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# Phenomenon of microbial pathogenicity as a function of bio-molecules

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## Abstract

The bacterial pathogenicity phenomenon is the poly-functional biological potency of germs that are realized by factors (determinants) of pathogenicity (PF) in multi-cellular organism.

Biological functions are responsible for bacterial pathogenicity in a multi-cellular host organism: the adhesive function, the function of invasion and penetration into the cell, the function of evasion of host defense, and the damage function. Factors of pathogenicity are representative bio-molecules possessed different functional activity. The ligand - receptor interaction of bacterial PF and receptors on eukaryotic cells is the basis of specific lesions caused by the pathogen.

**Keywords:** Bacterial Pathogenicity; Biological Function; Pathogenicity Islands; Infectious Diseases; Prokaryotic and Eukaryotic Organisms

## 1. Introduction

For a long time, the prevailing approach to the study of this phenomenon was focusing on identification of specific antigenic determinants in bacterial pathogens [1].

Unlike antigenic properties and metabolic peculiarities, the study of biological functions of germs opens an opportunity to explain the development of the infectious process from the point of view of the interaction of prokaryotic and eukaryotic organisms.

Systematic analysis of experimental and theoretical data obtained for the last decades, furthered accumulation the similar functionally active bio-molecules in separate groups which became the foundation of the modern understanding of bacterial pathogenicity [2].

## 2. Adhesive Function

It is known that the first step of interaction bacterial pathogen and cells of multi-cellular host organism starts from adhesive process. Many pathogens possess the special morphological structures that are located on the cell surface and are called *fimbria* or *common pili* [3]. These organelles are responsible for adhesion of pathogen to the host tissue cells. Despite their diversity in structure and biogenesis, pili/fimbriaes typically consist of a long fiber formed by homopolymerised subunits or pilins, and accessory pilins that often function as adhesions [4 some bacteria can produce nonpilus adhesive structures that mediate specific adherence to host tissues. The majority of nonpilus adhesions are proteins, but other structures such as lipopolysaccharides (LPS) and lipoteichoic acids also have adhesive function [5], Table 1.

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**Table 1** Components responsible for adhesive function

| Pathogen | Morphological structure | Somatic components |
|---|---|---|
| Gram – negative bacteria spp      Fimbriae/pili | Fimbriae/pili | Lipopolysaccharide (LPS) |
| Staphylococcus spp | | Lipoteichoic acids (LTA) |
| Streptococcus spp | | Protein M (?) |
| Lactobacillus spp | | Protein (?) |
| Micrococcus spp | | Protein (?) |

Among the adhesive macromolecules, some show high affinity to the process of physicchemical binding with eukaryotic cells. The ligand-receptor interaction of bacterial adhesions and the host cell surface demonstrates a high degree of specificity. For example, certain pathogenic bacteria infect only certain species of animals, e.g. Enteropathogenic *E. coli* K-88 infections are limited to pigs; *E. coli* K-99 strain infects calves. Other pathogens such as *Neisseria sp* and *E. coli* CFA I and CFA II infect humans; Group A streptococcal infections occur only in humans [6] [7] .

Biological features of some spore pathogens are belonging to *Bacillus* and *Clostridium* family showed that these bacteria have reduced adhesive function or not at all. Vegetable cells generated by spores that infected host organism immediately start production of extracellular toxin responsible for damaging function [6].

After adherence to a cell surface, microorganisms begin to reproduce intensively and increase their population while colonizing parts of the host tissue. Besides the very important role in colonization of the host tissue, some adhesions are also involved in cell aggregation, biofilm formation, DNA uptake, and phage transduction and gliding motility [40].

From point of view of evolutionary process, the appearance of microorganisms that could interact with living cells of multi-cellular tissues can be considered as a first step in the establishment of a new ecological space. Microbial cells that possessed such adhesive properties in relation to animal or plant tissues became commensals and potential pathogens. Natural selection completed formation of the new species and contributed to the promotion of the specificity of adhesive function. The adhesive function lead to extend microbial population in multi-cellular environment and it means that it was a new property allowing new germ species to broaden their habitat [7].

