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Review

Bacterial virulence factors: Review

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ABSTRACT

Bacterial pathogens have evolved a variety of strategies to live in the tissues of their vertebrate hosts. Despite the fact that some of these strategies are highly sophisticated and unique to a particular disease, others are shared by a number of bacterial species. The traits of microorganisms that confer virulence mainly fall into a few categories, such as the ability to enter a host (penetration), the ability to circumvent host protections (evasion), the ability to flourish in a host environment (capsule), the capacity to hinder host immune reactions, the capacity to consume nutrients and iron from the environment, and the capacity to recognize changes in the surroundings. Without a doubt, the concept of bacterial virulence factors has aided in the identification of important virulence features that have significantly improved our knowledge of microbial pathogenesis. As a result, the pathogenicity mechanisms and virulence factors of bacteria are the main focus of this review.

Keywords: Microbial, environment, virulence factor, bacteria.

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INTRODUCTION

The core tenet of the virulence factor concept is that pathogenic bacteria possess specific properties that enable them to be virulent. Although there are many conflicting definitions of what a virulence factor is (Casadevall and Pirofski, 1999), the hypothesis nonetheless has a strong hold on researchers' imaginations and despite the fact that it has been shown that commensal organisms can cause disease, the idea still drives a significant percentage of research and development in the field of microbial pathogenesis (Casadevall and Pirofski, 2001). The degree of pathogenicity produced by the microbial system is determined by the virulence factors at work as well as other intrinsic mechanisms, including the number of microbial entities delivered in the host system, the administration route, and host-specific defensive mechanisms (Casadevall and Pirofski, 2009; Khan et al., 2010).

Unquestionably, the idea of virulence factors has contributed to the discovery of significant virulence traits in microbes, enhancing microbial pathogenesis knowledge in a significant way. Additionally, applying the molecular postulates to the process of identifying virulence elements has given researchers studying virulence in some bacteria an experimentally rigorous approach (Falkow, 2004). For virulence factors, the establishment of pathogenic resistance against immune defense is aided by the complement system, phagocytosis, or offering evasion from adaptive immune responses. They can also act as dietary or metabolic variables, necrotic elements, or differences in phenotypic morphology can affect it. These factors dictate how the host and pathogen interact and whether the host survives or perishes during this host-pathogen interaction. Toxins, adhesions, and aggressions that encode and give the pathogenic host virulence-associated features are some significant factors involved in the gaining of virulence elements that lead to the emergence of pathogenic forms by horizontal gene transfer (Saunders et al., 2001; Keen, 2012). This review focuses mostly on the pathogenicity and virulence factors of bacteria.

VIRULENCE FACTORS OF BACTERIA

The microbial characteristics that confer virulence mainly

fall into a few categories, such as the being able to enter a host, the ability to avoid host defenses, the ability to flourish in a host environment, the ability to interfere with host immunological reactions, iron and nutrition uptake from the environment, as well as the ability to recognize environmental changes. Despite the fact that various categories and features can belong to more than one group, it is generally pointless to try to incorporate virulence factors into functionally organized categories. For instance, enzymes that break down host tissue cause damage to the host, the production of nutrients, and the potential for entrance. Similarly, bacterial defense strategies against phagocytosis allow it to survive in a host. The pathogenic nature of the bacterium makes its virulence a relative measure of the harm it can inflict when the result of these adaptations results in host damage (Casadevall and Pirofski, 2009; Khan et al., 2010).

Adhesins

Bacterial adhesins are necessary for an organism to adhere to host tissues. Adhesins are regarded as virulence factors since it is generally agreed that attachment is necessary for the majority of microorganisms to infect and multiply in a host. Adhesins are intricate chemical mixtures that include polysaccharides, proteins, and components of bacterial cell walls. The Gal/GalNAc lectin mediates *Entoamoebae histolytica's* adhesion to colonic cells. Some species, such as Streptococcus pyogenes, have several adhesions, such as M protein and lipoteichoic acids. Many bacterial species, such as Aeromonas spp. and E. coli, have flagella as adhesins (Patti et al., 1994; Schwarz-Linek et al., 2004).

The adherence of various bacteria is facilitated by a broad family of proteins known as microbial surface-component-recognizing adhesive matrix molecules (MSCRAMM), including *Staphylococcus aureus* (Wann et al., 2000) and *Enterococcus faecalis* (Sillanpaa et al., 2004), to host surfaces. Adhesins are molecules that are exposed to surfaces, like other virulence factors, and can trigger protective immune reactions. Therefore, in the instance of *E. histolytica*, the host may become more resistant to amoebiasis by inducing an IgA response to Gal/GalBAc (Houpt et al., 2004).

Binding proteins for integrin and fibronectin

Many interactions between cells and between cells and the matrix rely on the heterodimeric transmembrane glycoproteins known as integrins. It has been demonstrated that some integrins that bind to collagen are conserved across the metazoan tree of life, as well as crucial for the multi-cellularity of animals (Hoffmann et al., 2011). Many bacterial species have created adhesion mechanisms that engage with host integrin receptors directly or indirectly as a result of integrin signaling's widespread distribution through several essential cell signaling cascades, such as those involved in cell adhesion and cytoskeletal architecture, are made possible by the fact that it is present across the animal kingdom (Schwarz-Linek et al., 2004).

