# REGULATED ASSEMBLY OF LIPOPOLYSACCHARIDE AND ITS BALANCE WITH PHOSPHOLIPIDS IN *ESCHERICHIA COLI* REQUIRED A NEW THIOESTERASE TESD

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The outer membrane (OM) is essential for the viability of Gram-negative bacteria. This OM is asymmetric in nature due to the location of lipopolysaccharide (LPS) in its outer leaflet and phospholipids directed inwards. Maintenance of this asymmetry is crucial for bacterial cell envelope integrity. Bacteria keep a tight balance between the amounts of LPS and phospholipids because they use *R*-3-hydroxymyristate-ACP as the common metabolic precursor. This balance is achieved by regulating amounts of LpxC, which catalyzes the first committed step in LPS biosynthesis. The LpxC enzyme is unstable, and its amounts are determined by its FtsH-mediated proteolysis and several poorly defined signals such as bacterial growth rate, fatty acid composition, FabZ activity and accumulation of lipid A precursors. As FtsH cannot carry LpxC proteolysis by itself, our work discovered key players that either positively regulate FtsH-dependent proteolysis by identifying LapB as an adaptor or negatively by LapC. Based on our genetic and biochemical data, we show that the interaction between FtsH-LapB directs LpxC to the degradation pathway, while LapB-LapC complex formation inhibits this reaction. While addressing how bacteria balance these two pathways and couple them with phospholipid biosynthesis, we discovered additional factors that contribute to LpxC stability and potentially couple lipid A and fatty acid biosynthesis via LapD, the acyl carrier protein and a novel thioesterase TesD. We further show that LapD becomes essential for bacterial viability in the absence of either cardiolipin synthase A or myristoyl transferase LpxM. We show that this lethality can be overcome by mutations in different subunits of acetyl-CoA carboxylase enzyme or by overexpression of the *tesD* gene, due to reduction in fatty acid biosynthesis. Thus, these results reveal a pathway by which bacteria such as *Escherichia coli* balance phospholipids and LPS to maintain outer membrane homeostasis.

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