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Review Article

Immune Evasion Mechanism of Bacteria

Ebisa Mezgebu*
Animal Health Institute, Sebeta, Ethiopia

***Corresponding author: Ebisa Mezgebu**
Animal Health Institute, Sebeta, Po Box: 04, Ethiopia
Tel: +251 93 232 0809
Email: ebisamnaf@gmail.com

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Abstract

The co-evolution of pathogenic bacteria and hosts has led to the development of an array of virulence genes and a set of mechanisms of defense that constitute the immune system. However, successful microbial pathogens have in turn evolved complex and efficient methods to overcome innate and adaptive immune mechanisms, which can result in disease or chronic infections. Different mechanisms are used to subvert and exploit immune systems that are shared between these diverse microbial pathogens. The success of each pathogen is directly dependent on its ability to mount an effective anti-immune response within the infected host, which can ultimately result in acute or chronic infection or pathogen clearance. In this review, some of the mechanisms by which bacterial pathogens evade host immune systems like Biofilm formation and quorum sensing, bacterial surface modulators, inhibition of cytokines, blockade of Acquired Immunity, and other mechanisms are mentioned.

Keywords: Bacteria; Host; Immune evasion; Innate immunity; Phagocytes

Abbreviations: BDMCs: Bone-Marrow Derived Macrophages; DNA: Deoxyribonucleic Acid; GAP: Gtpase-Activating Protein; GEF: GTPase Exchange Factor; iNOS: Inducible Nitric Oxide Synthase; LPS: Lipopolysaccharide; LOS: Lipooligosaccharide; MHC: Major Histocompatibility Complex; MRSA: Methicillin-Resistant *S. aureus;* NFAT: Nuclear Factor of Activated T Cells; NO: Nitiric Oxide; PAMPs: Pathogen Associated Molecular Patterns; SCV: Salmonella-Containing Vacuole; PBMCs: Peripheral Blood Mononuclear Cells; PRRs: Pattern Recognition Receptors; QSSMs: Quorum Sensing Signal Molecules; Spi2: Salmonella Pathogenicity Island 2; T3SS: Type III Secretion Systems; T4SS: Type IV Secretion Systems; TLR: Toll-Like Receptor; V: Virulence

Introduction

The immune system is a collection of cells, chemicals, and processes that is used to protect the skin, respiratory passages, intestinal tract, and other areas from foreign antigens, such as microbes (organisms such as bacteria, fungi, and parasites), viruses, cancer cells, and toxins. The immune system can be categorized into two: innate and adaptive immunity. Innate immunity represents the first line of defense against an intruding pathogen. It is an antigen-independent (non-specific) defense mechanism that is used by the host immediately or within hours of encountering an antigen. Adaptive immunity, on the other hand, is antigen-dependent and antigen-specific and, therefore, involves a lag time between exposure to the antigen and maximal response. Innate and adaptive immunity are not mutually exclusive mechanisms of host defense, but rather are complementary, with defects in either system resulting in host vulnerability or inappropriate responses [1]. The immune system is a sophisticated and complex weapon that has evolved to destroy invading pathogens. The protective function of the immune system resides in the capacity of immune cells to discriminate between self and non-self antigens. Major Histocompatibility Complex (MHC) molecules expressed on the surface of all nucleated cells (class I), and "professional" antigen-presenting cells (class II) are an essential tool for the recognition of non-self antigens. These proteins bind to antigenic peptides and present them to T-cells [2].

To survive within the host, successful pathogens have evolved numerous effective evasion strategies to overcome attacks from the immune system [3]. All immune evasion mechanisms are deeply entrenched in the fine details of the molecular machinery that regulates the immune responses [4]. Pathogenic bacteria have been able to acquire genes encoding virulence factors, which not only allow colonization of host tissues but also block innate mechanisms of defense and provide escape from the at-

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tack of the specific responses. Virulence factors in bacteria may be encoded on chromosomal DNA (Deoxyribonucleic acid), bacteriophage DNA, plasmids, or transposons in either plasmids or the bacterial chromosome. The increasing specialization as pathogens is associated with a loss of metabolic versatility and with increased dependency on host metabolic pathways, which in turn is reflected in the reduction of the genome. The acquisition of virulence factors by lateral gene transfer and genome decay have key roles in the evolution of bacterial pathogens [5].

The mechanisms of both innate and specific immunity to bacteria are based on the recognition of bacterial structures. Receptors of innate immunity are known as Pattern Recognition Receptors (PRRs) since they recognize Pathogen-Associated Molecular Patterns (PAMPs) [6]. PRRs are fixed in the genome (their expression does not require rearrangement), the distribution in cells is non-clonal, and they only recognize foreign structures; on the contrary, receptors of specific immunity are encoded in gene segments (rearrangement is necessary for expression), are clonally distributed in B- and T-lymphocytes, and the self-nonself discrimination is imperfect so that tolerance mechanisms are required to avoid autoimmunity [7]. If pathogens were static entities, the regulatory mechanisms that avoid the over expression of the immune response might be enough to ensure the optimal functioning of the system. However, pathogens are evolving entities and, as such, they do respond to the selection pressures exerted by the immune system. Immune evasion can take several forms, such as hiding from and suppressing the immune response [2]. Therefore, this review focuses on different bacterial immune evasion mechanisms and is discussed below accordingly.

