AARHUS UNIVERSITY
DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS

DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

Mini-symposium

Friday 21 April 2023 from 11.00 – 12.00

Venue: MBG aud. (1871-120), Universitetsbyen 81, 8000 Aarhus
Dept. Molecular Biology and Genetics, Aarhus University

From 11.00-11.30

Chemo-mechanical coupling in an ATP-driven membrane transport complex

Prof. Dirk J. Slotboom
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Energy-coupling factor (ECF) type transporters, a mechanistically distinct group of ATP-binding cassette (ABC) transporters, mediate the uptake of micronutrients in a broad range of bacteria. The current model for the transport cycle includes two highly unusual steps. First, the substrate translocating transmembrane subunit (S-component) must topple over within the membrane to bring the substrate from the outside to the cytosol. Second, the substrate-free S-component must be expelled from the motor of the complex (ECF module) into the membrane, allowing it to topple back. How the expulsion of the integral membrane S-component is released, is a mechanistic enigma. I will present biochemical experiments and cryogenic electron microscopy (cryo-EM) reconstructions revealing that ATP binding charges a 'molecular spring' to expel the S-component into the membrane. The cryo-EM data, supported by molecular dynamics simulations, reveal that the lipid bilayer morphology depends strongly on the conformational state of the motor. Our work thus provides a picture of bilayer-assisted chemo-mechanical coupling in the transport cycle of ECF transporters.

From 11.30-12.00

Cerebrospinal fluid secretion occurs independently of conventional osmosis and is driven, in part, by the Na^+/K^+-ATPase and NKCC1

Prof. Nanna MacAulay
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Denmark

Disturbances in the brain fluid balance can lead to life-threatening elevation in the intracranial pressure (ICP), which represents a vast clinical challenge. Nevertheless, the details underlying the molecular mechanisms governing cerebrospinal fluid (CSF) secretion are largely unresolved, thus preventing targeted and efficient pharmaceutical therapy of cerebral pathologies involving elevated ICP. We here demonstrate lack of an osmotic gradient across the choroid plexus, no requirement for AQP1 for CSF secretion, and the ability of CSF to be secreted against a sizeable experimentally inflicted osmotic gradient. Mathematical modelling demonstrates that local osmotic gradients, proposed to arise between the abundant microvilli at the luminal surface of the choroid plexus, do not suffice to support CSF secretion of the observed rates. We therefore propose that the elusive local hyperosmotic compartment resides within the membrane transport proteins themselves and demonstrate the involvement of membrane transporters such as the Na^+,K^+,2Cl^- cotransporter NKCC1 and the Na^+/K^+-ATPase in the CSF secretion. The battery of plasma membrane transporters expressed in choroid plexus are thus proposed to sustain the choroidal CSF secretion via a molecular mode of water transport inherent in the proteins themselves, and thus in a manner independent of the prevailing osmotic gradient.

Hosted by: Prof. Poul Nissen