

Patogênese bacteriana III

Questões:

1) Um paciente chega ao hospital com as seguintes manifestações clínicas e histórico:

Teve recentemente um corte em arame farpado e após 24 horas começou a apresentar:

Espasmos e rigidez no maxilar

Rigidez nos músculos do pescoço e da nuca

Rigidez nos músculos do abdômen

Espasmos corporais que provocam dor e duram por vários minutos, geralmente causados por sons altos, toque físico e sensibilidade à luz

2) Outro paciente, com idade de 5 anos chega ao hospital com as seguintes manifestações clínicas:

Febre alta (mais de 39°C)

Pressão sanguínea baixa (sistólica <90 mmHg)

Vermelhidão, erupção difusa, branqueamento com descamação subsequente, especialmente das palmas e solas dos pés

Envolvimento de três ou mais sistemas:

Envolvimento gastrointestinal (vômito, diarreia)

Insuficiência renal

Inflamação hepática (AST, ALT > 2x normal)

Envolvimento cerebral (confusão, dor de cabeça ou convulsão)

Ambos os casos, foram relatadas a presença de bactérias, quais são os mecanismos de patogenicidade envolvidos? Explique as bases fisiológicas e moleculares dos mesmos



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 reesposáveis por causar os sintomas das doenças

Destruição dos tecidos

Produtos provenientes do metabolismo da bactéria

Enzimas degradativas



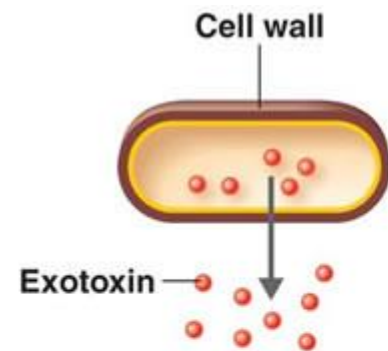
Clostridium perfringens

Tipos de toxinas

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

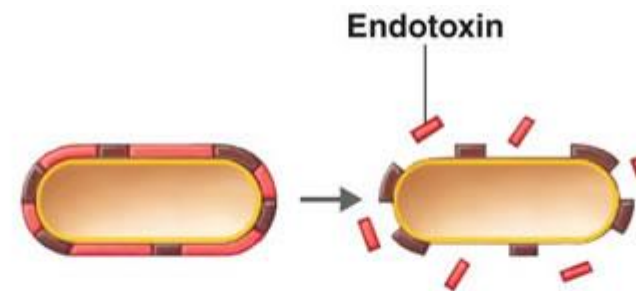
Exotoxinas – proteínas que podem ser produzidas pelas bactérias Gram positivas e Gram negativas que matam ou alteram uma função de uma célula hospedeira.

Endotoxinas – componentes da parede celular bacteriana Gram negativa (lipopolissacarídeo) 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.

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(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.

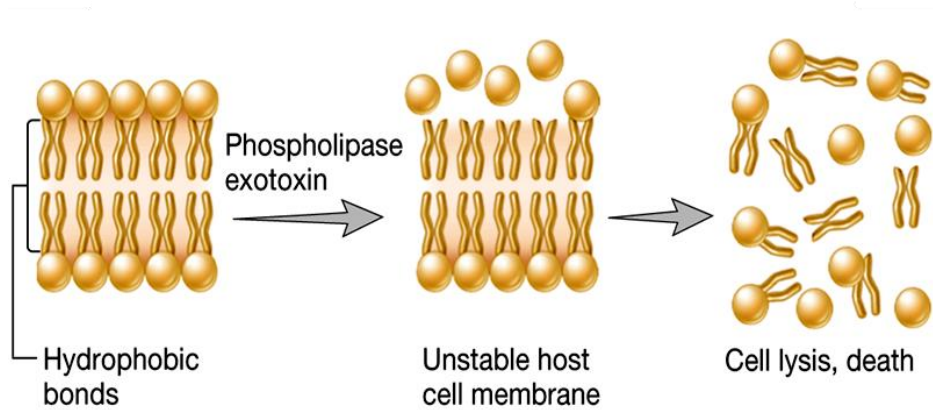
Key Concept

Toxins are of two general types: exotoxins and endotoxins.

Exotoxinas

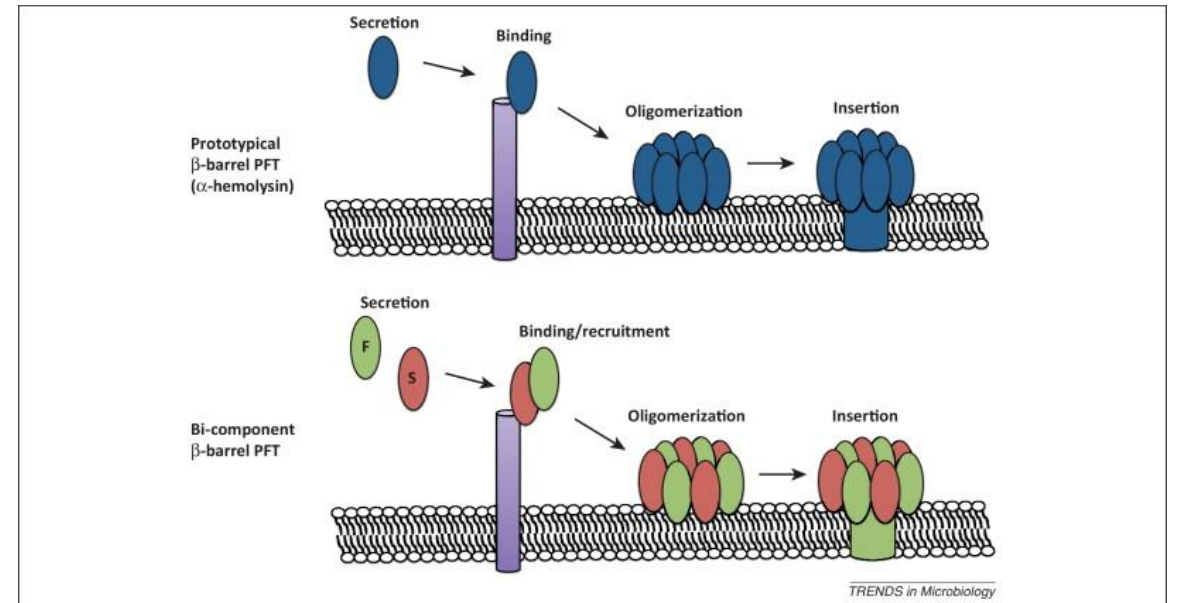
- Geralmente presentes em plasmídeos
- podem atuar localmente ou em locais distantes da infecção
- pode ser uma toxina pré-formada

Toxinas citolíticas:
Toxina α de *Clostridium perfringens* (fosfolipase C)

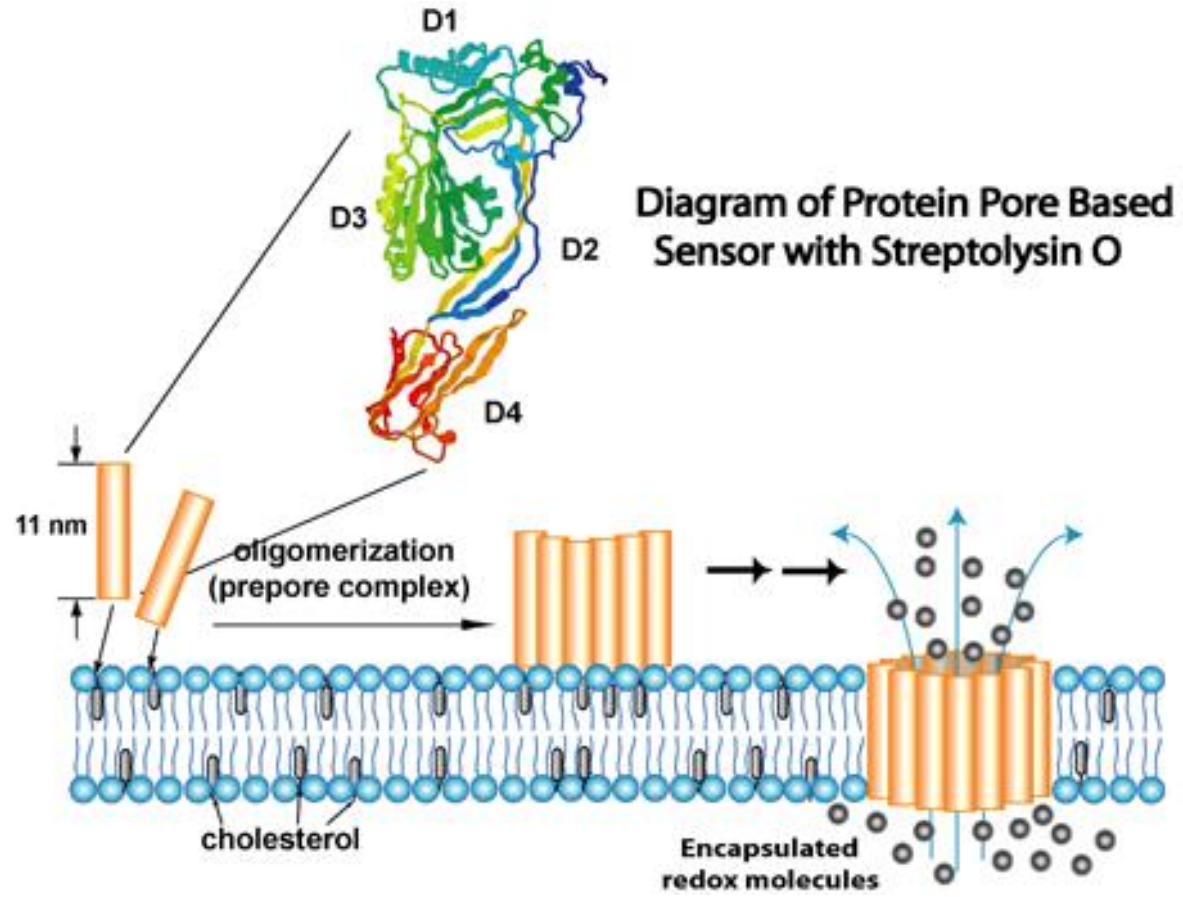


(b)

