Toxins

Toxins

- Toxins are bacterial products that directly harm tissue or trigger destructive biologic activities.
- Toxin and toxin-like activities are degradative enzymes that cause lysis of cells or specific receptor-binding proteins that initiate toxic reactions in a specific target tissue.

Toxins

- Cell wall components initiate a systemic response (e.g., fever) by promoting the inappropriate release of cytokines.

Toxins

- In many cases, the toxin is completely responsible for causing the characteristic symptoms of the disease.

Tissue Destruction

- *Byproducts of bacterial growth, especially fermentation,* include acids, gas, and other substances that are toxic to tissue.
- *Many bacteria release degradative enzymes to break down tissue, thereby providing food for* the growth of the organisms and promoting the spread of the bacteria.

Tissue Destruction

- *Clostridium perfringens organisms* are part of the normal flora of the GI tract but are also opportunistic pathogens that can establish infection in oxygen-depleted tissues and cause gas gangrene.
- These anaerobic bacteria produce enzymes (e.g., phospholipase C, collagenase, protease, and hyaluronidase), several toxins, and acid and gas from bacterial metabolism, which destroy the tissue.

Tissue Destruction

- Staphylococci produce many different enzymes that modify the tissue environment.
- These enzymes include hyaluronidase, fibrinolysin, and lipases.
- Streptococci also produce enzymes, including streptolysins S and 0, hyaluronidase, DNAases, and streptokinases; these enzymes facilitate the development of infection and spread into the tissue

Exotoxins

- Exotoxins are proteins that can be produced by grampositive or gram-negative bacteria and include cytolytic enzymes and receptor-binding proteins that alter a function or kill the cell.

- In many cases, the toxin gene is encoded on a plasmid (tetanus toxin of C. *tetani, LT and ST toxins of enterotoxigenic E. coli) or a lysogenic phage (Corynebacterium diphtheriae* and C. *botulinum).*

Cytolytic toxins

- Cytolytic toxins include membrane-disrupting enzymes such as the IX-toxin(phospholipase C) produced by C. *perfringens,* which breaks down sphingomyelin and other membrane phospholipids.
- Hemolysins insert into and disrupt erythrocyte and other cell membranes.
- Pore forming toxins, including streptolysin 0, can promote leakage of ions and water from the cell and disrupt cellular functions or cell lysis

A-B toxins

- Many toxins are dimeric with A and B subunits (A-B toxins).
- The B portion of the A-B toxins binds to a specific cell surface receptor, and then the A subunit is transferred into the interior of the cell, where cell injury is induced.
- The tissues targeted by these toxins are very defined and limited.

A-B toxins

- The biochemical targets of A-B toxins include:
- ribosomes
- transport mechanisms
- intracellular signaling (cyclic adenosine monophosphate [cAMP] production, G protein function)
- with effects ranging from diarrhea to loss of neuronal function to death.

Superantigens

- Superantigens are a special group of toxins.
- These molecules activate T cells by binding simultaneously to a T-cell receptor and a major histocompatibility complex class II (MHC II) molecule on an antigen presenting cell without requiring antigen.
- *Superantigens activate large numbers of T cells to release large amounts of interleukins (cytokine storm), including IL-1, TNF,* and IL-2, causing *life-threatening autoimmune-like responses.*

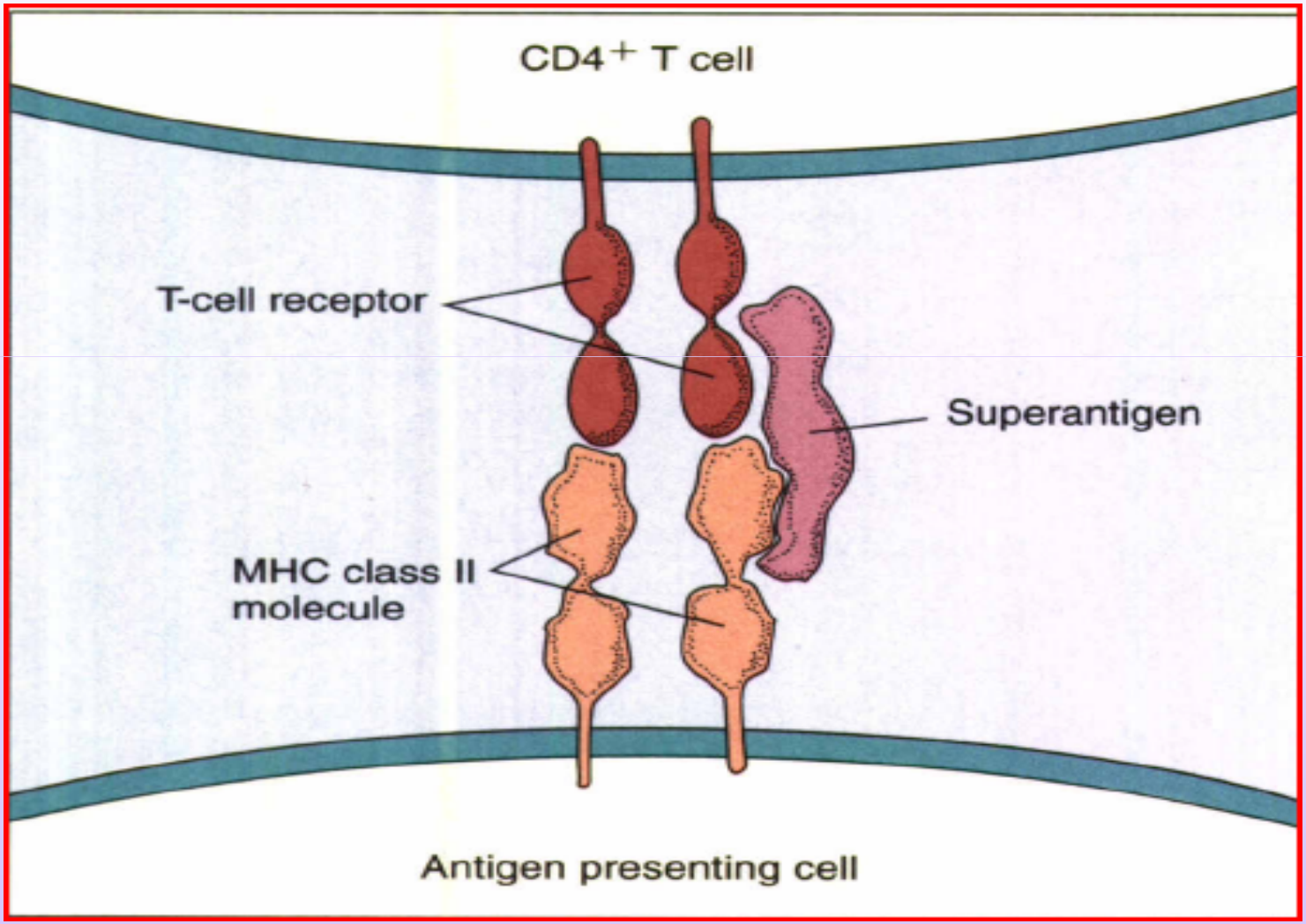
Superantigens

- This superantigen stimulation of T cells can also lead to death of the activated T cells, resulting in the loss of specific T-cell clones and the loss of their immune responses.

