Mon 12. Aug 2019
Time: 11:30 h

Institute of Biochemistry and Molecular Medicine (IBMM)
Seminar Room
Gertrud-Woker-Str. 5,
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Benjamin Lüscher is research fellow at the National Institute of Dental and Craniofacial Research, Bethesda (USA)

This lecture is hosted by Prof. Christine Peinelt (IBMM).

NCCR TransCure Lecture in Biology

by Benjamin P. Lüscher

Regulation of the Na^+-HCO_3^- Cotransporters NBCe1-B and the Cl^- Channel CFTR by the ER-PM Tether Protein Extended Synaptotagmin 3

Regulation of ion channels and transporters at membrane contact sites, such as the endoplasmic reticulum (ER) and plasma membrane (PM) junctions, by tether proteins in eukaryotic cells is poorly understood. Extended synaptotagmins (E-Syts), are a family of ER-PM contact site tethers. Key proteins in secretory epithelia, such as salivary glands and the pancreas, are the basolateral $1Na^+/2HCO_3^-$ co-transporter NBCe1-B and the luminal Cl^- channel CFTR. CFTR is mutated in cystic fibrosis and degraded in Sjögren's syndrome. I am interested in understanding the role of E-Syts and other tether and lipid transport proteins in the regulation of fluid and electrolyte secretion by studying their role in the function of NBCe1-B and CFTR. We have identified that, E-Syt3 will completely inhibit the activity of NBCe1-B and CFTR. E-Syt3 is anchored to the ER by an N terminal hairpin structure, while the C terminus is anchored in the PM by binding to PI(4,5)P2. Indeed, depletion of plasma membrane $PI(4,5)P_2$ eliminated transporters inhibition by E-Syt3. E-Syt3 also includes a Synaptotagmin-like Mitochondrial lipid-binding Protein (SMP) domain that mediates lipid exchange between membrane leaflets, and is followed by 3 Ca^{2+} and $PI(4,5)P_2$ binding C2 domains. Using alanine scanning of several positively charged regions of the C-terminal C2 (C2C) domain I identified two E-Syt3 regions that inhibit its function by preventing its interaction with $PI(4,5)P_2$. This results indicate that $PI(4,5)P_2$ binding is a key element for E-Syt3 inhibitory function. Deletion of the lipid transfer domain (E-Syt3(ΔSMP)) had no effect on localization of E-Syt3 but caused a loss of E-Syt3 inhibitory function, raising the possibility that the lipid transport function of E-Syt3 plays a role in the inhibition of NBCe1-B by E-Syt3. Alanine mutations in the lipid binding site resulted in loss of the inhibitory function. My findings to date suggest that E-Syt3 acts within the ER/PM junctions to regulate transport activity of NBCe1B and CFTR (and likely other transporters) and that localization within defined ER/PM junctions is a major regulatory modality of cellular transport function. Moreover there is strong evidence that the lipid transfer is an important function in the selective inhibition mediated by E-Syt3.

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