Single-Particle Cryo-EM Studies of Lipopolysaccharide Transport

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The transbilayer movement of most lipids is energetically unfavorable and requires the facilitation by lipid flippases. The mechanisms by which flippases recognize and translocate specific lipid molecules have remained elusive. Lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria is critical for their cell envelope assembly. LPS synthesized in the cytoplasmic leaflet of the inner membrane is flipped to the periplasmic leaflet by MsbA, an ATP-binding cassette transporter. We have used single-particle cryo-EM to elucidate the structures of lipid nanodisc-embedded MsbA in three functional states. Our study uncovers the long-sought-after structural basis for LPS recognition by MsbA, delineates the conformational transitions of MsbA to flip LPS, and paves the way for structural characterization of other lipid flippases.