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ON THE INTERPLAY BETWEEN COMPLEX LIPID BILAYER MEMBRANE AND MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 1 (MRP1) BY MEANS OF MOLECULAR DYNAMICS

In the context of pharmacology, drug membrane transporters play a central role in local pharmacokinetics, i.e., the intracellular drug concentrations of tissues of interest. Particular attention should be paid to membrane transporters located in liver and kidneys given their importance in drug metabolism and elimination. This is particularly true for multidrug-resistance associated proteins (ABCC/MRPs) which have been pointed out as of "emerging clinical importance" by the International Transporter Consortium (ITC). Unfortunately, only the bovine ortholog bMRP1/ABCC1 has been resolved by means of cryo-EM so far. However, given the conserved structural patterns within the ABCC family, the use of bovine MRP1 as a prototype appears relevant to investigate the overall dynamics of other ABCC transporters.

We here propose a dynamic and structural overview of bMRP1 from ca. 110 μs aggregated molecular dynamics simulations. This was achieved considering (i) several conformations along transport cycle (namely inward- and outward-facing) and (ii) different bound states (i.e., ATP, ADP and/or substrate). Systems were embedded in different lipid bilayers made of POPC, POPE and cholesterol due decipher the interplay between the membrane and bMRP1.

The asymmetric dynamics resulting from the sequence variability between nucleotide binding domains were highlighted by our simulations; confirming the differential role of ATP molecules proposed by the literature. Besides, our simulations strengthened the hypothesis about the active role of phospholipid and cholesterol molecules in ABC transport cycle, e.g., in the asymmetric allosteric communications between substrate- and ATP-binding sites.

Session

Structural biology

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