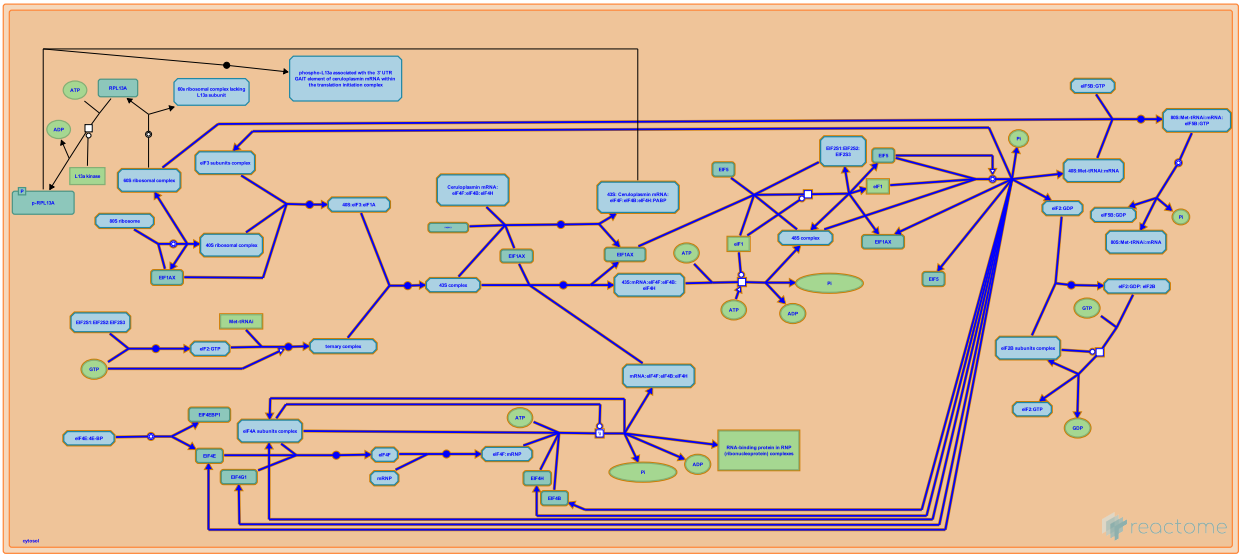
Cap-dependent Translation Initiation



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25/10/2020

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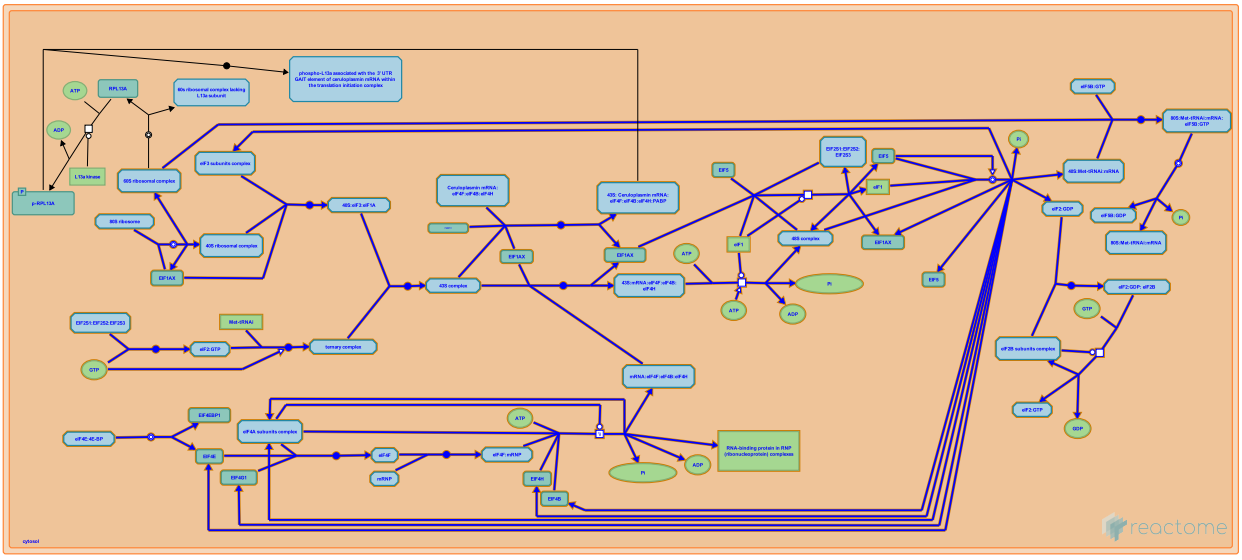
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Cap-dependent Translation Initiation ↗

