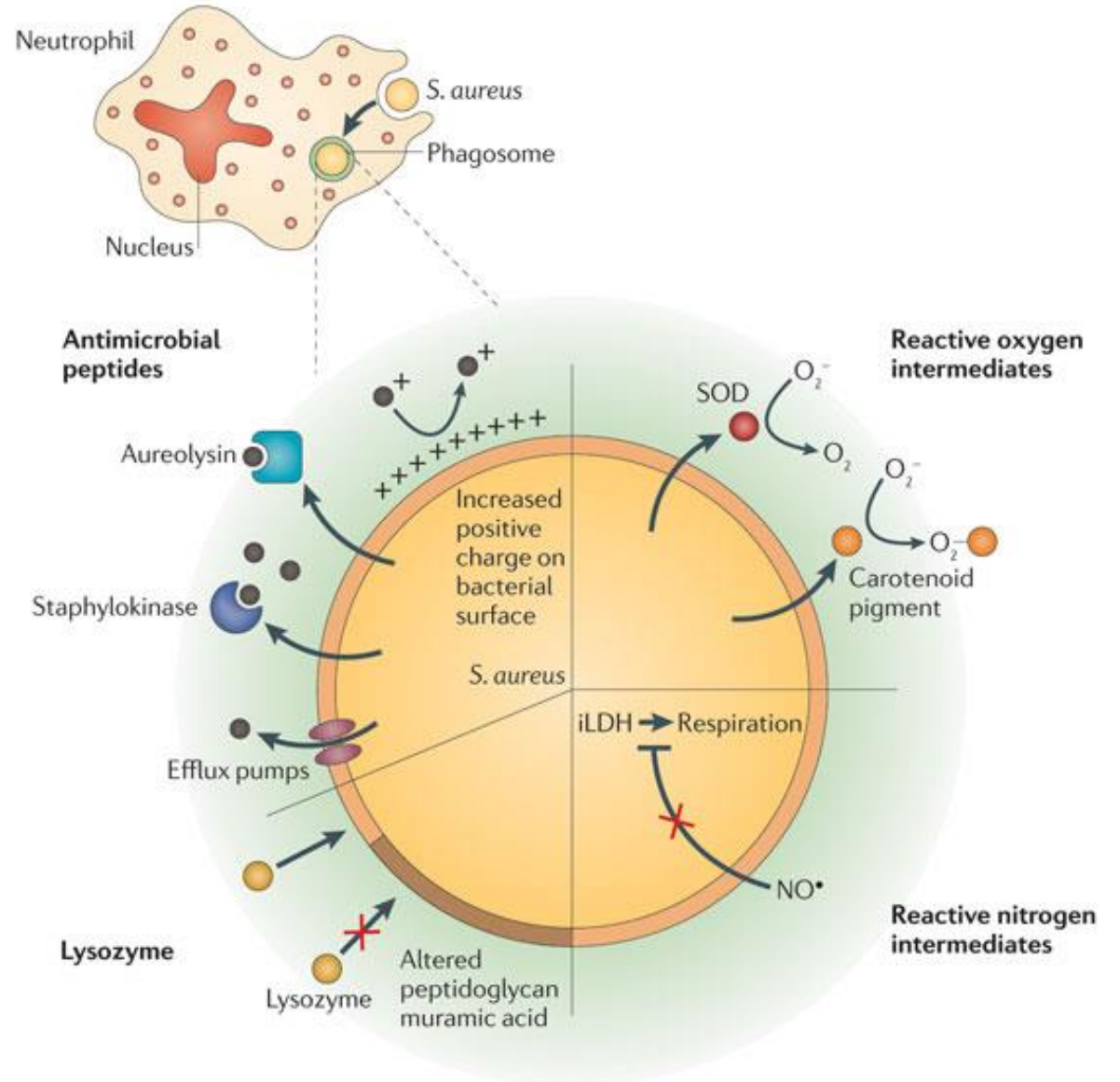


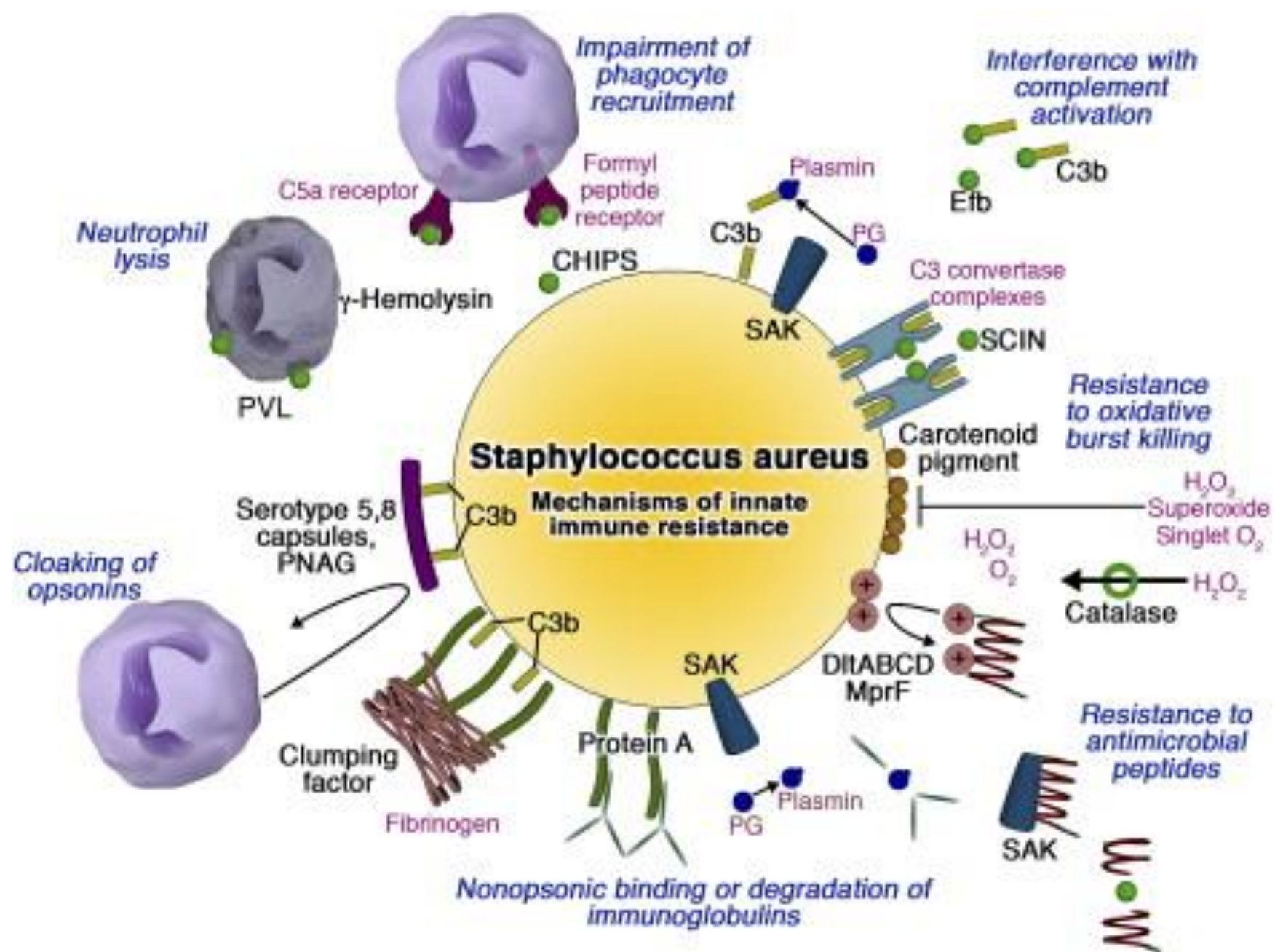
Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

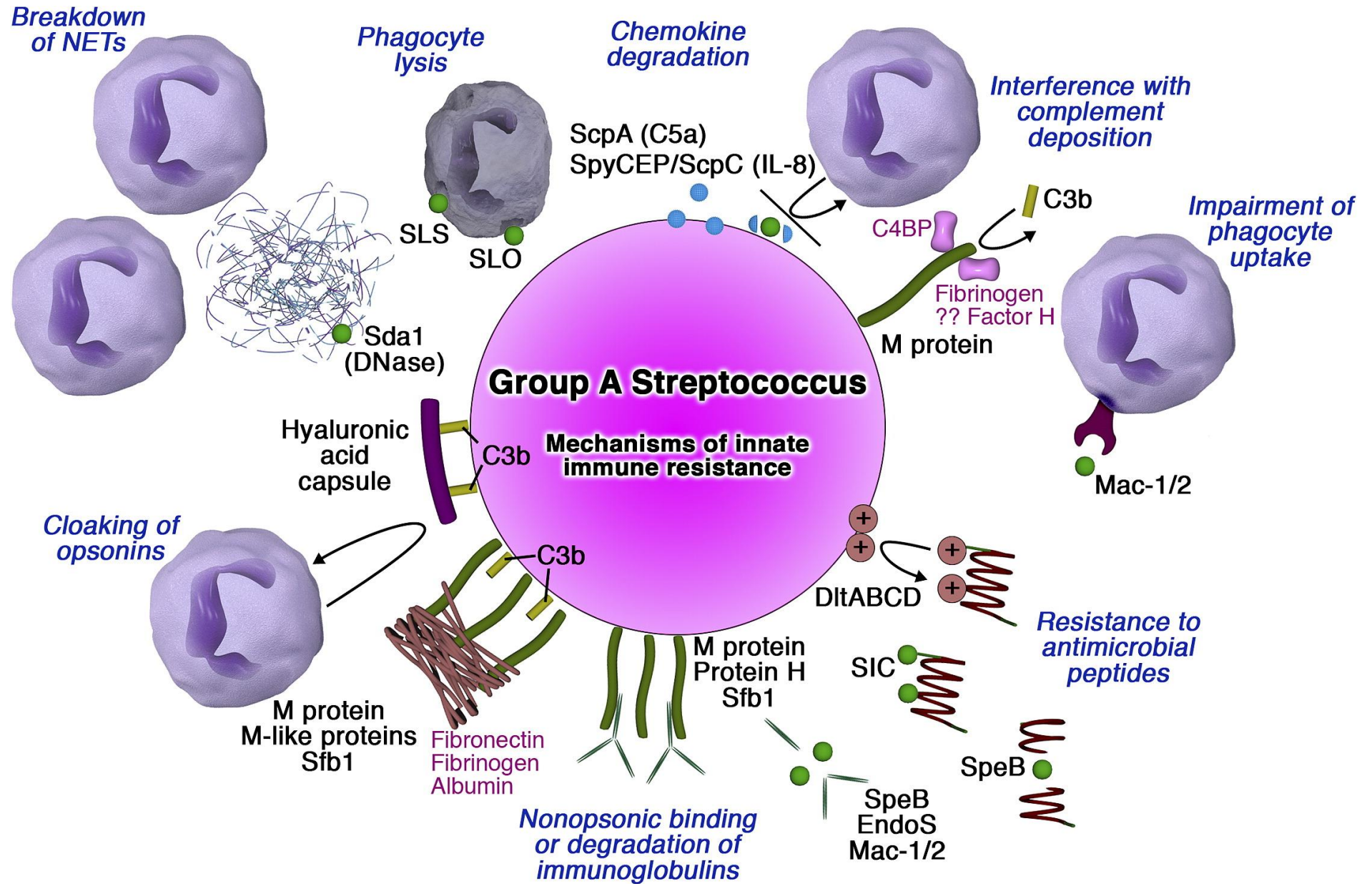


Destruição do peróxido de hidrogênio e outros componentes antimicrobianos do hospedeiro

