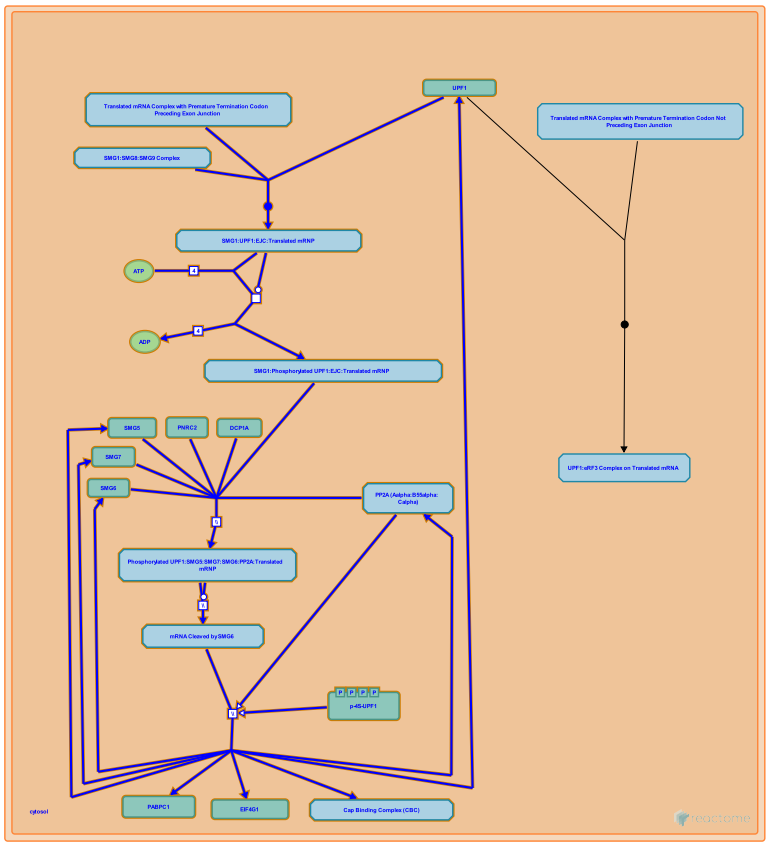
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)



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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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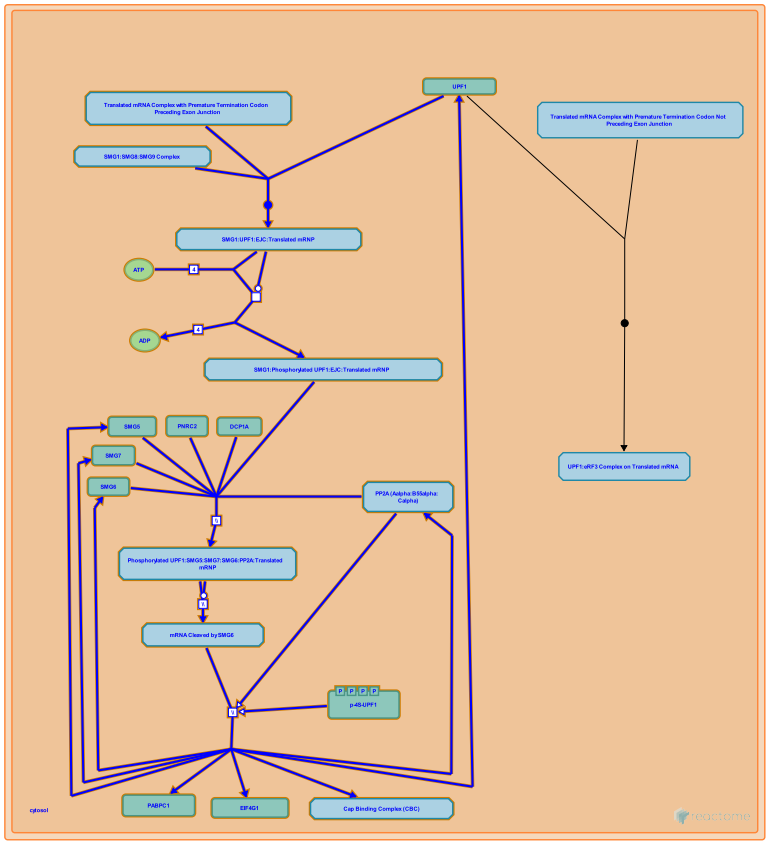
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC) ↗

