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Deciphering the structural defects from SNP variants of ABCB4 transporter by means of molecular dynamics simulations

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Bile secretion is an essential function of the liver for the elimination of xenobiotics and endogenous metabolites. This function mostly relies on membrane transporters located at the canalicular membrane of hepatocytes, such as the ATP-binding cassette (ABC) transporter ABCB4 responsible for phosphatidylcholine (PC) secretion into bile. Variations in the *ABCB4* gene were reported from patients with rare liver diseases. Most of them are missense variations which were associated with defects of *(i)* protein expression, *(ii)* intracellular trafficking, *(iii)*, secretion activity, or *(iv)* transporter stability. In this context, the present study aims to provide insights into structural defects of selected genetic variants of ABCB4 by means of molecular dynamics (MD) simulations, supported by cellular and molecular biology experiments.
Taking advantages of the recent cryogenic electron microscopy (cryo-EM) resolutions of ABCB4 in different conformations, μs-scaled MD simulations were performed considering: *(i)* different bound states (*i.e.*, ATP- and/or PC-bound ABCB4), and *(ii)* different lipid bilayer models (symmetric and asymmetric). The overall ABCB4 dynamics was monitored to decipher key structural features along transport cycle. Furthermore, local destabilization events arising from genetic variations were assessed by mutating wild type ABCB4 using alchemical calculations. Particular attention was paid to the local structural impact of mutations in order to provide hints associated with function impairment.

Session

Structural biology

Primary author: Ms CRESPI, Veronica (Inserm U1248 Pharmacology & Transplantation, University of Limoges, Limoges, France)

Co-authors: Ms TOTH, Agota (Inserm U1248 Pharmacology & Transplantation, University of Limoges, Limoges, France); Ms JANASZKIEWICZ, Angelika (Inserm U1248 Pharmacology & Transplantation, University of Limoges, Limoges, France); Dr FALGUIÈRES, Thomas (Inserm U1193 Physiopathogénèse et traitement des maladies du foie, Université Paris-Saclay, Orsay, France); Dr DI MEO, Florent (Inserm U1248 Pharmacology & Transplantation, University of Limoges, Limoges, France)

Presenter: Ms CRESPI, Veronica (Inserm U1248 Pharmacology & Transplantation, University of Limoges, Limoges, France)

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