DANDRITE

Topical Seminar

Examining disease-related human membrane protein (ABCG2, PMCA4b, SLC6A8) variants in cellular models

At the Membrane Transporter Laboratory, our research focuses on finding and characterizing naturally occurring variants in membrane proteins that may increase disease susceptibility or lead to diseases due to altered expression and function of the membrane protein. During my PhD studies, I worked on three key membrane transporters: the ABCG2 multidrug transporter, the PMCA4b calcium pump and the SLC6A8 creatine transporter.

The **ABCG2 multidrug transporter** protects cells and tissues from endo-and xenobiotic toxic substances in several tissues and tissue barriers in the human body. Unlike ABCB1 (or P-glycoprotein), ABCG2 is affected by several naturally occurring missense mutations, including a common variant found in nearly 20% of the global population. This variant, along with other rare mutations in ABCG2, leads to decreased protein expression and function, and it has been associated with increased susceptibility to gout. We characterized the expression, localization, and transport function of ABCG2 variants in HEK293, HeLa, and MDCKII cell lines.

The PMCA4b calcium pump, encoded by the *ATP2B4* gene has been linked to malaria severity. Our group showed that a haplotype in the *ATP2B4* gene leads to decreased PMCA4b protein levels in the red blood cell membrane. Genome-wide association studies have associated this minor haplotype with reduced malaria susceptibility and milder symptoms. Using erythroid cell lines HEL92 and K562, we investigated the effect of SNPs in the haplotype region and showed how the SNPs influence promoter activity in an erythroid-specific manner, likely through altered GATA-1 transcription factor binding.

Mutations in the **SLC6A8 creatine transporter** cause creatine transporter deficiency (CTD) syndrome, an X-linked mental disorder. The role of creatine in the brain is not fully uncovered, and there is a need for human brain models to study this rare disease. In collaboration with stem cell researchers at the Research Centre for Natural Sciences and at Paris-Saclay University, we introduced the WT-SLC6A8 into brain organoid models derived from CTD patients using induced pluripotent stem cells (iPSCs). The WT-SLC6A8 was stably introduced into the patient-derived iPSCs, and the generated brain organoids showed recovered creatine uptake, neuronal development and rescued differentiation markers.

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Date: **Friday 18 October 2024**
Time: **10:00 – 10:45**
Venue: **Meeting room 1872-647**
Address: **Universitetsbyen 81, 8000 Aarhus**

OPEN TO ALL INTERESTED

Hosted by: Poul Nissen group (DANDRITE)

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