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LIPOPOLYSACCHARIDE ENDOTOXINS

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■ **Abstract** Bacterial lipopolysaccharides (LPS) typically consist of a hydrophobic domain known as lipid A (or endotoxin), a nonrepeating "core" oligosaccharide, and a distal polysaccharide (or O-antigen). Recent genomic data have facilitated study of LPS assembly in diverse Gram-negative bacteria, many of which are human or plant pathogens, and have established the importance of lateral gene transfer in generating structural diversity of O-antigens. Many enzymes of lipid A biosynthesis like LpxC have been validated as targets for development of new antibiotics. Key genes for lipid A biosynthesis have unexpectedly also been found in higher plants, indicating that eukaryotic lipid A-like molecules may exist. Most significant has been the identification of the plasma membrane protein TLR4 as the lipid A signaling receptor of animal cells. TLR4 belongs to a family of innate immunity receptors that possess a large extracellular domain of leucine-rich repeats, a single *trans*-membrane segment, and a smaller cytoplasmic signaling region that engages the adaptor protein MyD88. The expanding knowledge of TLR4 specificity and its downstream signaling pathways should provide new opportunities for blocking inflammation associated with infection.

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ENDOTOXINS AS ACTIVATORS OF INNATE IMMUNITY

Lipid A (endotoxin), the hydrophobic anchor of lipopolysaccharide (LPS), is a glucosamine-based phospholipid that makes up the outer monolayer of the outer membranes of most Gram-negative bacteria (1–5). There are $\sim 10^6$ lipid A residues and $\sim 10^7$ glycerophospholipids in a single cell of *Escherichia coli* (6). The minimal LPS required for the growth of *E. coli* consists of the lipid A and Kdo (3-deoxy-D-*manno*-oct-2-ulosonic acid) domains (Figures 1, 2) (1, 7, 8). In wild-type strains, additional core and O-antigen sugars may be present (Figure 1) (5, 7, 9–11). Although generally not required for growth in the laboratory, these help bacteria resist antibiotics, the complement system, and other environmental stresses.

Many Gram-negative bacteria, including pathogens, synthesize lipid A species resembling the one found in *E. coli* (Figure 2) (1, 3, 4). Early ambiguities concerning the structure of lipid A have generally been resolved [see (1, 3, 4)]. Given their conserved architecture, most types of lipid A molecules are detected at picomolar levels by an ancient receptor of the innate immune system present on macrophages and endothelial animal cells (12, 13). The receptor, recently identified as TLR4 (toll-like receptor 4) (14, 15), is a membrane-spanning protein that is distantly related to the IL1 receptor (12, 13).

In macrophages, lipid A activation of TLR4 triggers the biosynthesis of diverse mediators of inflammation, such as TNF-α and IL1-β (16, 17), and activates the production of costimulatory molecules required for the adaptive

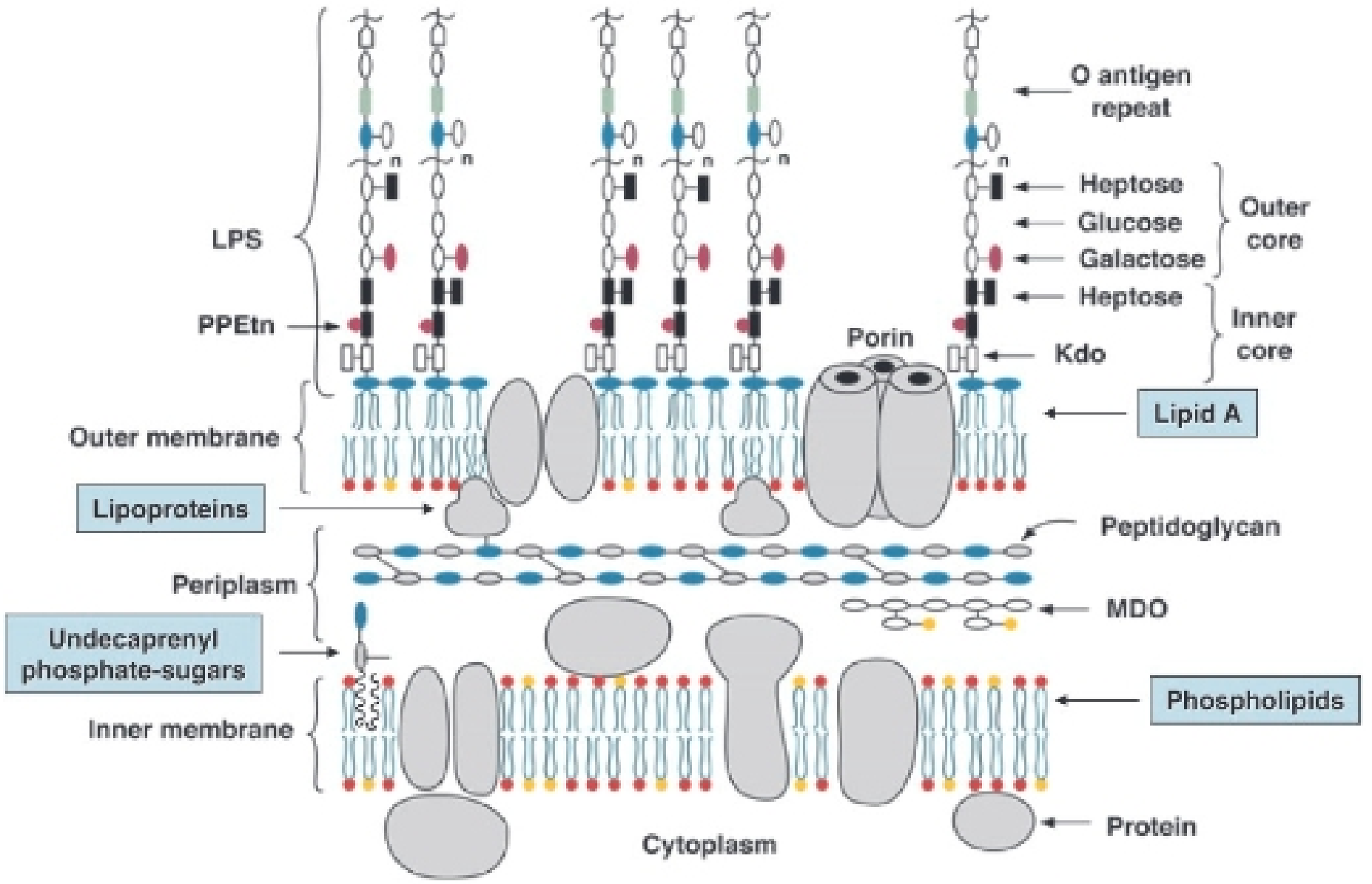

Figure 1 Model of the inner and outer membranes of *E. coli* K-12. Only the Kdo and lipid A regions of LPS are required for the growth of *E. coli* and most other Gram-negative bacteria (2). Exceptions to this general rule include certain spirochetes in which all lipid A biosynthesis genes are absent (141), *Thermotoga maritima* (137), and *Neisseria meningitidis* Type B in which lipid A-deficient *lpxA* knockouts can be constructed (133), provided the polysialic acid capsule is present (134a).