Immune Evasion Mechanisms of Bacteria

Antigenic Variation in Bacteria

Antigenic variation is appropriate for circumventing humoral and cellular responses. Even though 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 though the first infection was successfully cleared. The molecular mechanisms used by bacterial pathogens to cause antigenic variation are diverse. These mechanisms involve: having multiple but different copies of a molecule, each of which is under an independent on/off switch; having one expression locus plus many silent copies of the gene, and constantly changing which gene is expressed; and having a highly variable region in a molecule that is constantly changing [8].

Neisseria species are perhaps the best bacterial models of antigenic variation, using all of these three concepts and emphasizing why a vaccine for these organisms has not been successful. The gonococcus contains 10–11 outer membrane Opa proteins, each of which is antigenically different. Each gene is under a genetic switch that independently controls the expression of each Opa. During infection, multiple Opas are expressed in various combinations. 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. *Neisseria menigitidis (N. menigitidis)* also varies its lipooligosaccharide (LOS, similar to LPS) structure in a phase variation mechanism [8].

Subversion of Immune Response Pathways and Avoiding Immune Surveillance

A central component of the innate response is the deployment of specialized cells such as phagocytes to counter infectious agents that may have penetrated the initial physical barriers. Phagocytic cells have the ability to internalize microbes and kill them, recruit additional immune cells, and amplify the innate response if needed. Successful pathogens have developed a range of ways of countering phagocytic cells. The ability to avoid detection by either the innate or acquired immune system is a central feature of bacterial pathogens. One strategy is to cover up the surface of the microbe or the infected cell such that it is not recognized by host surveillance systems, while another is to dampen immune responses such that a complete immune response is evaded [8].

Bacterial Surface Modulators

Bacterial surfaces are complex structures that present many diverse antigenic targets. A major difficulty for bacterial pathogens is hiding this complex surface of proteins and carbohydrates from immune surveillance and Toll-Like Receptor (TLR) recognition yet exposing key molecules such as adhesins and invasins. A common mechanism of masking bacterial surfaces is to express a carbohydrate capsule. This mechanism is used by most extracellular bacterial pathogens that circulate systemically within the body, such as *Streptococcus pneumoniae* which relies extensively on its capsule to prevent antibody and complement deposition on its surface, thereby avoiding opsonization and phagocytic clearance. Similarly, bacteria such as *Haemophilus influenzae*, *Escherichia coli K1*, and *N. meningitidis* rely extensively on capsules to promote their extracellular lifestyle within the host by preventing antibody and complement deposition and insertion. Pathogens expressing surface capsules also often have filamentous adhesins that enter through the capsular surface, enabling the adhesins to bind to host receptors yet keeping the bacterial surface hidden [8].

Lipopolysaccharide is a major surface-exposed component of the Gram-negative bacteria. LPS is a key molecule from both the pathogens and hosts. The essential core component of LPS, lipid A, is highly conserved among most Gram-negative organisms and thus plays a vital role in the activation of TLRs such as TLR4. However, the outer part of LPS is made of highly variable carbohydrates, giving each strain its particular serotype (O antigen). Thus different strains of the same species can often reinfect the same host due solely to differences in O antigen. 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 [8].

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. In Gram-negative pathogens, both type III secretion systems (T3SS) and type IV secretion systems (T4SS) can insert various molecules directly into host cells [9].

There are suggestions that even Gram-positive organisms can form localized pores in host cells to deliver bacterial mol-

ecules into host cells. For instance, *Streptococcus pyogenes* has a cholesterol-dependent cytolysin that is needed to deliver a NAD-glycohydrolase into host cells to trigger cytotoxicity [10]. 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. 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 [11].

Hiding a complex bacterial surface is a major problem. Capsules are effective at hiding many bacterial surfaces and preventing opsonization. But, there are major 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. Bacterial pathogens have evolved ways of altering these molecules such that they are less well recognized by immune surveillance systems. Many Gram-negative pathogens modify lipid A to alter TLR4 responses [12]. 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-deacetylase (PagL) and a lipid A palmitoyltransferase (PagP). These modified forms of lipid a are up to 100-fold less active for TLR4 activation and NFkB production [13].

Genes involved in peptidoglycan synthesis, turnover, and recycling have been identified as virulence factors. For example, *Listeria monocytogenes (L. monocytogenes)* reside in the cytosol of macrophages and other host cells. Surface-located and secreted peptidoglycan hydrolases have been identified which are also virulence factors. This suggests that cleavage of peptidoglycan promotes a virulence mechanism involving the exploitation of Nod2 and the innate inflammatory response to promote *Listeria* pathogenesis [14].

