Of mice and men: linking cytoskeletal dynamics and spines to cognition

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The brain is a highly complex network of neurons, which serves to process information and enable adaptation of the organism to its environment. The structural (i.e., synaptic) connectivity of the network is an important determinant of its ability to process information, and will ultimately affect the cognitive abilities of the organism. We study the relationship between cognition and the structural connectivity of the brain by using genes which are causally involved in both neuronal network formation and human cognition (intelligence). Investigations of post-mortem cerebral cortex of persons with mental retardation (MR) have shown that MR is often associated with lower numbers of neurons, abberrant neuronal migration or alterations in the shape and density of dendritic spines and dendrites. These findings led to the hypothesis that in most cases MR is due to abnormal development or plasticity of *structural* cortical connectivity (TINS 25: 191-199), which causes deficient information processing. Thirteen genes have been cloned that cause non-specific MR in humans, when mutated. Three of these (OPHN1, ARHGEF6 and PAK3, encoding oligophrenin1, αPix and Pak3, resp.) are directly involved in signaling through Rho GTPases, which are central regulators of the dynamics of the actin cytoskeleton. Rho GTPases act as integrators of a large range of guidance cues, neurotrophic factors and neurotransmitters, to subsequently modulate the development of neuronal morphology and connectivity.
We will discuss the role of the cytoskeleton and Rho-associated MR genes in neurite outgrowth and synaptogenesis in cultured neurons and in knock-out mice. We find that manipulation of oligophrenin1 and αPix alters neurite outgrowth and spine formation/maintenance. Using multi-electrode arrays we investigate the functional consequences of the induced alterations in network connectivity. Finally, we will analyze how the mutations affect the behavior of the KO mice and the cognitive abilities of the persons in which these same genes are mutated.

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