UPF1 binds an mRNP with a termination codon preceding an Exon Junction Complex

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
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Literature references

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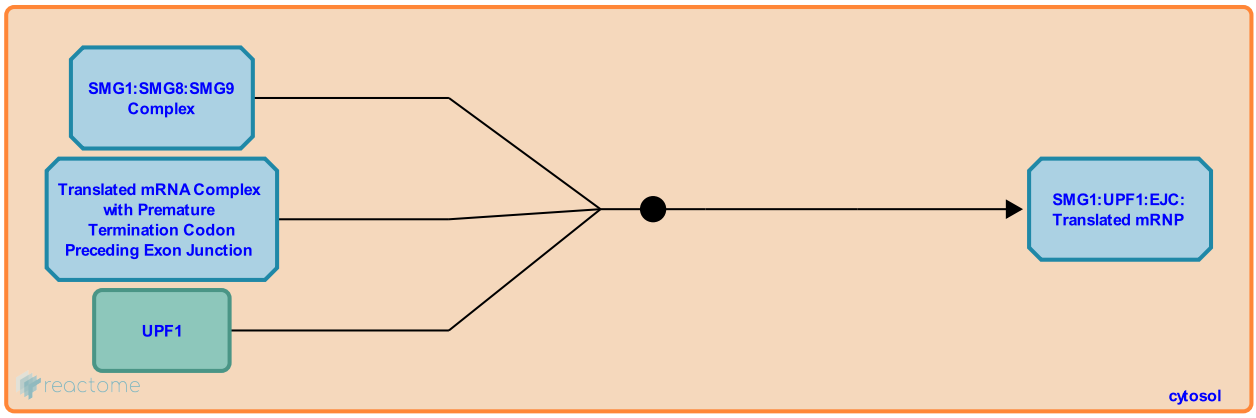
Stable identifier: R-HSA-927832

Type: binding

Compartments: cytosol



The presence of an exon junction complex (EJC) downstream of a termination codon enhances nonsense-mediated decay (NMD) but is not absolutely required for NMD. The EJC is deposited during splicing and remains bound to the mRNA until a ribosome dislodges it during the pioneer round of translation, distinguished by the presence of the cap-binding complex at the 5' end. If translation terminates at least 50-55 nucleotides 5' to an EJC during the pioneer round then termination factors (eRF1 and eRF3) and the EJC recruit UPF1 and other NMD machinery (Lykke-Andersen et al. 2001, Ishigaki et al. 2001, Le Hir et al. 2001, Gehring et al. 2003, Hosoda et al. 2005, Kashima et al. 2006, Singh et al. 2007, Chamieh et al. 2008, Ivanov et al. 2008, Buchwald et al. 2010).
A current model for NMD enhanced by the EJC posits recruitment of UPF1, SMG1, SMG8, and SMG9 to eRF3 at the ribosome to form the SURF complex (Kashima et al. 2006, Chang et al. 2007, Isken et al. 2008, Muhlemann et al. 2008, Stalder and Muhlemann 2008, Chamieh et al. 2009, Maquat and Gong 2009, Rebbapragada and Lykke-Andersen 2009, Hwang et al. 2010, Nicholson et al. 2010). UPF1 and SMG1 then interact with components of the EJC, activating phosphorylation of UPF1 by SMG1.
The model of the NMD mechanism is inferred from known protein interactions:
eRF1 and eRF3 interact with UPF1, the key regulator of NMD which also binds SMG1, UPF2, and UPF3 (UPF3a or UPF3b) to form the SURF complex (Kashima et al.2006, Ivanov et al. 2008, Clerici et al. 2009, Chakrabarti et al. 2011). UPF1 also interacts with CBP80 at the cap of the mRNA (Hwang et al. 2010).
SMG8 and SMG9 associate with SMG1 and the SURF complex and modulate the phosphorylation activity of SMG1 (Yamashita et al. 2009).
UPF2 and UPF3 are peripheral components of the EJC and thus may link the EJC to the SURF complex (Chamieh et al. 2008). UPF3b binds UPF1 and a composite surface formed by the Y14, MAGOH, and eIF4A3 subunits of the core EJC (Gehring et al. 2003, Kunz et al. 2006, Buchwald et al. 2010). SMG1 also interacts with the EJC (Kashima et al. 2006, Yamashita et al. 2009). UPF3a more weakly activates NMD than does UPF3b (Kunz et al. 2006) and UPF3a levels increase in response to loss of UPF3b (Chan et al. 2009).
The binding of UPF1 to translated RNAs may occur in two steps: Binding of the SURF complex to the terminating ribosome followed by transfer of UPF1 and SMG1 to the EJC (Kashima et al. 2006, Hwang et al. 2010).
The core EJC (Y14, MAGOH, eIF4A3, and BTZ) can activate NMD without UPF2, however RNPS1, another EJC subunit, requires UPF2 to activate NMD (Gehring et al. 2005). RNAs show differential dependence on RNPS1-activated NMD (Gehring et al. 2005). Also, NMD of some transcripts requires EJC component eIF4A3 but not UPF3b (Chan et al. 2007) therefore there may be more than one route to activating NMD via the EJC.

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Editions

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