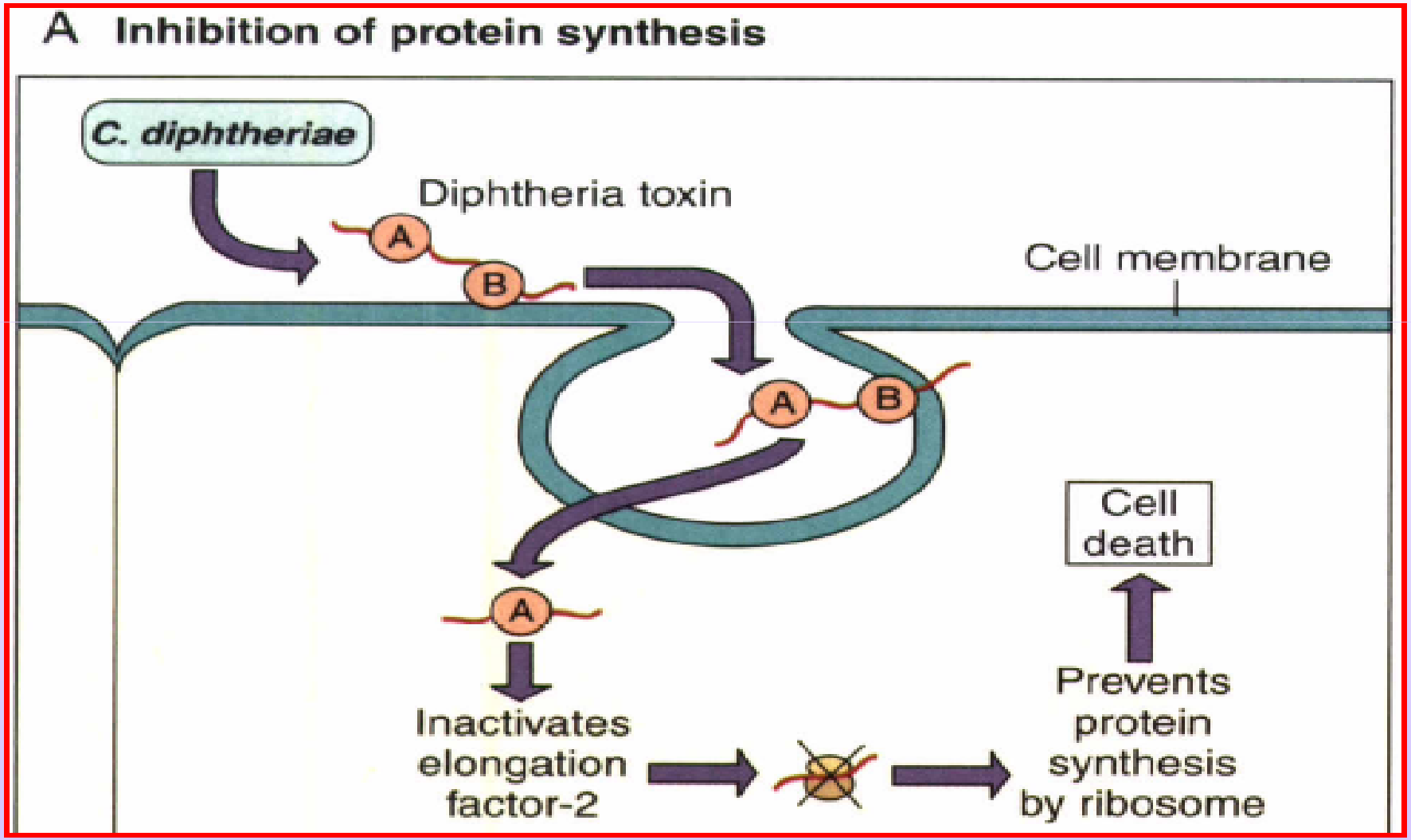
Superantigens include :

- toxic shock syndrome toxin of S. *aureus*
- *staphylococcal enterotoxins*
- erythrogenic toxin A or C of S. *pyogenes.*

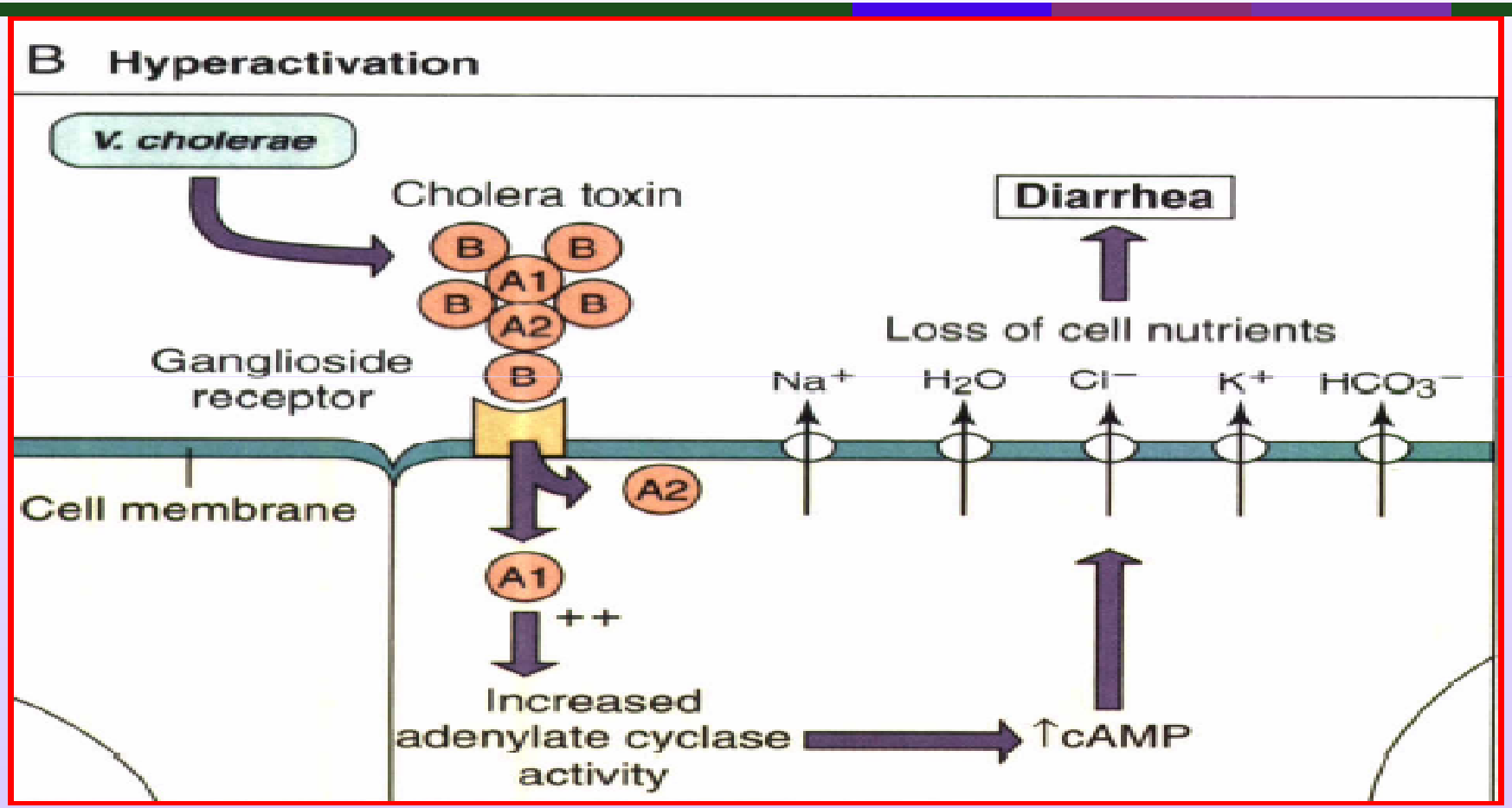
Superantigen binding to the external regions of the T-cell receptor and the major histocompatibility complex class II (MHC II) molecules.



Diphteria toxin



The mode of action of dimeric A-B exotoxins.



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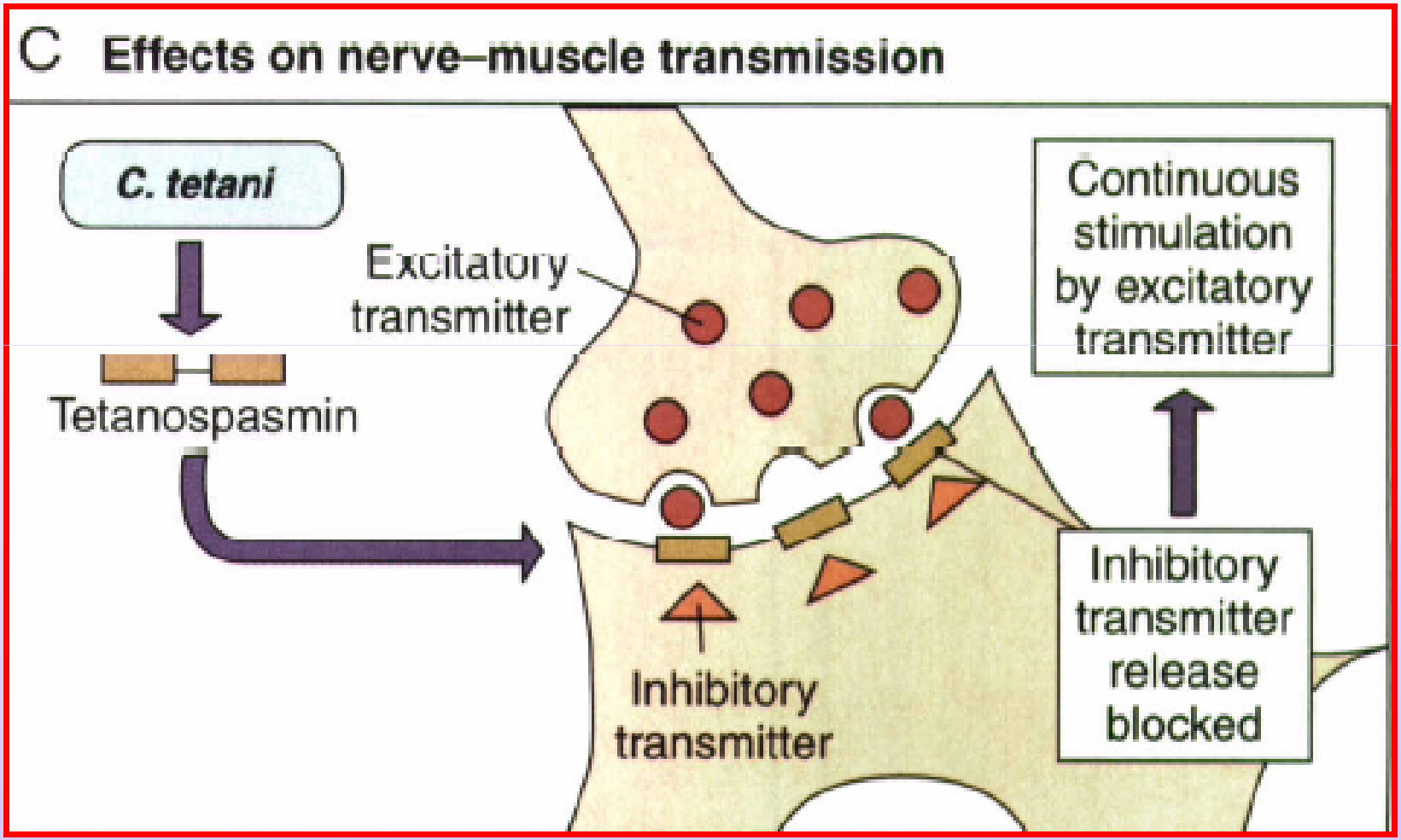

