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Biological Role of Legionella Pneumophila lipopolysaccharide

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Abstract

The lipopolysaccharide (LPS) localized in the outer membrane is the predominant molecule on the cell surface of Legionella pneumophila bacteria which contributes to the cell surface properties in an exceptionally important way. The chemical structure of L. pneumophila LPS is different from that of the endotoxins of other Gram-negative bacteria, despite the similar structure. Due to its complex structure and function as well as immunochemical and antigen variability, the L. pneumophila LPS plays an important role in the interaction with the host cell.

Introduction

Legionella pneumophila is an aquatic pathogen that is ubiquitously found in nature, both in anthropogenic structures and in environmental waters as parasites of free living protozoa. In evolution with protozoa, L. pneumophila acquired a rare ability among microorganisms to infect macrophages owing to their exceptional adaptation feature. The bacterium has been identified as one of the three most common causes of severe community-acquired pneumonia (CAP). Legionnaires' disease accounts for 2%-8% of CAP [1-3]. A review of 41 European studies of CAP identified Legionella as the causative agent in 1.9% of outpatients, 4.9% of hospitalized patients and 7.9% of ICU patients [4]. Among the 20,000-30 000 cases of Legionnaires' disease reported annually in the USA, approximately 25% are acquired in hospital [5]. More accurate estimates suggest that 56,000-113,000 cases occur in the US annually and most are not diagnosed [6].

Human infection usually occurs through inhalation of bacterium-contaminated water in the form of water-air aerosol via cooling towers, air-conditioning systems, and industrial and medical equipment. However, although humans have traditionally been considered a dead-end host for Legionella, one probable case of person-to-person transmission has recently been reported [7]. Legionella cause respiratory infections with varying severity: from flu-like infection called Pontiac fever, which does not require specialized treatment, to acute, multilobar pneumonia, which can result in death. The cause of this dichotomy is still unknown. Pontiac fever is probably due to exposure to low-dose live or dead Legionella bacteria incapable of causing pneumonia in the affected host [8]. The most common clinical manifestation of Legionella infection is pneumonia, which does not require hospitalization. Fatal courses of the disease occur when the bacteria disseminate deeper into the lung.

The infection progresses from bronchopneumonia to lobar pneumonia. Histopathology from infected lung tissue shows an infiltration of macrophages and granulocytes, fibrin-rich proteinaceous exudates in the alveoli and a diffuse alveolar damage, indicating inflammation and destruction of lung tissue after infection with L. pneumophila [9]. A radiographic examination of the chest shows infiltrates and nodules, but these changes are not distinctive enough to distinguished legionellosis pneumonia from pneumonia of different origin. Laboratory and histopathological analyses of lungs can only suggest the aetiology, but microbiological tests are the basis for the disease diagnosis. Appropriate confirmation of LD allows inclusive empirical treatment, changes in drug dosage or duration, or targeting of alternative antibiotics active against Legionella spp. Until recently, 62 species of bacteria from the family Legionellaceae have been isolated from environmental samples, and about half of the known species were also isolated from patients and have thus been associated with infection. Within the species, one or two serotypes were distinguished and L. pneumophila was subdivided into 16 serogroups.

In the US and Europe, the most common cause of LD is L. pneumophila serotype 1, responsible for approximately 70%-92%

of laboratory-confirmed cases; non-serogroup 1 L. pneumophila causes only 7% of legionellosis cases. Other species most commonly isolated were L. longbeachae (3.9%) and L. bozemanae (2.4%), followed by L. micdadei, L. dumoffii, L. feeleii, L. wadsworthii, and L. anisa (2.2% combined) [10]. However, in Australia and New Zealand, L. longbeachae represent 30.4% of cases community-acquired legionellosis [11]. Over 200 clinical Legionella isolates were subjected to comparative genome analysis using microarrays. It was found that the LPS biosynthesis gene cluster of serogroup 1 was the only common feature of L. pneumophila 1 strains. This suggests that the specific LPS of serogroup 1 is at least partly responsible for the predominance of this serogroup in human disease [12]. LPS is the major immunodominant antigen of all Legionella species including L. pneumophila [13]. It is the main component recognized by patient's sera and by diagnostic assays in urinary antigen detection [14]. The LPS molecule possesses a high degree of diversity and thereby provides the basis for the classification of L. pneumophila into serogroups and subgroups by monoclonal antibodies (mAb) [15].

