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ROLE OF LARG IN THE PATHOPHYSIOLOGY OF FRAGILE X SYNDROME

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Fragile X syndrome, the most common form of inherited mental retardation, is characterized by mild to severe cognitive dysfunction. In brain, alterations in dendritic spine morphology, such as increased spine density and more elongated, immature dendritic spines, were observed. Expression profiling in our group has shown under expression of *leukemia-associated Rhogef (Larg)* in the cortex of fragile X mice. LARG is a Rho guanine nucleotide exchange factor (RhoGEF) that specifically activates RhoA. RhoA is a member of RhoGTPases and in neurons it has a role in spine formation and maintenance by regulation of actin cytoskeleton. Constitutively active RhoA leads to very low densities of spines and spine retraction, while inhibition of RhoA activity leads to an increase in the number of elongated spines. Our hypothesis is that decreased expression of *LARG* leads to less activation of RhoA, causing the aberrant spine morphology observed in brain of fragile X subjects. Therefore the role of LARG in the pathophysiology of fragile X syndrome was further investigated. Additional genes in the LARG-RhoA pathway were analyzed for possible differential expression in cortex of fragile X mice. Preliminary results show under expression of 2 homologues genes of *Larg*, *p115-Rhogef* and *PDZ-Rhogef*, respectively, *RhoA*, *Insulin-like growth factor 1 receptor (Igf1-R)*, *Lysophosphatidic acid receptor 1 (Lpar1/Edg2)* and *Guanine nucleotide binding protein, alpha 13 and q (Gna13, Gnaq)*. In addition, we demonstrated decreased expression of orthologues of most of these genes in the fragile X fly model, *D. Melanogaster*: *Larg*, *Gna13*, *Gnaq* and *RhoA (Rhogef2, concertina, Ga49B and Rho1*, respectively), suggesting that this is an evolutionary conserved hallmark of fragile X syndrome. Using an electrophoretic mobility shift assay (EMSA) we showed that the C-terminus of Fragile X mental retardation protein (FMRP) is able to bind *Larg*-mRNA, suggesting a possible direct influence of FMRP on *LARG* mRNA transport and/or stability.