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Conformation of membrane-inserted P-glycoprotein

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Background

The human genome codes for 49 members of the large ABC protein family. Most of them are membrane transporters. The first structures of exporters have been solved in recent years. Although a remarkable achievement, some uncertainty remained with respect to the physiological conformation of the transporter, which seems not to be fully compatible with all biochemical evidence. During crystallization, the transporter is extracted from its native membrane environment and solubilized by surfactants. This procedure might have influenced the transporters' conformation and lead to the structures observed in the crystals. We focus on the multidrug resistance transporter P-glycoprotein, which prevents xenotoxic compounds from entering the body and from penetrating into the brain, and confers resistance to chemotherapy.

Methods

We used homology modelling and MD simulations to identify the equilibrium conformation of the membrane inserted transporter.

Results

An initial P-glycoprotein model was built using the Sav1866 template [1]. The model was in compliance with most experimental data; discrepancies were observed in the central pore, where biochemical evidence suggested a smaller distance between the two sides of the wing-like helical bundles of the transmembrane region. Bending the structure allowed us to create a model that showed a consistently better agreement with biochemical data [2]. MD simulations were used to probe for the equilibrium conformation in the membrane environment. Simulations were initiated from both the Sav1866-based and from the bend model. Analysis of the two trajectories revealed a tendency to converge to a common conformation, as the simulation started from the wing-like structure showed a motion that brought the two wings closer.

Conclusions

Our results therefore indicate that the membrane environment does have an effect on the equilibrium conformation and that this conformation differs from the one observed in the crystal structure of the bacterial homolog Sav1866.

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