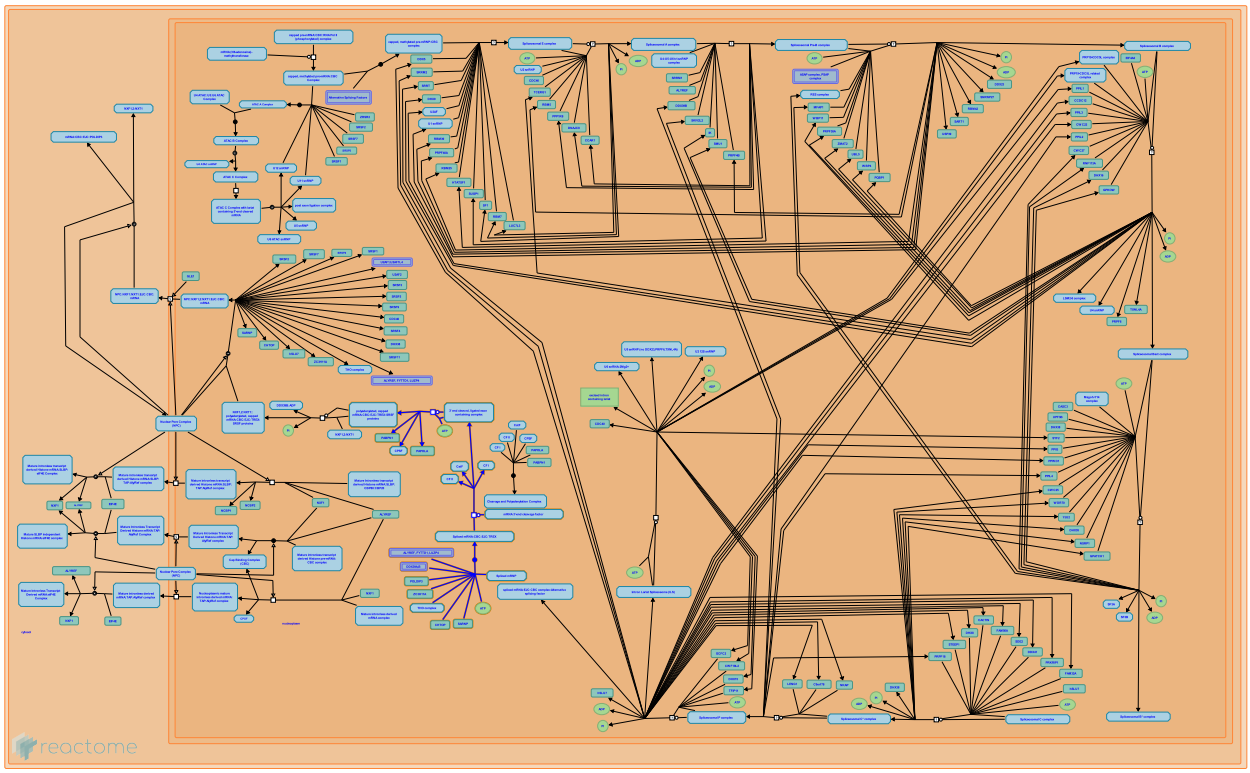
mRNA 3'-end processing



Joshi-Tope, G., May, B., Reed, R., Rondón, AG., Wahle, E.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

02/04/2024

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. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

