

# Patogênese Bacteriana – fatores de virulência

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Microbiologia Médica – Patrick Muray, Ken Rosenthal e Mechael Pfaller, 6 ed. ou posterior

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

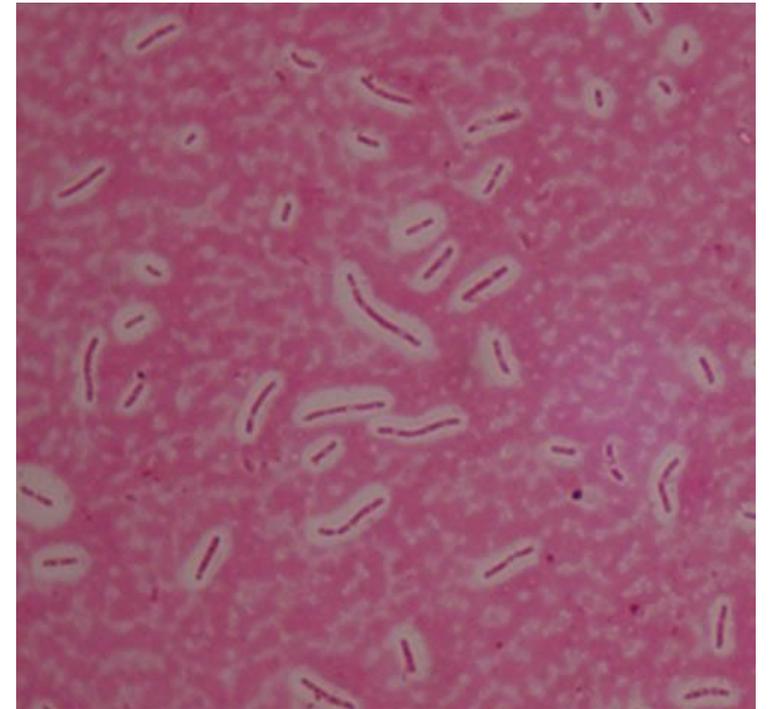
**Fatores de virulência** = fatores que aumentam a habilidade de uma bactéria em causar doença.

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?**



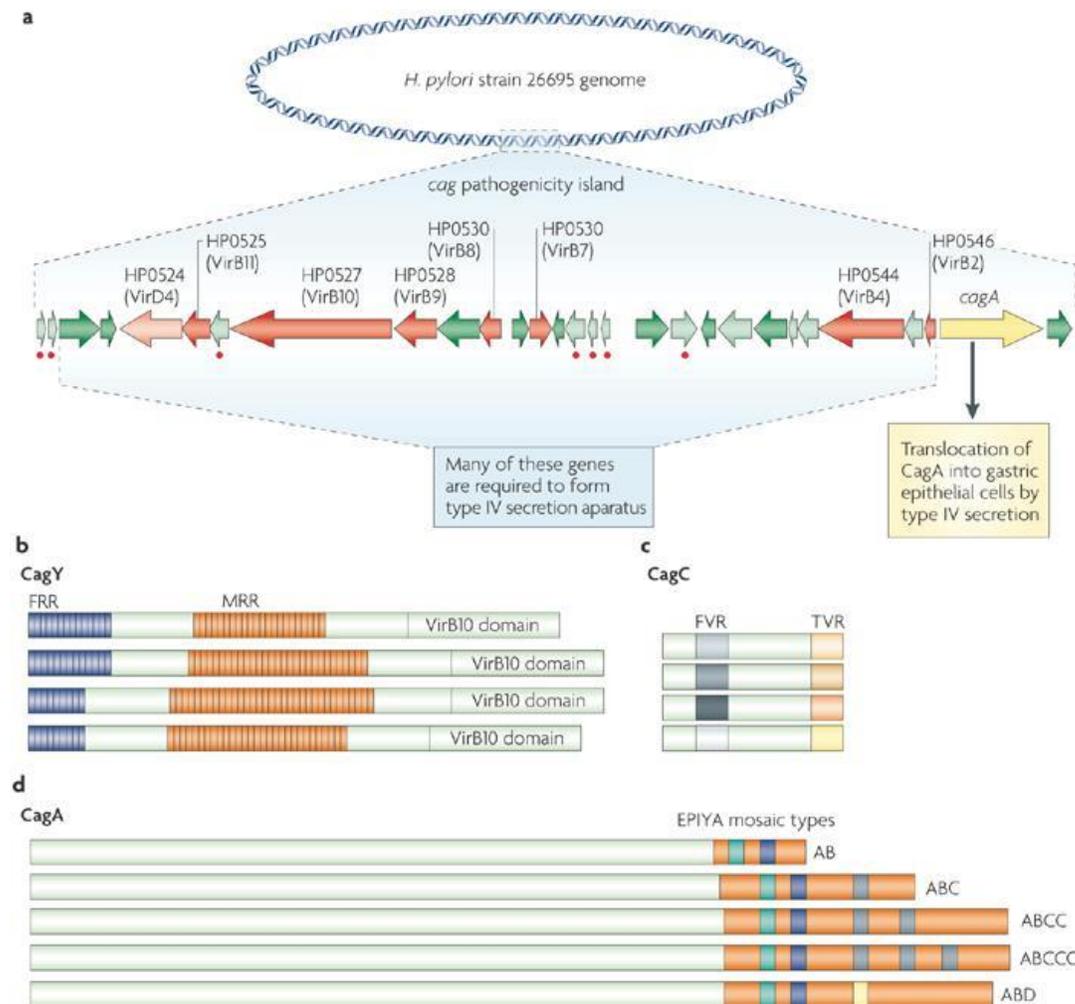
**Ilhas de patogenicidade = regiões cromossômicas que contêm conjunto de genes que codificam diversos fatores de virulência**



**Geralmente é um transposon inserido no cromossomo ou um plasmídeo**



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



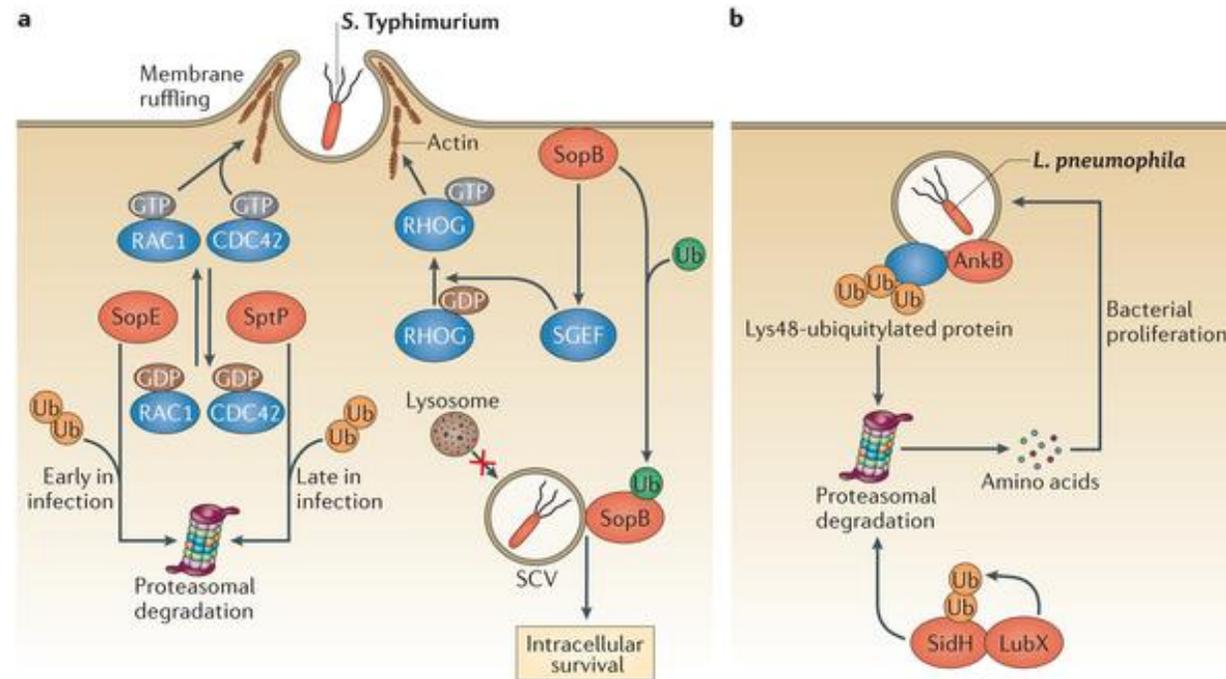
# 1. Mecanismos de evasão

# Estratégias de evasão bacteriana das defesas naturais, não adaptativas

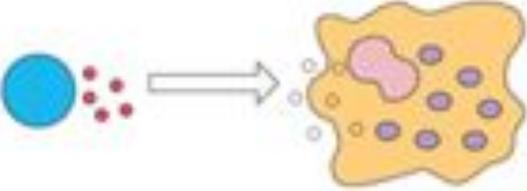
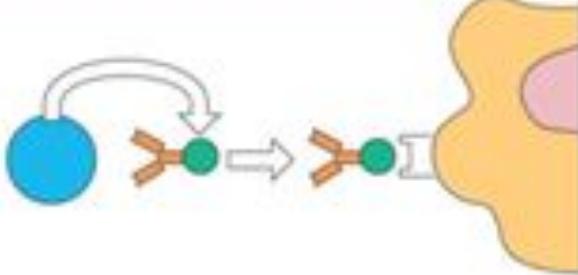
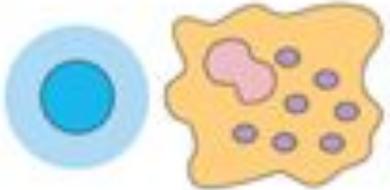
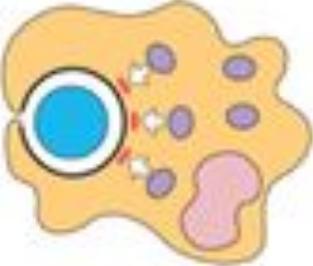
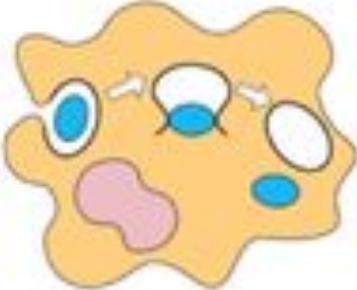
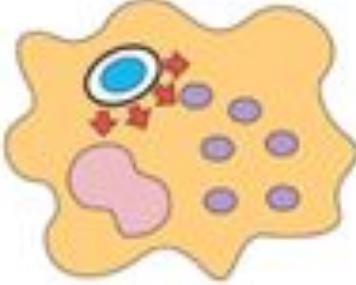
- Matar os fagócitos ou sobreviver à fagocitose
  - Interferir na ação ciliar
  - Interferir na ativação do complemento
  - Evitar o reconhecimento do sistema imune
- Clivagem do peróxido de hidrogênio e peptídeos antimicrobianos

# Alteração do citoesqueleto

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

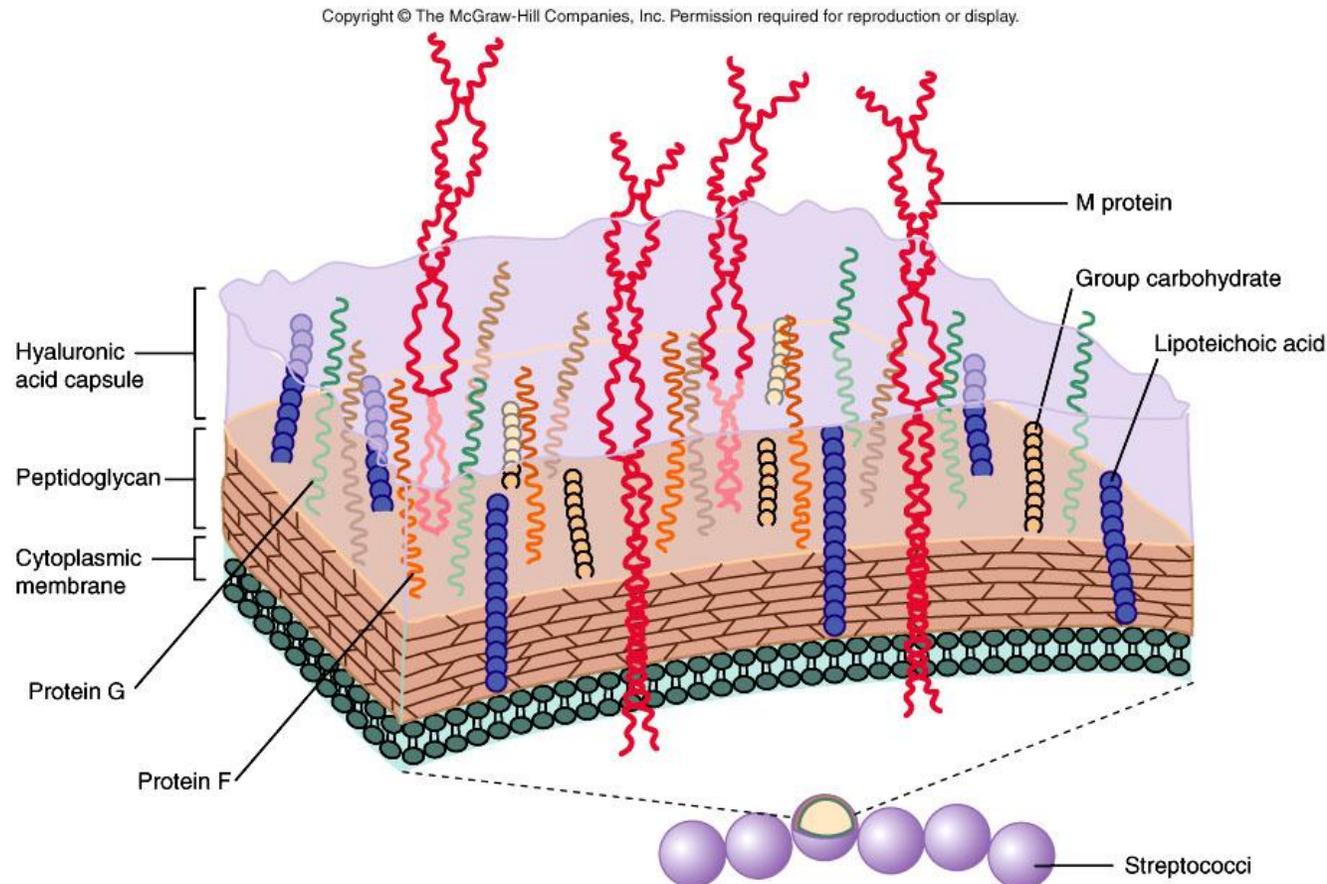


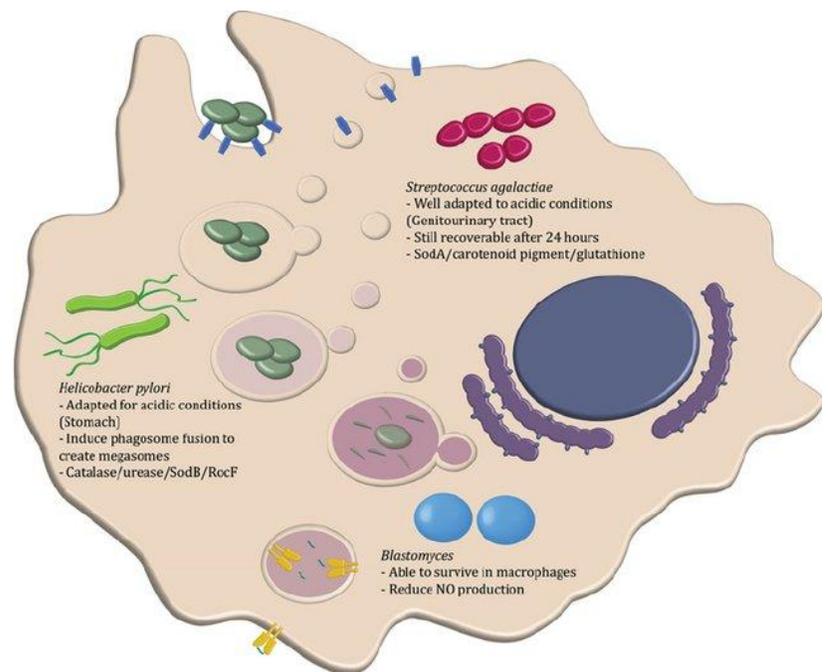
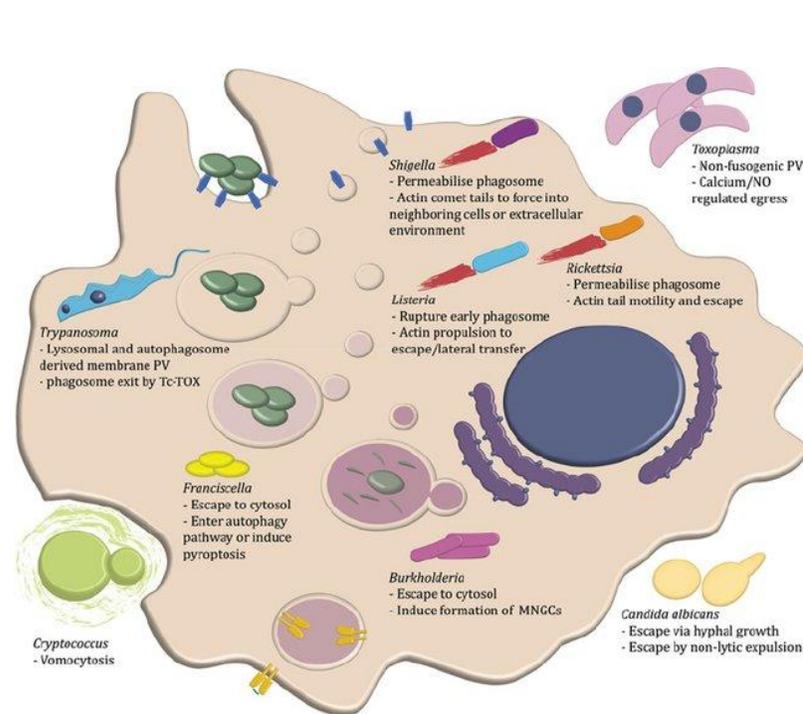
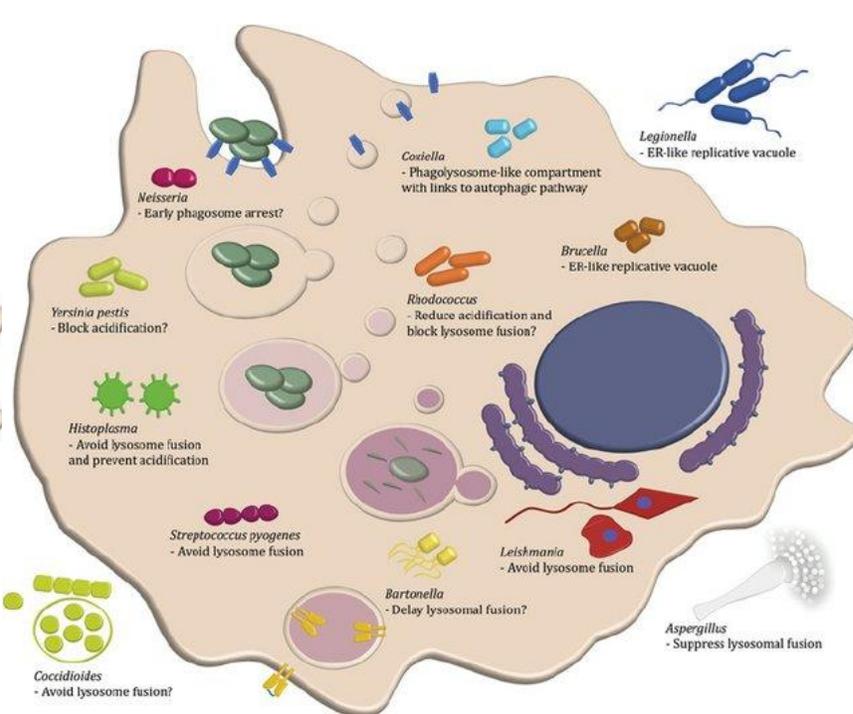
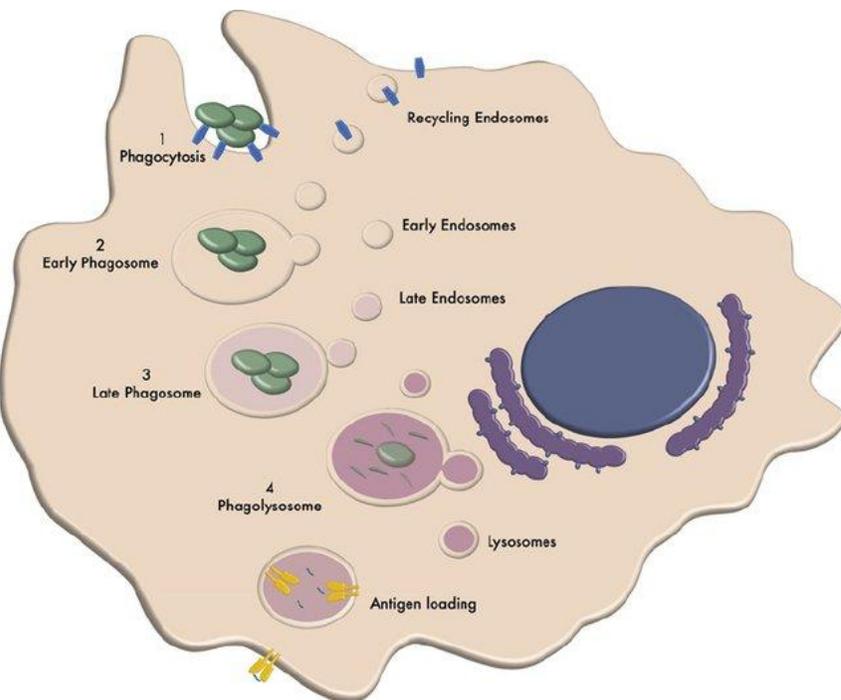
# Como evitar a fagocitose?