Stable identifier: R-HSA-72737



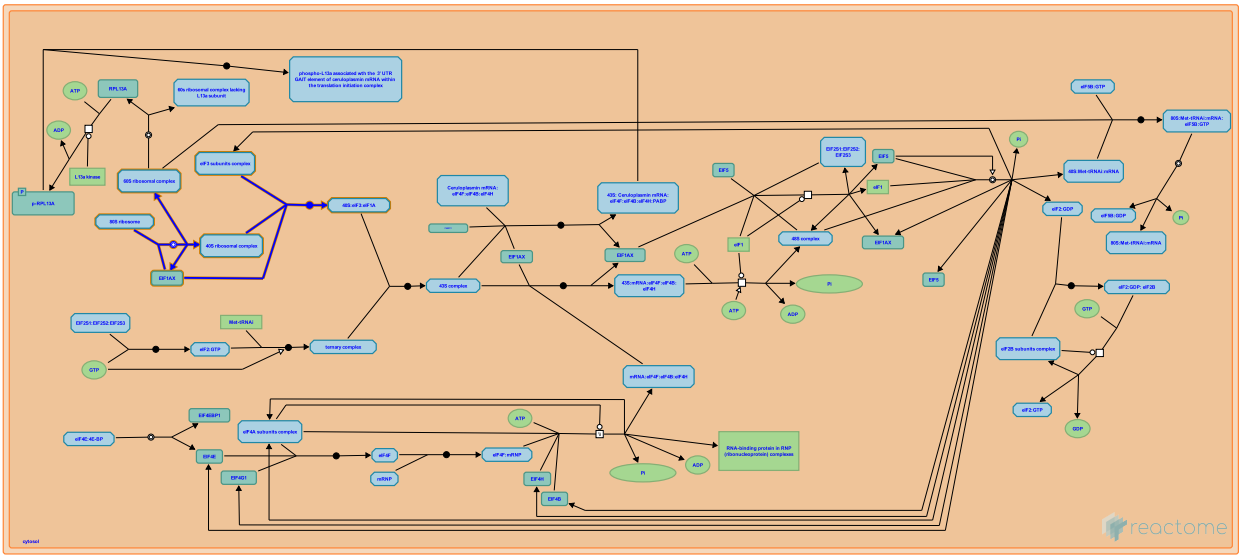
Translation initiation is a complex process in which the Met-tRNAi initiator, 40S, and 60S ribosomal subunits are assembled by eukaryotic initiation factors (eIFs) into an 80S ribosome at the start codon of an mRNA. The basic mechanism for this process can be described as a series of five steps: 1) formation 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.

Formation of a pool of free 40S subunits ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72689

Compartments: cytosol



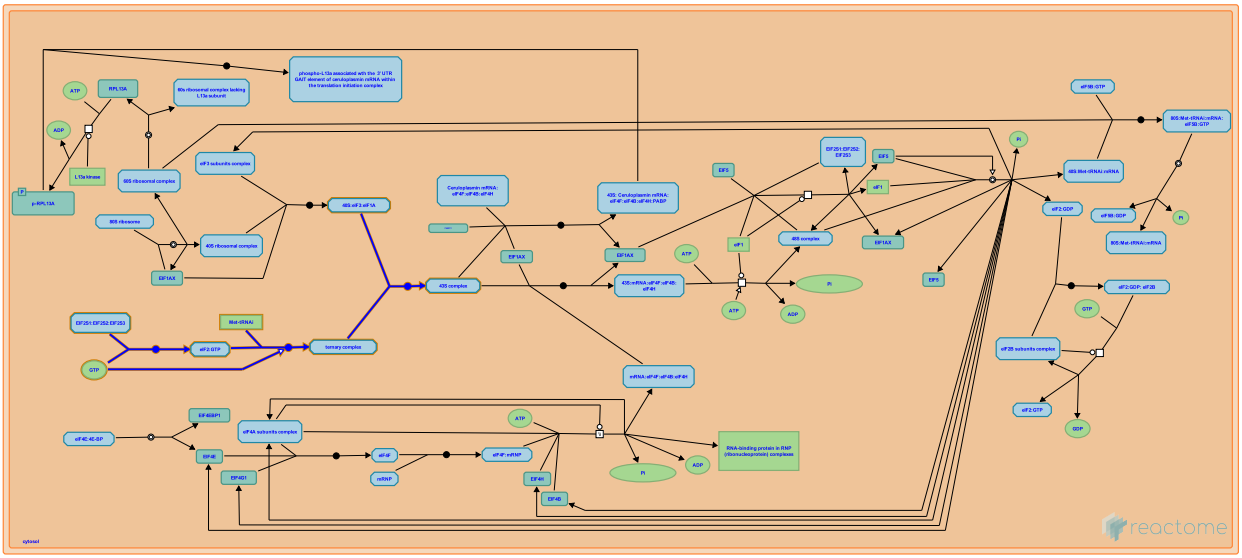
The 80S ribosome dissociates into free 40S (small) and 60S (large) ribosomal subunits. Each ribosomal subunit is constituted by several individual ribosomal proteins and rRNA.

