

The role of FMRP in local translation at synapses – analysis of underlying signaling pathways and proteomic identification of new target mRNAs

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In Fragile X patients, the normal function of the brain is severely impaired leading to mental retardation, autism and epilepsy. These symptoms indicate that in FXS, nerve cells do not communicate properly. Previous studies suggest that the lack of a single molecule, the Fragile X Mental Retardation Protein (FMRP), in the brain of FXS patients results in disturbed production of several proteins which are important for the function of nerve cells. Based on the observation that the communication between nerve cells is impaired in FXS, it is of special interest to investigate the role of FMRP in the dynamic regulation of the molecular composition directly at synapses, those sites through which a nerve cell makes specific connections to surrounding cells. I will use a mouse model for FXS to address this topic in two different ways: First, I will pharmacologically manipulate biochemical preparations of synaptic fractions of these mice to investigate which signaling molecules are involved in the aberrant protein synthesis at FMRP-deficient synapses. Previous research has shown that signaling through a specific metabotropic glutamate receptor is exaggerated in the absence of FMRP. My studies will provide a more detailed analysis of the signaling pathways which lie downstream of this receptor and are disturbed in FXS. As signaling molecules are valuable drug targets, results of these experiments may lead to the identification of new medical therapies that could ameliorate FXS symptoms in humans. Second, I will use an innovative technique to identify specific proteins whose activity-regulated expression at synapses is affected in FXS. Knowledge about proteins which are not expressed properly at FMRP-deficient synapses will help to reveal the molecular basis of the synaptic dysfunctions in Fragile X patients. Furthermore, these studies potentially result in the discovery of new drug targets. With both approaches I hope to contribute to the development of novel therapeutic strategies for the treatment of FXS in humans.