Nature Reviews Microbiology | AOP, published online 3 November 2008; doi:10.1038/nrmicro2037

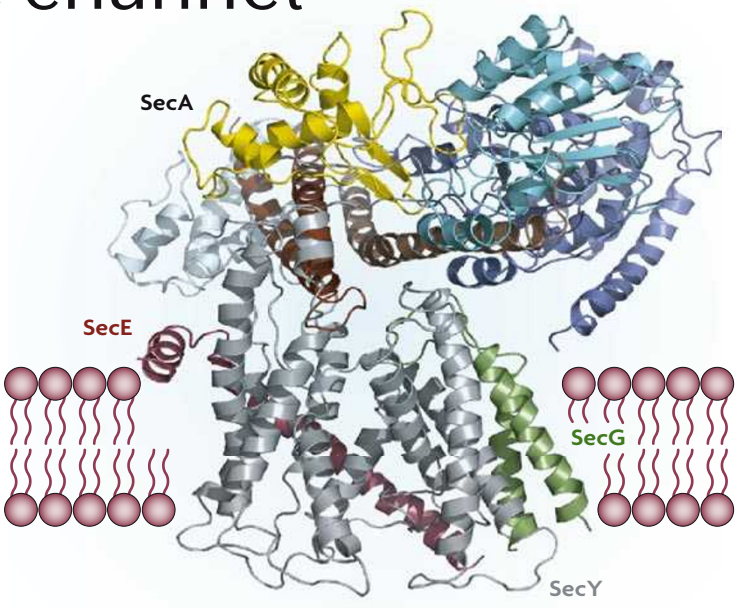
BACTERIAL SECRETION

Surfing the channel

Most bacterial proteins that are inserted into, or translocated across, the plasma membrane are targeted to the evolutionarily conserved SecY translocon complex. Three papers published in *Nature* now provide insight into how the cytoplasmic ATPase SecA moves polypeptides through the SecY channel.

A single copy of the SecY complex forms an hour-glass-shaped channel with a pore ring constriction midway across the membrane. The complex consists of two halves that are linked on the back and form a lateral gate at the front to allow release of transmembrane domains into the plasma membrane. In the closed state, the channel is blocked at the extracellular side of the pore ring by a short helix called the plug domain. In the open state, binding of a signal sequence or transmembrane domain of a translocating substrate to the lateral gate displaces the plug, which allows translocation to proceed. The driving force for translocation of polypeptides across the membrane depends on association of the translocon with different partners. Interaction with ribosomes allows co-translational translocation of emerging polypeptides, whereas post-translational translocation of fully synthesized polypeptides in bacteria requires binding to SecA.

Zimmer, Rapoport and colleagues now report crystal structures of SecA that are associated with SecY complexes. In the structures, a single copy of SecA was bound to each SecY complex, and this interaction led to substantial conformational changes in both partners. In the SecY-bound state, the SecA polypeptide cross-linking domain (PPXD) rotated from its original position to contact nucleotide-binding domain 2 (NBD2). This interface aligned perfectly with the channel opening in SecY, leading the authors to propose that PPXD and NBD2 form a clamp that captures and aligns substrates for insertion into the pore. Interestingly, upon binding to SecA, conformational changes in SecY led to the widening of the lateral gate but not complete displacement of the plug domain. A similar rearrangement was observed by Tsukazaki, Nureki and colleagues, who found that anti-SecY Fab fragments, which bind to the same site as SecA, promoted expansion of the lateral gate to form a hydrophobic crevasse. These observations point to formation of a 'pre-open' state, in which the translocation channel is primed but not yet completely open.



Cartoon of the SecA–SecY complex viewed from the side. Figure modified, with permission, from Zimmer, J. *et al.* Structure of a complex of the ATPase SecA and the protein-translocation channel. *Nature* **455**, 936–943 (2008).

> "…PPXD and NBD2 form a clamp that captures and aligns substrates for insertion into the pore."

In their second paper, Erlandson, Rapoport and colleagues investigated a two-helix finger-like structure that protrudes from SecA into the cytoplasmic funnel of the channel. Using a cross-linking approach, they showed that the loop between the two helices of the finger-like structure interacts with SecY at the entrance to the pore. Furthermore, mutation of this region blocked substrate translocation *in vitro*. The authors propose that a translocating polypeptide is positioned directly above the pore by the interaction of PPXD and NBD2, and that successive ATP hydrolysis cycles enable 'up and down' movements of the finger domain, which push polypeptides through the channel.

These structures provide valuable insights into the mechanisms for post-translational translocation through the SecY channel. However, the structure of a SecA–SecY complex that is bound to a translocating substrate must be determined to fully elucidate this process.

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ORIGINAL RESEARCH PAPERS Zimmer, J. *et al.* Structure of a complex of the ATPase SecA and the protein-translocation channel. *Nature* **455**, 936–943 (2008) | Erlandson, K. J. *et al.* A role for the two-helix finger of the SecA ATPase in protein translocation. *Nature* **455**, 984–987 (2008) | Tsukazaki, T. *et al.* Conformational transition of Sec machinery inferred from bacterial SecYE structures. *Nature* **455**, 988–991 (2008)