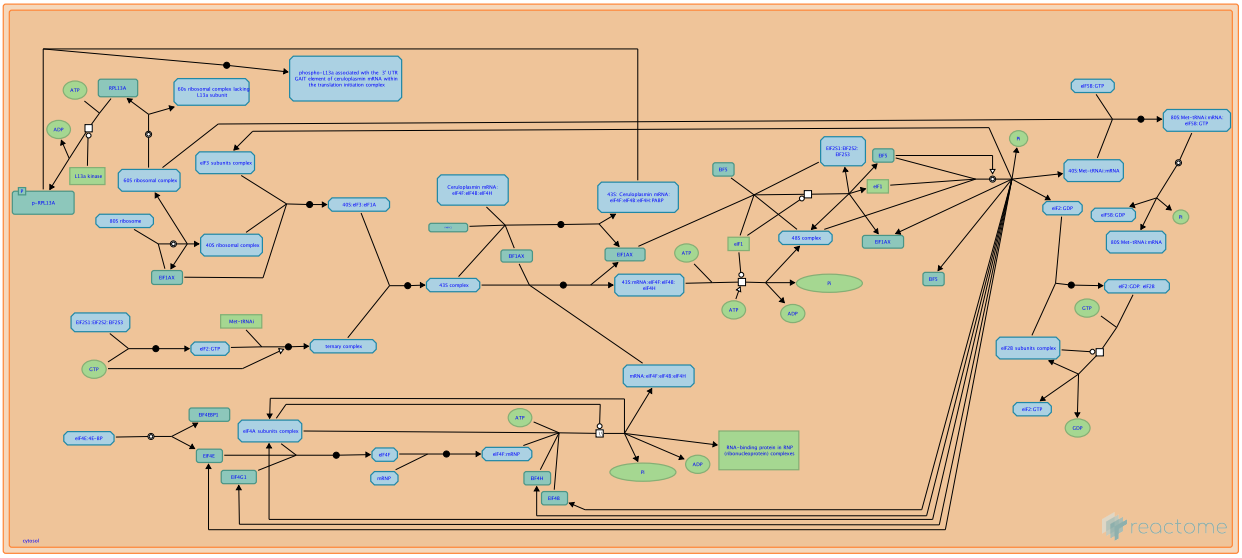
Eukaryotic Translation Initiation



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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

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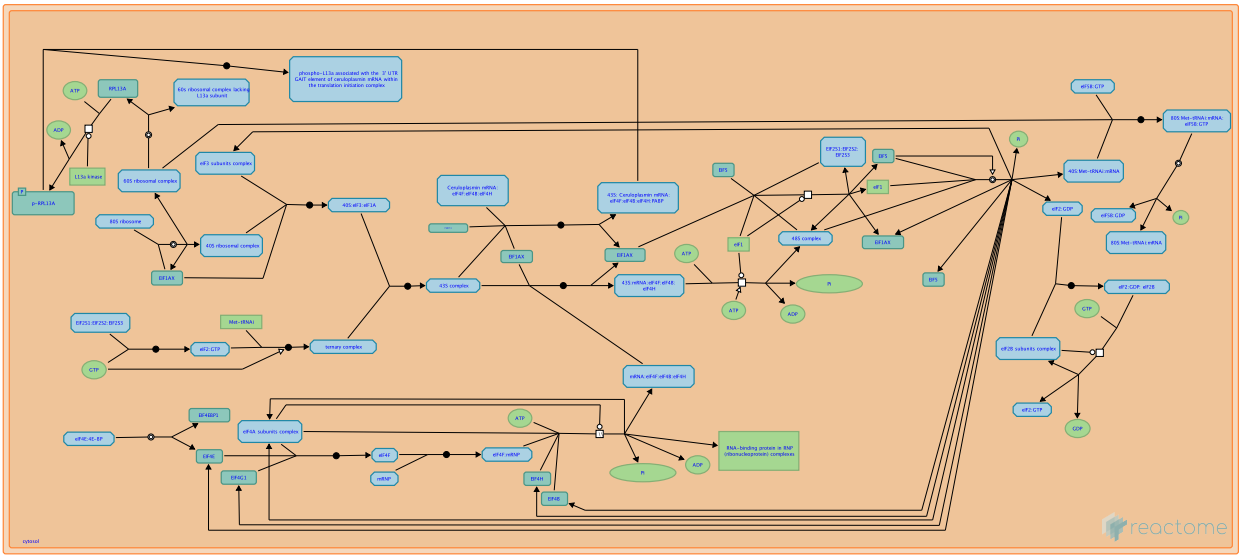
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 77

This document contains 3 pathways (see Table of Contents)

Eukaryotic Translation Initiation ↗

Stable identifier: R-HSA-72613



Initiation of translation in the majority of eukaryotic cellular mRNAs depends on the 5'-cap (m7GpppN) and involves ribosomal scanning of the 5' untranslated region (5'-UTR) for an initiating AUG start codon. Therefore, this mechanism is often called cap-dependent translation initiation. Proximity to the cap, as well as the nucleotides surrounding an AUG codon, influence the efficiency of the start site recognition during the scanning process. However, if the recognition site is poor enough, scanning ribosomal subunits will ignore and skip potential starting AUGs, a phenomenon called leaky scanning. Leaky scanning allows a single mRNA to encode several proteins that differ in their amino-termini. Merrick (2010) provides an overview of this process and hghlights several features of it that remain incompletely understood.

