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Bacterial Lipoproteins Diverse Role in Host-Pathogen Interactions

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Abstract

Lipoproteins have been identified in different strains of bacteria with vital functions and therefore these proteins are essential for their survival. Lipoproteins play roles in adhesion, conjugation, nutrition uptake, signal transduction, sporulation, transport, protein folding and virulence. The number of predicted lipoproteins in bacteria has increased in recent years. Lipoproteins present in bacteria are mainly confined to cell membrane and are involved in the bacterial-host interactions critical for the survival of bacteria. This paper reviews developments focusing interactions of bacteria with the host for their colonization within the host, adhesion to host surfaces and internalization of the host cells and tissues. Bacterial-host interactions involve sophisticated molecular mechanisms which are highly complex and adaptive in pathogenic organisms. The paper discusses, in particular, interactions involving lipoproteins of three strains, Neisseria meningitides, Mycobacterium tuberculosis and Streptococcus pneumoniae during the process of their pathogenesis. Advances leading to a better understanding of the role of lipoproteins in bacterial-host interaction are expected to lead to develop of novel therapeutic agents and vaccines.

Keywords: Lipoproteins; Bacteria; Bacterial-host interaction; Pathogenesis.

Introduction

In the recent years, primarily due to the advances in genome sequencing of bacteria, an increased number of lipoproteins have been predicted in the various strains of bacteria. Bacterial lipoproteins are critical for the survival of both the Gram-positive and Gram-negative bacteria. Bacteria are found on the surface of host or within the body as commensals or as pathogenic organisms. Survival of bacteria on or within the host is faced with challenges due to the host's defence mechanisms. Bacteria have evolved simple to complex mechanisms for their survival on or within the host. The mechanisms become even more complex when bacteria internalize within the host's cells during pathogenesis. The complex set of challenges at the levels of bacteria and the host are manifested in the form of molecular level interactions for an eventual fight for survival. Consequently, bacteria have evolved an armamentarium of molecules and mechanisms of which lipoproteins are an important constituent.

Lipoproteins play critical roles like helping bacteria in localization on host surfaces, survival within the host and protect bacteria against the host's defense mechanisms. At the molecular levels these roles are played by the involvement of

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lipoproteins in adhesion, conjugation, nutrition uptake, signal transduction, sporulation, transport, extra- cytoplasmic protein folding, and antibiotic resistance [1,2]. In case of pathogenic bacteria lipoproteins play a direct role in virulence by contributing to their enhanced powers for colonization, invasion, immunomodulation and resistance to host defence [3]. In Gram- negative bacteria, at least two enzymes responsible for biosynthesis of lipoproteins are critical for their survival, while in Gram-positive bacteria they seem to be dispensable [4,5]. As a result, mutations occurring in the enzymes taking part in the lipoprotein synthesis pathway are lethal in Gram-negative bacteria. In case of Gram-positive bacteria, mutations exhibit only mild growth defects [5,6]. This difference in the outcome of zyme mutations involved in the pathway of lipoprotein synthesis in Gram-negative and Gram-positive bacteria is explained by the functionality of enzyme precursors in the two classes of bacteria. In Gram-positive bacteria, the functionality of the precursors of necessary lipoproteins matches with the functionality of the mature lipoprotein [7,8]. In many Gram-positive bacteria, virulence is dependent on lipoproteins, and therefore such lipoproteins are necessary for virulence [9].

This review presents a description of the current understanding of the major roles of lipoproteins between the host and bacterial interactions and the involved underlying molecular level mechanisms. To begin, the review presents, in brief, developments related to lipoproteins structure and biosynthesis, followed by their roles in host – bacterial interactions during adhesion, colonization, pathogenesis and virulence. Examples of three specific organisms, namely, *Neisseria meningitides*, *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* are given to present a broader view of interaction during pathogenesis and virulence.