Bacterial Subversion of Phagocytes

Because of their size, bacteria make particularly proper phagocytic targets. Numerous bacterial pathogens have established ways of avoiding phagocytosis. For example, *Yersinia species*, including the causative agent of plague *Yersinia pestis* (*Y. pestis*), use their type III secretion system to inject several T3SS effectors that effectively neutralize phagocytic activity [15], because actin is central to phagocytosis, many of these effectors target this part of the cytoskeleton. For organisms that use insect bites to introduce organisms directly into the blood (such as *Y. pestis*, transmitted by flea bites), the first host immune cells that would be encountered are patrolling phagocytes. The ability to avoid internalization and killing plays a central role in their virulence strategy. For organisms that are internalized, they generally choose three strategies to avoid intracellular killing escape from the phagosome (moderately common), blockage of phagosome-lysosome fusion (most common), or utilization of mechanisms to allow survival ithe n phagolysosome. Species of Shigella and *Listeria monocytogenes (L. monocytogenes)* and some *Rickettsia species* secrete lysins that are highly effective at lysing the vacuolar membrane that engulfs internalized organisms. Lysteriolysin O is a key virulence factor for *L. monocytogenes*. Many intracellular pathogens reside within an intracellular vacuole that differs in composition from normally microbicidal phagolysosomes. However, the mechanisms by which these pathogens subvert and alter normal vesicle transport are not well understood. It is thought that intracellular bacterial pathogens secrete effectors via type III and type IV secretion systems into the host cytosol where they disrupt normal vesicular trafficking. *Legionella pnumophila* uses its type IV secretion system to target the organism to a privileged intracellular niche. The effector, RalF, is a GTPase Exchange Factor (GEF) that targets ARF-1, a small GTPase that is then activated on *Legionella phagosomes*. Similarly, *Salmonella species* use their Spi-2 type III secretion system to secrete effectors such as SifA into the host cytosol and membranes, which alter the composition of the *Salmonella*-containing vacuole [16].

The ability to alter inflammatory responses within phagocytic cells provides significant advantages to pathogens. Although blockage of inflammatory responses is the predominant survival strategy, ironically some pathogens activate inflammatory pathways. Recruitment of inflammatory cells may provide replicative niches for pathogens that cause serious inflammatory diseases [12].

There are increasing numbers of examples of pathogens that produce and secrete molecules that dampen inflammation. A common target of many of these pathways is to target the MAP kinase and NFkB signaling pathways. For example, *Yersinia species* have a type III effector, YopJ or YopP, which is a ubiquitin-like cysteine protease that targets and downregulates both of these pathways [17]. YopJ binds multiple members of the MAPK kinase superfamily, including MKKs and IkB kinase b. Cleavage of ubiquitin and ubiquitin-like proteins from these substrates blocks their ability to activate these inflammatory pathways. Similarly, *Bacillus anthracis* lethal factor cleaves MKKs that activate p38 MAPKs, also blocking the activation of NFkB target genes [18].

Bacterial Subversion of Innate Pathways

Evidence of bacterial pathogens that are capable of directly interfering with TLR signaling is restricted. However, there are several examples of downstream modulation of TLR responses, altering many of the cytokines that are key to efficient innate responses [19]. *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 emphasizing the contribution to V 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 via TLR2 [20].

Similar to antibiotic resistance, pathogens will alter their surface structure to decrease the insertion of peptides and resulting lysis, they can encode transport systems that remove the peptides, and they can secrete proteases that degrade these peptides. *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 [21].

Another very efficient way of controlling intracellular pathogens by phagocytic cells is the production of reactive species such as oxygen species and Nitric Oxide (NO). Inducible Nitric Oxide Synthase (iNOS) plays a central role in inflammation and immune regulation, both in terms of producing NO for killing organisms and also using NO as a key signaling molecule. Pathogens have evolved several ways of avoiding NO-mediated killing. Intracellular *Salmonella*, which resides within a special-

ized membrane compartment called the *Salmonella*-Containing Vacuole (SCV) in macrophages, use a T3SS called *Salmonella* Pathogenicity Island 2 (Spi2) to mediate protection from reactive nitrogen intermediates. If the bacteria lack Spi2, iNOS efficiently colocalizes with the intracellular organisms in the SCV. The ability to avoid colocalization with harmful host enzymes is a common theme for successful intracellular pathogens. Similarly, Spi2 is also required to evade phagocyte NADPH oxidase-mediated killing. Intra-cellular organisms have also developed mechanisms to detoxify NO-mediated effects [22]. These include the ability to repair damage caused by reactive nitrogen intermediates and methods to detoxify these molecules. Pathogens have evolved ways of not activating or inhibiting iNOS activity. For example, the murine intestinal mucosal pathogen *Citrobacter rodentium* causes a marked level of overall iNOS activity following infection. However, local iNOS activity in intestinal areas directly surrounding the adherent bacteria is very low, while in areas distant to the infection site iNOS activity is quite high [23].

Inhibition of Cytokines by Bacteria

There are many reported examples of bacterial pathogens altering downstream inflammatory cytokines, although in most cases the molecular mechanisms by which this is achieved have not been revealed. Because of the complexity of bacteria and the diverse array of effectors and other immune modulators produced by these organisms, it has been difficult to identify which components are responsible for triggering cytokines versus those which selectively inhibit cytokine production. However, there are now examples of pathogens specifically targeting cytokine pathways to enhance pathogenesis. For example, *Staphylococcus aureus* protein A binds directly to the TNFa receptor, TNFR1, on the respiratory epithelium, which then potentiates a chemokine and cytokine cascade and subsequent disease [24].