Formation of the ternary complex, and subsequently, the 43S complex ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72695

Compartments: cytosol



Binding of the methionyl-tRNA initiator to the active eIF2:GTP complex results in the formation of the ternary complex. Subsequently, this Met-tRNAi:eIF2:GTP (ternary) complex binds to the complex formed by the 40S subunit, eIF3 and eIF1A, to form the 43S complex.

Literature references

Peterson, DT., Merrick, WC., Safer, B. (1979). Binding and release of radiolabeled eukaryotic initiation factors 2 and 3 during 80 S initiation complex formation. *J Biol Chem, 254*, 2509-16. ↗

Safer, B., Adams, SL., Anderson, WF., Merrick, WC. (1976). Binding of MET-TRNAf and GTP to homogeneous initiation factor MP. *J Biol Chem, 250*, 9076-82. ↗

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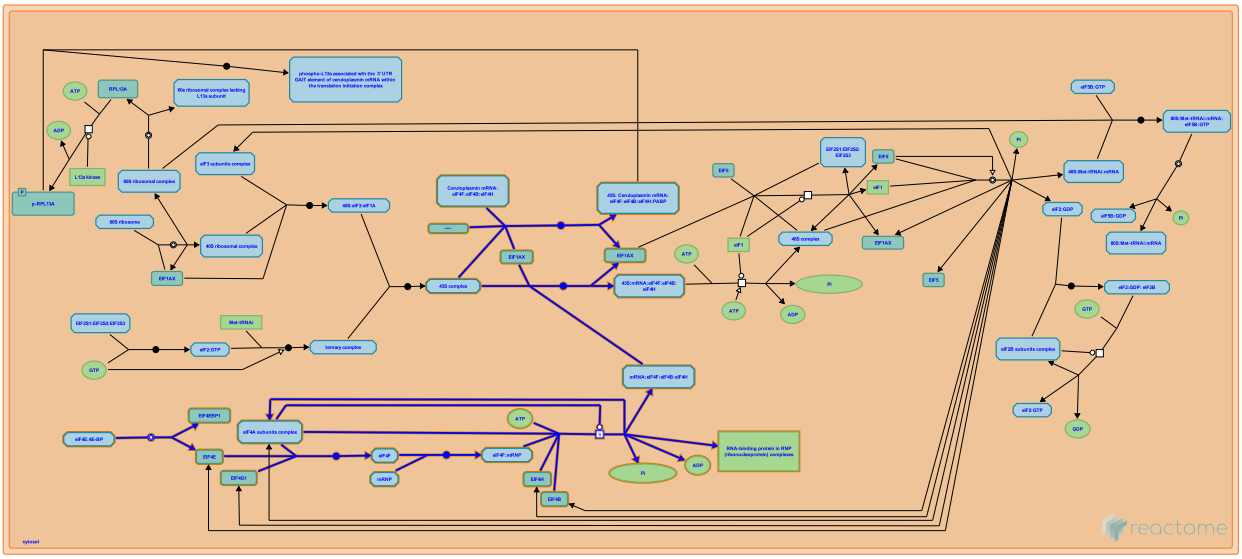
Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72662

Compartments: cytosol



The cap-binding complex is constituted by the initiation factors eIF4A, eIF4G and eIF4E. First, eIF4E must be released from the inactive eIF4E:4E-BP complex. Then eIF4A interacts with eIF4G, and eIF4E binds to the amino-terminal domain of eIF4G, resulting in the formation of the cap-binding complex eIF4F. eIF4A together with eIF4B or eIF4H is thought to unwind RNA secondary structures near the 5'-end of the mRNA. The translation initiation complex is formed when the 43S complex binds the cap-bound mRNA.