Phagocytosis of *Staphylococcus aureus*







Estratégias para evasão de defesas adaptativas

1- Mascaramento de antígenos

2- variação antigênica

3- imunossupressão

Mascaramento de antígenos

Estratégia adotada para microrganismos intracelulares

Colonização de “locais privilegiados”, como sistema nervoso central, articulações, testículos e placenta, ou mesmo aqueles gerados pelo próprio microrganismo

Mimetizar antígenos do hospedeiro

Absorção de antígenos

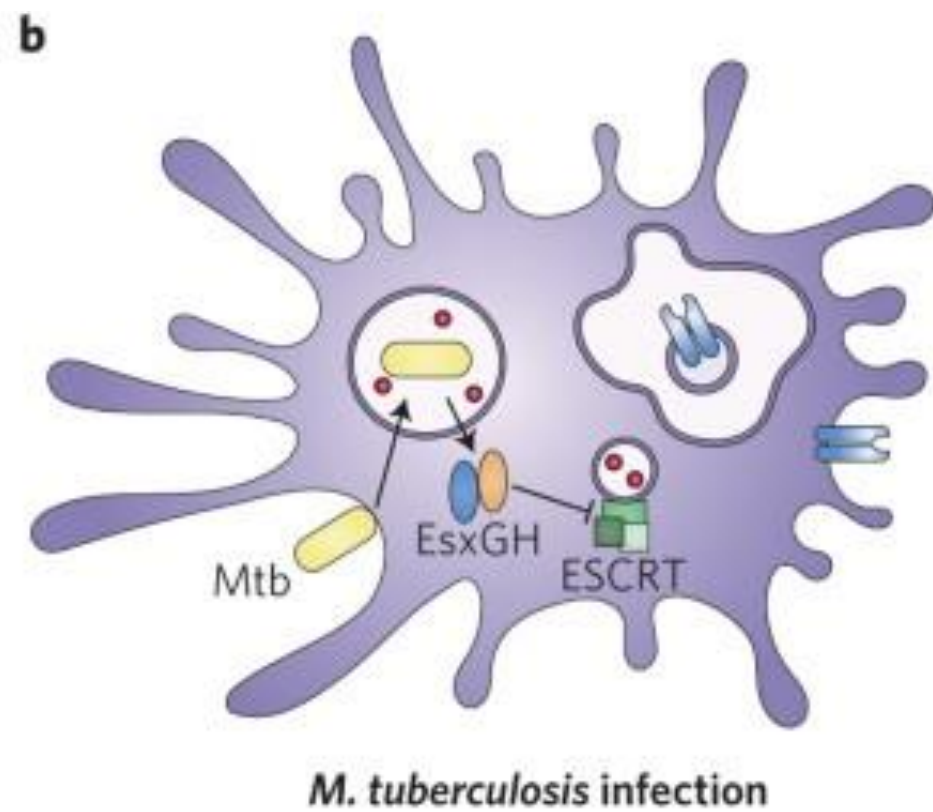
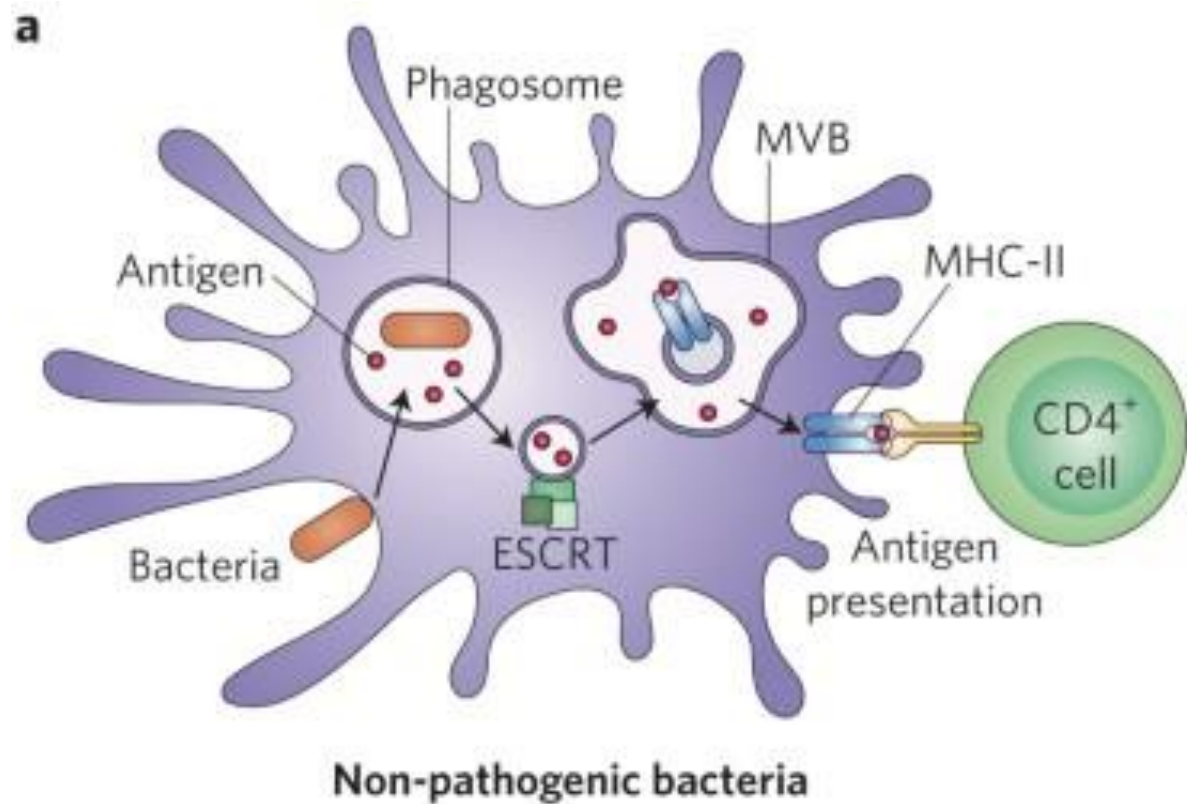
Imunomodulações: -

Perturbações no equilíbrio das respostas imunológicas

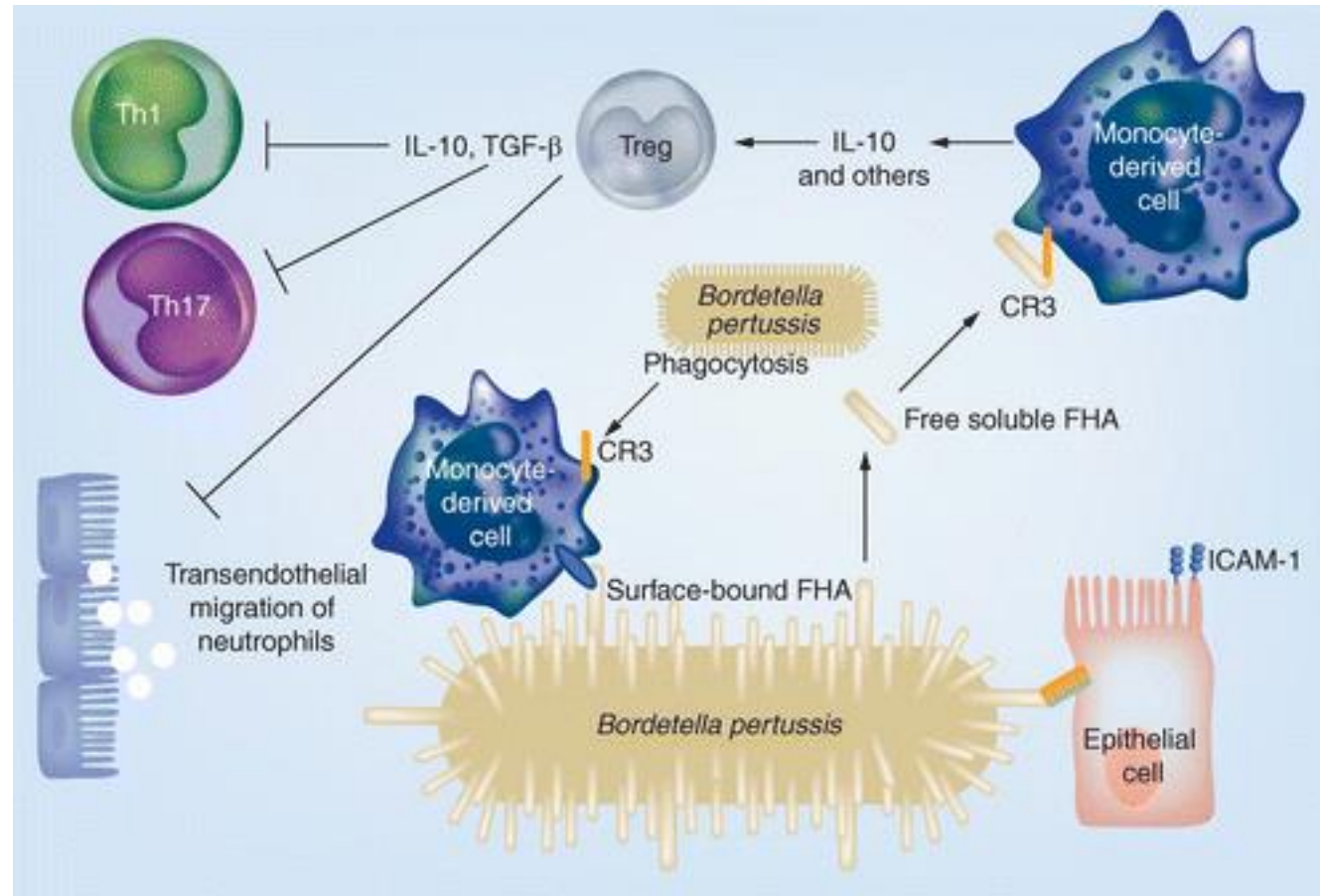
produção de grande quantidade de antígeno

produção de antígenos com receptores Fc (não desencadeia atividade)