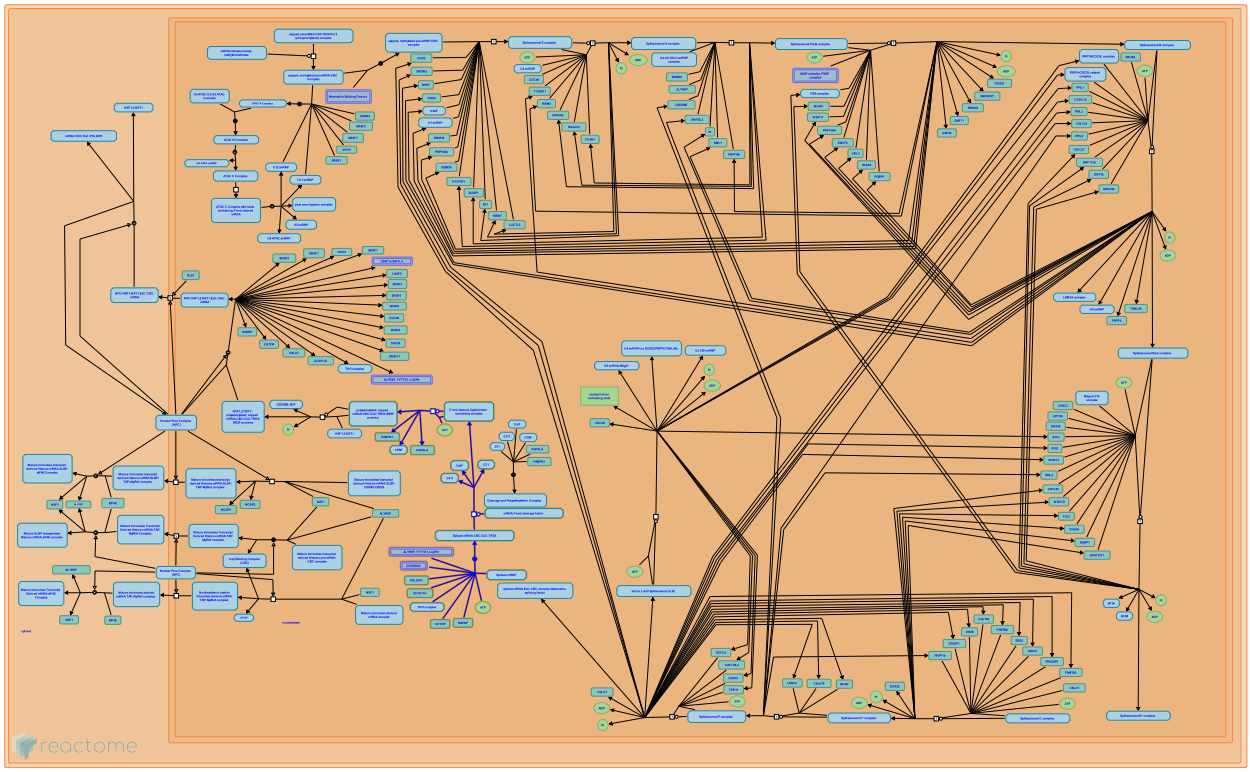
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

mRNA 3'-end processing ↗

Stable identifier: R-HSA-72187

Compartments: nucleoplasm



The 3' ends of eukaryotic mRNAs are generated by posttranscriptional processing of an extended primary transcript. For almost all RNAs, 3'-end processing consists of two steps: (i) the mRNA is first cleaved at a particular phosphodiester bond downstream of the coding sequence, (ii) the upstream fragment then receives a poly(A) tail of approximately 250 adenylate residues, whereas the downstream fragment is degraded. The two partial reactions are coupled so that reaction intermediates are usually undetectable. While 3' processing can be studied as an isolated event *in vitro*, it appears to be connected to transcription, splicing, and transcription termination *in vivo*.

The only known exception to the rule of cleavage followed by polyadenylation are the major histone mRNAs, which are cleaved but not polyadenylated.

Literature references

Rüegsegger, U., Wahle, E. (1999). 3'-End processing of pre-mRNA in eukaryotes. *FEMS Microbiol Rev, 23*, 277-95. ↗

Moore, CL., Sharp, PA. (1985). Accurate cleavage and polyadenylation of exogenous RNA substrate. *Cell, 41*, 845-55. ↗

Hyman, L., Zhao, J., Moore, C. (1999). Formation of mRNA 3' ends in eukaryotes: mechanism, regulation, and interrelationships with other steps in mRNA synthesis. *Microbiol Mol Biol Rev, 63*, 405-45. ↗

Furger, A., Dye, MJ., Proudfoot, NJ. (2002). Integrating mRNA processing with transcription. *Cell, 108*, 501-12. ↗

Editions

2003-06-05	Authored	Wahle, E.
2024-03-06	Edited	Joshi-Tope, G.

