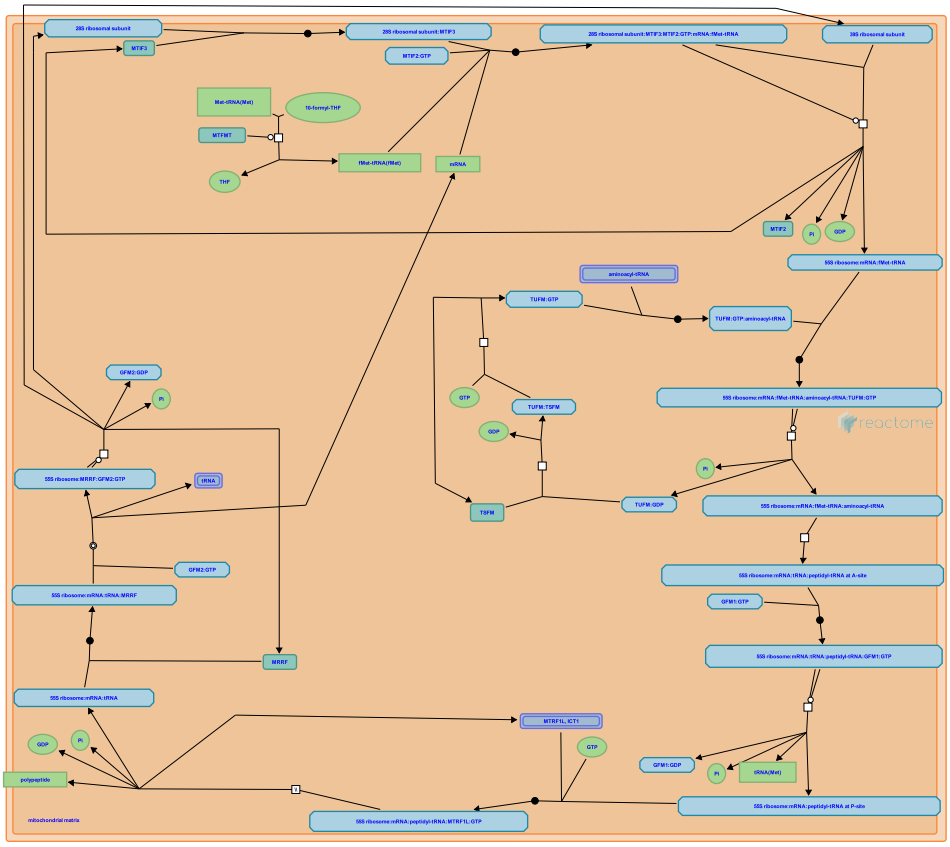
Mitochondrial translation



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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

