Bacterial toxins

Due to the action or breakdown of bacteria, toxic substances (toxins) are released into the environment. Such substances are capable of damaging, and in some cases even killing, the host. The ability to harm a host is called toxicity and is part of pathogenicity. It either acts directly or contributes to other pathogenicity factors.

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Toxins in general

Chemically, toxins are antigenic proteins that are neutralized (blocked) in the human body by specific antibodies . Boiling inactivation is also possible, they are so-called thermolabile . Toxins can also be turned into toxoids that are used for active immunization .

The toxicity of bacterial toxins produced within the body depends on their concentration and the susceptibility of the host. Toxins can also be introduced into the body from the external environment (eg in food - botulinum toxins, enterotoxins). These toxins depend not only on their concentration, but also on their absorption and resistance to digestive enzymes.

The mode of toxic action is characteristic of individual toxins (diphtheria, tetanus, botulism, cholera). Symptoms of clinical toxin disease are generally called toxinoses.

Bacterial toxins act on the host in two ways. The first is the reaction with the membranes of eukaryotic cells , which they damage. Hence, this group of toxins is referred to as cytolytic. The second way is the binding of the toxin to a specific receptor on the cell. By binding, the toxin penetrates into the cytoplasm, where it affects physiological mechanisms.

According to the target organs, we can divide toxins into

- neurotoxins (botulinum toxin, tetanospasmin);
- enterotoxins (choleragen , *E. coli* toxins);
- dermonecrotoxins (diphtheria , staphylococcal alpha toxin);
- cytotoxins (*Clostridium difficile*);
- cardiotoxins (diphtheria, streptolysin O);
- capillary toxin (*B. anthracis*);
- hemolysins, leukocidins;
- superantigen toxins (Streptococcus pyogenes, toxic shock syndrome toxin).

Exotoxins

Toxic bacterial proteins, secreted into the producer's environment. They are used in diseases caused by G + bacteria . Exotoxins are released from the bacteria into the environment during their growth .

Exotoxin genes are stored primarily on plasmids or on temperate bacteriophages . As a result, bacteria are not essential for life, but are useful for their survival and spread.

Mechanisms of action of exotoxins

Penetrating enzymes (factors)

Hydrolytic enzymes that disrupt the intercellular mass. It is used for invasion (so-called invasion factor), to gain nutrients and energy. These enzymes include, for example, hyaluronidase, elastase, DNase, streptokinase (dissolves blood clots).

Cytolytic enzymes (cytolysins)

Toxins interact with the membranes of eukaryotic cells, which they damage. Chemically, these are phospholipases . Membrane disruption can also occur through the formation of pores.

Hydrolysis of phospholipids by phospholipases C and D removes the polar group from the phospholipids. This destabilizes the membrane and lyses the cells. Examples of such bacteria are *Clostridium perfringens* , whose alpha toxin is phospholipase C. It causes intravascular hemolysis in myonecrosis or intravascular coagulopathy. Another example is sphingomyelinase (beta-hemolysin) in *Staphylococcus aureus*.

Toxins that form pores in the membrane are elongated molecules. They integrate into the membrane, creating channels through which water penetrates. This membrane disruption is non-enzymatic. *An example is Staphylococcus aureus* alpha-toxin . Another example is streptolysin O, which is produced by *Streptococcus*

pyogenes . Streptolysin disrupts the membrane of the granules inside the neutrophils. Another pore-forming toxin is Listeriolysin O, made by *Listeria monocytogenes* , which helps the bacterium escape from the phagosome .

Toxins affecting cell physiology

They do not kill cells directly, they modify their functions . ADP-ribose binds to the regulatory components of adenylate cyclase , which increases the concentration of cAMP. Increased cAMP concentration causes Cl- and water secretion and inhibits Na+ absorption . This will cause fluids to leak. Toxins therefore cause diarrhea (cholera toxin, thermolabile E. coli enterotoxin). Another example is *Bordetella pertussis* (pertussis toxin). It affects the level of cAMP in neutrophils . This will reduce chemotaxis and motility .