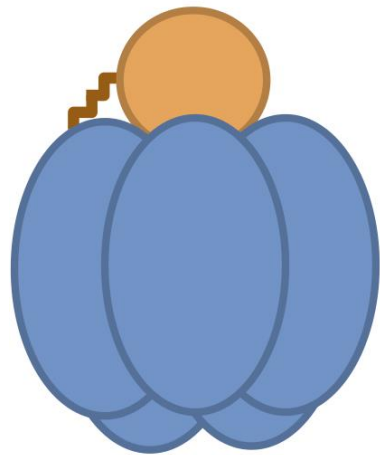
Hemolisina de *Streptococcus*



Estreptolisina O

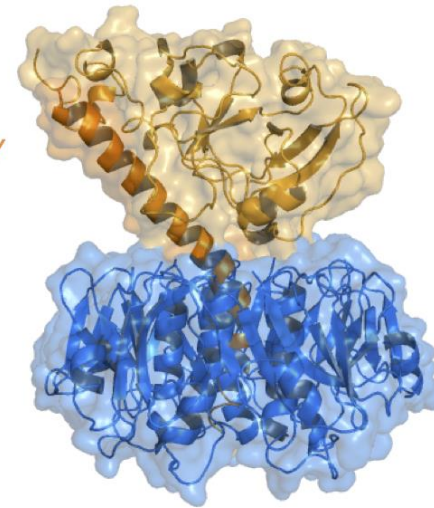


Toxinas diméricas com subunidades A-B

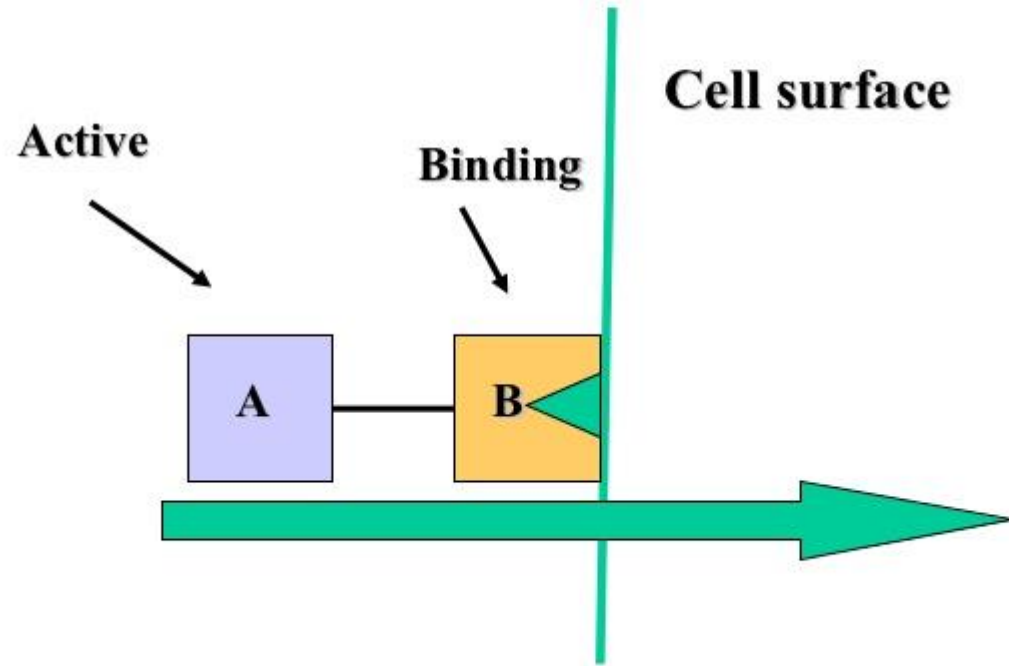


A subunit
enzymatic toxicity

B₅ subunit
cell binding



A-B toxins

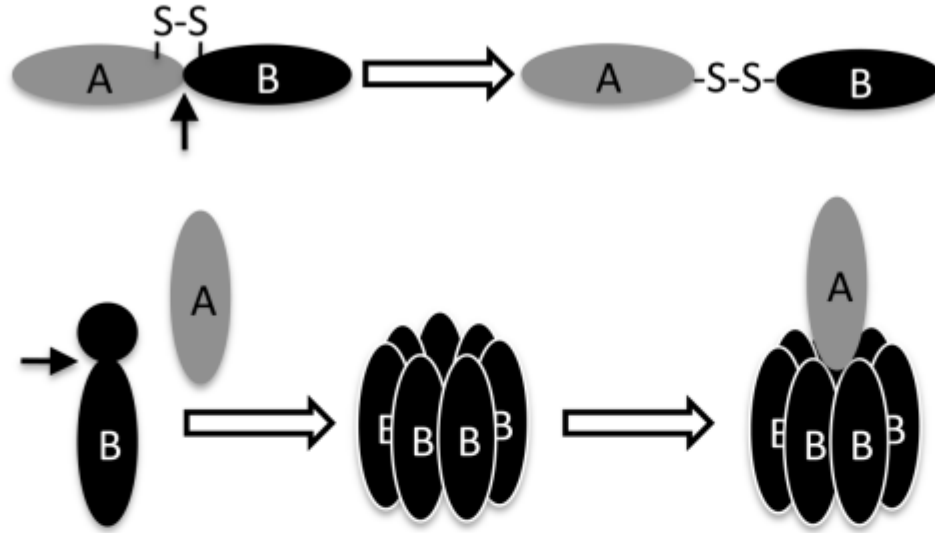


AB toxins

Molecular organization

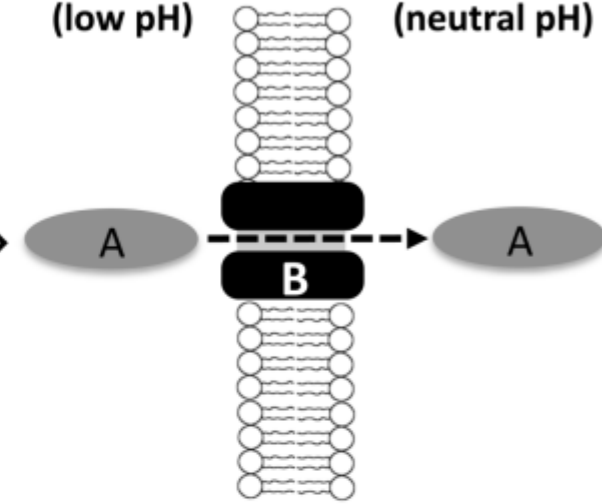
Translocation

Diphtheria toxin
Botulinum toxins
Tetanus toxin

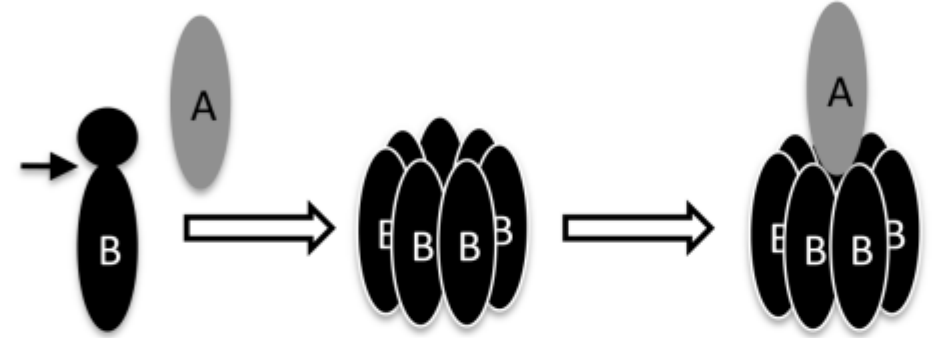


ENDOSOME
(low pH)

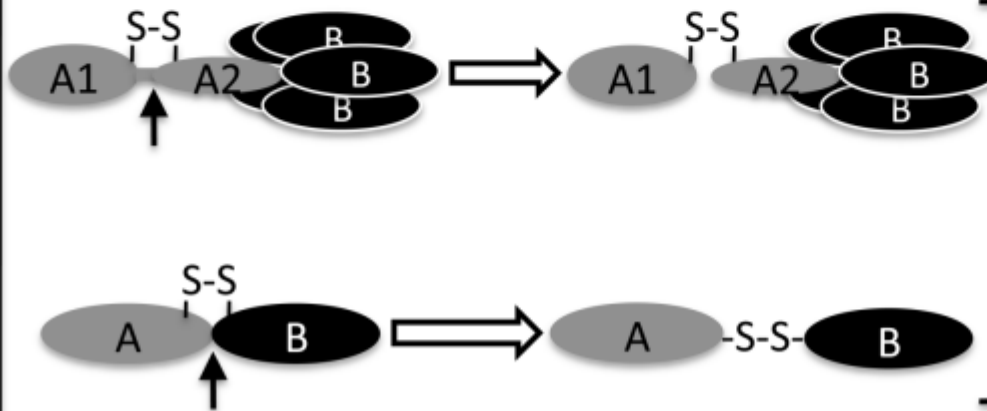
CYTOSOL
(neutral pH)



Anthrax toxin
C2 toxin

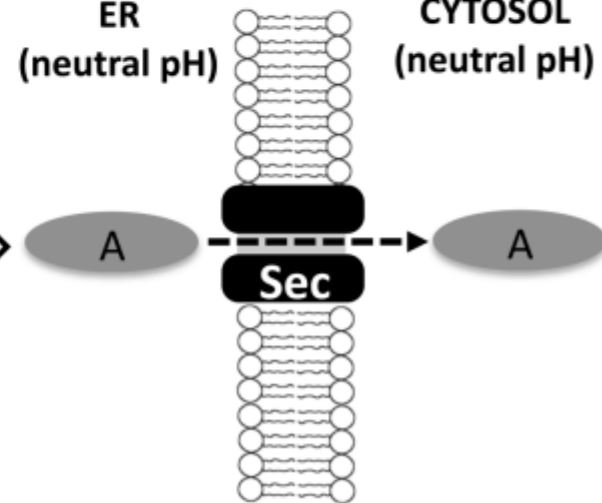


Cholera toxin
Shiga(like) toxins
Heat-labile toxin

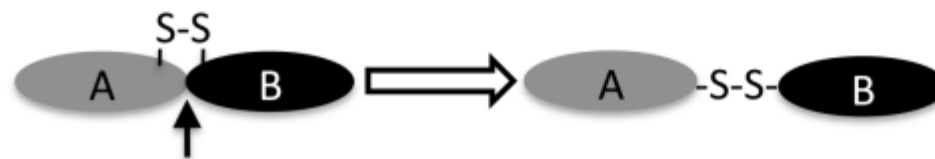


ER
(neutral pH)

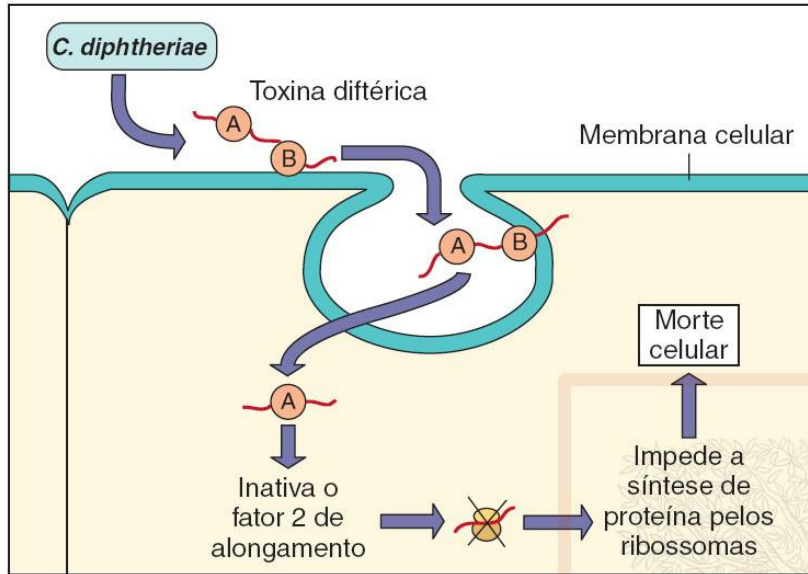
CYTOSOL
(neutral pH)