Bacterial Acquired Immunity Blockade

Most bacterial pathogens avoid the acquired immune response by avoiding its activation, and there are a few examples of direct interference with acquired immunity. For example, Helicobacter pylori LPS binds to the C-type lectin DC_SIGN on gastric dendritic cells to block Th1 development, thereby tilting the immune response from Th1 to a mixed Th1/Th2 response [25]. Helicobacter pylori also produces a vacuolating toxin, VacA, which blocks T cell proliferation by interfering with the T cell receptor/IL-2 signaling pathway, resulting in a decrease in nuclear translocation of Nuclear Factor of Activated T cells (NFAT), a global regulator of immune response genes [26].

Superantigens certainly alter the T cell response by affecting their subset distribution, but the actual contribution this plays in infection and disease is not well understood. However, there is evidence that indicates superantigens may play a role in disease severity. For example, streptococcal disease severity is correlated to the MHC haplotype, suggesting that the interaction between superantigens and MHC class II influences the severity of disease through their ability to regulate cytokine responses triggered by streptococcal superantigens [27].

Cell Death Manipulation by Bacteria

Many bacterial pathogens alter apoptotic pathways as part of their virulence strategies. Like viruses, obligate intracellular bacteria generally suppress apoptotic death. Because apoptotic death is generally less inflammatory than cytotoxic death, many nonobligate 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 [28]. Chlamydiae are 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. 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 type III secretion system that appears to be involved in modulating the intracellular environment and potentially apoptosis. Because of its obligate intracellular lifestyle, genetic experiments to further define bacterial factors are impossible [29].

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 sustained activation of host Akt/protein kinase B, which is a pro-survival kinase [30]. This results in 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 a release of 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. Thus this organism appears to drive apoptosis (and inflammation) as a mechanism to breach Peyer's patches and move to systemic sites [31].

However, at least in culture, these organisms mediate delayed apoptosis via the Spi-2 type III secretion-mediated system. Initially in infection, the organisms trigger apoptosis and inflammation via the Spi-1 system to facilitate subsequent interactions with macrophages, which leads to systemic spread. Then the Spi-2 system facilitates in- intracellular survival and growth in these macrophages while delaying the onset of apoptosis in these host cells. A hallmark of apoptotic cells is their phagocytosis by other phagocytic cells. Thus, as a host cell becomes depleted by intracellular Salmonella, the delayed apoptosis then enables the infected macrophage (and intracellular bacteria) to be phagocytosed by other macrophages, providing a fresh host cell reservoir for these organisms. Alternatively, an attractive host defense mechanism would be to deplete potential host cells (such as macrophages) by promoting extensive apoptosis within infected organs, thereby depriving the pathogens of additional host cells [31].

Biofilm Formation and Quorum Sensing

Biofilm Formation

In the interactions between host and pathogen, several host immune factors contribute to bacterial survival during persistent infection. For example, proteolytic enzymes and reac-

tive oxygen species have a dual role in bacterial clearance, as they not only destroy the bacteria but also enhance impaired pathogen recognition by degradation of *P. aeruginosa* surface molecules. In addition, the accumulation of extracellular DNA by the production of Neutrophil Extracellular Traps (NETs) also has beneficial effects on bacterial survival. Extracellular DNA facilitates biofilm formation, enhances LPS modification by Mg2+ chelation, and protects the bacteria from killing by Antimicrobial Peptides (AMPs) [32].

Biofilm development has been modeled to occur in three stages: (1) attachment, (2) proliferation/formation of the matured biofilm, and (3) detachment/dispersal. During attachment, staphylococcal surface-attached proteins known as Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) establish non-covalent interactions with device surfaces coated by host proteins and host tissues. After attachment, proliferation, and maturation of the biofilm follow, with the production of an extracellular matrix consisting of the staphylococcal biofilm exopolysaccharide, Polysaccharide Intercellular Adhesin (PIA), also called poly-N-acetylglucosamine (PNAG), teichoic acids, proteins, and Extracellular DNA (eDNA). During this second stage of biofilm expansion, channels and mushroom-shaped structures form to facilitate nutrient delivery to deeper layers of the biofilm. The last stage of biofilm development is characterized by the detachment and subsequent dispersal/dissemination of biofilm clusters to distal sites, a process mostly due to the activity of the surfactant-like Phenol-Soluble Modulin (PSM) peptides [33].

Biofilms are dense aggregates of microorganisms embedded in an exopolysaccharide matrix. Biofilms are ubiquitous in nature and biofilm formation is acknowledged to be a critical component of the pathogenesis of certain infectious diseases. Microbes in biofilms manifest different gene expression than microbes suspended in solution (planktonic forms), which translates into differences in cell surface properties, biosynthetic capacity, etc. The phenomenon of biofilm formation is closely linked to other processes involved in microbial pathogenesis, including quorum sensing, attachment, and signaling [34].