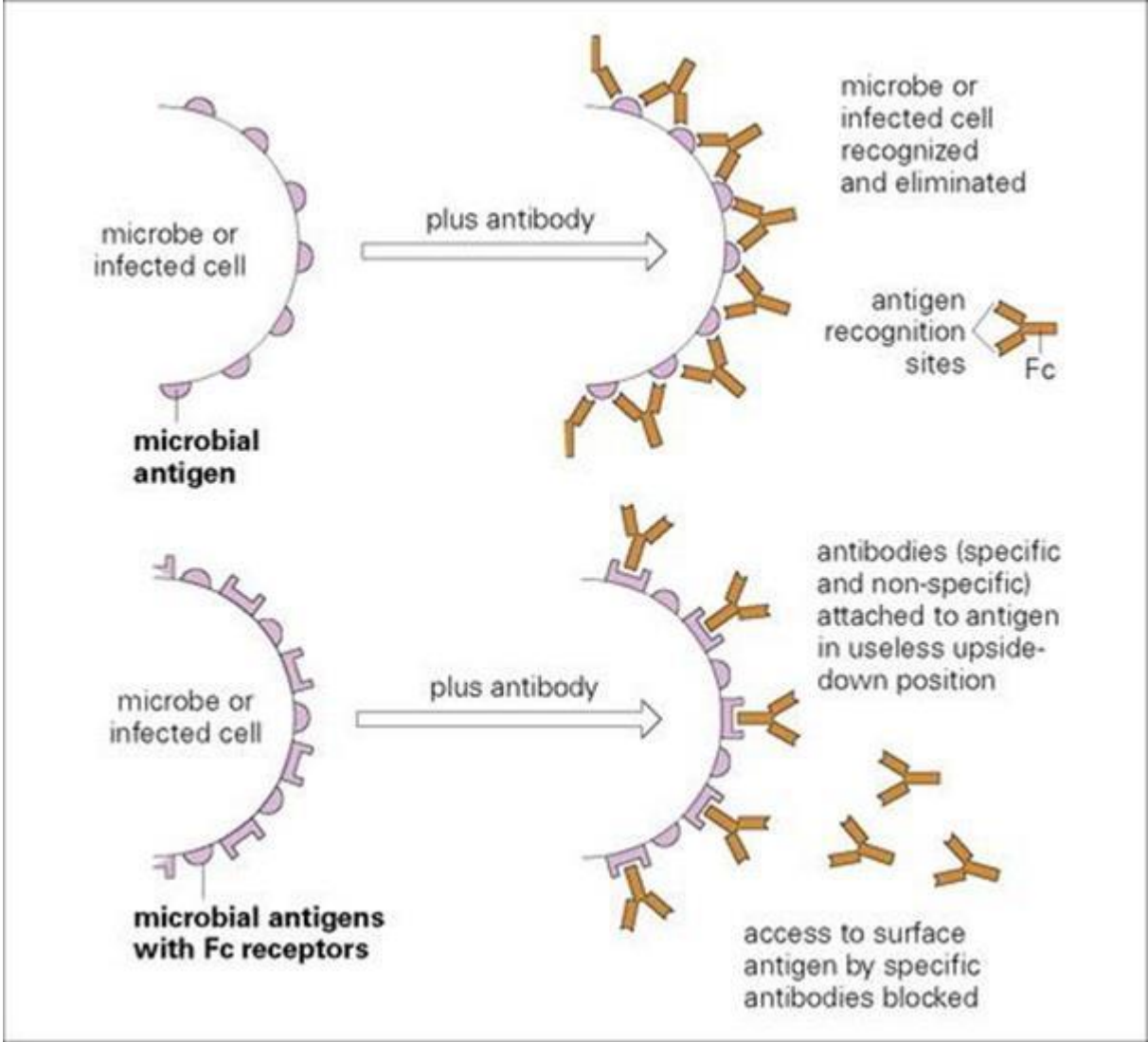
indução de células T reguladoras



Imunomodulação: *Bordetella pertussis*

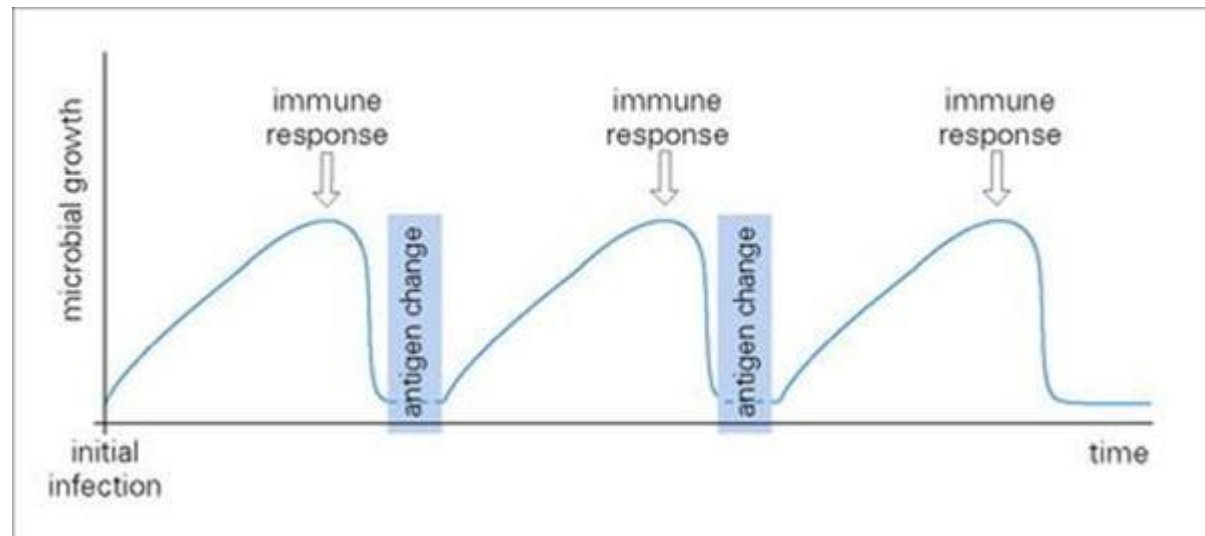


FHA = fragmento de hemaglutinina



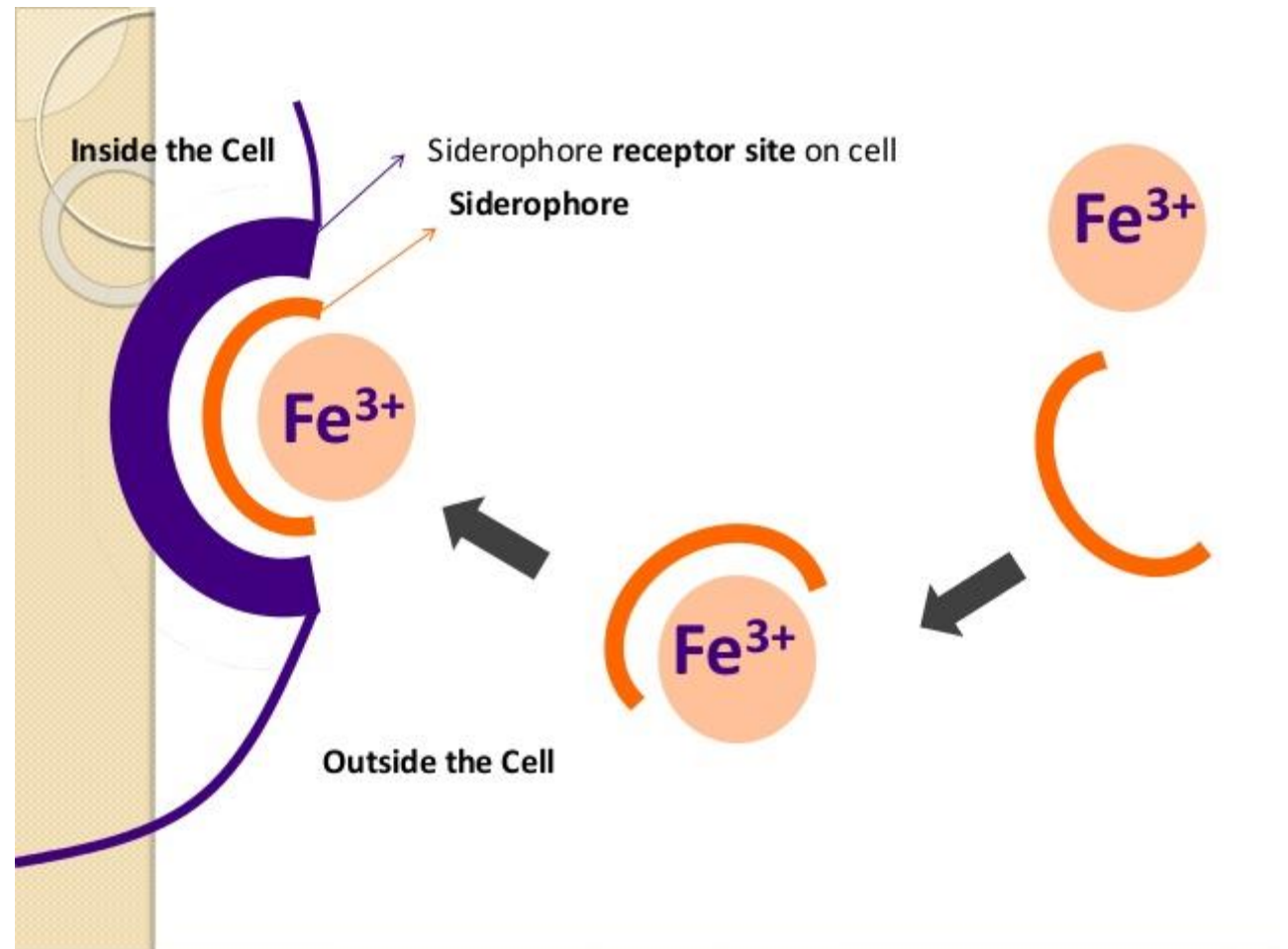
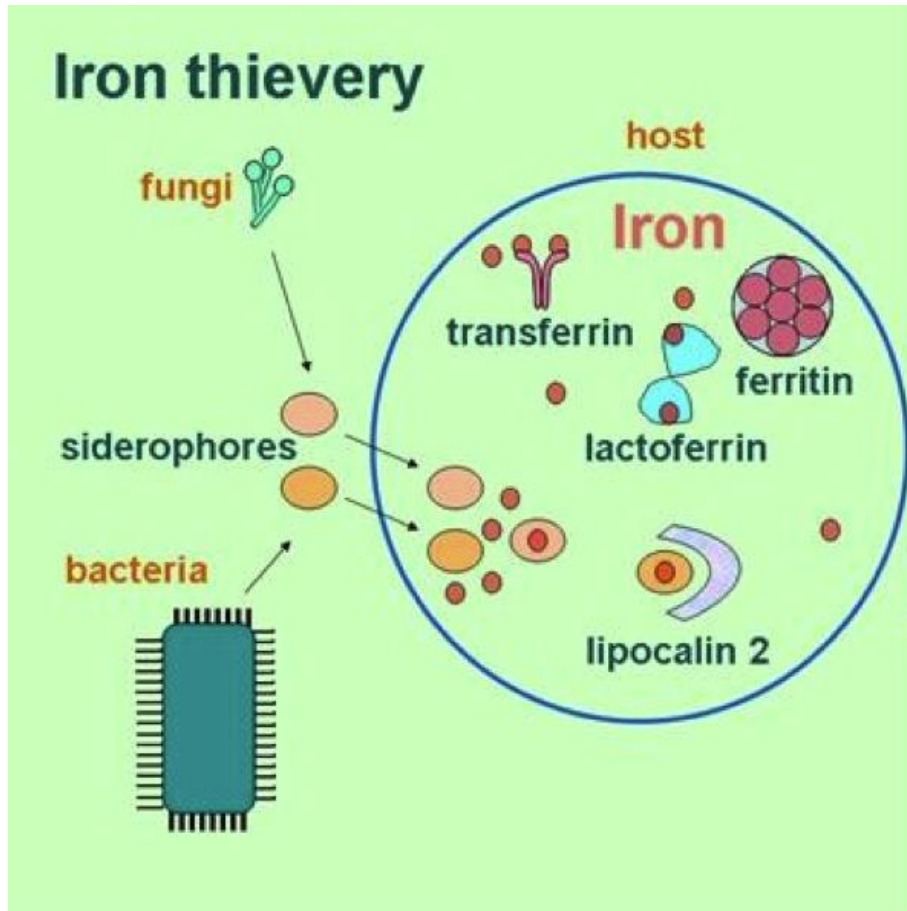
Variação antigênica