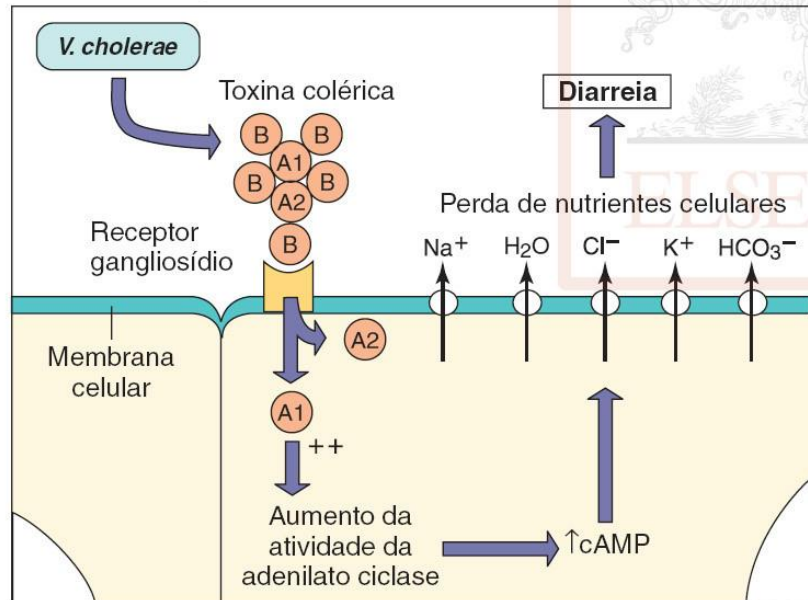
Exotoxin A
ricin



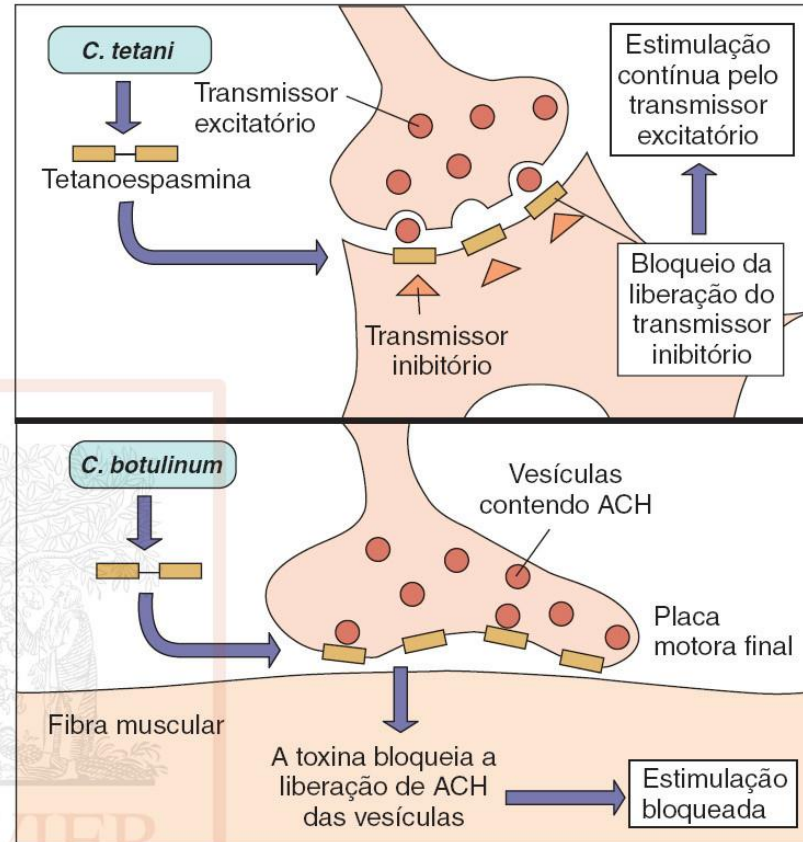
A Inibição da síntese de proteína



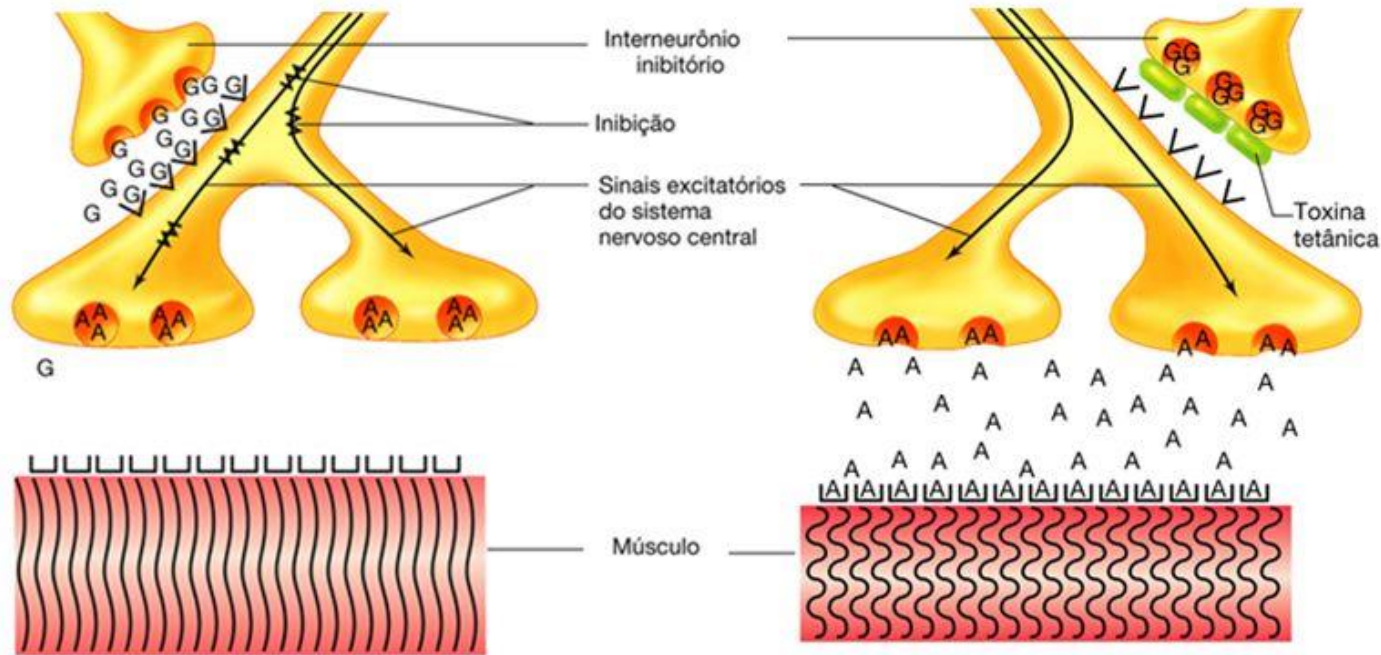
B Hiperativação



C Efeito na transmissão nervo-músculo



Ação da toxina tetânica de *Clostridium tetani*



Normal

A liberação de glicina (G) por interneurônios inibitórios bloqueia a liberação de acetilcolina (A) e permite o relaxamento do músculo

(a)

Tétano

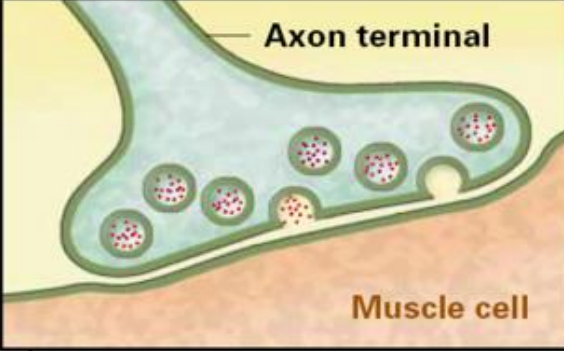
A toxina tetânica se liga a interneurônios inibitórios, impedindo a liberação de G e o relaxamento muscular

(b)



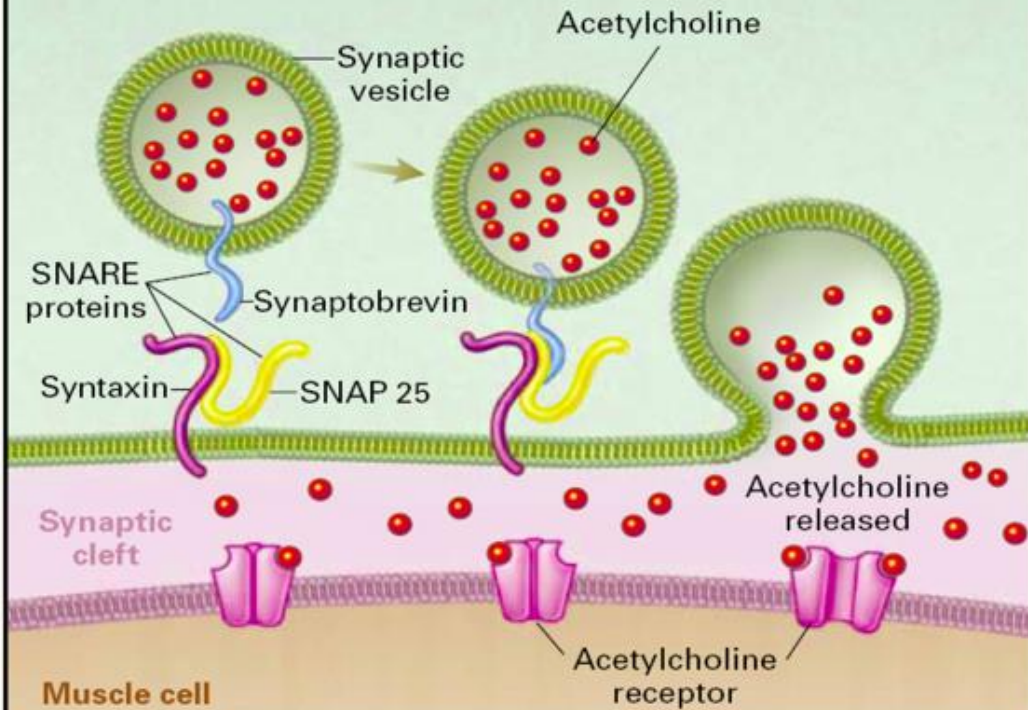
Paciente apresentando postura conhecida como "opistótono", decorrente da contratura muscular generalizada causada pela toxina tetânica (Fonte: Biblioteca Pública de Imagem de Saúde, Filadélfia, EUA). Fonte: Prophylaxis

