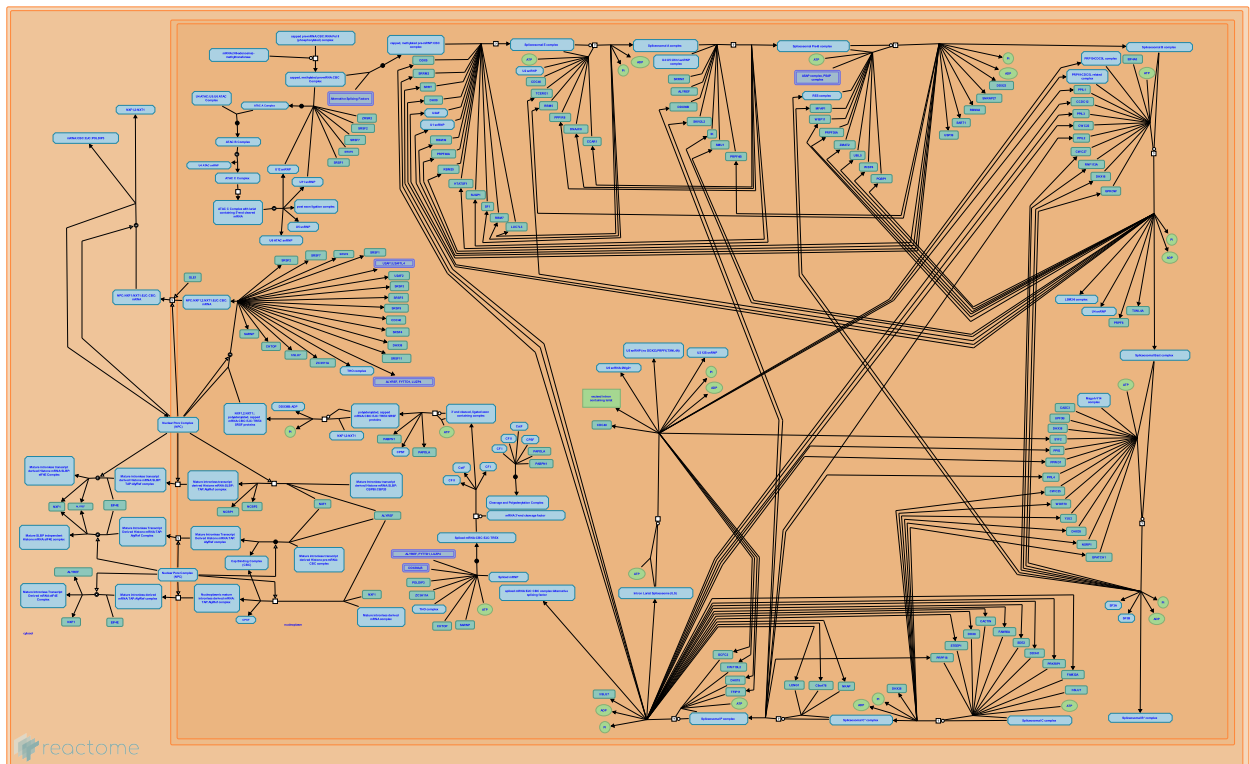


Processing of Capped Intron-Containing Pre-mRNA



Carmichael, GG., Gillespie, ME., Gopinathrao, G., Hammarskjold, ML., Hastings, ML., Joshi-Tope, G., Krainer, AR., Marzluff, WF., Nilsen, TW., Wahle, E., Zhang, Z.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

25/04/2024

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.