Algumas bactérias podem alterar seus antígenos de superfície escapando dos anticorpos produzidos pelo hospedeiro. *Neisseria gonorrhoeae*



Utilizando os nutrientes do hospedeiro

Captação de ferro



Toxinas e consequências patológicas das infecções



Toxinas



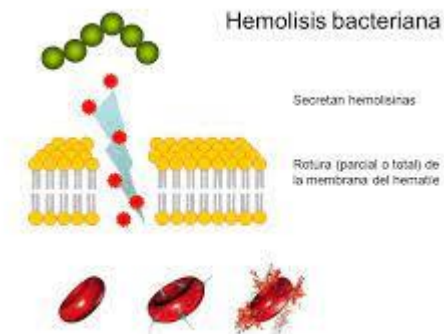
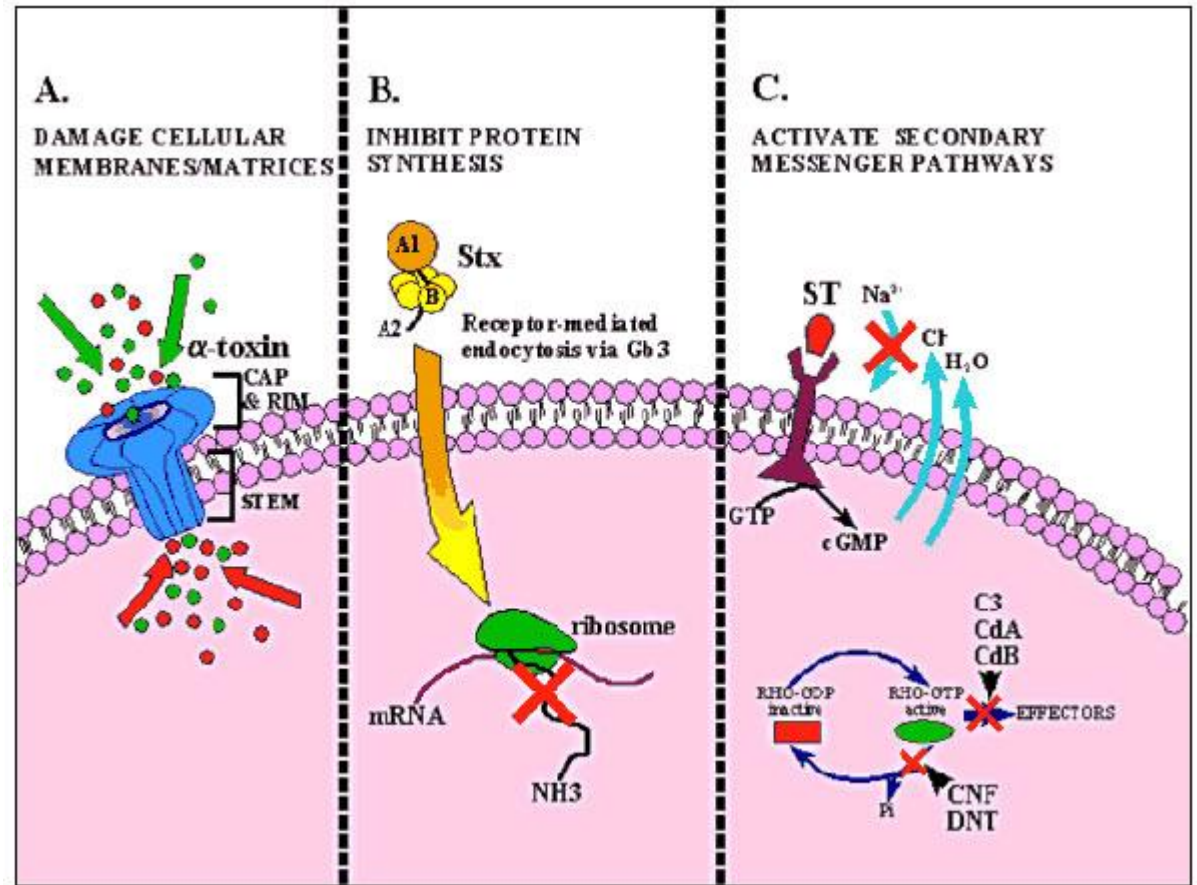
Toxinas

São produtos bacterianos que danificam diretamente o tecido ou promovem atividades biológicas destrutivas

Podem ser substâncias tóxicas ou enzimas degradativas que causam a lise celular ou se ligam a receptores específicos e desencadeiam uma reação tóxica em um tecido-alvo específico

Podem também ser componentes da parede celular que desencadeiam respostas sistêmicas

Muitas vezes as toxinas são as responsáveis por causar os sintomas das doenças



Enzimas como toxinas

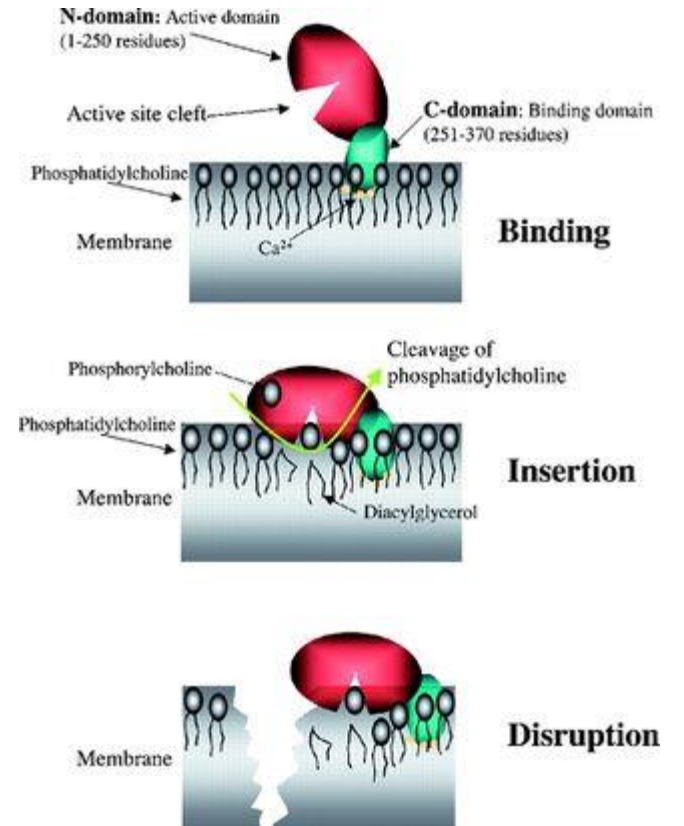
Enzimas podem digerir o material entre as células e induzir a formação ou a degradação de coágulos

- coagulases – enzimas bacterianas que coagulam o fibrinogênio no sangue. Comum em *Staphylococcus*
- quinases – degradam fibrina e digerem coágulos. Ex. fibronolisina (estreptocinase)
- Hilaronidase – hidrolisa ácido hialurônico de tecidos conectivos. Tem papel na necrose de ferimentos.
- Colagenase – hidrolisa colágeno de tecidos conectivos de músculos – ocasiona gangrena gasoso. Comum em *Chostridium*
- Proteases IgA – hidrolisam anticorpos. Enzima produzida por *N. gonorrhoeae*

