

Meliné Simsir

On the drug export mechanism by efflux pump Patched

M. Simsir, F. Cazals, I. Mus-Veteau

The Hedgehog receptor Patched is expressed in many cancers, and has been recently shown to have a drug efflux activity which confers resistance to chemotherapy [1, 2, 3]. However, its drug efflux mechanism is poorly understood. Patched is a member of the RND family which extrude drugs using the proton gradient [4]. The paradigm model of those proteins is AcrB, a protein responsible for antibiotic resistance in gram negative bacteria.

Patched structure was finally resolved by Cryo-EM in 2018 [5] which suggested a monomeric export mechanism and showed large structural differences compared to AcrB. This suggests differences of drug efflux mechanism compared to the later.

In this study, we use the available structures of Patched in order to inquire its efflux mechanism by using in silico tools such as Molecular Dynamics and Docking.

In order to learn more about the chemotherapy efflux mechanism by Patched, we started by addressing the cholesterol efflux mechanism depending on the protonation state of key amino-acids. We found which protonation state is necessary for the transport of cholesterol and gathered intel on the conformational changes necessary.

References

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