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Structure and function: Lipid A modifications in commensals and pathogens

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ABSTRACT

Lipopolysaccharides (LPS) of Gram negative bacteria are one of the most potent stimulators of the host innate immune system and LPS recognition is essential for the host organism to clear infections of invading bacterial pathogens. Here we review on the latest research on how LPS is sensed by host cells and how distinct LPS structures differentially modulate the strength of the host immune response. Much is known about host immunological reactions towards pathogens via recognition of their LPS, as well as strategies of pathogens to modulate their LPS structure in order to evade the immune system. However, less is known about differential sensing of lipopolysaccharides of commensal bacteria in the intestine and how this contributes to manifestation or destruction of the intestinal homeostasis. LPS sensing is necessary to fight pathogens. However, sensing of LPS of gut commensal bacteria can simultaneously be disadvantageous for the genetically predisposed host, since this might lead to damage of the intestinal homeostasis and therefore to chronic intestinal inflammation. However, less immunogenic LPS could also serve as therapeutics to antagonize an overreacting innate immune system. Therefore, commensal gut bacteria-derived LPS could prevent from uncontrolled intestinal immune response in the intestine which makes LPS an attractive therapeutical approach to treat e.g. IBD.

1. Introduction

Lipopolysaccharides fulfil two major functions. First, the LPS anchored in the outer bacterial membrane provides a protective function for Gram negative bacteria and therefore acts as a defence mechanism against harsh environmental conditions. It provides a barrier against surrounding stress factors which therefore makes LPS indispensable for bacterial viability in various distinct ecosystems (Silipo et al., 2012). By substituting the lipid A sugar moieties with phosphate groups, the bacterium achieves to create a negatively charged outer membrane which can therefore interact with divalent cations present in the surrounding milieu. This plays an important role for the rigidity and the tightness of the outer membrane and hence mediates bacterial resistance to external stress factors (Alexander and Rietschel, 2001). Second, LPS is one of the most conserved structures within all Gram negative bacterial species. This makes LPS an important pathogen associated molecular pattern (PAMP) to be recognized by the mammalian innate immune system which can subsequently initiate the clearance of a bacterial infection. This important immunological reaction contributes to the manifestation of relatively conserved molecular structures in mammals for the recognition of this PAMP (Akira and Takeda, 2004). A timely recognition and sensing of LPS of invading Gram negative bacteria strongly accounts for host immune system activation (Netea et al., 2002). However, the initiated immune response has to be balanced. Uncontrolled bacterial overgrowth within the mammalian body usually leads to the release of large amounts of non-membrane bound LPS which can, in turn, result in exaggerated systemic host immune responses. In severe cases, this leads to septic shock with fatal consequences for the host (Bone, 1991; Bone et al., 1997).

2. Structure of lipopolysaccharides

LPS consists of three genetically, biologically and chemically distinct domains (Alexander and Rietschel, 2001) (Fig. 1): (I) the more or less acylated and phosphorylated lipid A being anchored in the bacterial outer membrane, (II) the core oligosaccharide linked by 3-deoxy-D-*manno*-oct-ulosonic acid (Kdo) with lipid A and (III) the so-called O-antigen or O-specific polysaccharide, with the latter two pointing to the aqueous environment. Lipopolysaccharides that comprise all three regions are called smooth (S)-form LPS, while LPS lacking the O-antigen are named rough (R)-form LPS or lipooligosaccharide (LOS) (Fig. 1). The lipid A structure in

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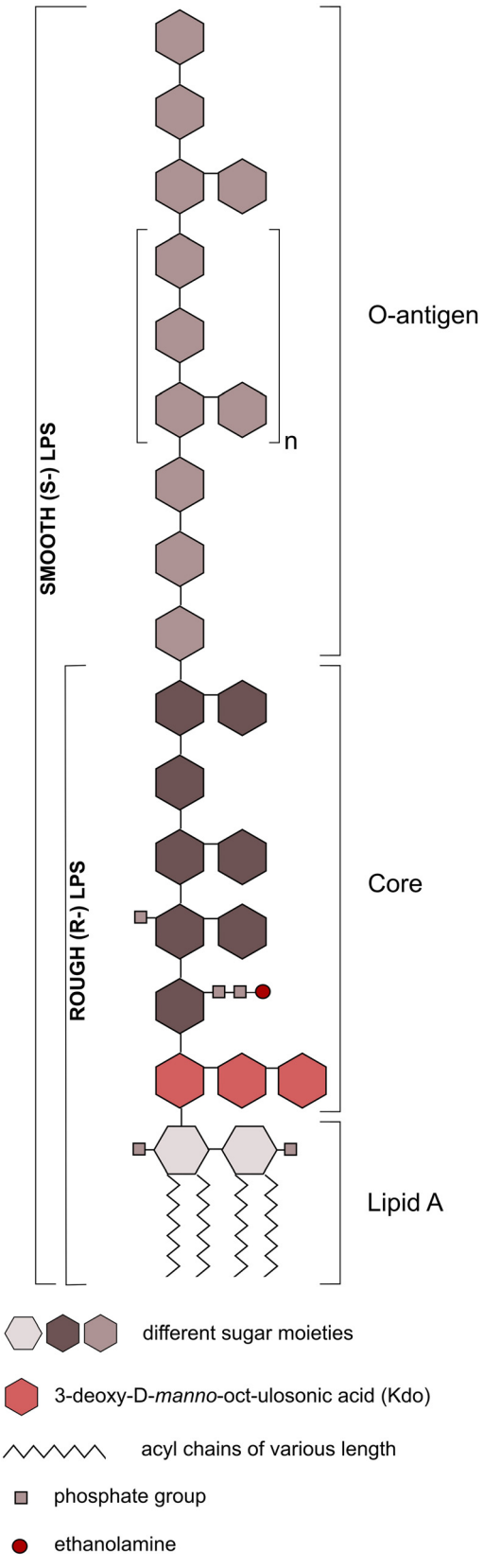