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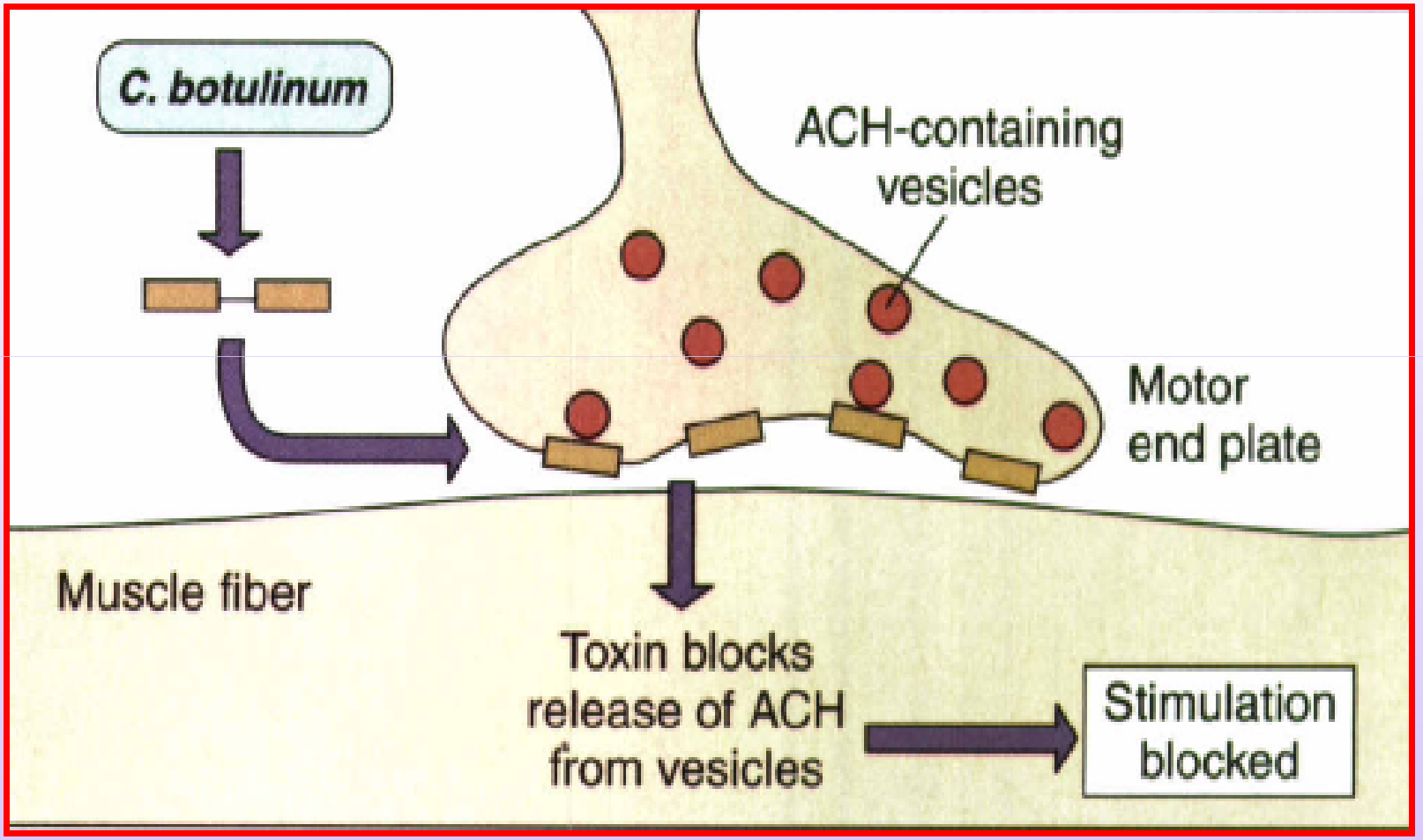
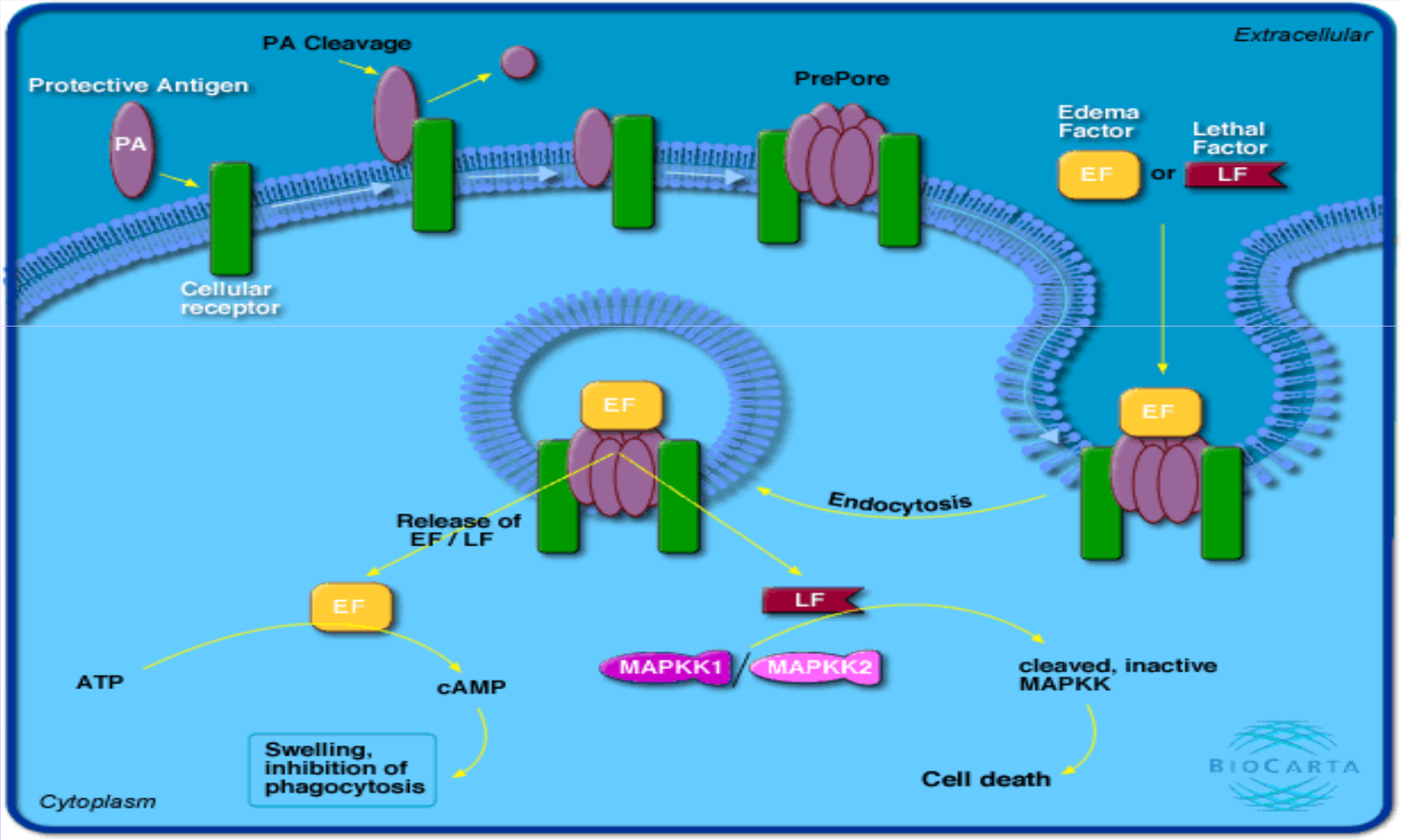


ACH, acetylcholine

Anthrax toxins

- *Bacillus anthracis*
- Plasmid
- Three separate proteins (EF, LF,PA)
- Target cell: Tumor endothelial marker-8 (TEM-8); capillary morphogenesis protein 2 (CMG2)
- EF + PA: increase in target cell cAMP level, localized edema; LF + PA: death of target cells and experimental anima

The toxins produced by anthrax bacteria are derived from three genes: lethal factor (LF), protective antigen (PA) and edema factor (EF).