Lipoprotein Structure and Synthesis in Bacteria

Bacterial lipoproteins characteristically possess a conserved modified N-terminal lipid- cysteine residue which allows the hydrophilic protein anchoring into bacterial cell membrane [10]. Lipoproteins are initially translated as preprolipoproteins both in Gram- negative and Gram-positive bacteria. These initial forms have an N-terminal signal peptide consisting of 20 aminoacids which show the common features of a typical signal peptides of secreted proteins [11]. The pathway for lipoprotein biogenesis involves a two- step process in Gram-positive bacteria. In Gram-negative bacteria the process involves three steps. The first step is catalysed by the enzyme diacylglyceryl transferase (Lgt) which is then followed by cleaving of signal peptide by Lsp. The third step of Gram-negative bacteria involves attachment of the enzyme N-acyl transferase (Lnt) to the mature lipoprotein. The synthesis of lipoprotein involves close interaction of all the three lipoprotein enzymes, Lgt, Lsp and the protein translocation apparatus. A conserved sequence,[LVI][ASTVI][GAS]C, called lipobox is positioned at the C end of signal peptides. It is modified by a diacylglycerol moiety through a covalent attachment to the thiol group of the cysteine residue [12]. This modification is catalysed by the enzyme lipoprotein, diacylglyceryl transferase (Lgt), leading to the formation of a prolipoprotein. Prolipoprotein consists of a diacylglycerol moiety and is linked through a thioester bond to the protein. Lgt transfers negatively charged phospholipids like phosphatidylglycerol to its lipid substrate [13]. Lgt is a certain enzyme in the formation of bacterial lipoproteins and most of its characteristic features need further evaluation. Phylogenetic studies on Lgt sequences of distantly related microorganisms have revealed some conserved regions which might be necessary for enzyme function.The two regions, His-103 and Tyr-235, have been found essential for Lgt activity [14]. In most bacterial genomes *lgt* is found as a single gene. Some bacteria like *Bacillus cereus*, *Coxiella burnetti*, *Clostridium perfringenes* and *Streptomyces coelicolor* have two putative *lgt* paralogues and multiple Lgt enzymes. The reasons for the presence of multiple Lgt enzymes are not known. The mature lipoproteins are targeted to various sites

within the cell wall by the lipoprotein localization machinery (Lol) which comprises a system involving a transmembrane protein complex (LolCDE), a chaperone located in periplasm (LolA) and a membrane receptor in the outer membrane (LolB) [15].

In recent years, the number of predicted and identified lipoproteins of bacteria has increased. A single bacterium can have a large number of lipoproteins which are translocated across the cytoplasmic membrane for localization in various places in the cells. In *Escherichia coli* over 90 lipoproteins have been reported. A majority of *E.coli*lipoproteins is localized at the periplasmic side of the outer membrane but some are found at periplasmic face of inner membrane [16]. In some cases it is not the acyl component alone which is responsible for anchorage of lipoprotein to the periplasmic face of the outer and inner membrane, or outer membrane external, through hydrophobic interactions. The peptidoglycan based lipoprotein (Pal) found in Gram-negative bacteria has a site for binding with *m*-Dap residue of peptidoglycan [17]. The first to be discovered lipoprotein, Braun's lipoprotein, is the most abundant lipoprotein found in Gram-negative bacteria, and is the only lipoprotein covalently linked to the cell wall. In *E.coli* all the known lipoproteins face the periplasm [18]. But in some Gram-negative bacteria and spirochetes lipoproteins are present in the outer membrane. The absence of outer membrane in Gram-positive bacteria causes lipoproteins to be anchored to the outer plasma membrane through hydrophobic interactions. As a result outer plasma membrane is directly exposed to the extracellular environment. Lipoproteins can also be shed from the cell membrane and may serve an extracellular role farther away from the cell [19].