Fig. 1. *Schematic diagram of the general structure of lipopolysaccharides of Gram negative bacteria.* Lipolysaccharides of Gram negative bacteria consist of three main subunits (from bottom to top): lipid A, the core region and the O-antigen. Lipid A and the core-region form rough (R)-type LPS. Lipid A, the core-region and the O-antigen together form smooth (S)-type LPS. The number and chemical structure of the acyl chains can vary. Sugar moieties are depticted as hexagons in different colours. The number and chemical structure of these sugar moieties can vary.

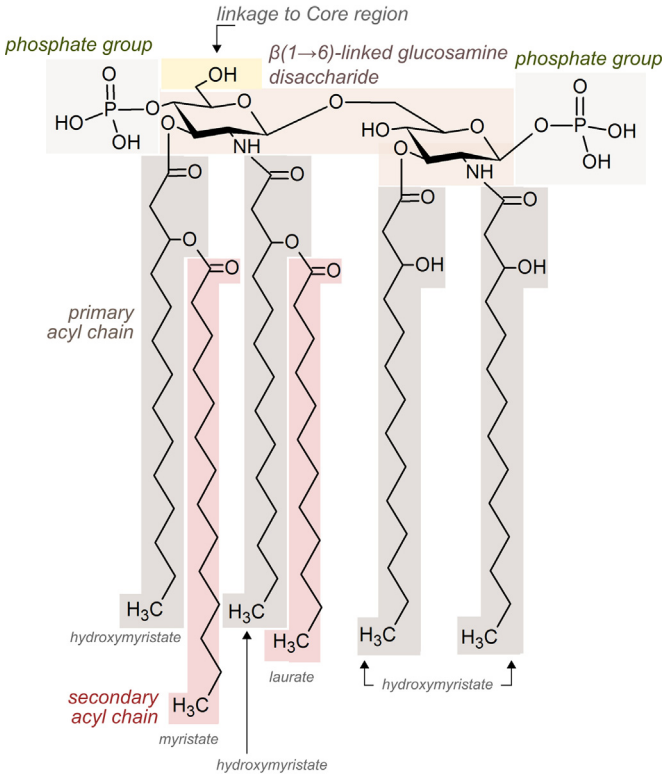

Fig. 2. *Detailed Structure of E. coli lipid A. E. coli* lipid A contains a β(1 → 6)-linked glucosamine disaccharide backbone (light brown). The hydroxyl group (light yellow) of the distal glucosamine links lipid A to the Core region. The two phosphate groups are depicted in light green. Primary acyl chains (light grey) are directly linked to the sugar moieties, secondary acyl chains (light red) are esterified with the hydroxyl groups of primary acyl chains. All primary acyl chains of *E. coli* lipid are hydroxymyristates, one of the two secondary acyl chains is myristate while the other one being laurate.

general is highly conserved, which is important for host receptor recognition.

3. Lipid A

Basically, lipid A is made up of a $\beta(1 \rightarrow 6)$-linked glucosamine disaccharide backbone which is mostly phosphorylated at position 1 and 4′ of the saccharides and acylated at positions 2 and 3 of each monosaccharide portion (Galanos and Freudenberg, 1993; Homma et al., 1985; Kotani et al., 1985).

Usually, lipid A is hexaacetylated, meaning that six acyl chains of variable length are esterified with the disaccharide backbone. Primary acyl chains are directly esterified with the sugar moiety while so-called secondary acyl chains form ester bonds with hydroxyl groups of primary acyl chains. “Symmetrically” acetylated lipid A means that each glucosamine moiety carries the same number of acyl chains. *Escherichia coli* LPS is an example for containing an “asymmetrically” acetylated lipid A, since 4 of its 6 acyl chains are carried by the first glucosamine. Lipid A is embedded in the outer leaflet of the bacterial outer membrane through electrostatic and mainly hydrophobic interactions. Here, the diglucosamine part of the lipid A is orientated towards the exterior environment while the lipid A acyl chains point to the hydrophilic interior of the membrane (Raetz and Whitfield, 2002). Fig. 2 illustrates the detailed structure of *E. coli* lipid A which is considered to be the prototype form of all lipid A structures. Its two glucosamine residues are each substituted by a phosphate residue at positions 1 and 4′, respectively. The hydroxyl groups at positions 2 and 3 of each monosaccharide are