Neuromuscular Junction

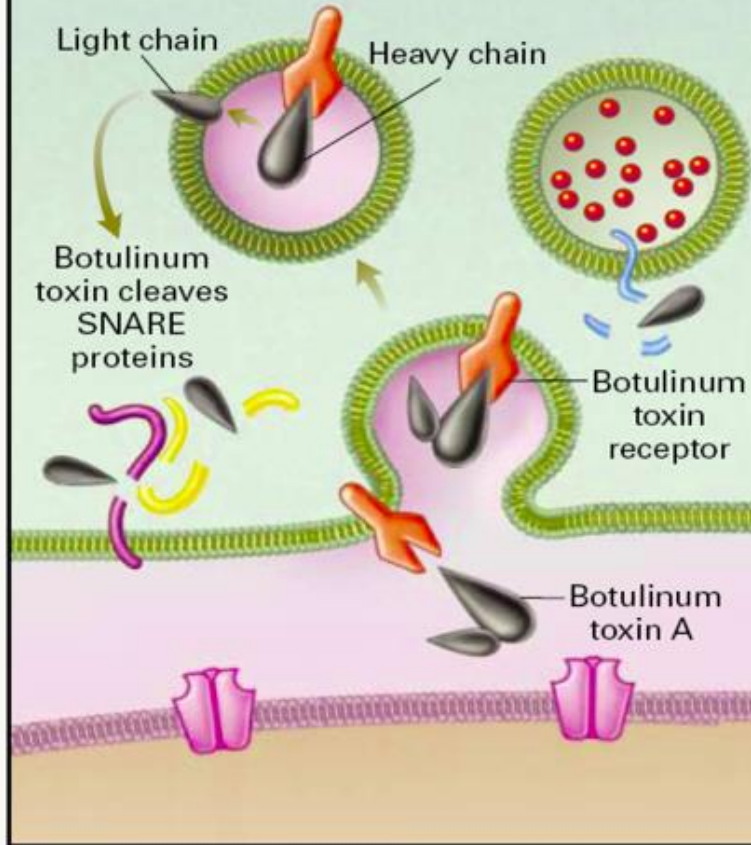


Normal Transmitter Release

Neuron



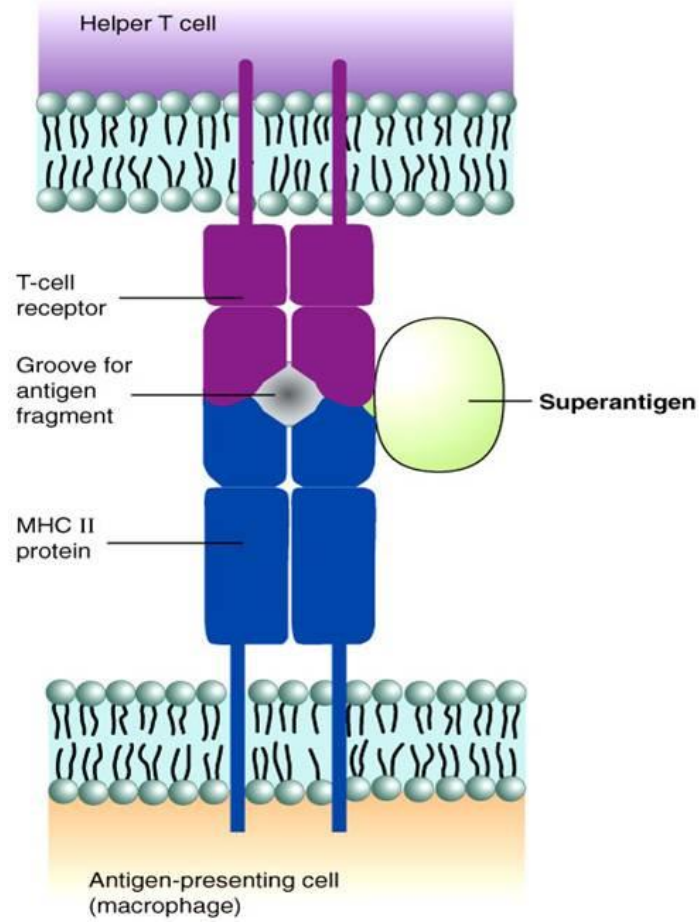
Action of Botulinum Toxin A



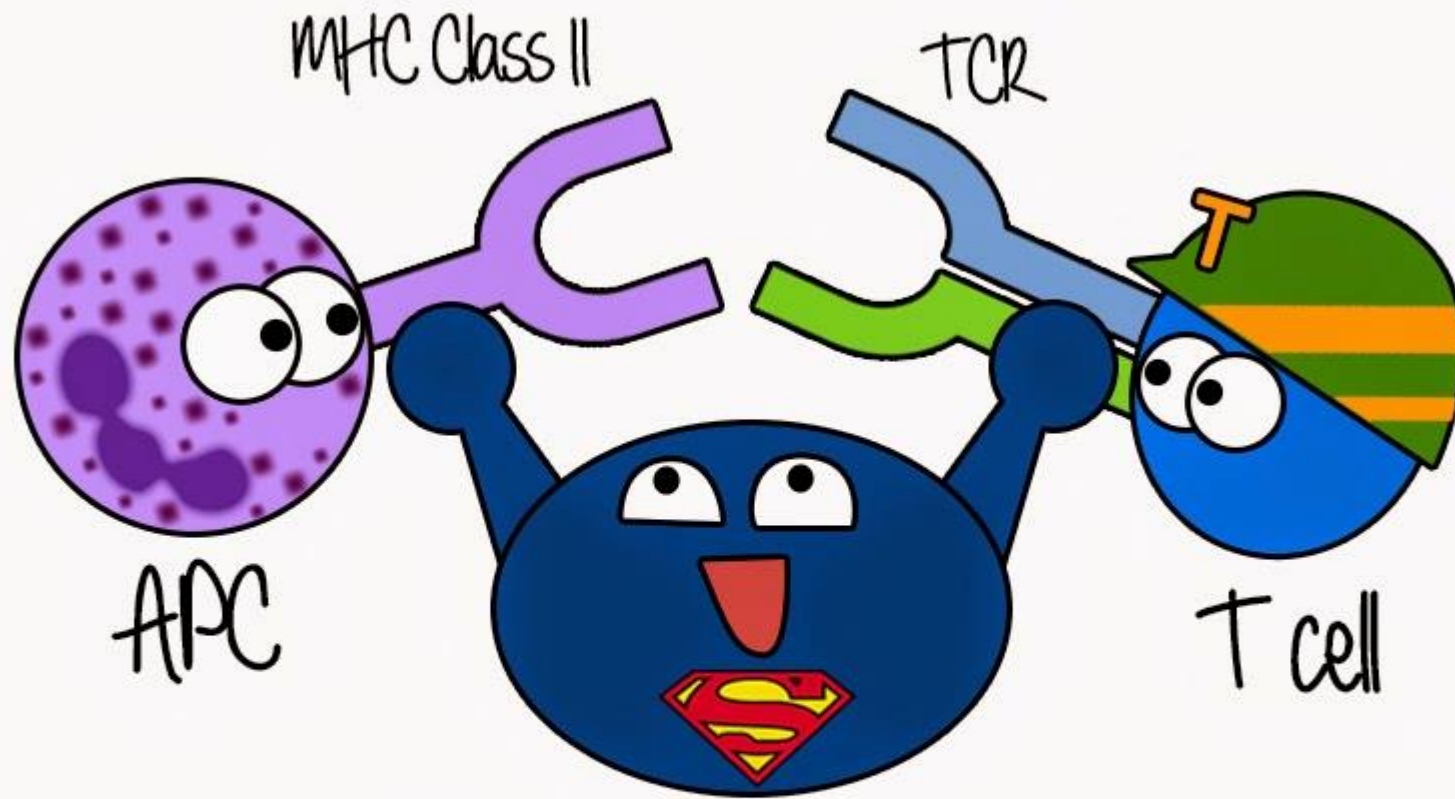
Superantígenos

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

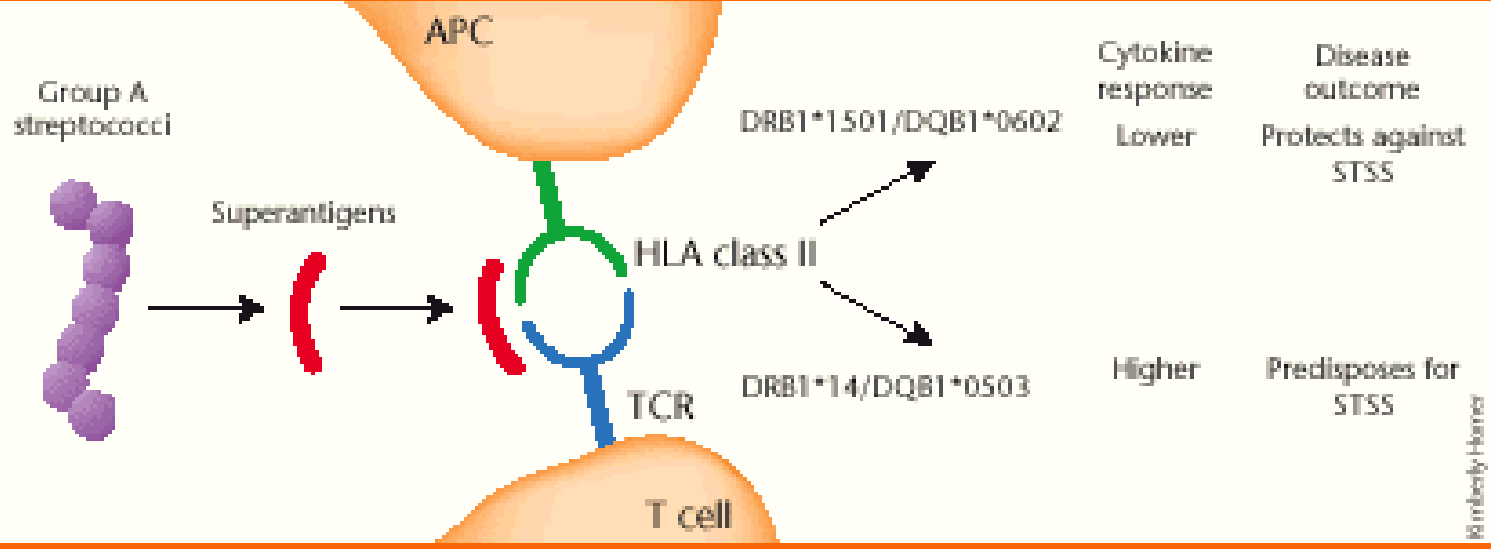
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Desencadeando a liberação de uma grande quantidade de interleucinas, principalmente IL-1



How super antigens work



Kimberly Horner

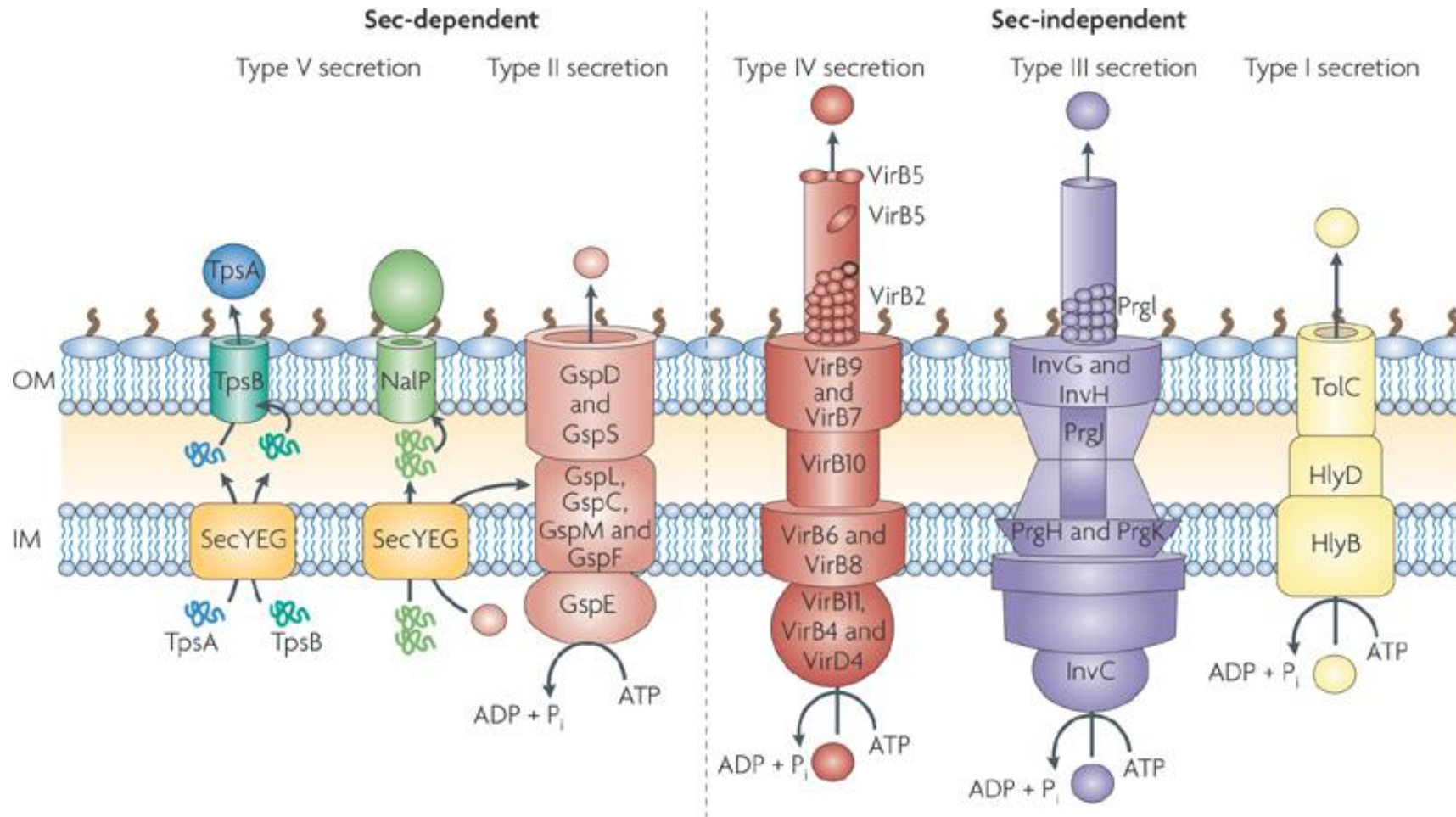
Source: Nat Med © 2002 Nature Publishing Group