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. ↗

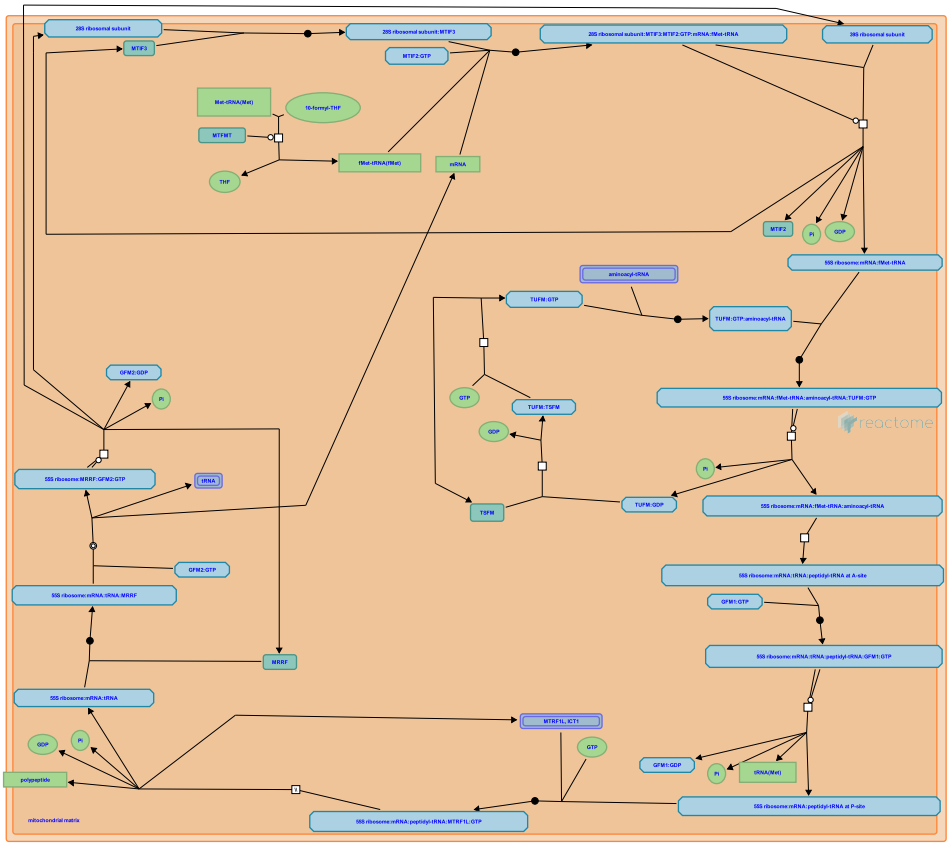
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Mitochondrial 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 (IF-2Mt: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 sub-

unit. 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

Kaushal, PS., Sharma, MR., Booth, TM., Haque, EM., Tung, CS., Sanbonmatsu, KY. et al. (2014). Cryo-EM structure of the small subunit of the mammalian mitochondrial ribosome. *Proc. Natl. Acad. Sci. U.S.A., 111*, 7284-9. ↗

Haque, ME., Elmore, KB., Tripathy, A., Koc, H., Koc, EC., Spremulli, LL. (2010). Properties of the C-terminal tail of human mitochondrial inner membrane protein Oxa1L and its interactions with mammalian mitochondrial ribosomes. *J. Biol. Chem., 285*, 28353-62. ↗

Rackham, O., Filipovska, A. (2014). Supernumerary proteins of mitochondrial ribosomes. *Biochim. Biophys. Acta, 1840*, 1227-32. ↗

Agrawal, RK., Sharma, MR. (2012). Structural aspects of mitochondrial translational apparatus. *Curr. Opin. Struct. Biol., 22*, 797-803. ↗

Koopman, WJ., Distelmaier, F., Smeitink, JA., Willems, PH. (2013). OXPHOS mutations and neurodegeneration. *EMBO J., 32*, 9-29. ↗