Chemical structure of L. pneumophila LPS

The chemical structure of L. pneumophila LPS is different from that of the endotoxins of other Gram-negative bacteria, despite the similar structure. This multi-functional macromolecule is composed of a polysaccharide part: an O-specific chain, an outer and inner core, and the lipid part, i.e. lipid A. The O-specific chain of L. pneumophila LPS is a homopolymer composed of 10 to 75 subunits of legionaminic acid, which is highly hydrophobic due to the presence of acetyl and acetylamide groups. The oligosaccharide core has a hydrophobic character as well. The high hydrophobicity of the L. pneumophila surface layer increases their survival in aerosols and facilitates adhesion to the host cell membrane. The saccharide backbone of Legionella lipid A is composed of 2,3-diamino-2,3-dideoxy-D-glucose linked via an amide bond with hydroxy acids, which are acylated by linear and branched (iso and anteiso), rarely encountered in nature long-chain fatty acids.

The high diversity of lipid A fatty acids has been used for distinguishing Legionella from other Gram-negative bacteria and in differentiation of species from one another. 27-oxo-octacosanoic acid is present in all examined Legionella species; it is regarded as a chemotaxonomic marker of this bacterial group [16-17]. Legionaminic acid in OPS of L. pneumophila serogroup 1 has the same configuration and the same C5 ring conformation as neuraminic acid, a common constituent of mammalian host-cell-surface glycoconjugates. It has been hypothesized that bacterial pathogens utilize legionaminic acid as a molecular mimic of sialic acid which is an important factor in immune system regulation and adhesion [18]. The presence of the deoxy groups and N- and O-acyl substituents in polylegionaminic acid makes LPS of L. pneumophila highly hydrophobic. It is known that the "hydrophobic bacteria" concentrate preferentially at the interface between water and air phase of a bubble. Bubbles, enriched with bacteria, can burst to produce aerosols containing viable bacteria. The formation of contaminated aerosols remains a crucial problem for the spread of the disease.

The role of L. pneumophila LPS in host-pathogen interaction

In comparison with the highly toxic Salmonella Minnesota LPS, L. pneumophila LPS is an over 1000-fold weaker inducer of proinflammatory cytokines produced by both MonoMac6 macrophages and bone marrow granulocytes. This is associated with the weak binding of LPS by lipopolysaccharide binding protein (LBP) present in plasma and by the CD14 receptor bound to both the macrophage membrane and its soluble sCD14 form [19]. Two Toll-like receptors (TLR4 and TLR2) are involved in the process of recognition of LPS related to development of inflammation [20]. LPS as well as live and formaldehyde-killed L. pneumophila cells stimulated murine C3H/HeJ bone marrow cells exclusively through TLR2. Macrophages and dendritic cells devoid of TLR2 after L. pneumophila induction were characterized by decreased production of IL-10 and TNF-α. Atypical activation of TLR2 by L. pneumophila LPS is probably a consequence of the increased stability of the outer membrane determined by the presence of long-chain, branched fatty acids. L.

pneumophila LPS is characterized by the presence of fatty acid chains twice the length of the corresponding chains found in high toxic enterobacterial LPS. Upon contact with the surface of the phagocytic cell, L. pneumophila LPS triggers a MyD88 adaptor protein-dependent signalling pathway. Protein MyD88-deficient murine mutants are unable to produce IL-6, IFN-γ, and chemokines responsible for rapid migration of leukocytes to the infection site. Consequently, mice develop an acute respiratory infection accompanied by dispersal of the bacteria to lymphatic vessels and spleen [21]. Additionally to TLR, LPS of L. pneumophila interacts with eukaryotic motifs leading to positive or negative effects for the bacterium. LPS of L. pneumophila is engaged in modulation of intracellular trafficking independently of the type IV Dot/Icm secretion system, which is also essential for intracellular multiplication of Legionella spp.During the E-phase, replicative noninfective phase growth, and during the PE transmissive growth phase characterized by preferential expression of genes required for virulence, L. pneumophila shed molecular-weight LPS and LPS-rich outer membrane vesicles [22].

In the E-phase, OMVs are attached to the bacterial cell wall but expel LPS structures, whereas in the PE-phase, the vesicles are profusely released [23]. Both OMV-bound and unbound LPS could participate to the inhibition of phagosome maturation [24]. L. pneumophila LPS specifically interacts with pulmonary collectins and hydrophilic surfactant proteins A and D, which play important roles in innate immunity in the lung. They promote localization of the bacteria to an acid compartment of lysosomes, thus suppressing intracellular growth of phagocytosed pathogens [25]. Human apolipoprotein E (ApoE) after interaction with LPS L. pneumophila impedes the penetration of host cells [26]. Cytoplasmic LPS derived from L. pneumophila triggers caspase-11-dependent pyroptosis via host guanylate binding proteins [27]. The lipopolysaccharide of L. pneumophila plays an important role in all stages of host cell infection.

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