Translation


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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


Reactome database release: 72

This document contains 7 pathways (see Table of Contents)
Translation

Stable identifier: R-HSA-72766

Protein synthesis is accomplished through the process of translation of an mRNA sequence into a polypeptide chain. This process can be divided into three distinct stages: initiation, elongation and termination. During the initiation phase, the two subunits of the ribosome are brought together to the translation start site on the mRNA where the polypeptide chain is to begin. Extension of the polypeptide chain occurs when a specific aminoacyl-tRNA, as determined by the template mRNA, binds an elongating ribosome. The protein chain is released from the ribosome when any one of three stop codons in the relevant reading frame on the mRNA is reached. Individual reactions at each one of these stages are catalyzed by a number of initiation, elongation and release factors, respectively.

Proteins destined for the endoplasmic reticulum (ER) contain a short sequence of hydrophobic amino acid residues (approximately 20 residues) at their N-termini. Upon protrusion of the signal sequence from the translating ribosome, the signal sequence is bound by the cytosolic signal recognition particle (SRP), translation is temporarily halted, and the SRP:nascent peptide:ribosome complex then docks with a SRP receptor complex on the ER membrane. There the nascent peptide:ribosome complex is transferred from the SRP complex to a translocon complex embedded in the ER membrane and reoriented so that the nascent polypeptide protrudes through a pore in the translocon into the ER lumen. Translation now resumes, the signal peptide is cleaved from the polypeptide by signal peptidase as the signal peptide emerges into the ER, and elongation proceeds with the growing polypeptide oriented into the ER lumen.

The 13 proteins encoded by the mitochondrial genome are translated within the mitochondrion by mitochondrial ribosomes (mitoribosomes) at the matrix face of the inner mitochondrial membrane. Mitochondrial translation reflects both the bacterial origin of the organelle and subsequent divergent evolution during symbiosis. Mitoribosomes have shorter rRNAs, mitochondria-specific proteins, and rearranged protein positions. Mitochondrial mRNAs have either no untranslated leaders or very short untranslated leaders of 1-3 nucleotides. Translation begins with N-formylmethionine, as in bacteria, and continues with cycles of aminoacyl-tRNA:TUFM:GTP binding, GTP hydrolysis and dissociation of TUFM:GDP. All 13 proteins encoded by the mitochondrial genome are hydrophobic inner membrane proteins which are inserted cotranslationally into the membrane by an interaction with OXA1L.
tion is terminated when MTRF1L:GTP recognizes a UAA or UAG codon at the A-site of the mitoribosome. The translated polypeptide is released and MRRF and GFM2:GTP act to dissociate the 55S ribosome into 28S and 39S subunits.

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tRNA Aminoacylation

Location: Translation

Stable identifier: R-HSA-379724

tRNA synthetases catalyze the ligation of tRNAs to their cognate amino acids in an ATP-dependent manner. The reaction proceeds in two steps. First, amino acid and ATP form an aminoacyl adenylate molecule, releasing pyrophosphate. The aminoacyl adenylate remains associated with the synthetase enzyme where, in the second step it reacts with tRNA to form aminoacyl tRNA and AMP. The rapid hydrolysis of pyrophosphate makes these reactions essentially irreversible under physiological conditions (Fersht and Kaethner 1976a). Specificity of the tRNA charging reactions is achieved both by specific recognition of amino acid and tRNA substrates by the synthetase, and by an editing process in which incorrect aminoacyl adenylate molecules (e.g., valyl adenylate associated with isoleucyl tRNA synthetase) are hydrolyzed rather than conjugated to tRNAs in the second step of the reaction (Baldwin and Berg 1966a,b; Fersht and Kaethner 1976b). The tRNA synthetases can be divided into two structural classes based on conserved amino acid sequence features (Burnbaum and Schimmel 1991).

A single synthetase mediates the charging of all of the tRNA species specific for any one amino acid but, with three exceptions, glycine, lysine, and glutamine, the synthetase that catalyzes aminoacylation of mitochondrial tRNAs is encoded by a different gene than the one that acts on mitochondrial tRNAs. Both mitochondrial and cytosolic tRNA synthetase enzymes are encoded by genes in the nuclear genome.