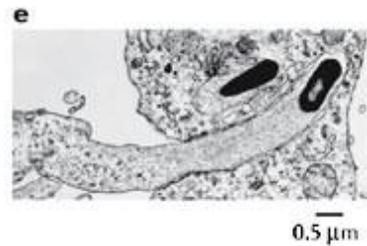
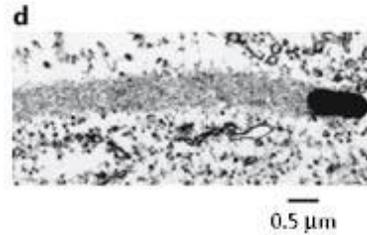
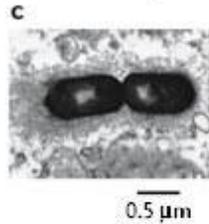
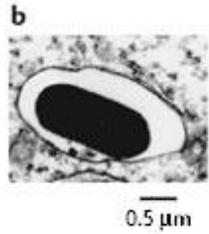
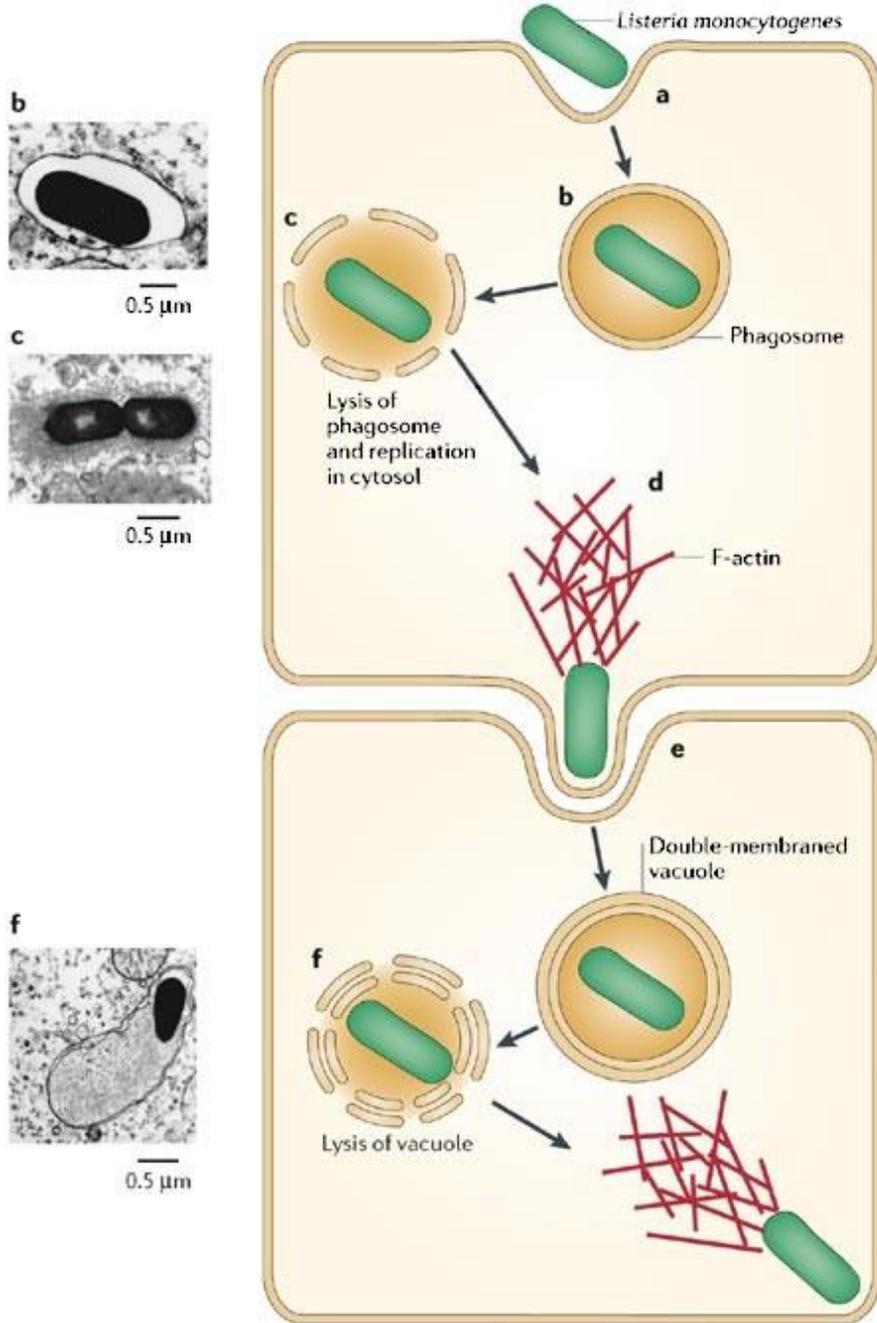
toxin release	opsonization prevented	contact with phagocyte prevented
 <p data-bbox="402 591 919 733">organism releases toxin, e.g. staphylococci, streptococci, amoebae</p> <p data-bbox="774 591 919 691">phagocyte killed by toxin</p>	 <p data-bbox="970 591 1600 733">organism (e.g. staphylococci) produces 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 1215 901 1358">fusion of phagosome and lysosome inhibited by organism, e.g. <i>Mycobacterium tuberculosis</i>, toxoplasma, chlamydia</p>	 <p data-bbox="970 1215 1589 1358">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 1215 2150 1396">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

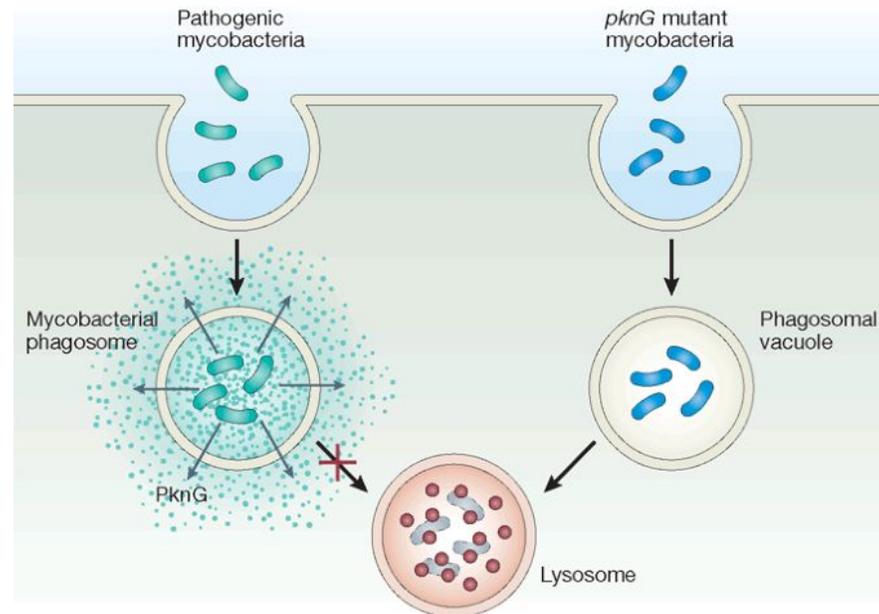
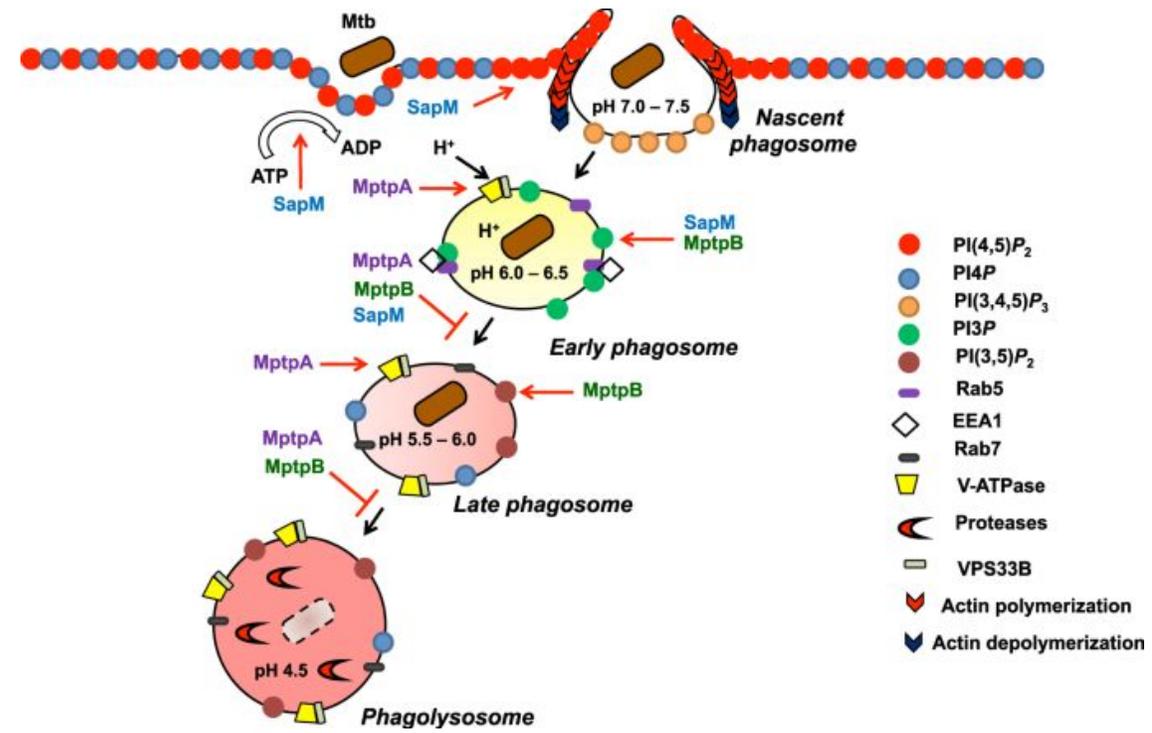
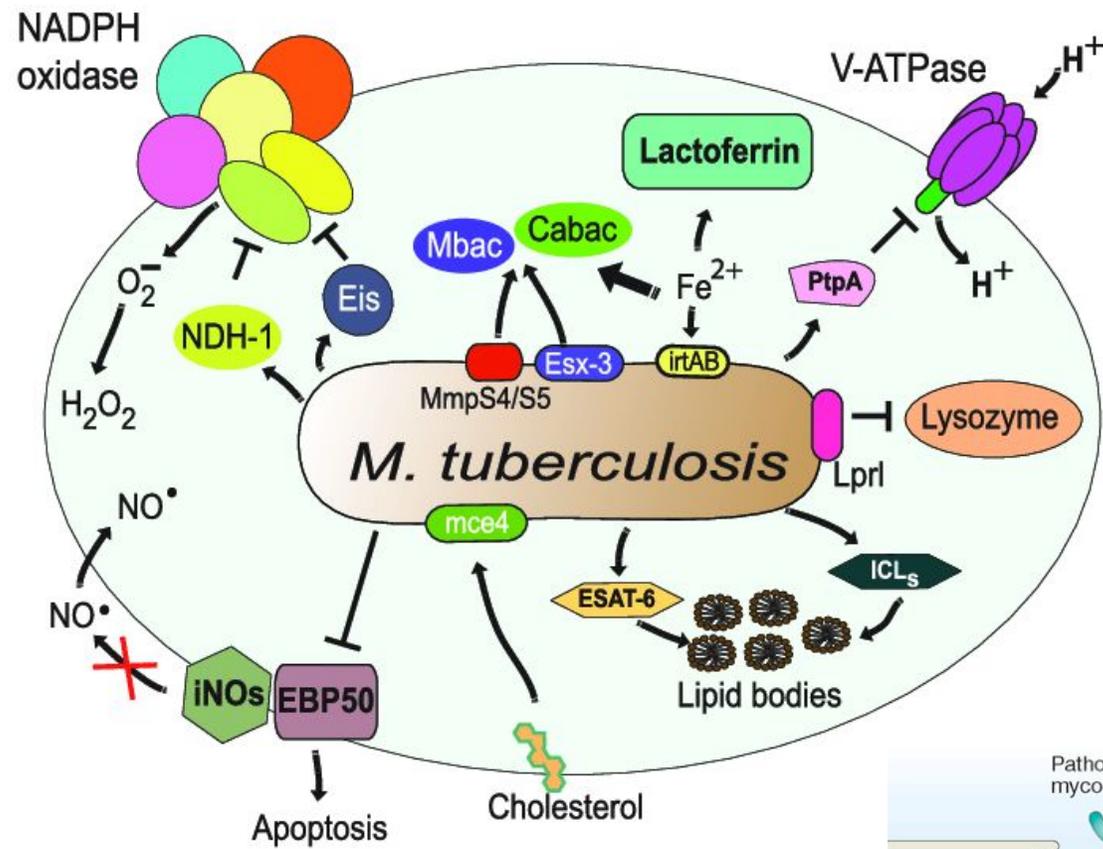
- Proteínas ou outras substâncias químicas: **proteína M** em *Streptococcus pyogenes* – impede a ação da fagocitose destruindo convertase C3 do sistema complemento. Assim como as **proteínas L** auxiliam no adesão.

