

3-Toxins

- **Poisonous substances produced by microorganisms.**
- Chemicals produced by pathogens that either harm tissues or trigger host immune responses that cause damage.

Two types of toxins;

a. Exotoxin

b. Endotoxin

Exotoxins

1. Exotoxins are a group of soluble proteins formed and secreted by the bacteria and found free in the surrounding medium.
2. **Exotoxin consists of two subunits.** usually one component is a **binding domain (B subunit)** associated with absorption to target cell surface and transfer of active component across cell membrane, the second component is an **enzymatic or active domain (A subunit)** that enzymatically disrupts cell function

3. Protein structure, strong poison
4. Soluble in body fluids, rapidly transported throughout body in blood or lymph.
5. Produced mainly by gram-positive bacteria. But also produced by Gram negative bacteria
6. Most genes for toxins are carried on plasmids or phages.
7. Produced inside bacteria and released into host tissue.

8. Responsible for disease symptoms and/or death. (Each toxin causes its own symptoms).
 - Cytotoxins: Kill or damage host cells.
 - Neurotoxins: Interfere with nerve impulses.
 - Enterotoxins: Affect lining of gastrointestinal tract.
9. Antibodies called antitoxins provide immunity. (Exotoxins are in the form of antigens and cause the formation of antibodies in the organism)
10. Toxoids (Anatoxin): Toxins that have been altered by heat or chemicals and lost toxic activity but have antigenic activity are defined as toxoids. This feature is used to obtain antitoxic serum and to treat toxic poisonings. Used as vaccines for diphtheria and tetanus.
11. it is released by the microorganism when it is alive.

Important Toxins

- ◆ **Diphtheria Toxin:** *Corynebacterium diphtheriae* when infected by a phage carrying toxin gene. **Cytotoxin** inhibits protein synthesis in eucaryotic cells. Two polypeptides: A (active) and B (binding).
- ◆ **Erythrogenic Toxins:** *Streptococcus pyogenes* produces three **cytotoxins** which damage blood capillaries, causing a red rash.
- ◆ **Botulinum Toxins:** Produced by *Clostridium botulinum*. **Neurotoxin** that inhibits release of neurotransmitter acetylcholine and prevents transmission of nerve impulses to muscles, causing flaccid paralysis. Extremely potent toxins.

- ◆ **Tetanus Toxin:** Produced by *Clostridium tetani*. A neurotoxin that blocks relaxation of skeletal muscles, causing uncontrollable muscle spasms and convulsions.
- ◆ **Vibrio Enterotoxin:** Produced by *Vibrio cholerae*. Two polypeptides: A (active) and B (binding). The A subunit of enterotoxin causes epithelial cells to discharge large amounts of fluids and electrolytes.
- ◆ **Staphylococcal Enterotoxin:** *Staphylococcus aureus* produces an enterotoxin similar to cholera toxin. Other enterotoxins cause toxic shock syndrome.
- ◆ **Enterotoxigenic *Escherichia coli* (ETEC) toxin:** heat labile enterotoxin, similar to cholera toxin

Endotoxins

1. Produced by gram-negative bacteria.
2. Endotoxin is lipid portion of lipopolysaccharides (LPS), called **lipid A**.
3. Effect exerted when gram-negative cells die and cell walls undergo lysis, liberating endotoxin.
4. Endotoxins do not promote the formation of effective antibodies.
5. They can not transform to anatoxin.
6. **All produce the same signs and symptoms:**
 - Chills, fever, weakness, general aches, blood clotting and tissue death, shock, and even death. Can also induce miscarriage.

- **FEVER:** Pyrogenic response is caused by endotoxins.
- **LEUKOPENIA/LEUKOCYTOSIS:** abnormal reduction in number of leukocytes in blood, ($\leq 5000/\text{mm}^3$) / abnormally large number of leukocytes in blood,
- **METABOLIC EFFECTS :** pathogenic organisms can affect any of the body systems with disruptions in metabolic processes, e.g.,hypotension, hypoglycemia, etc

- **CELLULAR DEATH:**

- **SEPTIC SHOCK:** associated with overwhelming infection resulting in vascular system failure with sequestration of large volumes of blood in capillaries and veins; activation of the complement and kinin systems and the release of histamines, prostaglandins, and other mediators may be involved
- **DISSEMINATED INTRAVASCULAR COAGULATION (DIC):** disorder characterized by a reduction in the elements involved in blood coagulation due to their utilization in widespread blood clotting within the vessels; late stages marked by profuse hemorrhaging
- **ORGAN NECROSIS:** the sum of morphological changes indicative of cell death and caused by the progressive degradative action of enzymes

- **Organisms that produce endotoxins include:**

- *Salmonella typhi*

- *Proteus spp.*

- *Pseudomonas spp.*

- *Neisseria spp.*

- **Medical equipment that has been sterilized may still contain endotoxins.**

- *Limulus* amoebocyte assay (LAL) is a test used to detect tiny amounts of endotoxin.

