Invited Lecture

Bacterial lipid transport through envelope-spanning tunnels and bridges

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Gram-negative bacteria acts as a physical barrier against antimicrobials. Therefore, understanding the mechanisms behind outer membrane biogenesis is essential to understand how we can disrupt this barrier. In order to build their outer membrane, bacteria must first transport hydrophobic molecules, including phospholipids, across the periplasm.
Recently, two proteins have emerged as candidate phospholipid transporters, LetB and YhdP, that could fulfil this role. First, using cryo-EM, we show that LetB consists of 7 stacked dynamic rings that form a continuous, hydrophobic tunnel. Second, using a combination of negative stain EM and AlphaFold, we show that YhdP is formed of repeated beta sheets that fold into a long bridge lined with hydrophobic residues. Furthermore, YhdP and LetB are both large enough to span the entirely of the periplasm, directly connecting the inner and outer membranes. Using site specific crosslinking, we have successfully captured putative phospholipids at locations within the tunnel of LetB and bridge of YhdP.
Overall, our data supports a model that LetB and YhdP form tunnels and bridges connecting the inner and outer membranes, creating a hydrophobic pathway for the translocation of phospholipids across the periplasm.