Quorum Sensing

Quorum sensing is a density-dependent mechanism for interbacterial communication, based on secreted inducers, often called 'Quorum Sensing Signal Molecules' (QSSMs), which bind to a bacterial receptor. Upon inducer-receptor interaction, target gene transcription is induced, including transcription of the QSSM. In a growing population with high density, more inducer is synthesized. In *P. aeruginosa,* three major QSSMs have been characterized, viz. the N-acyl-L-homoserine lactones N-(3-Oxododecanoyl)-L-Homoserine Lactone (3-oxo-C12-HSL) and N-Butanoyl-L-Homoserine Lactone (C4-HSL) and the Pseudomonas Quinolone Signal (PQS). These QSSMs act, together with less dominant QSSMs, on the complex *P. aeruginosa* QS systems. The QS systems regulate large domains of the *P. aeruginosa* genome, enhancing biofilm maturation, swarming motility, and secretion of many virulence factors. Therefore, *P. aeruginosa* QS systems strongly contribute to bacterial virulence and immune resistance in plants, insects, and mammals. QSSMs have a dual role during infection of *P. aeruginosa* biofilms and other bacteria, enhancing immune evasion directly and indirectly. Indirectly, QSSSMs are the main inducers of virulence during chronic infection, enhancing the secretion of immune evasive proteases and down-regulating flagellar motility [35].

Quorum sensing is a cell-to-cell communication mechanism by which bacteria can sense their population density by the production of small molecules. Quorum sensing regulation has three distinct phases: production of the signaling small molecules by bacteria, accumulation of the signaling molecules as a function of bacterial density, and the response by bacteria when a threshold concentration is reached. Bacterial responses to quorum-sensing molecules have global regulatory changes in microbial physiology and can affect virulence. Quorum-sensing-related regulation mechanisms have been associated with virulence in many microbes including *S. aureus*, *P. aeruginosa,* and *Streptococcus spp*. Quorum sensing affects the expression of many microbial traits associated with virulence, including biofilm formation and toxin production. Quorum-sensing molecules may actively participate in pathogenesis through effects on the host and some promote apoptosis of macrophages and neutrophils. There is increasing evidence that quorum-sensing mechanisms are targeted by innate and adaptive immune responses [34].

Surface Expressed Molecules

Pseudomonas flagellin and the lipid A subunit of Lipopolysaccharide (LPS) are the major inducers of immune responses. In mammalian cells, LPS and flagellin are recognized by TLR4 and TLR5, respectively. Upon TLR recognition in mammals, Myd88 signaling cascades are induced, leading to the production of inflammatory cytokines and inflammation. Both flagellar motility and LPS-based evasion mechanisms have been observed in different *P. aeruginosa* strains [36].

Flagellar Motility

Several studies suggest a TLR5-independent mechanism to evade the immune system by impaired flagellar motility. In these experiments, *P. aeruginosa* (strain PA14) was able to evade non-opsonic phagocytosis by murine Bone-marrow-Derived Macrophages (BDMCs) and human Peripheral Blood Mononuclear Clls (PBMCs) by loss of motility, independent of flagellar expression [37]. Numerous studies highlighted the critical role of flagellar interactions with TLR5 for effective inflammasome activation, chemotaxis, phagocytosis, and clearance of *P. aeruginosa* strain PAK. Also, TLR5-mediated immune evasion was demonstrated to enhance bacterial survival. Interestingly, this is not only mediated by loss of flagellar motility but also by degradation of monomeric flagellin [38].

Motility is a complex trait that has been associated with virulence in both bacteria and parasites. Motility is manifested by approximately 80% of known bacterial species and is critical for the adaptation of mobile microbes to new environments. Bacterial cells can move by the action of specialized organelles called flagella. Actin-based motility is used by several intracellular pathogens including Shigella spp., *Listeria monocytogenes,* and Rickettsiae for cell-to-cell spread. Flagellar synthesis is often coordinately regulated with other virulence factors within a common genetic regulatory network. Furthermore, flagella often induce strong immune responses and manifest antigenic variation. Flagella-dependent mobility in *Legionella pneumophila* and *Yersinia enterocolitis* contributes to virulence by facilitating the encounter of bacteria with host cells and enhancing cell-invasive capacity. For *Burkholderia cepacia*, flagellar movement is important for the penetration of epithelial barriers and may contribute to the establishment of systemic infections [34].

Flagellin is a highly conserved MAMP that can be recognized

by both animal and plant cells. This protein forms the major part of the bacterial flagellum that enables bacterial motility. Each flagellum consists of thousands of flagellin molecules. Flagellin monomers can surround the bacteria due to spills during flagellum construction or due to damage of the flagellar filaments. It is these monomers that are recognized by mammalian and plant cells. In mammals, the PRR Toll-Like Receptor 5 (TLR5) is required for detection of bacterial flagellin [39].

Tuf and Lpd

Elongation factors like Tuf are involved in translation and are commonly expressed intracellularly [40]. At the cell surface, Tuf is the first receptor of *P. aeruginosa* which was described to bind plasminogen. Plasminogen can be converted by host uPA into active plasmin, a key protease for degradation of extracellular matrix components. By degradation of extracellular matrix components, *P. aeruginosa* would hypothetically be able to invade the host tissue easier. Also, Tuf was described to bind complement regulator Factor H, which is still active upon interaction. By application of this host protease, *P. aeruginosa* uses acquired complement degradation for efficient evasion of the complement attack [41].

At the cell surface, Lpd contributes to bacterial survival in the host, as it binds plasminogen and complement regulator Factor H. These binding properties lead to degradation of the complement opsonin C3b, impairing neutrophilic phagocytosis and fibroblast growth. Next, binding of plasminogen leads to degradation of extracellular matrix, increasing invasion of the host tissue [42].

