

MS07 Membrane Proteins

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Mechanism of a proton-dependent lipid transporter involved in teichoic acid synthesis

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Abstract

Transport of lipids across membranes is fundamental for diverse biological pathways in cells. Multiple ion-coupled transporters take part in lipid translocation, but their mechanisms remain largely unknown. Major facilitator superfamily (MFS) lipid transporters play central roles in cell wall synthesis, brain development and function, lipids recycling, and cell signalling. LtaA is a flippase that mediates the translocation of the lipid-anchor of lipoteichoic acid, an essential cell wall biopolymer in the Gram-positive pathogen *Staphylococcus aureus*. We used X-ray crystallography, cysteine disulfide trapping, molecular dynamics simulations, mutagenesis analysis, and transport assays in vitro and in vivo, to elucidate the mechanism of LtaA and reveal its importance for bacterial fitness. We demonstrate that while the entire amphipathic central cavity of LtaA contributes to lipid binding, its hydrophilic pocket dictates substrate specificity. We show that cycling through outward- and inward-facing conformations is essential for transport, while LtaA lateral openings are asymmetric in their function. We propose that LtaA catalyzes lipid translocation by a 'trap-and-flip' mechanism that might be shared among MFS lipid transporters.