Bacterial-Host Interactions

Bacteria harbour the human body and thrive it's within and the outside. While in a healthy subject bacteria are restricted to thrive in selected areas like skin, mucosal linings of buccal cavity, nasal cavities, gastrointestinal tract (GIT) and vagina, the internal organs are normally sterile due to body's defence mechanisms. Once the body's defence barriers are damaged, opportunistic pathogens find way to internal organs and cause damage and disease leading to serious threat to life. Bacteria found within the body as commensals have evolved mechanisms to live in a friendly manner but as the physiological and health conditions within the host are changed, bacteria rapidly adapt to the changes and use the opportunity to grow fast and thrive by using a variety of mechanisms aided by an armamentarium of molecules. To survive outside and within the host, the bacteria havemechanisms through which they continuously interact with the host. In the process of continuous interaction with the host and its environment, which can vary from superficial existence for survival on the body surface to colonize mucosal linings of nasal cavity or GIT, lipoproteins found in bacteria serve a battery of useful functions for their survival.

Lipoproteins role in bacterial growth [20,21], colonization [22], as part of transport system [23,24] and signal transduction [25] are essential for the survival of bacteria. Lipoproteins also have a role in evading body's defence mechanisms and find way to deeper tissues and thrive there. The interactions are more intricate between bacterial mechanisms and the host's biological systems, in particular the defence mechanisms [22,24].

In progresion and establishing of inestinal disease,it is an essential requirement to create an intraction amoung commensal bacteria, enteric pathogens and host [25]. Host- bacterial interactions are of various types and are involved in processes leading to colonization, adhesion and internalization. Adhesion represents a crucial step for extracellular bacteria to persist in

the host. Adhesion is the first essential step to internalize within the host cells.

Interactions during Colonization

Bacteria have evolved mechanisms to hold on the surfaces of skin and tissues like respiratory, digestive and urogenital organs lined with mucosal linings [26]. Colonization of surfaces of these organs involves mechanisms involving glycoproteins. Pathogenic bacteria have evolved molecular strategies to adhere and proliferate on the surface as well as enter inside the host cells. Intestinal lining has a thick mucus layer which limits invasion by commensal micro flora or pathogenic bacteria finding way through food. Intestinal mucus is composed of mucins (glycoproteins), antimicrobial peptides, and immunoglobulins. Bacteria are mostly confined to the upper layer of mucus [27] and are absent in the deeper layers of mucus because it has antimicrobial substances. Mucinssecretion by goblet cells is modulated by the presence of microbial products and inflammation. Presence of microorganisms can also stimulate antimicrobial peptides secreted by Paneth cells from intestinal crypts. While antimicrobial peptides like α- defensins are constitutively expressed, peptides like REG3γ, an islet derived protein 3 γ , or cryptidins are produced following detection of pathogen-associated molecular patters (PAMPs). REG3 γ play the role of activating Toll-like receptors (TLRs) or signalling pathway of nucleotide-binding-oligomerization domain containing protein (NOD). IgA produced by B cells also play a critical role in limiting bacterial association with the intestinal epithelium [28].

The nature of interactions between host mucus and pathogenic bacteria constitutes the deciding mechanisms for host or the pathogen. While host can use shedding of mucus to prevent pathogenic *Helicobacter pylori* [29] colonizing gastric mucus, some bacterial pathogens have evolved mechanisms like production of proteases to target mucins, locomote through mucus using flagella, or counter antimicrobial products.

Microbiota, mainly constituted of commensal bacteria living on the surfaces of mucosal surface, constitutes another mechanism to prevent invasion by pathogenic bacteria. Microbiota plays an important role in digestion, intestinal epithelial metabolism and proliferation. It also plays an important role by directly competing with pathogenic enteric bacteria [30]. These commensal bacteria also release inhibitory metabolites like acetates and butyrate and compete with pathogens by utilizing nutrients present in the intestinal lumen.