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. ↗

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Editions

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

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

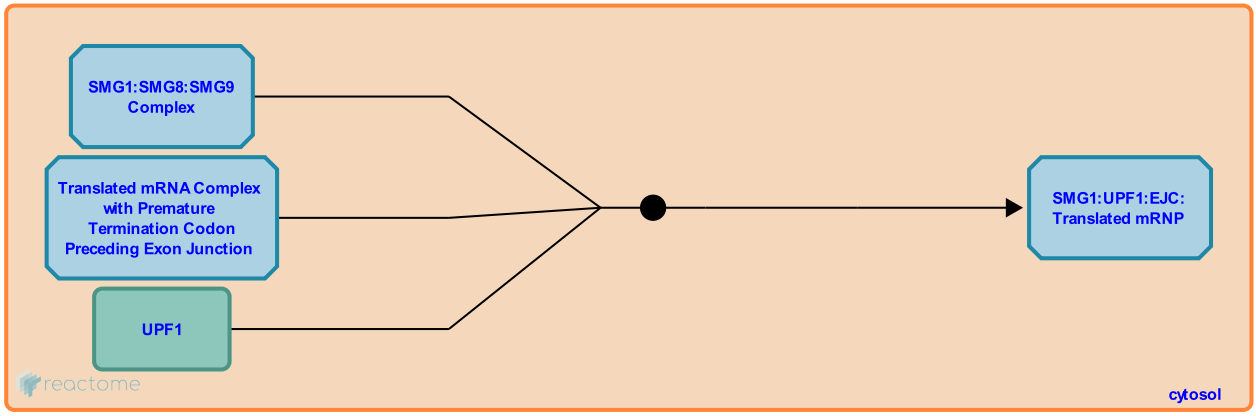
↗

Location: Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)

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.

Followed by: SMG1 phosphorylates UPF1 (enhanced by Exon Junction Complex)

Literature references

Le Hir, H., Moore, MJ., Gatfield, D., Izaurralde, E. (2001). The exon-exon junction complex provides a binding platform for factors involved in mRNA export and nonsense-mediated mRNA decay. *EMBO J, 20,* 4987-97. ↗

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Sauliere, J., Ebert, J., Bono, F., Buchwald, G., Conti, E., Le Hir, H. et al. (2010). Insights into the recruitment of the NMD machinery from the crystal structure of a core EJC-UPF3b complex. *Proc Natl Acad Sci U S A, 107*, 10050-5. ↗

Editions

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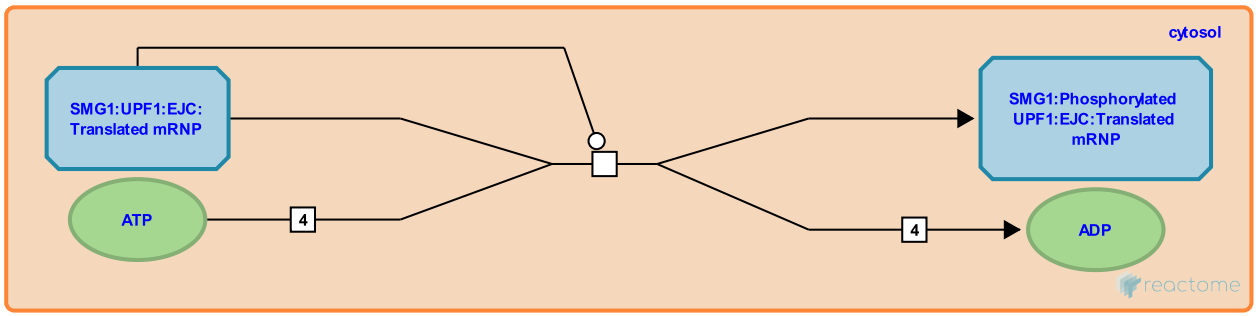
SMG1 phosphorylates UPF1 (enhanced by Exon Junction Complex) ↗