The extracellular matrix (ECM) protein fibronectin is bound by a variety of surface adhesins known as fibronectin-binding proteins (FnBPs). They, therefore, belong to a large family of bacterial adhesins that recognize sticky matrix molecules on microbial surfaces. This interaction with fibronectin within the ECM in the case of the Gram-positive bacterium *Staphylococcus aureus* is capable of promoting bacterial adherence to the surface of the host cell by taking advantage of fibronectin's binding to the host cell integrin-51 (Patti et al., 1994; Schwarz-Linek et al., 2004).

It has been demonstrated that through the use of fibronectin bridges, *S. aureus* FnBPA binds to integrin 51 and promotes bacterial absorption into host cells (Sinha et al., 1999). Additionally, it has been demonstrated that the Streptococcal FnBP Sfbl/F1 mediates the invasion of epithelial cells (Ozeri et al., 1998). Although the binding of FnBPs to fibronectin has been reported to be a strong interaction (2.5 nN), presumably because a single FnBP can bind up to 9 fibronectin molecules, the significance of FnBPs during infection when comparing wild-type versus FnBP mutant strains *in vivo* has been conflicting. There have been theories that this may be because of the diverse spectrum of illnesses that these organisms often cause, as well as the abundance of other virulence factors, some of which may play redundant roles (Schwarz-Linek et al., 2004; Herman et al., 2014). FnBPs, however, were discovered to be essential for the development of biofilms in the methicillin-resistant clinical isolate *S. aureus* strain LAC (McCourt et al., 2014).

By directly interacting with integrins, furthermore, bacteria have the ability to stick to and enter host cells. Invasin, a protein from Yersinia, has a high affinity for attaching to 1-integrin receptors on the surface of M cells and aids in the bacterium's initial adhesion (Isberg and Leong, 1990). After initial attachment and invasion, adhesion is maintained by the adhesins YadA and Ail, which mediate serum resistance and promote tight adherence to the ECM proteins fibronectin and collagen (Figure 1) (Felek and Krukonis, 2009).

Chaperone-Usher Pili: P pili and type I pili

Some of the most well-studied bacterial adhesins are chaperone-usher (CU) pili. Numerous Gram-negative bacteria as well as some Gram-positive bacteria produce

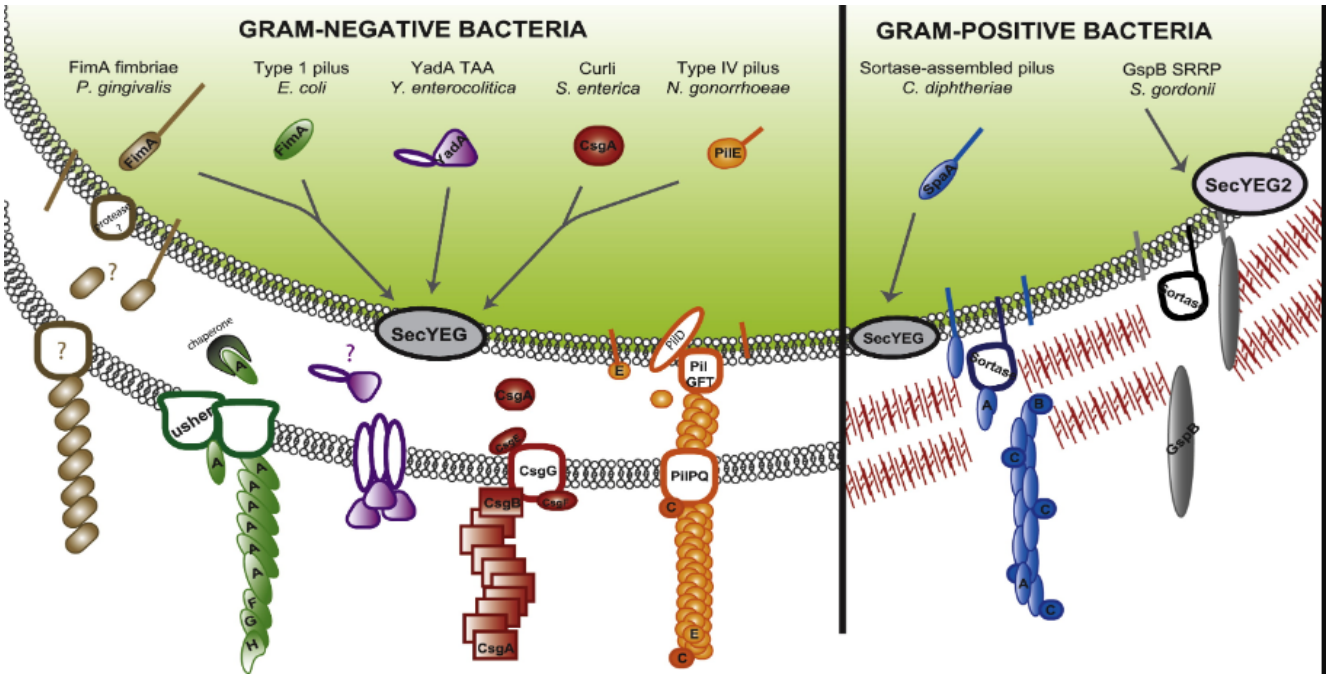

Figure 1. Effects of bacterial adhesins on host cell signaling (Patti et al., 1994).