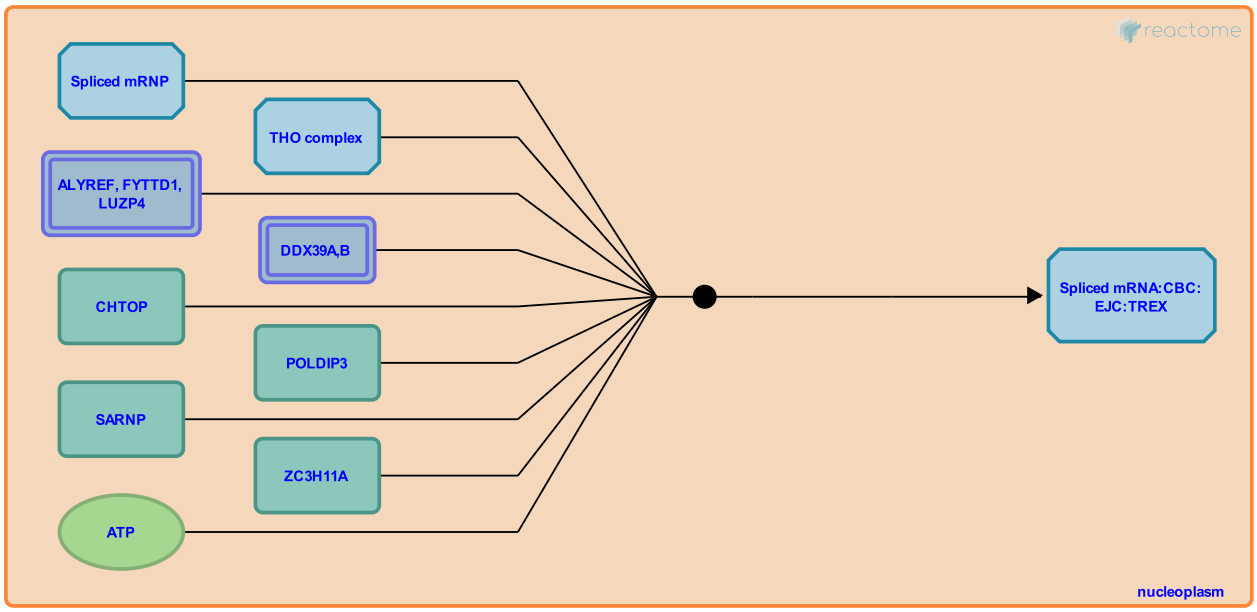
TREX complex binds spliced, capped mRNA:CBC:EJC cotranscriptionally ↗

Location: mRNA 3'-end processing

Stable identifier: R-HSA-8849157

Type: binding

Compartments: nucleoplasm



The THO subcomplex of the TREX complex initially interacts with the serine-2,5 phosphorylated C-terminal domain of RNA polymerase II (Strasser et al. 2002, Inferred from yeast in Meinel et al. 2013) then with CBP80 of the cap binding complex (Cheng et al. 2006, Dufu et al. 2010, Chi et al. 2013). A TREX complex binds spliced mRNA near the cap during transcription (Cheng et al. 2006). Recruitment is dependent on splicing of the mRNA (Masuda et al. 2005). THO/TREX is required for efficient mRNP biogenesis and export (reviewed in Luna et al 2012). In yeast, components of the THO/TREX complex also affect transcription and 3' processing of mRNA, (Rondon et al. 2003, Rougemaille et al. 2008, Johnson et al. 2011, reviewed in Katahira 2015), however the human TREX complex does not appear to affect transcription (Masuda et al. 2005). The AREX complex, which contains DDX39A (UHR49) rather than DDX39B (UAP56) appears to perform the same function as TREX in mRNA export, but acts on a different subset of mRNAs (Yamazaki et al. 2010).

Followed by: Cleavage of mRNA at the 3'-end

Literature references

Bentley, DL., Erickson, B., Johnson, SA., Kim, H. (2011). The export factor Yra1 modulates mRNA 3' end processing. *Nat. Struct. Mol. Biol., 18*, 1164-71. ↗

Gudipati, RK., Libri, D., Lemoine, S., Devaux, F., Jensen, TH., Rougemaille, M. et al. (2008). THO/Sub2p functions to coordinate 3'-end processing with gene-nuclear pore association. *Cell, 135*, 308-21. ↗

Reed, R., Masuda, S., Hurt, E., Das, R., Cheng, H., Dorman, N. (2005). Recruitment of the human TREX complex to mRNA during splicing. *Genes Dev., 19*, 1512-7. ↗

Aguilera, A., García-Rubio, M., Jimeno, S., Rondón, AG. (2003). Molecular evidence that the eukaryotic THO/TREX complex is required for efficient transcription elongation. *J. Biol. Chem., 278*, 39037-43. ↗

Aguilera, A., Luna, R., Rondón, AG. (2012). New clues to understand the role of THO and other functionally related factors in mRNP biogenesis. *Biochim. Biophys. Acta, 1819*, 514-20. ↗

Editions

2015-12-12	Authored, Edited	May, B.
2016-01-13	Reviewed	Rondón, AG.
2016-01-14	Reviewed	Reed, R.