A number of tRNA synthetases are known to have functions distinct from tRNA charging (reviewed by Park et al. 2005). Additionally, mutations in several of the tRNA synthetases, often affecting protein domains that are dispensable in vitro for aminoacyl tRNA synthesis, are associated with a diverse array of neurological and other diseases (Antonellis and Green 2008; Park et al. 2008). These findings raise interest into the role of these enzymes in human development and disease.
**Literature references**


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Eukaryotic Translation Initiation

**Location:** Translation

**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 highlights 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

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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, initiation 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**

SRP-dependent cotranslational protein targeting to membrane

Location: Translation

Stable identifier: R-HSA-1799339

Compartments: cytosol, endoplasmic reticulum lumen, endoplasmic reticulum membrane

The process for translation of a protein destined for the endoplasmic reticulum (ER) branches from the canonical cytosolic translation process at the point when a nascent polypeptide containing a hydrophobic signal sequence is exposed on the surface of the cytosolic ribosome:mRNA:peptide complex. The signal sequence mediates the interaction of this complex with a cytosolic signal recognition particle (SRP) to form a complex which in turn docks with an SRP receptor complex on the ER membrane. There the ribosome complex is transferred from the SRP complex to a translocon complex embedded in the ER membrane and reoriented so that the nascent polypeptide protrudes through a pore in the translocon into the ER lumen. Translation, which had been halted by SRP binding, now resumes, the signal peptide is cleaved from the polypeptide, and elongation proceeds, with the growing polypeptide oriented into the ER lumen.

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Eukaryotic Translation Elongation

Location: Translation

Stable identifier: R-HSA-156842

Compartments: cytosol

The translation elongation cycle adds one amino acid at a time to a growing polypeptide according to the sequence of codons found in the mRNA. The next available codon on the mRNA is exposed in the aminoacyl-tRNA (aa-tRNA) binding site (A site) on the 30S subunit.

A: Ternary complexes of aa-tRNA:eEF1A:GTP enter the ribosome and enable the anticodon of the tRNA to make a codon/anticodon interaction with the A-site codon of the mRNA. B: Upon cognate recognition, the eEF1A:GTP is brought into the GTPase activating center of the ribosome, GTP is hydrolyzed and eEF1A:GDP leaves the ribosome. C: The peptidyl transferase center of ribosome catalyses the formation of a peptide bond between the incoming amino acid and the peptide found in the peptidyl-tRNA binding site (P site). D: In the pre-translocation state of the ribosome, the eEF2:GTP enters the ribosome, physically translocating the peptidyl-tRNA out of the A site to P site and leaves the ribosome eEF2:GDP. This action of eEF2:GTP accounts for the precise movement of the mRNA by 3 nucleotides. Consequently, deacylated tRNA is shifted to the E site. A ribosome associated ATPase activity is proposed to stimulate the release of deacylated tRNA from the E site subsequent to translocation (Elskaya et al., 1991). In this post-translocation state, the ribosome is now ready to receive a new ternary complex.

This process is illustrated below with: an amino acyl-tRNA with an amino acid, a peptidyl-tRNA with a growing peptide, a deacylated tRNA with an -OH, and a ribosome with A,P and E sites to accommodate these three forms of tRNA.

Literature references

The arrival of any of the three stop codons (UAA, UAG and UGA) into the ribosomal A-site triggers the binding of a release factor (RF) to the ribosome and subsequent polypeptide chain release. In eukaryotes, the RF is composed of two proteins, eRF1 and eRF3. eRF1 is responsible for the hydrolysis of the peptidyl-tRNA, while eRF3 provides a GTP-dependent function. The ribosome releases the mRNA and dissociates into its two complex subunits, which can reassemble on another molecule to begin a new round of protein synthesis. It should be noted that at present, there is no factor identified in eukaryotes that would be the functional equivalent of the bacterial ribosome release (or recycling) factor, RRF, that catalyzes dissociation of the ribosome from the mRNA following release of the polypeptide.

