Australian National University

Structure and function of the multidrug resistance protein P-glycoprotein

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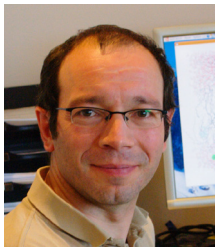
Dr Thomas Stockner Medical University of Vienna

Slatyer Seminar Room RN Robertson Building (46), ANU



The human genome contains 48 ATP-Binding Cassette (ABC) proteins. We focus on the multidrug resistance transporter P-glycoprotein, which is particularly expressed in barrier tissues. P-glycoprotein is expressed at the blood-brain-barrier, in the intestine, kidney, liver and in macrophages and transports an extraordinarily diverse range of substrates.

The bacterial homologue of P-gp, Sav1866 (Staphylococcus aureus), was the first ABC exporter crystallized and showed an unexpected domain interlinking architecture, later observed in homologue ABC transporters. Although ABC exporters have now been crystallized in several conformations, uncertainty remains regarding the physiological conformation of these structures. Non of the crystal structures is fully compatible with all biochemical evidence.

We combined modeling with experiments to address these issues. Homology modeling and MD simulations were used to determine the equilibrium conformation of ATP-bound P-glycoprotein in a membrane environment. In contrast to the conformations observed in crystal structures, we observed a conformations devoid of the wing-shape, in agreement with the bulk of the biochemical data. Site directed mutagenesis studies show the unexpected existence of two pseudo-symmetric substrate translocation paths. We start to identifyied molecular determinants for recognizing particular type of substrates by combining experiments with simulations.

Thomas Stockner studied chemistry at the University of Graz. In his PhD thesis he focused on protein structure using NMR and MD simulations, visiting the Utrecht University for a year. He then moved to the University of Calgary, joining the Tieleman group, where he worked on membranes and membrane proteins using MD simulations. He returned to Austria and joined the Austrian Institute of Technology, where he focused on predicting toxic effects of small organic molecules. In 2010 he joined the Medical University of Vienna. He now focuses on the function of the membrane transporter P-glucoprotein using computational and experimental methods.

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