- Liberação de grande quantidade de interleucinas, principalmente IL-1, TNF e IL-2

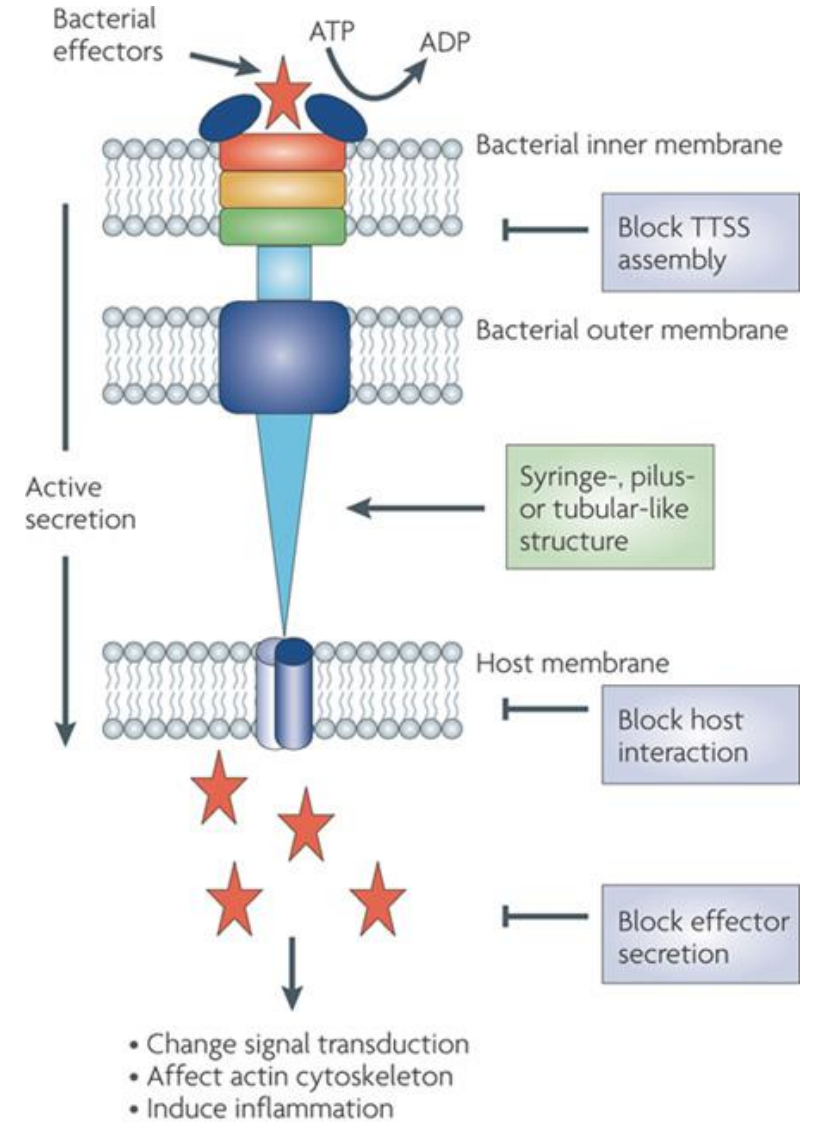
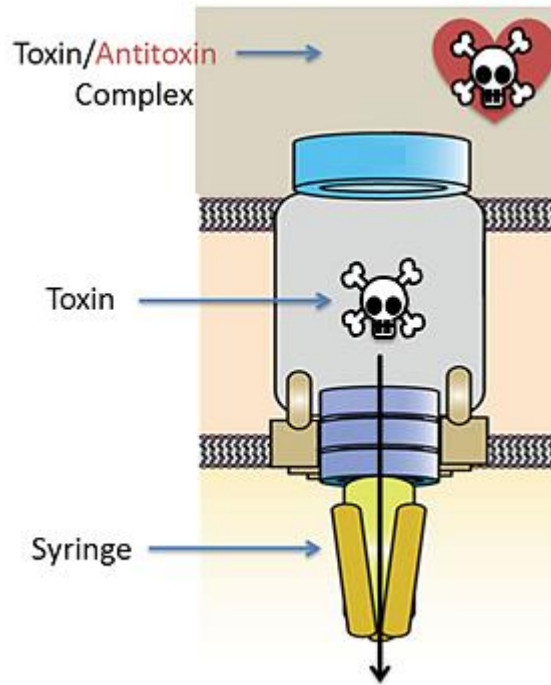
Table 15.2 Diseases Caused by Exotoxins

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.