long proteinaceous strands with multiple subunits that can be split into "tip" and "rod"-like domains that are helically twisted. Those pili are only employed for adherence because some pili can also be employed for the transfer of DNA during conjugation, host cell surfaces are frequently referred to as fimbriae (Lillington et al., 2014). The tip adhesion subunit PapG interacts with the P-pilus to bind to the -D-galactopyranosyl-(1-4)—D-galactopyranoside moiety of glycolipids found on upper urinary tract cells. The P-pilus was the first fimbria to be identified. It is produced by uropathogenic *E. coli* (UPEC) under the control of the pap operon (Lillington et al., 2014; Dreux et al., 2013).

Variations in PapG are also hypothesized since they can differentiate between diverse but related Gal (1-4) gal receptors that are unevenly distributed both within the host and within populations, they are thought to drive tissue and host specificity (Hultgren et al., 1991). The P-pilus' biogenesis has undergone extensive molecular analysis and is the model for chaperone-usher pilus formation.to drive tissue and host specificity since they can distinguish between various but related Gal (1-4) gal receptors that are variably distributed both within the host and within populations (Hultgren et al., 1991). The biogenesis of the P-pilus has been intensively investigated in molecular detail and is the archetype of chaperone-usher pilus development. The general secretory pathway is used to deliver specific unfolded subunits into the periplasm, where DsbA first forms a disulfide bond (Stathopoulos et al., 2000). The outer membrane usher PapC uses donor strand exchange to generate and extend the pilus from the tip after the subunits have been further transported and stabilized by the chaperone PapD (Lillington et al., 2014).

The type I pili, a different class of heteropolymeric fimbriae that can be seen on the surface of pathogenic *E. coli*, are encoded by the fim operon (UPEC and DAEC). Similar to the P-pilus, the type I pili are made by the CU pathway, which comprises FimC as the periplasmic chaperone and FimD as the outer membrane usher (Phan et al., 2011). The adhesin tip of the fimbria is made by the FimH subunit, which binds glycoproteins containing mono- and tri-mannose. The structural and biophysical analyses of type I and type P pili have revealed that the tip adhesins bind to their individual ligands via catch bonds, or bonds whose strength is increased by a force like shear stress, and that the helically wrapped rod domain may be unwound to regulate the binding strength. Additionally, FimH has been connected to studies that demonstrate it contributes significantly to pathogenicity. Point mutations in FimH caused by adherent-invasive *E. coli* linked to Crohn's disease have been found to alter adhesin conformation, increasing intestinal inflammation through an unexplained mechanism (Dreux et al., 2013; Zakrisson et al., 2013).

Type IV pili

There is another article that provides a thorough analysis

of type IV pili, a subcategory of polymeric surface organelles that are among the most common in both Gram-positive and -negative bacteria as well as Archaea (Giltner et al., 2012). Contrary to CU pili, type IV pili's precise biogenesis and adhesion characteristics are still poorly understood, in part due to the fact that a large number of different proteins are involved in pilus formation and that a large number of type IV pili exhibit a wide range of functional abilities, including adhesion, aggregation, DNA transfer, electron transfer, and motility (Carbonnelle et al., 2005). A mature pilin subunit is created when pre-pilin peptidase recognizes and cleaves a conserved type III signal sequence at the pre-N-terminus of pilin. Pre-pilins must pass the inner membrane in order to develop type IV pilus. After being liberated from the inner membrane along with many auxiliary protein molecules, the pilin subunit is next converted into a fiber by an ATPase-dependent mechanism (Siewering et al., 2014).

The ATPases PilF and PilT in *Neisseria meningitidis* are in charge of the pilin fiber's extension and retraction through the bacterial cell wall, respectively, while the pilus is still connected to the target surface (Wolfgang et al., 1998). It has been shown that PilT levels and force-mediated elongation, which can alter how the bacteria interact with their host cells by increasing pilus tension, affect the link between elongation and retraction. Additionally, research has demonstrated that the number of pili on the *N. meningitidis* surface can alter how the host cells communicate and interact (Maier et al., 2004; Imhaus and Duménil, 2014).