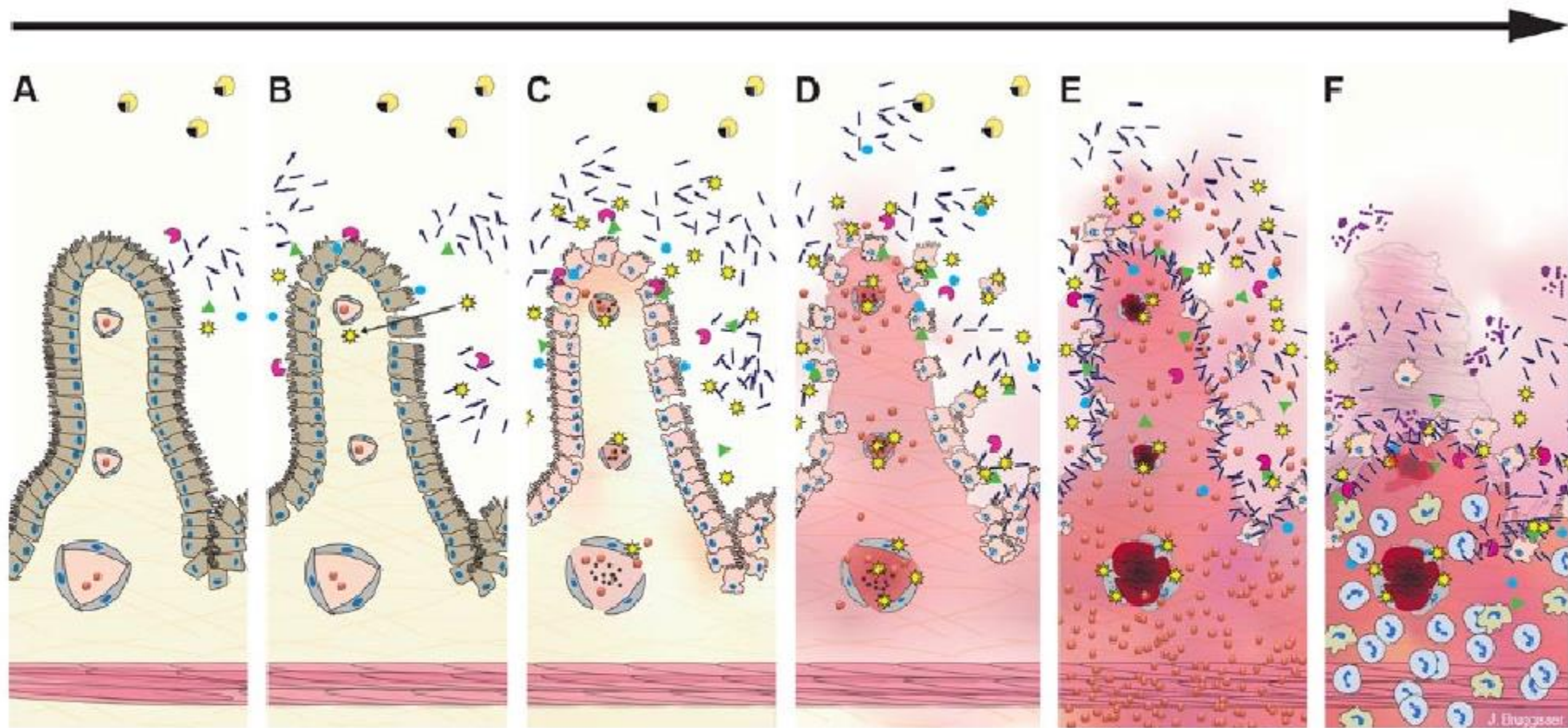
Destruição dos tecidos

Produtos provenientes do metabolismo da bactéria

Enzimas degradativas



Clostridium perfringens



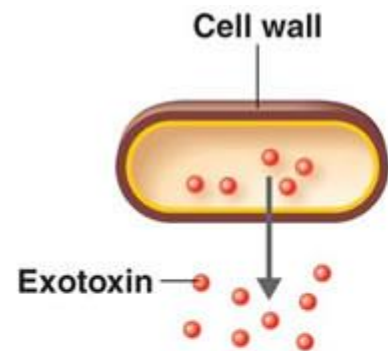
-  *C. perfringens* type C
-  β -toxin
-  Trypsin
-  Erythrocytes
-  Blood vessel
-  Neutrophil
-  Commensal bacterial flora
-  Additional major and minor toxins/enzymes
-  Trypsin inhibitor
-  Thrombocytes
-  Thrombus
-  Macrophage

Tipos de toxinas

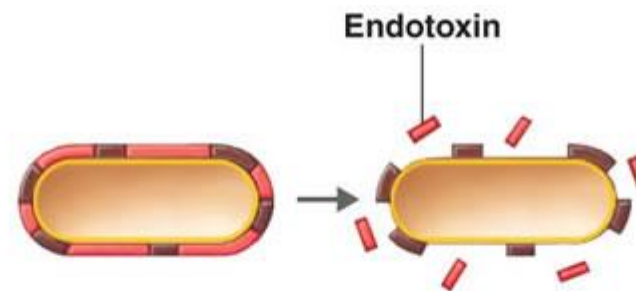
Toxina pré-formada – toxinas presentes nos alimentos antes da ingestão

Exotoxinas – proteínas que podem ser produzidas pelas bactérias Gram positivas e Gram negativas que matam ou alteram uma função de uma célula hospedeira.

Endotoxinas – componentes da parede celular bacteriana Gram negativa (lipopolissacarídeo, LPS) que causam uma reação imune extremamente potente, podendo levar ao choque



(a) Exotoxins are proteins produced inside pathogenic bacteria, most commonly gram-positive bacteria, as part of their growth and metabolism. The exotoxins are then secreted or released into the surrounding medium following lysis.



(b) Endotoxins are the lipid portions of lipopolysaccharides (LPSs) that are part of the outer membrane of the cell wall of gram-negative bacteria (lipid A; see Figure 4.13c). The endotoxins are liberated when the bacteria die and the cell wall breaks apart.

Key Concept

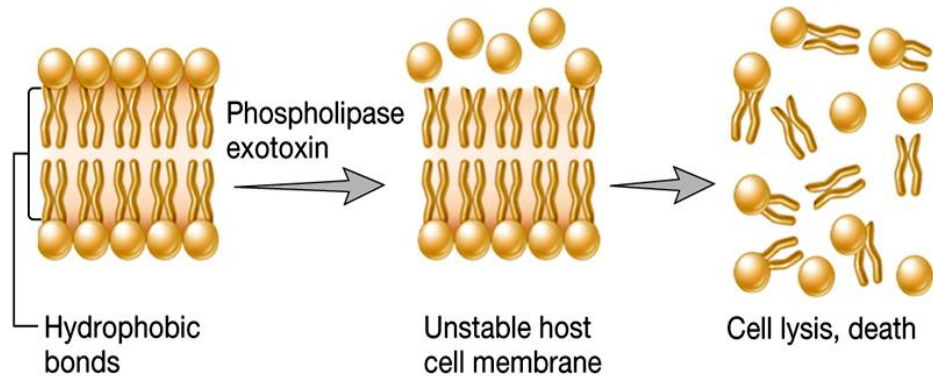
Toxins are of two general types: exotoxins and endotoxins.

Exotoxinas

- Geralmente presentes em plasmídeos
- podem atuar localmente ou em locais distantes da infecção
- pode ser uma toxina pré-formada

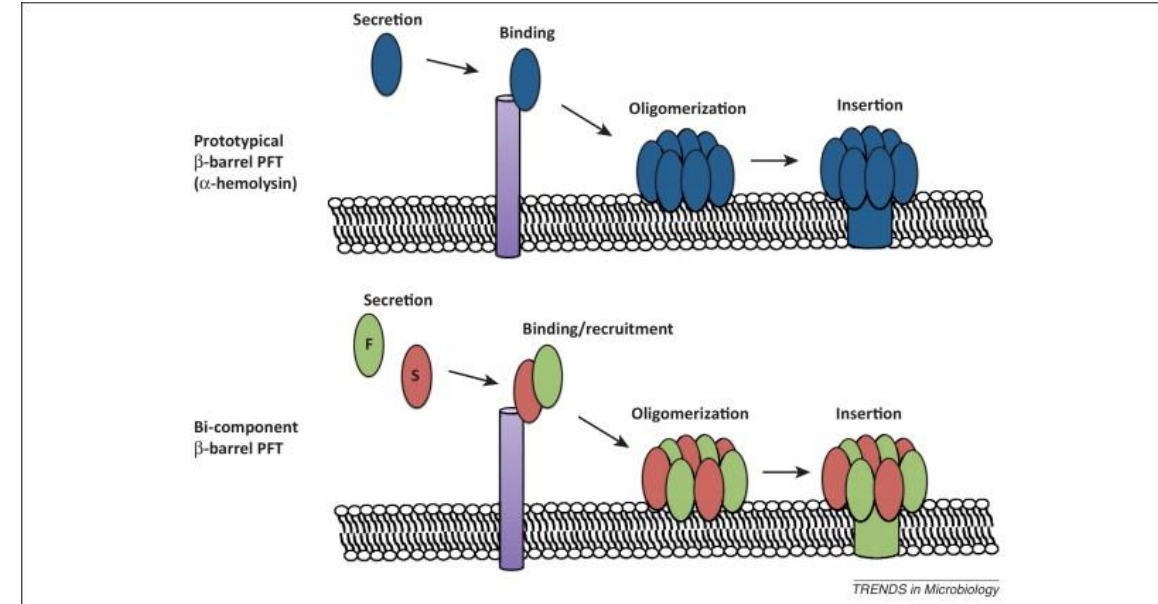
Toxinas citolíticas:

Toxina α de *Clostridium perfringens* (fosfolipase C)

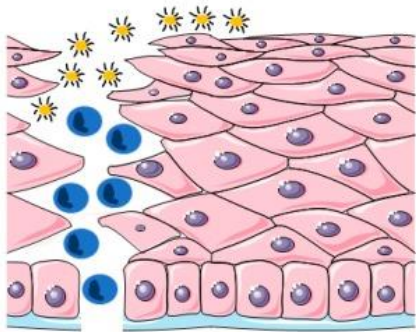


(b)

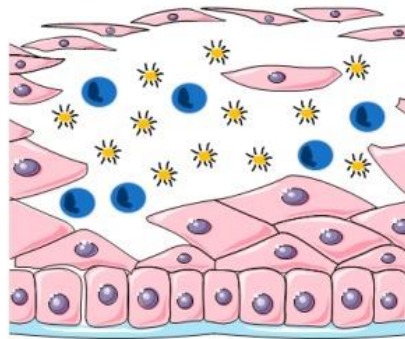
Hemolisina de *Streptococcus*



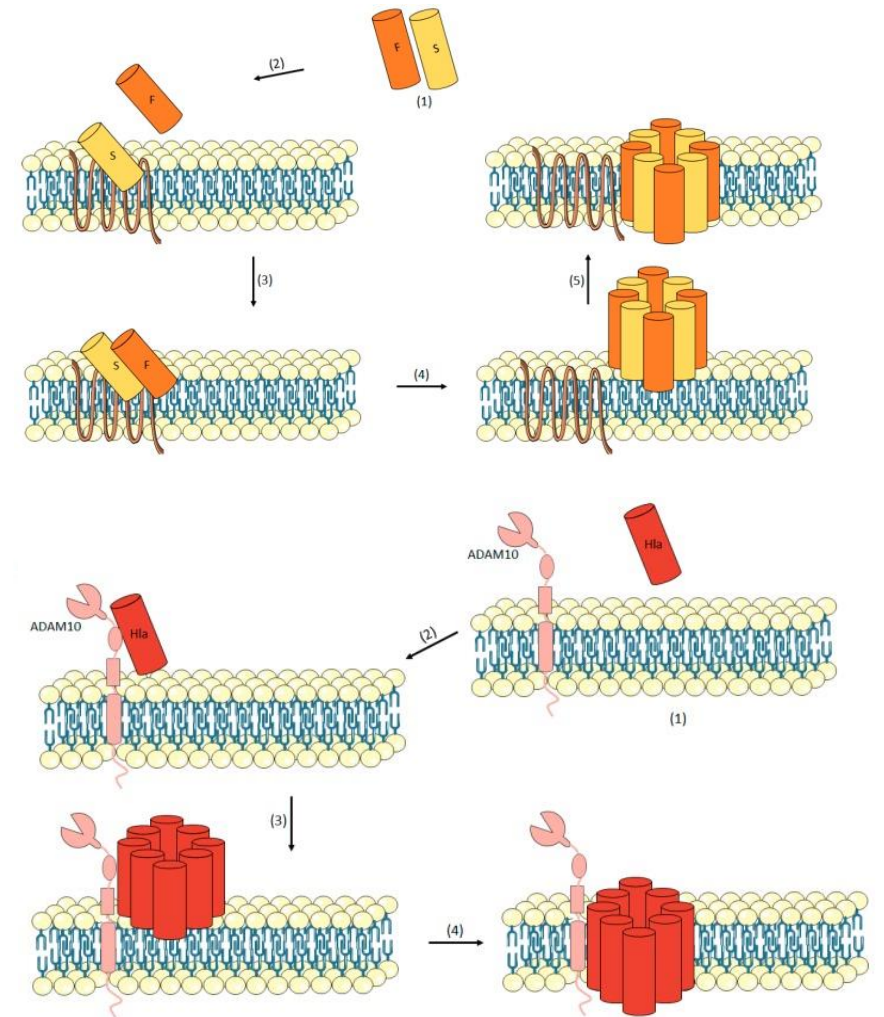
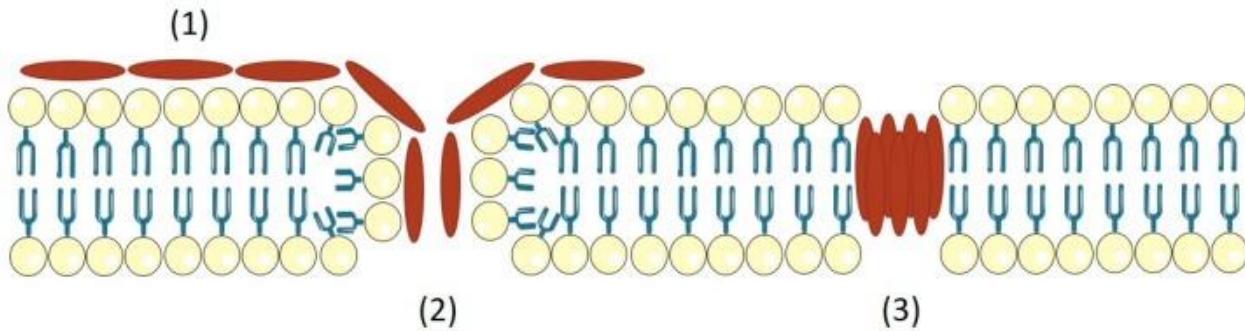
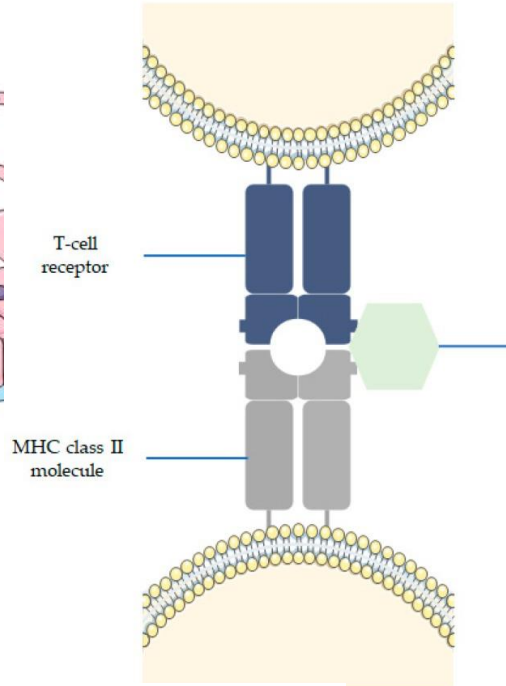
Toxins - *Staphylococcus aureus*