Bordetella adenylate cyclase toxin

- *Bordetella spp.*
- *Chromosomal*
- *A-B*
- Target Cell Receptor: Unknown, probably glycolipid

Biologic Effects:

- EF + PA: increase in target cell cAMP level, localized edema; LF + PA: death of target cells and experimental animals

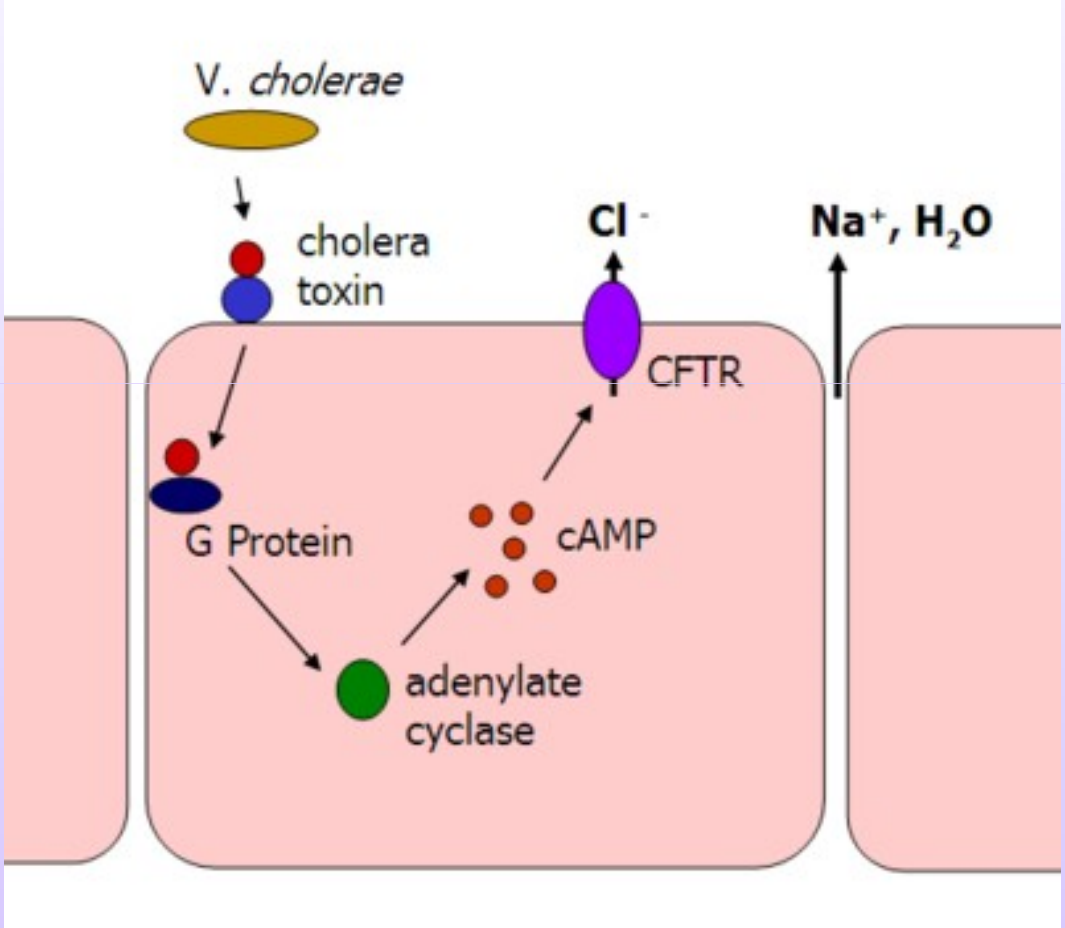
Botulinum toxin

- *Clostridium botulinum*
- Phage
- A-B
- Polysialogangliosides plus synaptotagmin (co-receptors)
- Decrease in peripheral presynaptic acetylcholine release, flaccid paralysis

Cholera toxin

- *Vibrio cholerae*
- *Chromosomal*
- *A-5B*
- Target Cell Receptor : Ganglioside (GM1)
- Activation of adenylate cyclase, increase in cAMP level,secretory diarrhea

Cholera toxin



Cholera toxin is released from bacteria in the gut lumen and binds via the B subunit to GM1 receptors on enterocytes, triggering endocytosis.
Following activation in the cytosol of an infected cell, the A subunit enzymatically activates a G protein and locks it into its GTP-bound form through an ADP-ribosylation reaction.

Diphtheria toxin

- *Corynebacterium diphtheriae*
- Phage
- A-B
- Target Cell Receptor: Growth factor receptor precursor
- Inhibition of protein synthesis, cell death

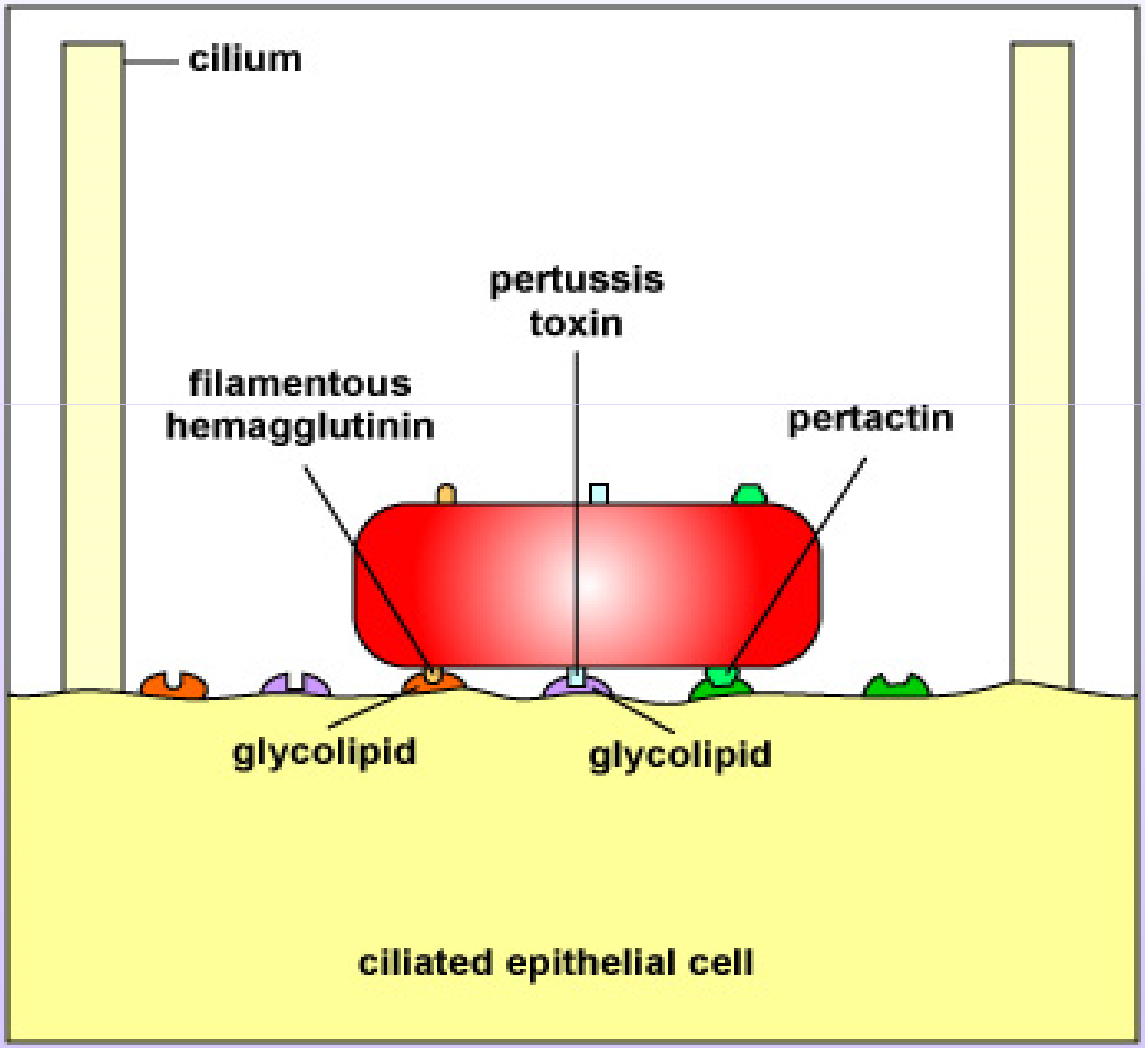
Heat-labile enterotoxins

- *Escherichia coli*
- *Plasmid*
- *Similar or identical to cholera toxin*
- Activation of adenylate cyclase, increase in cAMP level, secretory diarrhea

