REVIEW ARTICLE

Bacterial Strategy of Invading Host Immune System: A Review

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ABSTRACT

Bacteria are one of the infectious organisms and considered as threats to humans killing hundred thousand people worldwide annually. They have developed highly effective mechanisms to subvert the human immune system, which explains why developing vaccines and controlling these pathogens have been so difficult. Following infections by bacteria, the innate immune cells such as macrophages, dendritic cells, and neutrophils engulf and destroy microorganisms, while adaptive immunity is mediated through the generation of antigen-specific B and T lymphocytes, through a process of gene rearrangement resulting in the production and development of specific antibodies and killer T cell, respectively. However, many microbial pathogens avoid host recognition or dampen the subsequent immune activation through sophisticated interactions with host responses, but some pathogens benefit from the stimulation of inflammatory reactions against the host. Such mechanisms include capsule formation, secretion of toxins or modulator, avoiding immune surveillance, Antigenic variation, cell death manipulation, escape from phagocyte response, subversion of innate pathway, and blockage of acquired immune. Other strategies used by bacteria to invade host immunity include inhibition of complement, inhibition of cytokines, interferon or chemokines, interference with toll-like receptors, blockage of antimicrobial small molecules, and blockage of intrinsic cellular pathways. The paper reviews some strategies used by bacteria in evading host immune system.

Key words: Adaptive immunity, bacteria, immune system, innate immunity, strategy

INTRODUCTION

The bacteria are one of the infectious organisms and considered as threats to humans killing hundred thousands of people worldwide annually.[1,2] They have developed highly effective mechanisms to subvert the human immune system, which explains why developing vaccines and controlling these pathogens have been so difficult. Successful pathogens have evolved a range of anti-immune strategies to overcome both innate and acquired immunities, which play critical roles in their abilities to cause disease.[2]

The innate immune system constitutes the first line of host defense during infection and, therefore, plays a crucial role in the early recognition and subsequent triggering of a proinflammatory response to invading pathogens.[3] The innate immune response relies on recognition of evolutionarily conserved structures on pathogens, termed pathogen-associated molecular patterns, through a limited number of germ line-encoded pattern recognition receptors.[4] The adaptive immune system, on the other hand, is responsible for the elimination of pathogens in the late phase of infection and in the generation of immunological memory. Whereas the adaptive immune response is characterized by specificity developed by clonal gene rearrangements from a broad repertoire of antigen-specific receptors on lymphocytes, the innate immune response is mediated primarily by phagocytic cells and antigen-presenting cells, such as granulocytes,

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macrophages, and dendritic cells (DCs), and has been regarded as relatively nonspecific.[5]

The common features of pathogenic microorganisms are the exploitation of cytoskeleton and membranous structures to invade or gain motility inside the host cell and also the manipulation of key signaling pathways.[6] The pattern-recognition receptors confer to mammals an extremely efficient "detection system" of invading microorganism, triggering an intricate signaling network that ultimately orchestrates the establishment of an adequate immune response.[6] However, as part of their pathogenic strategies, several microorganisms evade the immune system by circumventing or distorting these signaling pathways and creating, therefore, conditions that facilitate their replication and spreading in the host.[6] The pathogens avoid host recognition or dampen the subsequent immune activation through sophisticated interactions with host responses, but some pathogens benefit from the stimulation of inflammatory reactions.[7]

THE IMMUNE SYSTEM

The immune system is classically divided into innate and adaptive (acquired) immunity.[8] The distinctive features of innate immunity commonly refer to a broadly distributed variety of myeloid and lymphoid cells that can exert rapid effector function through a limited repertoire of germ line-encoded receptors. Innate immunity represents a rapid and stereotyped response to a large but limited number of stimuli.[9] It is represented by physical, chemical, and biological barriers, specialized cells, and soluble molecules, present in all individuals, irrespective of previous contact with offending agents or immunogens, and does not change qualitatively or quantitatively after contact.[3] The main effector cells of innate immunity are macrophages, neutrophils, DCs, and natural killer cells. Phagocytosis, release of inflammatory mediators, activation of complement system proteins, as well as synthesis of acute phase proteins, cytokines, and chemokines are the main mechanisms in innate immunity.[3]

