Lecture (5)

● Superantigens: -

A particular class of bacterial toxins referred to as superantigens (enterotoxins, toxic shock syndrome toxins from Staphylococcus and Streptococcus) are characterized by their ability to bind both MHC class II molecules and T cell receptors. Unlike conventional antigens that are presented to the T cell receptor in complex with the MHC class II molecule, superantigens bind to the T cell receptors and MHC class II molecules outside the classical antigen-binding groove. This results in a massive antigen-independent proliferation of the targeted T lymphocytes, leading to the release of various cytokines and inflammatory factors.

●Ability to Produce Extracellular Toxins and Enzymes

Generally, disease from infection is noticeable only if tissue damage occurs. This damage may be from toxins, either **exotoxins** or **endotoxins**, or from inflammatory substances that cause host driven, immunologically mediated damage. The ability of organisms to produce exotoxins and extracellular enzymes is another major factor that contributes to the virulence and invasiveness of organisms. Toxins are poisonous substances produced by organisms that interact with host cells, disrupting normal metabolism and causing harm. Exotoxins are produced by both gram-negative and gram-positive bacteria and are secreted by the organism into the extracellular environment, or they are released on lysis of the organism.

Exotoxins can mediate direct spread of the microorganisms through the matrix of connective tissues and can cause cell and tissue damage. Some organisms produce soluble substances, such as proteases and hyaluronidases that liquefy the hyaluronic acid of the connective

tissue matrix, helping bacteria to spread in tissues, promoting the dissemination of infection. Endotoxins are a constituent, the lipopolysaccharide (LPS), of the outer cell membrane of gram-negative bacteria exclusively. Endotoxins, in contrast to exotoxins, do not have enzyme activity, are secreted in only very small amounts, do not have specificity in their activity on host cells, are not very potent, and are not destroyed by heating. Endotoxin is released in large amounts when the bacterial cell lyses.

●Exotoxins

Many bacterial exotoxins are highly characterized. Most are composed of two subunits: one is nontoxic and binds the toxin to the host cells and the other is toxic. The toxin gene is commonly encoded by phages, plasmids, or transposons. Only the organisms that carry the DNA coding for the toxin gene produce toxin. Isolates of *C. difficile,* for example, have to be tested for the presence of toxin genes, such as in the Case in Point. Diphtheria toxin inhibits protein synthesis and affects the heart, nerve tissue, and liver. Botulinum toxin is a neurotoxin that blocks nerve impulse transmission, causing flaccid paralysis, especially in infants. *Streptococcus pyogenes* and *S. aureus* both produce exfoliatin, which causes rash and massive skin peeling or exfoliation. Table 1 lists many bacterial exotoxins that are important in disease.

●Endotoxins

Endotoxins are composed of the LPS portion of the outer membrane on the cell wall of gram-negative bacteria. The cell wall of gramnegative microorganisms is composed of two layers—the inner peptidoglycan layer and an outer membrane. The LPS is contained in the outer membrane along with proteins and phospholipids. LPS contains three regions—an antigenic O–specific oligosaccharide, a core polysaccharide, and an inner lipid A (also called *endotoxin*). The lipid A portion of LPS is responsible for the toxic activity of endotoxin. LPS stimulates the release of proinflammatory cytokines, e.g., tumor necrosis factor and interleukin 1, chemokines and other inflammatory mediators that aid in mounting an innate immune response. These are the chemical mediators that produce the effects of endotoxin that consist of dramatic

changes in blood pressure, clotting, body temperature, circulating blood cells, metabolism, humoral immunity, cellular immunity, and resistance to infection. Endotoxin stimulates the fever centers in the hypothalamus, increasing body temperature within 1 hour after exposure. Endotoxin exposure also causes hypotension, producing severe hypotension within 30 minutes. Septic or endotoxic shock is a serious and potentially life-threatening problem. In contrast to shock caused by fluid loss, such as shock seen in severe bleeding, septic shock is unaffected by fluid administration. The endotoxin also initiates coagulation, which can result in intravascular coagulation. This process depletes clotting factors and activates fibrinolysis so that fibrin-split products accumulate in the blood. These fragments are anticoagulants and can cause serious bleeding. Another feature of patients with endotoxic shock is severe neutropenia, which can occur within minutes after exposure. It results from sequestration of neutrophils in capillaries of the lung and other organs. Leukocytosis follows neutropenia because neutrophils are released from the bone marrow.

Endotoxin also produces a wide variety of effects on the immune system. It stimulates proliferation of B lymphocytes in some animal species, activates macrophages, activates complement, and has an adjuvant effect with protein antigens. It also stimulates interferon production and causes changes in carbohydrates, lipids, iron, and sensitivity to epinephrine. A severe infection with gram-negative bacteria can lead to serious and often life-threatening situations.

TABLE 1 Examples of Exotoxins of Pathogenic Bacteria

Bacterium	Disease Caused in Humans	Toxins
Bacillus anthracis	Anthrax	Lethal, edema-producing toxins
Bordetella pertussis	Whooping cough	Lethal, dermonecrotizing toxin
Clostridium botulinum	Botulism	6 type-specific lethal neurotoxins[a]
Clostridium difficile	Antibiotic-associated diarrhea, pseudomembranous colitis	Toxin A, enterotoxin[a]
Clostridium novyi	Gas gangrene	Alpha, lethal,

		dermonecrotizing Beta, lethal, dermonecrotizing, hemolytic Gamma, lethal, dermonecrotizing, hemolytic Delta, hemolytic Epsilon, lethal, hemolytic Zeta, hemolytic
Clostridium perfringens	Gas gangrene, food poisoning, enteritis necroticans	Alpha, lethal, dermonecrotizing, hemolytica Beta, lethal Gamma, lethal Delta, lethal Epsilon, lethal, dermonecrotizing Iota, lethal, dermonecrotizing Theta, lethal, cardiotoxic, hemolytic Kappa, lethal, proteolytic Enterotoxin[a]
Clostridium septicum	Gas gangrene	Alpha, lethal, hemolytic, necrotizing
Clostridium sordellii	Gas gangrene	Lethal toxina Hemorrhagic toxin[a]
Clostridium tetani	Tetanus	Tetanospasmin, lethal, neurotoxic[a] Neurotoxin, nonspasmogenic Tetanolysin, lethal, cardiotoxic, hemolytic
Corynebacterium diphtheriae	Diphtheria	Diphtheria toxin, lethal, dermonecrotizing[a]
Escherichia coli	Diarrhea	Heat-labile enterotoxin[a] Heat-stable enterotoxin Shiga toxin
Pseudomonas aeruginosa	Pyogenic infections	Exotoxin A
Staphylococcus aureus	Pyogenic infections, enterotoxemia	Alpha, lethal, dermonecrotizing,

		hemolytic Beta, lethal, hemolytic Gamma, lethal, hemolytic Delta, hemolytic Exfoliating toxin[a] Enterotoxin[a]
Streptococcus pyogenes	Pyogenic infections, scarlet fever, rheumatic fever	Erythrogenic, nonlethal Streptolysin O, lethal, hemolytic, cardiotoxic Streptolysin S, lethal, hemolytic
Vibrio cholerae	Cholera	Cholera toxin, lethal, enterotoxic[a]
Salmonella Typhimurium	Enteritis	Enterotoxin? [a]
Shigella spp.	Dysentery	Enterotoxin[a]
Yersinia pestis	Plague	Murine toxin, cytotoxic pore-forming toxins[a]

[a]Toxins that produce harmful effects of infectious disease.