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A NOVEL FUNCTION OF FRAGILE X MENTAL RETARDATION PROTEIN IN TRANSLATIONAL ACTIVATION

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Fragile X syndrome, the most frequent form of inherited mental retardation, is due to the absence of FMRP (Fragile X Mental Retardation Protein), an RNA-binding protein involved in several steps of RNA metabolism. Up to date, two RNA motifs have been found to mediate FMRP/RNA interaction: the G-quartet and the “kissing complex”, which both induce translational repression in the presence of FMRP. We show here a new role of FMRP as a positive modulator of translation. FMRP specifically binds *Superoxide Dismutase 1* (*Sod1*) mRNA with high affinity through a novel RNA motif, SoSLIP (*SoSLIP* mRNA Stem Loops Interacting with FMRP), which is folded as three independent stem-loop structures. FMRP induces a structural modification of the SoSLIP motif upon its interaction with it. SoSLIP also behaves as a translational activator, whose action is potentiated by the interaction with FMRP. We propose that the deregulation of *Sod1* expression may be at the basis of several traits of the physiopathology of the Fragile X syndrome, such as anxiety, sleep troubles and autism. Indeed, the absence of FMRP results in a decreased expression of *Sod1*. Interestingly it has been observed that brain metabolism of *FMR1* null mice is more sensitive to oxidative stress. Chronic pharmacological treatment with alpha-tocopherol reversed pathophysiological hallmarks including free radical overproduction, oxidative stress, macro-orchidism, and also behaviour and learning deficits, suggesting that the restoration of the oxidative status in the *Fmr1* null mice could be a new approach for further therapeutic research in fragile X syndrome. In conclusion, our study suggests a role of *Sod1* in physiopathology of Fragile X syndrome and proposes a new function and novel mechanism of action for FMRP.