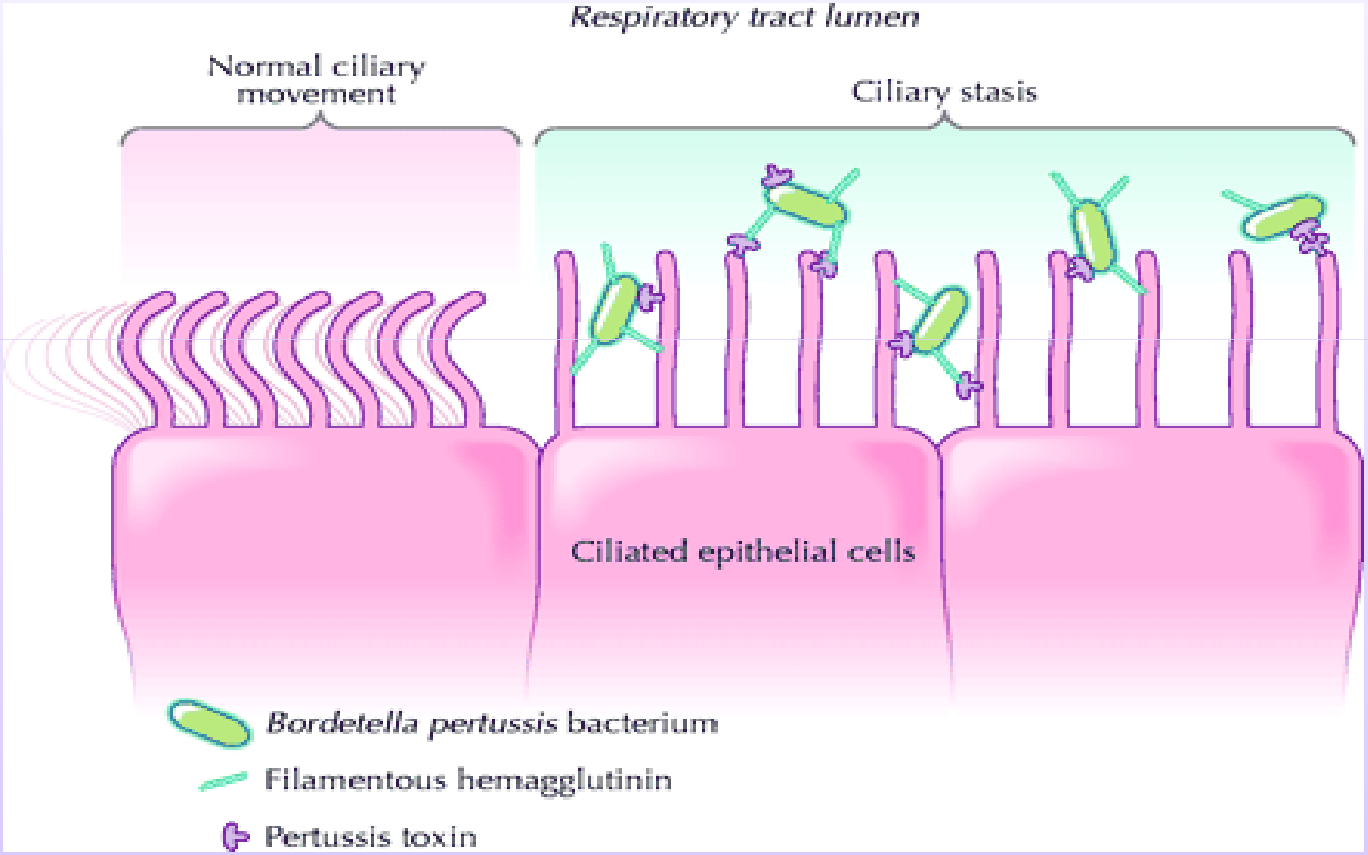
Pertussis toxin

- *Bordetella pertussis*
- *Chromosomal*
- *A-5B*
- Target Cell Receptor : Surface glycoproteins with terminal sialic acid residues
- Block of signal transduction mediated by target G proteins

Bordetella pertussis using Adhesins to Adhere to a Ciliated Epithelial Cell



Synergy between pertussis toxin and filamentous hemagglutinin in binding to ciliated respiratory epithelial cell



Pseudomonas exotoxin A

- *Pseudomonas*
- *Chromosomal*
- *A-B*
- α2-macroglobulin receptor (α 2MR)
- Similar or identical to diphtheria toxin

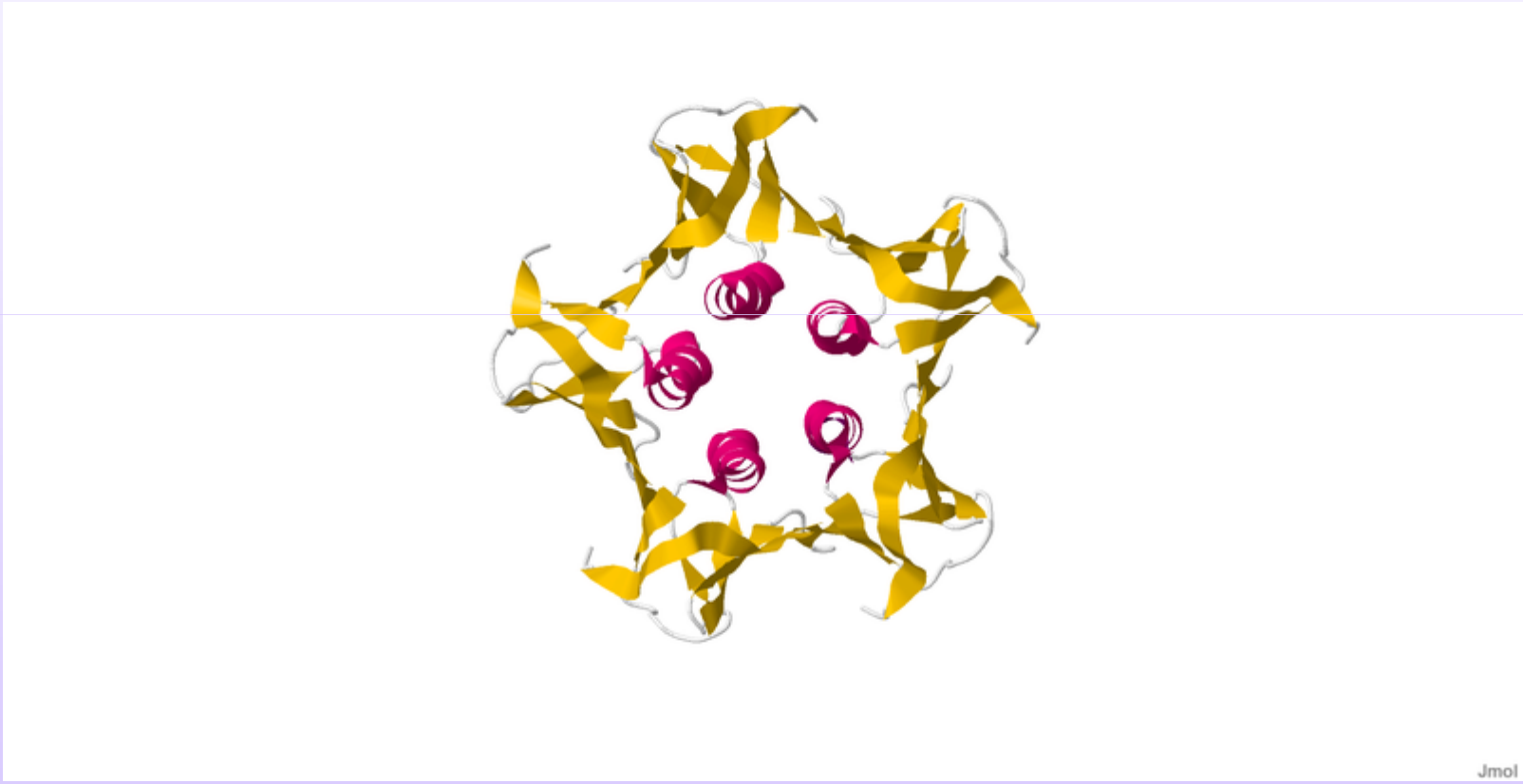
Shiga toxin

- *Shigella dysenteriae*
- *Chromosomal*
- *A-5B*
- Globotriasoyl ceramide (Gb3)
- Inhibition of protein synthesis, cell death

