UPF1

Regulator of nonsense transcripts 1 is a protein that in humans is encoded by the UPF1 gene.

Function

This gene encodes a protein that is part of a post-splicing multiprotein complex, the exon junction complex, involved in both mRNA nuclear export and mRNA surveillance. mRNA surveillance detects exported mRNAs with truncated open reading frames and initiates nonsense-mediated mRNA decay (NMD). When translation ends upstream from the last exon-exon junction, this triggers NMD to degrade mRNAs containing premature stop codons. This protein is located only in the cytoplasm. When translation ends, it interacts with the protein that is a functional homolog of yeast Upf2p to trigger mRNA decapping. Use of multiple polyadenylation sites has been noted for this gene.

Neuronal mRNAs can be packaged in reversibly stalled polysome granules prior to their transport to distant synaptic locales. Stimulation of synaptic metabotropic glutamate receptors (mGluRs) reactivates translation of these particular mRNAs to produce plasticity-related protein; a phenomenon exhibited during mGluR-mediated long-term depression (mGluR-LTD). This form of plasticity is deregulated in Fragile X Syndrome, a monogenic form of autism in humans, and understanding the stalling and reactivation mechanism could reveal new approaches to therapies. Here, we demonstrate that UPF1, known to stall peptide release during nonsense-mediated RNA decay, is critical for assembly of stalled polysomes in rat hippocampal neurons derived from embryos of either sex. Moreover, UPF1 and its interaction with the RNA binding protein STAU2 are necessary for proper transport and local translation from a prototypical RNA granule substrate and for mGluR-LTD in hippocampal neurons. These data highlight a new, neuronal role for UPF1, distinct from its RNA decay functions, in regulating transport and/or translation of mRNAs that are critical for synaptic plasticity.SIGNIFICANCE STATEMENTThe elongation and/or termination steps of mRNA translation are emerging as important control points in mGluR-LTD, a form of synaptic plasticity that is compromised in a severe monogenic form of autism, Fragile X Syndrome. Deciphering the molecular mechanisms controlling this type of plasticity may thus open new therapeutic opportunities. Here, we describe a new role for the ATP-dependent helicase UPF1 and its interaction with the RNA localization protein STAU2 in mediating mGluR-LTD through the regulation of mRNA translation complexes stalled at the level of elongation and/or termination [1)].

1)

Graber TE, Freemantle E, Anadolu M, Hébert-Seropian S, MacAdam R, Shin U, Hoang HD, Alain T, Lacaille JC, Sossin WS. UPF1 governs synaptic plasticity through association with a STAU2 RNA granule. J Neurosci. 2017 Aug 18. pii: 0088-17. doi: 10.1523/JNEUROSCI.0088-17.2017. [Epub ahead of print] PubMed PMID: 28821679.