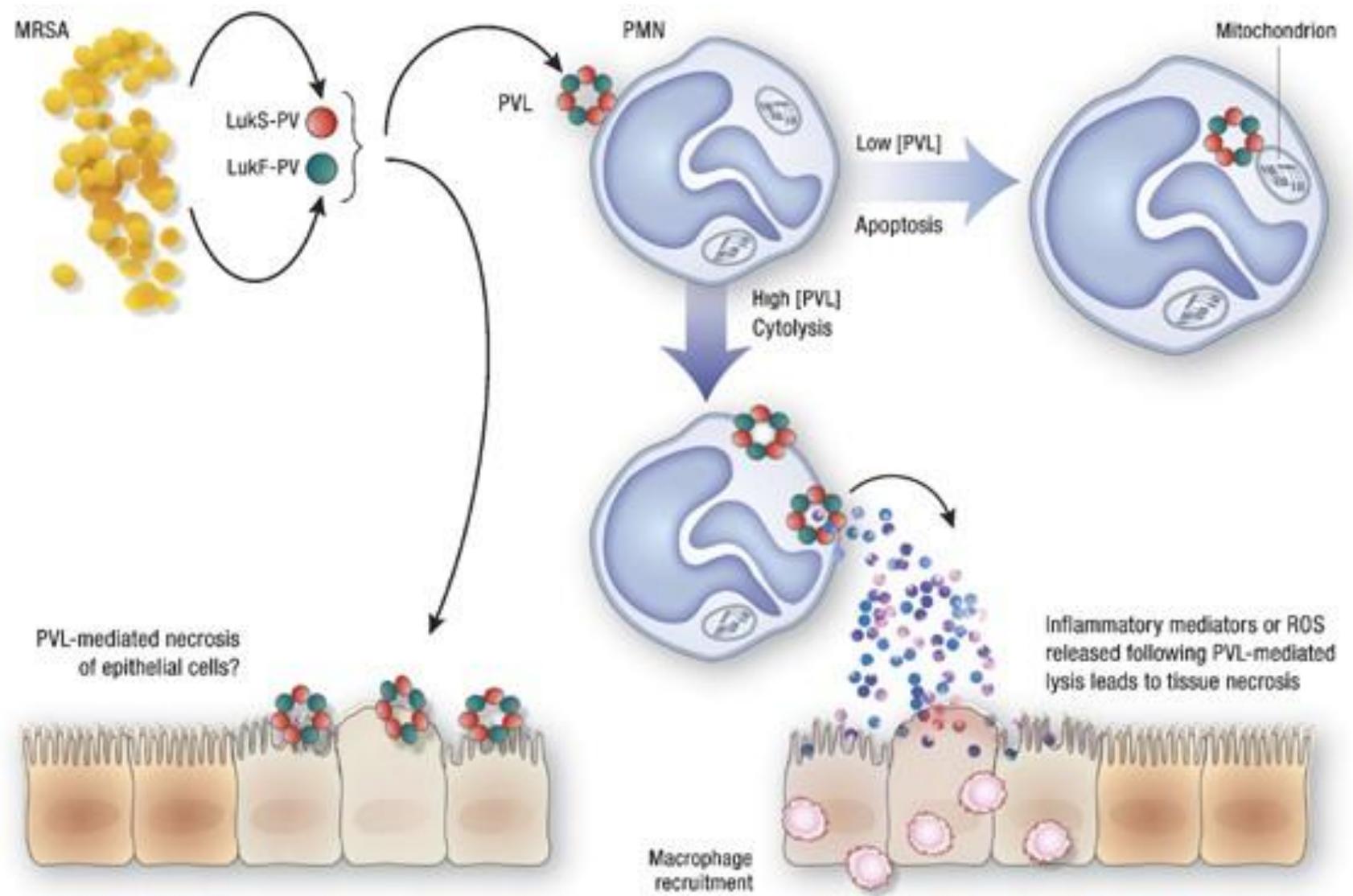




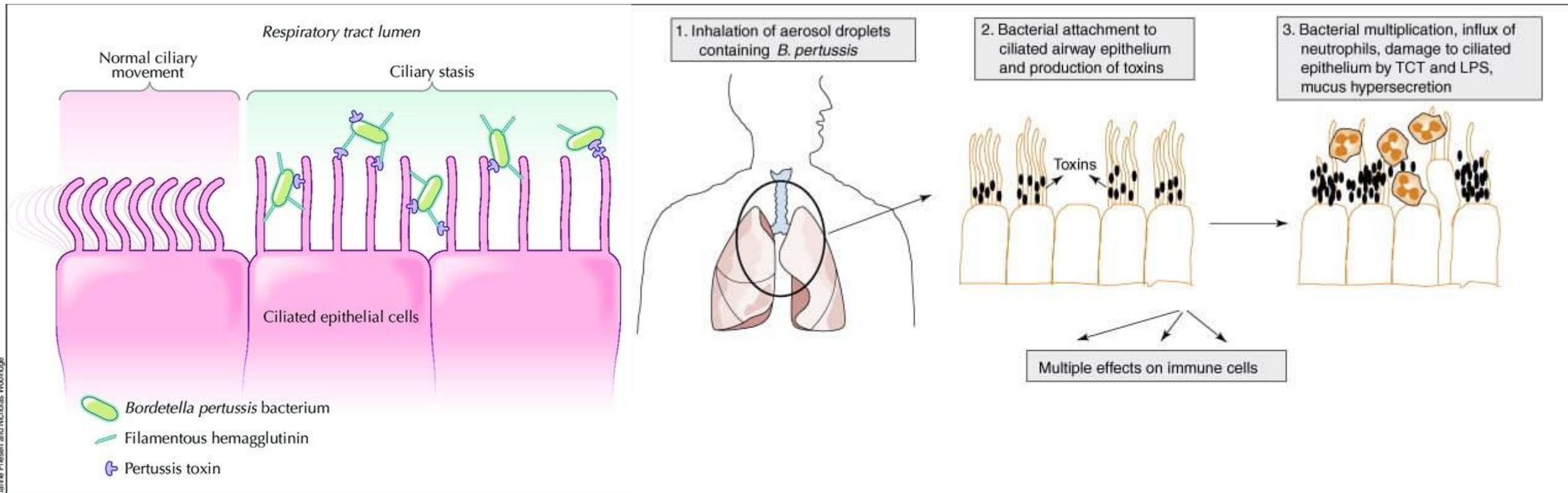


<https://youtu.be/4JWpG8XPku4>





# Interferência na ação ciliar por *Bordetella*



# Interferência na ativação do complemento

1 – presença de cápsula previne a ativação;

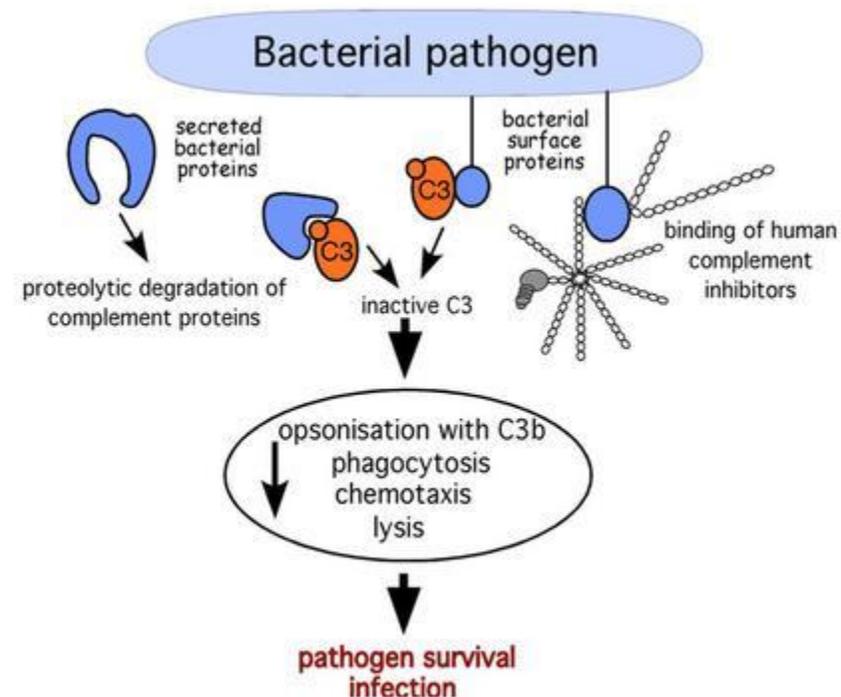
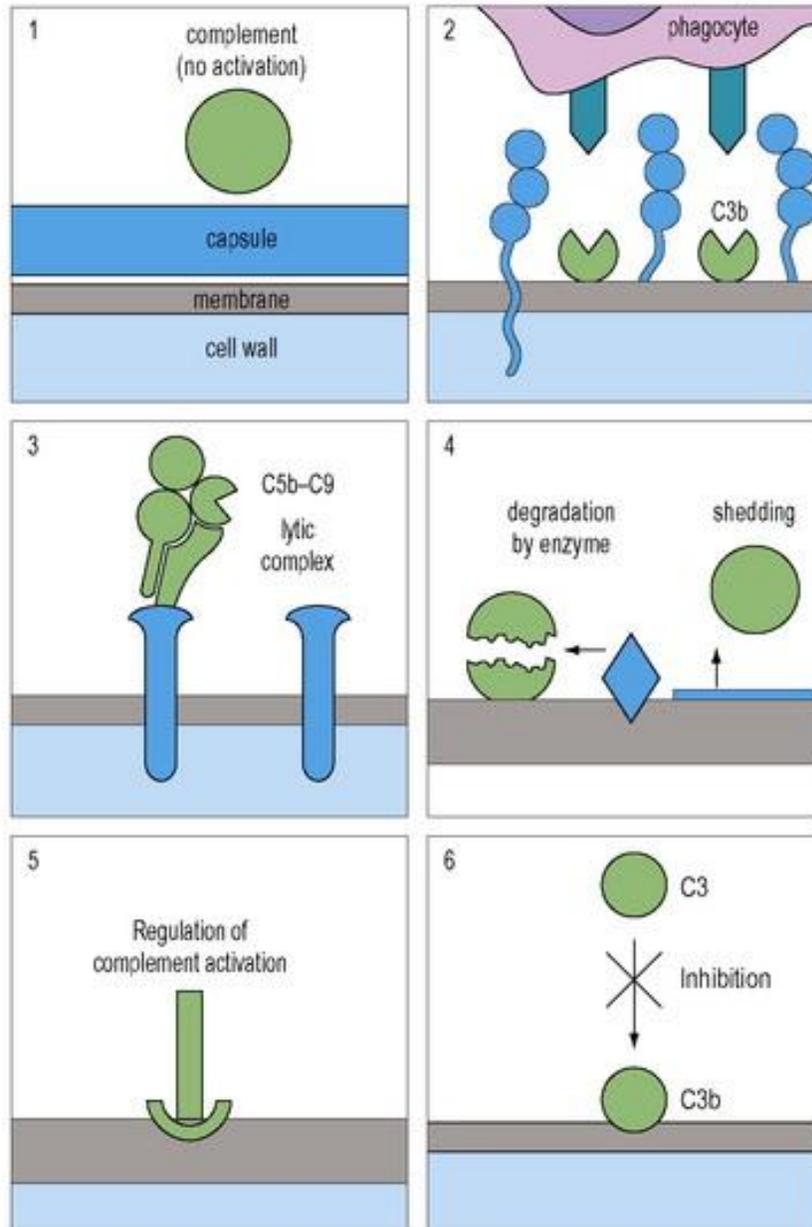
2 – configuração da superfície bacteriana evitando que receptores celulares não tenham acesso a C3b;

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

4- proteases ligadas a membrana degradam o complemento

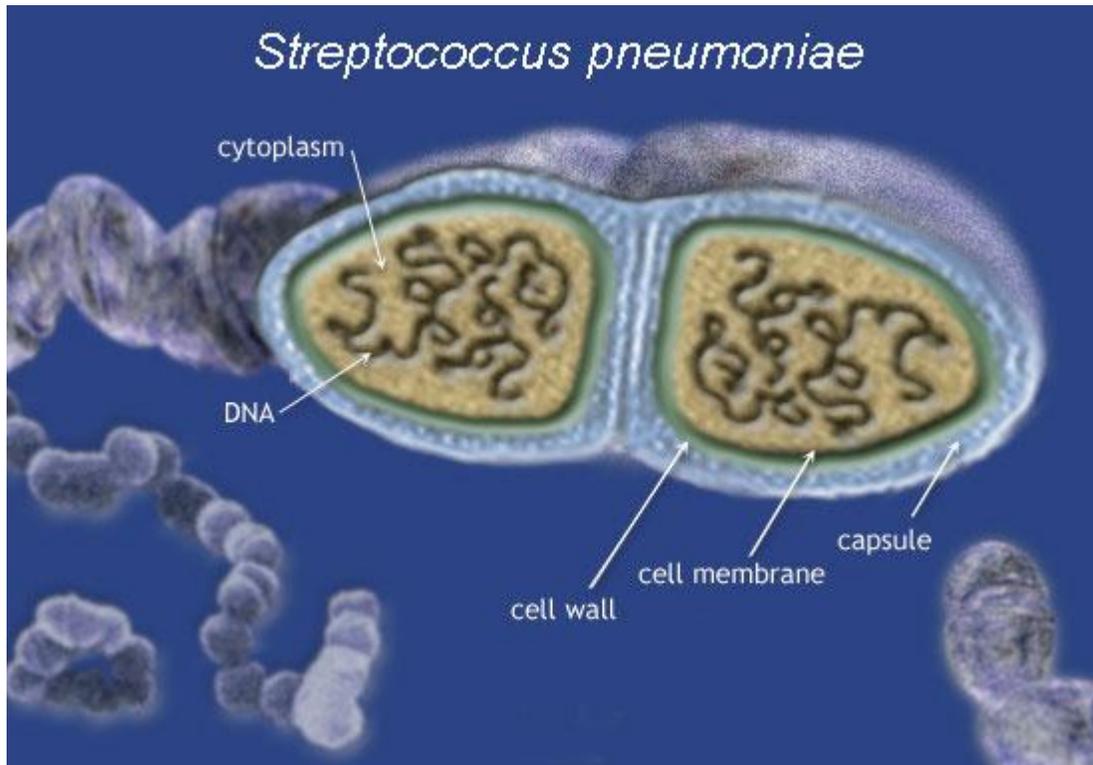
5- a superfície bacteriana pode apresentar inibidores da ativação do complemento

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

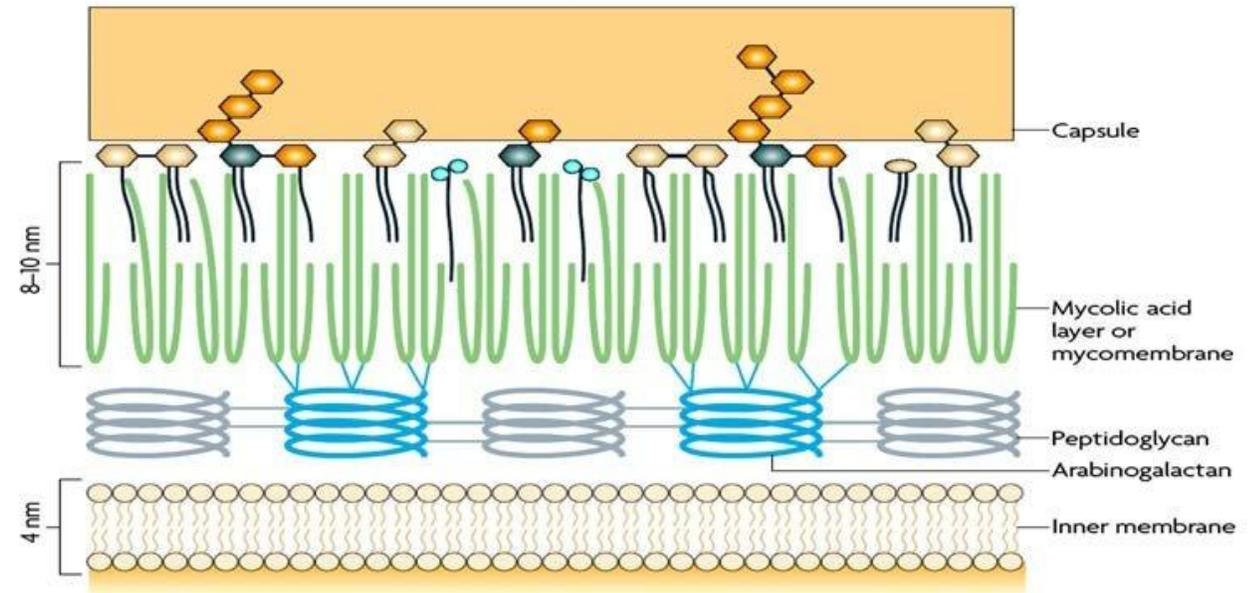


# Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

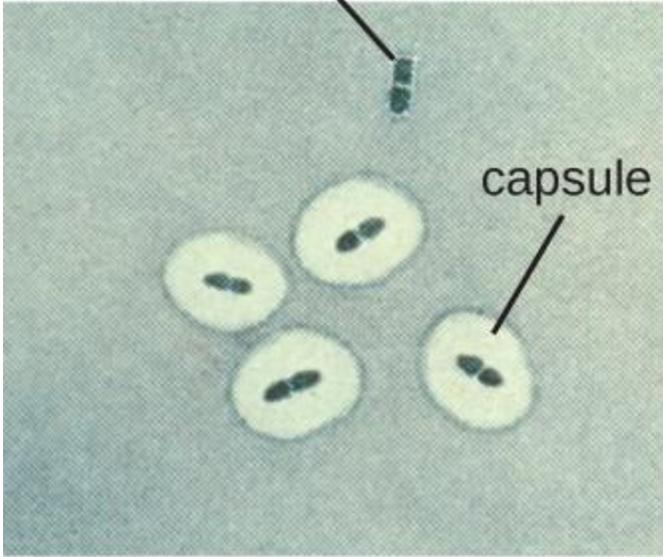
- Cápsula = impede a fagocitose



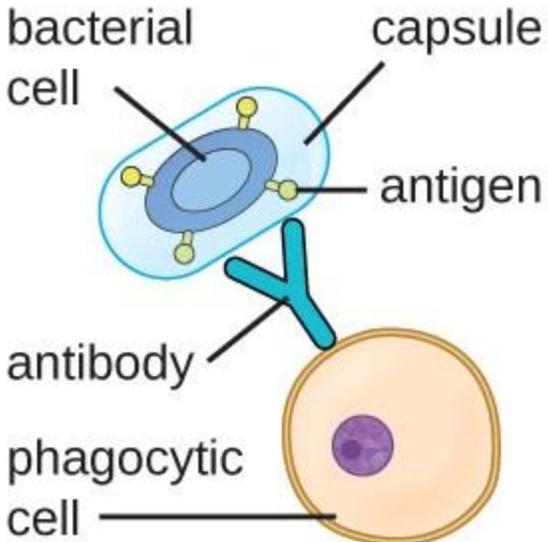
Parede celular micobacterina



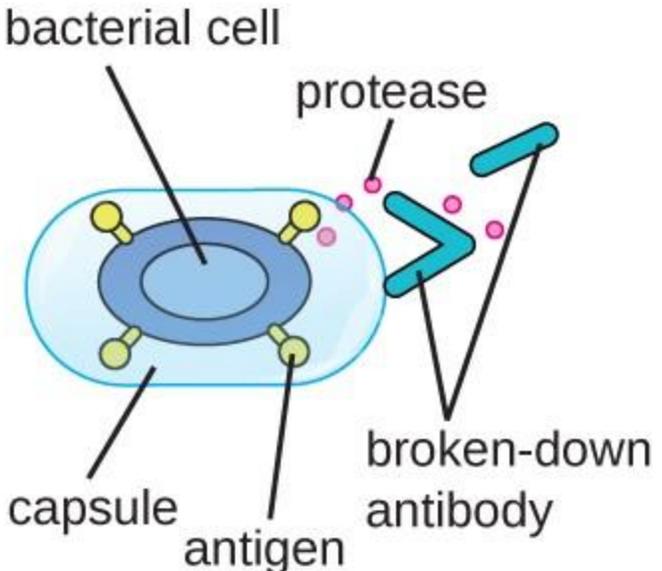
nonencapsulated bacteria



(a)



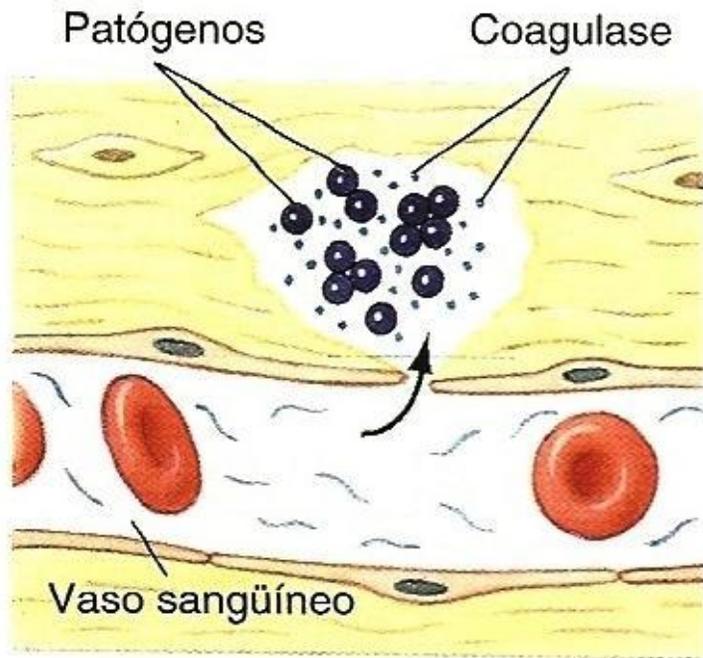
(b)



