Host –Parasite Interaction

Parasitism is a type of relationship between two organisms- a parasite usually the smaller of the two and a host, upon which the parasite is physiologically dependent.

Parasite is defined as one organism lives in or on other organisms which is commonly harmed. The organisms that feeds on the cells and tissues of other organisms is called parasite and the second organism is called host which is commonly harmed.

Microbial Pathogenicity

Many microbial interactions are harmful to the host and cause disease. Disease is an impairment of the normal state of organisms or any of its components that inhibit the function of important activity. Infection refers to any situation in which a microorganism is established and growing in a host whether or not the host is harmed.

Pathogenicity or the ability to cause disease requires the attributes of transmissibility from one host or reservoir to a fresh host, survival in the new host, infectivity or the ability to destroy the new host defences and virulence, a variable that denotes the capacity of pathogen to harm the host.

Bacterial pathogens can be classified into major groups – primary and opportunistic pathogen.

Primary pathogens are capable of establishing infection and causing disease in previously healthy individual with intact immunological defences. On the contrary opportunistic pathogen rarely causes disease in individual with intact immunological defences. They are present in healthy individual and don't cause any disease. When the defences are impaired, these pathogens cause disease.

Pathogenesis or the ability of a microorganism to cause disease starts with exposure and adherence of the microorganism to host cell followed by invasion, colonization and growth resulting in damage to the host. Pathogenic microorganisms elicit host changes using several different strategies to established virulence, the relative ability of a pathogen to cause disease.

- ***Steps of pathogenesis:***

  1. ***Entry of the pathogen into the host:***

     A pathogen must usually gain access to host tissues and multiply before damage can be done, this require that the organism penetrate the skin, mucus membrane or intestinal epithelium.

  2. ***Specific adherence:***

     Most microbial infection begins at breaks or wounds in the skin or on the mucus membrane of the respiratory, digestive or genitor-urinary tract. Bacteria able to initiate infection adhere specifically to epithelial cell by different factors –

     - *Adherence factor-*

       Pathogenic bacteria may adhere to epithelial cell surface through protein-protein interaction. For e.g. *Neisseria gonorrhoeae*, the causative agent of gonorrhoea, adhere to urogenetial epithelium by a surface protein called 'Opa' the host cell binds specifically to Opa with a protein called 'CD66' found on the surface of human epithelial cell. Thus the bacteria interact with the target cell through a cell surface receptor – ligand pair.

Some bacteria adherence macromolecules are not covalently attached to the bacteria. These are usually polysaccharides synthesized and secreted by the bacteria like capsule, glycocalyx, slime layer etc. are involved in bacterial adherence. For e.g. *Streptococcus mutans* produce a polymer of glucose (glucan) that helps the bacteria to adhere to tooth surface and cause dental caries.

Pilli and fimbriae are bacterial surface structures that also function in the attachment process. For e.g. *Neisseria gonorrhoeae* play a key role in the attachment of the organism to urogenetial epithelium and fimbriated strains of *E. coli* are much more frequent cause of urinary tract infection, than strains lacking fimbriae.

3. Invasion:

Most pathogens penetrate the epithelium to initiate pathogenicity, a process called 'invasion'. Although penetration of the epithelial layer is not always essential to infection, the microorganisms may multiply on the epithelial surface, causing damage without penetration into the body. For e.g. *Vibrio cholerae*, the causative agent of cholera multiply on the epithelial layer of small intestine where it produces a toxin that causes loss of fluid from the epithelial cell and kill that cells.

Penetration to body surfaces may be achieved not only actively i.e. by the penetration mechanism of the pathogen itself but also passively by mechanism having nothing to do with the properties of the microorganism. Any mechanically caused cut or wound in the body surface may introduce pathogen directly into the underlying tissues.

Wound or burn represents one passive mechanism, for e.g. soldiers wounded may develop gas gangrene if the wound contaminated by *Clostridium perfringens*. Another mode of passive penetration is by arthropods. For e.g. *Borellia burgdorferi* cause relapsing fever in human when the pathogens are introduced through the bite of a tick.

