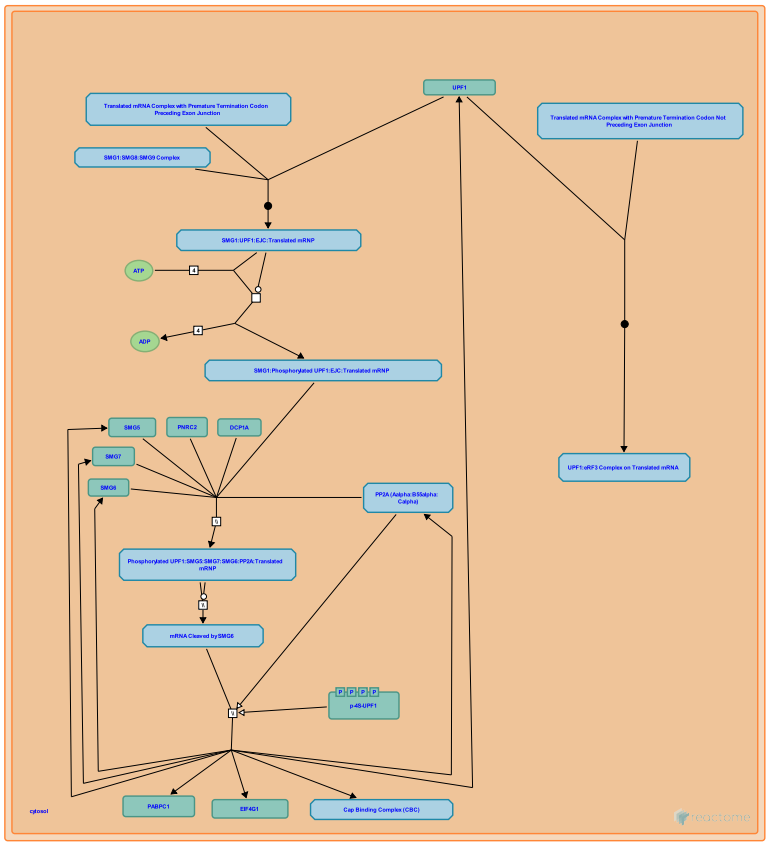
Nonsense-Mediated Decay (NMD)



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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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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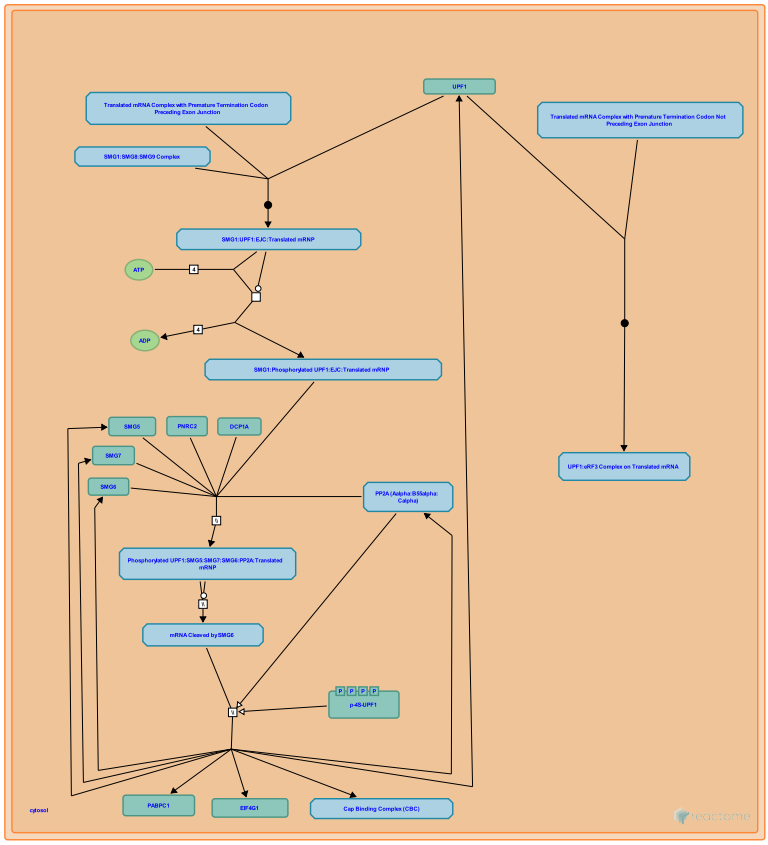
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Nonsense-Mediated Decay (NMD) ↗