## 3. Function of Invasion and Cell Penetration

Another function that was responsible to spread bacterial pathogens in multi-cellular media was the ability to penetrate intercellular space or invasive capacity. Some extracellular bacteria can employ the enzymes that their saprophyte predecessors used to degrade organic remains in water and soil. For example, enzymes such as hyaluronidase, lecithinase, proteases and some glycopeptidases cellular media was the ability to penetrate intercellular space or invasive capacity. Some extracellular bacteria can employ the enzymes that their saprophyte predecessors used to degrade organic remains in water and soil. For example, enzymes such as hyaluronidase, lecithinase, proteases and some glycopeptidases which produced by *Clostridium* pathogens were able to split intercellular concreted compounds and invade the tissue [2] [10].

At the entry site, activated signaling pathways regulated the fate of the invading microorganism. Bacteria may then replicate in either cytoplasmic or vacuolar niches [10]. Vacuoles are acting membrane-bounded compartments have unique specificity to a given bacteria in its composition and behavior. Under the action of intracellular pathogens their vacuoles transform into a favorable niche where they undermine the anti-bacterial host defense mechanisms. This is mainly achieved through the action of bacterial proteins (*effectors*) that are translocated out of the vacuoles into the host cytoplasm [12] [13].

The invasive and penetrative function is another property of the pathogenicity complex, in addition to selective adhesion to host eukaryotic cells that led to occupy new ecological space.

## 4. Function of evasion of host Defense

To develop infectious process, the entered pathogen needs to defeat the action of the nonspecific immune system machinery. This essential component is the compliment system. Compliment activation (through the classical, the lectin,

and the alternative pathways) tags microbes for destruction by phagocytic cells causing microbial lysis. Many pathogens have developed strategies to evade the complement system [7] [17].

Some pathogenic bacteria possess special morphological structures (capsules) or biochemical features which allow them to resist the main lines of host internal defense against them. The capsule is located on the surface of a bacterial cell and has a gelatinous consistence usually reinforced by chains or threads of linear polymers. To resist compliment activation and absorption by phagocytes, the capsule of microbial cells needed certain chemical traits. For example, the vegetative forms of *Bacillus anthracis* that had a capsule consisting of *D*-isomers glutamic acid became invulnerable to host phagocytes because it is known that the *D*-amino acids isomers peptides are resistant to the action of proteolytic degradation [9].

Many pathogens, however, produce diverse biochemical features which are responsible for evasion the complement system. These bacterial substances had different molecular and chemical structure. This group of pathogenicity factors mainly consists of peptides or proteins. Thus, staphylococcal protein A and streptococcal protein M, LPS produced by Gram-negative bacteria, glycoproteins and other mixed polymers are included in the group. Some pathogens such as *Streptococcus pyogenes*, *Staphylococcus aureus* and *Treponema pallidum* use fibronectinbinding proteins to provide an antigenic disguise if they clotted fibrin on the cell surface to avoid host defenses. Pathogenic *Mycobacterium* has a waxy cell wall that resists attack or digestion by most tissue bactericides. Intact LPS of some Gram-negative pathogens may protect the bacterial cells from complement-mediated lysis or the action of lysozyme [6] [17].

**Table 2** Cell components responsible for evasion function

| Pathogen | Component |
|---|---|
| Pneumococcus sp | capsule polysaccharide |
| Bacillus anthracis | capsule D-glutamile polypeptide |
| Pseudomonas aeruginosa | slime polysaccharide |
| Staphylococcus aureus | Protein A |
| Streptococcus sp | Protein M |
| Trepanema pallidum | Fibronectin binding protein (FBP) |
| Staphylococcus aureus | FBP |
| Streptococcus pyogenes | FBP |
| Mycobacteriun spp | waxy cell |
| *Yersinia pestis* | capsule protein F-1 |

Despite different mechanisms of resistance to the host cell activity, these substances played the same functional role: they protected microbial germs from host non-immune and immune system. Table 2

Recently, an original function of S-layer proteins as a defense against antibacterial peptides has been demonstrated. The defense peptides of host are small cationic, amphypathic molecules produced all organisms as a first line of defense against microbial invasion and are found at host-microbe interfaces, such epithelial layers. Initially it was established that the role of the peptides was to control microbial levels through direct antimicrobial activity. Actually, mechanisms of bacterial resistance to S-layer proteins are not yet clear [15] [17].

