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Multidrug Efflux Pumps of Gram-Negative Bacteria: Molecular Basis for Their Wide Substrate Specificity

Hiroshi Nikaido

Dept. of Molecular and Cell Biology, University of California, Berkeley, CA 94720-3202, USA

Multiple antibiotic resistance in pathogenic bacteria is one of the major problems in health care today. In many cases, such resistance results from the expression of multidrug efflux pumps, each of which may pump out an astonishingly wide range of compounds. For example the AcrAB-TolC complex of *Escherichia coli* (an RND family transporter) is known to transport practically all classes of antibiotics (except aminoglycosides) and chemotherapeutic agents in addition to dyes, detergents, and solvents. These substrates may be uncharged, anionic, cationic, or zwitterionic. Another surprising feature of the pump of this type is its ability to extrude drugs that have difficulty in crossing the cytoplasmic membrane, for example carbenicillin. The most important advance in this area was achieved by Murakami et al. in Prof. A. Yamaguchi's laboratory, who solved the crystal structure of the AcrB trimer. We have recently solved the crystal structure of liganded AcrB, with bound substrates, including ethidium, rhodamine 6G, dequalinium, and ciprofloxacin. These structures suggest that the substrates first bind to a composite binding site, which is composed of the walls of the central cavity of AcrB trimer, as well as of the phospholipids that fill this cavity. I will discuss the results of structural studies, as well as biochemical studies based on reconstitution of purified transporters and genetic studies using site-directed mutagenesis, with the ultimate aim of understanding how the pump recognizes and transports such a diverse range of compounds.

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Profile: M.D. ('55), D.Med.Sc. ('61), Associate then Assistant Professor, Harvard Medical School ('63-69), Associate Professor and then Professor, University of California, Berkeley ('69-present).