BACTERIAL PHYSIOLOGY

# Pump action

Research published in the latest issues of the *Journal of Molecular Biology* and the *Journal of Biological Chemistry* sheds new light on our understanding of multidrug efflux in pathogenic bacteria.

To expel antibiotics, antiseptics and other toxic compounds, Gram-negative bacteria use specialized systems that pump the offending molecules across two membranes and the periplasmic space that exists between them. One example of this transport machinery is the complex formed by an inner-membrane proton antiporter, an outer-membrane channel and a periplasmic protein that consolidates the assembly by coupling the interaction of the inner- and outer-membrane components. These tripartite pumps have been implicated in the multidrug resistance observed in some clinically important Gram-negative species. Previous studies have characterized a number of representative tripartite-system pump complexes, including the AcrAB–TolC assembly of *Escherichia coli* and the MexAB–OprM system of *Pseudomonas aeruginosa*. Now, Adrian Walmsley and co-workers extend our understanding of these structures to the causative agent of cholera, *Vibrio cholerae*. This pathogen encodes a tripartite pump that consist of an inner-membrane protein, VceB, a periplasmic adaptor, VceA, and an outer membrane channel, VceC. Reporting in the *Journal of Biological Chemistry*, Federici *et al.* describe the crystal structure of the trimeric VceC. Although sharing the same overall fold as other outer-membrane channel proteins, including TolC and OprM, there is no obvious conservation of residues that are predicted to be functionally important, indicating that different types of efflux pumps have quite different assemblies and stoichiometries. Interestingly, two detergent molecules associating with the protein structure are present in an orientation that would be expected for lipopolysaccharides of the bacterial outer membrane and could mimic the natural protein-channel–membrane architecture.

In a second paper, Borges-Walmsley and colleagues also investigate the dynamics of genetic regulation of the Vce tripartite pump. The expression of efflux pumps is often under the tight control of transcriptional regulators, which frequently bind the substrate drug as well as their target DNA. VceR, which the authors confirmed as a repressor of the *vce* operon, was shown to bind to a 28-bp inverted repeat within the operon and could be dissociated from the site with a drug substrate. Using various techniques, Borges-Walmsley *et al.* were further able to show that the equilibrium between the free — and therefore available to bind DNA — VceR molecule and VceR bound to the drug substrate was crucial in controlling expression of the pump. The authors contend that the cooperative transition between these two states affords an exquisite degree of control by allowing the repressor to respond to minor changes in drug concentrations that could prove toxic to the cell.

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## References and links

**ORIGINAL RESEARCH PAPERS** Federici, L. *et al.* The crystal structure of the outer membrane protein VceC from the bacterial pathogen *Vibrio cholerae* at 1.8 Å resolution. *J. Biol. Chem.* **280**, 15307–15314 (2005) | Borges-Walmsley *et al.* VceR regulates the vceCAB drug efflux pump operon of *Vibrio cholerae* by alternating between mutually exclusive conformations that bind either drugs or promoter DNA. *J. Mol. Biol.* 2 April 2005 (doi:10.1016/j.jmb.2005.03.045)