SFB 35 Colloquia in Membrane Transport

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"Regulation of the serotonin transporter by interacting proteins"

The neurotransmitter serotonin (5-hydroxytrytamine, 5-HT) exerts broad modulatory control over many fundamental aspects of physiology and behavior. Alterations in whole blood 5-HT levels are associated with a variety of neuropsychiatric disorders, suggesting that conserved molecular mechanisms regulate 5-HT homeostasis in brain and blood. One such example is the serotonin transporter (SERT), responsible for the maintenance of 5-HT levels in both the brain and in platelets. Peripheral findings suggest that genetic variation impacting both platelet and brain 5HT levels contributes to multiple brain disorders and may underlie comorbidity with peripheral symptoms. We recently characterized a number of regulatory partners that dictate SERT trafficking and function, including integrins and focal adhesion proteins. Hic-5 is an adaptor protein responsible for the molecular organization of signaling complexes downstream of integrin activation. Hic-5 binding to the carboxy-terminal of SERT leads to inactivation and internalization of the trans-porter. The interaction between SERT and Hic-5 is regulated by intracellular signaling pathways and 5HT availability. Integrins are cell surface receptors that interact with extracellular matrix proteins and mediate the signal transduction cascades necessary for cell motility and shape change. Activation and clustering of integrins activate SERT transport activity through previously characterized p38MAPK-dependent mechanisms. Importantly, integrin genetic variation associated with 5HT blood levels also influence SERT uptake activity. These are but two examples of SERT-interacting proteins that dynamically interact and regulate transport function that are conserved in platelets and in the brain. Our latest efforts aim to parallel changes in 5HT signaling in adult brain with altered 5HT blood homeostasis and map the molecular changes in SERT interactions in disease. These studies reveal a framework for understanding the comorbidity of depression and cardiovascular disease.