Targeting the dynamic BAM–SurA holo insertase complex with novel antibiotics

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The β-barrel assembly machinery (BAM) complex is essential for folding and inserting outer membrane proteins (OMPs) in Gram-negative bacteria. This process relies on the substrate insertion into the membrane by BamA but also on the prior chaperone-mediated substrate delivery to the complex, an essential yet poorly understood mechanism. We determined the structure of the holo insertase complex, where SurA, the major periplasmic chaperone, binds BAM for substrate delivery. High-resolution cryo-EM structures and 3D variability analysis show that the holo insertase complex has a large motional spectrum. This motion is independent of the conformational flexibility of the BamA barrel, which can open and close, but is coupled to conformational changes of the C-terminal helix grip domain of BamC. Substrate delivery by SurA to BAM thus appears to follow a concerted motion that encodes a gated delivery pathway through the BAM accessory proteins to the membrane entry site. This conformational motion may present various new approaches for inhibition and development of novel antibiotics against BAM. Furthermore, we identified a novel family of bamabactins, the xenorceptides, that selectively kill drug-resistant Enterobacteriaceae. Mode of action studies revealed that xenorceptides integrate into the BamA barrel as an additional β-strand, locking BamA in a closed-like conformation, blocking its function and leading to bacterial cell death. This study advances the understanding of bacterial outer membrane protein assembly and paves the way for future research aimed at targeting the BAM complex for the development of novel antibiotics, offering advanced strategies to combat multi-resistant Gram-negative bacteria.