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The adhesion and invasion of bacteria on the host cells by producing surface secreting protein

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Abstract
Adhesion and invasion of pathogenic bacteria represent the important initial step of infection. Pathogen utilize surface located adhesion and invasion for specific interaction with host cell receptors. The three-dimensional structure of several adhesion and invasion show that many are elongated molecules containing domains commonly found in eukaryotic proteins. Similar folds are employed repeatedly to target different receptors. The successful establishment of infection by bacterial pathogens requires adhesion to host cells colonization of tissue and cellular invasion followed by intracellular multiplication and dissemination to other tissue.

Keywords: Bacteria, pathogens, adhesion, invasion, proteins and enzymes

Introduction

The bacteria adhere to host cells and secrete product or structural products complementary to host. Hence, bacteria are found adhered to host's epithelial cells due to direct adhesion to host cells or binding to secretory products that coat host cells or bacteria. Besides, bacteria also adhere to phagocyte cells of the host and trigger immune system and may or may not be phagocytosed.

A wide variety of surfaces are available for adherence of microbial cells such as polymers of extracellular matrix as collagen, proteoglycans bones, endothelial cells. Bacteria possess several surface molecules and structures which facilitate to adhere these surfaces. Moreover, a particular bacterium can adhere to only specific surface. It means that there exists tissue-tropism of bacteria. Some of the bacteria e.g. *Neisseria meningitidis* and *Salmonella* spp. encounter many types of surfaces to cause infection. But at least two facts of bacterial adhesion are very important, the physicochemical forces facilitating invasion and the specificity of process to guide specific surfaces. Bacteria and host cells interact and affect the activity of one another by the secretion of toxins low molecular weight metabolites, hormones, enzymes and antibacterial peptides. The behaviour of eukaryotic cells is affected by LPS, peptidoglycan and membrane protein on outer wall.

Bacterial Adhesion

1. Forces in Adhesion

There are different types of forces which operate between bacteria and host cell surface before adhesion of bacterial cells. Van der Waals and electrostatic forces apply when microbial cells are at a distance of tens of nanometres. Bacterial cell and host cell surface are mutually attracted due to Van der Waals forces. The electrostatic forces result in repulsion of these two objects. Hydrophobic interactions result in adhesion of bacterial and host cells and the former is brought closer to host cell surface for other adhesive interactions such as hydrogen bonding, cation bridging and specific bonding of a molecule ligand on the bacterial surface to a receptor molecule present on host surface. Adhesin molecules present on bacterial surface are responsible for adhesion.

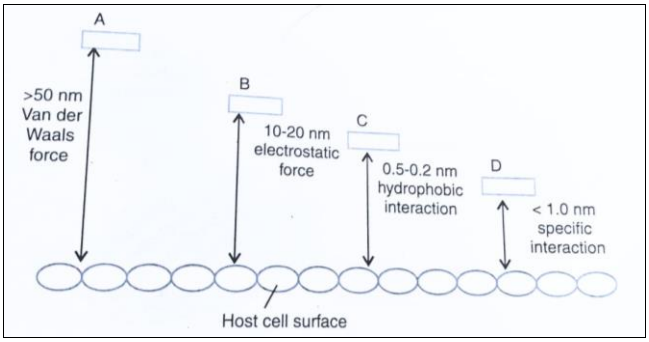

Fig 1: Force operating between bacteria and host surface

2. Structure in Adhesion

Bacteria possess several structures which help in adhesion of cells for example fimbriae pili, fibrils, flagella, capsule and S-layer. All these structures consist of adhesins. Capsule components of certain bacteria e.g. *Streptococcus sp., Staphylococcus sp., Klebsiella sp., Neisseria sp.* and *Haemophilus sp.* mediate adhesion to host cell surface. S - layer consists of glycoprotein and self-assembling units external to cell wall which also help in adhesion. Fimbriae are present on cell surface and cause bacterial adhesion.