Exotoxin	Endotoxin
Made of two components (A and B)	Lipopolysaccharide complex on the outer membrane; lipid A portion is toxic
Proteins; excreted by certain gram-positive or gram negative bacteria (living cell)	Released on cell lysis as part of the outer membrane of gram negative bacteria
Heat-labile	Heat-stable
Highly toxic often fatal	Weakly toxic, rarely fatal (Factor XII)
Highly variable effect on host of different toxins Diphtheria toxin, Botulinum toxin, Tetanus toxin, <i>Vibrio cholerae</i>	Similar effect of all toxins; fever, diarrhea, vomiting
Highly immunogenic; stimulate the production of neutralizing antibody (antitoxin)	Relatively poor immunogen; immune response not sufficient to neutralize toxin
Exposure of toxin with formaldehyde will destroy toxicity, but exposed toxin (toxoid) remains immunogenic	None

ENDOTOXINS

1. Integral part of cell wall
2. Endotoxin is **LPS**;
lipid A is toxic
3. Heat stable
4. Antigenic; questionable immunogenicity
5. Toxoids not be produced
6. Many effects on host
7. Produced **only by gram-negative** organisms

EXOTOXINS

1. Released from the cell before or after lysis
2. **Protein**
3. Heat labile
4. Antigenic and **immunogenic**
5. **Toxoids** can be produced
6. Specific in effect on host
7. Produced by gram-positive & gram-negative organisms

4-Hemolysins

- Hemolysins are lipids and proteins that cause lysis of red blood cells by destroying their cell membrane. Hemolysins are thought to be responsible for many events in host cells. For example, iron may be a limiting factor in the growth of various pathogenic bacteria. Since free iron may generate damaging free radicals, free iron is typically maintained at low concentrations within the body. Red blood cells are rich in iron-containing heme. Lysis of these cells releases heme into the surroundings, allowing the bacteria to take up the free iron.

Hemolysin Patterns:

- alpha hemolysis; partially breaks down RBC membranes. Turn blood agar green
- beta hemolysis; completely ruptures RBCs. Turns blood agar clear
- gamma hemolysis is no RBC lysis; no color change on blood agar

- **5- Leucocidin:** Substances firstly that stop movement of leukocytes , then kill and melt them. It can be occured in vivo and in vitro. It can be separated by filtration. Antigenic. They form pus.
- **6- Fibrinolytic kinases (Lysokinase):** found especially in pathogenic streptococci (primarily group C and G with group A) and some staphylococci.

Secreted kinase => activates plasminogen (profibrinolysin) => Fibrinolytic plasmin is formed.

Streptokinase → The specific effect to the fibrin of the mammal from which the bacteria are isolated.

- **7- Deoxyribonuclease (Streptodornase):** The enzymes are formed by Streptococci and that depolymerize DNA.
- Normally, pus has its own unique consistency and this is provided by deoxyribonucleoproteins. It prevents the spread of bacteria. Streptodornase increases the liquidity of pus and facilitates its spread.
- *Staphylococcus aureus*
- *Corynebacterium diphtheriae*
- Bazı Proteus ve Alcaligenes'ler
- *Moraxella catarrhalis*

- **8- Hyaluronidase:** Hyaluronic acids and mucopolysaccharides form the connective tissue. Hyaluronidase melts this tissue and allows the bacterium to spread through the tissue. It is an extracellular substance and antigenic. It is mainly produced by *Clostridium perfringens*.
- **9- Coagulase:** An enzyme that is formed by pathogenic staphylococci and coagulates the blood plasma that has been prevented from clotting. Coagulase-producing staphylococci are protected from phagocytosis. Coagulase=> Clots human, rabbit, horse plasmas. But not clotting chicken, guinea pig, mouse plasmas.

- **10- Neuroaminidase:** (Mucin melter): orthomyxovirus and in some bacteria.
- Melts and dilutes the mucus. It provides easy adherence to the receptors.
- **11- Capsule** : prevents phagocytosis. Antigenic, Non-toxic

The other factors:

- Collagenase: invasion factor, destroy collagen under the skin
- Lecithinase
- hypothermic agent
- Protease
- genetic and environmental factors

Increase of Virulence

1- It may be genetically mutated or recombined with chromosomal or extrachromosomal changes.

2- It may increase with the influence of environmental factors. Eg:

Transferring the microorganism with decrease virulence to rich medium.

Decrease of the virulence

- The change in the virulence of a pathogenic microorganism induced by passage through another host species, This is the basis for the development of live vaccines.
- E.g., that of Bacille Calmette Guerin (BCG), a strain of *Mycobacterium bovis* that has been weakened by multiple (238- 13 year) subcultures on a bile- glycerine medium. The resulting bacterium is immunogenic , capable of eliciting antibody formation, but not virulent. Live attenuated organisms are used to produce the poliomyelitis vaccine.

Virulence can be reduced with;

1. Genetically missing some chromosomal or extrachromosomal genes.
2. Passages in unsuitable mediums.
- 3- Insensitive tissue culture and animal passages.
- 4 - Various physical (heat, radiation) and chemical (paint) agents.

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