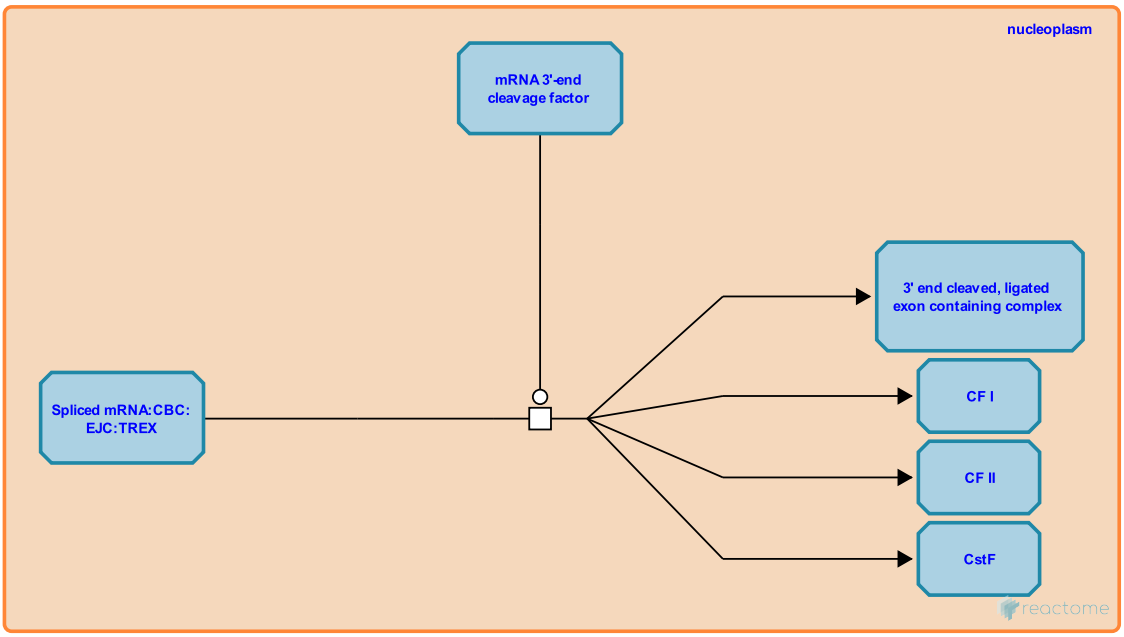
Cleavage of mRNA at the 3'-end ↗

Location: mRNA 3'-end processing

Stable identifier: R-HSA-72180

Type: transition

Compartments: nucleoplasm



Endonucleolytic cleavage separates the pre-mRNA into an upstream fragment destined to become the mature mRNA, and a downstream fragment that is rapidly degraded. Cleavage depends on two signals in the RNA, a highly conserved hexanucleotide, AAUAAA, 10 to 30 nucleotides upstream of the cleavage site, and a poorly conserved GU- or U-rich downstream element. Additional sequences, often upstream of AAUAAA, can enhance the efficiency of the reaction. Cleavage occurs most often after a CA dinucleotide. A single gene can have more than one 3' processing site.

Cleavage is preceded by the assembly of a large processing complex, the composition of which is poorly defined. ATP, but not its hydrolysis, is required for assembly. Cleavage at the 3'-end of mRNAs depends on a number of protein factors. CPSF, a heterotetramer, binds specifically to the AAUAAA sequence. The heterotrimer CstF binds the downstream element. CF I, which appears to be composed of two subunits, one of several related larger polypeptides and a common smaller one, also binds RNA, but with unknown specificity. RNA recognition by these proteins is cooperative. Cleavage also requires CF II, composed of at least two subunits, and poly(A) polymerase, the enzyme synthesizing the poly(A) tail in the second step of the reaction. The polypeptide catalyzing the hydrolysis of the phosphodiester bond remains to be identified.

Cleavage produces a 3'-OH on the upstream fragment and a 5'-phosphate on the downstream fragment. At some unknown point after cleavage, the downstream RNA fragment, CstF, CF I and CF II are thought to be released, whereas CPSF and poly(A) polymerase remain to carry out polyadenylation.