Some pathogenic microorganisms are capable of penetrating the epithelial layer to which they have become attached by producing certain enzymes or toxins. For e.g. in bacillary dysentery *Shigella dysenteriae* penetrate into and kill the epithelial cell of the colon, then spreads to adjacent cell which are then killed. The result is the formation of lesions (damaged area) known as 'ulcers'.

4. Colonization:

If a pathogen gains access to tissue it may multiply a process called 'colonization'. Because the initial inoculums of a pathogen is rarely sufficient to cause damage. A pathogen must find appropriate nutrient and environmental condition in order to grow. For e.g. *Brucella abortus* grows very slowly in most tissues of infected cattle but grows very rapidly in the placenta. The placenta is the only tissue that contains high concentration of erythritol, a sugar i.e. readily metabolised by *Brucella abortus*. The erythritol enhances *Brucella abortus* growth causing abortion in cattle.

♣ ***Localised infection:***

In some infection that microorganisms may simply grow in the tissue in which it attaches itself, causing a localised infection. An e.g. of this type of infection is caused by *Staphylococcus aureus* where the characteristic lesions is abscesses i.e. a walled off cavity in the tissue containing

staphylococci numerous WBC and dead disintegrating tissue cells that collectively formed a pasty mass called 'pus'.

♣ ***Systematic infection:***

In other infection the organism may not remain localised by may spread through the tissues. An e.g. is anaerobic bacteria *Clostridium perfringens* which causes gas gangrene. Initiation of gas gangrene depends on the occurrence of anaerobic condition in the wound as occurs in the crushed tissues or clotted blood. As *Clostridium perfringens* begins to grow the bacteria secret toxins that kill some of the surrounding healthy tissue. This dead tissue becomes anaerobic and can support the growth of more bacteria which in turn secret more toxins that kill more tissue and allow the organism to spread further.

5. Mechanism of damage to host cell:

Virulence is the relative ability of an organism to cause disease. Virulence is due to the ability of a pathogen to cause damage through toxicity and invasiveness.

Toxicity is the ability of an organism to cause disease by means of a preformed toxin that inhibit host cell function or of kill host cell. For e.g. the disease tetanus is caused by *Clostridium tetani* through a potent (highly active) exotoxin. The cells of *Clostridium tetani* rarely leave the wound where it was first deposited. Yet the bacteria are able to bring about the disease because it produces tetanus toxin that move to distant part of the body and initiates irreversible muscle contraction and death of the host.

Invasiveness is the ability of an organism to grow in the host tissue in such large number that the pathogen inhibits host function. A microorganism may still be able to produce disease through invasiveness even if it produces number of toxins. For e.g. capsulated strains of *Streptococcus pneumoniae* are able to cause extensive host damage because they are highly invasive. They grow in lungs in enormous number where it initiates host responses that lead to pneumonia.

Toxigenicity

Toxins are defined as a microbial substance i.e. able to induce host damage. There are two types of toxin – 'exotoxin' and 'endotoxin'.

Exotoxin:

They are protein in nature, released extracellularly as the organisms grow. The toxin may travel from a locus of infection to distant part of the body and cause damage. Some exotoxins have extraordinarily high potency (activity) with only minute amount being needed to kill animals.

Exotoxins have generally A-B type structure that means there are no subunits. The A subunit is responsible for toxic activity and the B subunit is responsible for binding of the toxin with the specific cell surface receptor. The two subunits are joined by disulfide bonds. Some exotoxins having an AB type structures are diphtheria toxin, cholera toxin, botulinum toxin etc.

Exotoxins are often divided into various categories based on the site of damage that they cause or the kind of cells that are affected. For e.g. botulinum and tetanus toxin affects nerve tissue and are termed as 'neurotoxin'. Diphtheria toxin kills several kinds of cells and termed as 'cytotoxins'. Cholera toxin affects the gastro-intestinal tract and termed as 'enterotoxin'. Some cytotoxins may kill leukocytes and are

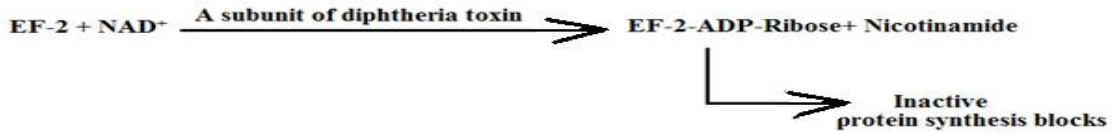
known as 'leukocidins'. Some may cause lysis of red blood cells and therefore are termed as 'haemolysin'.

