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Structure and Mechanism of the Tripartite Multidrug Exporter

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Background

Bacterial multidrug exporters are responsible for multidrug resistance of gram negative bacteria currently emerging in the modern chemotherapy. The most significant characteristic is their extraordinary broad substrate specificity. We succeeded to solve the crystal structure of a bacterial major multidrug exporter AcrB in 2002 and revealed that the drug recognition is based on the membrane vacuum cleaning mechanism. However, our first structure did not contain bound substrates. We have solved the drug-bound structure of AcrB in 2006 and revealed the structural basis of multidrug export mechanism.

Results

Our new crystal of AcrB has no crystallographic three-fold symmetry. Each monomer in the AcrB trimer has a different conformation to the others. Only one substrate binds to the AcrB trimer. The substrate binding pocket is a phenylalanine-rich cluster located in the porter domain. Multidrug recognition is based on the multisite binding, that is, different drugs interact with different residues in the same pocket. Three monomers represent the conformations of the three intermediate steps of the drug export function, access, binding and extrusion. In the binding monomer, exit is closed by the inclined central a -helix of the extrusion monomer and the entrance is open due to the unfolding of the top of TM8. In contrast, in the extrusion monomer, the vacant substrate binding site is shrunk and the exit is open because the central a -helix is inclined away. The entrance is closed by the a -helix of the top of TM8. The access monomer shows the intermediate structure; entrance is open but the binding site is still shrunk.

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Conclusion

Crystal structure of AcrB revealed the functionally-rotation mechanism of multidrug export.

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