Lecture (3)

●Secretion of Exotoxins from the Bacterium: -

Most bacteria secrete exotoxins across the cell membrane by the type II secretion pathway. Type II secretion is also called the general secretion pathway. Type II secretion involves the coordinate translation and secretion of a nascent polypeptide across the cell membrane. During the translation of the mRNA that encodes a type II-secreted protein, the nascent polypeptide encodes an N-terminal leader sequence that is targeted to and secreted across the cell membrane. After secretion across the cell membrane, the nascent protein folds into its native conformation and the leader sequence is cleaved by a periplasmic leader peptidase to yield a mature exotoxin. Some Gram-negative bacteria export the assembled exotoxin from the periplasm into the external environment via a complex export apparatus. While the heat-labile enterotoxin (LT) of *Escherichia coli* remains localized within the periplasmic space, *V. cholerae* and *Bordetella pertussis* assemble their respective exotoxins, cholera toxin and pertussis toxin, within the periplasm and then transport the mature exotoxin into the external environment.

●Specific Host Site Exotoxins: -

The second type of exotoxin is categorized on the basis of the site affected: neurotoxins (nerve tissue), enterotoxins (intestinal mucosa), and cytotoxins (general tissues). For example; neurotoxins (botulinum toxin and tetanus toxin), enterotoxins (cholera toxin, *E. coli* heatlabile toxins), and cytoxins (diphtheria toxin, Shiga toxin).

Neurotoxins usually are ingested as preformed toxins that affect the nervous system and indirectly cause enteric (pertaining to the small intestine) symptoms. Examples include staphylococcal enterotoxin B, *Bacillus cereus* emetic toxin [Greek *emetos,* vomiting], and botulinum toxin.

True enterotoxins [Greek *enter,* intestine] have a direct effect on the intestinal mucosa and elicit profuse fluid secretion. The classic enterotoxin, cholera toxin (choleragen), has been studied extensively.

Cytotoxins have a specific toxic action upon cells/tissues of special organs and are named according to the type of cell/tissue or organ for which they are specific. Examples include nephrotoxin (kidney), hepatotoxin (liver), and cardiotoxin (heart).

●Membrane-Disrupting Exotoxins: -

The third type of exotoxin lyses host cells by disrupting the integrity of the plasma membrane. There are two subtypes of membrane-disrupting exotoxins. The first, is a protein that binds to the cholesterol portion of the host cell plasma membrane, inserts itself into the membrane, and forms a channel (pore). This causes the cytoplasmic contents to leak out. Also, because the osmolality of the cytoplasm is higher than the extracellular fluid, this causes a sudden influx of water into the cell, causing it to swell and rupture. Two specific examples of this type of membrane-disrupting exotoxin are now presented.

Some pathogens produce membrane-disrupting toxins that kill phagocytic leukocytes. These are termed leukocidins [*leuko*cyte and Latin *caedere,* to kill]. Most leukocidins are produced by pneumonococci, streptococci, and staphylococci. Since the poreforming exotoxin produced by these bacteria destroys leukocytes, this in turn decreases host resistance. Other toxins, called hemolysins [*haima,* blood,

and Greek *lysis*, dissolution], also can be secreted by pathogenic bacteria. Many hemolysins probably form pores in the plasma membrane of erythrocytes through which hemoglobin and/or ions are released (the erythrocytes lyse or, more specifically, hemolyze). Streptolysin-O (SLO) is a hemolysin, produced by *Streptococcus pyogenes*, that is inactivated by O2 (hence the "O" in its name). SLO causes beta hemolysis of erythrocytes on agar plates incubated anaerobically. A complete zone of clearing around the bacterial colony growing on blood agar is called beta hemolysis, and a partial clearing of the blood is called alpha hemolysis. Streptolysin-S (SLS) is also produced by *S. pyogenes* but is insoluble and bound to the bacterial cell. It is O2 stable (hence the "S" in its name) and causes beta hemolysis on aerobically incubated blood-agar plates. SLO and SLS act as leukocidins and kill leukocytes. It should also be noted that hemolysins attack the plasma membranes of many cells, not just erythrocytes and leukocytes.

The second sub-type of membrane-disrupting toxins are the phospholipase enzymes. Phospholipases remove the charged head group from the lipid portion of the phospholipids in the host-cell plasma membrane. This destabilizes the membrane and the cell lyses and dies. One example of the pathogenesis caused by phospholipases is the disease gas gangrene. In this disease, the *Clostridium perfringens* α-toxin almost totally destroys the local population of white blood cells.

●Roles of Exotoxins in Disease: -

Bacterial exotoxins affect a human host three main ways:

(1) Ingestion of preformed exotoxin,

(2) Colonization of a mucosal surface followed by exotoxin production.

(3) Colonization of a wound or abscess followed by local exotoxin production. Each of these is now briefly discussed.

In the first example, the exotoxin is produced by bacteria growing in food. When food is consumed, the preformed exotoxin is also consumed. The classical example is staphylococcal food poisoning caused solely by the ingestion of preformed enterotoxin. Since the bacteria (*Staphylococcus aureus*) cannot colonize the gut, they pass through the body without producing any more exotoxin; thus, this type of bacterial disease is self-limiting.

In the second example, bacteria colonize a mucosal surface but do not invade underlying tissue or enter the bloodstream. The toxin either causes disease locally or enters the bloodstream and is distributed systemically where it can cause disease at distant sites. The classical example here is the disease cholera caused by *Vibrio cholerae*. Once the bacteria enter the body, they adhere to the intestinal mucosa where they are not invasive but secrete the cholera toxin, which is an AB exotoxin that catalyzes an ADP– ribosylation similar to that of diphtheria exotoxin. As a result, cholera toxin stimulates hypersecretion of water and chloride ions and the patient loses massive quantities of water.

The third example of exotoxins in disease pathogenesis occurs when bacteria grow in a wound or abscess. The exotoxin causes local tissue damage or kills phagocytes that enter the infected area. A disease of this type is gas gangrene in which the exotoxin (α-toxin) of *Clostridium perfringens* causes the tissue destruction in the wound.