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DYSFUNCTION OF PROTEIN SYNTHESIS MEDIATED BY mTOR-DEPENDENT SIGNALING IN FRAGILE X SYNDROME

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Multiple studies have revealed the important role played by the mTOR (mammalian target of rapamycin) signaling pathway in learning and memory. All components of the mTOR pathway, which is involved in protein synthesis-dependent phase of synaptic strengthening, are present in dendrites suggesting a role for mTOR in local translation. mTOR drives local translation through phosphorylation of its downstream targets, including the eukaryotic initiation factor 4E-binding protein (4E-BP)s, which permits eIF4E to bind to eIF4G and be phosphorylated by Mnk1. The 70kD ribosomal protein S6 kinase (S6K1) and the eukaryotic elongation factor 2 (eEF2) are two additional mTOR substrates involved in translation control. These substrates in turn regulate translational initiation and rates of peptidyl elongation. Hypophosphorylated 4E-BPs inhibit translation of a number of mRNAs, mRNAs by sequestering eIF4E. Loss of eIF4E activity especially impacts mRNAs with high CGG content and complex 5'UTR structure via steric hindrance. The mRNA encoded by the Fragile X gene (*FMR1*) bears these features. *FMR1* contains a CGG repeat element in the 5'UTR. Expansion above 200 CGG repeats leads to Fragile X syndrome (FXS) through hypermethylation of the promoter, silencing and consequent absence of the encoded protein, FMRP. FMRP is an RNA-binding protein, which plays an important role in translational repression. Thus, we have investigated whether altered mTOR signaling is present in subjects with FXS. Our preliminary findings indicate that translation control mediated by the mTOR pathway is compromised in FXS. Peripheral blood leukocytes of FXS subjects, who lack of FMRP, displayed phosphorylation of translation factors and kinases involved in translation control. Specifically, a significant increase in the phosphorylation of both S6K1 and eIF4E, which is consistent with elevated basal translation, was detected in FXS subjects. The observed increases in translational signaling suggest excessive basal translation in FMRP-deficient cells, and this activity may contribute to the cognitive and behavioral deficits observed in subjects with FXS. Thus, altered phosphorylation of mTOR substrates and their effectors could represent putative biological markers of cognitive impairment in FXS and the assessment of their levels in FXS lymphocytes could complement existing molecular testing.