

## **Perspectives on multidrug resistance in membrane transporters**

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Membrane proteins constitute about 30% of all proteins and among these are a large cohort of transporters, receptors, and enzymes. Membrane transporters have become the subject of intense research over the past two decades, chiefly because many of them are responsible for a process known as drug efflux in which the drug is captured at the cell membrane and extruded to the outside, thereby protecting the cell from the action of the drug. This is best and most simply illustrated by the resistance of many bacteria to antibiotics by drug efflux. Though this is one of many mechanisms of cellular resistance to drugs, it is perhaps the most perplexing as it most often appears in the guise of multidrug resistance. In all, there are five major classes or families of membrane drug transporters, namely, the Major Facilitator Superfamily (MFS), Small Multidrug Resistance (SMR), Multidrug and Toxin Extrusion (MATE), Resistance Nodulation Division (RND), and ATP-Binding Cassette Transporter (ABC) families.

The failure of cancer chemotherapy in humans is a noted example of efflux-mediated resistance. A most insidious feature of multidrug resistance is that it is often triggered by exposure to a single drug. For example, if human tumours are treated with a cytotoxic drug, the drug will bring about unbridled expression of an ABC transporter called P-glycoprotein. Though this protein has seen only one drug, it elaborates an efflux mechanism for all known cytotoxic drugs thereby rendering chemotherapy irrelevant as a curative treatment for cancerous tumours. A single membrane transporter is capable of extruding a large number of unrelated drugs, making the cells multidrug resistant. That this mechanism is ubiquitous among all phyla makes it a major investigative topic. It was thought that recent resolved structures of some of these transporters would quickly yield the mechanistic details of multidrug resistance, but the reality is less promising. However, some important studies have given clues about the way in which specific transporters are able to extrude a diverse range of drugs.