Adhesive amyloids

Insoluble polymeric proteins are called amyloids that fibrils with a cross-stacked arrangement of folded -sheets in common. They were initially identified in human illnesses like Prion, Alzheimer's, and Huntington's encephalopathies, but it has now been discovered that they are incredibly widespread and demonstrate a wide range of functional diversity (Pham et al., 2014). Curli are a family of functional amyloids that are perhaps the best described. They are made by enteric bacteria such Shewanella, Citrobacter, *E. coli*, and Salmonella. Additionally, 5 to 40 percent of organisms isolated from natural biofilms exhibit amyloid fibers. There are two distinct operons, the csgBAC operon and the csgDEFG operon, are involved in the development of curli in *E. coli*. The csgDEFG operon codes in favor of the chaperones CsgE and CsgF, which collaborate with CsgG to create a special secretion system, as well as the soluble transcription regulation subunit CsgD (Hufnagel et al., 2013).

CsgA and CsgB are curli subunits that are subsequently transported to the surface of cells by the secretion system, where CsgB initiates CsgA to form the extremely stable fibril polymer. The engaged complex created by the un-gated, non-selective protein secretion channel generated by CsgG and CsgE restricts the conformational space within the channel, according to structural data. Entropy-driven, diffusion-based protein translocation is made possible by this caging, which over the channel results in an entropic free-energy gradient (Goyal et al., 2014). By interacting with fibronectin and laminin, among other host ECM proteins, amyloid fiber adhesion plays its primary role in increasing biofilm stability during biofilm development, which also increases resistance to protease breakdown. Mycobacterium tuberculosis Mtp amyloid fibers there have been demonstrated that can bind to laminin in the ECM and aid bacterial colonization and adhesion (Alteri et al., 2007).

Autotransporters

Numerous Gram-negative bacteria have a large family of outer membrane and secreted proteins known as autotransporters, which can exist as a monomeric or trimeric form. The majority of the time, they promote bacterial aggregation and biofilm development as well as adherence to accommodate ECM and cell surfaces. The conserved C-terminal translocation domain inserts into the outer membrane, the variable passenger domain, which can be either free or anchored to the cell surface and affects the protein's adhesive properties, and the N-terminal signal sequence of all auto-transporters allows the protein to be secreted across the inner membrane via the general secretory pathway, are shared structural features that are common to all auto-transporters (Totsika et al., 2012; El-Kirat-Chatel et al., 2013).

YadA of *Yersinia* sp. was the first described trimeric auto-transporter. It is believed that different *Yersinia* sp. YadA attaches to different ECM components (Bölin and Wolf-Watz, 1984). There are still several auto-transporter proteins without clear definitions. specific molecular mechanisms of action, while playing a significant and widespread role in bacterial pathogenicity. Antigen 43, an auto-transporter from uropathogenic *E. coli*, has a recently discovered twisted L-shape-helical structure that is expected to provide a molecular "Velcro-like" mechanism of self-association that enhances bacterial clumping (Heise and Dersch, 2006; Heras et al., 2014).

According to a study examining the binding interactions of Burkholderia cenocepacia trimeric auto-transporters, the homophilic and heterophilic connections produced by auto-transporter BCAM0224 are of low affinity. This poor adhesion may be biologically significant because, during lung colonization, adhesion and would be able to interact dynamically with a reduced affinity bacterial mobility,

facilitating the dissemination of the infection and binding to new sites (El-Kirat-Chatel et al., 2013).

Multivalent adhesion molecules

A variety of Gram-negative bacteria engage in high-affinity binding with the recently identified multivalent adhesion molecules (MAMs), a class of adhesins, in the early stages of infection (Krachler et al., 2011). Mammalian cell entry (MCE) domains are found at the N-terminus of MAMs and can be either six (MAM6) or seven (MAM7) in number (Figure 1). MAM6 and MAM7 molecules are only found in Gram-negative bacteria, although single MCE domain-containing proteins are more widely conserved and are also present in Mycobacteria, some Gram-positive bacteria, algae, and higher plants (Chitale et al., 2001).

The MCE domain was first described in Mycobacteria, which has four different operons that each encode an MCE protein. The majority of them are believed to play a role in lipid metabolism, despite the fact that Mce1A has been shown to increase M. tuberculosis adherence and internalization into non-phagocytic host cells (Chitale et al., 2001). It has been proposed that variations in Mce1A between *M. leprae* and M. TB reflect a potential mechanism of tissue-specific infection in the two species (Kumar et al., 2005). Gram-negative bacteria have six or seven MCE domains in their MAMs, as previously mentioned, and it has been shown that six domains are the bare minimum required for efficient binding to host cells (Krachler et al., 2011).

Intriguingly, it has been discovered that three to five MCE domains in tandem are found in recombinant MAMs to produce misfolded or extremely unstable proteins, explaining why nature does not show this domain arrangement. However, it is still unclear what the molecular causes of this discovery are. According to secondary structural predictions, MAMs are similar to FnBPs in that they contain a lot of -strands coupled by adaptable loop regions. The host ligands for MAM7 adhesion are phosphatidic acid and fibronectin, according to an analysis of *Vibrio parahaemolyticus* MAM7 binding interactions (Krachler et al., 2011).