The epithelial surface secretes antimicrobial compounds e.g. lysozyme and antibacterial peptides. The epithelium of respiratory tract is coated with mucin in which bacteria are trapped, brought to back of pharynx by ciliary action. Also, several antimicrobial compounds are found in mucin e.g. lysozyme, lactoferrin, secretory Ig A, superoxide radicals and antibacterial peptides. The urinary tract and oral cavity are always flushed by secretions of respective tissues. Even then epithelium is colonised by bacteria.

Using broad-spectrum antibiotics, normal microflora is disturbed, and undesirable microorganisms may be present such as *Candida albicans*, *Clostridium difficile* and *Pseudomonads* which can infect the organs. It seems that normal microflora of human exerts protective effect.

Adhesin is located at the tip or along the whole length of fimbriae. Fimbriae are widely distributed among the gram-negative bacteria such as *Bordetella sp., Salmonella sp., Neisseria sp., Pseudomonas sp., Yersinia sp.* etc. Fimbriae have been classified into the five types:

Type 1 -rigid fimbriae that exhibit mannose-sensitive haemagglutination e.g. *E. coli*. Type 2- not induce haemagglutination e.g. *Actinomyces naeslundii*, Type 3 - flexible and mannose resistant fimbriae they are common among the Enterobacteriaceae e.g. *Klebsiella pneumoniae*, Type 4- they consist of N-methyl-phenylalanine in the amino terminus region of the major subunits e.g. *Pseudomonas aeruginosa*, and Type 5-thinner than type one mannose-sensitive and a few in number.

3. Enzymes in Adhesins

The different type of molecule presents on bacterial cell surface act as adhesins and facilitate the attaching bacteria to host cell surface. One of the most extensively explored adhesion is the glycoprotein. Glycoproteins are present at the end of pili capsule of gram-negative bacteria, etc. Examples of bacteria comprising of lectins are E *coli*, N acetyl D galactosamine N-acetylmuramic acid and N-acetyl-D-glucosamine, *S. saprophyticus*, N-acetylglucosamine. In Gram-negative bacteria lipoteichoic acid act as an important adhesin. A glycoprotein fibronectin produced by many epithelial cells and other host cells act as receptor for lipoteichoic acid.

S. aureus produces a surface protein 210 KDa which acts as adhesin and mediates the adhesion to fibronectin. The bacterium also attaches to the other host proteins e.g. fibrinogen and laminin. A proline-rich protein of *Mycoplasma* sp. also acts as adhesin. Carbohydrates present on bacterial cell surfaces act as adhesins in certain bacteria. Eexample, *P. aeruginosa* secretes an exopolysaccharide alginate that acts as adhesin for attachment to tracheal cells and mucin and binds to both.

Lipopolysaccharide LPS of gram-negative bacteria play an important role in adhesion. Example, LPS of *C. jujeni, E. coli, P. aeruginosa, S. typhi, S. flexneri* etc. mediate the bacterium to attach to host's epithelial cells.

Bacterial enzymes e.g. glyceraldehyde 3-phosphate-dehydrogenase of *Strep. Pyogenes*, cell surface urease of *H. pylori*, glucosyl transferase of cell surface of mutant *streptococci h*ave been found to function as adhesins in attaching to epithelial cells of various tissues.

Bacterial Invasion

The mechanism that bacteria use for infection of host cell. Bacteria have evolved several invasive mechanisms. Most of them involve the manipulation of normal host cell cytoskeletal components such actin and tubulin resulting in the investigation of host cell membrane to enclose the bacterium within the vacuole. This occurs by interfering the inhibition of signal transduction or both.

1. Mechanism of Invasion

Bacterial invasion of host cells is broadly classified into the three groups based on involvement of microfilament or microtubule of host cell The type of host cells to be invaded also govern the invasion process.

1.1. Invasion on Epithelial Cell

The outer integument of our body is constituted by the epithelial cells. A varying population of microbes contributing the normal microflora colonises the epithelial interface. Thus, epithelium acts as the first physical barrier for commensal microorganisms. Many bacteria enter epithelial cells of the host by inducing the rearrangement of microfilament of the cytoskeleton.

