Molecular, Cellular and Brain Imaging Studies on Fragile X Syndrome reveal disease convergence with Autism and Schizophrenia

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ABSTRACT
One fourth of the population worldwide is estimated to develop a mental or behavioral disorder, including major depression, schizophrenia (SCZ), autism spectrum disorder (ASD) and intellectual disability (ID). These pathologies are typically associated with disturbed early neurodevelopment, but the molecular mechanisms are not yet fully understood. The Fragile X Syndrome (FXS) is the most common cause of inherited intellectual disability with symptoms manifesting during infancy and early childhood. FXS is due to absence or mutation of the Fragile X Mental Retardation Protein (FMRP), an RNA-binding protein involved in different aspects of mRNA metabolism regulating synaptic mRNA translation and stability in different brain regions and at synapses. During synaptogenesis a series of events, including increased local protein synthesis, upregulation of mGluR and downregulation of GABA signaling, ultimately affect spine shaping and reshaping of FXS synapses. Over the past years we have identified one of the molecular mechanisms regulating mRNA translation at synapses and showed that it is indeed impaired in FXS. Recently we discovered a role of FMRP in regulating the positioning of neurons in the cortical plate during embryonic development and show that regulation of mRNA metabolism in the developing cerebral cortex and alterations in synaptic communication and neuronal network connectivity affect the development and progression of FXS. Furthermore, we have identified an affected molecular pathway in FXS that can be tackled with a peptide-therapy and that leads to the amelioration of important deficits observed in a mouse model for FXS. Interestingly, we connected FXS with other disabilities through the FMRP cytoplasmic interactor CYFIP1, a protein independently associated to ASD and SCZ. We could show that CYFIP1 orchestrates two molecular cascades, protein translation and actin polymerization, each of which is necessary for correct spine morphology in neurons. Finally we identified the CYFIP1 interactome that reveals many interactors associated with brain disorders such as ASD, MDD, AD, and IDs opening new perspectives to define regulatory pathways shared by neurological disabilities characterized by spine dysmorphogenesis.

We believe that the knowledge we acquire examining molecular mechanisms at the synapses will offer a major inroad into the understanding of processes that govern not only learning and memory, but also human behavior, neurodevelopment and neurodegenerative diseases that arise from malfunctioning synapses “synaptopathies”.

Fragile X Syndrome, Autism and Schizophrenia are still without an effective cure. Using different mouse and fly models, stem cells and in collaboration with clinical researchers, we are developing possible pharmacological approaches to modulate some aspects of FXS, ASD and SCZ.

References

