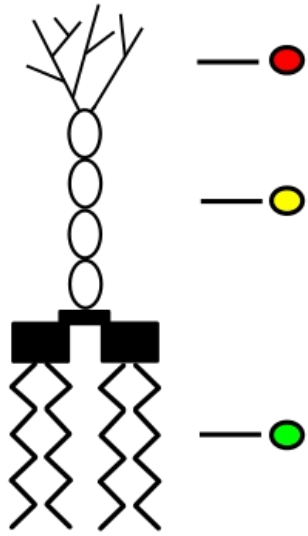
Endotoxin

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



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

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.

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

- Bacterial toxins
- Bacteria
- Gram stain
- Pseudomembranous enterocolitis

Resource

- JANSKÝ, Petr. *Zpracované otázky z mikrobiologie* [online]. [cit. 2012-01-30]. <https://www.yammer.com/wikiskripta.eu/uploaded_files/3804405>.
- VOTAVA, Miroslav. *Lékařská mikrobiologie obecná.* 2. edition. Brno : Neptun, 2005. ISBN 80-86850-00-5.
- Foca A, Liberto MC, Quirino A, Matera G: Lipopolysaccharides: From Erinyes to Charites, Mediators of Inflammation, Volume 2012 (2012), Article ID 684274, 6 pages
- Lerner KL, Lerner BW: World of Microbiology and Immunology, Gale, Farmington Hills, 2003, s. 351-352