In contrast, adaptive immunity in mammals is characterized by two types of lymphocytes, T and B cells, clonally expressing a large repertoire of antigen receptors that are produced by site-specific somatic recombination, i.e., T cell receptor (TCR) and antibody B cell receptor. Functionally, naive T and B cells encounter antigens in specialized lymphoid organs and undergo a process of cell division and maturation before exerting their effector function.[10]

IMMUNE SYSTEM AND INVADING MICROORGANISMS

Following infection, innate immune cells such as macrophages, DCs, and neutrophils, which are collectively called phagocytes, engulf and destroy microorganisms, and this represent the first defense barrier against infection.[8] In turn, adaptive immunity is mediated through the generation of antigen-specific B and T lymphocytes, through a process of gene rearrangement resulting in the production and development of specific antibodies and killer T cell, respectively. Adaptive immunity is also behind immunological memory, allowing the host to rapidly respond when exposed again to the same pathogen. Contrarily to the original thought, the innate immune response is not completely nonspecific, but rather is able to discriminate between self-antigens and a variety of pathogens.[11] Furthermore, much evidence has demonstrated that pathogen-specific innate immune recognition is a prerequisite to the induction of antigen-specific adaptive immune responses,[5,12] being DC central players in this linking.[13] DCs are specialized antigen presenting cells that function as sentinels, scanning changes in their local microenvironment, and transferring the information to the cells of the adaptive immune system.[14,15] On activation by microorganisms or microorganism components, immature DCs suffer a complex process of morphological, phenotypical, and functional modifications to become mature DCs that enter draining lymphatic vessels and migrate to the T-cell zones of draining lymph nodes where they present antigens to T lymphocytes. Depending on their maturation/activation profile, DCs will polarize and expand distinct T-cell subsets (T-helper cells which include Th1, Th2, and Th17, regulatory T cells, and cytotoxic T cells)[16] and given that the recognition of different microorganisms leads to distinct DC maturation or activation profiles, and the adaptive immune response is, therefore, modulated to match the nature of the pathogen.[17]

MECHANISMS OF OVERCOMING HOST IMMUNE SYSTEM

Capsule formation

Bacterial surfaces are complex structures which present many diverse antigenic targets to the host body surface.[18] A common mechanism of masking bacterial surfaces is to express a carbohydrate capsule. Capsules are effective at hiding many bacterial surfaces and preventing opsonization. This mechanism is used by most extracellular bacterial pathogens that circulate systemically within the body. For example, the pneumococcus (*Streptococcus pneumoniae*) relies extensively on its capsule to prevent antibody and complement deposition on its surface, thereby avoiding opsonization and phagocytic clearance.[19]

Similarly, bacteria that cause meningitis (*Haemophilus influenzae*, *Escherichia coli* K1, and *Neisseria meningitidis*) rely extensively on capsules to promote their extracellular lifestyle within the host by preventing antibody and complement deposition and insertion.[18,19] Pathogens expressing surface capsules also often have filamentous

adhesins (fimbriae and pili) that protrude through the capsular surface, enabling the adhesins to bind to host receptors yet keeping the bacterial surface hidden.[18,19]

SECRETION OF TOXINS OR MODULATOR

Lipopolysaccharide (LPS) is a major surface-exposed component of the Gram-negative bacteria. LPS is a key molecule from both the pathogens' and hosts' points of view. [18] The essential core component of LPS, lipid A, is highly conserved among most Gram-negative organisms and thus plays a central role in the activation of toll-like receptors (TLRs) such as TLR4. However, the outer part of LPS is made of highly variable carbohydrates, giving each strain with their particular serotype (O antigen). Thus, different strains of the same species can often reinfect the same host due solely to differences in O antigen.[18] LPS is surface exposed, and a LPS is surface exposed and a target of complement, but since it protrudes from the surface membrane, insertion by the membrane attack complex does not occur in the cellular membrane.[15] Bacterial pathogens, especially Gram-negatives, have developed secretion systems to export virulence factors across the bacterial membranes and either into the supernatant or even directly into host cells. In Gram-negative organisms, these are named according to the type, and there are at least seven secretion systems in addition to the general secretion system. Secretion of virulence factors such as toxins and immune modulators is a major use of these secretion systems, as well as conjugal DNA transfer.[19]

