ABSTRACT

INVESTIGATING NOVEL THERAPEUTIC TARGETS FOR THE TREATMENT OF FRAGILE X SYNDROME

By

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Fragile X syndrome (FXS) is the most common form of inherited mental retardation and a leading cause of autism. Most cases of FXS result from CGG repeat expansion in the 5' UTR of the FMR1 gene, which results in lack of expression of its protein product, FMRP. FMRP is an mRNA binding protein, which predominantly suppresses the translation of its targets. The absence of FMRP thus leads to excessive protein synthesis and altered synaptic signaling, which are believed to underlie the pathophysiology of FXS. There is currently no cure for FXS and often multiple drugs are administered to manage the symptoms. This highlights the importance of understanding the molecular mechanisms that are altered in FXS brains, in order to develop better therapeutic targets. My study identifies that translation of the brain-specific type-1 adenylyl cyclase (AC1) mRNA is controlled by FMRP and that AC1 protein is overexpressed in the absence of FMRP. Using genetic knockdown and pharmacological inhibition of AC1, I show that reducing AC1 activity can rescue several cellular and behavioral phenotypes in the Fmr1 knockout mouse model. My research also reveals calmodulin inhibitor can rectify several cellular and behavioral phenotypes in Fmr1 KO mice. In summary this thesis describes the identification and validation of a novel therapeutic target and an FDA approved drug for treatment of FXS using the Fmr1 KO mouse model.