- ***Cytotoxin:***

The exotoxins that affect various types of cells are called 'cytotoxin'. They may cause damage either by inhibiting eukaryotic protein synthesis or may damage host cytoplasmic membrane causing cell lysis and death.

Diphtheria toxin is an A-B type as well as a cytotoxin that inhibit eukaryotic protein synthesis. The bacteria *Corynebacterium diphtheriae* secret the toxin only when it is lysogenised with β- bacteriophage in its genome. It is an example of lysogenic conversion. The toxin is a large protein released from the bacteria in an inactive form. The B chain attaches to specific receptor on the host cell membrane and the entire molecule taken into the cell by endocytosis. Cells that lack the appropriate receptor do not take up the toxin and are affected by it. This receptor specificity explains why some tissue of the body are not affected in diphtheria while others such as heart, kidney are damaged.

Once the toxin molecule is inside the cell, the A chain separates from the B chain and becomes an active enzymes. The A subunit then catalyses the transfer of an ADP-ribose unit from NAD^+ to EF-2. EF-2 is required during the elongation phase of eukaryotic protein synthesis. ADP ribosylated EF-2 becomes inactive, this blocks eukaryotic protein synthesis and the cell dies.



Various pathogens produce proteins that damage the host cytoplasmic membrane causing cell lysis and death. They are called 'cytolytic toxin' and also one type of cytotoxin.

Some cytolytic toxins involve the lysis of RBC. They are called haemolysin.

Some may attach the phospholipids of the host cytoplasmic membrane. Because the phospholipid lecithin (phosphatidyl choline) is often used as a substrate. These toxins are called lecithinase or phospholipase. An e.g. is α-toxin of *Clostridium perfringens*, a lecithinase that dissolves membrane lipids resulting in cell lysis.

Some cytolytic toxins for e.g. Streptolycin-O produced by streptococci affects the sterols of the host cytoplasmic membrane.

Leukocidins lyses WBC and may decrease host resistance. Staphylococcal α-toxin kills nucleated cells and lyses erythrocytes. The toxin subunits first bind to the lipid bilayer. The subunits then oligomerised into heptamers. Following oligomerization each heptamar undergoes conformational changes to produce a membrane spanning pore, releasing the contents of the cell and allowing influx of extracellular material, disrupting cell function and causing death.

- ***Enterotoxin:***

Enterotoxins are exotoxins that affect the gastro intestinal tract for e.g. cholera toxin.

Cholera toxin is an A-B type toxin consists of one A subunit and 5 B subunits. The B subunit is responsible for binding of the toxin irreversibly to specific ganglioside receptor (GM1) on the epithelial cells of small intestine. The A subunit is responsible for toxic activity. As the B subunit binds to specific cell surface receptor, the disulfide bond that held the two subunits break and the A subunit enters the cell. Inside the cell A subunit catalyses transfer of ADP-ribose unit from NAD^+ to a G protein.

G protein is a regulatory protein and exists in two forms – an active GTP binding form and an inactive GTP binding form. ADP ribosylated G protein normally binds to GTP but the bound GTP never hydrolyses to GDP. So the G protein is always in the active state. In its active form G protein activates the enzyme adenylate cyclase which catalyses the production of cAMP from ATP. cAMP is a mediator of different regulatory system in cell including ion balance. Under normal condition G protein switches back and forth from active state to regulate adenylate cyclase activity and fluid secretion. In presence of cholera toxin, the G protein becomes permanently active, thus causing maximum cAMP production. The increased cAMP level induce secretion of Cl^- and HCO_3^- and inhibition of influx of Na^+ ions, resulting in massive water and electrolyte loss from intestinal lumen.

- ***Neurotoxin:***

The exotoxins that affect nervous systems are called 'neurotoxin'. For e.g. Botulinum toxin.