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Literature references

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

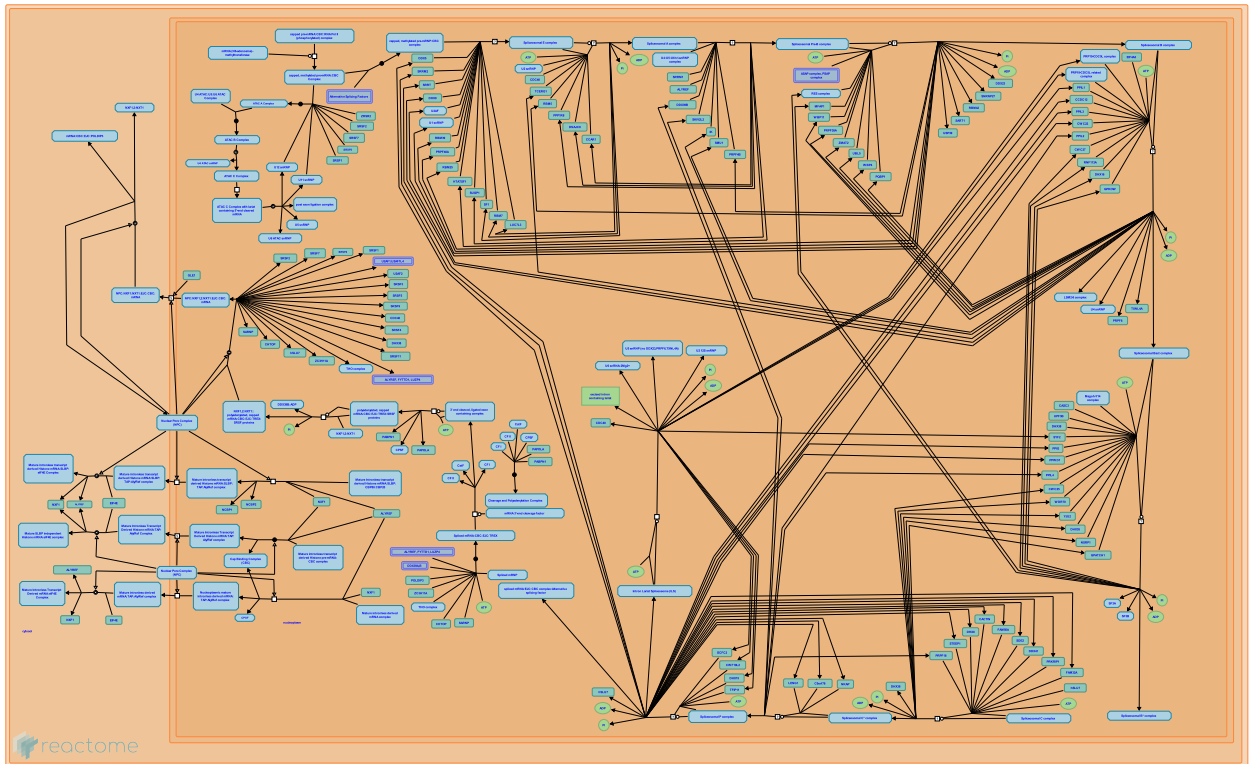
Reactome database release: 88

This document contains 4 pathways and 3 reactions ([see Table of Contents](#))

Processing of Capped Intron-Containing Pre-mRNA ↗

Stable identifier: R-HSA-72203

Compartments: nucleoplasm, nuclear envelope, cytosol



Co-transcriptional pre-mRNA splicing is not obligatory. Pre-mRNA splicing begins co-transcriptionally and often continues post-transcriptionally. Human genes contain an average of nine introns per gene, which cannot serve as splicing substrates until both 5' and 3' ends of each intron are synthesized. Thus the time that it takes for pol II to synthesize each intron defines a minimal time and distance along the gene in which splicing factors can be recruited. The time that it takes for pol II to reach the end of the gene defines the maximal time in which splicing could occur co-transcriptionally. Thus, the kinetics of transcription can affect the kinetics of splicing. Any covalent change in a primary (nascent) mRNA transcript is mRNA Processing. For successful gene expression, the primary mRNA transcript needs to be converted to a mature mRNA prior to its translation into polypeptide. Eucaryotic mRNAs undergo a series of complex processing reactions; these begin on nascent transcripts as soon as a few ribonucleotides have been synthesized during transcription by RNA Polymerase II, through the export of the mature mRNA to the cytoplasm, and culminate with mRNA turnover in the cytoplasm.