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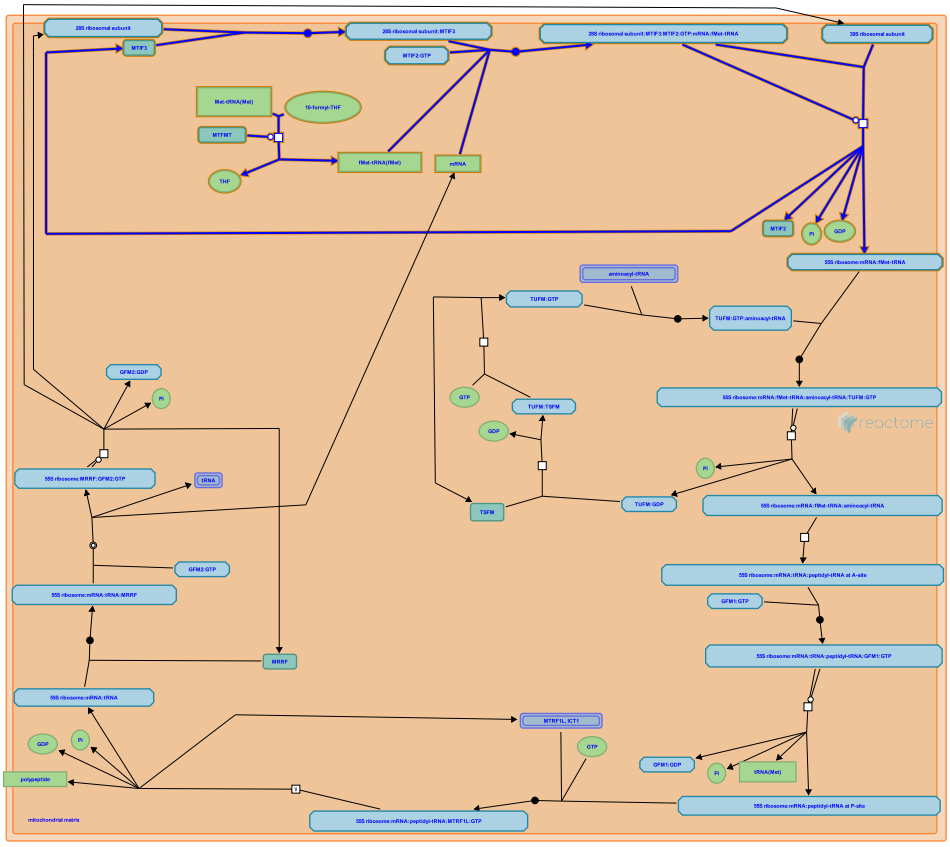
Mitochondrial translation initiation ↗

Location: Mitochondrial translation

Stable identifier: R-HSA-5368286

Compartments: mitochondrial matrix, mitochondrial inner membrane



Translation initiates with the mitochondrial mRNA binding the 28S subunit:MTIF3 (28S subunit:IF-3Mt, 28S subunit:IF3mt) complex together with MTIF2:GTP (IF-2Mt:GTP, IF2mt:GTP) (reviewed in Christian and Spremulli 2012, Kuzmenko et al. 2014). As inferred from bovine homologs, the 28S subunit, 39S subunit, and 55S holoribosome associate with the matrix-side face of the inner membrane and the translation products are inserted into the inner membrane as translation occurs (Liu and Spremulli 2000). 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.. Binding of N-formylmethionine-tRNA to the start codon results in a stable complex between the mRNA and the 28S subunit while absence of a start codon at the 5' end of the mRNA causes the mRNA to slide though the 28S subunit and eventually dissociate. The 39S subunit then binds the 28S subunit:mRNA complex, GTP is hydrolyzed, and the initiation factors MTIF3 and MTIF2:GDP dissociate.

Literature references

Christian, BE., Spremulli, LL. (2012). Mechanism of protein biosynthesis in mammalian mitochondria. *Biochim. Biophys. Acta, 1819*, 1035-54. ↗

Kuzmenko, A., Atkinson, GC., Levitskii, S., Zenkin, N., Tenson, T., Hauryliuk, V. et al. (2014). Mitochondrial translation initiation machinery: conservation and diversification. *Biochimie, 100*, 132-40. ↗

Liu, M., Spremulli, L. (2000). Interaction of mammalian mitochondrial ribosomes with the inner membrane. *J. Biol. Chem., 275*, 29400-6. ↗