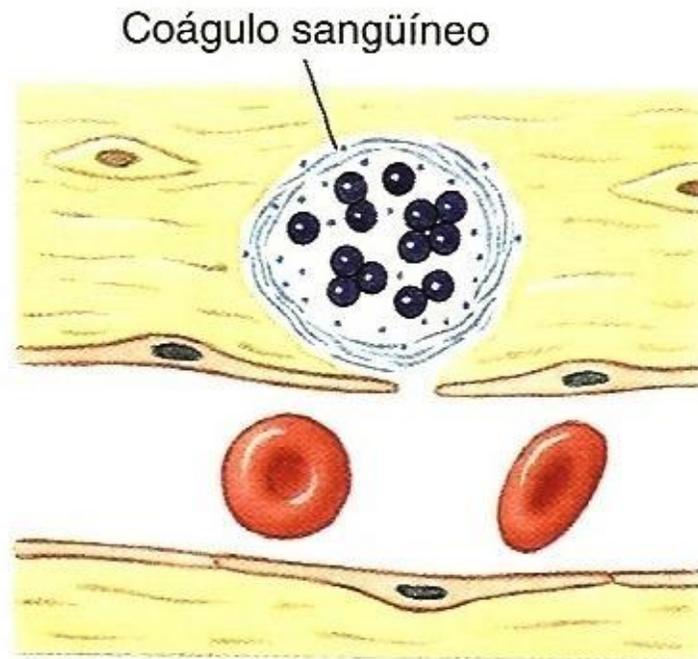
(c)

# Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

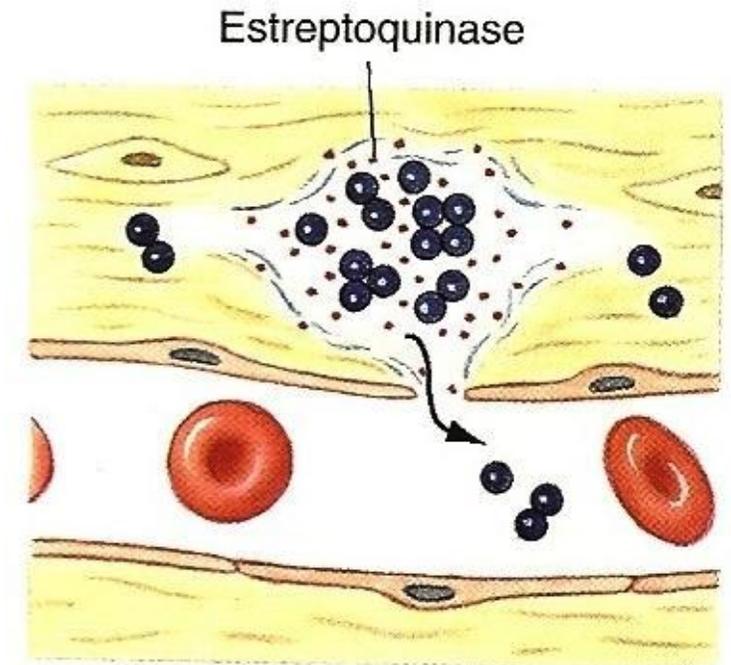
## Presença de coagulase – *Staphylococcus aureus*



1. Patógenos produzem coagulase



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

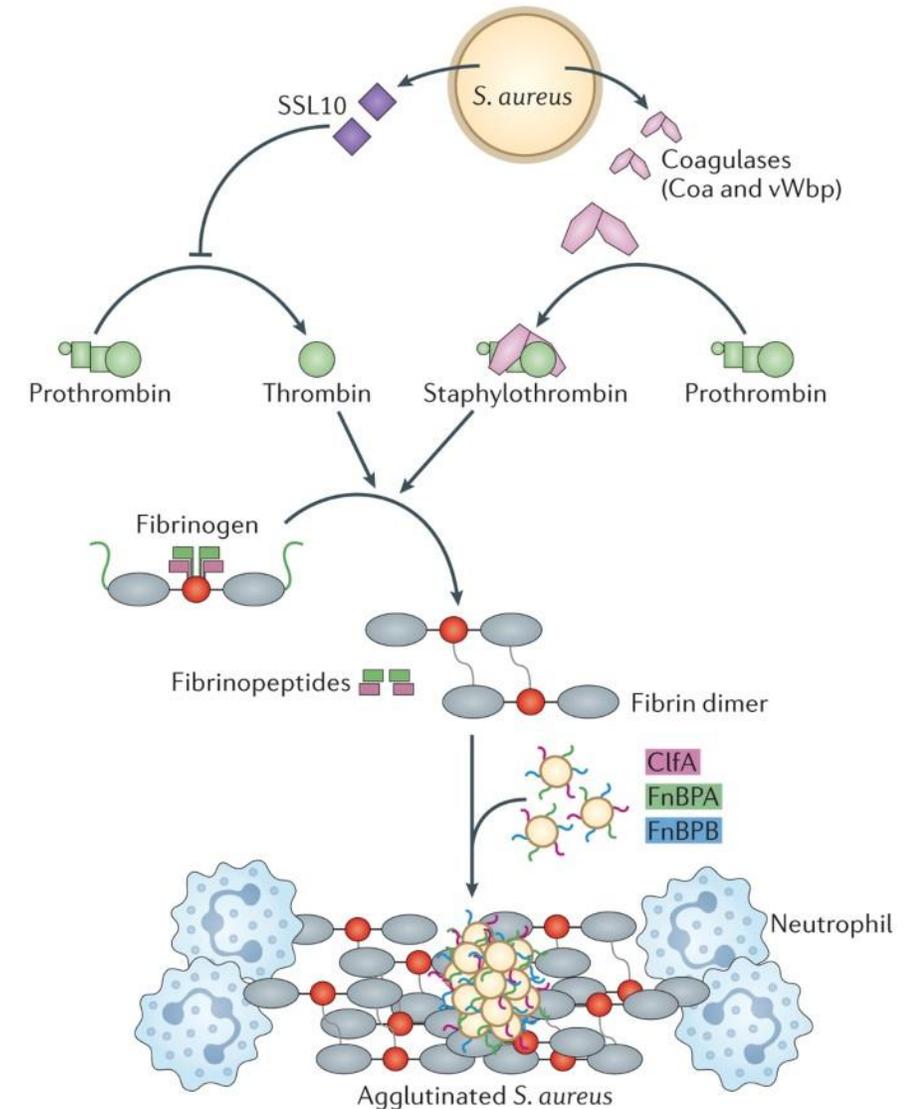
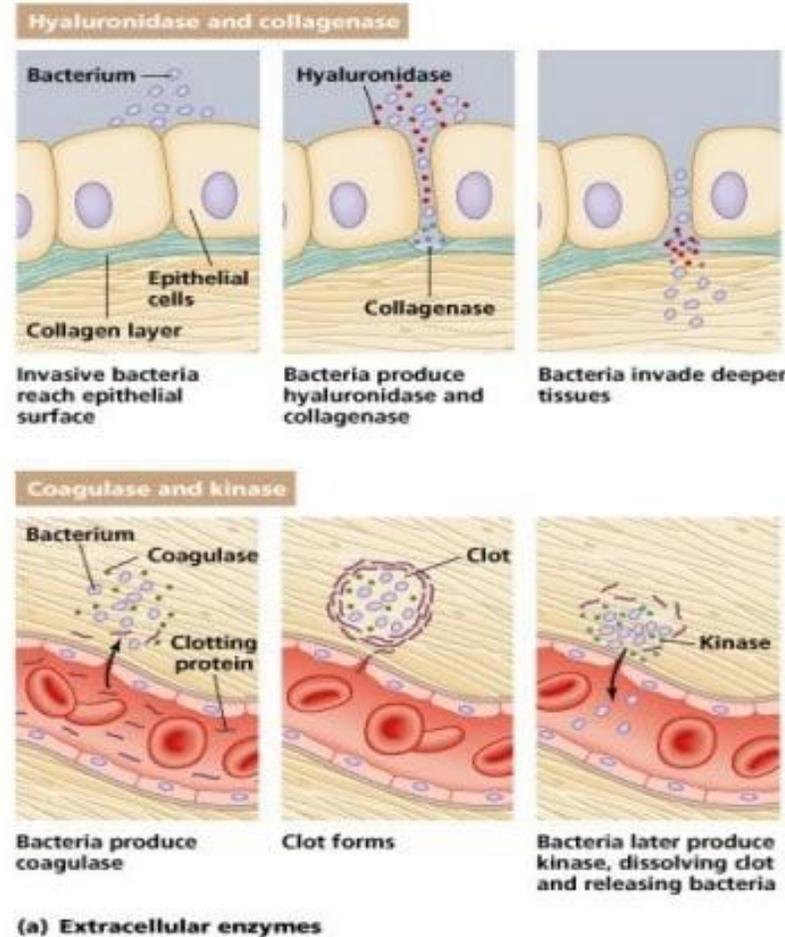


3. Patógenos produzem estreptoquinase, ocorrendo a dissolução do coágulo e liberando as bactérias

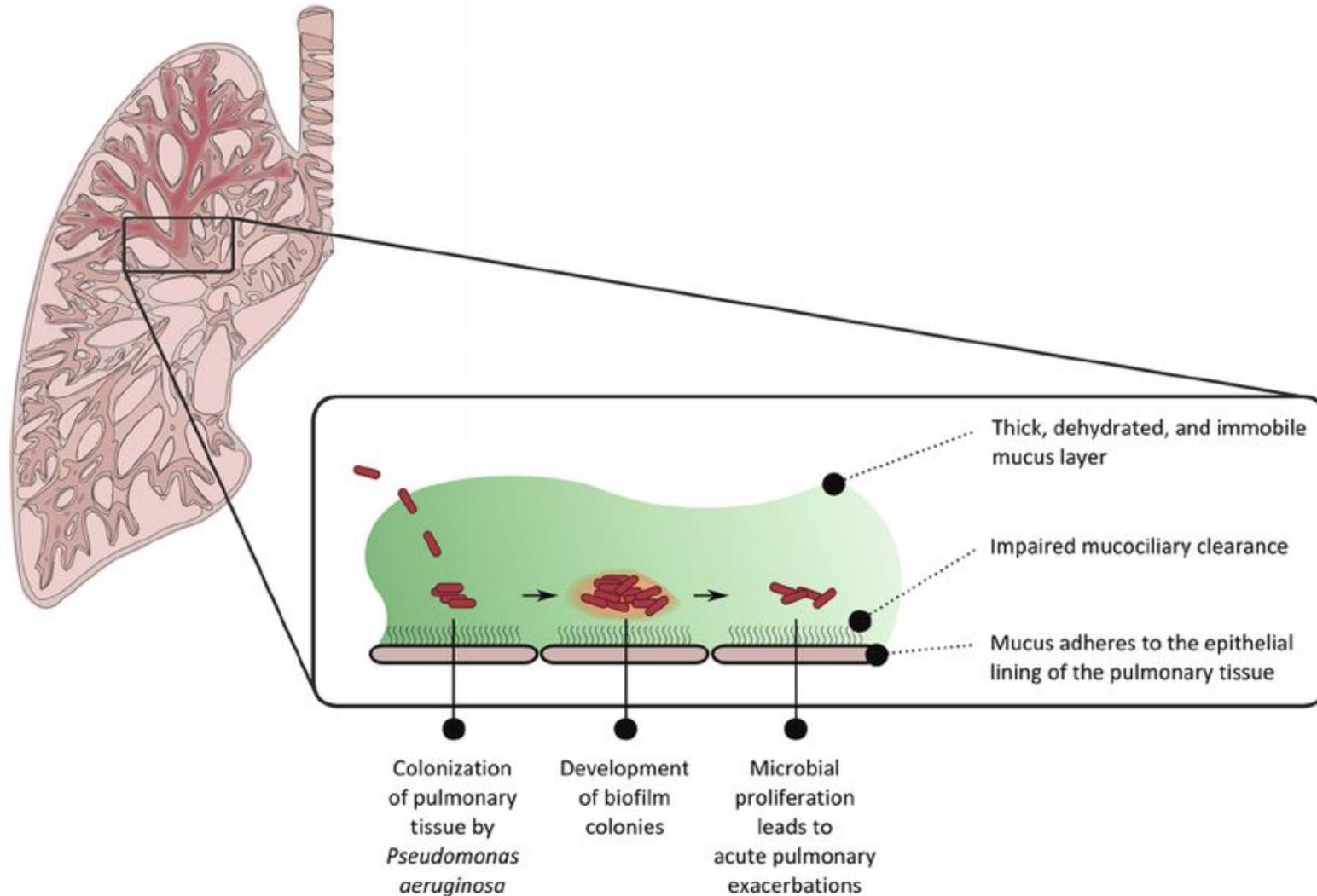
# Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

## Invasiveness

- Hyaluronidase
- Coagulase
- Streptokinase (dissolves Clots)

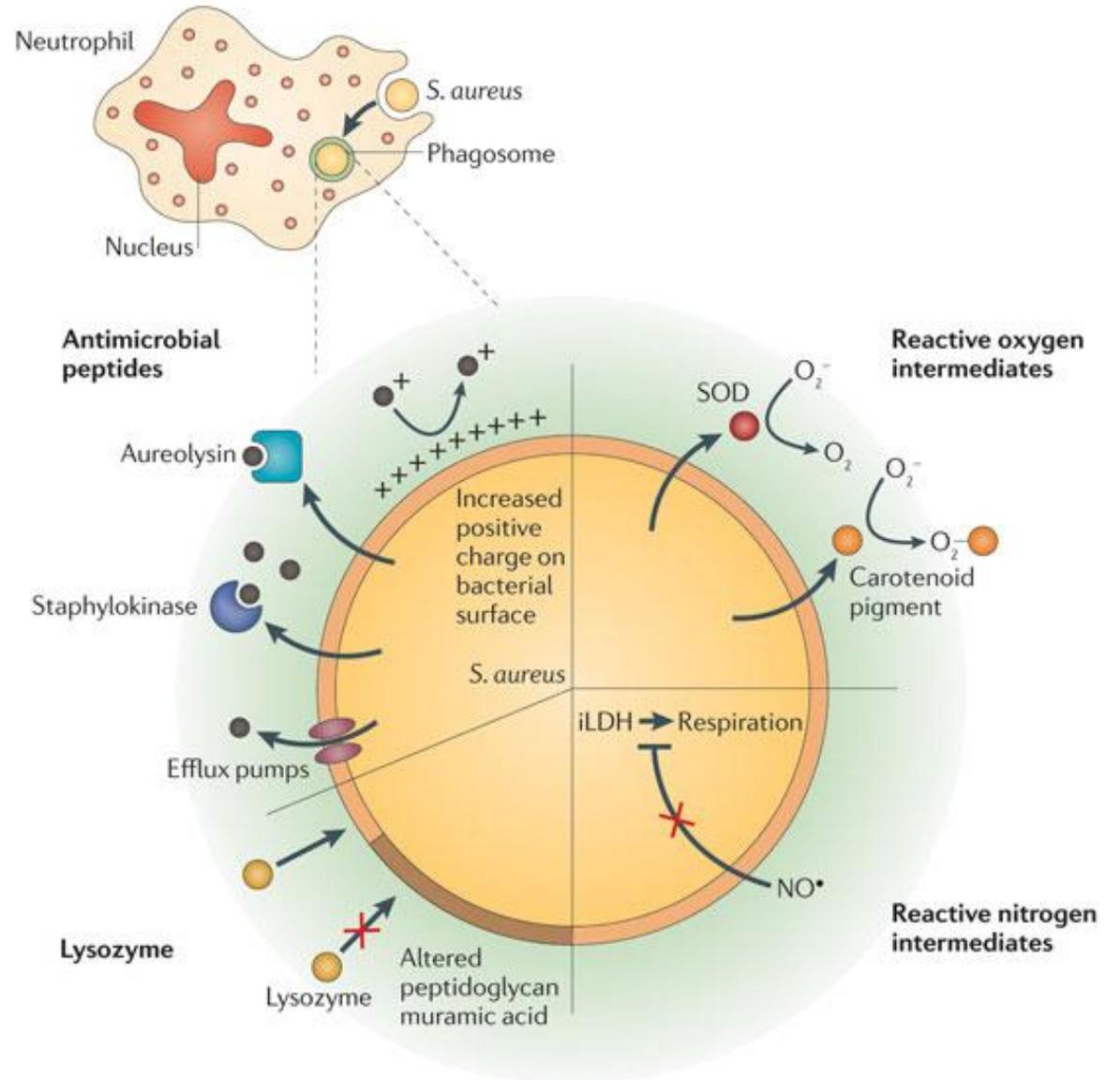


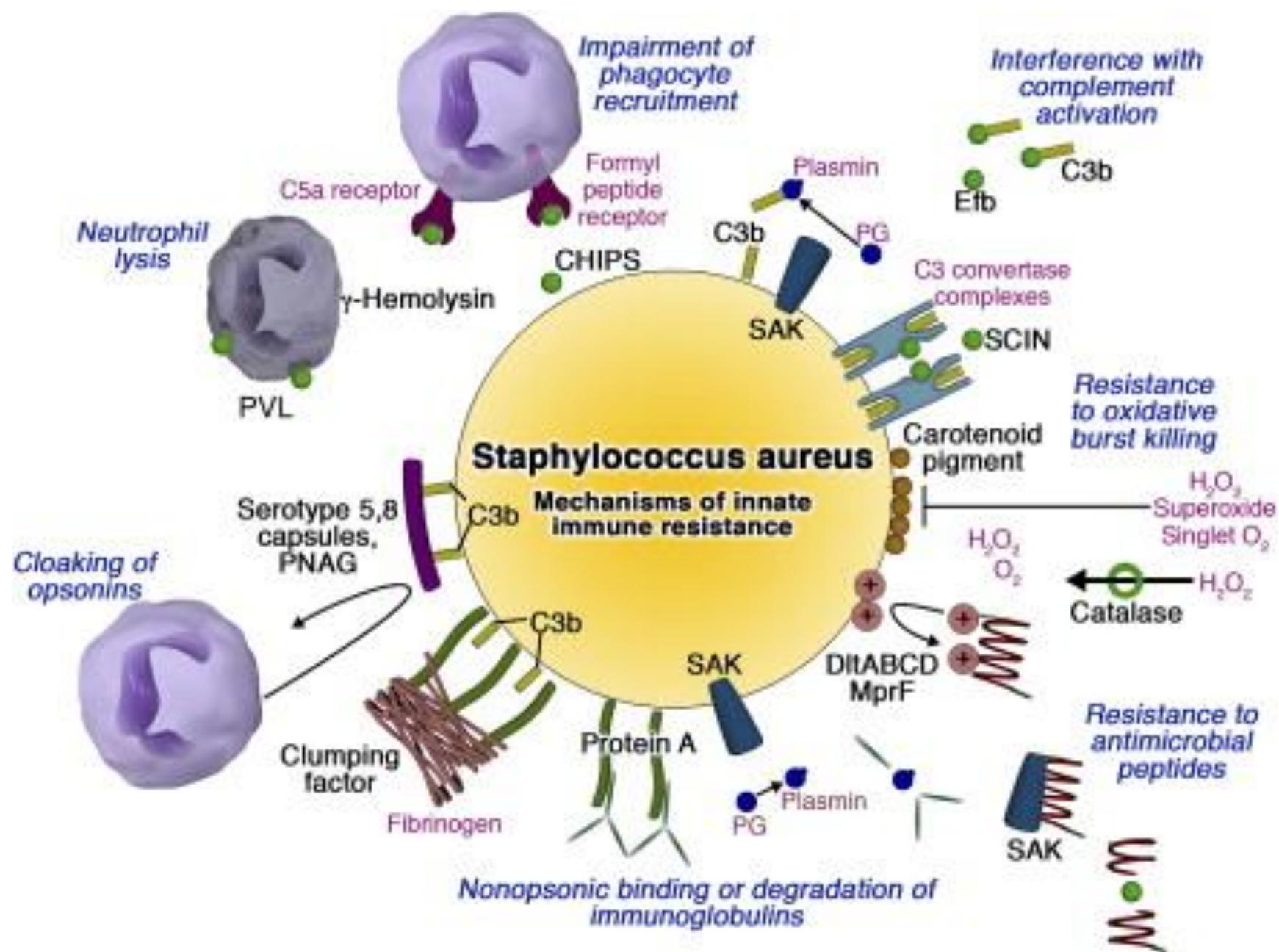
# Evitar o reconhecimento pelo constituintes celulares e humorais do sistema imune