Preceded by: TREX complex binds spliced, capped mRNA:CBC:EJC cotranscriptionally

Followed by: mRNA polyadenylation

Literature references

Rüegsegger, U., Wahle, E. (1999). 3'-End processing of pre-mRNA in eukaryotes. *FEMS Microbiol Rev, 23*, 277-95. ↗

Hyman, L., Zhao, J., Moore, C. (1999). Formation of mRNA 3' ends in eukaryotes: mechanism, regulation, and interrelationships with other steps in mRNA synthesis. *Microbiol Mol Biol Rev, 63*, 405-45. ↗

Editions

2003-06-05	Authored	Wahle, E.
2024-03-06	Edited	Joshi-Tope, G.

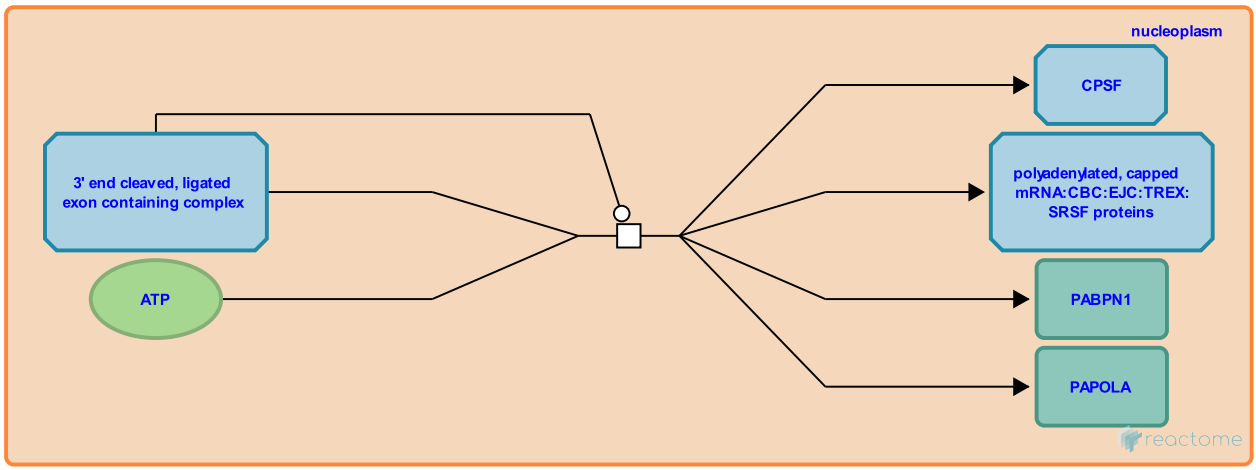
mRNA polyadenylation ↗

Location: mRNA 3'-end processing

Stable identifier: R-HSA-72185

Type: transition

Compartments: nucleoplasm



The upstream fragment generated by 3' cleavage of the pre-mRNA receives a poly(A) tail of approximately 250 AMP residues in a reaction depending on the AAUAAA sequence 10 to 30 nucleotides upstream of the 3' end. Polyadenylation is carried out by three proteins: Poly(A) polymerase carries the catalytic activity. The enzyme has no specificity for any particular RNA sequence, and it also has a very low affinity for the RNA.

Under physiological conditions, the activity of poly(A) polymerase thus depends on two auxiliary factors, both of which bind to specific RNA sequences and recruit the enzyme by a direct contact. One of these proteins is the heterotetrameric CPSF, which binds the AAUAAA sequence and is also essential for 3' cleavage. The second is the nuclear poly(A) binding protein (PABPN1), which binds the growing poly(A) tails once this has reached a length of about ten nucleotides. Stimulation of poly(A) polymerase by both proteins is synergistic and results in processive elongation of the RNA, i.e. the polymerase adds AMP residues without dissociating from the RNA. The processive reaction is terminated when the tail has reached a length of about 250 nucleotides.

Preceded by: Cleavage of mRNA at the 3'-end

Literature references

Moore, CL., Sharp, PA. (1985). Accurate cleavage and polyadenylation of exogenous RNA substrate. *Cell, 41*, 845-55. ↗

Hyman, L., Zhao, J., Moore, C. (1999). Formation of mRNA 3' ends in eukaryotes: mechanism, regulation, and interrelationships with other steps in mRNA synthesis. *Microbiol Mol Biol Rev, 63*, 405-45. ↗

Editions

2003-06-05	Authored	Wahle, E.
2024-03-06	Edited	Joshi-Tope, G.

Table of Contents