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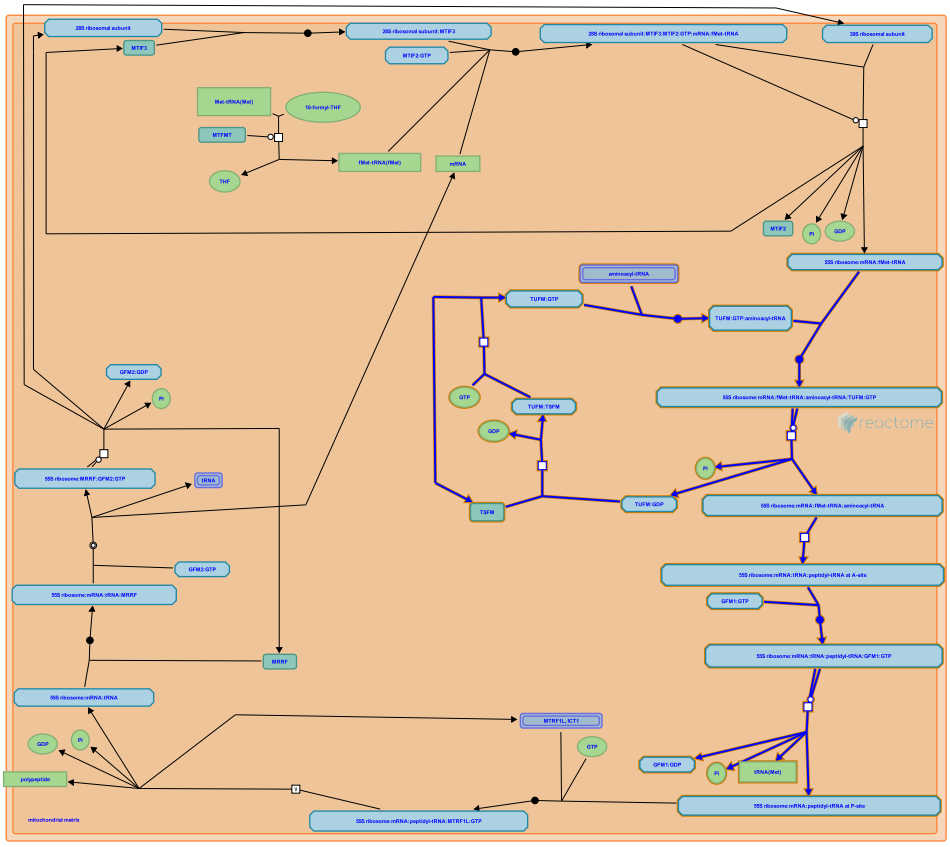
Mitochondrial translation elongation ↗

Location: Mitochondrial translation

Stable identifier: R-HSA-5389840

Compartments: mitochondrial matrix, mitochondrial inner membrane



Translation elongation proceeds by cycles of aminoacyl-tRNAs binding, peptide bond formation, and displacement of deacylated tRNAs (reviewed in Christian and Spremulli 2012). In each cycle an aminoacyl-tRNA in a complex with TUFM:GTP (EF-Tu:GTP) binds a cognate codon 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, leaving a deacylated tRNA at the P-site and the elongating polypeptide attached to the tRNA at the A-site. GFM1:GTP (EF-Gmt:GTP) binds, GTP is hydrolyzed, GFM1:GDP dissociates, and the ribosome translocates 3 nucleotides in the 3' direction, relocating the peptidyl-tRNA to the P-site and allowing another cycle to begin. Mitochondrial ribosomes associate with the inner membrane and polypeptides are co-translationally inserted into the membrane (reviewed in Ott and Herrmann 2010, Agrawal and Sharma 2012). TUFM:GDP is regenerated to TUFM:GTP by the guanine nucleotide exchange factor TSFM (EF-Ts, EF-TsMt).

Literature references

Christian, BE., Spremulli, LL. (2012). Mechanism of protein biosynthesis in mammalian mitochondria. *Biochim. Biophys. Acta, 1819*, 1035-54. ↗

Ott, M., Herrmann, JM. (2010). Co-translational membrane insertion of mitochondrially encoded proteins. *Biochim. Biophys. Acta, 1803*, 767-75. ↗

Agrawal, RK., Sharma, MR. (2012). Structural aspects of mitochondrial translational apparatus. *Curr. Opin. Struct. Biol., 22*, 797-803. ↗

