Crystal Structure of the EmrE Multidrug Transporter with a Substrate

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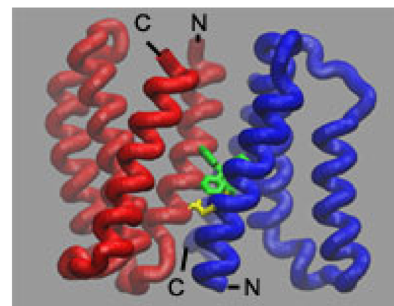
A major obstacle to effective treatment of bacterial infections is the emergence of drug-resistant strains. Multidrug resistance arises, in part, through the action of integral membrane proteins called multidrug transporters. Multidrug resistance transporters threaten to reverse the progress in treating infectious disease by extruding a wide range of drug and other cytotoxic compounds. Proteins that pump drugs out of bacterial cells contribute to the problem of multidrug resistance in diseases such as tuberculosis. One such drug transporter, EmrE, from the small multidrug resistance family, utilizes proton gradients as an energy source to drive substrate translocation. EmrE makes bacteria resistant to tetracycline, ethidium, and other cationic antibiotics. Developing inhibitors of such proteins could make old drugs effective again.



View of the EmrE homodimer. The N and C termini of the two subunits are colored. The bound substrate (TPP) is shown in green. The glutamine 14 which is implicated in the proton-depended drug translocation is shown in yellow.

Using the x-ray diffraction data collected on BL11-1 at SSRL, ALS, and APS, Geoffrey Chang's group at The Scripps Research Institute has solved the crystal structure of EmrE multidrug transporter in complex with a substrate, tetraphenylphosphonium (TPP). The data for the selenomethionine labeled protein was collected at SSRL. The structure was determined to 3.7 Å resolution by anomalous dispersion methods, using the arsonium analog of TPP and selenomethionine-susbstituted protein. This membrane protein is a homodimer made of two chemically but not structurally identical polypeptides that align themselves in an inverted, antiparallel fashion. Although the subunits have the same amino acid sequence, they adopt different conformations, making the protein asymmetric. Each subunit has four helices. The arrangement of the first three helices is nearly identical in each subunit; the fourth helix, however, is packed differently. The difference between the fourth helices provides the structural basis for the asymmetry and explains how the transporter could have a function that's unidirectional. Two EmrE polypeptides from a homodimeric transporter bind the substrate at the dimerization interface. The structure also shows the location of two glutamates that have previously been shown through biochemical experiments to be essential for drug efflux.

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References

Pornillos, O., Chang, G. (2006). Inverted Repeat Domains in Membrane Proteins. *FEBS Letters*, **580**, 358-362.
Ma, C. and Chang, G. (2004). Structure of the Multidrug Resistance Efflux Transporter EmrE from *Escherichia coli*. *PNAS* **101**, 9, 2852-2857.

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