Editions

2003-06-05	Authored	Wahle, E., Carmichael, GG., Hammarskjold, ML., Hastings, ML., Marzluff, WF., Krainer, AR. et al.
2024-03-06	Edited	Gillespie, ME., Gopinathrao, G., Joshi-Tope, G.
2024-03-06	Reviewed	Nilsen, TW.

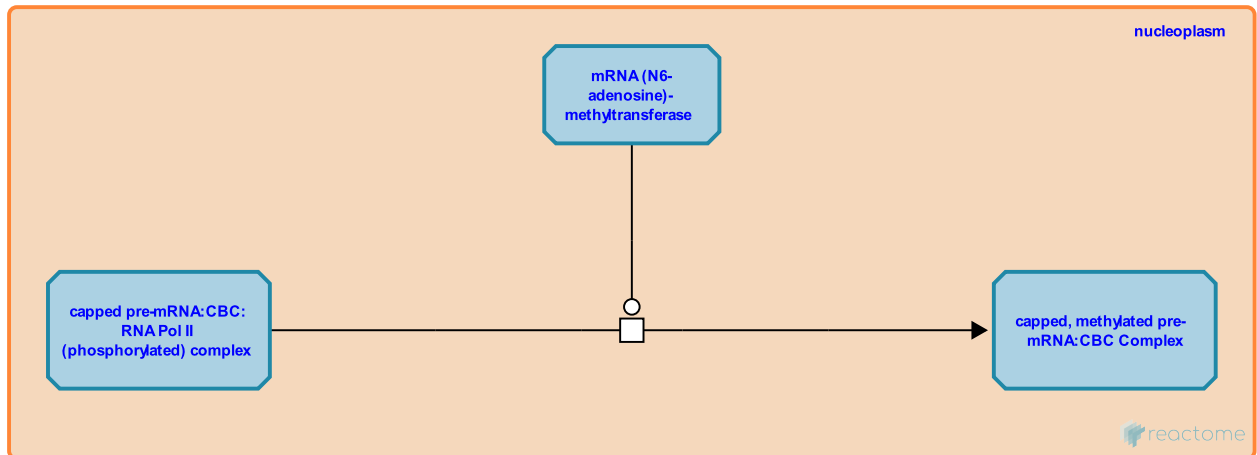
Internal Methylation of mRNA ↗

Location: [Processing of Capped Intron-Containing Pre-mRNA](#)

Stable identifier: R-HSA-72095

Type: transition

Compartments: nucleoplasm



In addition to the methylation of the 5'-cap, there is methylation of internal nucleotides in the mRNA. This methylation can occur in translated and untranslated regions. One to three methyl groups have been seen per mRNA molecule, but methylation is non-stoichiometric. The most frequent methylation observed is at the N6 position of adenosine. The function of mRNA internal methylation, if any, is unknown.

Literature references

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- Bushkin, GG., Mumbach, MR., Satija, R., Wang, T., Pacold, ME., Sanjana, NE. et al. (2014). Perturbation of m6A writers reveals two distinct classes of mRNA methylation at internal and 5' sites. *Cell Rep*, 8, 284-96. ↗
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Editions

2024-03-06

Edited

Joshi-Tope, G.