Despite the fact that multiple bacterial receptors have been discovered to bind fibronectin, this is the first bacterial adhesin to be shown to directly bind to lipid ligands present in the host cell membrane. The binding to fibronectin was found to have a moderate affinity with an equilibrium dissociation constant (KD) of 15 M; however, the binding to PA was demonstrated to have a significantly higher KD of 200 nM. Investigation of this relationship has shown that PA is required for cellular adhesion and is primarily an important basic residue in MCE-1, 2, 3 and 4 to mediate this process. In contrast, fibronectin is not required and only serves to speed up host cell attachment. It was discovered binding showed only needed a 30 KDa N-terminal portion of fibronectin and that the interaction with fibronectin required at least 5 MCE domains. Sadly, the molecular basis Because of this, it is yet unknown how MAM proteins produce simultaneous protein-protein and protein-lipid interactions, as well as the crucial residues involved (Krachler et al., 2011; Kumar et al., 2005).

Invasins

The term "invasin" has historically been used to refer to virulence factors that specifically encourage bacterial internalization by a host cell. This label may also be applied collectively to the broad virulence tactics necessary for host colonization. A typical pathogen must invade the host by one or a combination of methods. The functional diversity of factors that encourage colonization can range from the release of poison into the environment to the manifestation of a specific surface ligand that stimulates receptor binding on a host cell. Numerous pathogens have developed specific macromolecular structures that are intended to transport effector chemicals right into the target cells' cytoplasm. These injection methods appear to be extremely effective pathogenic tactics because they avoid the necessity of a toxin's connection with a target through diffusion. Together, these strategies enable the pathogen to influence host cell molecular functions to increase adhesion, cytotoxicity, occasionally phagocytosis, and frequently general subversion of immunological systems, both innate and adaptive (Isberg and Leong, 1990; Krachler et al., 2011; Cambronne and Schneewind, 2005).

In the end, the bacteria will be able to survive by creating an environmental niche in the tissues of the host. Most pathogenic techniques share the requirement of secreting polypeptides from the bacterial cytosol to targets inside or outside the cell wall envelope. In order to accommodate these virulence methods, generalized secretion pathways are used or altered, creating specialized systems devoted to the invasion of host tissues (Cambronne and Schneewind, 2005).

Exotoxins

When various toxigenic bacteria, such as *Vibrio cholera*, *Clostridium tetani* and *Corynebacterium diphtheria*, the causative agents of cholera, tetanus and diphtheria respectively, were linked to disease, toxins were considered as contributing to pathogenicity. Exotoxins produced by these bacteria are necessary for the development of disease but not for the survival of cells (Collier and Young, 2003).

These poisons are typically produced by genes carried by plasmids, pathogenicity islands, or phages, and the cessation of toxin synthesis is typically accompanied by the cessation of virulence. Through disruption of cellular homeostasis, bacterial toxins increase virulence, and for toxigenic bacteria, the sickness can typically be wholly attributable to the toxin's action on the host. Edema factor, deadly factor, and other *Bacillus anthracis* toxins are enzymes that render mitogen-activated protein kinase and calcium- and calmodulin-dependent adenylate cyclase inactive. Both enzymes help *B. anthracis* become more virulent by impairing macrophage activity and preventing an efficient immunological response (Saunders et al., 2001; Cambronne and Schneewind, 2005; Collier and Young, 2003; Cox et al., 2000).

Modulins

Numerous microbial substances have the ability to harm a host by inducing inflammatory reactions. The fact that these substances are essential to bacterial cells means that they frequently do not fit the traditional standards for virulence factor definition. A pathogenic substance that can seriously harm the host by engaging with Toll-like receptors and setting off an inflammatory cascade is bacterial lipopolysaccharide. Modulins are microbial substances like lipopolysaccharide that cause unfavorable cytokine reactions. Even though many chemicals that cause cytokine reactions, like toxins and adhesins, also have additional functions in the pathogenic process, the idea that they are also modulins has arisen because of their capacity to harm via similar host-mediated inflammatory pathway substances (Henderson et al., 1996).

Enzymes

Bacterial pathogenicity has been linked to a variety of enzymes. Despite the large number of enzymes that fall under this group. The majority of enzymes that improve virulence by damaging host tissues attack host components and increase virulence. When tissue is damaged, the host is more receptive to microbial infection. Proteases, neurominidases, and phospholipases are examples of enzyme virulence factors that harm tissue. By breaking down substrates into nutrients that bacteria may absorb, these enzymes both damage cells and produce nutrition. They also change microbial activity to improve host cellular receptors in a way that can prevent the binding of their usual ligands, such as complement, as well as increase invasiveness, serum resistance, and evasion of host immunological responses. By enabling survival inside phagocytic cells, other enzymes, such as urease, increase virulence (Cox et al., 2000; Henderson et al., 1996; Modun et al., 2000).