Botulinum toxin is an AB type toxin. The B subunit attaches to specific receptor on motor nerve endings and the A subunit is responsible for toxic activity. The circulatory neurotoxin attaches to motor nerves, blocking transmission of nerve signals to the muscles and thereby causing paralysis. Normally nerve signals are transmitted by a type of chemical known as 'neurotransmitter' present in the nerve in tiny vesicle. The neurotoxin probably acts by preventing vesicles from attaching to the cytoplasmic membrane of the nerve cell; thereby preventing the release of the neurotransmitter by exocytosis.

Botulinum toxin binds to presynaptic membrane of the neuromuscular junction, blocking the release of acetyl choline. Transmission of the nerve impulse to the muscle requires acetyl choline interaction with a muscle receptor and botulinum toxin prevents the muscle from receiving the excitatory signal. This prevents muscle contraction and leads to flaccid paralysis.

- ***Super antigen exotoxin:***

Super antigens are the antigens that provoke drastic immune response. Certain exotoxins function as super antigen and hence called 'super antigen exotoxin'. They act indirectly on the host cell, using a novel immune mechanism to cause expensive host tissue damage. They directly stimulate large number of immune response cells resulting in extensive inflammatory reaction. Several diseases can be attributed to super antigen exotoxin. Staphylococcal enterotoxins

are good example of super antigen exotoxins that cause staphylococcal food poisoning (caused by *Staphylococcus aureus*) characterised by fever, vomiting and diarrhoea. *Staphylococcus aureus* also produces super antigen exotoxin responsible for toxic shock syndrome.

Endotoxin:

Gram negative bacteria produce lipopolysaccharide as part of the outer membrane of their cell wall which under various conditions becomes toxic. These are called 'endotoxin'. Endotoxins are studied in different Gram negative bacteria such as *Salmonella*, *Shigella* etc. Lipopolysaccharides consist of lipid A, core polysaccharide and O-antigen. Both the lipids and polysaccharide components are necessary for in vivo toxic activity.

Endotoxins cause a variety of physiological effect –

1. ***Pyrogenicity:***

   This is the ability to cause changes in body temperature. In human endotoxin cause an increase in temperature i.e. a fever response. The pyrogenic effect is indirect; the active chemical agent that causes the temperature changes is called endogenous pyrogens i.e. released from the blood leukocytes under the influence of endotoxins. These pyrogens affect the hypothalamus of the brain which regulates the body temperature.

2. ***Blood changes:***

   When administered to experimental animals endotoxin causes increase in the number of leukocytes in the blood. Endotoxin also damage blood platelets or thrombocytes which release factor that may cause blood to clot within blood vessels (Intravascular clotting). Moreover endotoxins cause an increase in the permeability of blood capillaries, causing them to leak the fluid portion of the blood and sometimes even the whole blood (haemorrhage); these effects can cause serious changes in circulation and blood pressure.

3. ***Shock:***

   When Gram negative bacteria are present in the blood in large number or when endotoxin is injected intravenously, severe shock may occur as evidenced by a decreased blood pressure, rapid pulse, decreased respiration and sometime unconsciousness. A high dose can result in circulatory collapse and death.

♣ ***Difference between endotoxin and exotoxin:***

Properties	Endotoxin	Exotoxin
1. Chemical nature	Lipopolysaccharides, present endogenously as the integral part of outer membrane of cell wall of Gram negative bacteria.	Protein, secreted extracellularly by certain bacteria.
2. Producer organism	Only Gram negative bacteria.	Both Gram positive and Gram negative bacteria.
3. Heat stability	Generally heat stable.	Generally heat labile.

4. Mode of action	Non- specific.	Highly specific, affects only particular tissues.
5. Toxicity	Weakly toxic.	Often highly toxic.
6. Immunogenicity	Poorly immunogenic.	Highly immunogenic.
7. Fever potential	Always pyrogenic.	May be pyrogenic or not.
8. Toxoid available	Not available.	Available.