Inhibition of proteosynthesis

Intracellular toxins that cause subsequent cell death. The toxin has two components. The A (*active*) component is toxic, the B (*binding*) component binds to a specific cell membrane receptor. Binding will allow the toxin to endocytose into the cell. Enzymatic activation occurs inside the cell. Toxins cause the transfer of the adenosine diphosphate ribosyl group from NAD to the target molecule (elongation factor 2 - diphtheria toxin). This stops proteosynthesis, which causes cell death.

Neurotoxins

They act as peptidases. It acts at nerve synapses on proteins that are responsible for releasing neurotransmitters. These are tetanus toxin and botulinum toxin.

Tetanus toxin (tetanospasm) is a toxin that is formed by *Clostridium tetani* . Bacteria are present in the digestive tract of animals. With the droppings of these animals, they get into the soil, where they sporulate. Spores enter the human body when the infected soil comes into contact with an open wound (most often deep injuries). Spores in the wound germinate (ideal conditions - heat, humidity, anaerobic environment). Bacteria begin to produce toxins. They penetrate the blood and lymph into the nerve cells. Along their axons, they can reach the CNS (motor neurons). In the CNS, they can disrupt transmission on inhibitory neurons, where they inhibit GABA release. Continuous stimulation with excitatory neurotransmitters causes muscle cramps, and thus respiratory arrest, heart failure, and subsequent death.

Botulinum toxin is a toxin *of Clostridium botulinum* . It is probably the most effective poison known - the LD 50 is 10 ng/kg. Bacteria multiply in uncooked food. Heat treatment destroys the bacterium itself, but the toxin remains. It usually causes serious fatal poisoning. It is most often present in canned food (bacteria form gases → bulging can), especially meat (sausage poison).

From the intestinal mucosa, it enters the PNS through the blood . It acts on the neuromuscular discs, where it blocks the release of acetylcholine. It causes polio . If it attacks the respiratory muscles (diaphragm), death can lead to suffocation.

Superantigens

A subset of exotoxins that are able to induce polyclonal T-cell activation (mitogens). They bind to T-lymphocytes and macrophages. After binding, they induce an overall defense response (release of large amounts of cytokines). This contributes to the development of autoimmune diseases. They increase the sensitivity to the action of G− endotoxins. Examples are staphylococcal enterotoxins (food poisoning) and *Streptococcus pyogenes* superantigens (pyrogenic fever toxins).

Endotoxins

Endotoxin is a lipopolysaccharide complex (LPS) that is part of the cell wall of Gram-negative bacteria.

Characteristics

The term endotoxin was introduced as a contrast to exotoxin, which is a toxin released by bacteria into the environment (endotoxin is released only after the bacterial cell wall has collapsed). Today, the term endotoxin is synonymous with lipopolysaccharide (LPS), which is an important component of the outer membrane of Gram-negative bacteria.

However, lipopolysaccharides are not only harmful substances. They also play an important role for the bacterium itself - they contribute to structural stability and protect the membrane from certain chemical attacks. Because of the importance of lipopolysaccharide to the bacterial cell, this molecule has become a target for research into bactericidal agents.

Composition

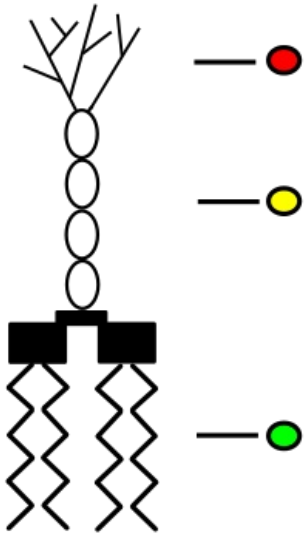
Lipopolysaccharide consists of 3 parts:

1. lipid A,
2. oligosaccharide core,
3. O-antigen.

Lipid A – forms the lipid component of the endotoxin responsible for the toxicity of gram-negative bacteria. Due to its hydrophobic nature (glycolipid) it anchors in their outer membrane. However, despite its toxic effect, the recognition of lipid A by the human immune system is crucial for initiating and subsequently managing the immune response. It activates mainly monocytes and macrophages, for which a concentration of picograms per milliliter of blood is sufficient. If it is present in high concentrations in the human body, it is possible to cause endotoxic shock, which can be fatal

Oligosaccharide core - consists of a short chain of carbohydrate residues (often heptose, ketodeoxyoctulosonic acid also occurs) and connects lipid A to the O-antigen.