Motility

In both bacteria and parasites, virulence has been linked to a complicated feature called motility. About 80% of known bacterial species exhibit some form of mobility, which is essential for mobile microorganisms to adapt to new habitats (Soutourina and Bertin, 2003). Flagella are specialized organelles that allow bacterial cells to migrate. Many bacteria use host actin to drive themselves forward in intracellular regions (Goldberg, 2001). Several intracellular infections, including Listeria monocytogenes, Rickettsiae and *Shigella* spp., utilise actin-based motility for cell-to-cell dissemination. While some amoebae utilize pseudopodia to crawl, certain protozoa use flagella to move. A myosin-actin motor's action is connected to the translocation of surface adhesins in other protozoa, such as *Toxoplasma gondii*, to produce gliding motility, a specialized kind of movement (Goldberg, 2001; Sibley, 2003).

The capacity for movement is closely related to other features that are thought to be associated with virulence, just as other virulence characteristics. For instance, many bacteria are mobile thanks to their flagella, which are also employed for adhesion, biofilm formation, and tissue colonization. The flagellar devices are utilized for the export of compounds linked to pathogenicity. Within the same genetic regulatory network, flagellar synthesis is frequently coordinatedly controlled with other virulence factors (Soutourina and Bertin, 2003). Additionally, flagella frequently exhibit antigenic diversity and significant immunological responses. In *Legionella pneumophila* and *Yersinia enterocolica*, flagella-dependent mobility increases the ability of the bacteria to invade host cells and contributes to their pathogenicity. Pathogenic organisms frequently exhibit motility, which increases virulence by enabling the bacteria to travel to advantageous niches, come into contact with host cells, cross cell membranes, and emerge from the intracellular space. Almost all motile microbes depend on several genes that are subject to intricate regulatory regulation in order to move, and virulence is commonly reduced by motility-related mutations (Young et al., 2000; Dietrich et al., 2001).

Capsules

In mammalian hosts, polysaccharide capsules are essential for pathogenicity and are present in a large number of harmful bacteria. *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are some of the bacteria that are encapsulated in

polysaccharide capsules. Among the eukaryotes, only *C. neoformans* contains a polysaccharide capsule. Even though some capsular structures can act as adhesins, most capsules play a role in microbial pathogenicity by shielding the bacterium from host immune systems (Schembri et al., 2004).

The anti-phagocytic and weak immunogenic properties of polysaccharide capsules, for instance, shield microorganisms from intracellular degeneration and phagocytosis. But there is mounting proof that the capsular polysaccharide that dissolves, produced by bacteria that are encapsulated can potentially increase virulence by having immunomodulatory effects. For instance, it has been demonstrated that the capsular polysaccharide of *C. neoformans* mediates a variety of adverse impacts on immunological cells, including modifications to cytokine synthesis and obstructions to leukocyte migration (Vecchiarelli, 2000).

Although polysaccharides make up the majority of microbial capsules, some also include interconnected amino acids. In this way, the poly-gamma-D-glutamic acid that makes up the Bacillus anthracis capsule works to prevent phagocytosis. However, antibodies against anthrax-prone mouse models, gamma-D-glutamic acid is opsonic and protective against *B. anthracis*, similar to the results with polysaccharide capsules (Kozel et al., 2004).

Complement evasion

Integral to both host defense against microbes and innate immunity is the complement system. Direct antibacterial activity, influencing opsonization, which encourages phagocytosis, and encouraging the inflammatory mediators to be released are just a few of the many activities that complement proteins do for the host. Numerous microbial organisms have the ability to avoid the harmful consequences of complement activation in the host by expressing determinants. Numerous impacts of microbial complement inhibition include leukocyte chemotaxis inhibition, opsono-phagocytosis inhibition, and serum resistance of Gram-negative pathogens. The capacity of Gram-negative lipopolysaccharides (LOS) to bind complement elements, preventing them from attaching to membranes and reducing complement-mediated cell lysis, is a key mechanism of serum resistance (Rautemaa and Meri, 1999).

While pneumococci may digest C3b without the aid of host proteins, Group A and B streptococci have a C5a peptidase that inhibits leukocyte recruitment. Microbiological determinants, such as Factor H, CD55 (decay-accelerating factor, DAF), CD21 (CR2), and CD46, that bind to or resemble the ligands of human regulators of complement activation (RCA) (MCP), are used in other methods of complement suppression (Lindahl et al., 2000). These determinants come in a variety of forms, but they always contain molecules that are exposed to the surface. Sialic acid residues on gonococci and type III group B streptococci's capsule, promote Factor H's inactivation of C3b; pneumococcal surface protein C (PspC), which binds Factor H; pneumococcal surface protein A (PspA), which prevents activation of the alternative complement pathway; and the streptococcal M protein, which binds C4 bp (Jarva et al., 2003).

Pigments

Production of pigments, especially those that resemble melanin, has been linked to virulence in a number of bacteria. Melanotic organisms have the ability to defend themselves against a range of host defensive mechanisms, including phagocytosis, defensins, and free radical fluxes (Nosanchuk and Casadevall, 2003). The prototype bacterium, *Cryptococcus neoformans*, whose laccase catalyzes melanization, is the one for which the role of melanin in virulence has received the most research. Mutants lacking laccase are less virulent and show poor initial pulmonary infection spread (Noverr et al., 2004).