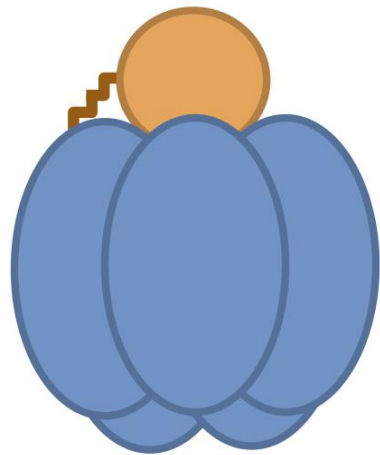
S. aureus adhere to the epidermis and then penetrate through neutrophil-created intercellular gap between superficial keratinocytes.



Expansion of blisters by ETs.

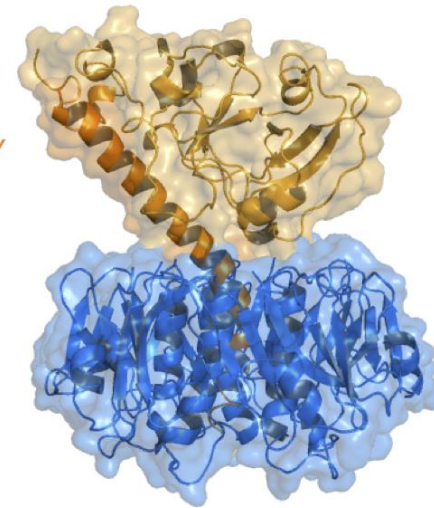


Toxinas diméricas com subunidades A-B

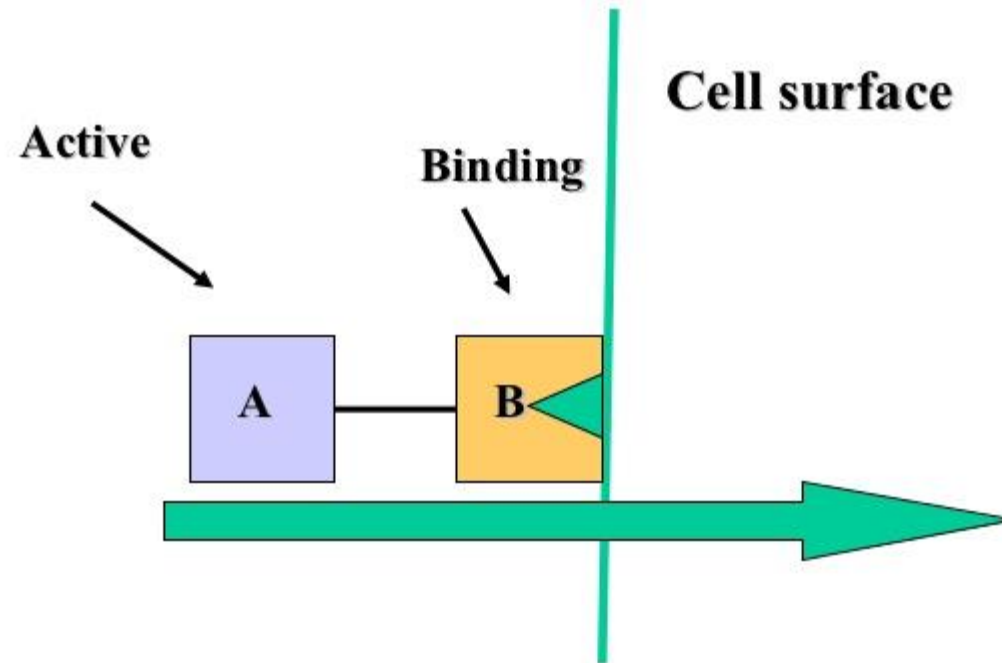


A subunit
enzymatic toxicity

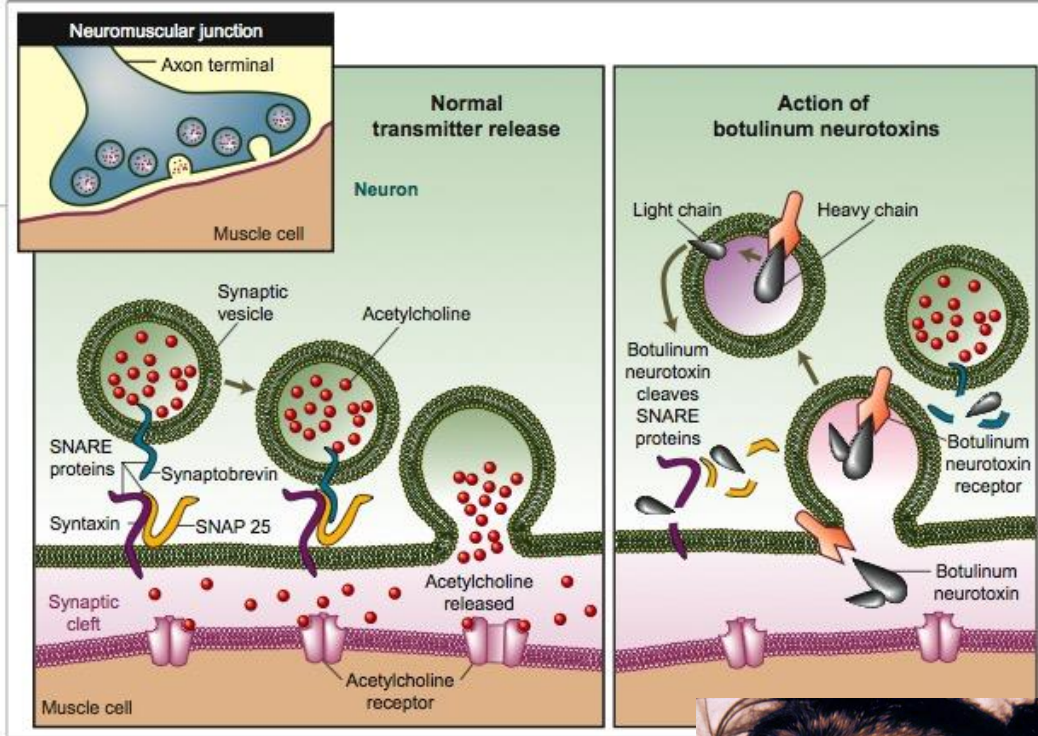
B₅ subunit
cell binding



A-B toxins



Toxina botulínica e tetânica



Mechanism of Action of Tetanus Toxin

