More than Anagrams: MsbA and SbmA, a Link Between Primary and Secondary Transporters

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SbmA is a membrane transporter from *Escherichia coli* that imports antimicrobial peptides. Although the protein is a secondary transporter that is energized by the proton gradient, it is structurally related to the transmembrane domain (TMD) of ATP-binding cassette (ABC) transporters. SbmA therefore bridges the structural divide between primary and secondary transporters. While SbmA has likely evolved from the TMD of an ABC transporter, it remains unclear if SbmA also shares the mechanism of alternating access with ABC transporters, because only a single (outward-open) state has been resolved. We determined the cryogenic electron microscopy structures of SbmA in occluded and inward-facing states. These conformations closely resemble equivalent states found in ABC transporters, indicating a shared structural mechanism of transport. In contrast to ABC transporters, where nucleotide binding, hydrolysis and release steer conformational changes necessary for substrate translocation, electron paramagnetic resonance (EPR) spectroscopy and molecular dynamics (MD) simulations reveal how pH changes induce conformational transitions in SbmA, consistent with a mechanism of substrate internalization that uses the transmembrane proton gradient.

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