Antibodies against melanin have been demonstrated to offer protection in infection-modeling animals, and interference with melanization in vivo has been proven to extend survival (Rosas et al., 2001). Pyocyanin in *P. aeruginosa* and *Plasmodium falciparum's* malarial pigment are two other pigments that have been linked to virulence in a variety of microorganisms (Lau et al., 2004; Lyke et al., 2003).

Mechanisms of pro-apoptotic

A type of non-inflammatory cell death called apoptosis contributes to the preservation of healthy host tissue. While microbial suppression of apoptosis has the potential to boost virulence by preventing the down-regulation of the inflammatory response, enhancing apoptosis has the potential to promote microbial persistence by eliminating antimicrobial effector inflammatory cells (Weinrauch and Zychlinsky, 1999). However, by reducing or enhancing the inflammatory response to the host's advantage, microbial modulation of apoptosis additionally may reduce pathogenicity. Toxins such as the diphtheria toxin, exotoxin A from *P. aeruginosa*, shiga-like toxins, exotoxins from B. pertussis and H. pylori, listerolysin O from Listeria monocytogenes, alpha hemolysin from *E. coli*, listerolysin O from Listeria monocytogenes, listerolysin O from *S. aureus* (Weinrauch and Zychlinsky, 1999).

Pro-apoptotic pathways have a complex and poorly understood impact on the host-microbe relationship.

While *P. aeruginosa* exotoxin-mediated neutrophil apoptosis has been proposed to promote Pseudomonas persistence by allowing the organism to evade neutrophil absorption, Yersinia YopJ-mediated induction of macrophage apoptosis has been connected to the evasion of host defense responses (Usher et al., 2002). These findings support the idea that pro-apoptotic pathways may benefit persistent or intracellular bacteria while potentially harming extracellular microorganisms. Therefore, the relationship between the host and the germ determines how pro- or anti-apoptotic pathways affect the virulence's of microbial and host defense (Griffin and Hardwick, 1997).

Biofilm formation

Exo-polysaccharide-based biofilms are dense collections of bacteria (Cvitkovitch et al., 2003). Biofilm production is accepted to be a crucial step in the pathogenesis of some infectious diseases, and biofilms are found everywhere in nature (Donlan, 2001; Parsek and Singh, 2003). Due to the intimate connections between the biofilm formation phenomena and other bacterial pathogenic mechanisms analyzing various processes, including quorum sensing, adhesion, and signaling separately inevitably entail an unnatural level of simplification and reductionism. The pathogenic process for various diseases, including dental caries, some types of nephrolithiasis, cystic fibrosis, and bacterial endocarditis, depends heavily on the production of biofilm. Both bacterial and host components make up the biofilm in these disorders, which isolates the microorganisms from host defenses and antimicrobial therapy. For instance, the bacteria that cause bacterial endocarditis are coated in fibrin threads that produce vegetations, the anatomical name for inflammatory developments on heart valves that are resistant to host defense processes and can only be treated for a long time with antimicrobial medications (Parsek and Singh, 2003).

A single bacteria may make up a medically significant biofilm (as in the case of endocarditis), or a variety of microbial species may form a biofilm (e.g. dental plaque). Persistent infections are caused by biofilm development on catheters and other medical prosthetic devices, which invariably results in catheter loss because antimicrobial therapy cannot be used to sanitize the tools (Donlan, 2001). The development of biofilms is linked to the propensity of several commensal microorganisms to colonize catheters and prosthetic devices, comprised of coagulase-negative both Candida albicans and Staphylococcus. The formation of biofilms in intravascular catheters for coagulase-negative staphylococci is a two-step, multigene-driven process in which the bacteria initially attach and then grow to form multilayered colonies encased in microbial polysaccharide and host components, such as fibrin (von Eiff et al., 2002).

However, it seems that the system and the organism are being studied for pathogenicity to determine how important biofilm development is to the pathogenic process. No link has been found between a bacteria's propensity for formation of biofilm *in vitro*, and pathogenicity in animal models for different bacteria like Listeria monocytogenes (Borucki et al., 2003) and *Staphylococcus aureus* (Kristian et al., 2004). In actuality, the relationship between the development of biofilms and other virulence variables may be complex or even conflicting. Capsule induction prevents the function of self-recognizing adhesion proteins, which are essential for the creation of biofilms in Gram-negative bacteria like *E. coli* (Schembri et al., 2004).

Bacterial secretion systems

Export of bacterial effector proteins required for pathogenicity by bacterial secretion systems. The secretion systems classified as Forms I–IV have been linked to at least four different types of pathogenicity. The export of specific toxins and drug efflux are both carried out via the protein-mediated Type I secretion system (Remaut and Waksman, 2004).