In Gram-negative pathogens, both Type III secretion systems (T3SS) and Type IV secretion systems can insert various molecules directly into host cells.[18,19] These two types of systems are not genetically related, although they both have a very diverse repertoire of secreted molecules (called effectors) that can be delivered into host cells.[19] These include toxins (to kill host cells), molecules that mediate bacterial uptake (invasion), effectors that reprogram vesicular transport to enhance intracellular parasitism, mechanisms to paralyze phagocytosis, molecules that form receptors for bacteria to adhere to, and many diverse effectors that alter immune functions to enhance immune evasion.[18,19]

The secretion of bacterial toxins impairs protective functions and facilitates colonization. For example, *Bordetella pertussis*, the agent that causes whooping cough, paralyzes the ciliary clearance function of the respiratory tract through the release of cell wall constituents that induce nitric oxide-mediated ciliostasis.[20] Biofilm formation by the opportunistic pathogens *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* or the production of a protective bacterial extracellular matrix by *E. coli* shield bacteria from the hostile environment and might facilitate resistance against the host surface protective mechanisms.[21]

Although Gram-positive surfaces are more simple (one membrane surrounded by peptidoglycan), there are suggestions that even Gram-positive organisms can form localized pores in host cells to deliver bacterial molecules into host cells. For example, *Streptococcus pyogenes* has a cholesterol-dependent cytolysin that is needed to deliver a NAD-glycohydrolase into host cells to trigger cytotoxicity.[22] Similarly, *Mycobacterium tuberculosis* has a specialized secretion system that is needed to deliver major T cell antigens (ESAT-6 and CFP-10) and presumably other proteins that are needed for bacterial replication inside macrophages and virulence.[23] The ability to drive bacterial molecules directly into host cells is a major strategy used by diverse bacterial pathogens to subvert and overcome host defenses.[23]

AVOIDING IMMUNE SURVEILLANCE

The ability to avoid detection by either the innate or acquired immune system is a central feature of bacterial pathogens. One strategy is to camouflage the surface of the microbe such that it is not recognized by host surveillance systems, while another is to dampen immune responses such that a complete immune response is avoided.[24] There are predominant molecules on bacterial surfaces that the host's immune system uses as key signatures. These are often TLR agonists such as lipid A of LPS, flagella, and peptidoglycan. However, the bacterial pathogens have evolved ways of altering these molecules such that they are less well recognized by immune surveillance systems.[24] Many Gram-negative pathogens modify lipid A to alter TLR4 responses.[25] For example, *Salmonella* has a two-component sensor (PhoP/PhoQ) that senses host environments, regulating many virulence genes. Some of these genes are enzymes involved in lipid A modification, including a 3-O-deacylase (PagL) and a lipid A palmitoyltransferase (PagP).[26] These modified forms of lipid A are up to 100-fold less active for TLR4 activation and NFkB production. Although lipid A is fairly well conserved, some organisms produce lipid A structures that are not efficient TLR2 and 4 activators. For example, *Porphyromonas gingivalis*, a major dental pathogen, contains multiple lipid A species which function as both agonists and antagonists of TLR2 and 4 selectively moderating the inflammatory response.[27]