One of the pathogenicity factors with evasion function is the ability that also can alter host cell apoptosis or cause other forms of cell death [14].

Thus, all three biological functions played a very important role in the colonization of the new ecological niche by microbial pathogen and guaranteed its necessary life in the host organism. At this stage, pathogen was devoid of aggressive features and did not induce any specific damage to human or animal multi-cellular systems. This type of interaction between the prokaryotic pathogen and the eukaryotic tissue cells of the host organism can be characterized as a kind of a symbiotic like balance [9].

## 5. Damaging function

The pathogenicity complex was further complicated after the damaging function developed in the pro-pathogens, which possessed the above mentioned properties. The tox-genes appeared in the bacterial genome were responsible for production of aggressive substances directed to induce various types of dysfunction in the host tissue cells. According to chemical structure and mechanism of damaging action, bacterial toxins can be divided to two categories: endo- and exo-toxins. Depends on specific biological activity of toxic molecules, the host target cells can be undergoing by direct or indirect mechanism of destructive action.

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Endotoxons (*LPS*) of Gram-negative bacteria are constituents of the outer membrane of the bacterial cell wall. Toxicity of the cell unbound *LPS* is associated with the lipid component activity (*Lipid A*). *Lipid A* is known to react at the surfaces of macrophages causing them to release tumor necrosis factor (*TNF-α*) and probably other cytokines. In contrast to the protein exotoxins, endotoxins do not act enzymatically and they are less potent and less specific in their action. We can assume that the induction of lipid A cytokines play the leading role in the indirect mechanism of damaging action developed by endotoxins. Blood and lymphoid cells as well as immune system cells and compliment system, are targets that undergo endotoxin action [14] [19].

Besides endotoxins, some Gram-negative pathogens can produce exo-toxin proteins. For example, enteropathogenic *E. coli* strains synthesized extra-cellular LT- and ST- enterotoxins or cytolytic molecules [9].

**Table 3** Components responsible for damaging function

| S/ no | Direct action toxin type | Indirect action toxin type |
|---|---|---|
| 1. | Poreforning toxins: | Lipid A (Gram-negative LPS) |
| | leukocidins, hemolysins | Superantigenic toxins |
| 2. | AB subunit tox: | *Staphylococcal enterotoxins, TSST* |
| | A subunit – affect cyclic AMP | *Streptococcal pyrogenic toxins* |
| | A subunit – inactivate protein synthesis | |
| | B subunit – receptor binding function | |

A family of staphylococcal and streptococcal exotoxins, such as enterotoxins, toxic shock syndrome toxin (*TSST*), pyrogenic toxins and others, belong to the group of toxic bio-molecules with indirect mechanism of damaging action and they are named superantigens. These toxins are represented by peptide molecules that have the distinct domain structure. They are able to elicit massive activation of the *T* lymphocytes but induce weakly antibody response in the host organism. The molecular mechanism of the *T* cell proliferation is realized by interaction with *Class II MHC* molecules

on *APC*s and specific *Vß* chains of the *T* cell receptor. The process of activation under the action of superantigens results to production of lymphokines such as *IL- 1, TNF* and others [20].

Thus, we can suppose that endtoxins of Gram-negative bacteria and superantigen exotoxins produced by Gram-positive pathogens have similar mechanism of indirect damaging action on the host immune system.

Another group of damaging macro-molecules is represented by toxin exo-proteins that were able to inactivate or to destroy the vitally important physiological systems in the organ tissue cells by direct way. Both Gram-positive and Gram-negative bacteria produce soluble protein toxins. Most exotoxins possess an enzymatic activity that can be realized in contact with the host tissue target cells. Bacterial protein exotoxins are different in their molecular structure; some of them are represented by simple polypeptide molecules and others have a complicated subunit structure [21].

Certain simple protein toxins have broad cytotoxic activity and cause both very specific as well as nonspecific damage of tissue cells. Poreforming mechanism of action underlies cytotoxicity of some exotoxins, such as hemolysins and leukocidins produced by both Gram-positive and Gram–negative bacteria. The essential functional feature of cytolysins is their capacity to provoke the formation of hydrophobic pores in the cytoplasmic membranes of target eukaryotic cells. The process results from the binding of the toxins with membrane receptor on the cell surface, followed by their oligomerization, which lead to insertion of the oligomers into the membrane and formation of protein-lined channels. This insertion provokes the impairment of the osmotic balance of the cell and subsequent cytolysis [16].