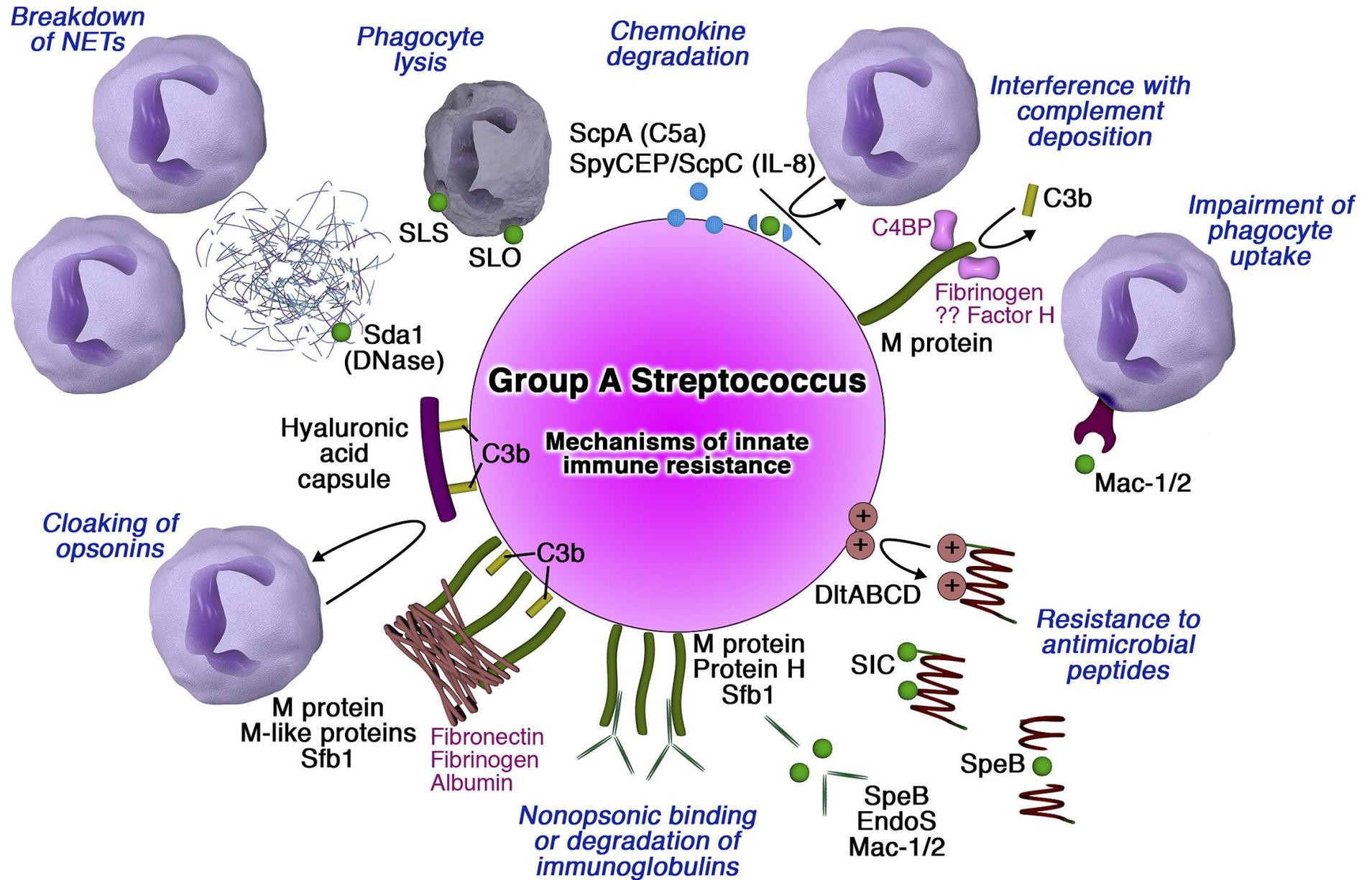


# Destruição do peróxido de hidrogênio e outros componentes antimicrobianos do hospedeiro

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**

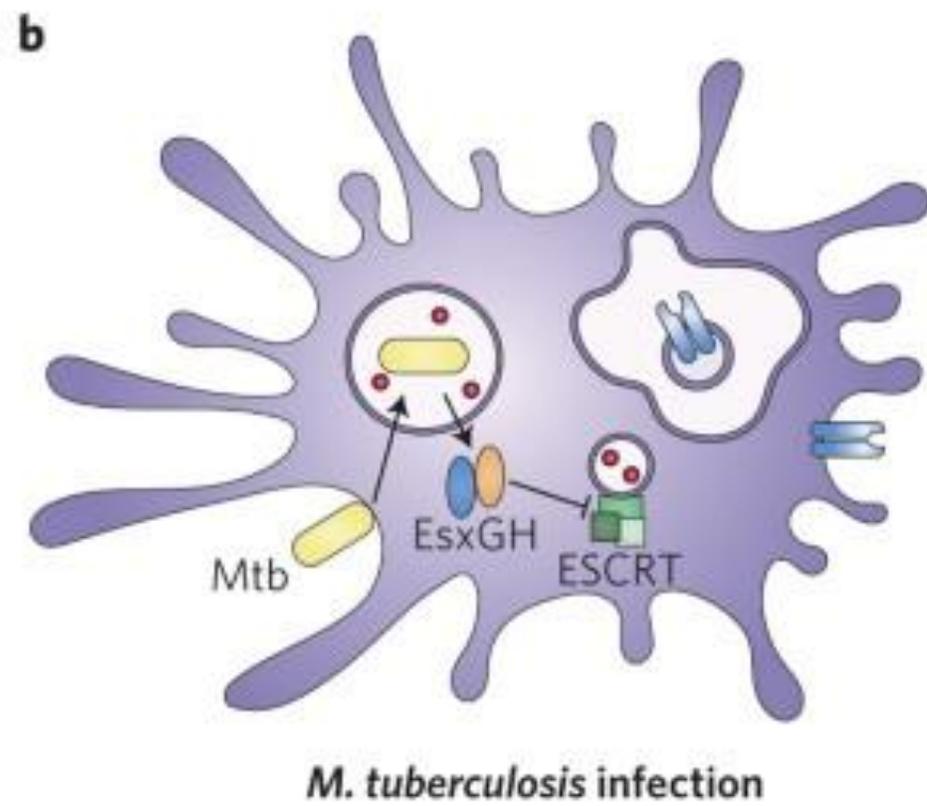
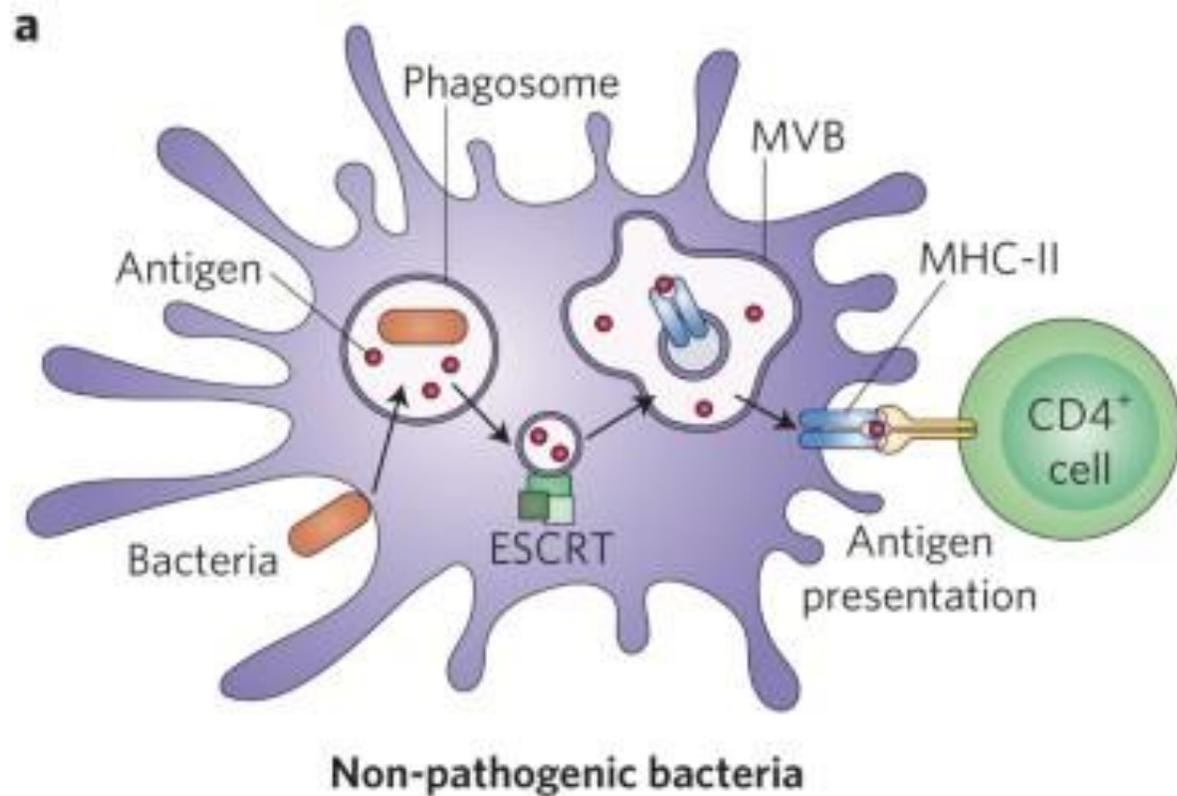
**Imunomodulações: -**

**Perturbações no equilíbrio das respostas imunológicas**

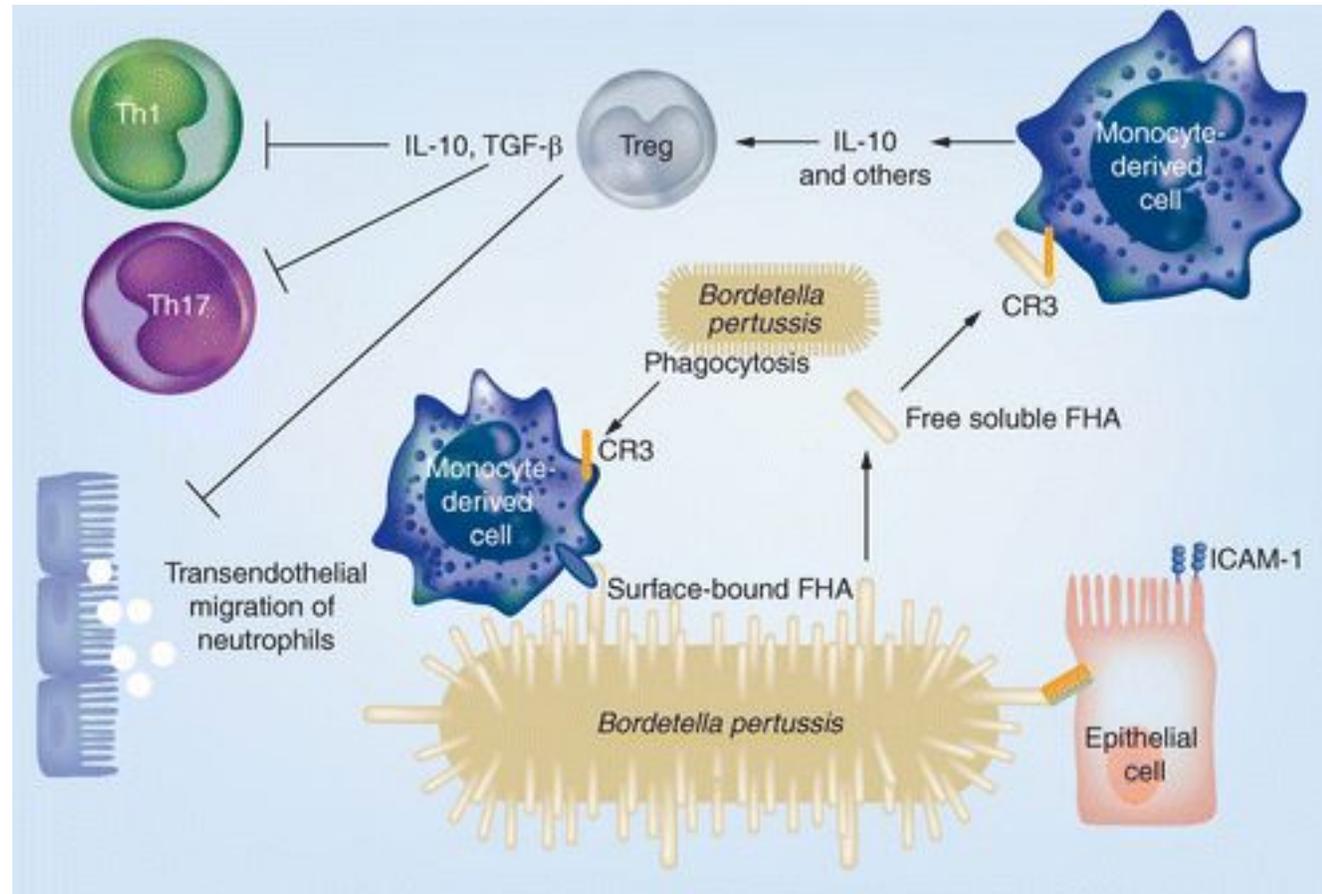
**produção de grande quantidade de antígeno**