Another major signature of bacterial pathogens is peptidoglycan. Nod1 and Nod2 are leucine-rich repeat intracellular proteins that function analogously to TLRs to detect peptidoglycan inside host cells.[28,29] Human Nod1 detects N-acetylglucosamine-N-acetylmuramic acid, a tripeptide motif characteristic of Gram-negative organisms,[30] while Nod2 detects a N-acetylglucosamine-N-acetylmuramic

acid dipeptide.[30] Activation of either Nod leads to NFkB activation and inflammatory responses. Bacterial pathogens have developed ways to avoid peptidoglycan processing and recognition by Nods.[31] Genes involved in peptidoglycan synthesis, turnover, and recycling have been identified as virulence factors. For example, *Listeria monocytogenes* resides in the cytosol of macrophages and other host cells. Surface-located and -secreted peptidoglycan hydrolases have been identified that are also virulence factors.[32,33] This work suggests that cleavage of peptidoglycan promotes a virulence mechanism involving exploitation of Nod2 and the innate inflammatory response to promote Listeria pathogenesis.[32]

ANTIGENIC VARIATION IN BACTERIA

Another classic mechanism viral, bacterial, and parasitic pathogen use to avoid immune responses is to vary immunodominant molecules known as antigenic variation. Acquired immunity relies on memory of previous exposure to antigens, and thus, antigenic variation is, especially, appropriate for circumventing humoral and cellular responses.[24] There are few, if any, examples of antigenic variation being used to escape innate immunity. Although strain-to-strain variation in antigenic molecules is common, antigenic variation refers to a single strain specifically changing a subset of its antigens, either to sustain an ongoing infection or reinfect hosts even though the first infection was successfully cleared. The molecular mechanisms used by bacterial pathogens to cause antigenic variation are diverse but very well studied.[34] These mechanisms usually involve one of three mechanisms:

i. Having multiple but different copies of a molecule, each of which is under an independent on/off switch;
ii. Having one expression locus plus many silent copies of the gene, and constantly changing which gene is expressed; or
iii. Having a highly variable region in a molecule that is constantly changing.[24]

Neisseria species are, perhaps, the best bacterial models of antigenic variation, using all three of these concepts and emphasizing why a vaccine to these organisms has not been successful.[24] The *Neisseria* pilus is expressed at the pilE locus. However, these organisms have many silent copies of partial pilin genes stored in "silent" (pilS) loci. By genetically recombining various pil alleles into the expression locus, a constantly shifting pilus is made. As these organisms are naturally competent, they acquire additional pilin gene sequences and incorporate them into pilS loci. *N. menigitidis* also varies its lipooligosaccharide structure in a phase variation mechanism.[24] It can express up to 13 different immunotypes by switching various terminal sugar structures. This is achieved by varying expression of various carbohydrate biosynthesis genes. For example, glycosyltransferase activity is regulated by slipped-strand mispairing, resulting in incorporation of different sugars in LOS.[35]

CELL DEATH MANIPULATION BY BACTERIA

Many bacterial pathogens also alter apoptotic pathways as part of their virulence strategies. Like viruses, obligate intracellular bacteria generally suppress apoptotic death. As apoptotic death is generally less inflammatory than cytotoxic death, many non-obligate intracellular pathogens choose this strategy to neutralize a variety of host cells. For example, *Salmonella enterica* utilizes a variety of strategies to both promote and inhibit host cell apoptosis as part of their virulence strategy during enteric infections.[36]