O-antigen – forms repeating oligosaccharide units. It is found most superficially, attached at one end to the oligosaccharide core and protrudes from the surface of the microbe. It carries the greatest variability and determines antigen specificity. If the lipopolysaccharide has a complete O-chain, the colonies appear smooth and moist when cultured on solid growth medium. However, if the O-chain is shortened, the colonies appear rough and dry. Such bacteria often have more vulnerable membranes to hydrophobic antibiotics. The polysaccharide chain is highly variable between different bacteria and determines their serotype. The sugar chains of smooth lipopolysaccharides can overlay the outer membrane proteins and mask them from the host immune system.



Lipopolysaccharide: red circle - side chains; yellow circle - core; green circle-lipid A

Endotoxin release

Endotoxin release can occur:

- after phagocytosis and intracellular destruction of the bacterium
- during the breakdown of the bacteria by the action of its own **autolytic** enzymes;
- as a result of cytolysis by **complement**;
- by the effect of membrane-acting **antibiotics.**

Biological effects

It acts as a pyrogen (temperature increase). The toxin stimulates mononuclear phagocytes to produce endogenous pyrogens (interleukin-1 and TNF) - induces fever and vasodilation. Activates the complement system (alternative pathway). The result is cell cytolysis associated with further toxin release.

It stimulates the immune system response - activation of macrophages, neutrophils, B lymphocytes. A local inflammatory reaction occurs. At higher concentrations, endotoxic shock may occur.

May cause clotting disorders. Activates f. XII - triggers the clotting cascade. Affects platelets - release of granule contents (platelet degranulation). It affects neutrophils - release of proteins that stabilize fibrin clots. Affects the endothelium.

It acts chemotactically on polymorphonuclear cells. At high concentrations, **endotoxemia** (presence of endotoxin in the blood) - sepsis caused by G− bacteria can occur. Low levels of endotoxin in the body have a positive effect (stimulation of immunity). At high concentrations, there is a risk of toxic shock and DIC (often resulting in death).

Endotoxic shock

- **Hypotension**
- **disseminated intravascular coagulation (DIC),**
- **vasodilation,**
- **reduced cardiac output (oxidative disorders).**

  25-40% of these cases end in death. There is no effective treatment to reverse the toxic activity of lipid A. In infections with Gram-negative bacteria, endotoxins are largely responsible for the severe clinical manifestations. For example, in meningococcal infections and Waterhouse-Friderichsen syndrome (adrenal failure due to haemorrhage) caused predominantly by Neisseria meningitidis.

Endotoxin also acts as a potent B-cell mitogen and activator of polyclonal B-cells, which plays a role in the development of an appropriate chronic immune response if the bacterium has not been destroyed in the acute phase.

Endotoxin contamination

Endotoxins can often contaminate substances that are included in a research or otherwise used medically. This may include, for example, plasmid DNA for use in gene therapy, ovalbumin in research or laboratory equipment.

A single Escherichia Coli bacterium contains around 2 million lipopolysaccharide molecules. In addition, endotoxins are very heat stable (they cannot be destroyed by conventional sterilization methods or autoclaving). Due to their hydrophobicity, they show a high affinity for other hydrophobic materials such as plastics. If the contamination were left and transmitted to the human body, an inflammatory reaction would break out, which could be dangerous

or could interfere with test results. It is therefore necessary to remove the endotoxins. **Depyrogenation** is used for this purpose. This method involves heating up to 250-300 ˚C for 30 minutes, which safely destroys the endotoxins.

A very sensitive test for the presence of endotoxin is called the Limulus test, which is based on the principle of coagulation of the blood of the horseshoe crab. It precipitates in the presence of even a small amount of lipopolysaccharide due to its very strong amplifying effect on the enzymes of the coagulation cascade.

Possible applications

Enzymes involved in the biosynthesis or modification of lipid A may provide access not only to new lipid A derivatives that may be useful as adjuvants or endotoxin antagonists, but may also be used for new bacterial vaccines. Monophosphorylated lipid A derived from *Salmonella minnesota* is used as an adjuvant in combination with alum and has recently been approved as a vaccine for human papillomavirus and viral hepatitis B.

Links

Related articles

- Bacteria
- Gram staining
- Pseudomembranous enterocolitis

Sources

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