Stable identifier: R-HSA-927802

Compartments: cytosol



The Nonsense-Mediated Decay (NMD) pathway activates the destruction of mRNAs containing premature termination codons (PTCs) (reviewed in Isken and Maquat 2007, Chang et al. 2007, Behm-Ansmant et al. 2007, Neu-Yilik and Kulozik 2008, Rebbapragada and Lykke-Andersen 2009, Bhuvanagiri et al. 2010, Nicholson et al. 2010, Durand and Lykke-Andersen 2011). In mammalian cells a termination codon can be recognized as premature if it precedes an exon-exon junction by at least 50-55 nucleotides or if it is followed by an abnormal 3' untranslated region (UTR). While length of the UTR may play a part, the qualifications for being "abnormal" have not been fully elucidated. Also, some termination codons preceding exon junctions are not degraded by NMD so the criteria for triggering NMD are not yet fully known (reviewed in Rebbapragada and Lykke-Andersen 2009). While about 30% of disease-associated mutations in humans activate NMD, about 10% of normal human transcripts are also degraded by NMD (reviewed in Stalder and Muhlemann 2008, Neu-Yilik and Kulozik 2008, Bhuvanagiri et al. 2010, Nicholson et al. 2010). Thus NMD is a normal physiological process controlling mRNA stability in unmutated cells.
Exon junction complexes (EJCs) are deposited on an mRNA during splicing in the nucleus and are displaced by ribosomes during the first round of translation. When a ribosome terminates translation the A site encounters the termination codon and the eRF1 factor enters the empty A site and recruits eRF3. Normally, eRF1 cleaves the translated polypeptide from the tRNA in the P site and eRF3 interacts with Polyadenylate-binding protein (PABP) bound to the polyadenylated tail of the mRNA.
During activation of NMD eRF3 interacts with UPF1 which is contained in a complex with SMG1, SMG8, and SMG9. NMD can arbitrarily be divided into EJC-enhanced and EJC-independent pathways. In EJC-enhanced NMD, an exon junction is located downstream of the PTC and the EJC remains on the mRNA after termination of the pioneer round of translation. The core EJC is associated with UPF2 and UPF3, which interact with UPF1 and stimulate NMD. Once bound near the PTC, UPF1 is phosphorylated by SMG1. The phosphorylation is the rate-limiting step in NMD and causes UPF1 to recruit either SMG6, which is an endoribonuclease, or SMG5 and SMG7, which recruit ribonucleases. SMG6 and SMG5:SMG7 recruit phosphatase PP2A to dephosphorylate UPF1 and allow further rounds of degradation. How EJC-independent NMD is activated remains enigmatic but may involve competition between PABP and UPF1 for eRF3.

Literature references

Yepiskoposyan, H., Kleinschmidt, N., Zamudio Orozco, R., Metze, S., Muhlemann, O., Nicholson, P. (2010). Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. *Cell Mol Life Sci, 67*, 677-700. ↗

Saulière, J., Wittkopp, N., Behm-Ansmant, I., Izaurralde, E., Rehwinkel, J., Kashima, I. (2007). mRNA quality control: an ancient machinery recognizes and degrades mRNAs with nonsense codons. *FEBS Lett, 581*, 2845-53. ↗

Durand, S., Lykke-Andersen, J. (2011). SnapShot: Nonsense-Mediated mRNA Decay. *Cell, 145*, 324-324.e2. ↗

Bhuvanagiri, M., Kulozik, AE., Hentze, MW., Schlitter, AM. (2010). NMD: RNA biology meets human genetic medicine. *Biochem J, 430*, 365-77. ↗