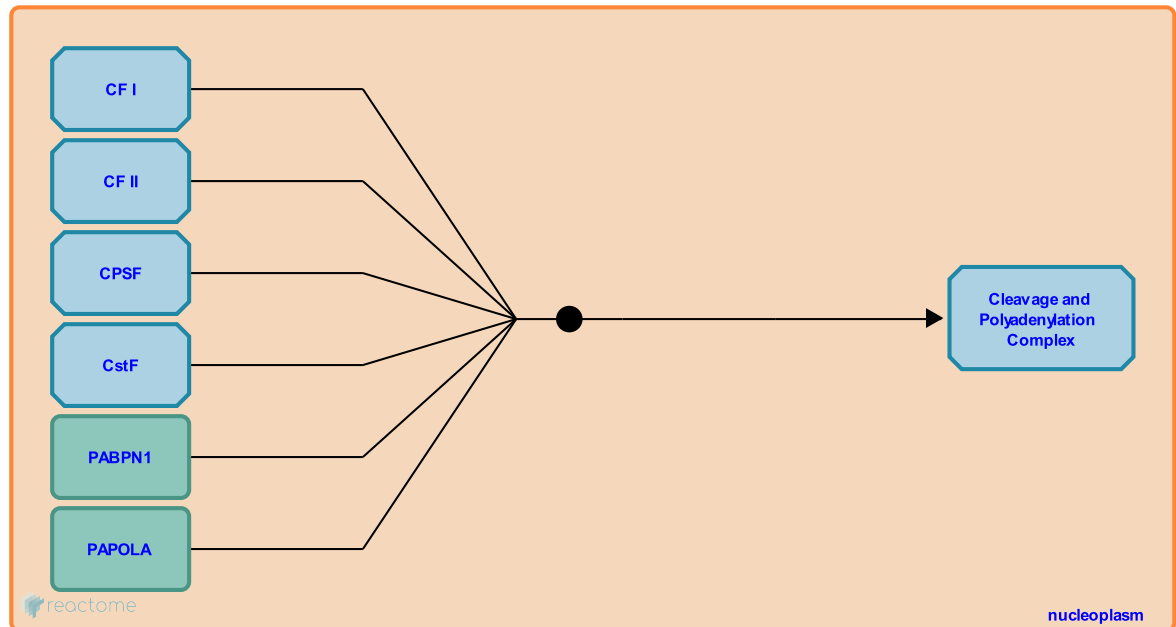
Formation of the Cleavage and Polyadenylation Complex ↗

Location: [Processing of Capped Intron-Containing Pre-mRNA](#)

Stable identifier: R-HSA-72231

Type: binding

Compartments: nucleoplasm



The cleavage and polyadenylation complex includes proteins that recognize the polyA addition signal of the nascent mRNA as well as the endonuclease that cleaves the RNA and other RNA binding elements (Charlesworth et al. 2013).

Literature references

Charlesworth, A., Meijer, HA., de Moor, CH. (2013). Specificity factors in cytoplasmic polyadenylation. *Wiley Interdiscip Rev RNA*, 4, 437-61. ↗

Editions

2024-03-06

Edited

Joshi-Tope, G.

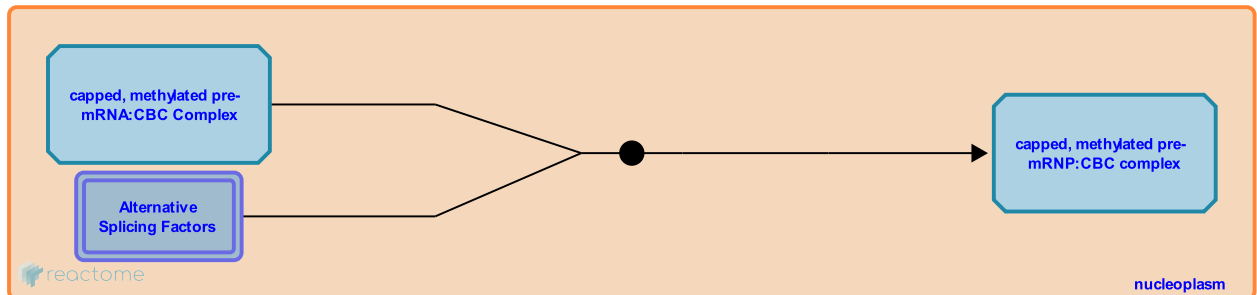
Formation of pre-mRNPs ↗

Location: Processing of Capped Intron-Containing Pre-mRNA

Stable identifier: R-HSA-72103

Type: binding

Compartments: nucleoplasm



After the nascent pre-mRNA undergoes the initial capping and methylation reactions, it gets associated with numerous factors, including the various heterogeneous nuclear ribonucleoproteins (hnRNPs), the nuclear Cap-Binding Complex, and many splicing factors that make the pre-mRNA a substrate for splicing, 3'-end processing, and in some cases editing.

