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In vitro Screening for Modulators of Synaptic Development in a Model of Fragile X Syndrome

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Fragile X Syndrome (FXS) is the most common genetic cause of intellectual disability, caused by an X-linked mutation in the gene Fmr1, which encodes for Fragile X Mental Retardation Protein (FMRP). FMRP is essential for normal cognitive development and function, and across species, mutations in Fmr1 drive mutant phenotypes at the synapse. Accordingly, the function of FMRP is highly conserved across species; FMRP is a translational repressor with over 800 mRNA targets identified in the mouse. In the absence of FMRP, loss of translational repression over target mRNAs results in overexpression of the respective protein products. In mammals, there are obvious and functionally relevant defects in the development of dendritic spines, which are the sites at which a neuron receives excitatory synaptic input from other neurons. Cortical neurons of Fmr1-knockout (KO) mice, a well-established mammalian model of FXS, have immature, thin dendritic spines. A virtually identical malformation of dendritic spines has been observed in the brains of humans who had FXS, indicating that proper spine development is a conserved and critical aspect of FMRP function. This phenotype also affects synaptic function; cortical neurons from Fmr1-KO mice are hyperexcitable. We developed an assay to culture Fmr1-KO mouse embryonic cortical neurons to screen for genetic and pharmacological manipulations that can reverse these defects. The goal is to discover novel genes and proteins that, when knocked down or inhibited, reverse the *in vitro* immature spine phenotype of Fmr1-KO neurons, suggesting they are normally targeted by FMRP. We hypothesize that overexpression of these key targets may drive Fmr1-KO mutant phenotypes at the synapse. FXS is a developmental and intellectual disorder of entirely genetic origin; because it is frequently linked and shares similarities to Autism Spectrum Disorders (ASD), a hit from our screen could have therapeutic potential for the larger class of disorders.