Abstract workshop 2013 Bern

Investigating Notch and Reelin crosstalk in mature neuronal function.

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Notch and Reelin signaling, which are respectively specification and patterning signals during neuronal development, have been recently found to be essential in higher brain function and are affected in Alzheimer's disease. Previous studies indicate that Notch1 and Reelin crosstalk intracellularly during neuronal maturation. In addition, reduction in Reelin transduction causes spine deficit and learning impairment. Our work showed that the loss of Notch1 in the mature hippocampus leads to more immature spines and a memory acquisition defect. Based on the commonalities between Reelin and Notch1 signaling we hypothesize that the two pathways act synergistically to display their function in mature neurons. The aim of our work is to elucidate the interaction between the Notch1 receptor and the Reelin receptor complex, ApoER2, VLDLR and APP, which have been implicated as causative factors in Alzheimer's disease. Fluorescent immunohistochemistry on long term mouse primary neuronal cultures indicates that Notch1 is co-expressed with ApoER2 and its secondary messenger Dab1 in NMDAR positive puncta. This suggests an interaction between the two pathways at the postsynaptic density. Co-immunoprecipitation from cortical lysate, using specific antibodies against Notch1 and ApoER2, confirms the physical interaction between the two trans-membrane receptors. To further clarify the interaction between Notch1 and Reelin pathway we performed western blot analysis on crude synaptosomal fractions of Reelin+/- mice and wildtype littermates. Our preliminary results show that in the synaptosomal fraction (P2) of Reelin +/- cortices Notch1 processing is more pronounced than in wt controls. Interestingly, Dab1 is also increased in the synaptosomal fraction of heterozygous mice. This suggests that imbalances in Reelin signaling can affect the Notch1 cascade likely through the direct interaction of Notch1 with Reelin pathway components. Further studies manipulating these two pathways using brain specific KO mice will help to unravel this functional crosstalk and may have clinical relevance.