Secreted Products

Alkaline Protease A

A major enzyme involved in *P. aeruginosa* immune evasion is the metalloprotease Alkaline Protease (AprA). AprA is secreted by the type 3 secretion system and high levels have been reported in sputa of chronically infected CF patient. Interestingly, AprA has been shown to degrade complement components and cytokines for years [43]. An effect of AprA was also found in a Drosophila melanogaster infection model, where AprA protected Pseudomonas against antimicrobial peptides and contributed to persistent infections [44].

The opportunistic pathogen Pseudomonas aeruginosa secretes an alkaline protease, designated AprA, which belongs to the serralysin family of the zinc metalloproteases. This protease is secreted by a type I secretion system and has been associated with virulence. Recently, we demonstrated that AprA actively degrades flagellin monomers [39].

IMPa (Immunomodulating Metalloprotease of Pseudomonas Aeruginosa)

IMPa was described as a new immune-modulating metalloprotease of *P. aeruginosa*. Secreted IMPa cleaves PSGL-1, an important mediator in neutrophil recruitment. Functionally, IMPa treated neutrophils show impaired PSGL-1 mediated rolling, indicating a protective effect of IMPa against neutrophilic attack [45]. Protection from neutrophilic evasion by degradation of PSGL-1 has also been observed for Staphylococcus aureus secreted SSL5 [46].

Protease IV and LasA

Other secreted proteases, like Protease IV and LasA also contribute to bacterial virulence. Some studies reported cleavage of complement factors, surfactant proteins and Immunoglobulins (Ig) by protease IV. Also some preliminary data indicate a role for Protease IV in complement degradation, but more experiments have to reveal the exact targets and the immune-modulating properties of this protease during infection [47].

Type III Secretion Systems and Pore-Forming Toxins

Pathogenic bacteria evolved a wide repertoire of virulence mechanisms that promote immune evasion and bacterial persistence, including the use of Type III Secretion Systems (T3SSs). T3SSs are complex, macromolecular transport machines found on many pathogenic Gram-negative bacteria including members of Yersinia, Shigella, and *Salmonella species*, which subvert host cell immune responses by injecting bacterial effector proteins directly into the host cell, to modify their functionality [48]. It was originally thought that the species of Shigella and Salmonella used T3SSs to gain entry to cells. However, research evolved to show that T3SSs work at a different level, by altering the phagocytic properties of macrophages and possibly their killing capacities [49]. As such, proteins secreted by T3SSs can be classed as manipulators of innate defense mechanisms, endowing bacterial pathogens with the ability to alter inflammatory responses from within phagocytic cells. Shigella use T3SSs to secrete effector proteins, such as IpaB, which binds to and activates Caspase-1 in macrophages, through a process involving the IPAF/ASC inflammasome, which enables them to evade the phagosome and induce pyroptosis [50]. Such exploitation of the IPAF/ASC inflammasome is thought to help Shigella to escape macrophages, enabling them to invade the intestinal epithelium. The evasive techniques employed here by Shigella, enable it to establish infectious processes. Moreover, Shigella evolved to inhibit the production of certain antimicrobial peptides, which are key effector molecules in bacterial host defense. Indeed, early in Shigella infections, expression of peptides LL-37 and human β-defensin-1 were found to be dramatically reduced or turned off. This down regulation of immediate defense effectors might encourage bacterial adherence and invasion into host epithelium, and could be an important virulence parameter. Such T3SS-driven evasion strategies act to guard against innate immunity, but in terms of defending against adaptive immune responses, bacteria can use T3SSs to modify T cell behavior. *S. flexneri* evolved to use T3SSs to invade CD4+ T cells to "paralyze" their migratory patterns and utilizes injected effector proteins to induce inhibitory signals that alter cellular dynamics [51]. *Salmonella enterica serovars* use a unique T3SS that is capable of injecting up to 30 effector proteins with the ability to disrupt cell signaling pathways, interfere with MHC-dependent antigen presentation in DCs, and slow the migration of infected DCs with a downstream effect on T cell activation. Salmonella-encoded T3SSs can also directly contact T cells, inhibit their proliferation and augment co-inhibitory signaling between T cells and APCs [52]. *S. aureus*, which displays various levels of virulence, can manipulate host T cell responses that limit bacterial growth but do not eliminate the pathogen during persistent infections. Along with producing potent, T-cell-targeting SAgs, *S. aureus* produces extracellular, pore-forming toxins that lyse T cells upon cellular engagement. *S. aureus* α-toxin forms heptameric pores that destroy T cells [53], whilst leukocidin DE binds to CCR5 to kill T cells. Furthermore, during persistent *S. aureus* infection, T cells can become anergic through a failure in TCR signaling events, which render the T cells unable to respond to antigenic stimulation. The presence of T3SSs and pore-forming toxins, arms bacterial pathogens, such as Shigella and *S. aureus*,

with an attack and evasion "arsenal", which acts to dampen host innate and adaptive immune responses and aids their virulence and survival [54]. For pathogen survival, suppression and evasion of host immune responses is of utmost importance. Many bacterial pathogens possess a type III secretion system that allows them to transfer proteins directly into host cells. These proteins are called effectors and generally contribute to virulence by sup- pressing host defense responses. Besides suppression of host immunity, evasion of host immunity is an important virulence strategy as well [39].