Location: Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)

Stable identifier: R-HSA-927889

Type: transition

Compartments: cytosol



SMG1 phosphorylates UPF1 in vitro and in vivo (Denning et al. 2001, Yamashita et al. 2001, Kashima et al. 2006). Serines 1073, 1078, 1096, and 1116 in isoform 2 (Serines 1084, 1089, 1107, 1127 in isoform 1) are phosphorylated in vitro and phosphorylation at serines 1078 and 1096 has been confirmed in vivo (Yamashita et al. 2001, Ohnishi et al. 2003, Kashima et al. 2006). UPF1 also contains additional serine and threonine residues that could be phosphorylated. SMG8 and SMG9 associate with SMG1 and regulate the kinase activity of SMG1 (Yamashita et al. 2009). The phosphorylation reaction is rate-limiting in nonsense-mediated decay and is therefore regarded as a licensing step (reviewed in Rebbapragada and Lykke-Andersen 2009). Phosphorylation is enhanced by the exon junction complex, which can interact with UPF1 via UPF2 and/or UPF3 (Kashima et al. 2006, Ivanov et al. 2008) or via Y14:Magoh (Ivanov et al. 2008). SMG8 and SMG9 bind SMG1 and regulate its kinase activity (Yamashita et al. 2009, Fernandez et al. 2011).

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

Followed by: p-4S-UPF1 recruits SMG5, SMG7, SMG6, PNRC2, DCP1A, and PP2A

Literature references

Ohno, S., Katsuhata, Y., Yamashita, A., Ohnishi, T., Iwamatsu, A., Anderson, P. et al. (2009). SMG-8 and SMG-9, two novel subunits of the SMG-1 complex, regulate remodeling of the mRNA surveillance complex during nonsense-mediated mRNA decay. *Genes Dev, 23*, 1091-105. ↗

Jamieson, L., Thompson, EA., Maquat, LE., Denning, G., Fields, AP. (2001). Cloning of a novel phosphatidylinositol kinase-related kinase: characterization of the human SMG-1 RNA surveillance protein. *J Biol Chem, 276*, 22709-14. ↗

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Bartolomé, RA., Ohno, S., Bamba, Y., Llorca, O., Yamashita, A., Teixidó, J. et al. (2011). Characterization of SMG-9, an essential component of the nonsense-mediated mRNA decay SMG1C complex. *Nucleic Acids Res, 39*, 347-58. ↗

Editions

2010-08-06	Authored, Edited	May, B.
2011-05-19	Reviewed	Neu-Yilik, G.

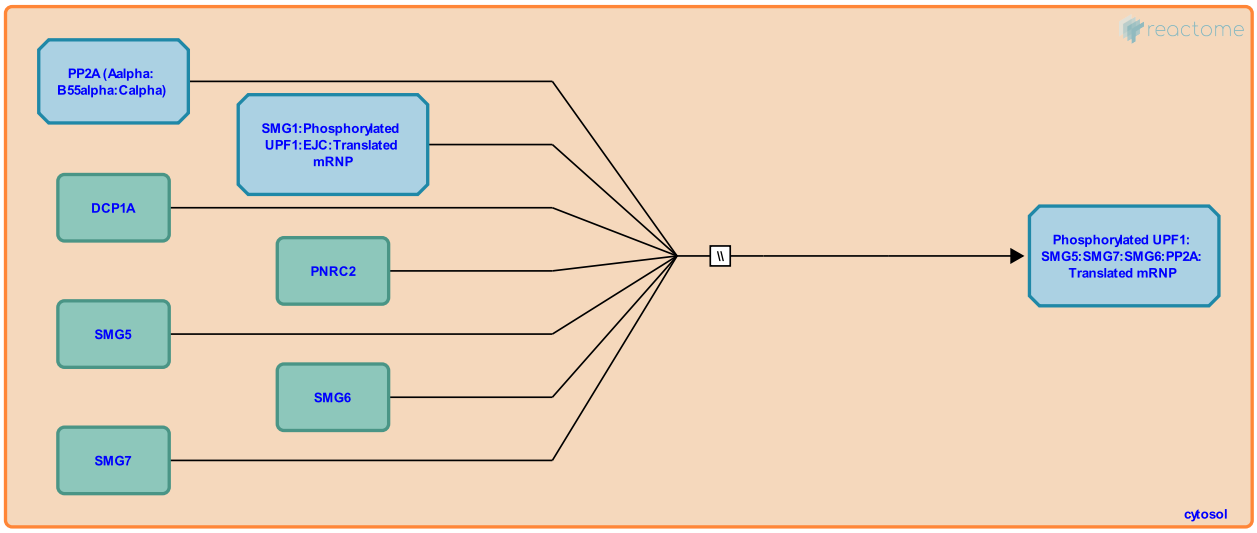
p-4S-UPF1 recruits SMG5, SMG7, SMG6, PNRC2, DCP1A, and PP2A ↗