Chlamydia is obligate intracellular bacteria that reside within a membrane-bound inclusion in host cells. Not surprisingly, they have devised several strategies to avoid the host immune response and to avoid triggering apoptosis in infected cells. These mechanisms include blocking mitochondrial cytochrome C release and inhibiting Bax, Bak, and caspase-3 activation.[37] They also degrade proapoptotic factors such as BH3-only proteins Bim/Bod, Puma, and Bad, as well as several other reported mechanisms. Although the bacterial factors are not known, *Chlamydia* possesses a T3SS that appears to be involved in modulating the intracellular environment and potentially apoptosis. Due to its obligate intracellular lifestyle, genetic experiments to further define the bacterial factors are impossible. The first cells encountered by *Salmonella* in the gut are thought to be intestinal epithelial cells, which the organisms enter into and replicate within. This is mediated mainly by the Spi1 T3SS and several injected effectors. SopB/SigD is a phosphoinositide phosphatase that, following T3SS injection into the host cytosol, causes a sustained activation of host Akt/protein kinase B, which is a pro-survival kinase.[38] This results in the decreased levels of apoptosis within epithelial cells, which presumably prolongs the life of the epithelial cells harboring intracellular *Salmonella*. These pathogens then normally escape intestinal epithelial cells and enter the underlying reticuloendothelial system. The interactions with macrophages are more complex than epithelial cells. The Spi1 T3SS delivers an effector (SipB), which activates caspase-1 and causes the release of interleukin (IL)-1b and IL-18, which facilitates a rapid cell death that has features of both apoptosis and necrosis. Ironically, animals lacking caspase-1 are more resistant to *Salmonella* infection, and these pathogens cannot disseminate to systemic tissues in these mice.[39] Thus, this organism appears to drive apoptosis (and inflammation) as a mechanism to breach Peyer's patches and move to systemic sites. However, at least in culture, these

organisms mediate a delayed apoptosis through the Spi-2 Type III secretion-mediated system.[39]

ESCAPE FROM PHAGOCYTE RESPONSES

On arrival at the subepithelial space, bacteria encounter locally resident as well as newly infiltrated professional phagocytic cells that are attracted by the chemokine response of the overlying epithelial cells.[40] Phagocytes are equipped with a number of receptors that detect the presence of invading microbes and bind opsonized microbial surfaces. Membrane-bound scavenger receptors, lectins, Fc receptors, and complement receptors as well as signaling through TLRs may cooperate to determine the ultimate cellular response.[40] This may lead to phagocyte maturation, activation of antimicrobial substances, and secretion of pro-inflammatory cytokines, as well as phagocytosis and microbial degradation.[41]

Consequently, bacteria use a variety of strategies to avoid engulfment and degradation by phagocytes and facilitate proliferation and spread among host tissues.[40] Examples are the inhibition of phagocytosis by capsule formation or toxin-mediated cellular destruction and necrosis. In contrast, induction of apoptosis avoids the release of pro-inflammatory signals.[41] Host-induced apoptosis of lung epithelial cells during infection with *P. aeruginosa* plays an important role in reducing leukocyte infiltration and maintaining the essential function of the lungs. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* which both cause enterocolitis and abdominal lymphadenitis can inhibit phagocytosis by the translocation of bacterial mediators that specifically disorganize the host cell cytoskeleton preventing bacterial uptake by macrophages and polymorphonuclear leukocytes.[41]

BACTERIAL SUBVERSION OF INNATE PATHWAYS

Evidence of bacterial pathogens that are capable of directly interfering with TLR signaling is limited. However, there are several examples of downstream modulation of TLR responses, altering many of the cytokines that are keys to efficient innate responses[40] *Yersinia* species secrete a virulence (V) antigen, LcrV. This molecule signals in a CD-14- and TLR2-dependent manner to, ironically, trigger IL-10 secretion and mediate immunosuppression.[42] Emphasizing the contribution to virulence is the observation that TLR2-deficient mice are more resistant to infection with *Y. enterocolitica*. It has recently been shown that a particular residue in the N-terminal region of LcrV targets TLR2 and is required for altering IL-10 induction through TLR2.[42]

Small cationic peptides are a major component of the innate response in controlling diverse infections.[43] They have significant antimicrobial activity, which appears to be mediated by direct insertion of cationic and amphipathic peptides into negatively charged bacterial membranes, as well as many additional immunomodulatory activities central to innate responses.[43] Such peptides include defensins and cathelicidins.[24]

Resisting the antimicrobial activity of these peptides is critical to overcome host innate defenses. Analogous to antibiotic resistance, pathogens will alter their surface structure to decrease insertion of peptide and resulting lysis, they can encode transport systems that remove the peptides, and they can secrete proteases that degrade these peptides.[24] *Salmonella* species provide an excellent example of pathogens that utilize all three of these defense strategies. *Salmonella* species are intracellular pathogens, and macrophages and neutrophils produce several cationic antimicrobial peptides to control intracellular organisms. Intracellular *Salmonella* is capable of resisting these activities.[44]