❖ ***Virulent factor:***

A number of factors produced by pathogenic bacteria may contribute to virulence, although they are not toxins. They may increase virulence by helping the spread of the pathogen through tissues by enhancing tissue damage, to protect the pathogen against host defences by allowing the pathogen to compete more efficiently with the host for an essential nutrient etc. Some are as follows –

i. ***Hyaluronidase:***

The enzyme is produced by *Clostridium perfringens*. It hydrolyses hyaluronic acid, an essential tissue connecting material, thus helps the pathogen to spread through tissues.

ii. ***Streptokinase:***

It is produced by β-haemolytic streptococci. It converse blood plasminogen to plasmin, a protease that dissolve the fibrin of blood clots. Thus streptococci may spread through tissue by dissolving blood clots that binds to wall off areas of tissues damaged by infection.

iii. ***Coagulase:***

It is produced by *Staphylococcus aureus*. This converts soluble fibrinogen to insoluble fibrin, thus stimulates the clotting process. The fibrin coats the cell wall of the cocci and thus preventing their phagocytosis.

iv. ***Collaginase:***

It is produced by *Clostridium perfringens*. It degrades tissue supporting collagen network, enabling these organisms to spread through the body.

v. ***Capsules:***

Many bacterial pathogens avoid phagocytosis by producing an extracellular capsule. It is produced by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*. Polysaccharide capsules reduce the efficiency of host defences in a number of ways. The hydrophilic nature of the capsule may prevent engulfment by phagocytic cells, a process that occurs more readily at hydrophobic surfaces. Capsules also prevent efficient opsonisation of the bacterium by compliment of specific antibody, events that promote interaction with phagocytic cells.

vi. ***Streptococcal M protein:***

The M protein present on the surface of *Streptococcus pyogenes*. It functions in a similar manner to prevent compliment deposition at the bacterial surface. The M protein binds both fibrinogen and fibrin deposition of these materials on the streptococcal surface prevents the access of compliments.

vii. ***Meningococcal factor H binding protein:***

The compliment system is a powerful diffuse mechanism against bacterial pathogens but can potentially damage host cell as well. The host must therefore protect itself against the damaging activities of compliment. The serum glycoprotein factor H is a negative regulator of the compliment system that protects host cells by binding to glucosaminoglycans present on

the surface of host but not to bacterial cells. It can down regulate the activity of compliment and thus protect the host cell. *Neisseria meningitidis* express a factor H binding protein on its surface which recruits this compliment regulator, thus affording similar protection to the bacterial pathogen.

viii. ***Immunoglobulin-A proteases:***

Several species of pathogenic bacteria that cause disease on mucosal surface produce a protease that specifically cleaves immunoglobulin A (IgA) the principal antibody type produced at these sites.

ix. ***Resistance to killing by phagocytic cells:***

Some pathogens not only survive within phagocytic cells but may actually multiply intracellularly. Different organs use different strategies for survival. *Mycobacterium tuberculosis* resist intracellular killing by preventing phagosome-lysosome fusion. Production of catalase by *Streptococcus aureus* and *Neisseria gonorrhoeae* protect these organisms from toxic oxygen radicals. The smooth lipopolysaccharide of many bacterial pathogens contribute to their resistance to the effects of bacterial cationic peptides present in the phagolysosome.

x. ***H_2O_2 and NH_3:***

Mycoplasma and *Ureaplasma* adhere firmly to the epithelial cells of respiratory and urogenital tract where they secrete toxic by-products like NH_3 and H_2O_2 which cause damage to epithelial cells. *Proteus sp.* that cause urinary tract infections produce urease that breakdown urea in the urine and the release of NH3 may contribute to the pathology. The urease produced by *Helicobacter pylori* is similarly involved in the virulence of the organism.

xi. ***Microbial iron chelators:***

Aerobic or aerotolerant microorganisms continually faced with the difficult of obtaining enough iron for growth. Most of the iron i.e. available for aerobic or aerotolerant organisms is present in the Fe^{+3} form which is extremely insoluble. Aerobic organisms evolve Fe^{+3} binding compounds called 'siderophores' which reduce Fe^{+3} to Fe^{+2} in order to make utilization by the microbial cell. For e.g. enterochelin produced by *E. coli*. Some pathogenic bacteria don't produce siderophores themselves but are able to obtain iron from siderophores produced by other species or use host molecules such as noradrenalin which has siderophore like activity. Some other pathogenic bacteria have specific receptors for transferrin or lactoferrin (host siderophores or Fe binding protein) on their surfaces and are able to bind these proteins and remove the bound Fe directly from these host proteins.

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