Location: Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)

Stable identifier: R-HSA-927813

Type: omitted

Compartments: cytosol



SMG6, SMG5 and SMG7 contain 14-3-3 domains which are believed to bind phosphorylated SQ motifs in UPF1 (Chiu et al. 2003, Ohnishi et al. 2003, Unterholzner and Izaurralde 2004, Fukuhara et al. 2005, Durand et al. 2007). SMG7 has been shown to bind UPF1 directly, target UPF1 for dephosphorylation by PP2A, and recruit enzymes that degrade RNA (Ohnishi et al. 2003, Unterholzner and Izaurralde 2004, Fukuhara et al. 2005). UPF3AS (the small isoform of UPF3A) also associates with the complex (Ohnishi et al. 2003). SMG6 is an endoribonuclease that cleaves the mRNA bound by UPF1 and also recruits phosphatase PP2A to dephosphorylate UPF1 (Chiu et al. 2003, Glavan et al. 2006, Eberle et al. 2009). PNRC2 binds both phospo-UPF1 and the decapping enzyme DCP1A, thereby facilitating decapping of the mRNA (Cho et al. 2009, Lai et al. 2012, Cho et al. 2013).
Though immunofluorescence in vivo indicates that SMG5 and SMG7 exist in separate complexes from SMG6 (Unterholzner and Izaurralde 2004) immunoprecipitation shows that SMG6 is present in complexes that also contain SMG5, SMG7, UPF1, UPF2, Y14, Magoh, and PABP (Kashima et al. 2010). SMG5, SMG6, and SMG7 are therefore represented here together in the same RNP complex. It is possible that some complexes contain only SMG6 or SMG5:SMG7 (reviewed in Nicholson et al. 2010, Muhlemann and Lykke-Andersen 2010). Note that "Smg5/7a" in Chiu et al. 2003 actually refers to SMG6.
Phosphorylated UPF1 also inhibits translation initiation by inhibiting conversion of 40S:tRNAmet:mRNA to 80S:tRNAmet:mRNA complexes (Isken et al. 2008)

Preceded by: SMG1 phosphorylates UPF1 (enhanced by Exon Junction Complex)

Followed by: SMG6 hydrolyzes mRNA with premature termination codon

Literature references

Ebert, J., Conti, E., Fukuhara, N., Lindner, D., Unterholzner, L., Izaurralde, E. (2005). SMG7 is a 14-3-3-like adaptor in the nonsense-mediated mRNA decay pathway. *Mol Cell, 17*, 537-47. ↗

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Ohno, S., Grimson, A., Yamashita, A., Ohnishi, T., Anderson, P., Hachiya, T. et al. (2003). Phosphorylation of hUPF1 induces formation of mRNA surveillance complexes containing hSMG-5 and hSMG-7. *Mol Cell, 12*, 1187-200. ↗

Unterholzner, L., Izaurralde, E. (2004). SMG7 acts as a molecular link between mRNA surveillance and mRNA decay. *Mol Cell, 16*, 587-96. ↗

Lai, T., Song, H., Cho, H., Bowler, MW., Liu, Z., Parker, R. et al. (2012). Structural basis of the PNRC2-mediated link between mrna surveillance and decapping. *Structure, 20*, 2025-37. ↗

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2011-05-19	Reviewed	Neu-Yilik, G.