Literature references

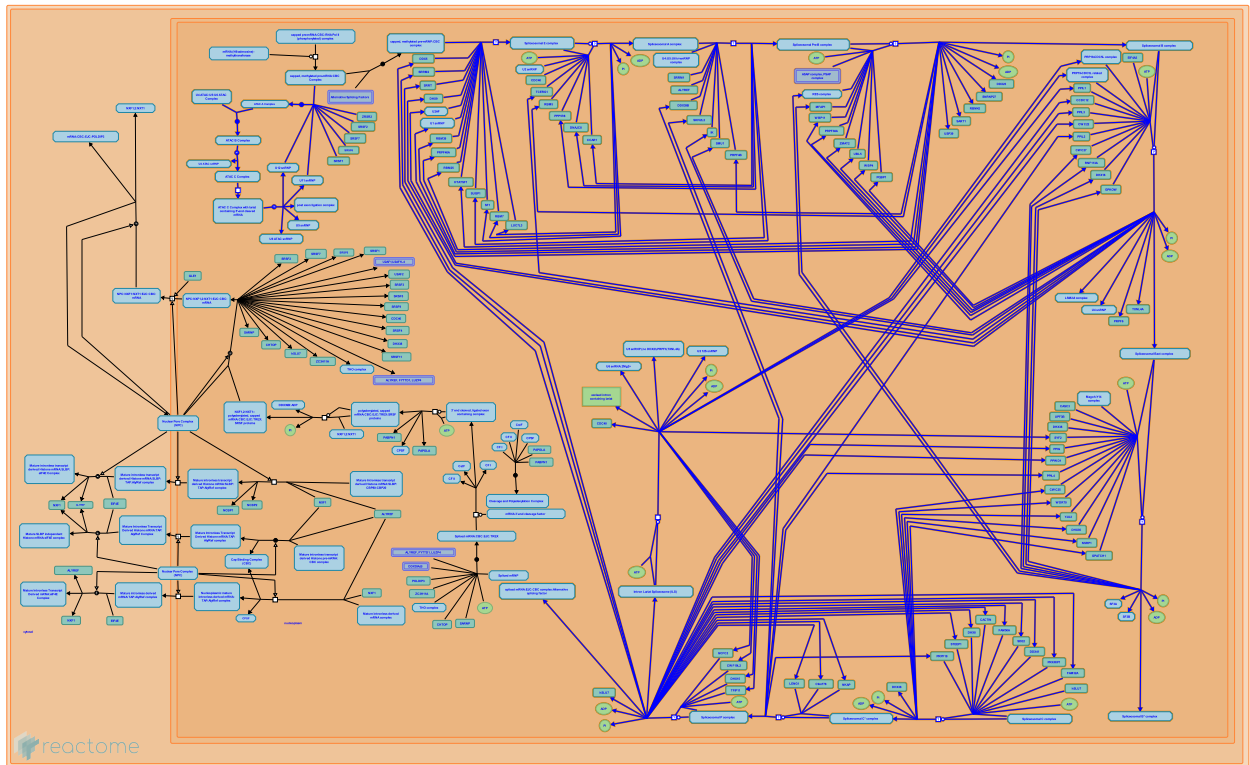
Piñol-Roma, S., Matunis, MJ., Burd, CG., Dreyfuss, G. (1993). hnRNP proteins and the biogenesis of mRNA. *Annu. Rev. Biochem.*, 62, 289-321. ↗

mRNA Splicing ↗

Location: Processing of Capped Intron-Containing Pre-mRNA

Stable identifier: R-HSA-72172

Compartments: nucleoplasm



The process in which excision of introns from the primary transcript of messenger RNA (mRNA) is followed by ligation of the two exon termini exposed by removal of each intron, is called mRNA splicing. Most of the mRNA is spliced by the major pathway, involving the U1, U2, U4, U5 and U6 snRNPs. A minor fraction, about 1 %, of the mRNAs are spliced via the U12 dependent pathway.