Y. enterocolitica Integrin adhere to an epithelial cell. Adhesion is mediated by many adhesin between the Ail protein and Yad A protein. Close contact between bacterium and host cell is made at any point on the bacterium-host cell interface a process described as zippering. This induces the uptake of the organism into an endocytic vacuole.

The bacteria sink into the membrane of the epithelial cell. The host cells show a normal appearance within a few minutes of entry.

Binding of invasion zippering induces the uptake of bacterium. Clustering of integrins induces tyrosine kinase activity which is required for invasion. Cytochalasin inhibits endocytosis employing the involvement of actin microfilaments. During early stages of in-eternalization, clathrin lattices are soon formed beneath the bacteria. The polymerized actin and other proteins filamin and talin surround the vacuole. The internalized bacteria survive inside the vacuole but not reproduce.

Yersinia sp., Salmonella sp. invade the epithelial cells after adhesion to microvilli within one minute of contact, microvilli form pseudopods extending from cell surface of host epithelium, engulf bacteria and internalise within a vacuole. Mannose-specific type one fimbriae mediate the adhesion of *Salmonella* sp. to epithelial cells of intestine. After invasion, intracellular level of Ca ion increases which polymerises actin synthesis and inhibits bacterial invasion. Fimbriae-mediated adhesion of *Salmonella sp.* takes place.

Besides, cytoskeletal proteins actin, talin, tubulin, tropomyosin and ezrin accumulate in host cell at the site of bacterial adhesion. Several proteins of host cell membrane form aggregates in the vicinity of bacterial attachment. Consequently, bacterium is taken up by micropinocytosis a process which involves intake of large quantity of extracellular fluid. Thus, bacterium resides on a large fluid filled vacuole called spacious phagosome surrounded by polymerised actin, talin and actinin

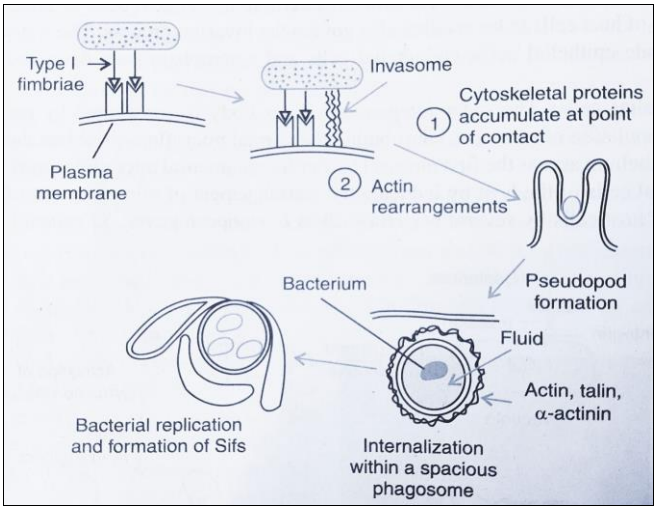

Fig 2: Invasion of epithelial cell by *Salmonella* sp.

1.2. Invasion of Non-Epithelial Cells

There are several pathogenic bacteria which enter at a site of host cell and spread throughout the body, for example *H. Influenzae, N. Gonorrhoea, S. dysenteries, S. pneumoniae,*

S. typhi, etc. They enter the blood stream and cross the cellular barrier the endothelium. Invasion takes place by one of the four main routes:
1.invasion followed by intracellular persistence without multiplication e.g. *S. Aureus, P. Aeruginosa* 2. invasion followed by intracellular replication *Rickettsia rickettsia* 3. traversed without cell disruption spirochaetes. 4. invasion within phagocytes *Listeria monocytogenes*.
E. coli causes diarrhoea, urinary tract Infection and neonatal meningitis. It is having been found that an outer membrane protein Omp A of the bacterium play a central role in invading the host cells. Bacterial Omp A protein mediates binding of bacteria to the receptors N-acetylglucosamine, B1-4-N-acetylglucosamine epitope present on BMEC brain microvascular endothelial cells. The polymers of ß1-4-linked N-acetylglucosamine prevent the entry of *E. coli* into the cerebrospinal fluid of neonatal rats. Hence, meningitis caused by it can be controlled by using receptor analogue