Microbiota is also involved in the regulation of host immune system. In germ–free mice, which are devoid of microbiota, mucosal lymphoid follicles called Payer's pathches are poorly developed. They also present an altered composition of CD4pT cells and IgG producing B cells in the lamina propria. Enteric pathogenic bacteria overcome protection provided by microbiota by triggering inflammation [25]. Inflammation alters microbiota composition thereby allowing pathogens to outcompete commensals harbouring. During the inflammation of gut there is an increase of antimicrobial peptides in mucosa. Pathogenic bacteria are more adapted to resist antimicrobial peptides than the commensals [30] and this provides pathogenic bacteria an advantage to outgrow commensals. Certain compounds produced during inflammation, such as glycosylated proteins or tetrathionate, may be used by pathogens during anaerobic respiration giving them a growth advantage over the fermenting commensal bacteria in the inflamed environment [31].

Renewal of epithelial cells also plays an important role in the colonization of bacteria [32]. The gut lining involves

continuous turnover at a high rate. The new cells formed migrate upwards along the villi and finally are extruded at the tip of villi in about a week. Renewal of epithelial cells and their elimination works as a homeostatic mechanism for integrity of epithelium. This also serves as a defensive mechanism of the host to limit infection caused by pathogenic bacteria. Some bacteria use mechanisms to target epithelial cells to protect their replication sites or to invade the underlying tissues [32].

Bacterial-Host Interactions during Adhesion

Bacteria have evolved certain specialized mechanisms to adhere and colonize on the host surfaces. They possess an arsenal of molecular mechanisms to target and adhere to host cells. Pili are hair-like organelles protruding from the surface of bacteria which are involved in binding the organism to the host cells [33]. Initially discovered in Gram- negative bacteria, the base of pili is anchored to the bacterial outer membrane and the free tip has an adherence factor conferred with specificity to bind specific target. In uropathogenic strains of *Escherichia coli* (UPEC) which colonize urinary tract, and are involved in kidney infections, display pyelonephritis –associated (P) pili at their surface. The tips of these pili possess an adhesion factor named PapG which links to glycosphingolipids of the kidney epithelium [34]. Some UPEC strains also have Type I pili on their surface which have specificity to link with uroplakins of bladder [35]. In some Gram-negative bacteria, the expressed Type-IV pili contains several hundred copies of pilin protein, which is synthesized in the cytoplasm of bacteria [36].

The bacterium *Neisseria meningitides* normally inhabits human nasopharynx but occasionally enters the bloodstream and causes sepsis and meningitis. It possesses type IV pili which help it attach to the endothelial cells of blood vessels and help in formation of micro colonies [37]. Blood and its components move in capillaries at a high speed causing a hydrodynamic force which does not allow any bacterium to lodge on the endothelium lining of capillaries due to sheer stress. A drop in this sheer stress, such as those observed in brain capillaries, may initiate attachment of *Meningitides* to the endothelium [38]. Once attached, these bacteria are more resistant to sheer stress and are able to proliferate and establish microcolonies. This resistance is due to tiny cell projections or pili and a host of proteins underneath bacteria [39**]**. The type IV pili continue to hold cells aggregated even after division. Some bacteria may modify their pili and these may be detached and released from the parent colony to lodge at distant places to form similar microcolonies [40]. New variants of *Neisseria* type IV pili are formed to escape immune system. Pili structures have also been detected in Gram-positive bacteria, which are primarily of two types: ‘sortaseassembled pili” and “type IV-like pili”, the latter are similar to type IV pili of gram-negative bacteria. However, they differ in assembly mechanisms of their filaments. In addition to pili, a large number of bacterial cell surface factors called adhesins are also involved in binding to the host cell surface. The adhesins are able to recognize various classes of host molecules such as transmembrane proteins, integrins or cadherins or components of extracellular tissue matrix such as collagen, fibronectin or elastin [41]. After binding with cell surface, some adhesins also help in facilitating internalization of bacteria inside the host cells.