Shiga-like toxins

- *Shigella spp., E. coli*
- *Phage*
- *Similar or identical to Shiga toxin*
- Inhibition of protein synthesis, cell death

Shiga-like toxin subunit B



Tetanus toxin

- *Clostridium tetani*
- *Plasmid*
- *A-B*
- Polysialogangliosides plus 15-kDa glycoprotein (coreceptors)
- Decrease in neurotransmitter release from inhibitory neurons, spastic paralysis

Endotoxin and Other Cell Wall Components

- The presence of bacterial cell wall components acts as a signal of infection that provides a powerful multi alarm warning to the body to activate the host's protective systems.
- The molecular patterns in these structures (pathogen-associated molecular patterns [PAMPs]) bind to Toll-like receptor (TLR) molecules and stimulate the production of cytokines.
- In some cases, the host response is excessive and may even be life threatening.

Endotoxin and Other Cell Wall Components

- On infection with gram-positive bacteria, peptidoglycan and its breakdown products, as well as teichoic and lipoteichoic acids, are released, and these stimulate endotoxin-like pyrogenic (fever) acute-phase responses.

Endotoxin and Other Cell Wall Components

- The lipopolysaccharide (LPS) produced by gram-negative bacteria is an even more powerful activator of acute-phase and inflammatory reactions and is termed endotoxin.

Endotoxin and Other Cell Wall Components

- The lipid A portion of LPS is responsible for endotoxin activity.
- It is important to appreciate that endotoxin is not the same as exotoxin and that *only gram-negative bacteria make endotoxin.*

Endotoxin

- Gram-negative bacteria release endotoxin during infection.
- Endotoxin binds to specific receptors (CD 14 and TLR4) on macrophages, B cells, and other cells and stimulates the production and release of acute-phase cytokines such as IL-l, TNF-α, IL-6, and prostaglandins.
- Endotoxin also stimulates the growth (mitogenic) of B cells.

Endotoxin

- At low concentrations, endotoxin stimulates the mounting of protective responses, such as fever, vasodilatation,and the activation of immune and inflammatory responses.
- However, the endotoxin levels in the blood of patients with gram-negative bacterial sepsis (bacteria in the blood) can be **very high**, and the systemic response to these can be **overpowering**, resulting in **shock** and possibly **death**.

Endotoxin

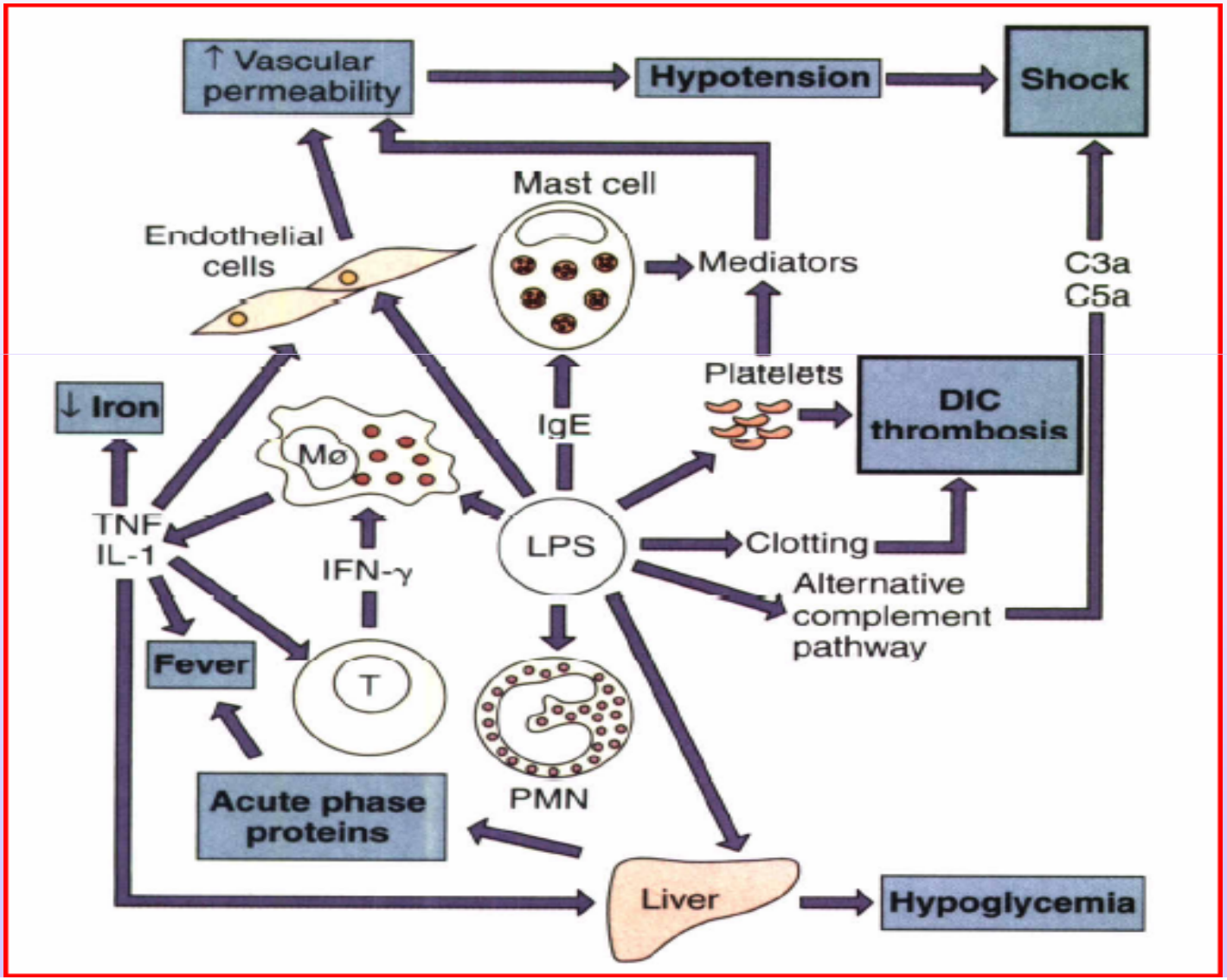
- High concentrations of endotoxin can also activate the alternative pathway of complement and production of anaphylotoxins (C3a, C5a), contributing to vasodilatation and capillary leakage.

- In combination with TNF and IL-1, this can lead to hypotension and shock.

Disseminated intravascular coagulation

- DIC can also result from the activation of blood coagulation pathways.
- The high fever, petechiae (skin lesions resulting from capillary leakage), and potential symptoms of shock (resulting from increased vascular permeability) associated with *Neisseria meningitidis* infection can be related to the large amounts of endotoxin released during infection.

The many activities of lipopolysaccharide (LPS).
This bacterial endotoxin activates almost every immune mechanism, as well as the clotting pathway, which together make LPS one of the most powerful immune stimuli known.



Endotoxin-Mediated Toxicity

- Fever
- Leukopenia followed by leukocytosis
- Activation of complement
- Thrombocytopenia
- Disseminated intravascular coagulation
- Decreased peripheral circulation and perfusion to major organs
- Shock
- Death

Mechanisms for Escaping Host Defenses

- Bacteria are parasites, and evasion of host protective responses is a selective advantage.
- Logically, the longer a bacterial infection remains in a host, the more time the bacteria have to grow and also cause damage.
- Therefore bacteria that can evade or incapacitate the host defenses have a greater potential for causing disease.
- Bacteria evade recognition and killing by phagocytic cells, inactivate or evade the complement system and antibody, and even grow inside cells to hide from host response.