Several eukaryotic cell and viral mRNAs initiate translation by an alternative mechanism that involves internal initiation rather than ribosomal scanning. These mRNAs contain complex nucleotide sequences, called internal ribosomal entry sites, where ribosomes bind in a cap-independent manner and start translation at the closest downstream AUG codon.

Initiation on several viral and cellular mRNAs is cap-independent and is mediated by binding of the ribosome to internal ribosome entry site (IRES) elements. These elements are often found in characteristically long structured regions on the 5'-UTR of an mRNA that may or may not have regulatory upstream open reading frames (uORFs). Both of these features on the 5'-end of the mRNA hinder ribosomal scanning, and thus promote a cap-independent translation initiation mechanism. IRESs act as specific translational enhancers that allow translation initiation to occur in response to specific stimuli and under the control of different trans-acting factors, as for example when cap-dependent protein synthesis is shut off during viral infection. Such regulatory elements have been identified in the mRNAs of growth factors, protooncogenes, angiogenesis factors, and apoptosis regulators, which are translated under a variety of stress conditions, including hypoxia, serum deprivation, irradiation and apoptosis. Thus, cap-independent translational control might have evolved to regulate cellular responses in acute but transient stress conditions that would otherwise lead to cell death, while the same mechanism is of major importance for viral mRNAs to bypass the shutting-off of host protein synthesis after infection. Encephalomyocarditis virus (EMCV) and hepatitis C virus exemplify two distinct mechanisms of IRES-mediated initiation. In contrast to cap-dependent initiation, the eIF4A and eIF4G subunits of eIF4F bind immediately upstream of the EMCV initiation codon and promote binding of a 43S complex. Accordingly, EMCV initiation does not involve scanning and does not require eIF1, eIF1A, and the eIF4E subunit of eIF4F. Nonetheless, ini-

tiation on some EMCV-like IRESs requires additional non-canonical initiation factors, which alter IRES conformation and promote binding of eIF4A/eIF4G. Initiation on the hepatitis C virus IRES is simpler: a 43S complex containing only eIF2 and eIF3 binds directly to the initiation codon as a result of specific interaction of the IRES and the 40S subunit.

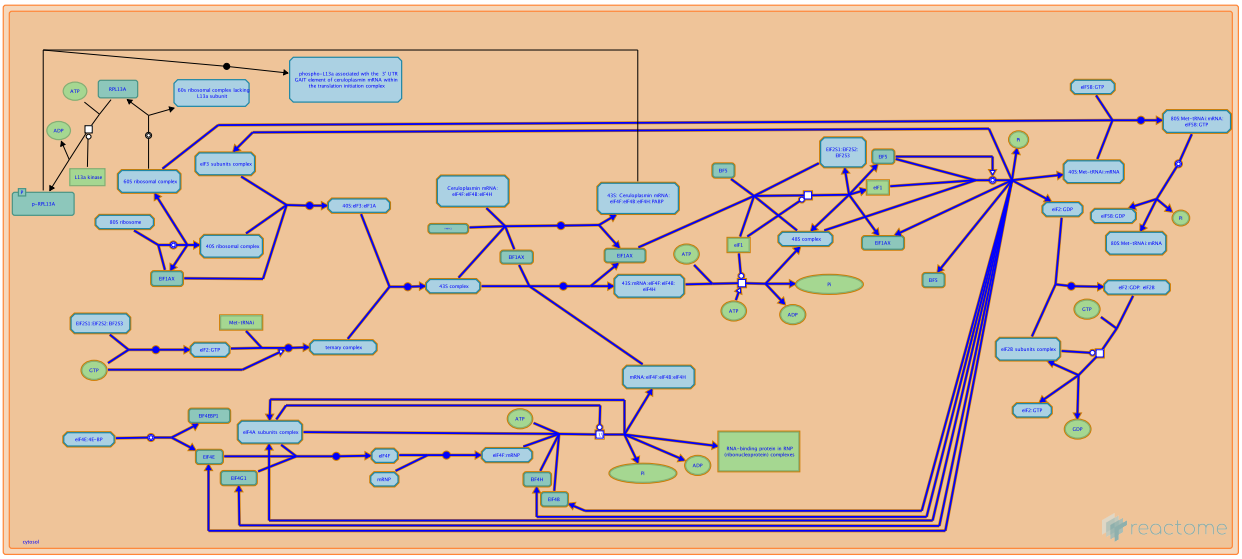
Literature references

Merrick, WC. (2010). Eukaryotic protein synthesis: still a mystery. *J Biol Chem, 285*, 21197-201. ↗