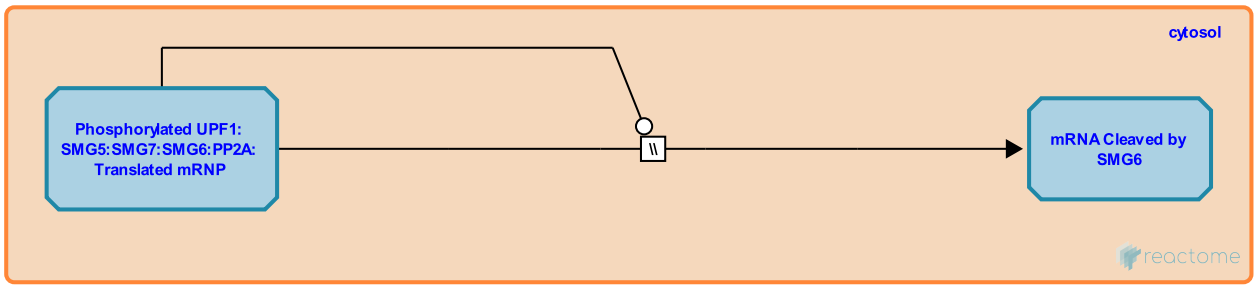
SMG6 hydrolyzes mRNA with premature termination codon ↗

Location: Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)

Stable identifier: R-HSA-927836

Type: omitted

Compartments: cytosol



SMG6 is an endoribonuclease which cleaves the mRNA bound by UPF1 near the premature termination codon (Glavan et al. 2006, Eberle et al. 2009).

Preceded by: p-4S-UPF1 recruits SMG5, SMG7, SMG6, PNRC2, DCP1A, and PP2A

Followed by: Decay of mRNA in SMG6:SMG5:SMG7:mRNA complex

Literature references

Conti, E., Behm-Ansmant, I., Glavan, F., Izaurralde, E. (2006). Structures of the PIN domains of SMG6 and SMG5 reveal a nuclease within the mRNA surveillance complex. *EMBO J, 25*, 5117-25. ↗

Saulière, J., Fauser, M., Huntzinger, E., Izaurralde, E., Kashima, I. (2008). SMG6 is the catalytic endonuclease that cleaves mRNAs containing nonsense codons in metazoan. *RNA, 14*, 2609-17. ↗

Jensen, TH., Eberle, AB., Lykke-Andersen, S., Muhlemann, O. (2009). SMG6 promotes endonucleolytic cleavage of nonsense mRNA in human cells. *Nat Struct Mol Biol, 16*, 49-55. ↗

Editions

2010-08-06	Authored, Edited	May, B.
2011-05-19	Reviewed	Neu-Yilik, G.

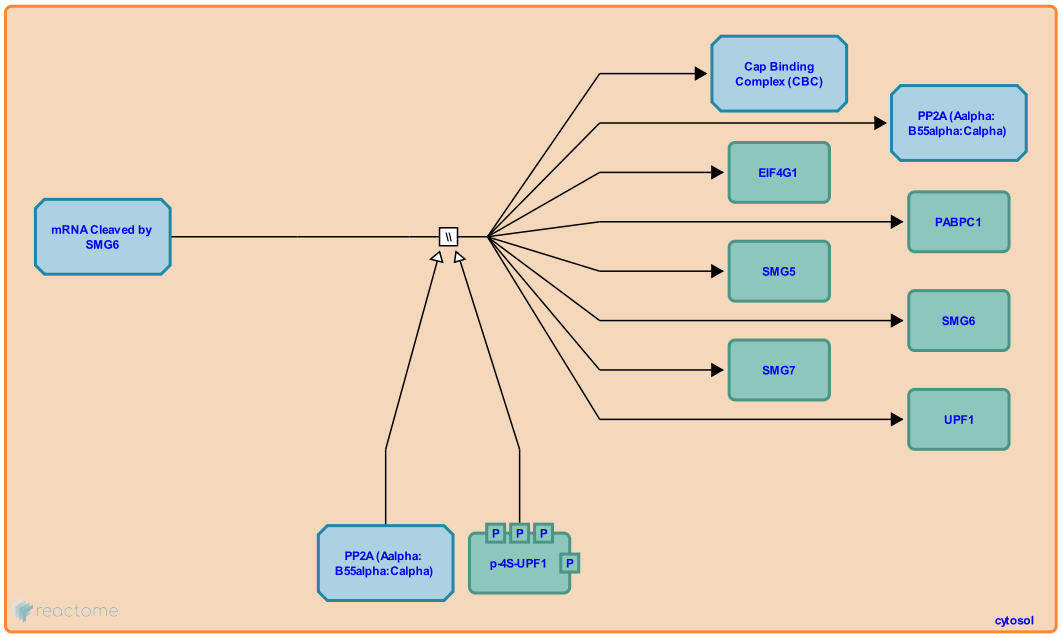
Decay of mRNA in SMG6:SMG5:SMG7:mRNA complex ↗

