Online links

Salmonella enterica serovar Typhimurium: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomemap&cmd=Retrieve&dopt=Overview&list_uids=241

STRUCTURAL BIOLOGY

The flip side of MsbA

Two recent *Science* papers have revealed detailed structural evidence for the mechanism of action of the ATP-binding cassette (ABC) 'flip-pase' MsbA.

Lipopolysaccharide (LPS) is synthesized in the inner leaflet of the inner membrane as a precursor molecule. It must be transported first to the outer leaflet, where mature LPS is formed, and then to the outer

membrane. The essential ABC transporter MsbA is responsible for the transport of LPS across the inner membrane. Two crystallographic structures were already available for MsbA, one in an open and one in a closed conformation; however, the absence of ligands made it difficult to interpret these structures in terms of function and the ATPase cycle. A new crystal structure in the presence of substrate and site-directed spin labelling (SDSL) analysis now provides a more dynamic picture of the conformational changes in MsbA during substrate transport and ATP hydrolysis.

Reyes and Chang present the structure of MsbA from *Salmonella enterica* serovar Typhimurium complexed with magnesium, ADP and inorganic vanadate, and LPS at an average resolution of 4.2 Å. Compared with the previous structures, these MsbA molecules appear to be in post-hydrolysis mode. ATP hydrolysis causes a large, rigid body shift of the two transmembrane domains (TMDs), so that an inner chamber is created that can only be accessed from the periplasm. The structural shifts observed also suggest a possible mechanism for transmitting conformation change from the TMDs to the nucleotide-binding domains (NBDs).

The SDSL analysis of Dong *et al.* largely confirmed the structural observations of Reyes and Chang, with a few notable exceptions, such as the accessibility and mobility of

the periplasmic loops.

Both groups go on to propose models based on their structural data to support a 'flip-flop' mechanism of action for MsbA. The substrate LPS binds MsbA at a high-affinity surface-binding site. This conformational change is transmitted from the TMDs to the NBDs, resulting in ATP binding and hydrolysis. The free energy that is generated by hydrolysis of one ATP closes the inner chamber, trapping the LPS sugar head groups, which are then 'flipped' 180° by the rigid body shift in the TMDs, with the hydrophobic tails being dragged through the membrane. Hydrolysis of the second ATP molecule moves the NBDs apart, restoring the native conformation of MsbA.

Both of these papers represent a significant step forward, not only for the ABC transporter field and the corresponding implications for tackling multidrug resistance, but also for membrane proteins in general.

Sheilagh Molloy

References and links

ORIGINAL RESEARCH PAPERS Dong, J., Yang, G. & McHaourab, H. S. Structural basis of energy transduction in the transport cycle of MsbA. *Science* **308**, 1023–1028 (2005) | Reyes, C. & Chang, G. Structure of the ABC transported MsbA in complex with ADP-vanadate and lipopolysaccharide. *Science* **308**, 1028–1031 (2005)