DYSREGULATED ERK SIGNAL PATHWAY AND IMMUNE PROFILES IN FRAGILE X SYNDROME

BY

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DISSERTATION

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ABSTRACT

Fragile X Syndrome (FXS) is the leading cause of inherited mental retardation, and the most common identified genetic cause of autism. Lack of production of the Fragile X Mental Retardation Protein (FMRP) leads to changes in dendritic morphology and resultant cognitive and behavioral manifestations characteristic of individuals with FXS. FMRP is an RNA-binding protein that is believed to regulate the translation of a large number of other proteins, leading to a complex and variable set of symptoms in FXS. In a mouse model of FXS, we previously observed delayed initiation of synaptically localized protein synthesis in response to neurotransmitter stimulation, as compared to wild-type mice. We now likewise have observed delayed early-phase phosphorylation of extracellular-signal regulated kinase (ERK), a nodal point for cell signaling cascades, in both neurons and thymocytes of *fmr-1* KO mice. We further reported that early-phase kinetics of ERK activation in lymphocytes from human peripheral blood is delayed in a cohort of individuals with FXS, relative to normal controls, suggesting a potential biomarker to measure metabolic status of disease for individuals with FXS. Furthermore, dysregulated phosphatases, especially Protein phosphatase 2A (PP2A) may account for the delay in ERK activation.

FXS and immune dysregulation is an emerging area in FXS research. We hypothesize that immune cells from FXS patients may have different gene expression and protein profiles. We first analyzed genome-wide microarray data from FXS lymphoblastoid cell, and found several immune gene sets are differentially expressed in FXS patients. We further reported that the cytokine profiles and cytokines activation

profiles are dysregulated in FXS patients. These results could be used as potential cellular markers for FXS patients.

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