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

DANDRITE Topical Seminar

by visitor Ana Oliveira

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From 12:00 – 13:00

Aud. 6, 3rd floor, building 1170
Aarhus University, Ole Worms Allé 3, 8000 Aarhus C

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Regulation of the Ras pathway by neurofibromin in dendritic spines

Synaptic plasticity is thought to underlie learning and memory formation. In dendritic spines, Ras plays a critical role in many forms of synaptic plasticity and, therefore, many neuropsychiatric disorders that involve learning deficits, such as Neurofibromatosis Type I (NF1), are associated with abnormal Ras signaling. NF1 is caused by loss-of-function mutations on the *Nf1* gene, which encodes neurofibromin, a Ras inactivator. While it has been shown that neurofibromin is localized in dendritic spines, its function in these subcellular compartments is not well understood.

Using a combination of fluorescence lifetime imaging microscopy (FLIM) and 2-photon glutamate uncaging, we observed that loss of neurofibromin disrupted Ras inactivation in dendritic spines of pyramidal neurons in the CA1 region of the rat hippocampus, suggesting that neurofibromin acts as a RasGAP in these subcellular compartments. Loss of neurofibromin caused sustained Ras activation in spines, which led to impairment of spine structural plasticity and loss of spines in an activity-dependent manner. In line with these findings, loss of neurofibromin also resulted in a loss of functional excitatory synapses. Taken together, our results provide evidence that postsynaptic Ras hyperactivation following loss of neurofibromin may explain, at least in part, the cognitive deficits associated with NF1.

Host: Group Leader Keisuke Yonehara, DANDRITE