Salmonella modifies lipid A by various mechanisms including deacylation, palmitoylation, addition of aminoarabinose, and other modifications to its LPS.[45] *Salmonella* also expresses an outer membrane protease, PgtE, which promotes resistance to ahelical cationic antimicrobial peptides by cleaving these molecules. *Salmonella* also encodes a locus (sapA-F) that mediates cationic peptide resistance. SapD and SapF exhibit homology to members of the ATP-binding cassette family of transporters and are thought to transport cationic peptides to the cytosol.[46] To fully coordinate these various resistance mechanisms, all of the above resistance mechanisms are all under the control of a global two-component regulator, PhoP/Q.[47] It has recently been shown that PhoQ, the sensor domain, directly binds cationic peptides, which then activate the various transcriptional programs which mediate the variety of antimicrobial resistance mechanisms.[48] Thus, these pathogens actually sense innate immune molecules to promote their virulence in a highly programmed manner.[49]

BLOCKADE OF ACQUIRED IMMUNITY

Most bacterial pathogens avoid the acquired immune response by avoiding its activation, and there are few examples of direct interference with acquired immunity.[50] For example, *Helicobacter pylori* LPS binds to the C type lectin DC_SIGN on gastric DCs to block Th1 development, thereby tilting the immune response from Th1 to a mixed Th1/Th2 response.[51] *H. pylori* also produces a vacuolating toxin, VacA, which blocks T cell proliferation by interfering with the TCR/IL-2 signaling pathway, resulting in a decrease in nuclear translocation

of nuclear factor of activated T cells, a global regulator of immune response genes.[52] Despite triggering an inflammatory response, there is little specific immune response to *Neisseria gonorrhoeae*, and there are decreased T lymphocytes. The Opa proteins of this organism bind to CEACAM1, which is expressed on CD4+ T cells, thereby suppressing their activation and proliferation.[53,54] Superantigens certainly alter the T cell response by affecting their subset distribution, but the actual contribution that superantigens plays in infection and disease is not well understood.[24]

However, there is evidence that indicates superantigens which may play a role in disease severity. For example, streptococcal disease severity is correlated to major histocompatibility complex (MHC) haplotype, suggesting that the interaction between superantigens and MHC Class II really influences the severity of disease through their ability to regulate cytokine responses triggered by streptococcal superantigens. [43] Another strategy employed by several mucosal pathogens, including dental pathogens, is to secrete enzymes such as IgA proteases that degrade immunoglobulins. IgA is a secretory antibody that is found on mucosal surfaces and thought to play a key role in the humoral defense of these surfaces. Bacterial examples include *Neisseria* species, *H. influenzae* (causes meningitis), and various Streptococci. For Gram-negative pathogens, the IgA protease uses an autotransporter mechanism, including a self-cleavage reaction, to facilitate its secretion out of the bacterium.[24]

Other strategies used by bacteria to invade host immunity include inhibition of complement, inhibition of cytokines, interferon or chemokines, interference with TLRs, blockage of antimicrobial small molecules, and blockage of intrinsic cellular pathways.[24]

CONCLUSION

In higher organisms such as human, different types of host defense mechanisms were used to control the resident microflora and, in most cases, effectively prevent invasive microbial disease. However, many microbial pathogens avoid host recognition or dampen the subsequent immune activation through sophisticated interactions with host responses, but some pathogens benefit from the stimulation of inflammatory reactions against the host. Such mechanisms include capsule formation, secretion of toxins or modulator, avoiding immune surveillance, antigenic variation, cell death manipulation, escape from phagocyte response, subversion of innate pathway, and blockage of acquired immune. Other strategies used by bacteria to invade host immunity include inhibition of complement, inhibition of cytokines, interferon or chemokines, interference with TLRs, blockage of antimicrobial small molecules, and blockage of intrinsic cellular pathways.

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