Microbial Defenses against Host Immunologic Clearance

- Encapsulation
- Antigenic mimicry
- Antigenic masking
- Antigenic shift
- Production of antiimmunoglobulin proteases
- Destruction of phagocyte
- Inhibition of chemotaxis
- Inhibition of phagocytosis
- Inhibition of phagolysosome fusion
- Resistance to lysosomal enzymes
- Intracellular replication

Examples of Encapsulated Microorganisms

- ***Staphylococcus aureus***
- ***Streptococcus pneumoniae***
- ***Streptococcus pyogenes (group A)***
- ***Streptococcus agalactiae (group B)***
- ***Bacillus anthracis***
- ***Bacillus subtilis***
- ***Neisseria gonorrhoeae***
- ***Neisseria meningitidis***
- ***Haemophilus influenzae***
- ***Escherichia coli***
- ***Klebsiella pneumoniae***
- ***Salmonella spp.***
- ***Yersinia pestis***
- ***Campylobacter fetus***
- ***Pseudomonas aeruginosa***
- ***Bacteroides fragilis***
- ***Cryptococcus neoformans (yeast)***

Methods That Circumvent Phagocytic Killing

- Inhibition of phagolysosome fusion
- *Legionella spp.,*
- *Mycobacterium tuberculosis*
- *Chlamydia spp.*

Methods That Circumvent Phagocytic Killing

- Resistance to lysosomal enzymes
- *Salmonella typhimurium*
- *Coxiella spp.,*
- *Ehrlichia spp.,*
- *Mycobacterium leprae*
- *Leishmania spp.*

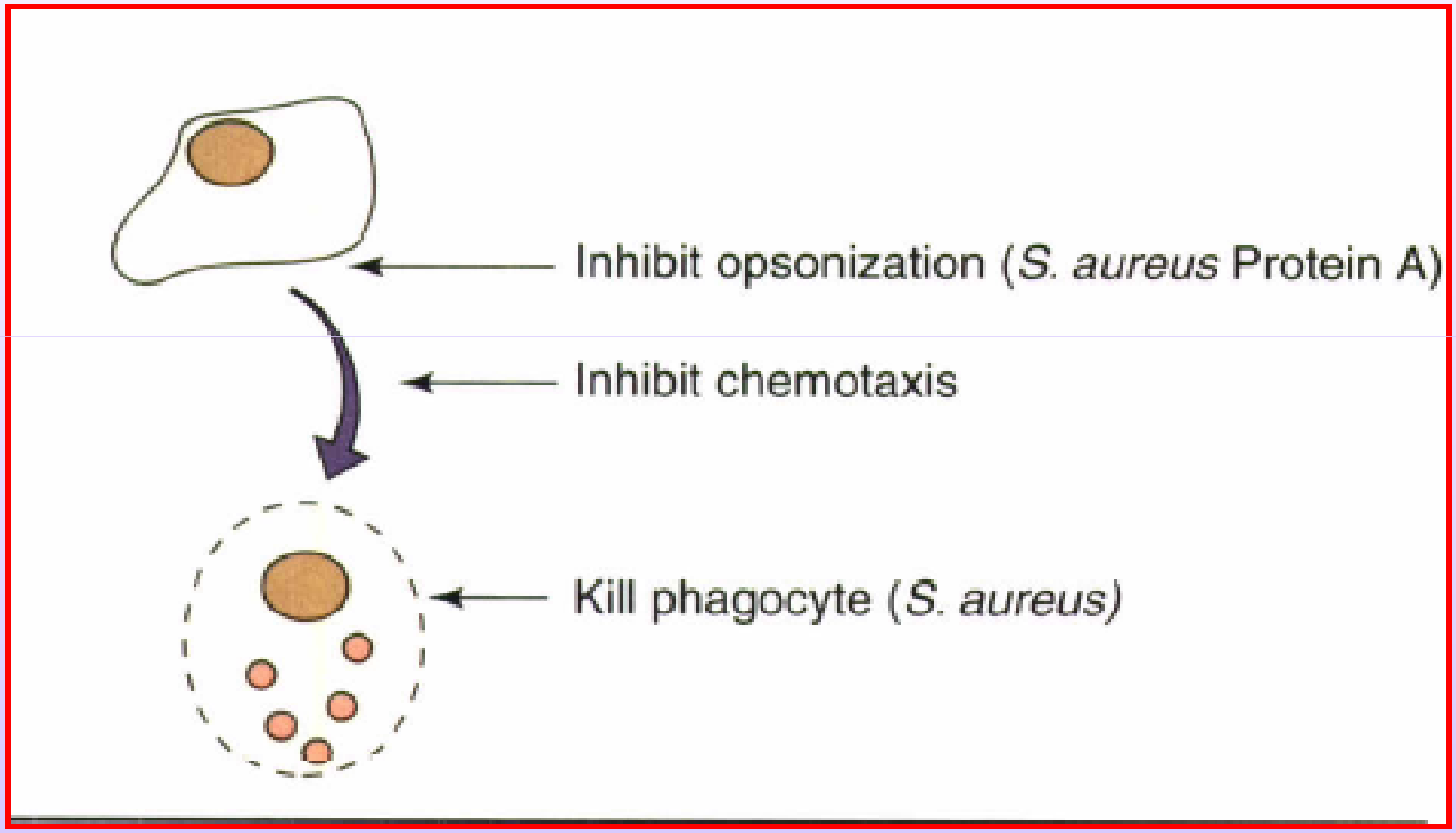
Methods That Circumvent Phagocytic Killing

- Adaptation to cytoplasmic replication
- *Listeria*
- *Francisella*
- *Rickettsia spp.*

Examples of Intracellular Pathogens

- *Mycobacterium spp.*
- *Brucella spp.*
- *Francisella spp.*
- *Rickettsia spp.*
- *Chlamydia spp.*
- *Listeria monocytogenes*
- *Salmonella Typhi*
- *Shigella dysenteriae*
- *Yersinia pestis*
- *Legionella pneumophila*

Bacterial mechanisms for escaping phagocytic clearance.



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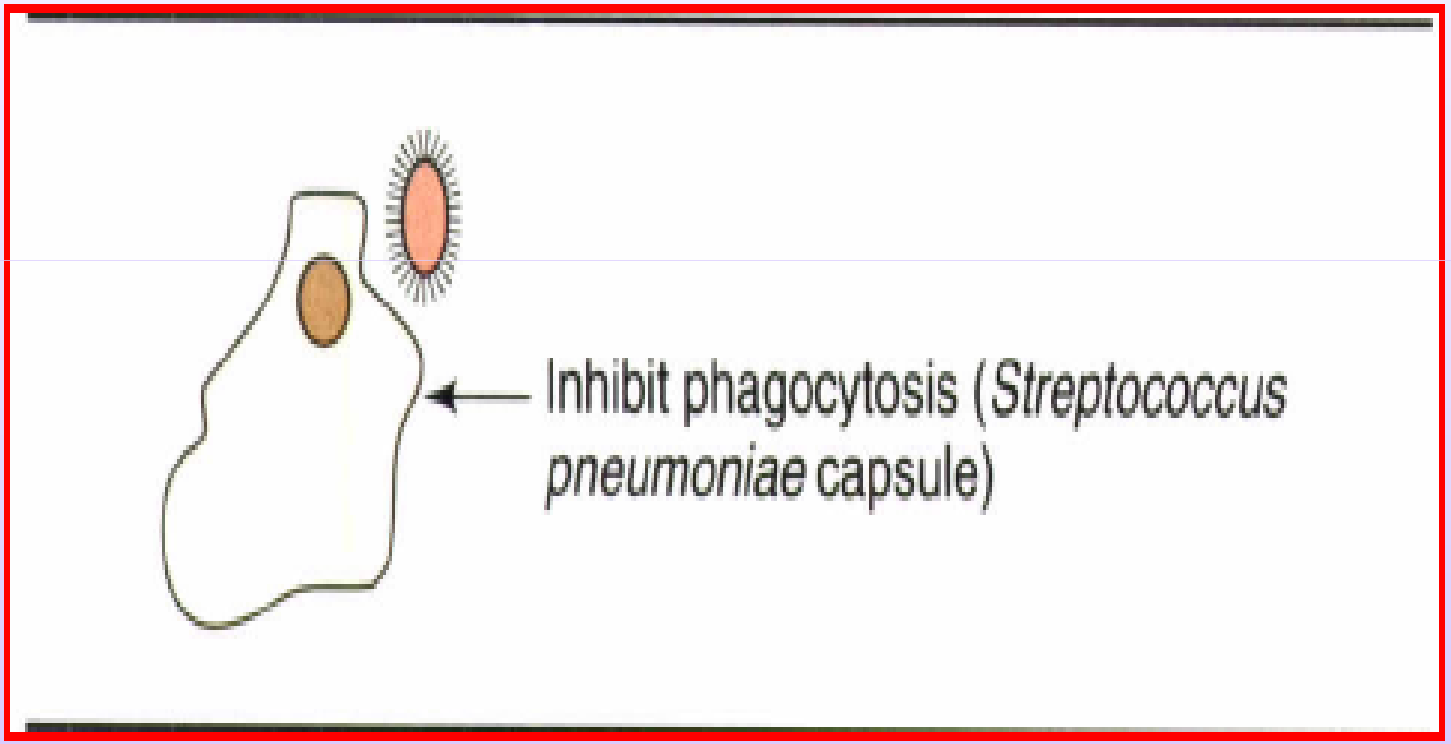