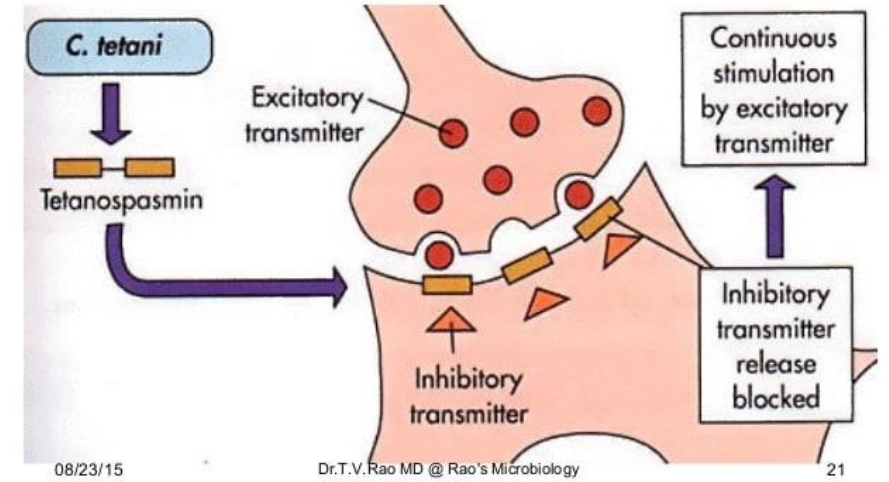


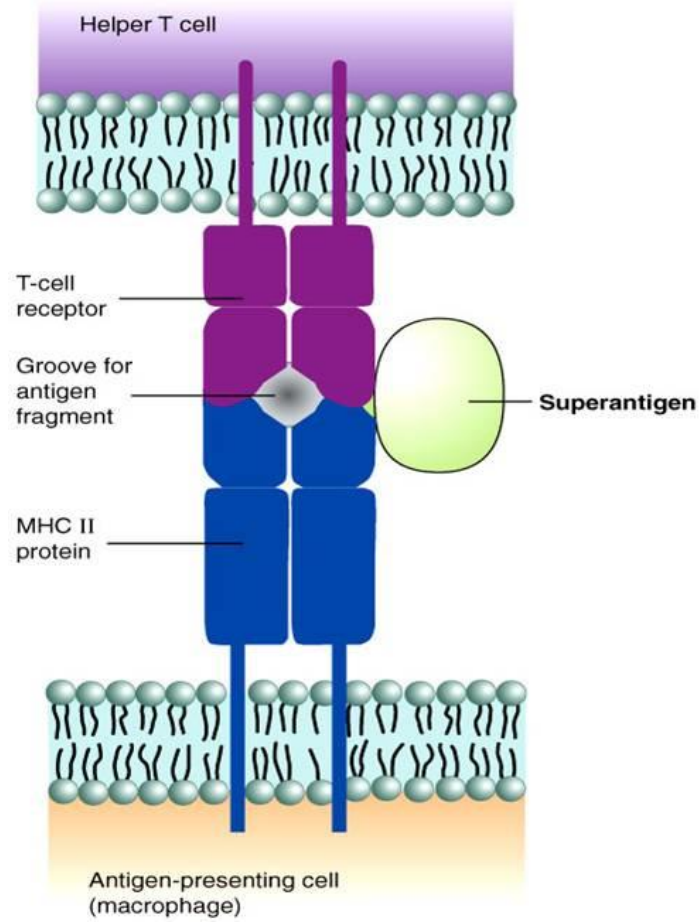
FIGURE 1
Opisthotonus



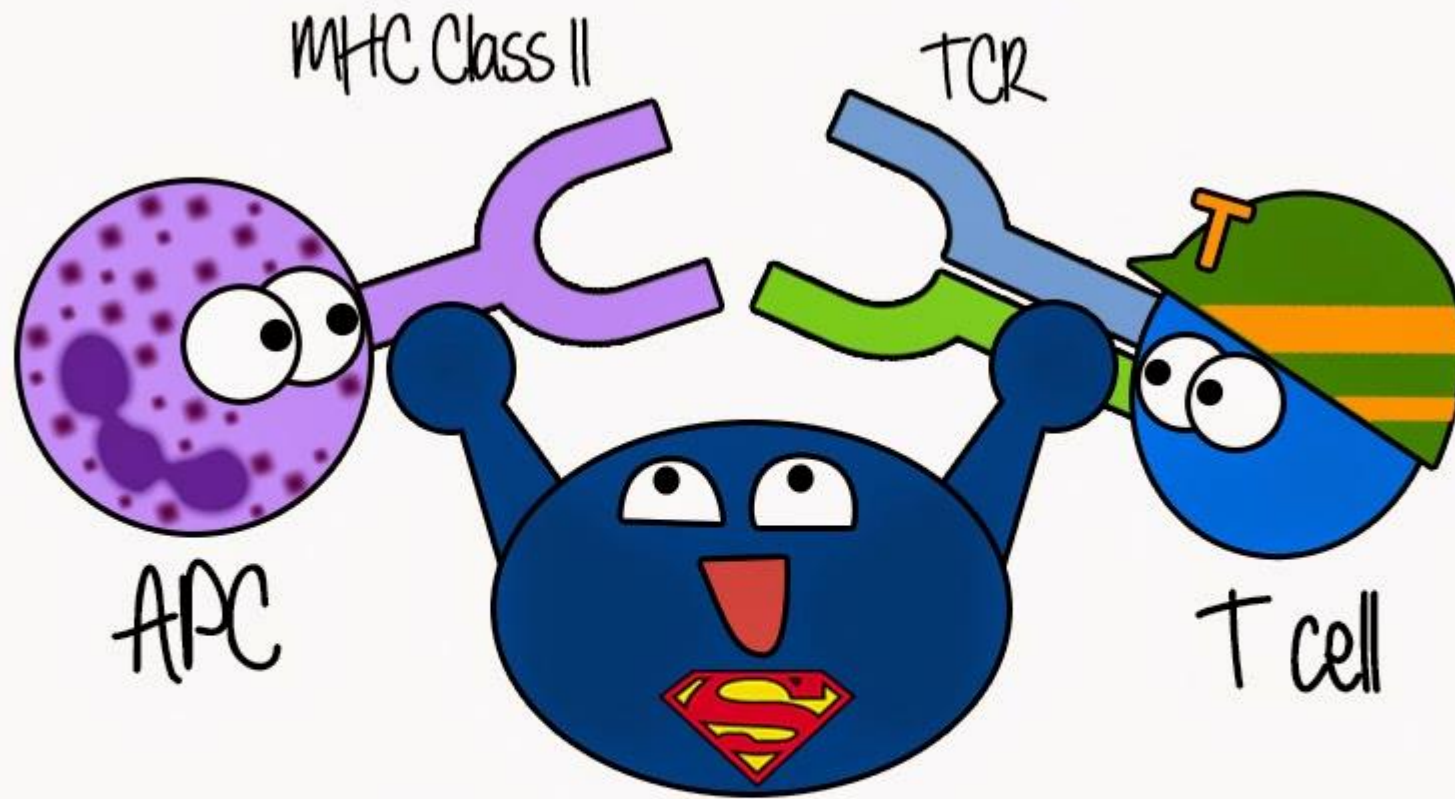
Superantígenos

São moléculas que ativam as células T por ligarem simultaneamente à um receptor de célula T e a uma molécula do MHC II

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Desencadeando a liberação de uma grande quantidade de interleucinas, principalmente IL-1

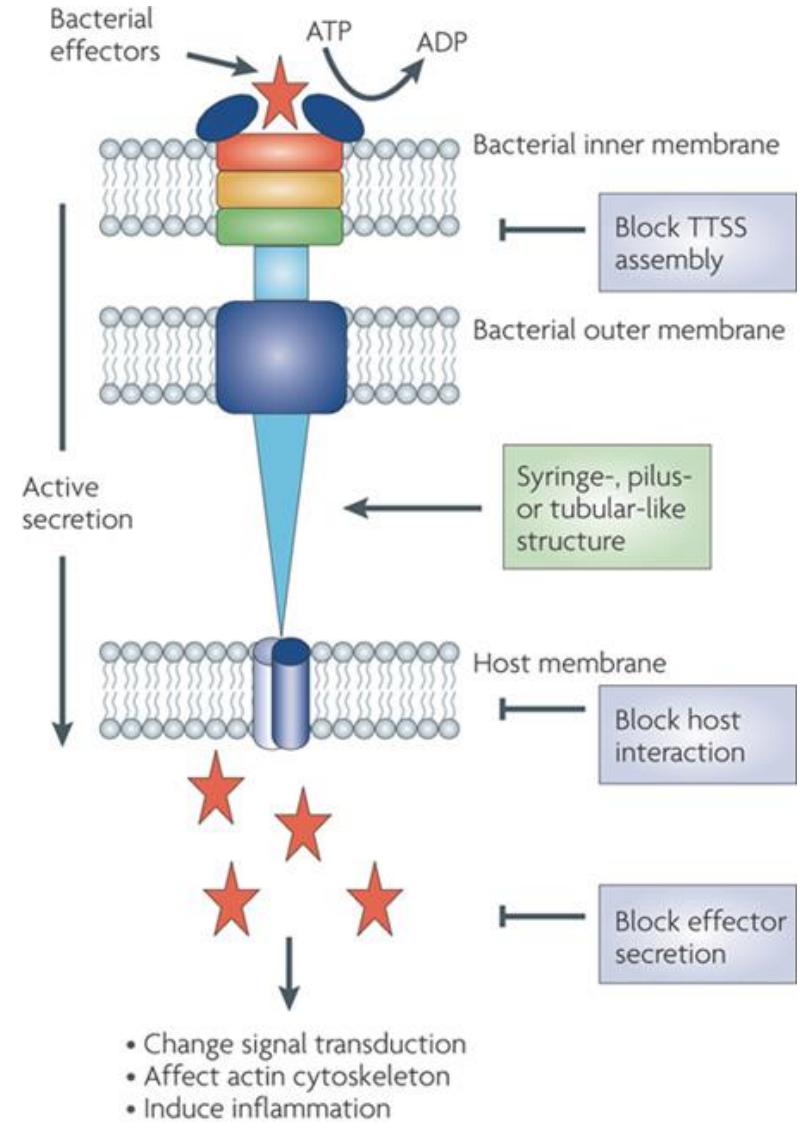
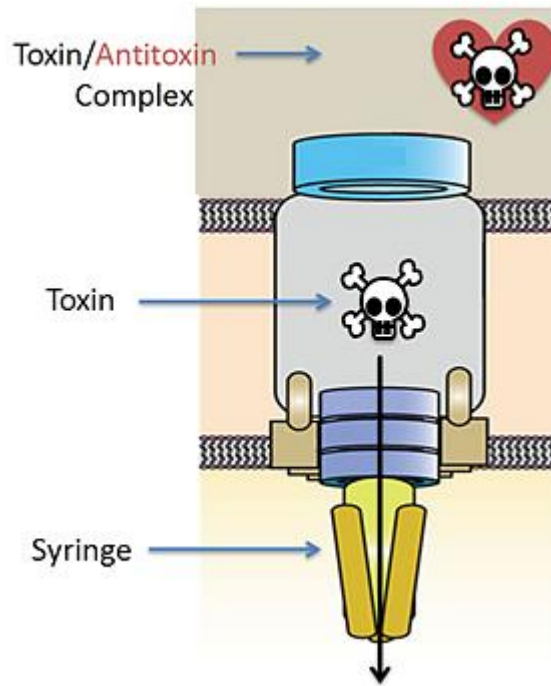


