The role of Rho-GTPases in the neuropathology of mental retardation

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Mental retardation (MR) is a developmental disability, defined by an IQ below 70, an onset during childhood and an inability to cope with everyday life. Causes of MR can be both environmental and genetic. For the genetic causes two subclasses are distinguished. If the MR is accompanied by various body and brain malformations, by psychiatric or metabolic abnormalities, it is called syndromic MR. If not, we speak about non-syndromic MR. For studying the neurobiological basis of MR these non-syndromic forms are specifically interesting.
Until now, 12 X-linked genes are found to cause non-specific MR in humans, of which three interact directly with Rho-GTPases. The Rho-GTPases integrate many types of environmental cues to regulate the actin cytoskeleton, thereby playing a key role in the morphological development of neurons. During development, Rho-GTPases affect neurite outgrowth, branching and pathfinding. In the adult brain they are also involved in the formation and maintenance of dendritic spines. A disturbance in the regulation of this pathway will lead to changes in neuronal morphology, which are likely to change the connectivity of the neuronal network. This probably will lead to the impaired information processing in MR.
We are investigating the effects of the Rho-associated MR genes (Oligophrenin1, αPIX, PAK3 and GDI1) on the development of neuronal morphology and connectivity. Dissociated neuronal cultures of embryonic rats were transfected with different constructs of these genes, coupled to GFP. During development, neuronal morphology is quantified at different time points. In this way potential effects are studied on neurite outgrowth, dendritic complexity and spine densities. Quantitation of spine densities in αPIX knock out mice revealed lower spine densities in the αPIX knock out mouse compared to controls, while overexpression of αPIX WT in cultured neurons increased spine density. These observations are consistent with reduced network connectivity upon loss-of-function mutation of αPIX.

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