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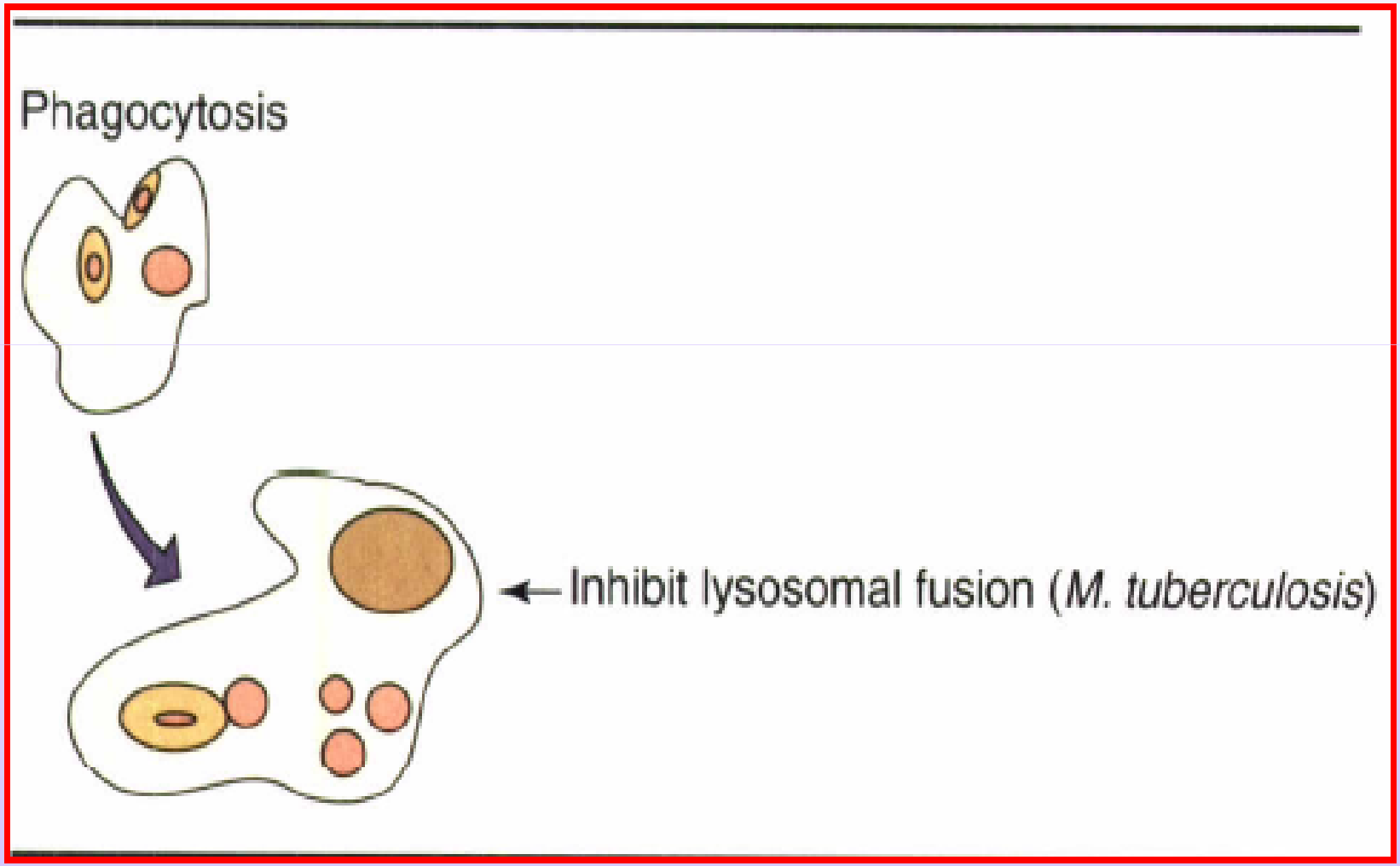

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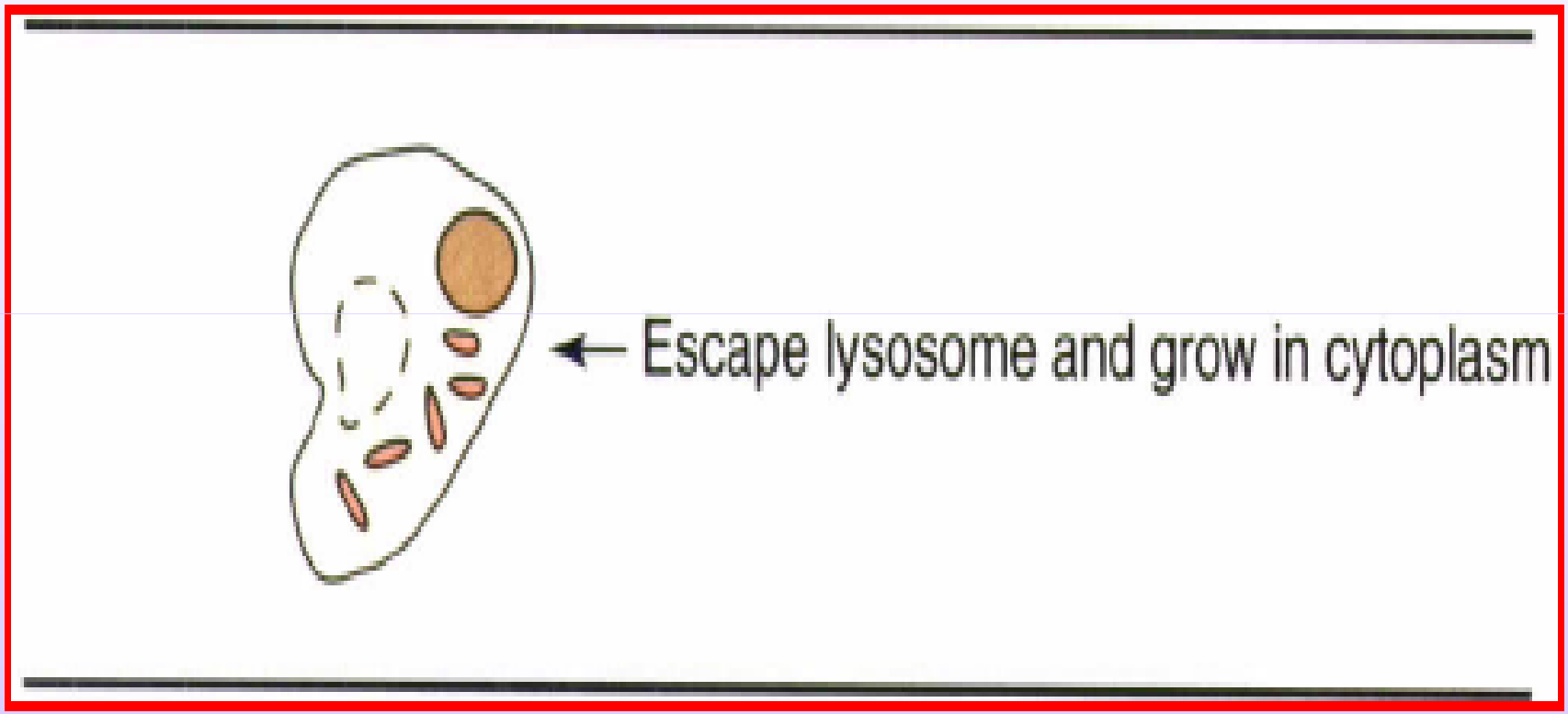

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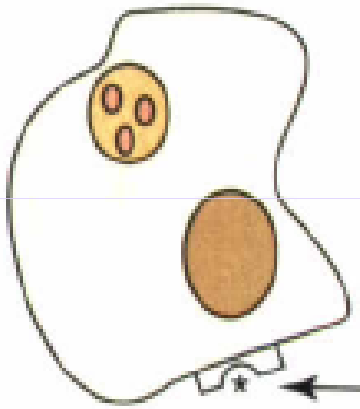

Resist antibacterial lysosomal action and multiply within cell (*M. leprae*, *Salmonella* species, *S. aureus*)

Block activation by interferon-γ (Mycobacteria)

virulence factors

The primary virulence factors of bacteria are:

- Capsule
- Adhesins
- Invasins
- Degradative enzymes
- Toxins
- Mechanisms for escaping elimination by host defenses producing a spectrum of diseases

virulence factors

- Different strains within a bacterial species may express different virulence mechanisms.
- The symptoms and sequelae of gastroenteritis (diarrhea) caused by *E. coli* may include invasion and bloody stools, cholera-like watery stools, and even severe hemorrhagic disease, depending on the specific infecting strain.