**produção de antígenos com receptores Fc (não desencadeia atividade)**

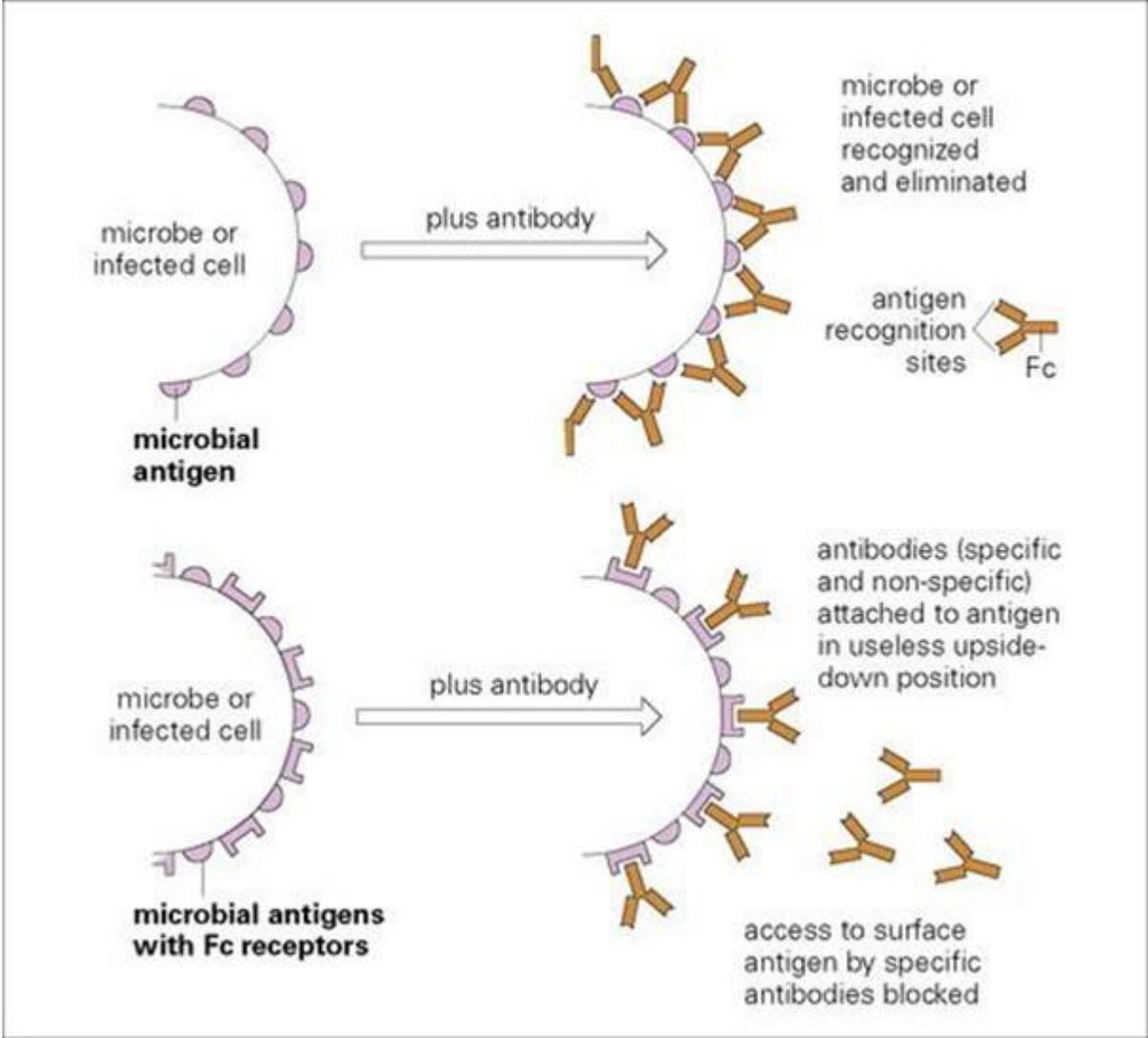
**indução de células T reguladoras**



## Imunomodulação: *Bordetella pertussis*

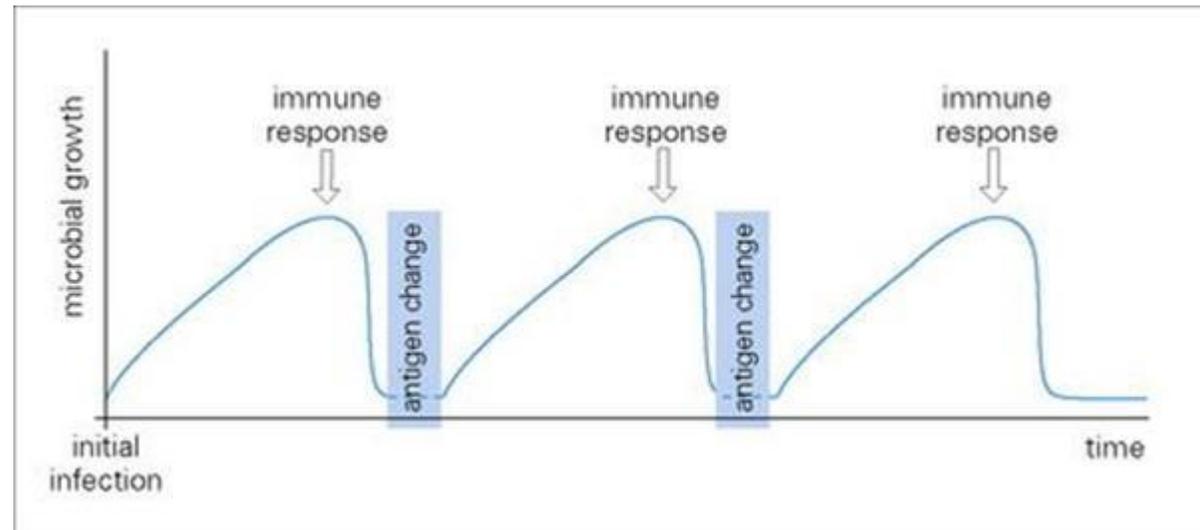


FHA = fragmento de hemaglutinina



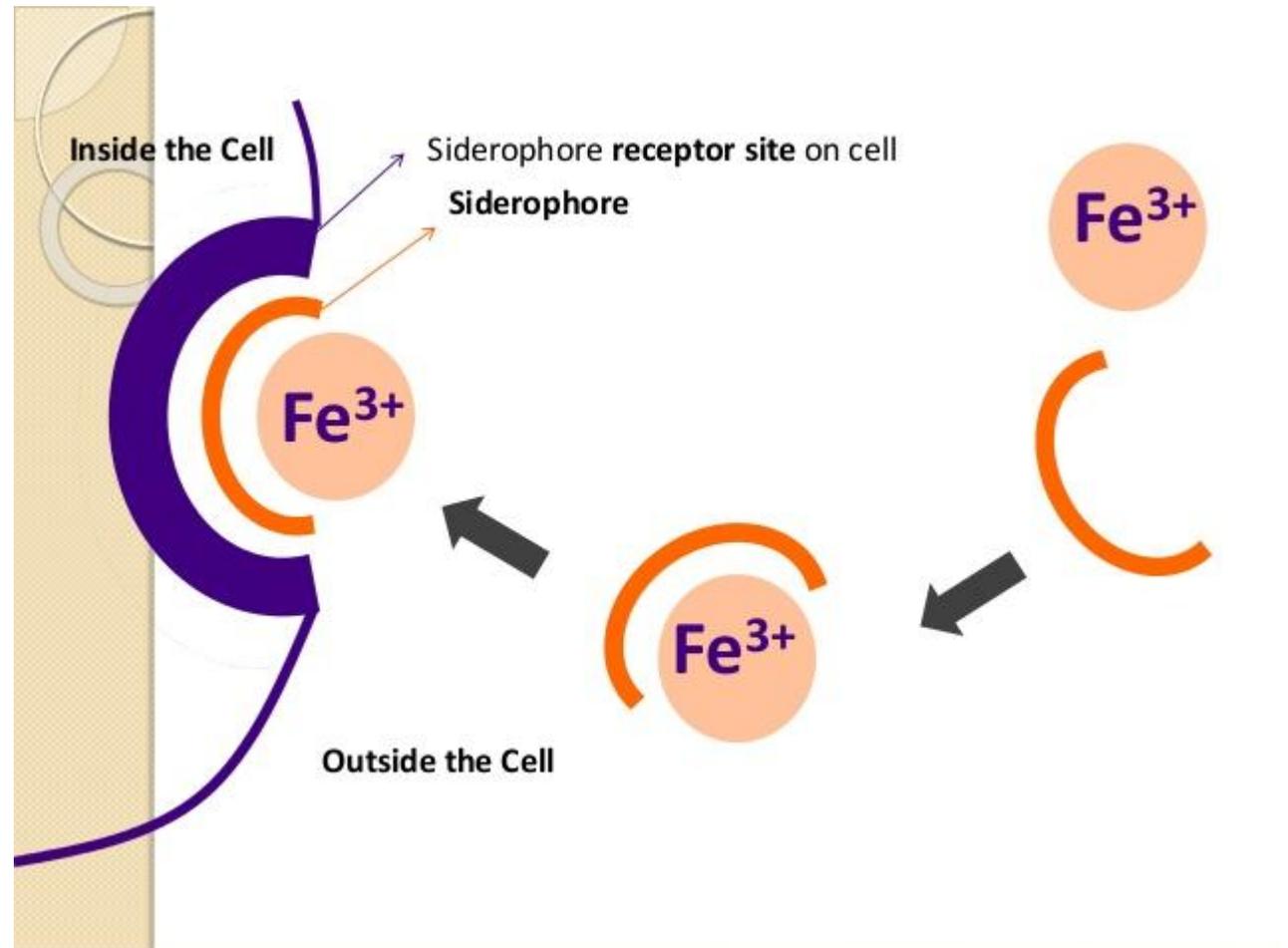
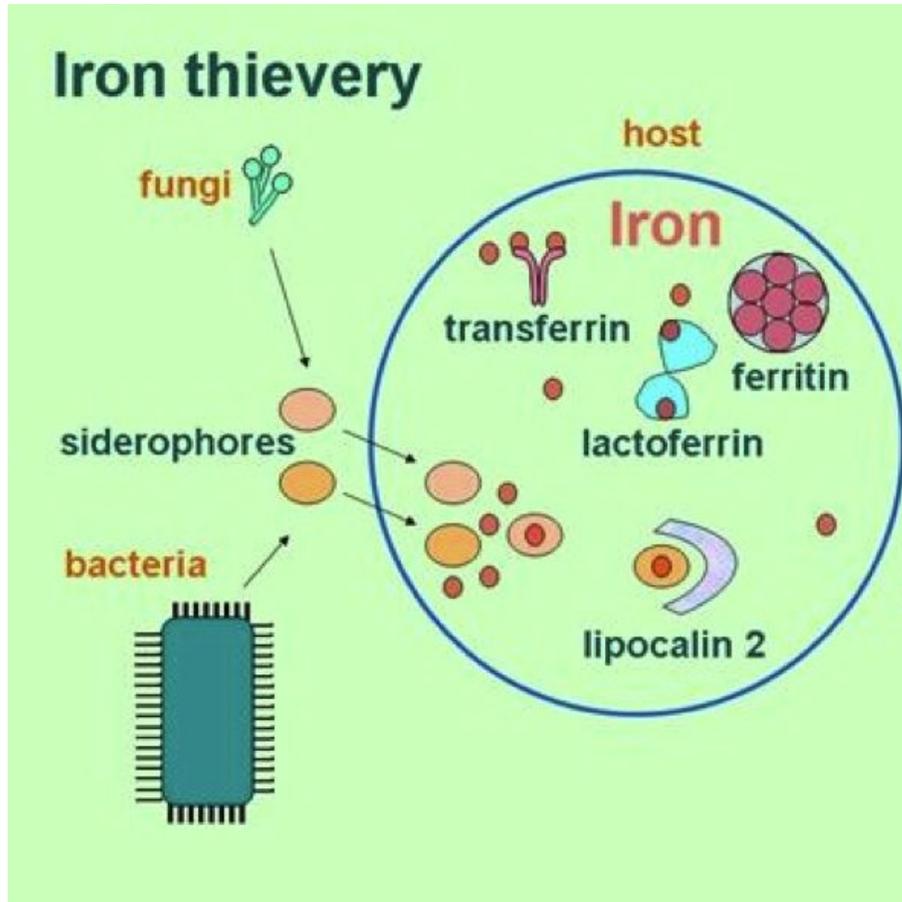
# Variação antigênica

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



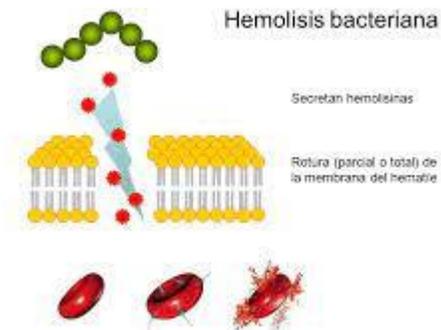
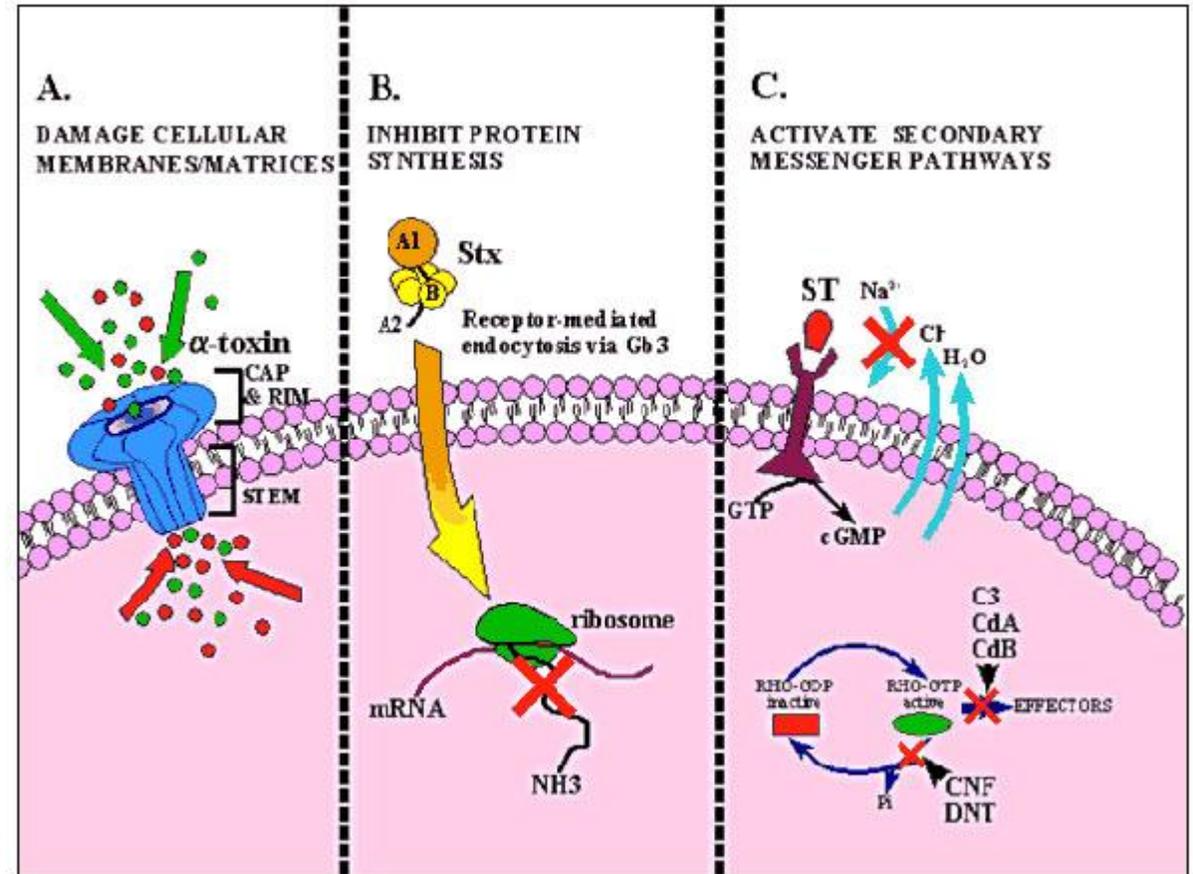
# Toxinas

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

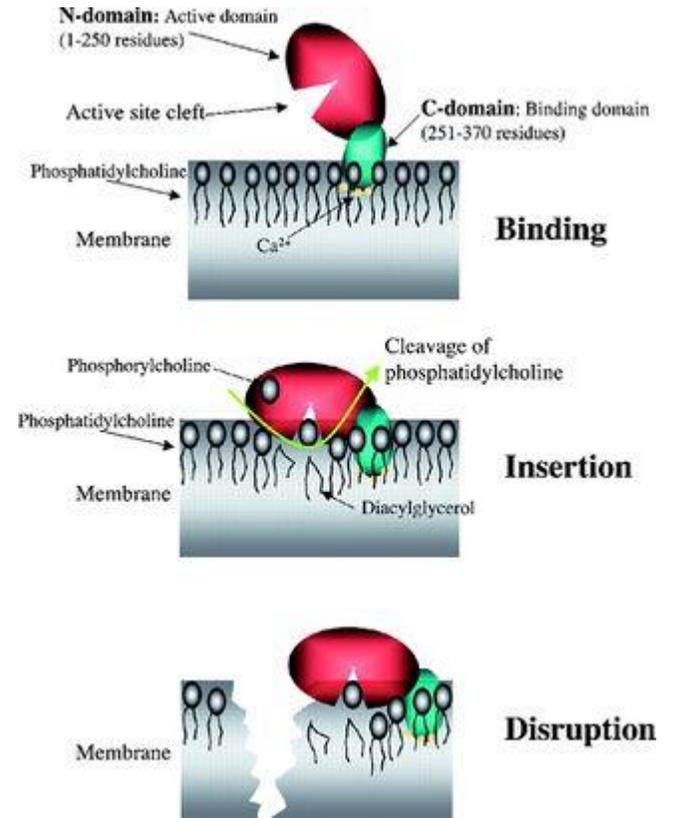
Enzimas podem digerir o material entre as células e induzir a formação ou a degradação de coágulos

- coagulases – enzimas bacterianas que coagulam o fibrinogênio no sangue. Comum em *Staphylococcus*
- quinases – degradam fibrina e digerem coágulos. Ex. fibronolisina (estreptocinase)
- Hialuronidase – 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*

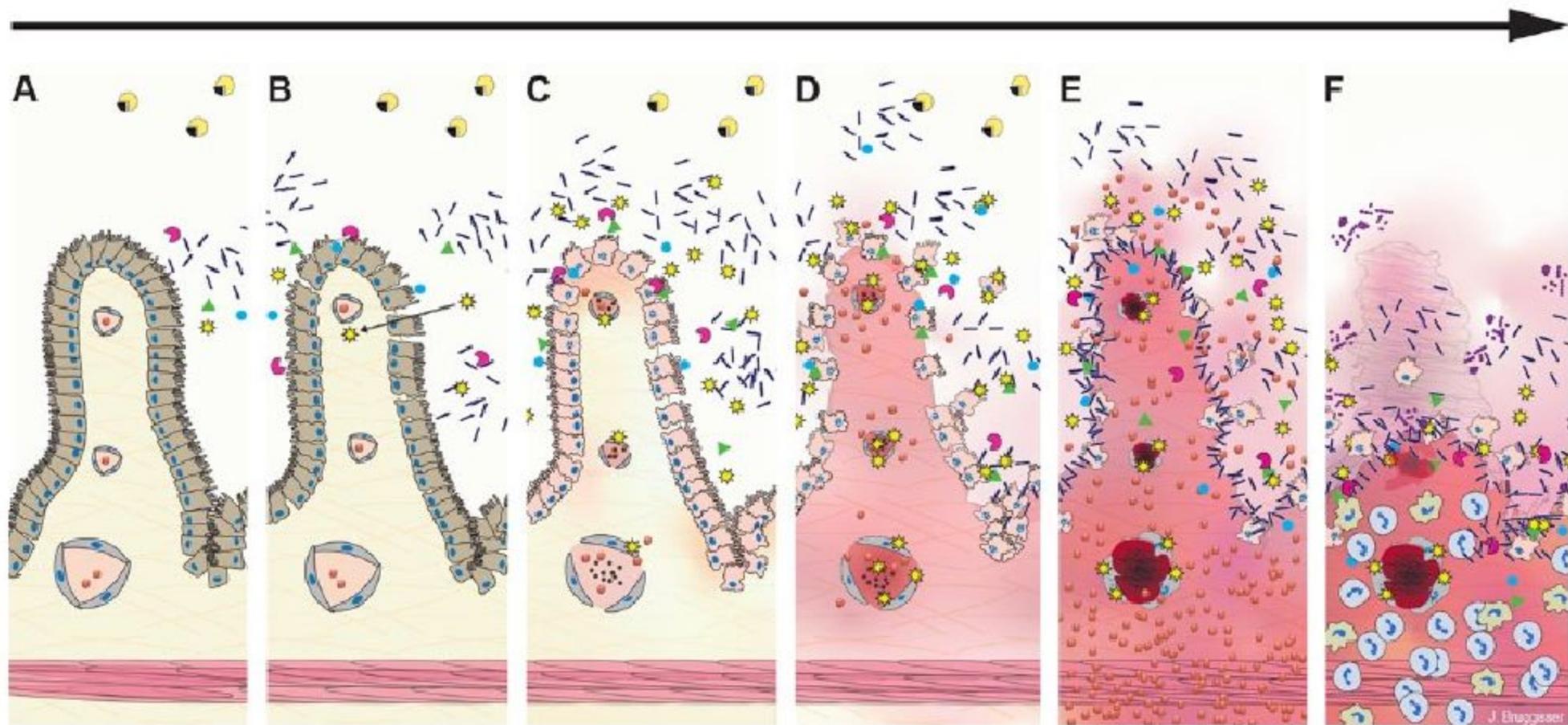
# Destruição dos tecidos

Produtos provenientes do metabolismo da bactéria

Enzimas degradativas



*Clostridium perfringens*



 *C. perfringens* type C

  $\beta$ -toxin

 Trypsin

 Erythrocytes

 Blood vessel

 Neutrophil

 Commensal bacterial flora

 Additional major and minor toxins/enzymes

 Trypsin inhibitor

 Thrombocytes

 Thrombus

 Macrophage

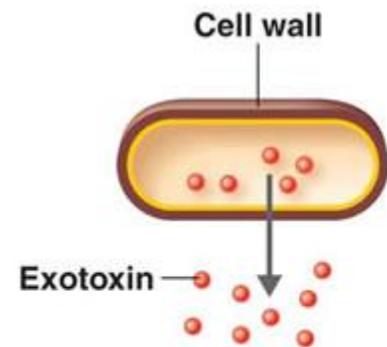
J. Ehrig

# Tipos de toxinas

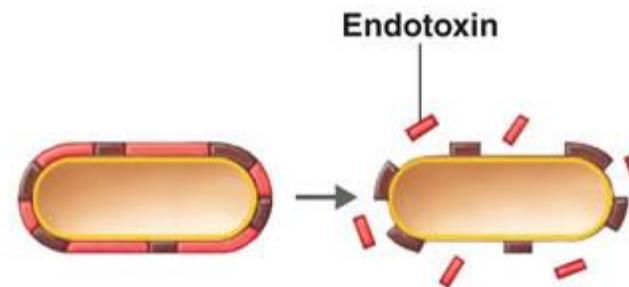
Toxina pré-formada – toxinas presentes nos alimentos antes da ingestão

**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

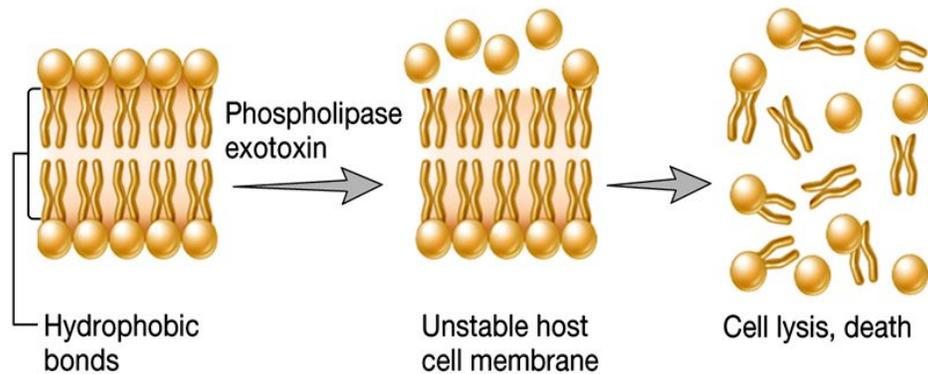
Toxins are of two general types: exotoxins and endotoxins.