The export of specific poisons and enzymes is carried out by the Type II secretion system, sometimes referred to as the general secretion system. A multi-subunit protein assembly known as the Type II secretion system, which covers the periplasmic space, is responsible for exporting proteins to the extracellular compartment (Sandkvist, 2001). Some bacterial infections have unique methods besides the normal secretion pathway, secreting proteins into host cells. The syringe-like Type III secretion systems of a number of Gram-negative bacterial pathogens are used to deliver microbial effector proteins straight into the cytoplasm of the host cell (Buttner and Bonas, 2002). The Type III needle complex seen in *Salmonella* spp. is a complex structure made up of up to 20 proteins that might be related to flagella in terms of evolution (Kimbrough and Miller, 2002).

The payload carried by the Type III secretion system includes a large number of effector proteins that have detrimental effects on host cells. *Salmonella enterica* effector molecules SopE, SopE2, and SopB cause actin rearrangements while the Salmonella-actin binding proteins SipA and SipC coordinately alter host actin dynamics to aid bacterial uptake (Zhou and Galan, 2001). Pathogenic *Yersinia* spp. inject tyrosine phosphatase YopH into the cytoplasm of phagocytic cells via a Type III secretion pathway to resist phagocytosis (Fallman et al., 2001). This enzyme impairs cellular function and encourages cell rounding up. The Yersinia Type III secretion system thus demonstrates a relationship and overlap between the traits that promote inducible

resistance to phagocytosis and those that enable survival in a host. Type IV secretion systems are another mode of protein delivery to eukaryotic cells that has an evolutionary heritage with bacterial conjugation systems (Christie, 2001). The host cellular processes are disrupted or taken over by a variety of bacterial effector chemicals delivered by Type IV secretion channels (Nagai and Roy, 2003).

Iron acquisition

Microbial growth and metabolism depend on iron. Prokaryotic and eukaryotic germs that infect people find it difficult to get iron, yet limiting the host's ability to defend itself against several Gram-positive and Gram-negative organisms, protozoa, and fungi depend heavily on the availability of iron. Humans have iron-binding proteins such transferrin, lactoferrin and ferritin that limit the quantity of accessible free iron. Examples of the close relationship between iron acquisition and virulence include associations between iron overload circumstances and infectious diseases and experimental models showing that iron administration improves lethality for bacteria like *Neisseria menigitidis* (Weinberg, 1999; Holbein, 1980).

Contrarily, iron uptake mutants have the potential to be avirulent (Genco et al., 1991) and iron shortage is linked to greater infection resistance. In host-microbe interactions, the host's iron-withholding mechanisms and/or the microbe's decreased iron uptake processes can diminish microbial virulence, whereas the microbe's iron acquisition mechanisms and/or enhanced host iron can boost it (Litwin and Calderwood, 1993). The generation of siderophores is coordinately modulated by iron together with other virulence factors such as the oxidative stress response and toxins (Litwin and Calderwood, 1993; Ratledge, 2004). Organisms that do not express siderophores can obtain iron through species-specific, surface-exposed receptors for transferrin, lactoferrin, and other iron-containing substances (Litwin and Calderwood, 1993).

Several human iron sources, including hemoglobin, haptoglobin-hemoglobin complexes, lactoferrin, transferrin, and lactoferrin, can be used by *Neisseriae* spp. (Genco et al., 1991). Heme transport is a crucial component of Yersinia pestis' intricate iron acquisition system, which is necessary for virulence (Perry, 1993). ABC transporter and related genes are involved in the mechanisms that transport iron from the cell's outside to its cytoplasm (Modun et al., 2000).

Intracellular survival

A portion of harmful bacteria possess the ability to live inside phagocytic cells and the intracellular survival mechanisms. Some microorganisms have evolved to the point of obligatory intracellular pathogenesis, which is characterized by genome reduction and total reliance on the host cell. These other microbes are classified as facultative intracellular pathogens because they still have the ability to replicate and survive without the assistance of their hosts. To ensure intracellular survival, each intracellular pathogen has a distinct strategy, with the caveat that all changes aim to reduce phagocytic cells' capacity to destroy microbes. Given that phagocytic cells kill ingested bacteria through a well-orchestrated mechanism that involves phagosome formation, maturation, and acidification, it makes sense that the so-called intracellular pathogens use just a few basic approaches for avoiding intracellular killing. By impairing cellular homeostasis and antimicrobial defenses, intracellular infections persist inside phagocytic cells. A variety of microbial characteristics, each of which can be regarded as a virulence factor, allowing for the possibility of intracellular survival should be seen as a specialized phenotype (Casadevall and Pirofski, 2009).

CONCLUSION

The virulence factor is a key concept in the fields of microbial pathogenesis and infectious diseases, hypothesis has been a potent force behind research and the flow of ideas. Practically speaking, the discovery that virulence components are frequently the target of efficient immune responses offers a guide for upcoming vaccine design. But this idea has some serious drawbacks, which stem from the fact that in the absence of host factors and host reactions, pathogenicity and virulence factors cannot be determined. In actuality, commensal organisms with the capacity to cause disease and bacterial pathogens seem to benefit from this idea the most.

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