Location: Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)

Stable identifier: R-HSA-927830

Type: omitted

Compartments: cytosol



SMG6 endonucleolytically cleaves an mRNA it is believed that the resulting fragments are degraded by exonucleases, possibly XRN1, a 5'-to-3' nuclease, and the exosome complex, a 3'-to-5' nuclease (Huntzinger et al. 2008, Eberle et al. 2009). Inhibition of XRN1 is observed to cause accumulation of SMG6-cleaved intermediates therefore XRN1 is postulated to act downstream of SMG6 (Huntzinger et al. 2008).
In general, during Nonsense-Mediated Decay mRNAs are observed to be deadenlyated (implicating the PAN2 complex, PARN complex, and CCR4 complex), decapped (implicating the DCP1:DCP2 complex), and exoribonucleolytically digested (implicating the XRN1 5'-to-3' exonuclease and exosome 3'-to-5' exonuclease) (Lykke-Andersen 2002, Chen et al. 2003, Lejeune et al. 2003, Couttet and Grange 2004, Unterholzner and Izaurralde 2004, Yamashita et al. 2005). UPF1 is observed to associate with the decapping enzymes DCP1a and DCP2, however the specific decay reactions that occur after SMG6, SMG5 and SMG7 have associated with an mRNA are unknown (Lykke-Andersen et al. 2002). Likewise, SMG6 may be present in complexes separate from SMG5 and SMG7 and these complexes may have different routes of decay (reviewed in Nicholson et al. 2010, Muhlemann and Lykke-Andersen 2010).
ATPase activity of UPF1 is necessary for NMD and may reflect ATP-dependent helicase activity that disassembles the mRNA-protein complex (Franks et al. 2010). UPF1 must be dephosphorylated by PP2A for NMD to continue (Ohnishi et al. 2003, Chiu et al. 2003). Presumably the dephosphoryation recycles UPF1 for interaction with other mRNA complexes.

Preceded by: SMG6 hydrolyzes mRNA with premature termination codon

Literature references

Lykke-Andersen, J., Muhlemann, O. (2010). How and where are nonsense mRNAs degraded in mammalian cells?. *RNA Biol, 7*, 28-32. ↗

Ohno, S., Grimson, A., Yamashita, A., Ohnishi, T., Anderson, P., Hachiya, T. et al. (2003). Phosphorylation of hUPF1 induces formation of mRNA surveillance complexes containing hSMG-5 and hSMG-7. *Mol Cell, 12*, 1187-200. ↗

Zhu, W., Chang, TC., Yamashita, A., Zhong, Z., Yamashita, Y., Chen, CY. et al. (2005). Concerted action of poly(A) nucleases and decapping enzyme in mammalian mRNA turnover. *Nat Struct Mol Biol, 12*, 1054-63. ↗

Grange, T., Couttet, P. (2004). Premature termination codons enhance mRNA decapping in human cells. *Nucleic Acids Res, 32*, 488-94. ↗

Unterholzner, L., Izaurralde, E. (2004). SMG7 acts as a molecular link between mRNA surveillance and mRNA decay. *Mol Cell, 16*, 587-96. ↗

Editions

2010-08-06	Authored, Edited	May, B.
2011-05-19	Reviewed	Neu-Yilik, G.

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