1.3. Invasion of Macrophages

Macrophages are a part of our immune system. They engulf antibody or complement-coated opsonised bacteria, internalise is mediated by in vacuole and kill them. Adhesion interaction between Fe region of antibodies and Fer receptors on macrophage surface. Binding causes internalisation of bacteria within a vacuole. Then it fuses with lysosome to form phagosome inside which bacterium is killed by enzymes, antimicrobial peptides, reactive oxygen species and low pH.

2. Consequences of Invasion

2.1. Effect of Host Cells

It is a difficult task to describe all the changes occurring in host cells due to bacterial invasion. Bacteria affect the host cells in many ways finally resulting in death. After invasion several cells respond by secreting cytokines which activate the immune system. Over production of cytokines may adversely affect the host cells e.g. *S. dysenteries*. The diarrhoeal response to infection is mediated by prostaglandin which is an important regulator for secretion of gastro-intestinal fluid by inducing Cl secretion from mucosa. Infection by enterobacteria of intestinal epithelial cells results in secretion of prostaglandins.

2.2. Effect on Bacterial Cell

The bacteria have several options after invading the host cells. They may live within the vacuole of host cell e.g. *M. tuberculosis, S. typhimurium, Brucella sp., Burkhulderia cepacian*, within the cytoplasm e.g. *Shigella spp., Rickettsia spp. Listeria monocytogenes* or may exit the cell and live extracellular life e.g. *Yersinia* spp.
Irrespective of above option, the bacteria adapt the new environmental conditions by expressing gene products that help their survival in new habitats. The bacterial regulatory system responds to changes of environmental factors e.g. pH, osmolarity and concentration of O_2, CO_2 micro and macro nutrients and antibacterial substances.

2.3. Survival of Bacteria

Once the bacterium has invaded the epithelial cell, it may proliferate within the cell and come out of cell or infect deeper tissues and spread the outer sites. Thus, the bacterium leads two types of lifestyles: extracellular and intracellular lifestyles.
If the bacteria remain extracellular, they face secretions of blood or tissues such as complements. antibodies, antimicrobial molecules discharge by phagocytes and phagocytic cells. Bacteria have evolved various ways to deal with these antimicrobial substances and phagocytic cells through production of toxins.
There are many bacteria which lead intracellular lifestyle surviving inside the vacuole, phagolysosome or cytoplasm of infected host cells.

- **Survival in Phagosome**

It may be exemplified by *Coxiella brunette* causing Q fever. Its main habitat is macrophage inside which it grows and multiplies. It exists in two phases: I and II. Phase I bacteria have a smooth form of lipopolysaccharide and are highly virulent, whereas phase II bacteria have a rough lipopolysaccharide and have reduced virulence.
After adhesion, phase I bacteria bind to a leukocyte, response integrin a membrane protein and integrin-associated protein. The bacterium is internalised by microfilament-dependent process. Then phagosome and lysosome get fused to form apparent normal phagolysosome-containing membrane proton ATPase and lysosomal enzymes. The infected host cell is capable of asymmetric division resulting in two daughter cells, one containing the vacuole inside which bacterium is present and the other parasite-free cell. The vacuole containing cell is broken liberating the bacterium, whereas the other cell may be invaded by bacterium repeating the similar cycle.