Avoiding Lp Recognition Molecules

Masking of PAMPs

The surface structure of a pathogen provides a signature for recognition by the host; example, MBL and ficolins recognize Pathogen Associated Molecular Patterns (PAMPs) on the microbial surface, which lead to LP complement activation. Accordingly, one evasion strategy employed by pathogens is to camouflage or alter the surface of the microbe (or the infected cell) to hide from the host surveillance systems. This strategy is used by certain *Klebsiella pneumoniae* strains that can alter their capsular composition to prevent recognition by the LP. It was shown that Klebsiella-induced respiratory burst in phagocytes occurs via AP and LP. However, Klebsiella serotypes that lack expression of capsular polysaccharides containing mannobiose or rhamnobiose, which are recognized by LP PRMs, induce lower respiratory burst in phagocytes than those expressing the glycoepitopes. Additionally, these serotypes are more likely to evade intracellular killing by phagocytes. Therefore, lack of these glycoepitopes benefits the pathogen [55].

Complement Inhibitors

The complement system is part of the innate immune defense. It constitutes an extensive network of plasma proteins that trigger a proteolytic cascade upon recognizing the PAMP microbial patterns often found on the bacterial cell wall [56].

Escherichia coli and *Bordetella pertussis* are examples of pathogens that recruit and utilize C1-INH to evade complement. C1-INH was discovered as an inhibitor of the C1 complex (C1qr2s2: C1q and its associated proteases), but it also targets LP complexes consisting of PRMs and MASPs. Thus, if a pathogen manipulates C1-INH it will probably disturb both pathways if these are active [57]. C4b-binding protein works as a cofactor in cleavage and inactivation of C4b and C3b and many pathogens exploit C4BP as part of their survival strategy, *Leptospira interrogans* binds C4BP via its surface molecule Lsa23 and induce C4b and C3b degradation. Interestingly, Lsa23 is also able to attract plasminogen, which after activation into plasmin was shown to directly cleave C4b and C3b. This demonstrates that cross- talk between complement and coagulation also exists in immune evasion [58].

Utilizing LP Components to be Phagocytized

Mycobacterium tuberculosis binds MBL and has developed a strategy of hiding inside macrophages by preventing lysosomal degradation [59]. Case-control studies of tuberculosis infection showed that MBL increases susceptibility. MBL is also protective or insignificant. The reason for the discrepancy could perhaps be found in the differences of assessing MBL genotypes and timing of the blood sampling for measuring MBL serum levels. Hence, the role of MBL in tuberculosis remains an open question [60].

Blocking of C4b

The bacteria *Staphylococcus aureus* causes severe diseases like toxic shock syndrome and includes Methicillin-Resistant *S. Aureus* (MRSA) strains. *S. aureus* has a palette of evasion mechanisms and possibly one is to reduce the LP and CP activity using a protein called extracellular adherence protein (Eap). Eap binds C4b and blocks assembly of the C3 convertase C4b2a. After secretion, a fraction of Eap rebinds *S. aureus*, but it is the fluid phase Eap that forms complexes with C4b. Experiments showed that only exogenously added Eap reduced opsonization/phagocytosis and *S. aureus* were not more susceptible to phagocytosis after knocking out endogenous Eap. This questions whether the purpose of Eap is to inhibit LP and CP. It has been shown that patients with *S. aureus* infections have high titers of anti-Eap antibodies confirming the importance of the protein, but Eap is a multifaceted protein with many functions in *S. aureus* virulence, which can explain the reported antibody titers [61].

Bacterial Resistance to Phagocyte Killing

Despite the presence of the antimicrobial host factors, many pathogens can survive inside the host cell. Such pathogens, which include bacteria, fungi and viruses, have evolved a multitude of strategies to counteract host defences. Some bacterial species interfere with the ability of phagocytes to engulf them, either by scavenging, inhibiting or even degrading opsonic antibodies or complement, or by directly impairing the phagocytic machinery of macrophages and neutrophils [62]. Other bacteria have become resistant to one or more of the antimicrobial factors of phagocytes. Some species have developed metabolic pathways to counteract acid accumulation inside phagosomes or have acquired uniquely resistant proteins to withstand the low pH. Yet other bacteria protect themselves by actively degrading or shielding themselves from the antimicrobial peptides and proteins produced by phagocytes, or by expressing detoxifying enzymes, such as catalase, that neutralize ROS and/or RnS. Alternatively, some bacterial species prevent RnS and ROS formation by impairing recruitment of the proteins that mediate their synthesis [63]. Other species have devised means of overcoming the scarcity of iron by secreting specialized iron-scavenging molecules called siderophores, which sequester and target the cation for bacterial use, or by expressing iron storage or transport proteins. Lastly, many bacteria improve their intraphagosomal survival by mounting a vigorous stress response to dispose of and replace damaged proteins [64].

Although most bacteria use one or more resistance mechanisms, only a select group of bacteria are 'professional' intracellular pathogens. These species survive and replicate inside phagocytes, effectively avoiding attack by their antimicrobial factors. To accomplish this feat, such pathogens have evolved multiple strategies towards one common goal: to perturb phagosomal maturation. These different strategies are exemplified by the mechanisms used by *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Legionella pneumophila* and *Coxiella burnetii*. These bacteria parasitize host cells by arresting or reprogramming phagosomal maturation, by escaping maturing phagosomes or by withstanding the microbicidal properties of the phagolysosome [65].