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Editions

2010-08-06	Authored, Edited	May, B.
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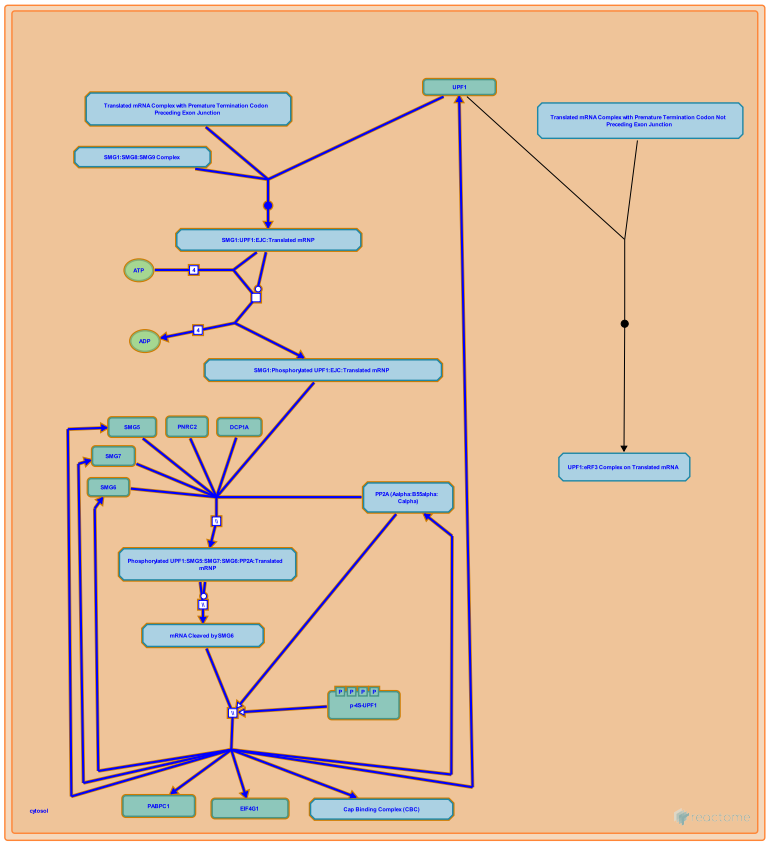
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC) ↗

Location: Nonsense-Mediated Decay (NMD)

Stable identifier: R-HSA-975957

Compartments: cytosol



During normal translation termination eRF3 associates with the ribosome and then interacts with PABP bound to the polyadenylate tail of the mRNA to release the ribosome and allow a new round of translation to commence. Nonsense-mediated decay (NMD) is triggered if eRF3 at the ribosome interacts with UPF1, which may compete with PABP (reviewed in Isken and Maquat 2007, Chang et al. 2007, Behm-Ansmant et al. 2007, Rebbapragada and Lykke-Andersen 2009, Bhuvanagiri et al. 2010, Nicholson et al. 2010, Durand and Lykke-Andersen 2011). An exon junction located 50-55 nt downstream of a termination codon is observed to enhance NMD.
Exon-junction complexes (EJCs) are deposited on the mRNA during splicing in the nucleus, remain on mRNAs after transport to the cytosol, and are dislodged by the ribosome as it progresses along the mRNA during the pioneer round of translation (Gehring et al. 2009). EJCs contain the core factors eIF4A-III, Magoh-Y14, and CASC3 as well as the peripheral factors RNPS1, UPF2, and UPF3. UPF2 and UPF3 recruit UPF1 to eRF3 at the terminating ribosome. Thus an EJC downstream of a termination codon will not have been dislodged during translation and will recruit UPF1, triggering NMD.
UPF1 is believed to form a complex containing SMG1, SMG8, and SMG9. In the key regulatory step of NMD SMG1 phosphorylates UPF1. The phosphorylated UPF1 then recruits either SMG6 or SMG5 and SMG7. SMG6 is itself an endoribonuclease that cleaves the mRNA. SMG5 and SMG7 do not have endoribonuclease activty, but are thought to recruit ribonucleases. Nonsense-mediated decay has been observed to involve deadenlyation, decapping, and both 5' to 3' and 3' to 5' exonuclease activities, but the exact degradative pathways taken by a given mRNA are not yet known.
UPF1 also plays roles in Staufen-mediated decay, histone mRNA decay, telomere maintenance, genome integrity, and may play a role in normal termination of translation.