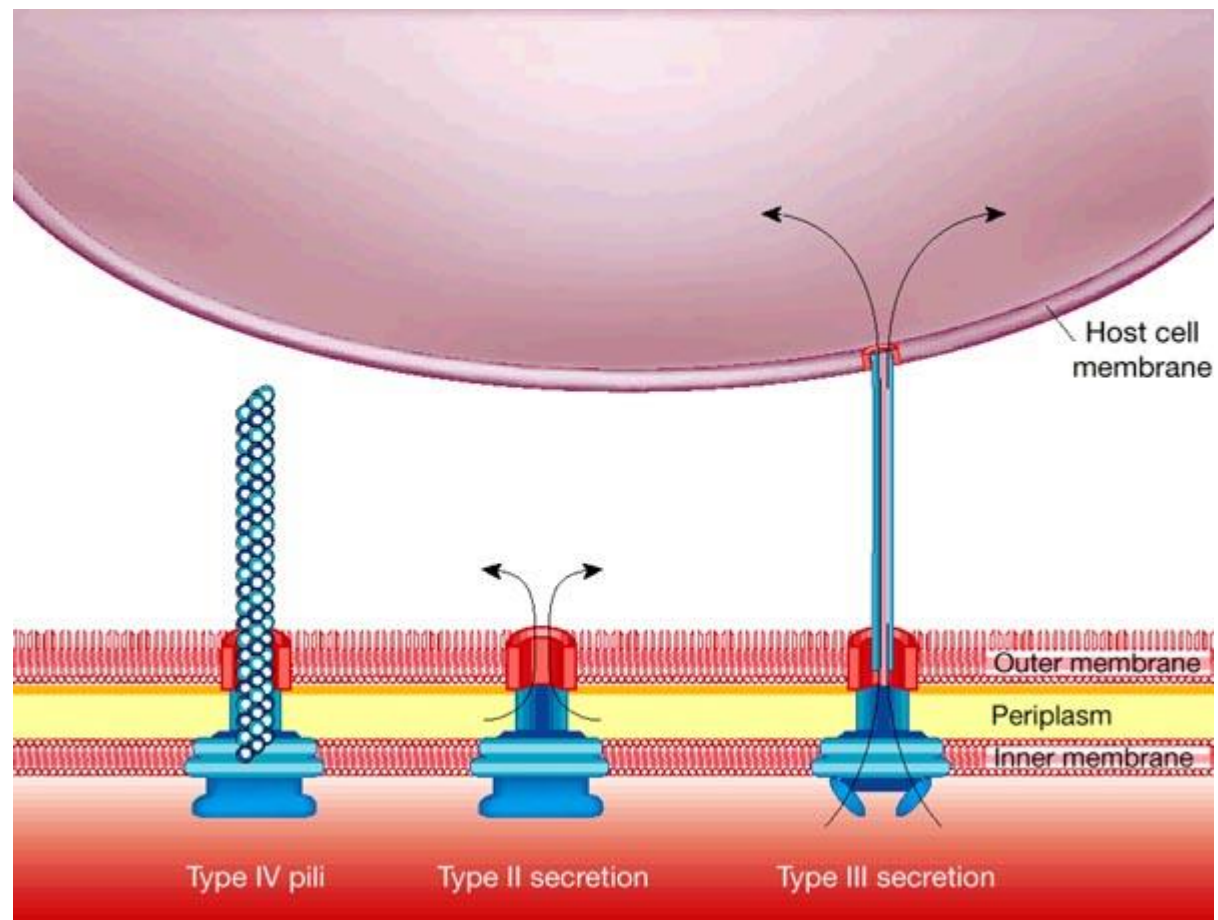
Sistema de secreção bacteriano

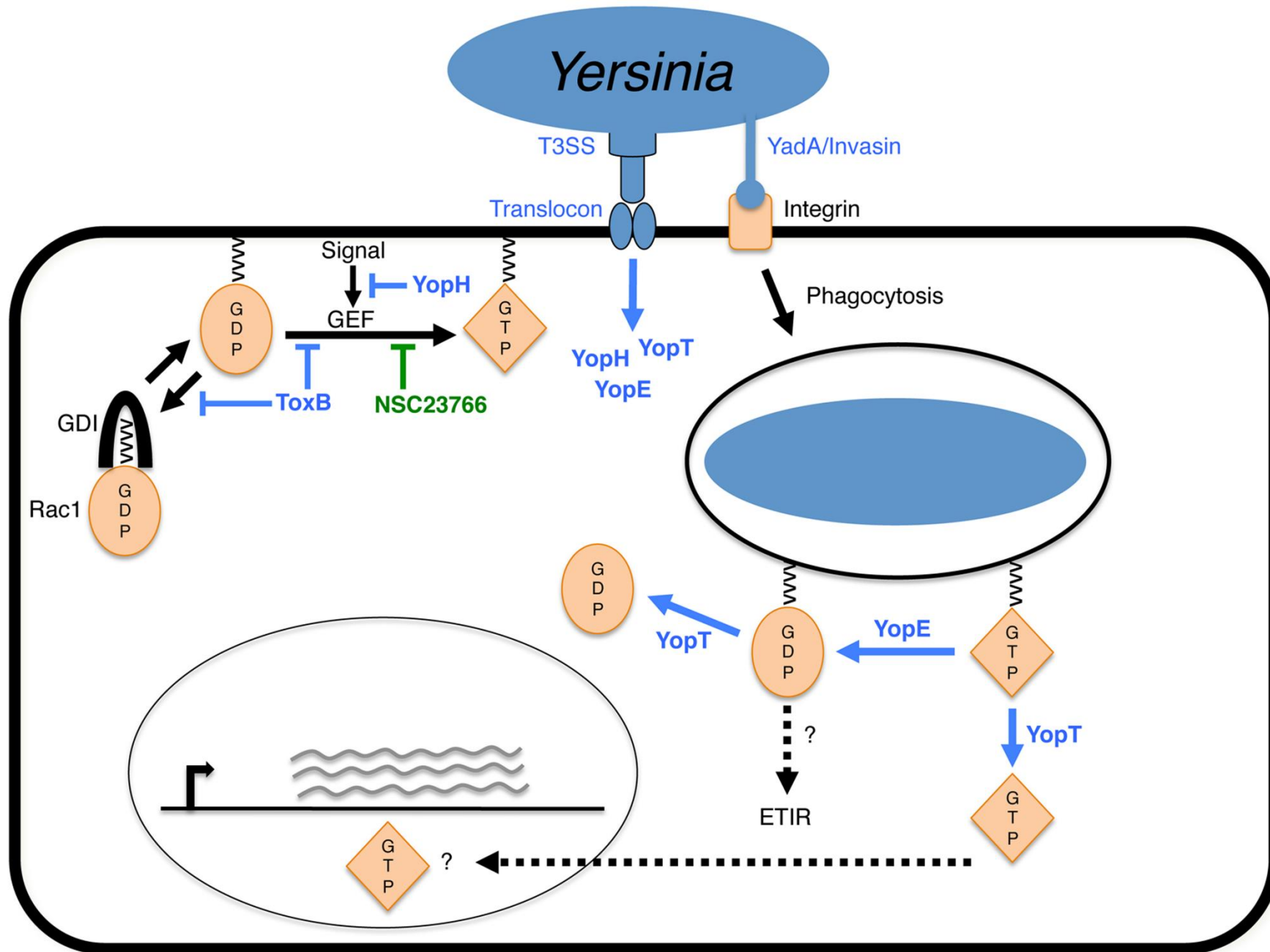


As proteínas secretadas pelas bactérias podem ser toxinas ou realizar a modulação do sistema imune