A key characteristic of many pathogens is persistence the continued presence of pathogen in environments that are considered stressful or hostile conditions, which might have limited nutrients and might be shared with antimicrobial regents or threatening immune cells. During persistence, the pathogen

is non-infectious, having stopped progressive activities, such as cell development and reproduction, and thus remains undetected by the host, while it 'hides' in a non-replicating state. Until a more comfortable environment can be secured, such persistence will continue where the pathogen remains viable but does not thrive. However, the pathogen can play 'hide and seek' and re-appear once the immune system is evaded and possibly deceived at the infection or colonization site. One pathogenic bacterium that excels at this is *M. tuberculosis*, which evades host immune responses to establish a chronic infection [66]. *M. tuberculosis* is a facultative intracellular pathogen that is known to reside inside a variety of APCs, including macrophage and DC subsets. Upon invading host cells through phagocytosis, *M. tuberculosis* can replicate within the infected cells by arresting phagosome maturation. This is accomplished by *M. tuberculosis* changing its composition, as the structure of the cell wall and specific molecules on its surface serve as a barrier that allows the macrophages to maintain a neutral pH [67]. This mechanism allows the pathogen to avoid exposure to lysosomal hydrolases, unfavorable low pH conditions produced by the immune response, and other bactericidal lysosomal components. Additionally, *M. tuberculosis* is capable of producing factors that modulate the expression of pro-apoptotic and anti-apoptotic genes in macrophages, which has implications for innate immune responses. Inhibition of apoptosis might be a major mechanism, whereby *M. tuberculosis* delays the acquisition of bacteria by DCs and the onset of adaptive immunity. *M. tuberculosis* not only hides from the immune system but can also modulate adaptive immune responses by inhibiting T cell activities. *M. tuberculosis* can chronically stimulate antigen-specific CD4+ T cells (i.e., ESAT6-specific) to drive functional exhaustion [68].

Many pathogenic bacteria have developed strategies to evade ingestion and killing by phagocytes. Extracellular pathogens generally try to avoid ingestion. Exotoxins of hemolysin and leukocidins of *S. aureus* and streptolysins of *S. pyogenes* promote leukocyte lysis. *S. pyogenes* produces a protease that inactivates IL-8, preventing the recruitment of phagocytes in response to the chemokine. Through a type III secretion system, virulent strains of *Y. enterocolitica* introduce six effector proteins named Yops in the cytoplasm of phagocytes: YopE, YopH, YopO, and YopT disrupt the actin cytoskeleton and inhibit phagocytosis; YopM inhibits cytokine production, and YopP blocks NF-kB signaling pathways and suppress the release of chemokines and proinflammatory cytokines. Gram-positive cocci produce several proteases that degrade IgG, thus preventing antibody-mediated opsonization [69].

Once phagocytosed, intracellular bacteria can choose between three different strategies to prevent intracellular killing: (a) *Shigella spp*. and *Listeria monocytogenes* secrete membranolytic lysins that destroy the membrane of phagosome, and therefore engulfed bacteria are released into the cytoplasma of phagocytic cell; (b) *Salmonella spp*. and *Legionella pneumophila* use type III and IV secretion systems, respectively, to inject effector proteins that avoid phagosome-lysosome fusion; and (c) the unusual components of *Mycobacterium tuberculosis* cell wall protect it from intracellular killing [8].

Besides its beneficial role for the host, inflammation also contributes to pathogenesis. During intracellular killing of ingested bacteria lysosomal enzymes are released, causing tissue damage. Inflammation is a substantial component of the pathogenesis in most bacterial infections. For example, gastric infection with *Helicobacter pylori* results in a chronic inflammation that can evolve into an acid gastritis with development of peptic ulcers or lead to a gastric atrophy with achlorohydria and development of gastric carcinoma [70]. The most severe manifestation of the adverse effects of inflammation is sepsis. Sepsis is a systemic inflammatory syndrome in response to severe infection. The main fraction responsible for sepsis induction by Gram-negative bacteria is endotoxin (LPS), whereas Gram-positive bacteria can induce sepsis through interactions between superantigenic exotoxins and T cells. Excessive release of pro-inflammatory cytokines into the systemic circulation causes endothelium injury that is followed by coagulation disorders and organ dysfunction [71]. Therefore, deleterious effects of inflammation necessitate an efficient control over the process. Macrophages play an important role in regulating inflammation. Macrophages have been classified into two groups: M1 and M2 macrophages. The M1 program of macrophages is usually associated with protection against acute bacterial infections and includes the up-regulation of genes encoding cytokines, cytokine receptors, chemokines, chemokines receptors, iNOS, and costimulatory molecules (a bridge with the specific immunity); M2 macrophages are immunoregulatory cells and produces the anti-inflammatory and immunosuppressor cytokines IL-10 and transforming growth factor-beta. When an excessive or prolonged M1 program treats to the host, macrophage reprogramming toward a M2 profile contributes to the resolution of inflammation. However, some bacterial pathogens can take advantage of the M2 profile to cause chronic infections [72].

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