Literature references

Pestova, TV., Borukhov, SI., Hellen, CU. (1999). Eukaryotic ribosomes require initiation factors 1 and 1A to locate initiation codons. *Nature, 394*, 854-9. ↗

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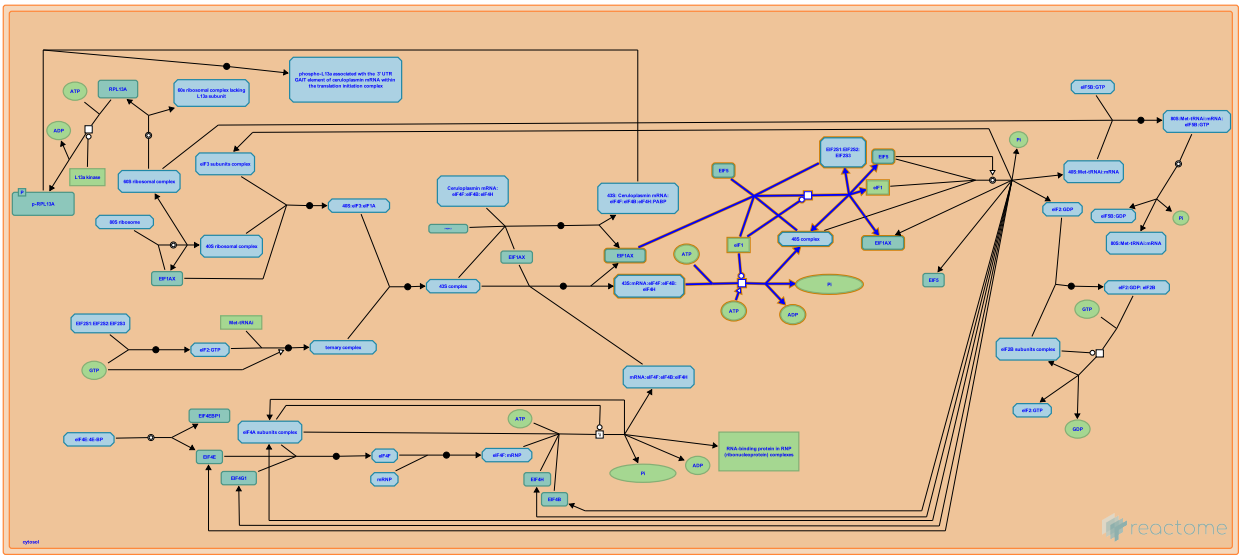
Benne, R., Hershey, JW. (1978). The mechanism of action of protein synthesis initiation factors from rabbit reticulocytes. *J Biol Chem, 253*, 3078-87. ↗

Ribosomal scanning and start codon recognition ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72702



The 80S ribosome bound to the mRNA moves along the mRNA molecule from its initial site to the initiation codon and forms a 48S complex, in which the initiation codon is base paired to the anticodon of the Met-tRNAi. Proper recognition of the AUG initiation codon depends on base pairing with the anticodon of the Met-tRNAi and requires eIF1, eIF1A, eIF2 and eIF5.

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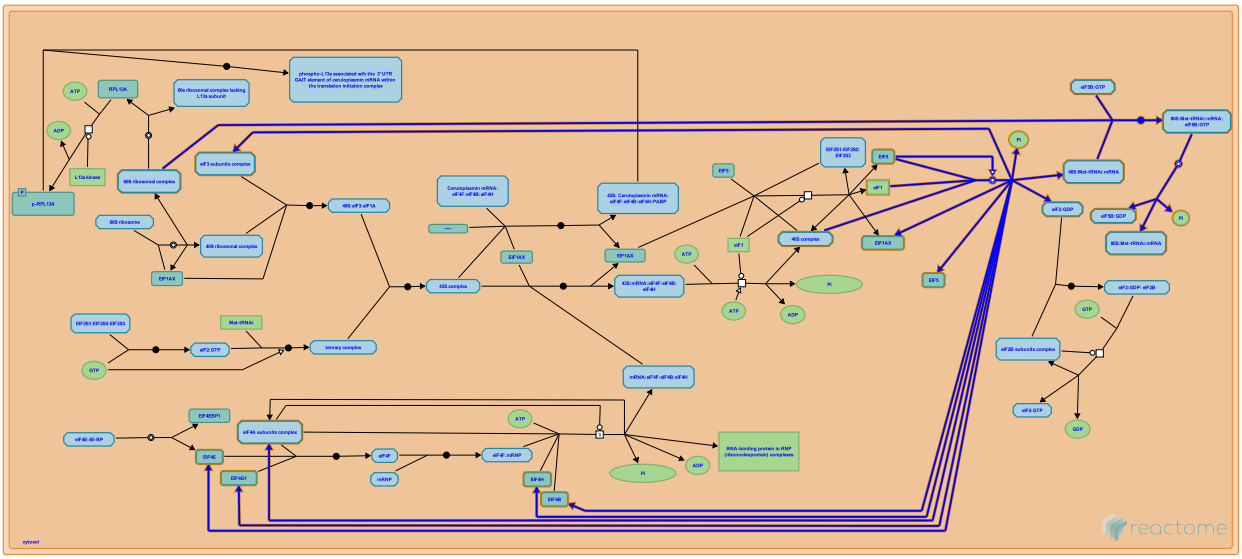
GTP hydrolysis and joining of the 60S ribosomal subunit ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72706