# Exotoxinas

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

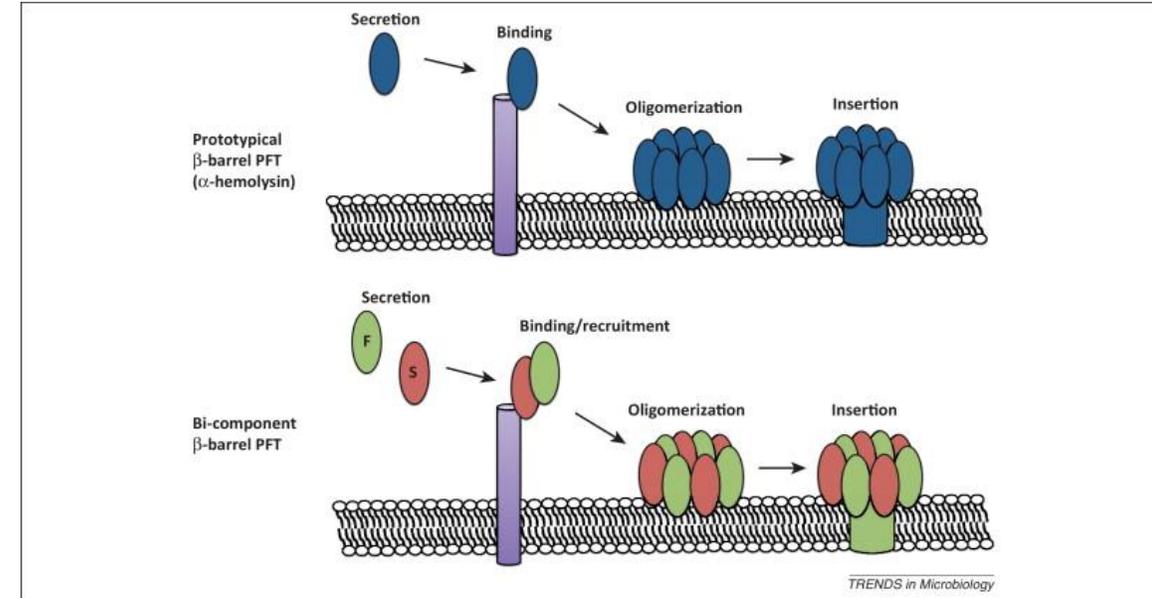
Toxinas citolíticas:

Toxina  $\alpha$  de *Clostridium perfringens* (fosfolipase C)

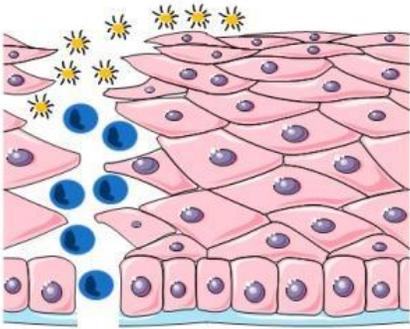


(b)

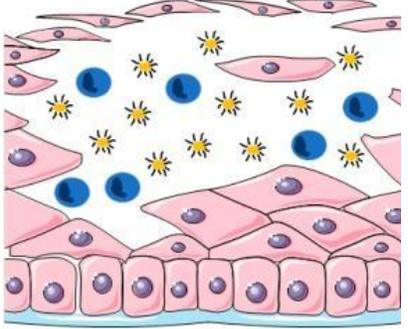
## Hemolisina de *Streptococcus*



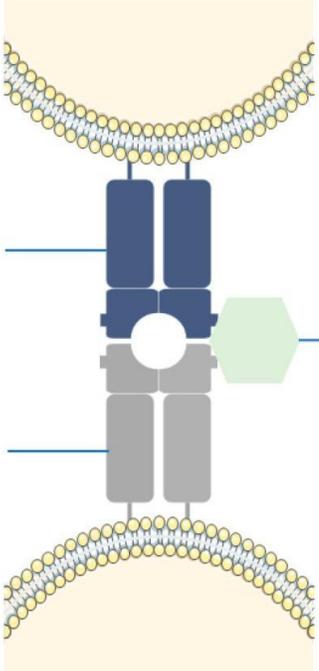
# Toxinas - *Staphylococcus aureus*



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

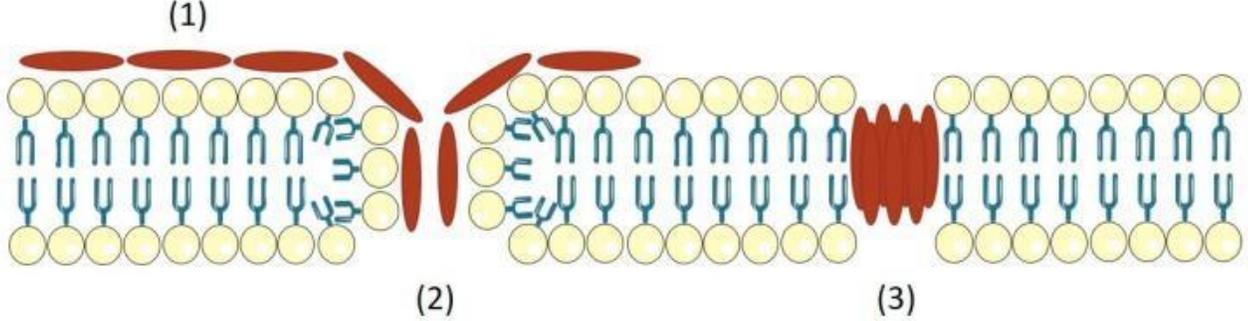


Expansion of blisters by ETs.



T-cell receptor

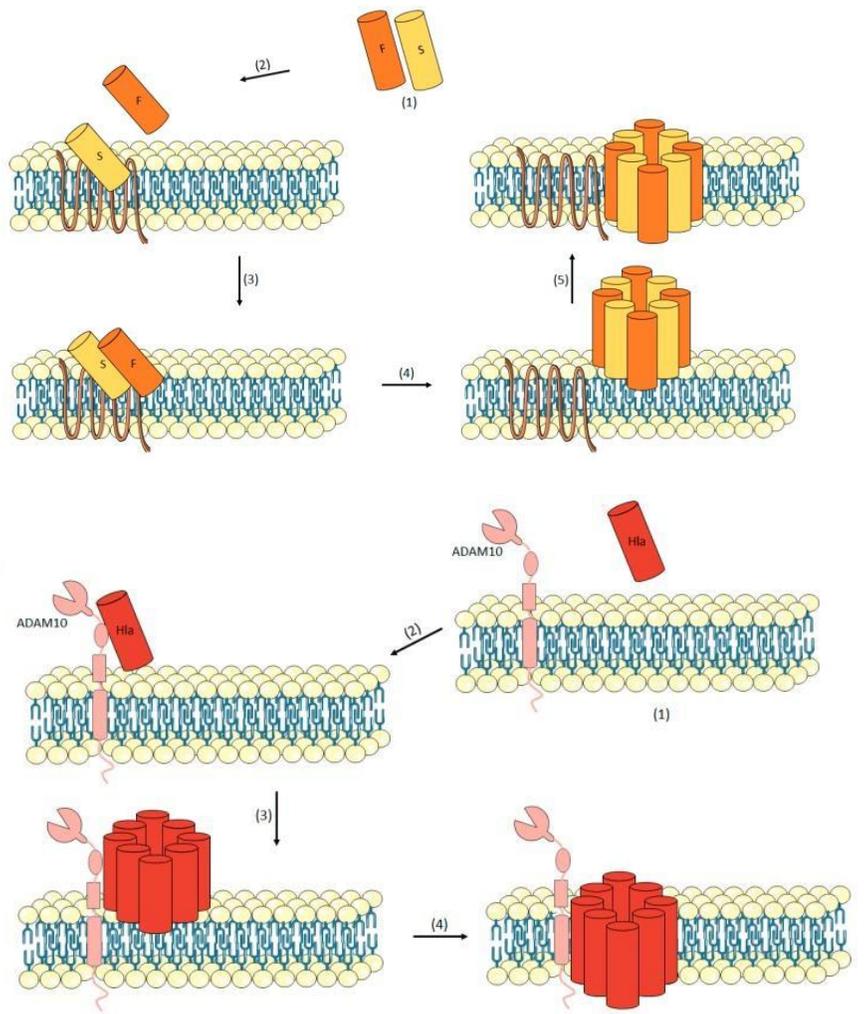
MHC class II molecule



(1)

(2)

(3)



(1)

(2)

(3)

(4)

(5)

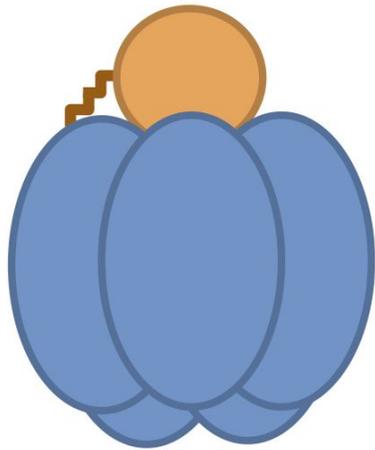
(1)

(2)

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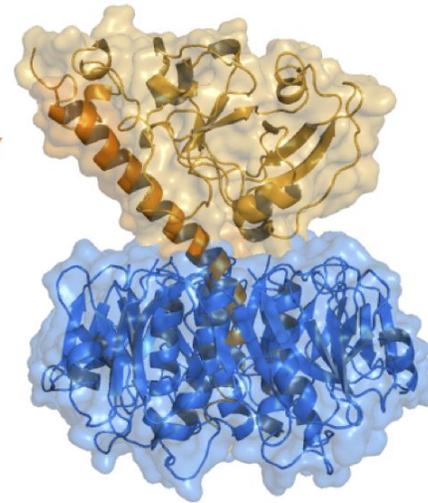
(4)