Cap-dependent Translation Initiation ↗

Location: Eukaryotic Translation Initiation

Stable identifier: R-HSA-72737



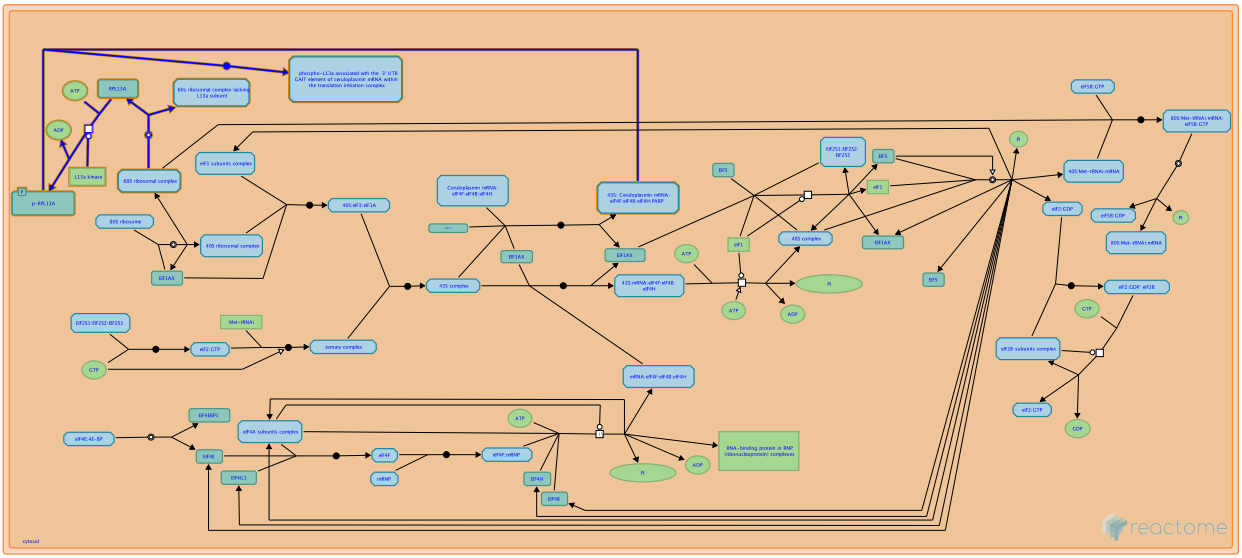
Translation initiation is a complex process in which the Met-tRNAi initiator, 40S, and 60S ribosomal subunits are assembled by eukaryotic initiation factors (eIFs) into an 80S ribosome at the start codon of an mRNA. The basic mechanism for this process can be described as a series of five steps: 1) formation of a pool of free 40S subunits, 2) formation of the ternary complex (Met-tRNAi/eIF2/GTP), and subsequently, the 43S complex (comprising the 40S subunit, Met-tRNAi/eIF2/GTP, eIF3 and eIF1A), 3) activation of the mRNA upon binding of the cap-binding complex eIF4F, and factors eIF4A, eIF4B and eIF4H, with subsequent binding to the 43S complex, 4) ribosomal scanning and start codon recognition, and 5) GTP hydrolysis and joining of the 60S ribosomal subunit.

L13a-mediated translational silencing of Ceruloplasmin expression ↗

Location: Eukaryotic Translation Initiation

Stable identifier: R-HSA-156827

Compartments: cytosol



While circularization of mRNA during translation initiation is thought to contribute to an increase in the efficiency of translation, it also appears to provide a mechanism for translational silencing. This might be achieved by bringing inhibitory 3' UTR-binding proteins into a position in which they interfere either with the function of the translation initiation complex or with the assembly of the ribosome (Mazumder et al 2001). Translational silencing of Ceruloplasmin (Cp) occurs 16 hrs after its induction by INF-gamma (Mazumder et al., 1997). Although the mechanism by which silencing occurs has not yet been determined, this process is mediated by the L13a subunit of the 60s ribosome and thought to require circularization of the Cp mRNA (Sampath et al., 2003; Mazumder et al., 2001; Mazumder et al., 2003). Between 14 and 16 hrs after INF gamma induction, the L13a subunit of the 60s ribosome is phosphorylated and released from the 60s subunit. Phosphorylated L13a then associates with the GAIT element in the 3' UTR of the Cp mRNA inhibiting its translation.

Literature references

Mazumder, B., Sampath, P., Seshadri, V., Maitra, RK., DiCorleto, PE., Fox, PL. (2003). Regulated release of L13a from the 60S ribosomal subunit as a mechanism of transcript-specific translational control. *Cell, 115*, 187-98. ↗

Editions

2004-12-13	Authored	Matthews, L.
2013-11-25	Edited	Matthews, L.

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