How super antigens work

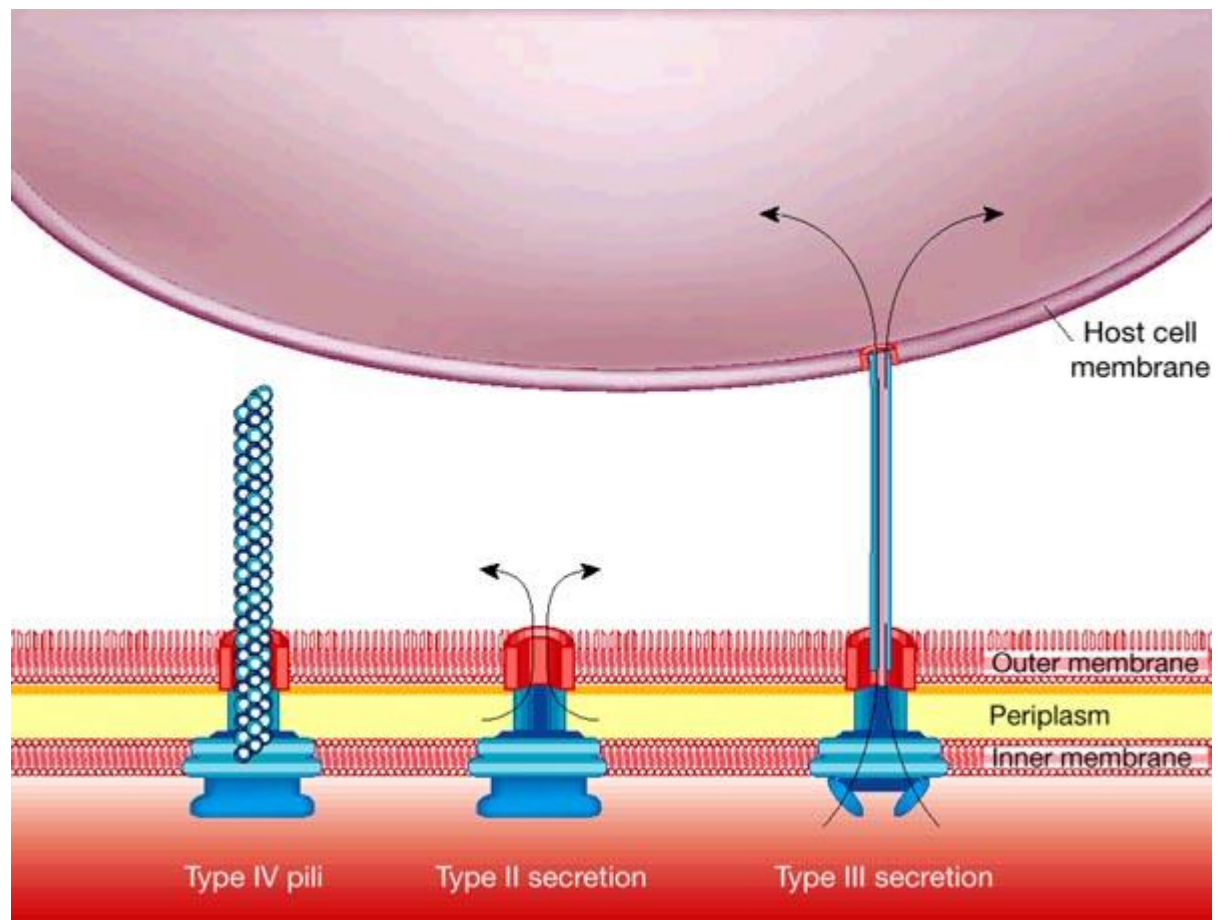
Table 15.2 Diseases Caused by Exotoxins

Disease	Bacterium	Type of Exotoxin	Mechanism
Botulism	<i>Clostridium botulinum</i>	A-B	Neurotoxin prevents the transmission of nerve impulses; flaccid paralysis results.
Tetanus	<i>Clostridium tetani</i>	A-B	Neurotoxin blocks nerve impulses to muscle relaxation pathway; results in uncontrollable muscle contractions.
Diphtheria	<i>Corynebacterium diphtheriae</i>	A-B	Cytotoxin inhibits protein synthesis, especially in nerve, heart, and kidney cells.
Scalded skin syndrome	<i>Staphylococcus aureus</i>	A-B	One exotoxin causes skin layers to separate and slough off (scalded skin).
Cholera	<i>Vibrio cholerae</i>	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Traveler's diarrhea	Enterotoxigenic <i>Escherichia coli</i> and <i>Shigella</i> spp.	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Anthrax	<i>Bacillus anthracis</i>	A-B	Two A components enter the cell via the same B. The A proteins cause shock and reduce the immune response.
Gas gangrene and food poisoning	<i>Clostridium perfringens</i> and other species of <i>Clostridium</i>	Membrane-disrupting	One exotoxin (cytotoxin) causes massive red blood cell destruction (hemolysis); another exotoxin (enterotoxin) is related to food poisoning and causes diarrhea.
Antibiotic-associated diarrhea	<i>Clostridium difficile</i>	Membrane-disrupting	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea; cytotoxin disrupts host cytoskeleton.
Food poisoning	<i>Staphylococcus aureus</i>	Superantigen	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea.
Toxic shock syndrome (TSS)	<i>Staphylococcus aureus</i>	Superantigen	Toxin causes secretion of fluids and electrolytes from capillaries that decreases blood volume and lowers blood pressure.

As proteínas secretadas pelas bactérias podem ser toxinas ou realizar a modulação do sistema imune

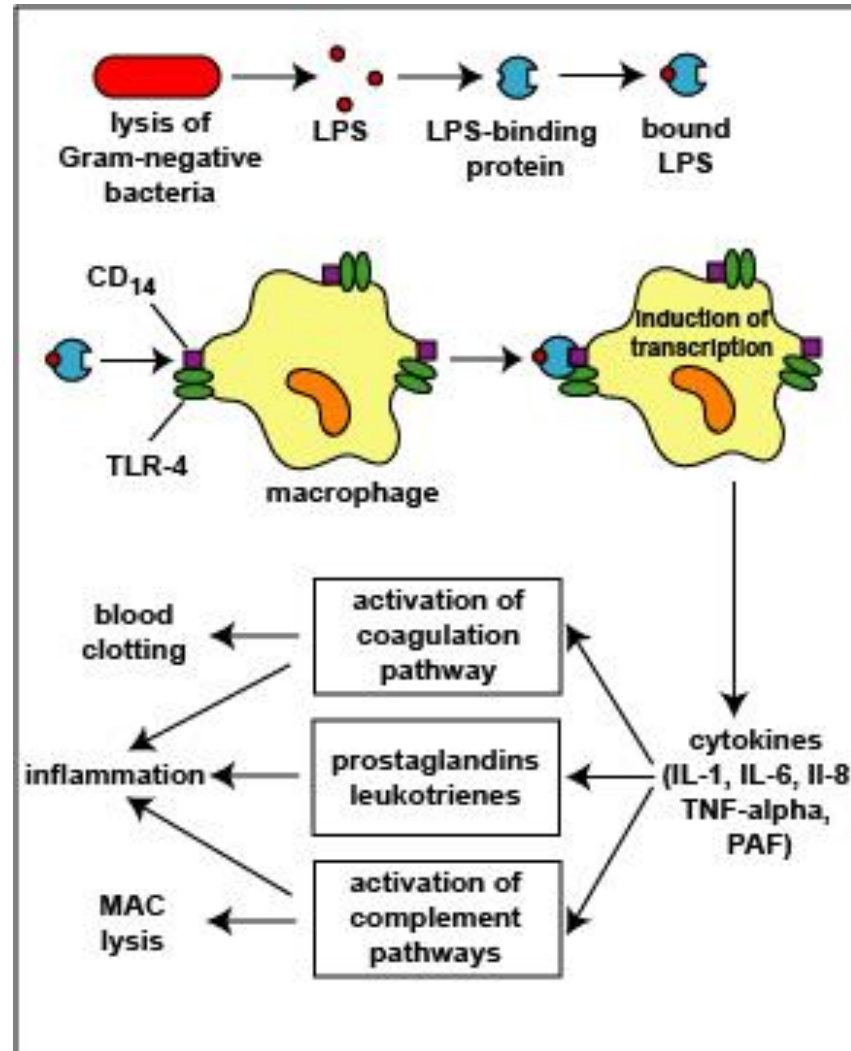


Sistema de secreção do tipo III



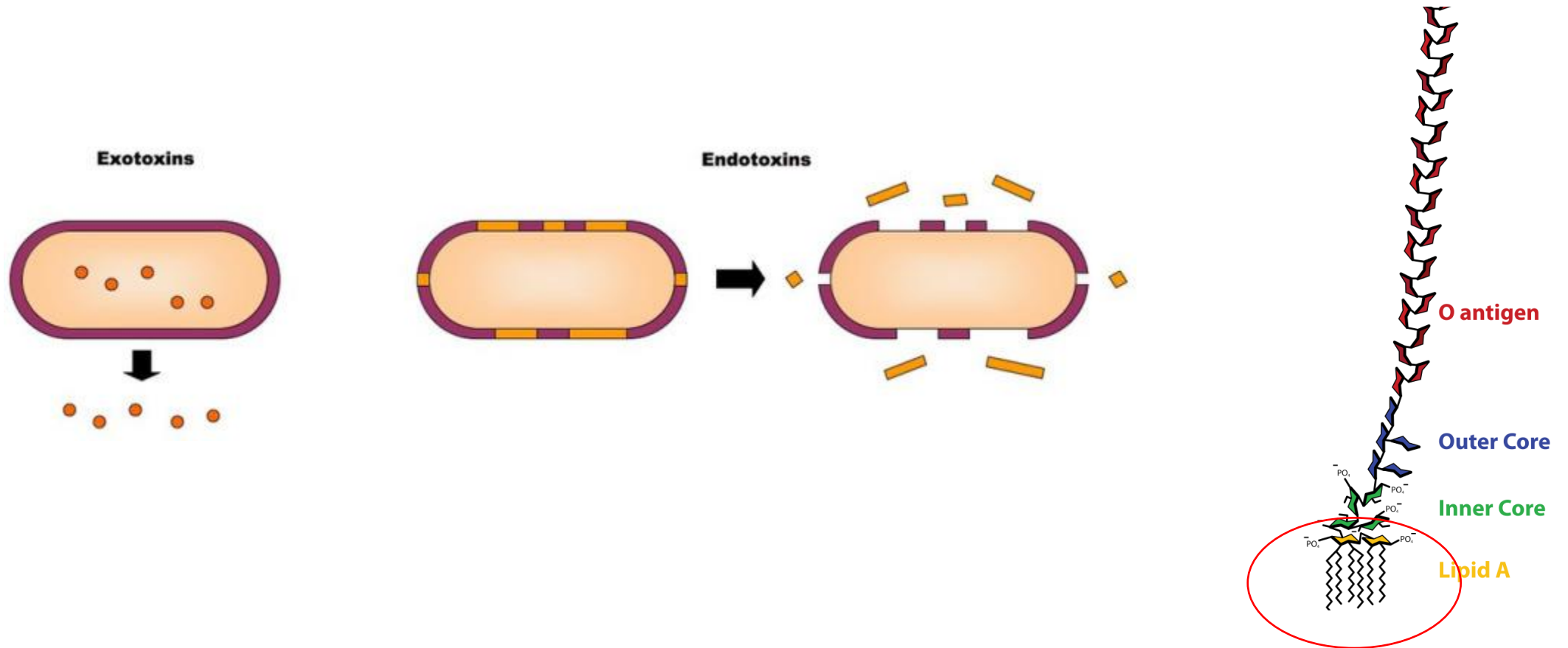
Endotoxinas

Endotoxinas são referentes a componentes do LPS e são somente presentes em bactérias Gram negativas



Endotoxinas e outros componentes da parede celular bacteriana

-Endotoxinas - componentes da parede celular de bactérias Gram negativas que atuam como sinal para ativar o sistema de defesa



Bactérias gram negativas liberam endotoxinas durante a infecção



Endotoxinas ligam-se a receptores específicos (CD14 e TLR4)



Liberão de de citocinas de fase aguda



Crescimento de células B



Febre e vasodilatação

