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„Die funktionelle Bedeutung der Serin/Threonin-Kinase Ndr2 in Integrin-Signalwegen für die Differenzierung neuronaler Zellen“

Summary

In the developing nervous system neuronal differentiation processes such as the outgrowth and branching of neurites are regulated by various protein kinases and phosphatases. Previously, members of the Ndr serine/threonine kinase family in D. melanogaster (Warts and Tricornered) and C. elegans (SAX-1) have been shown to regulate actin-dependent growth and morphogenesis, including dendritic branching and tiling. In this study I investigated the potential role of the mammalian Ndr-kinase Ndr2 in dendritic outgrowth of neurons of the central nervous system. I could show that in hippocampal primary neurons overexpression of Ndr2 induces an increase, whereas an inhibition of Ndr2 expression with small hairpin RNA resulted in a decrease in dendritic branching. The Ndr2-dependent outgrowth proved to depend on integrin-mediated cell adhesion. Moreover, I could demonstrate that Ndr2 regulates the amount of activated β1-integrin in growth cones of differentiated PC12 cells and further, that Ndr2 binds to the GTPase Dynamin and associates with the recycling pathway of integrins in both primary hippocampal neurons and PC12 cells. Thus I suggest that Ndr2 controls the outgrowth and branching of neurons in the developing nervous system through an involvement in inside-out signalling and recycling pathways of integrins. In addition to these cellular studies, a biochemical and morphological characterisation of a novel conditional Ndr2-transgenic mouse model exhibited a prominent transgene expression in the hippocampus. Most notably, in these mice a decreased density of the suprapyramidal mossy fibre terminals became evident. This indicates that Ndr2 is also involved in the regulation of axonal outgrowth *in vivo.*

In addition to its role in neuronal development, structural rearrangement of the actin cytoskeleton is critically important for neural plasticity in the adult brain. In fact, the expression of β -actin and Ndr2 has been shown to transiently increase in the BLA 6 hours after fear conditioning. Therefore in a further part of this study I addressed the question whether this regulation may coincide with a critical phase of actin filament dynamics in the BLA. Indeed I could show, that a phalloidin-mediated actin filament arrest in the BLA leads to a disruption of auditory cued fear memory when induced between 6 to 12 hours after its acquisition and reactivation, respectively. Thus, both the consolidation and the reconsolidation of fear memory appear to involve a temporally coordinated dynamic of actin filaments in the BLA. Changes of Ndr2 expression fall into a sensitive phase of actin dynamics in the BLA and hence Ndr2 may be involved in processes of emotional memory formation.