There are organisms which utilize tensile force to promote adhesion. This bonding is enforced by forcestrengthened bonds called ‘catch bonds’ [42]. *E.coli* FimH adhesion exhibits such a bonding to mannose. Pathogenic E.coli like the EPEC (Entero-Pathogenic *E.coli*) and EHEC (Entero-Hemorragic *E.coli*), which are respectively responsible for diarrheal diseases in children and foodborne infections, utilize a novel mechanism using an effector called Tir. Bacteria insert Tir in the plasma membrane of host cells and this insert serves as an exogenous receptor for the bacterial surface protein intimin [43]. Tir is delivered to host cell by using a complex delivery system involving the utilization of complex proteins. Following the

binding of bacterial intimin to Tir on host membrane surface, host cell cytoskeleton regulators, such as the Wiskott- Aldrich syndrome protein (N-WASP) and actin related protein 2/3 (Arp2/3), are recruited. These regulators remodel the actin cytoskeleton [43] leading to the retraction of the host cell absorption microvilli forming a pedestal under the attached bacterium. Tir therefore provides a direct connection between the bacteria and the host cytoskeleton [44].

Bacterial-Host Interactions during Infection and Virulence

Role of lipoproteins in virulence has been demonstrated through studies using lgt and lsp mutants [45]. *Lsp* mutants of *Streptococcus pyrogenes* have demonstrated reduced levels of adhesion and internalization [46]. Studies involving animal models of infections have shown attenuation of virulence following mutation of pathogen. The *lgt* mutant of *Streptococcus pyrogenes* was found to be avirulent in a mouse model of infection [6]. Loss of Lsp in *M.tuberculosis* reduced virulence. but it had no effect on the virulence of *Streptococcus suis* [47]. The *lsp* mutant of *L. monocytogenes* was found to have low virulence, whereas the *lgt* mutant of *Staphylococcus aureus* expressed as a hypervirulent type [48].

Internalization of bacteria in host cells provides a lifestyle with several advantages. The bacteria avoid stress-induced clearance and have access to a wide variety of nutrients. Thus, the pathogenic bacteria become inaccessible to humeral and complement mediated attack from the host defense system. Some bacteria also induce their internalization through nonprofessional phagocytosis by zipper and trigger mechanisms. The process involves activation of signalling cascades which causes reorganisation of the actin cytoskeleton of the host plasma membrane. During the zipper mechanism, bacterial proteins such as catherins or integrins, which are involved in cellular adhesion, engage with several host factors involved in strengthening of cell matrix. The trigger mechanism involves injection of effectors by the bacterium into the host cell cytoplasm triggers cytoskeletal rearrangement and formation of ruffles allowing engulfment and internalization of the bacterium [35].

Lipoproteins of Neisseria Meningitides

The various strains of pathogen *Neisseria meningitides* Z2491 [49] contain the genes encoding Lo1ABCD (NMA0830, -1091, 1403, and -1402), an essential machinery for the transportation of lipoproteins to the outer cell membrane [50]. Base on an annotation on the bacterium reveals that its genome can encodes for 53 lipoproteins [51]. In the pathophysiology of meningitis caused by *N. meningitides,* type IV pili play a key role [52]. The *N. meningitides* lipoprotein PilP (NMA0651) has an integral role to the formation of type IV pili, so that introducing a nonpilated strain of the bacterium is the result mutation of pilP [53]. The functionality of type IV pili is lost if two of three lipoproteins of the disulphide-bonded system (Dsb system) are absent [21]. Efforts to develop vaccines against *N. meningitidis* have led to identification of several immunogenic lipoproteins [54]. Antibodies raised against decorin binding protein DbpA of *B.burgdorferi* are unusually not bactericidal, raising question as to why antibodies raised against are not bactericidal.