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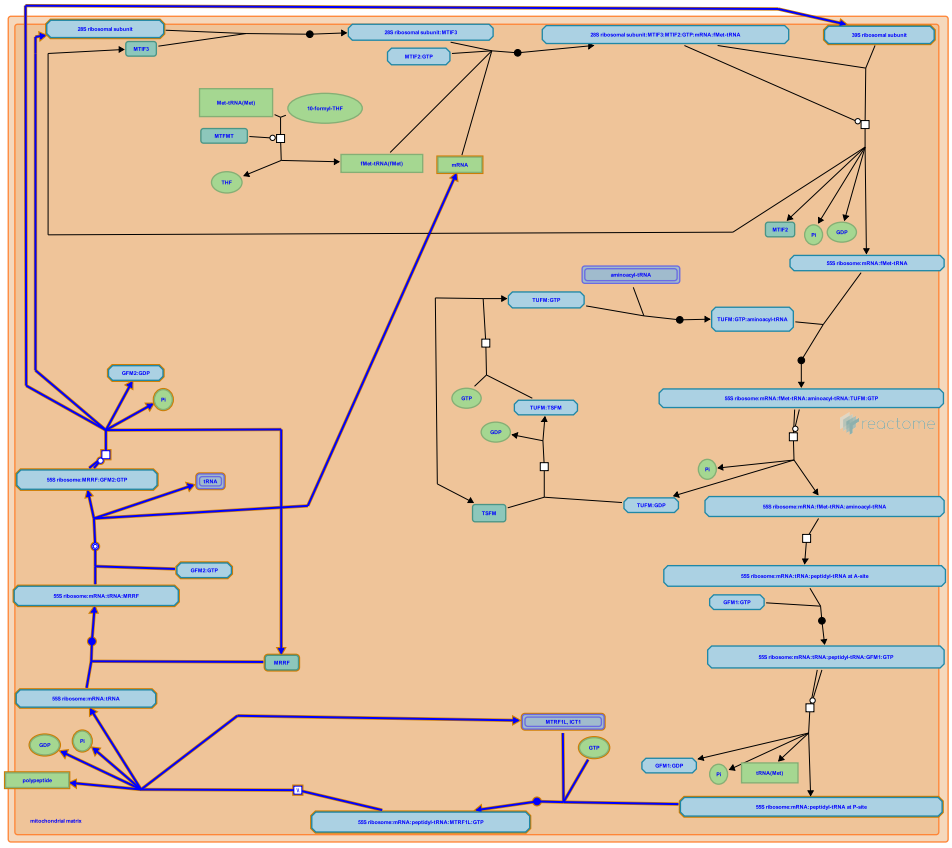
Mitochondrial translation termination ↗

Location: Mitochondrial translation

Stable identifier: R-HSA-5419276

Compartments: mitochondrial matrix, mitochondrial inner membrane



Translation is terminated when MTRF1L:GTP (MTRF1a:GTP) recognizes a UAA or UAG termination codon in the mRNA at the A site of the ribosome (Soleimanpour-Lichaei et al. 2007, reviewed in Richter et al. 2010, Chrzanowska-Lightowlers et al. 2011. Christian and Spremulli 2012). GTP is hydrolyzed, and the aminoacyl bond between the translated polypeptide and the final tRNA at the P site is hydrolyzed by the 39S ribosomal subunit, releasing the translated 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.

Literature references

Christian, BE., Spremulli, LL. (2012). Mechanism of protein biosynthesis in mammalian mitochondria. *Biochim. Biophys. Acta, 1819*, 1035-54. ↗

Richter, R., Pajak, A., Dennerlein, S., Rozanska, A., Lightowlers, RN., Chrzanowska-Lightowlers, ZM. (2010). Translation termination in human mitochondrial ribosomes. *Biochem. Soc. Trans., 38*, 1523-6. ↗

Chrzanowska-Lightowlers, ZM., Pajak, A., Lightowlers, RN. (2011). Termination of protein synthesis in mammalian mitochondria. *J. Biol. Chem., 286*, 34479-85. ↗

Soleimanpour-Lichaei, HR., Kühl, I., Gaisne, M., Passos, JF., Wydro, M., Rorbach, J. et al. (2007). mtRF1a is a human mitochondrial translation release factor decoding the major termination codons UAA and UAG. *Mol. Cell, 27*, 745-57. ↗

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