**Literature references**


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Mitochondrial translation

Location: Translation

Stable identifier: R-HSA-5368287

Compartments: mitochondrial matrix, mitochondrial inner membrane

Of the roughly 1000 human mitochondrial proteins only 13 proteins, all of them hydrophobic inner membrane proteins that are components of the oxidative phosphorylation apparatus, are encoded in the mitochondrial genome and translated by mitoribosomes at the matrix face of the inner membrane (reviewed in Herrmann et al. 2012, Hallberg and Larsson 2014, Lightowlers et al. 2014). The remainder, including all proteins of the mitochondrial translation system, are encoded in the nucleus and imported from the cytosol into the mitochondrion. Translation in the mitochondrion reflects both the bacterial origin of the organelle and subsequent divergent evolution during symbiosis (reviewed in Huot et al. 2014, Richman et al. 2014). Human mitochondrial ribosomes have a low sedimentation coefficient of only 55S, but at 2.71 MDa they retain a similar mass to E. coli 70S particles. The 55S particles are protein-rich compared to both cytosolic ribosomes and eubacterial ribosomes. This is due to shorter mt-rRNAs, mitochondria-specific proteins, and numerous rearrangements in individual protein positions within the two ribosome subunits (inferred from bovine ribosomes in Sharma et al. 2003, Greber et al. 2014, Kaushal et al. 2014, reviewed in Agrawal and Sharma 2012).

Mitochondrial mRNAs have either no untranslated leader or short leaders of 1-3 nucleotides, with the exception of the 2 bicistronic transcripts, RNA7 and RNA14, which have overlapping orfs that encode ND4L/ND4 and ATP8/ATP6 respectively. Translation is believed to initiate with the mRNA binding the 28S subunit:MTIF3 (28S subunit:IF-3Mt, 28S subunit:IF2mt) complex together with MTIF2:GTP (IF2Mt:GTP, IF2mt:GTP) at the matrix face of the inner membrane (reviewed in Christian and Spremulli 2012). MTIF3 can dissociate 55S particles in preparation for initiation, enhances formation of initiation complexes, and inhibits N-formylmethionine-tRNA (fMet-tRNA) binding to 28S subunits in the absence
of mRNA. Binding of fMet-tRNA to the start codon of the mRNA results in a stable complex while absence of a start codon at the 5' end of the mRNA causes eventual dissociation of the mRNA from the 28S subunit. After recognition of a start codon, the 39S subunit then binds the stable complex, GTP is hydrolyzed, and the initiation factors MTIF3 and MTIF2:GDP dissociate.

Translation elongation then proceeds by cycles of aminoacyl-tRNAs binding, peptide bond formation, and displacement of deacylated tRNAs. In each cycle an aminoacyl-tRNA in a complex with TUFM:GTP (EF-Tu:GTP) binds at the A-site of the ribosome, GTP is hydrolyzed, and TUFM:GDP dissociates. The elongating polypeptide bonded to the tRNA at the P-site is transferred to the aminoacyl group at the A-site by peptide bond formation at the peptidyl transferase center, leaving a deacylated tRNA at the P-site and the elongating polypeptide attached to the tRNA at the A-site. The polypeptide is co-translationally inserted into the inner mitochondrial membrane via an interaction with OXA1L (Haque et al. 2010, reviewed in Ott and Hermann 2010). After peptide bond formation, GFM1:GTP (EF-Gmt:GTP) then binds the ribosome complex, GTP is hydrolyzed, GFM1:GDP dissociates, and the ribosome translocates 3 nucleotides in the 3' direction along the mRNA, relocating the polypeptide-tRNA to the P-site and allowing another cycle to begin. TUFM:GDP is regenerated to TUFM:GTP by the guanine nucleotide exchange factor TSFM (EF-Ts, EF-TsMt).

Translation is terminated when MTRF1L:GTP (MTRF1a:GTP) recognizes an UAA or UAG termination codon at the A-site of the ribosome (Tsuboi et al. 2009). GTP hydrolysis does not appear to be required. The tRNA-aminoacyl bond between the translated polypeptide and the final tRNA at the P-site is hydrolyzed by the 39S subunit, facilitating release of the polypeptide. MRRF (RRF) and GFM2:GTP (EF-G2mt:GTP) then act to release the remaining tRNA and mRNA from the ribosome and dissociate the 55S ribosome into 28S and 39S subunits.

Mutations have been identified in genes encoding mitochondrial ribosomal proteins and translation factors. These have been shown to be pathogenic, causing neurological and other diseases (reviewed in Koopman et al. 2013, Pearce et al. 2013).

**Literature references**


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