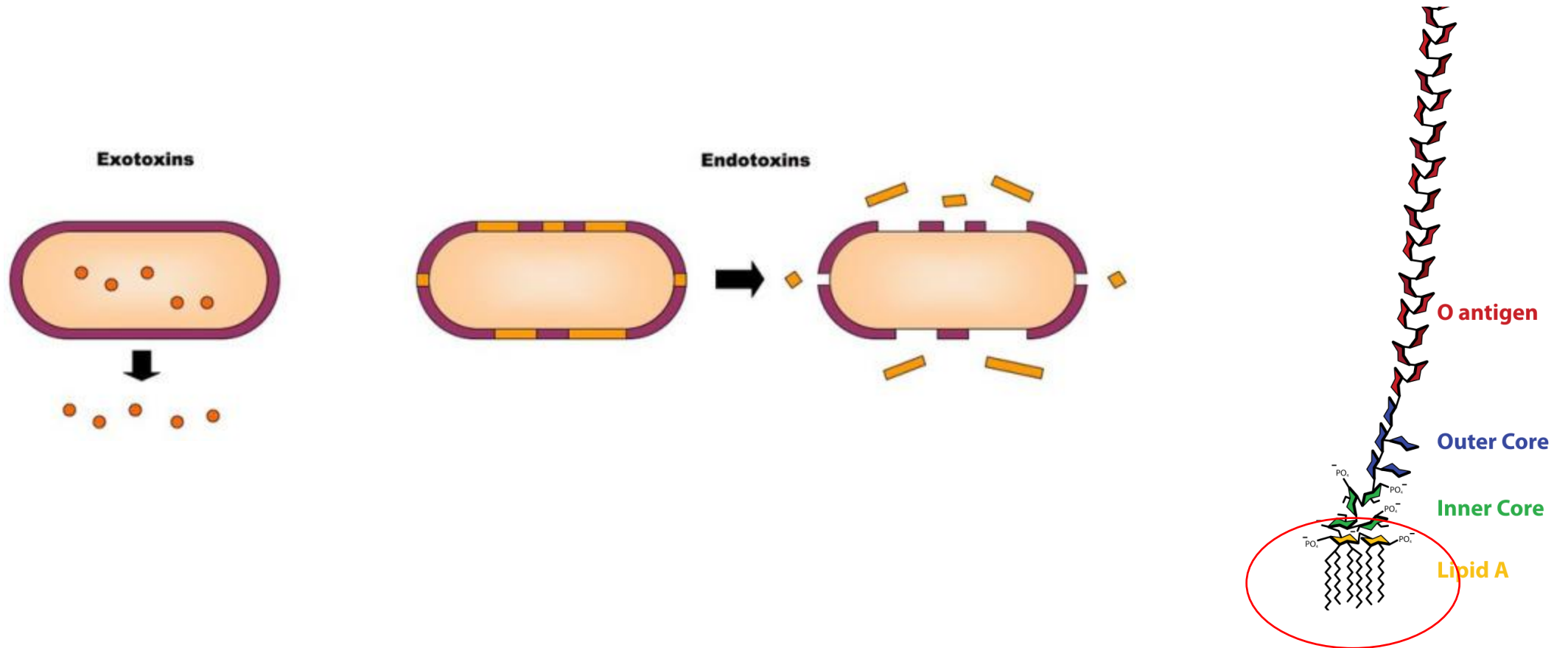
Sistema de secreção do tipo III



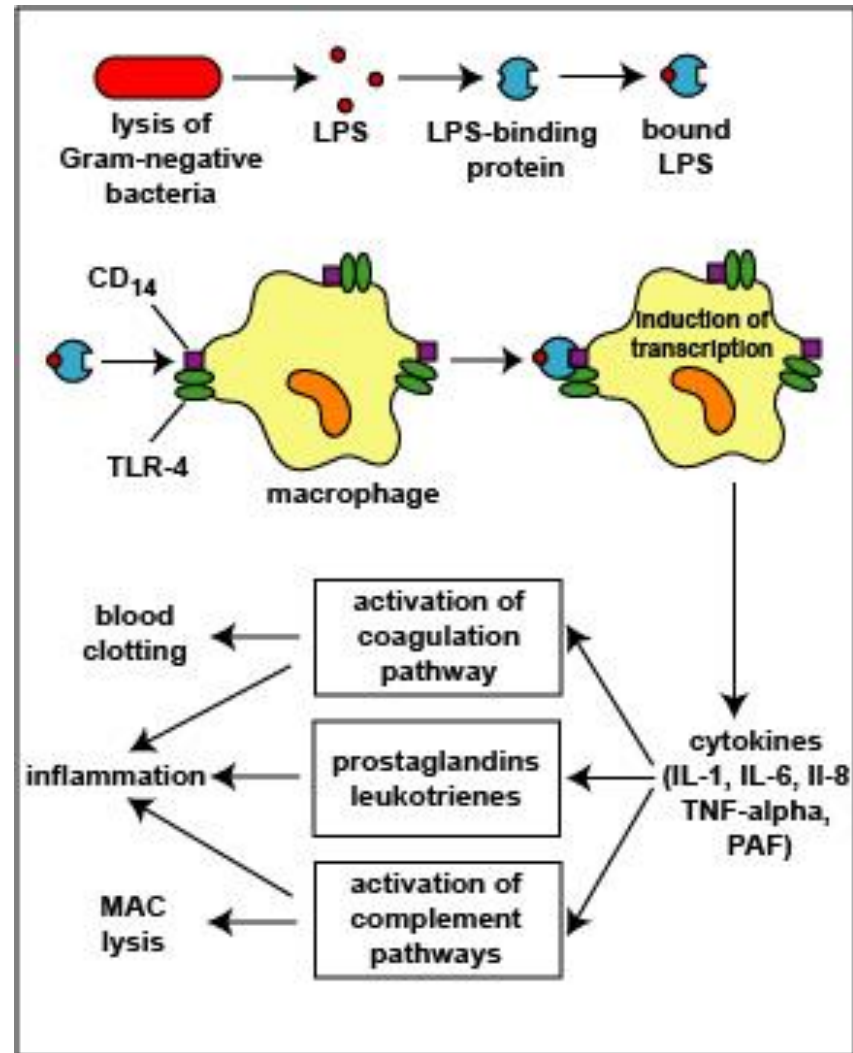


Endotoxinas e outros componentes da parede celular bacteriana

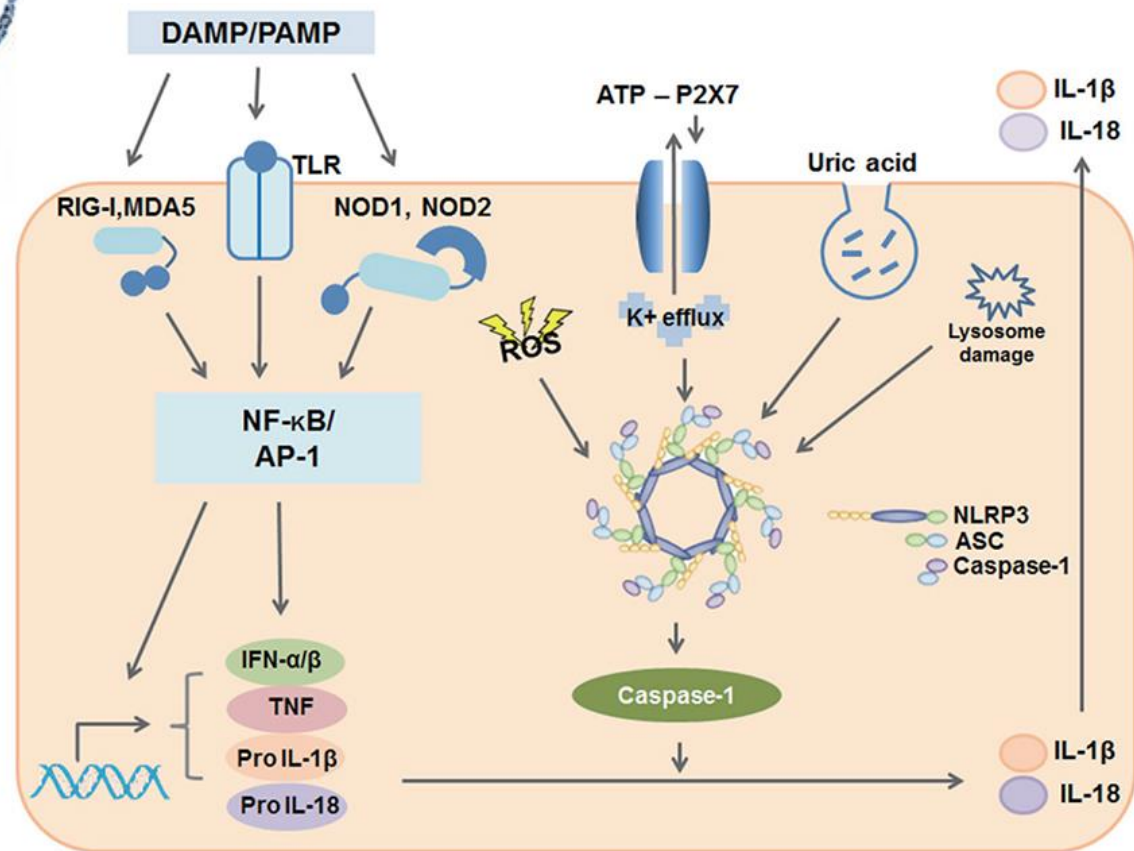
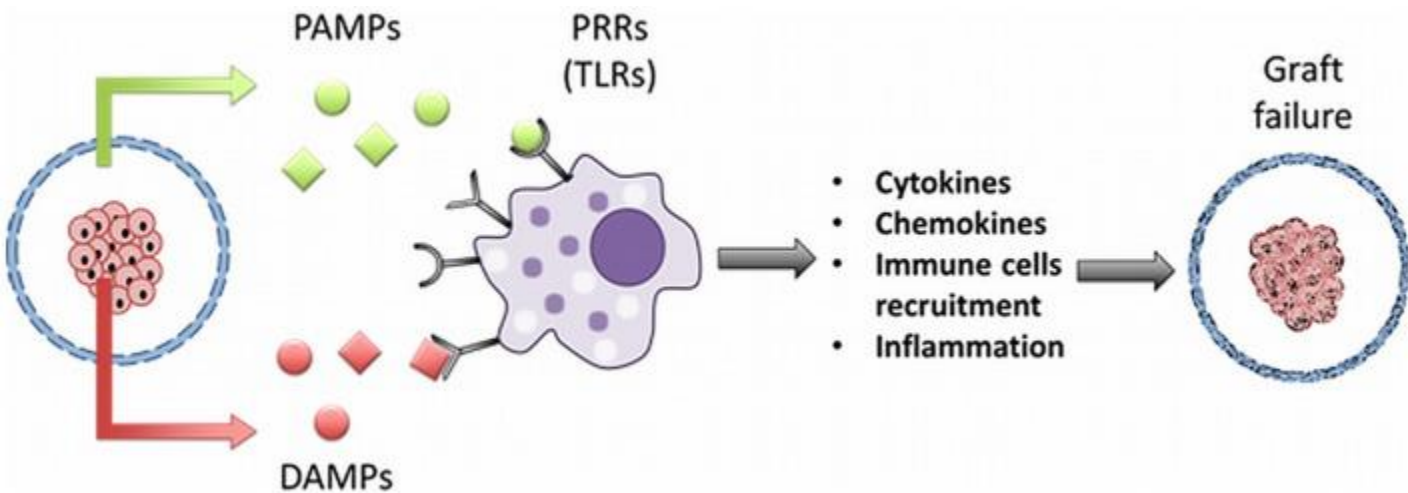
-Endotoxinas - componentes da parede celular de bactérias Gram negativas que atuam como sinal para ativar o sistema de defesa



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



Padrões moleculares associados aos patógenos/ padrões moleculares associados ao dano



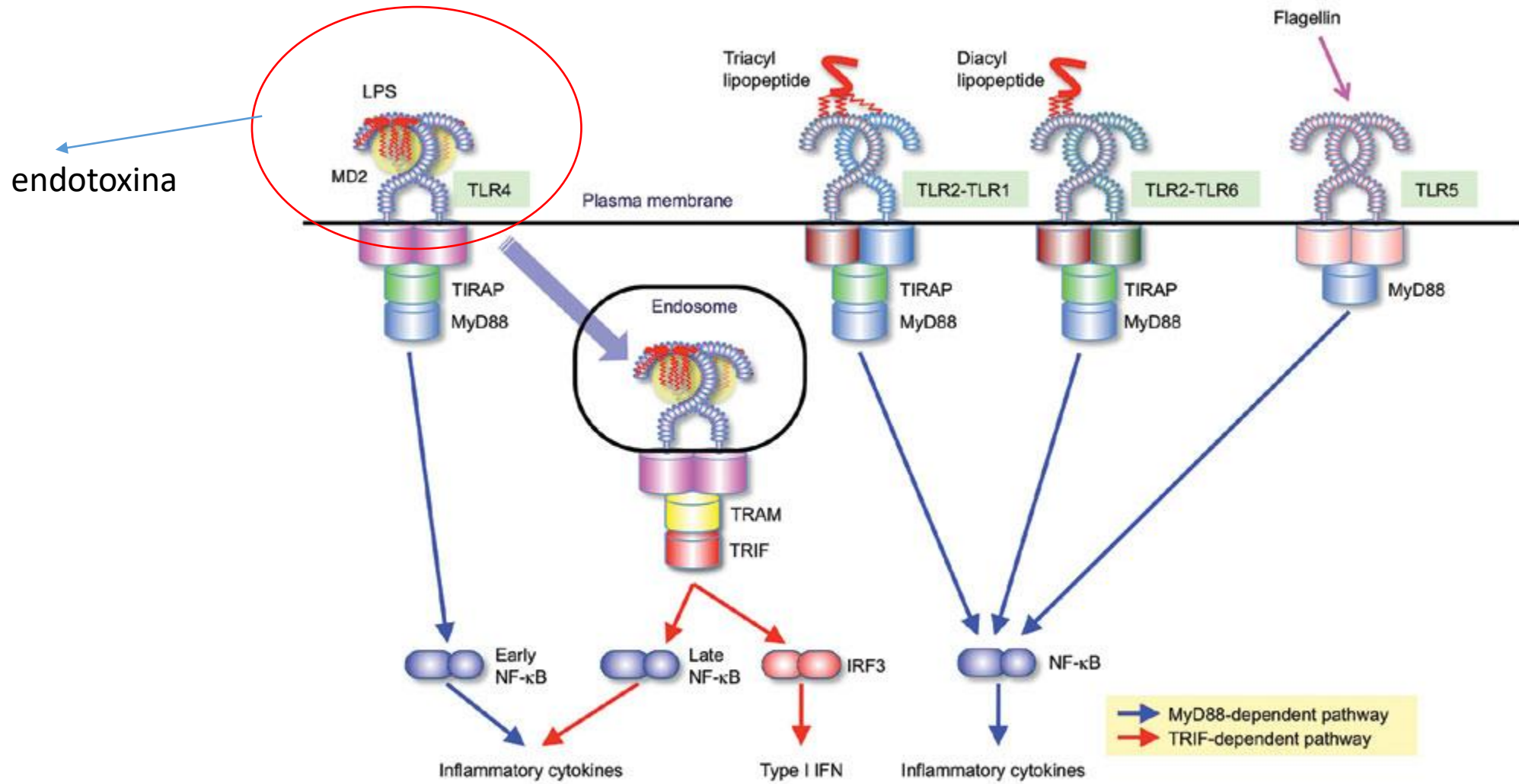


Fig 1

Table 1 PAMPs and pattern recognition receptors

PAMP	Pathogen(s)	Essential ligand	Pattern recognition receptors	Biological sequelae
LPS	Most Gram-negative bacteria	Lipid A	LBR, CD14 TLR4, TLR2* Scavenger receptor	Enhance inflammatory response mediated by TLRs Recognize LPS and initiate inflammatory response Endocytosis of LPS (non-inflammatory), ?phagocytosis
Lipoproteins	Eubacteria	Amino-terminal tripalmitoylated cysteine† generated by the signal peptidase II cleavage system	TLR2	Initiates inflammatory response
Peptidoglycan	Most bacteria	Undefined	CD14 TLR2	Enhances inflammatory response Initiates inflammatory response
Lipoteichoic acid	Many Gram-positive bacteria	Undefined	TLR2, TLR4‡	Initiates inflammatory response
CpG	Many microbial pathogens	Unmethylated CpG-containing oligonucleotides§	Undefined	Initiates inflammatory response
Lipoarabinomannan	Mycobacteria	Undefined	TLR2 CD1	Initiates inflammatory response Presents glycolipid to $\alpha\beta$ T cells
N-formyl-Met	Prokaryotes	Amino-terminal N-formylmethionine of proteins synthesized de novo	f-Met receptors 1 and 2	Chemotaxis and release of inflammatory mediators (?)
Mannans and mannoproteins	Yeast	Undefined	Mannose receptor Mannose-binding protein	Phagocytosis, endocytosis and initiation of inflammatory response Opsonization and complement fixation
Zymosan (yeast cell wall)	Yeast	Undefined	Mannose and β -glucan receptors TLR2	Phagocytosis Initiates inflammatory response
Heat shock proteins	Prokaryotes and eukaryotes	Undefined	Undefined	Initiate inflammatory response and promote T cell dependent immune responses

* TLR2's role as an LPS receptor is based on studies in vitro, and, although TLR2 may function as a physiological receptor for LPS, evidence to support this function in vivo has not yet been demonstrated.

† Mycoplasma lipoproteins have been shown to have a dipalmitoylated amino-terminal cysteine residue, which is also recognized by TLR2. These findings indicate that not all three fatty acid ester-linked chains are necessary for recognition.

‡ LTA is recognized by TLR2 in systems in vitro, and by TLR4 in studies with knockout mice. These differences have not been reconciled.

§ Flanking sequences are also influential.

|| Studies with Hsp60 family members have shown that C3H/HeJ mice are defective in inflammatory signaling in response to these proteins, implicating TLR4 as a pattern recognition receptor for foreign and endogenous Hsp60 family gene products.