Literature references

Yepiskoposyan, H., Kleinschmidt, N., Zamudio Orozco, R., Metze, S., Muhlemann, O., Nicholson, P. (2010). Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. *Cell Mol Life Sci, 67*, 677-700. ↗

Saulière, J., Wittkopp, N., Behm-Ansmant, I., Izaurralde, E., Rehwinkel, J., Kashima, I. (2007). mRNA quality control: an ancient machinery recognizes and degrades mRNAs with nonsense codons. *FEBS Lett, 581*, 2845-53. ↗

Durand, S., Lykke-Andersen, J. (2011). SnapShot: Nonsense-Mediated mRNA Decay. *Cell, 145*, 324-324.e2. ↗

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Bhuvanagiri, M., Kulozik, AE., Hentze, MW., Schlitter, AM. (2010). NMD: RNA biology meets human genetic medicine. *Biochem J, 430*, 365-77. ↗

Editions

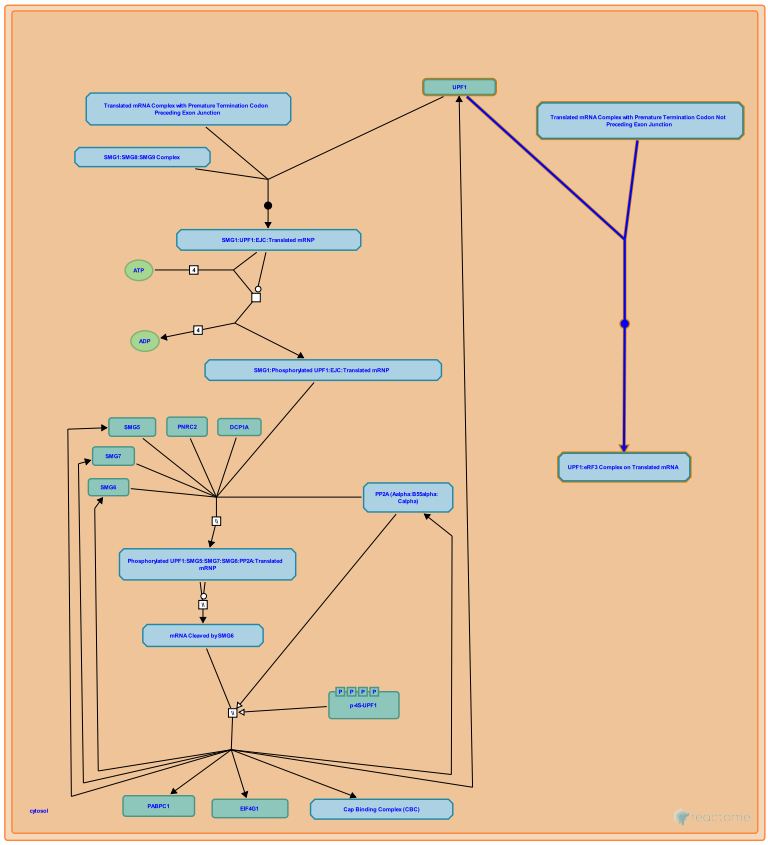
2010-10-08	Authored, Edited	May, B.
2011-05-19	Reviewed	Neu-Yilik, G.

Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC) ↗

Location: Nonsense-Mediated Decay (NMD)

Stable identifier: R-HSA-975956

Compartments: cytosol



Nonsense-mediated decay has been observed with mRNAs that do not have an exon junction complex (EJC) downstream of the termination codon (reviewed in Isken and Maquat 2007, Chang et al. 2007, Behm-Ansmant et al. 2007, Rebbapragada and Lykke-Andersen 2009, Nicholson et al. 2010). In these cases the trigger is unknown but a correlation with the length of the 3' UTR has sometimes been seen. The current model posits a competition between PABP and UPF1 for access to eRF3 at the terminating ribosome (Ivanov et al. 2008, Singh et al. 2008, reviewed in Bhuvanagiri et al. 2010). Abnormally long 3' UTRs may prevent PABP from efficiently interacting with eRF3 and allow UPF1 to bind eRF3 instead. Long UTRs with hairpin loops may bring PABP closer to eRF3 and help evade NMD (Eberle et al. 2008).
The pathway of degradation taken during EJC-independent NMD has not been elucidated. It is thought that phosphorylation of UPF1 by SMG1 and recruitment of SMG6 or SMG5 and SMG7 are involved, as with EJC-enhanced NMD, but this has not yet been shown.

Literature references

Yepiskoposyan, H., Kleinschmidt, N., Zamudio Orozco, R., Metze, S., Muhlemann, O., Nicholson, P. (2010). Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. *Cell Mol Life Sci, 67*, 677-700. ↗

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Editions

2010-10-08	Authored, Edited	May, B.
2011-05-19	Reviewed	Neu-Yilik, G.

Table of Contents