Hydrolysis of eIF2-GTP occurs after the Met-tRNAi has recognized the AUG. This reaction is catalyzed by eIF5 (or eIF5B) and is thought to cause dissociation of all other initiation factors and allow joining of the large 60S ribosomal subunit. The 60S subunit joins - a reaction catalyzed by eIF5 or eIF5B - resulting in a translation-competent 80S ribosome. Following 60S subunit joining, eIF5B hydrolyzes its GTP and is released from the 80S ribosome, which is now ready to start elongating the polypeptide chain.

Literature references

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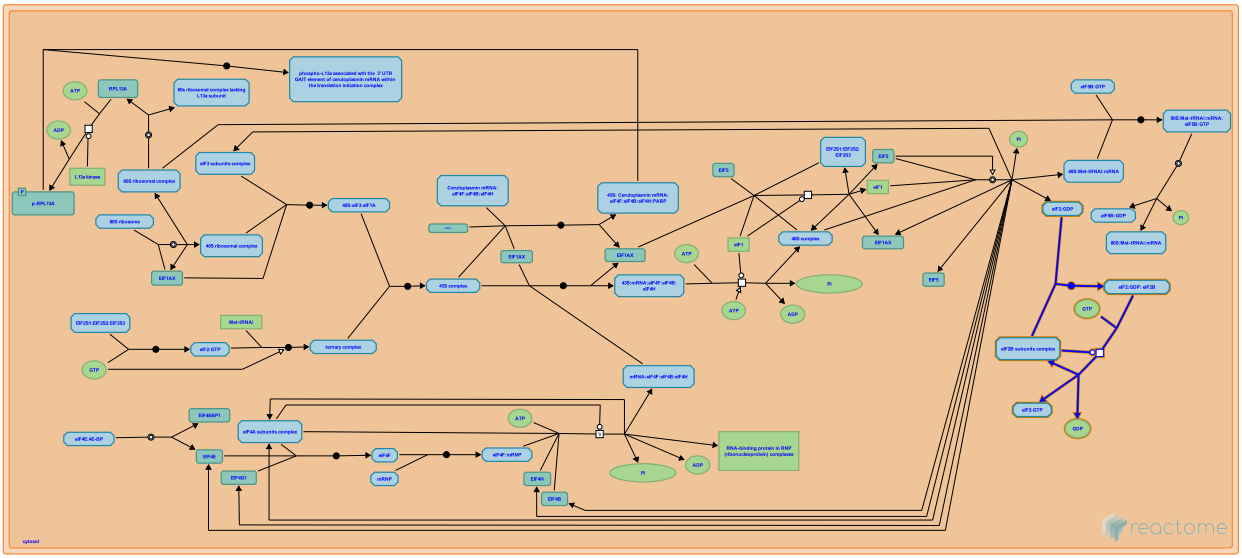
Recycling of eIF2:GDP ↗

Location: Cap-dependent Translation Initiation

Stable identifier: R-HSA-72731

Compartments: cytosol



The active eIF2:GTP complex may be formed by direct binding of GTP to free eIF2 or by GDP-GTP exchange on the eIF2:GDP:eIF2B complex. The eIF2:GDP complex binds eIF2B forming an eIF2:GDP:eIF2B intermediate complex. eIF2B is a guanine nucleotide releasing factor required to cause GDP release so that a new GTP molecule can bind and activate eIF2. Phosphorylated eIF2:GDP sequesters all eIF2B as an inactive complex, and thus, reuse of eIF2 is inhibited as a consequence of the tight bond it forms with eIF2B, which prevents nucleotide exchange. Therefore, in the absence of free eIF2B, excess eIF2 remains in its inactive GDP-bound form and protein synthesis slows dramatically.

Literature references

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