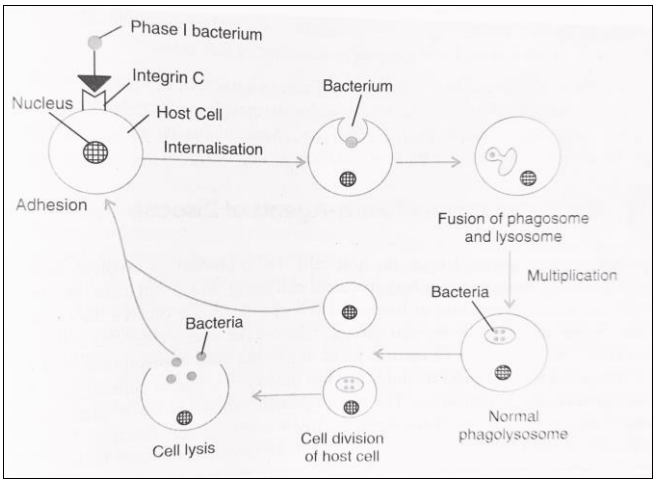

Fig 3: Life cycle of *Coxiella* sp.

- **Survival in Vacuoles**

Legionella pneumophila causing legionnaire's disease invades the macrophages and gets internalised by coiled phagocytosis. After 15 minutes of internalisation, phagosome is surrounded by smooth vesicles and after one hour by mitochondria. The phagosome does not fuse with lysosome. Hence, it lacks endosomal receptor transferrin and endosomal lysosomal markers. Phagosome-lysosomal fusion is prevented by the polycationic protein of the bacterium. After 4 to 8 hours of internalisation, the phagosome is surrounded by ribosome and ribose-containing vesicles. Bacterium multiplies exponentially with the doubling time of two hours using bacterial cell organelles resulting in cell lysis.

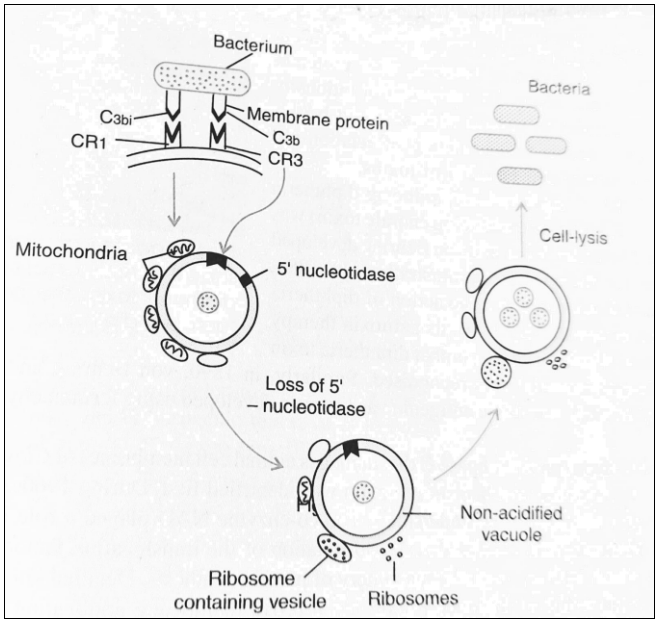

Fig 4: Multiplication of *Legionella* sp. Inside macrophage

- **Survival in Cytoplasm**

There are several bacteria which escape from vacuole after invading the host cell and remain within the cytoplasm, for example *L. monocytiogenes, Shigella sp., S. aureus, Streptococci sp., Rickettsia sp., Haemophilus sp.* of these only *Rickettsia* spp. are the obligate intracellular parasite.

Conclusion

Bacteria live in complex environments that require rapid responses to changing condition as well as continued adaption to new niches and hosts. Genome damage and resulting instability due to exposure to DNA damaging agents such as chemical mutagenesis and endogenous metabolic by products is generally considered a threat to bacterial survival. Bacteria have harnessed genome instability as an important element in regulating their dynamic lifestyle by controlling gene expression in response to various stress and stimuli. Genome instability is an important part of generation of genetic diversity especially by horizontal gene transfer and represent an important component of bacterial adaption and evolution.

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