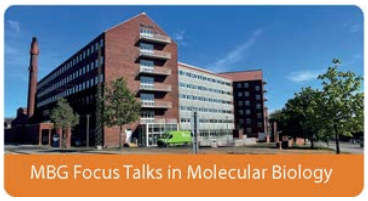
MBG FOCUS TALK

hosted by Bjørn Panyella Pedersen



Tuesday 9th May 2023 from 13:00-13:45

MBG Auditorium (1871-120)

By Principal Investigator Chloé Martens

Dept of Chemistry, Université Libre de Bruxelles, Belgium

Interrogating dynamics and allostery of transporters with H/D exchange coupled to mass spectrometry

Membrane transporters participate in a myriad of vital biological processes, including nutrient and drug import, cell-cell signaling and toxin export. This central role makes them an attractive class of drug targets and uncovering their molecular mechanism is an intense area of research. They are, however, notoriously difficult to work with, mainly due to their localization within the heterogeneous environment of the biological membrane and instability once extracted from the lipid bilayer.

Hydrogendeuterium exchange coupled to mass spectrometry (HDXMS) has recently emerged as a powerful method to investigate aspects eluding traditional biophysical tools, such as the dynamics of membrane proteins and their interactions with substrates, ions and lipids. This technique measures the rate of H/D exchange of labile protons from backbone amides. This exchange rate is directly correlated to solvent accessibility and local structural dynamics. A summary of the insights that HDX-MS applied to membrane transporters can reveal, as well as the practical means to obtain those will be presented.

Transporters undergo important structural rearrangements, alternating between inward-facing (IF) and outward-facing (OF) states to actively shuttle their substrate across the biological membrane. Such changes in the conformational landscape lead to changes in global and local dynamics measurable by HDX-MS. In combination with predictions from Molecular Dynamics simulations, we show how specific lipid-modulated changes in the conformational dynamics can be identified at the molecular level. In addition, we observe that the coupling between a substrate and an ion in a secondary transporter leads to a specific "dynamic fingerprint" and that the difference between substrate and inhibitor is encoded in local dynamics of the transporter. Finally, we uncover how a specific set of mutations in a neurotransmitter homolog causes a local increase in protein dynamics that ultimately translates into a faster rate of conformational switching and substrate release, providing a molecular level explanation for the gain-of function phenotype. These various examples illustrate the importance of measuring dynamics to update our current understanding of transport mechanisms.

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