Literature references

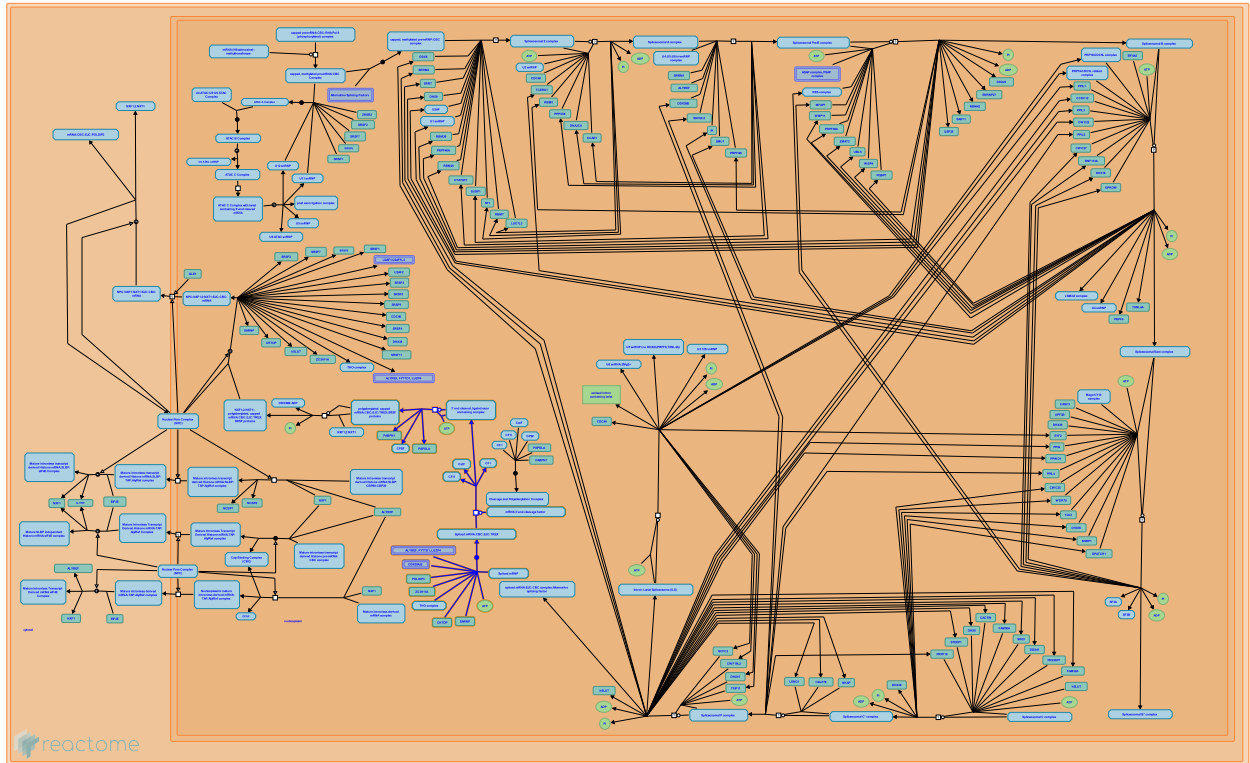
Reed, R., Gygi, SP., Licklider, LJ., Zhou, Z. (2002). Comprehensive proteomic analysis of the human spliceosome. *Nature*, 419, 182-5. ↗

mRNA 3'-end processing ↗

Location: Processing of Capped Intron-Containing Pre-mRNA

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. ↗
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Editions