# Toxinas diméricas com subunidades A-B

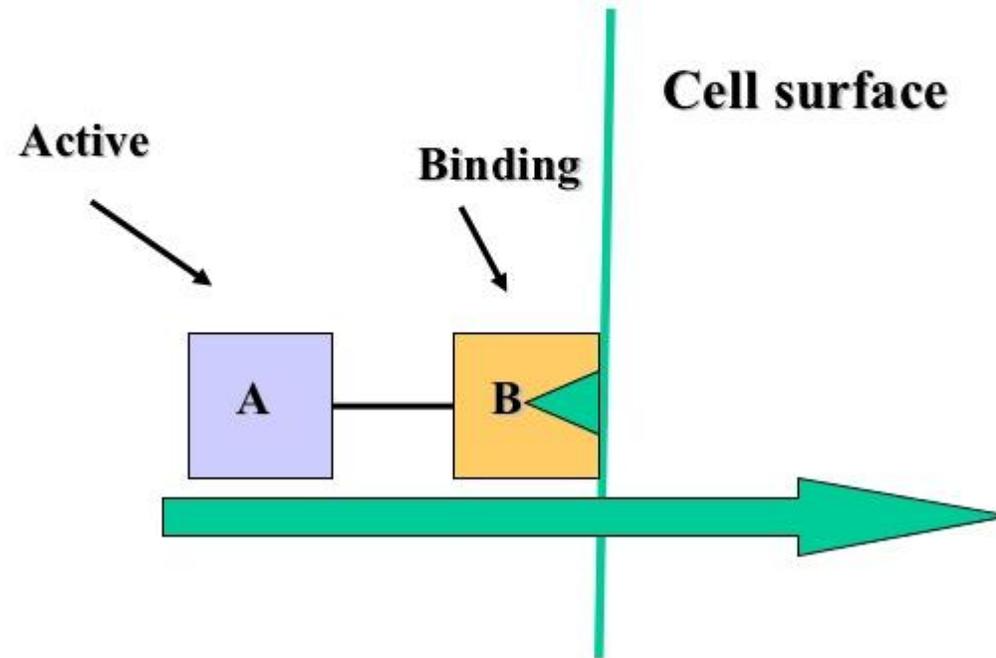


A subunit  
*enzymatic toxicity*

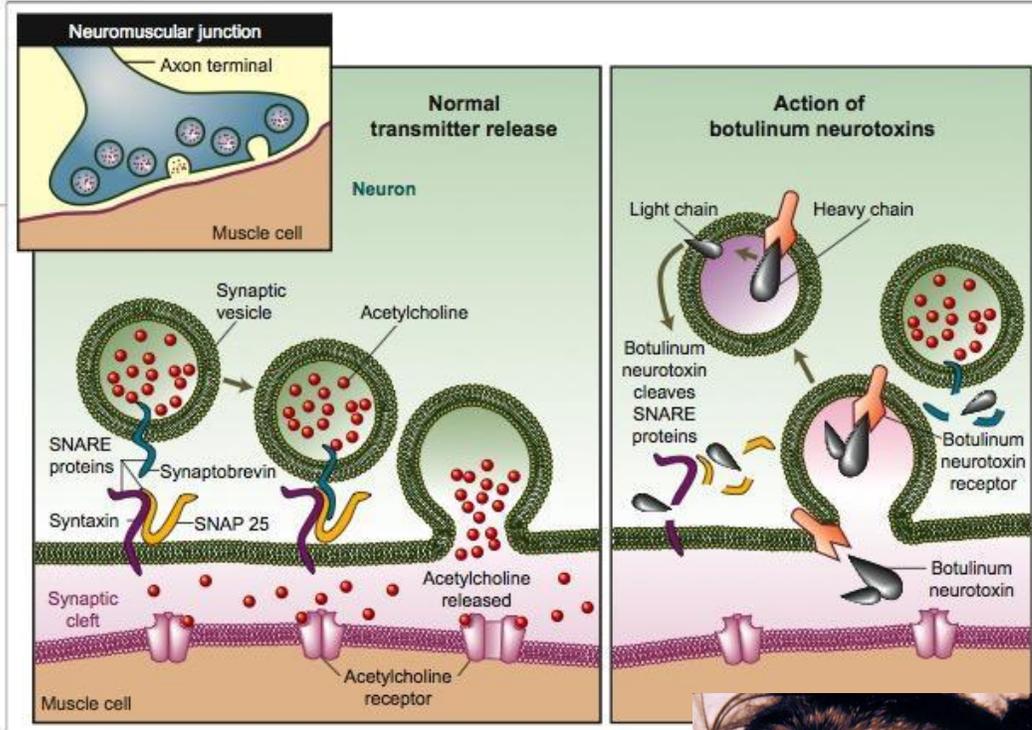
B<sub>5</sub> subunit  
*cell binding*



# A-B toxins



# Toxina botulínica e tetânica



## Mechanism of Action of Tetanus Toxin

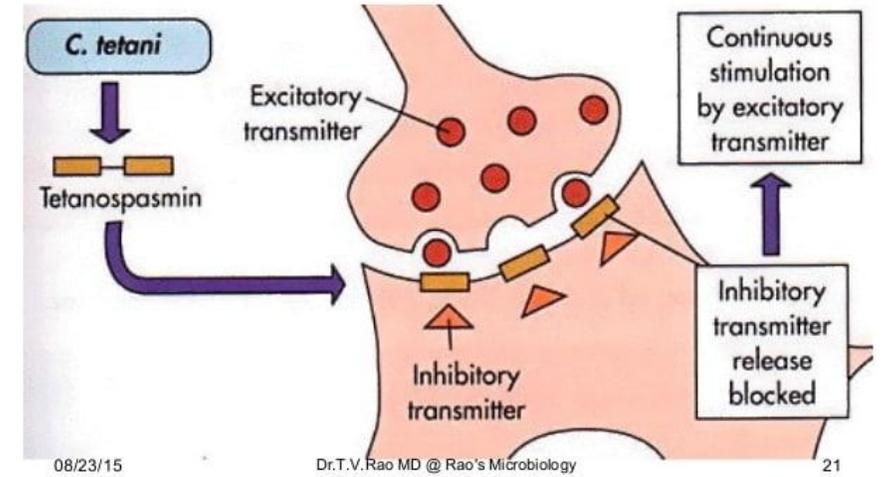


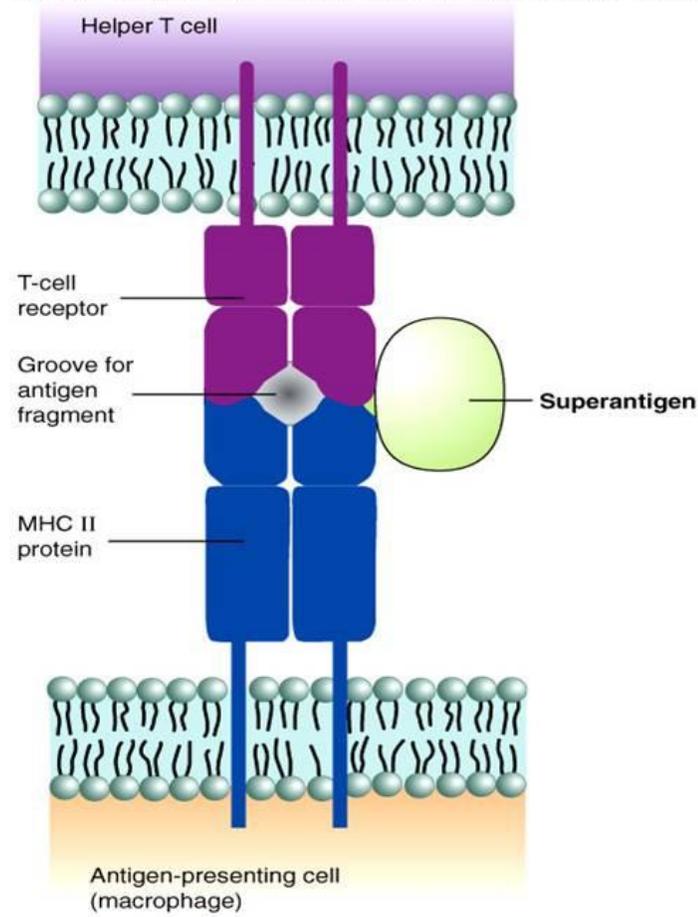
FIGURE 1  
Opisthotonus



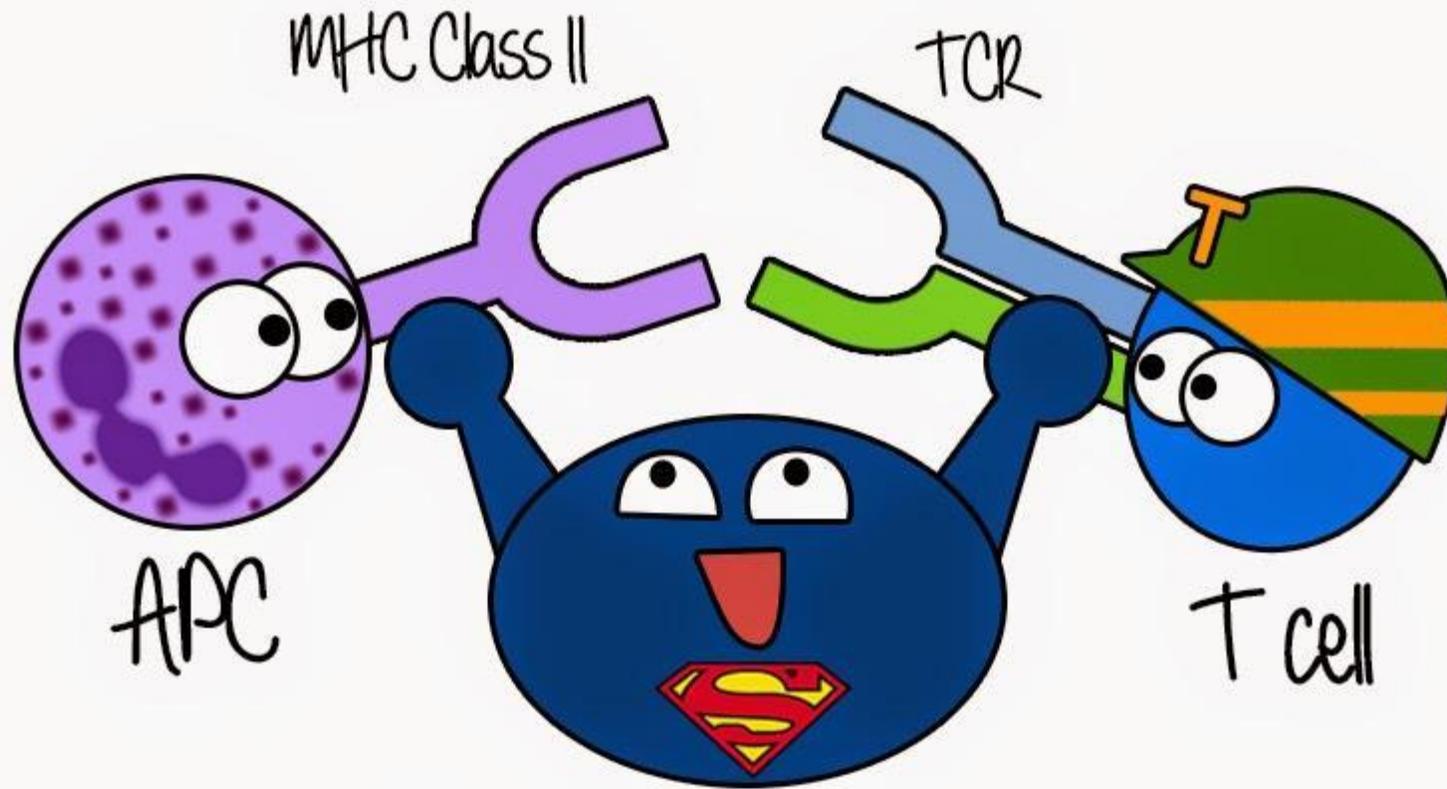
# Superantígenos

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

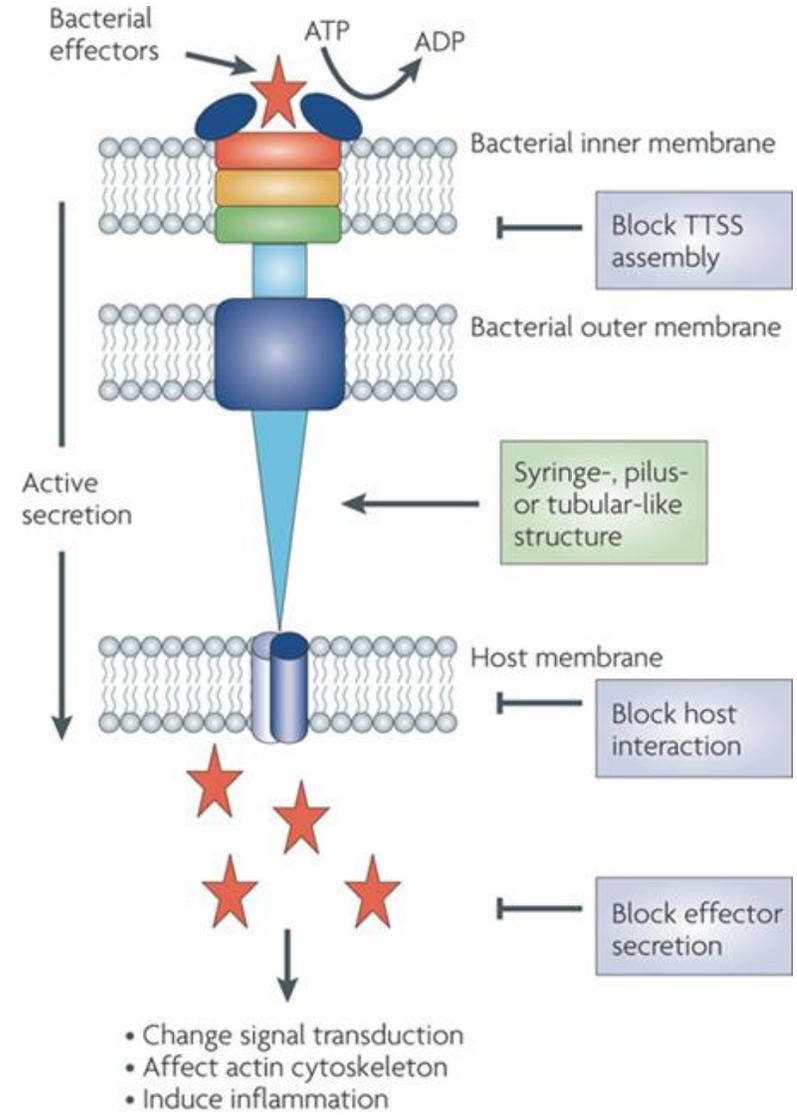
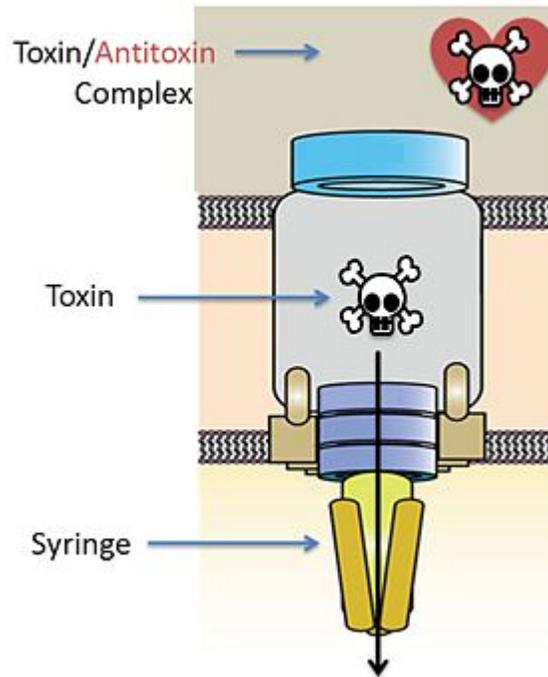


How super antigens work

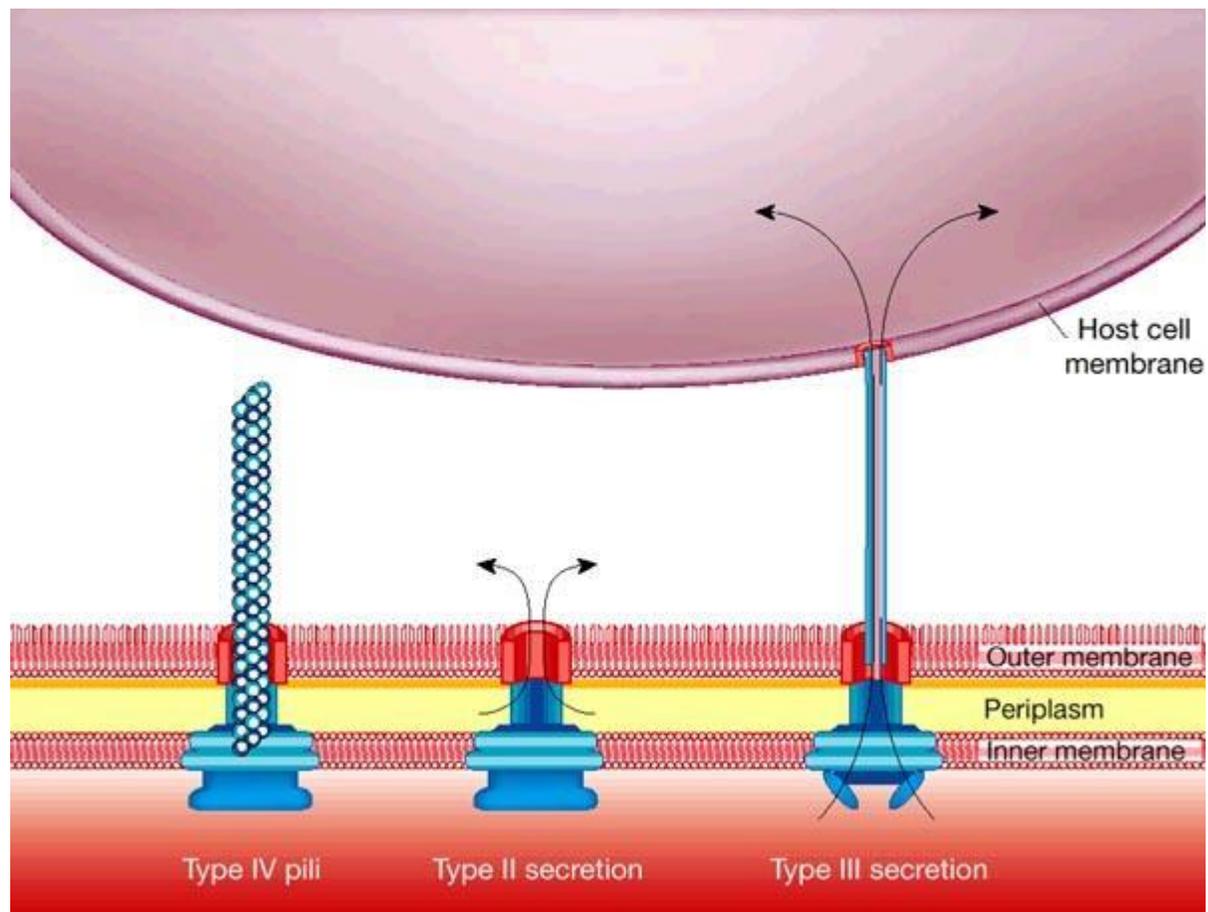
**Table 15.2 Diseases Caused by Exotoxins**

<b>Disease</b>	<b>Bacterium</b>	<b>Type of Exotoxin</b>	<b>Mechanism</b>
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

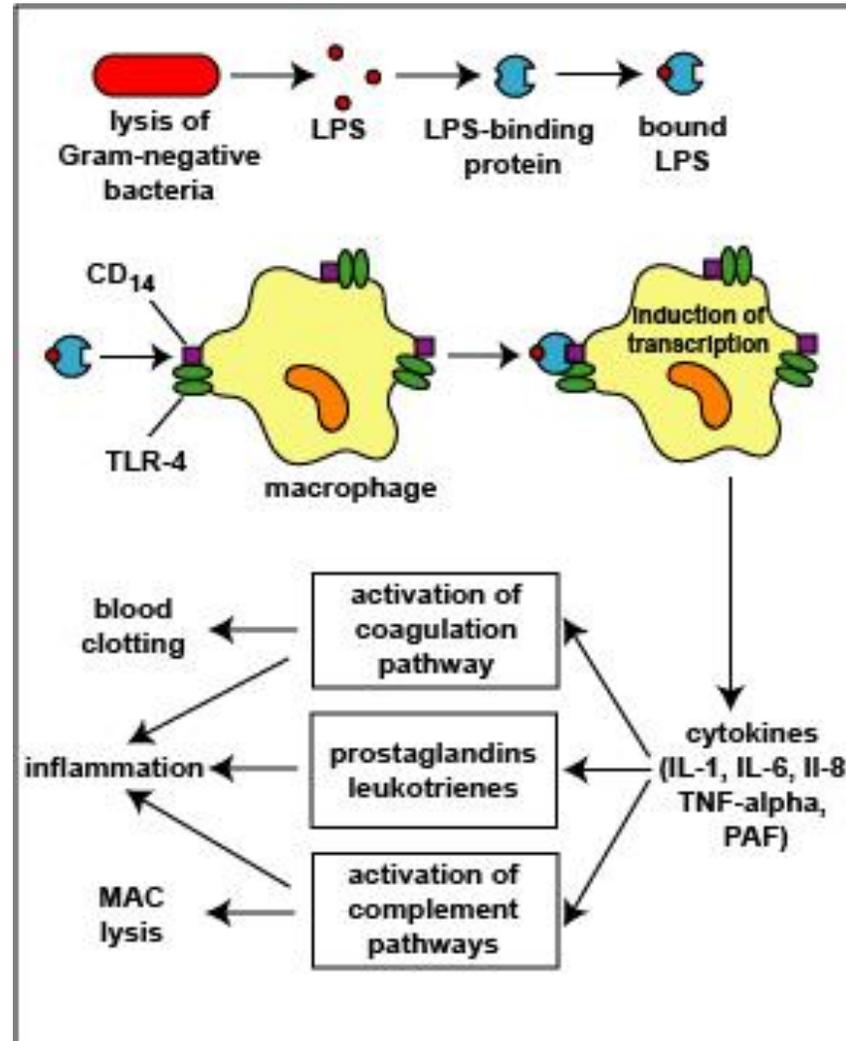


### Sistema de secreção do tipo III



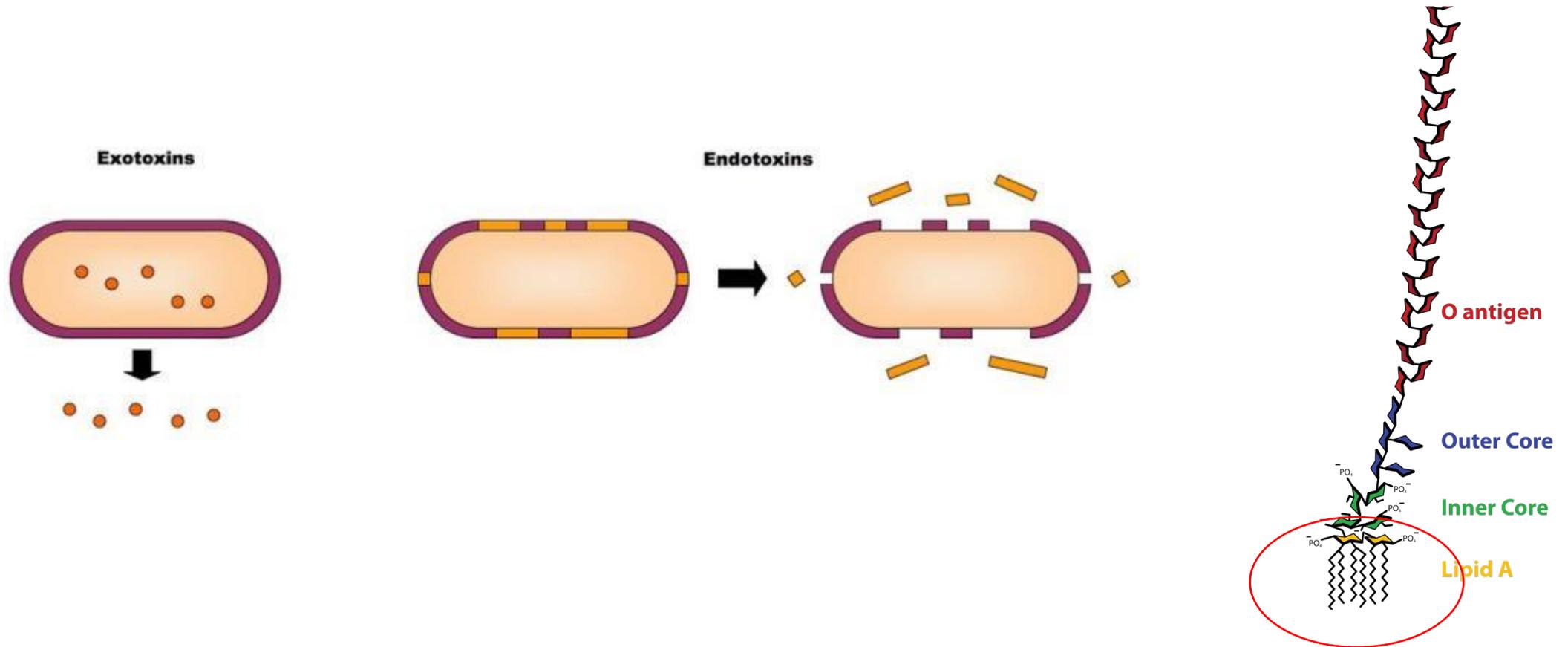
# Endotoxinas

**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**

