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Autism-like phenotype caused by a neuronal-microexon mis-splicing impairing kinetic stability of ribonucleoprotein condensates and regulation of mRNA translation in neurons

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The inclusion of microexons by alternative splicing is frequent in neuronal proteins. The roles of these sequences are in most cases unknown, but changes in their degree of inclusion are associated with neurodevelopmental diseases. We recently found that the decreased inclusion of an 24-nucleotide neuron-specific microexon in CPEB4, an RNA-binding protein that regulates translation through cytoplasmic changes in poly(A) tail length, is linked to idiopathic autism spectrum disorder (ASD). Why this microexon is required and how small changes in its degree of inclusion generate a dominant negative effect on the expression of ASD-linked genes is not clear. Here we show that neuronal CPEB4 forms condensates that dissolve upon depolarization, a phase transition associated with a switch from translational repression to activation. Heterotypic intermolecular interactions between the microexon and a cluster of histidine kinetically stabilize the condensates by competing with homotypic interactions between clusters, that lead to the irreversible aggregation of CPEB4. We conclude that microexon 4 in neuronal CPEB4 is required to preserve the reversible regulation of CPEB4-mediated gene expression in response to neuronal stimulation.

Reference

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