Universität Basel

Research Project

The role of mTOR complex 1 and mTOR complex2 in synapse function and plasticity

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Synapses are the sites of contact between neurons and their postsynaptic target cells. During development, synapses are formed independent of electrical activity in response to trophic interactions. In contrast, ”activity” of synapses triggers changes in synaptic strength and structure in the adult brain, which can occur in the process of learning and memory. There is ample evidence that the formation of new synapses during the course of learning and memory requires new protein synthesis. A candidate signaling pathway that controls protein translation is the mTOR (mammalian target of rapamycin) signaling complex, which integrates multiple signals to regulate local mRNA translation and the cytoskeleton. We propose here to test the role of mTOR in synapse function and plasticity.

mTOR is a protein kinase, which associates with several proteins to form two multi-protein complexes, called mTORC1 (mTOR complex 1) and mTORC2 (mTOR complex 2). mTORC1, which is inhibited by the immunosuppressant drug rapamycin, is thought to control protein translation; in contrast, mTORC2, which is insensitive to rapamycin, is thought to regulate the actin cytoskeleton. We have recently generated mice that carry conditionally targeted alleles for *raptor* or *rictor*, which are the two genes that define mTORC1 and mTORC2, respectively. Removal of raptor in skeletal muscle or adipocytes causes major changes in cell size and metabolism (Bentzinger et al., 2008; Polak et al., 2008). Moreover, mice lacking raptor in skeletal muscle develop a muscle dystrophy and eventually die at the age of approximately 5 months. In contrast, mice that lack rictor in their skeletal muscle do not show any obvious phenotype. In unpublished work, we also eliminated raptor and rictor during early brain development and found that raptor deficiency causes perinatal death concomitant with microcephaly and alterations in the cortical layering. In contrast, rictor deficiency resulted in mice that survived but also showed major alteration in brain size, had signs of seizures and of strong neurodegeneration.

Although these results are highly interesting, these mouse models do not allow addressing the question of the role of raptor and rictor on synapse function and plasticity. We therefore propose to generate new models by using mice that express Cre recombinase under the control of the calcium/calmodulin-dependent protein kinase (CaMK) II. This will allow analyzing the consequence of raptor and rictor deficiency in postnatal neurons of the forebrain and the hippocampus. Using such mice, we will investigate the role of the two complexes for synapse homeostasis. Specifically, we will test the influence of the inactivation of mTORC1 or mTORC2 on the development of neural circuits *in vivo*. This will be done by examining the structure (axons, dendrites and synapses) of neurons using immunohistochemistry and histological methods. In addition, the mice will be tested in learning and memory paradigms, such as the Morris water maze, that are the dependent on synaptic plasticity of CaMKII-positive neurons. In addition, synaptic function and plasticity in response to presynaptic stimulation will be evaluated using

electrophysiological and imaging methods on cultured hippocampal neurons and hippocampal slices in conjunction with gene inactivation in single neurons.

As the experimental evidence for a role of mTOR signaling in learning and memory are quite strong in cultured neurons, we believe that the set of experiments proposed here will likely unravel an important role of this signalling pathway *in vivo*. Thus, our experiments have the potential to provide first time *in vivo* evidence that local protein synthesis at synapses is regulated by mTORC1 and/or mTORC2. As rapamycin is generally used as an immunosuppressant, our experiments may also provide new insights into potential side effects during long-term use of this drug.

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