The peculiarity of so-called "chimera" toxin proteins is that they have both hormone-like and enzyme-like properties. Molecular model of the "chimera" toxin complex is sometimes described as a *A+ B* (?) formula where the subunit *B* is the peptide (or peptides) responsible for the membrane receptor binding, and the subunit "*A*" is the peptide that is able to penetrate the cell and damage the intracellular target. The hormone-like component of the macromolecule was able to recognize specific membrane receptors on the sensitive tissue cell and bind to the cell surface. After the ligand-receptor binding, the enzymatic active components of the bifunctional structure were subjected to endocytosis or pore-forming mechanism and targeted one of the vital systems of the host cell [15]. For instance, the active enzyme subunit A of toxins produced by *Vibrio cholerae, Bordetella pertussis* and *Bacillus anthracis* can affect cyclic AMP and disturb a critical regulatory process of the host tissue cell. These above mentioned pathogens are completely nonrelated bacteria but their toxins function in a similar way, although the host target cells differ and thus the effect [21] [22].

Other enzyme active subunits A from AB toxins elaborated by *Corynebacterium diphtheria, Pseudomonas aeruginosa* and *Shigella dysenteriae* can inactivate protein syntheses in the eukaryotic target cells. The Elongation factor- 2 is the intracellular target damaged by diphtheria toxin and the ribosome is the sensitive host tissue cell's target affected by Shiga toxin [9] [23].

Membrane receptors for many AB bacterial toxins are the same lipid-containing components, for example, gangliosides, that are used by hormone molecules [21] [22].

The bacterial cell produces toxin molecules that are not toxic for the prokaryotic organism, but their damaging actions are aimed at eukaryotic cells. There is no direct connection between production of the toxin macromolecules and viability of pathogenic bacteria. Facts show that the capacity of exotoxin synthesis is caused by a biological stimulus to an increasing number of the microbial population.

## 6. Discussion

The use of molecular biology in the experimental study of phenomenon of pathogenicity brought us closer to understanding the mechanism of the cell – cell interaction in prokaryotic and eukaryotic organisms. It was found that some factors of pathogenicity (PF) have a complex molecular structure, for example domain or subunit.

The ligand - receptor interaction of bacterial PF and receptors on eukaryotic cells is the basis of specific lesions caused by the pathogen.

Some biological functions that were acquired by bacteria during the occupation of new ecological niche in the multi-cellular host organism are fundament of the pathogenicity phenomenon.

The arsenal of pathogenicity factors allowed pathogens to colonize and replicate within hostile niches. It consists of bacterial adhesion to the cell surface and extracellular matrix of host tissue, cellular invasion by pathogens and bacterial evasion of host defenses.

There are three approaches in consideration of pathogenicity phenomenon: biological, medical and applied aspects.

Biology of pathogenicity is based on the study of evolution, speciation of pathogens, ecology, genetic determination and encoding of biosynthesis of macromolecules possessing the function of pathogenicity factors (PF). The mechanism of interactions of PF and the host target-cells are also an important part in the biological process of pathogenicity.

The medical aspect of bacterial pathogenicity indicates a realization of pathogenic potency in the host organism. It is a problem of infectious disease, diagnostic, prophylactic and treatment of illness induced by the pathogen.

In the applied area, the knowledge of PF, their structure and functions may have important practical implication such as providing delivery systems for vaccination, tools for cell biology, and tools for the development of new strategies for therapy of bacterial infections.

## 7. Conclusion

Experimental data accumulated over the last two decades demonstrates the poly-functional feature of the phenomenon of bacterial pathogenicity. The main biological functions including adhesion, invasion, evasion, and damaging function are responsible for the interaction between the prokaryotic pathogen and the eukaryotic host tissue. Factors of pathogenicity (FP) are representative bio-molecules possessed different functional activity. The ligand - receptor interaction of bacterial FP and receptors on eukaryotic cells is the basis of specific lesions caused by the pathogen.

The damaging function plays the leading role in the development of the disease specific syndrome. From an ecological point of view, the phenomenon of pathogenic bacteria can be considered as a factor in regulating the size of the population and at the same time the pathogen and the host organism.

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