Lipoproteins of Mycobacterium Tuberculosis

The genome of this bacterium encodes 99 putative lipoproteins and functions of several of them have been verified [55]. *M.tuberculosis* lipoproteins involved in virulence include solute binding proteins (SBPs) which serve as components of the ABC transporter machinery (PstS and ModA) [20] or are involved in bacterial growth (SubI and GlnH) [56]. Three lipoprotein antigen of *M.tuberculosis,* namely, LpqH, LprG and LprA, contribute to virulence by induction of

immunosuppressive responses and/or humoral and suppressive responses. The transporter ModA, which functions as a molybdenum transporter, is also potentially involved in virulence [20]. It has been reported that members of the Mce family of proteins, which enable *M.tuberculosis* to invade mammalian cells, contain high proportion of lipoproteins. A 19 kDa antigen of M.tuberculosis, which is a lipoglycoprotein, is recognised by TLR2 thus serving a role in the activation of immune responses at an early stage of infection [57]. In contrast,it has been found the 19 kDa antigen to have a role in antimicrobial inhibition processing such as inhibition of gamma interferon-depended responses like antigen processing [58]. Inhibition of different molecular mechanisms allows *M.tuberculosis* to survive and it is possible that the 19kDa antigen alone can't do it. The 19kDa antigen is involved in modulating CD4-T cell responses and also in the inhibition of IFN-gamma signalling [59].

Role of Lipoproteins of Streptococcus Pneumoniae

A total of 42 lipoproteins are predicted in the virulence determinants such as capsules, surface and surface proteins of *Streptococcus pneumoniae*. Out of these lipoproteins, 5 lipoproteins are considered immunogenic [60]. All typical strains of *S. pneumoniae* contain two lipoproteins, namely, PiaA (pneumococcal iron acquisition) and PiuA (pneumococcal iron uptake). Antibodies have been generated against both these lipoproteins [61]. Anti-PiaA and anti-PiuA antibodies have promoted opsonophagocytosis against *S.pneumoniae* [62]. Expression of PsaA (pneumococcal surface adhesion A) by all the serotypes of S.pneumoniae plays a major role in the pathogenesis of infection caused by *S.pneumoniae* [63]. Immunization with PsaA protected against carriage of *S.pneumonieae* but it did not protect against systemic disease [64].

Two lipoproteins of the peptidyl isomerases (PPIases) family, namely, putative proteinase maturation protein A (PpmA) and streptococcal lipoprotein rotamase A (SlrA) promote colonization by the bacterium, *S. pneumoniae,* and thereby help in its virulence. **A** 37kDa antigen of lipoprotein receptor-associated antigen I (LraI) has the role of an adhesin. Use of antibodies developed against PsaA affected the ability of *S.pneumoniae* to adhere to the nasopharyngeal epithelial cells [65]. This function of PsaA has been demonstrated by its upregulation during attachment to the pharyngeal epithelial cells [66].

Many pathogens depend on Fe (II) for their cellular functions while some require Mn (II) for growth and pathogenesis [64,67]. Because Mn (II) concentration is very low, high affinity transporters are required for survival. PsaA seems to serve this role of transporter in *S.pneumonieae.* Studies on bacteria containing mutations in manganese transporters revealed that mutants were vulnerable to oxidative stress. These studies indicate a key role of manganese in oxidative environment [68]. Inactivation of psaA genes follows *S.pneumonieae* hypersensitivity to oxidative stress [69]. SodA (superoxide dismutase) requires Mn (II) and is involved in the detoxifying mechanisms to protect against hydrogen peroxide and reactive radicals generated by the Fanton reaction [70]. Virulence studies on soda and psa mutants of *S.pneumonieae* have revealed that absence of SodA caused only a partial impairment of virulence whereas the absence of Psa made the strain avirulent. PsaA stimulates immune response leading to the formation of antibodies (IgA, IgG and IgM) by the type B cells [71]. PsaA is a highly conserved antigenic protein from amongst the various serotypes of *S. pneumonieae* found in the world. PsaA is indicated as a potential candidate to provide protection against *S.pneumoniae* serotypes. The immunogenicity of PsaA was enhanced when it was combined with another immunogenic protein (PspA), commonly found in *S. pneumonieae* [72].

So far, the progress made in the understanding of bacterial lipoproteins and their interaction with the host have opened new

vistas for the development of vaccines based on antigens identified from *S.pneumoniae* and *N.meningitides* [73]. Further advances in this area are expected to provide opportunities for development of novel pharmaceutical agents and vaccines.

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