Cryo-EM structure of human P-glycoprotein in the outward-facing conformation

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The Multidrug resistance to chemotherapeutics is a major obstacle to successful cancer treatment. ATP-binding cassette (ABC) transporter are often the culprits. These membrane bound transporter utilize the energy of ATP binding and hydrolysis to activity pump chemotherapy drugs from cells before they can reach their intracellular target, thus shielding the cells from the drug's cytotoxic effects. Several different ABC transporters have been implicated in the phenomenon including P-glycoprotein (P-gp), the breast cancer resistance protein (ABCG2), and the multidrug resistance protein (MRP1). P-glycoprotein extrudes toxic molecules and drugs from cells through ATP-powered conformational changes. Despite decades of effort, only the structures of the inward-facing conformation of P-glycoprotein are available.

To better understand the physiological roles of P-glycoprotein, we have solved high-resolution electron cryo-microscopy (cryo-EM) structure of human P-glycoprotein in the outward-facing conformation. The two nucleotide-binding domains form a closed dimer occluding two ATP molecules. The drug-binding cavity observed in the inward-facing structures is re-orientated toward the extracellular space and compressed to preclude substrate binding. Those features of structure elucidate the role of ATP in substrate release from the transporter. The structure evokes a model in which the dynamic nature of P-glycoprotein enables translocation of a large variety of substrates.

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