Bactérias gram negativas liberam endotoxinas durante a infecção



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



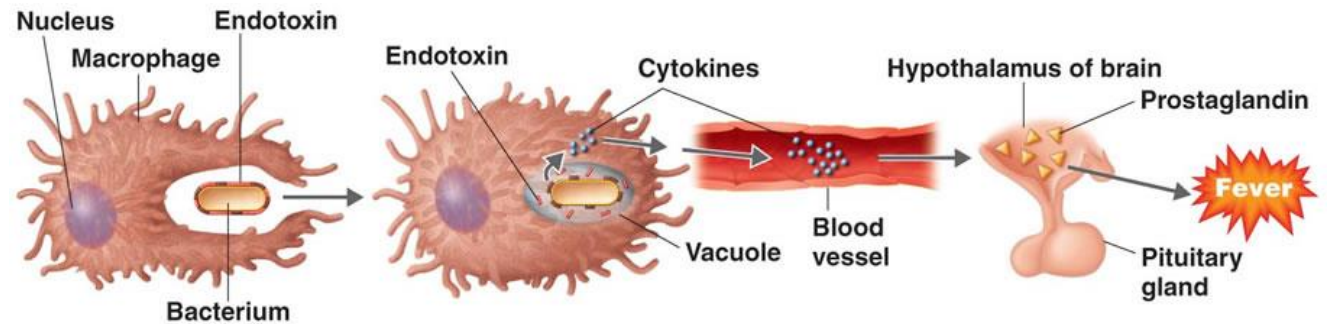
Liberão de de citocinas de fase aguda

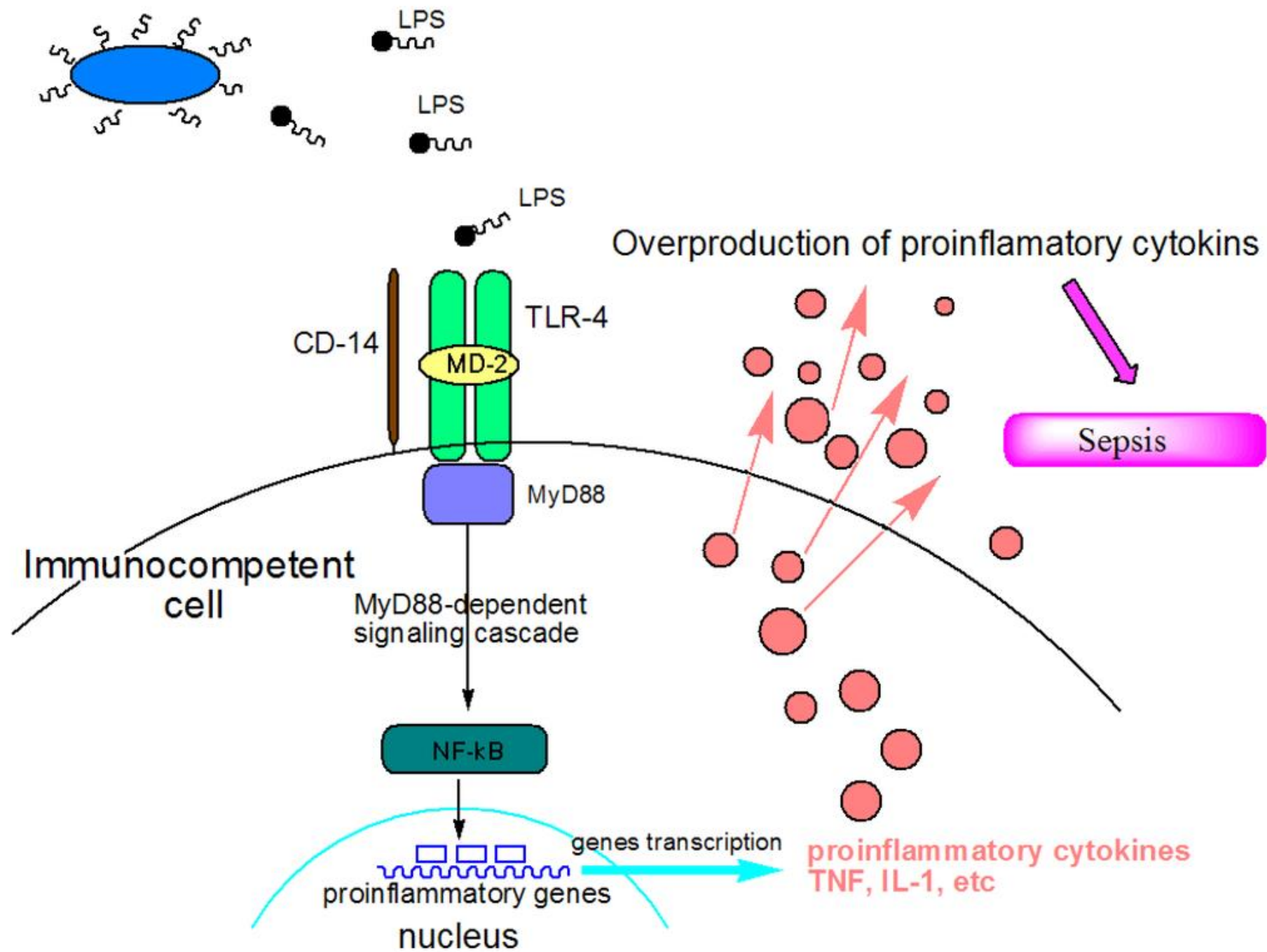


Crescimento de células B



Febre e vasodilatação



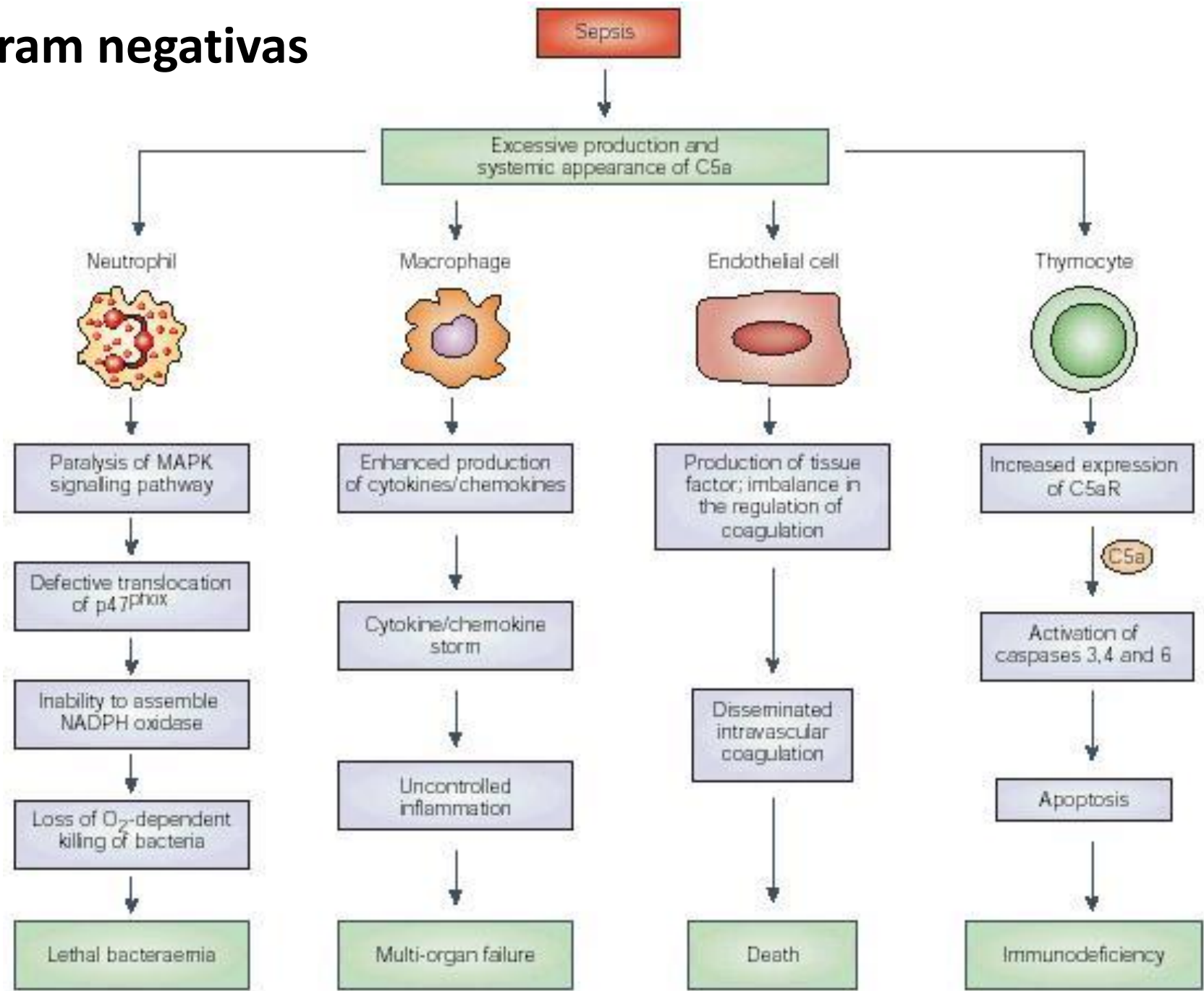


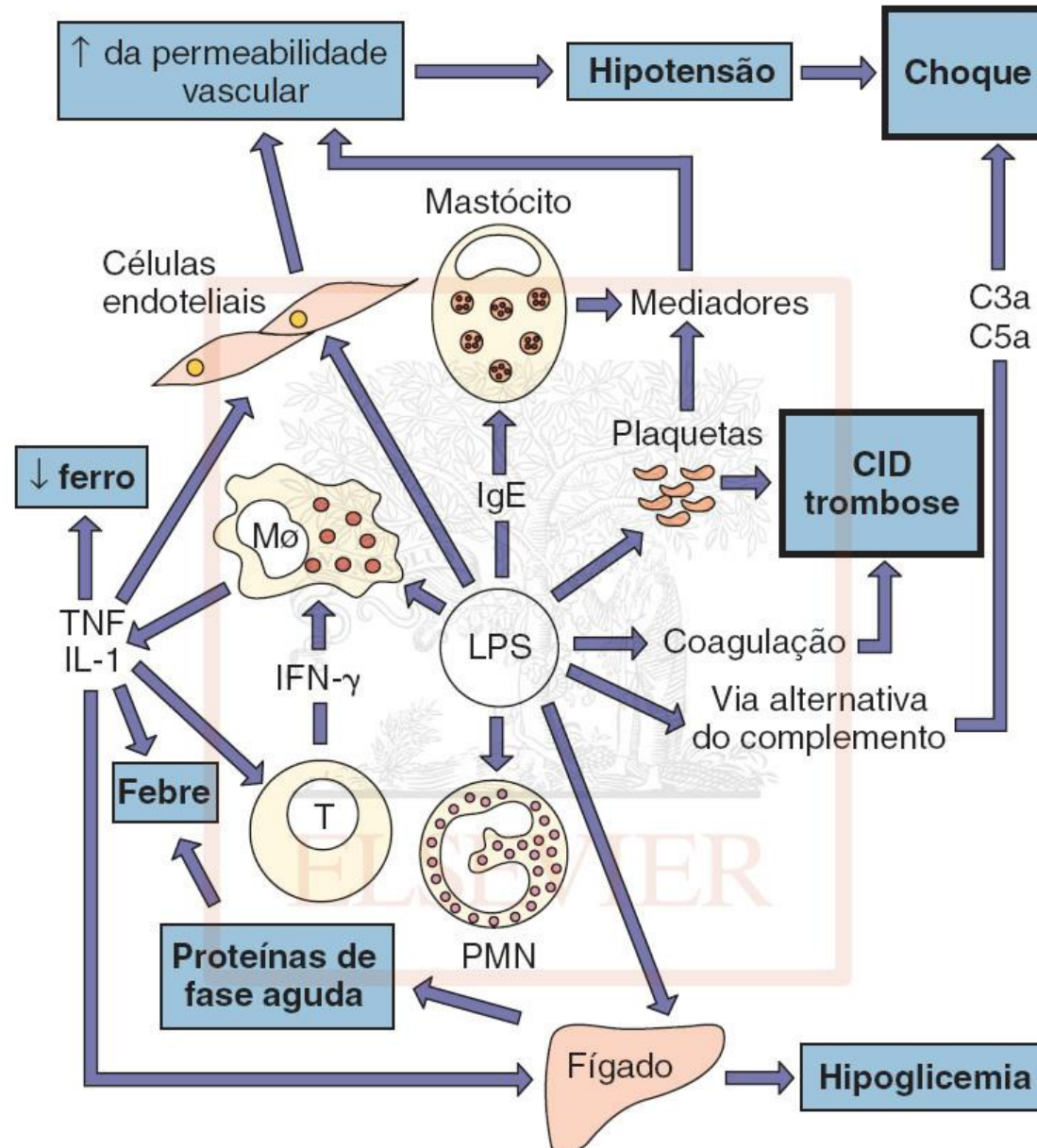
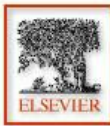
Septicemia por bactérias Gram negativas

Produção de anafilotoxinas

Vasodilatação e extravasamento dos vasos sanguíneos

Hipotensão e choque





<https://www.youtube.com/watch?v=5yGbxyOpZRk>