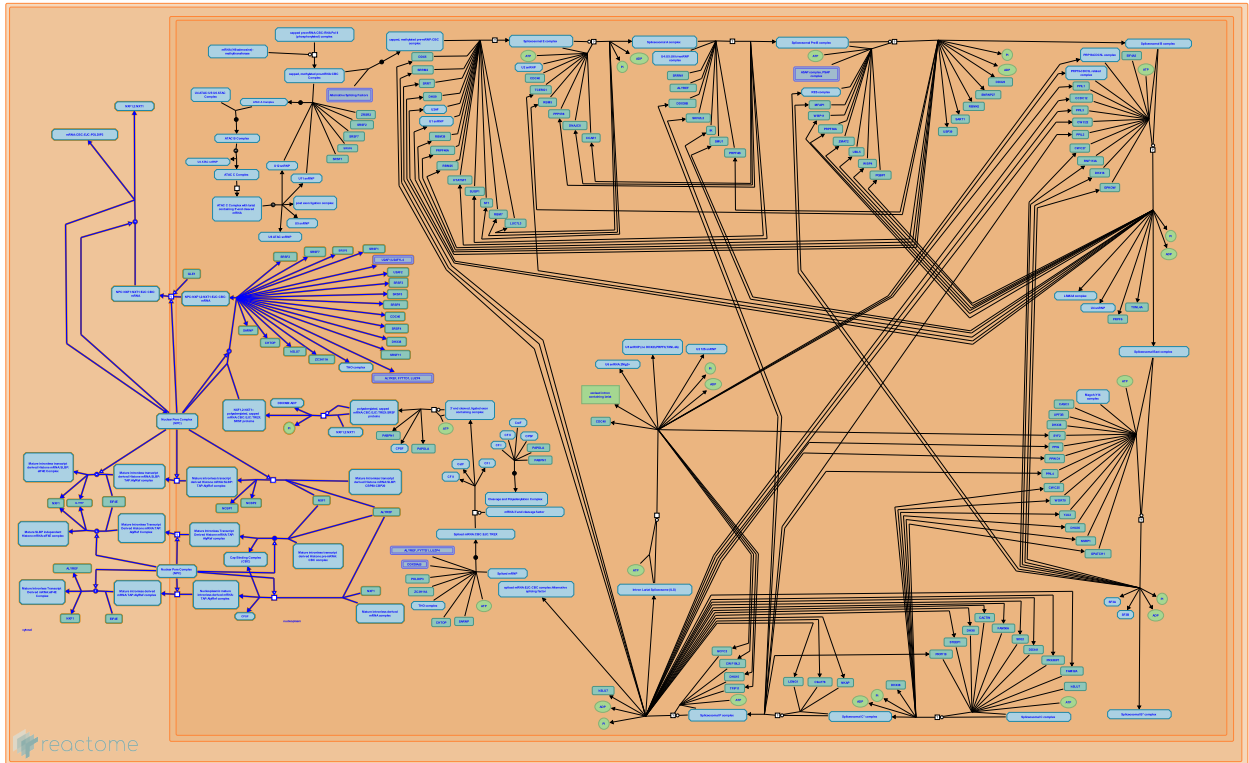
2003-06-05	Authored	Wahle, E.
2024-03-06	Edited	Joshi-Tope, G.

Transport of Mature Transcript to Cytoplasm ↗

Location: Processing of Capped Intron-Containing Pre-mRNA

Stable identifier: R-HSA-72202

Compartments: nuclear envelope, nucleoplasm, cytosol



Transport of mRNA through the Nuclear Pore Complex (NPC) is a dynamic process involving distinct machinery and receptor subsets. The separation of the two compartments and the regulation of this transport provide spatial and temporal control over mRNA expression and ultimately control over translation. It should be noted that mRNA export does not rely on a specific motif in the mRNA molecule, but rather transport appears to be coupled to processing and regulation. The specific proteins that are bound to the mRNA determine when it will be transported to the cytoplasm. This limitation insures that transport overwhelmingly favors transport of fully processed mRNA molecules.

Editions

2003-09-02

Authored

Joshi-Tope, G.

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