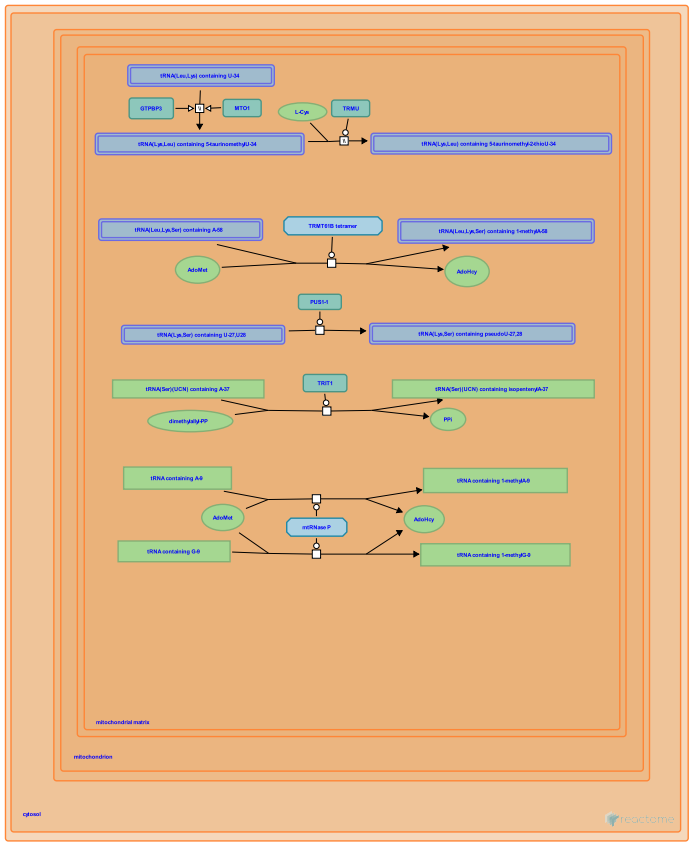
tRNA modification in the mitochondrion



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17/09/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

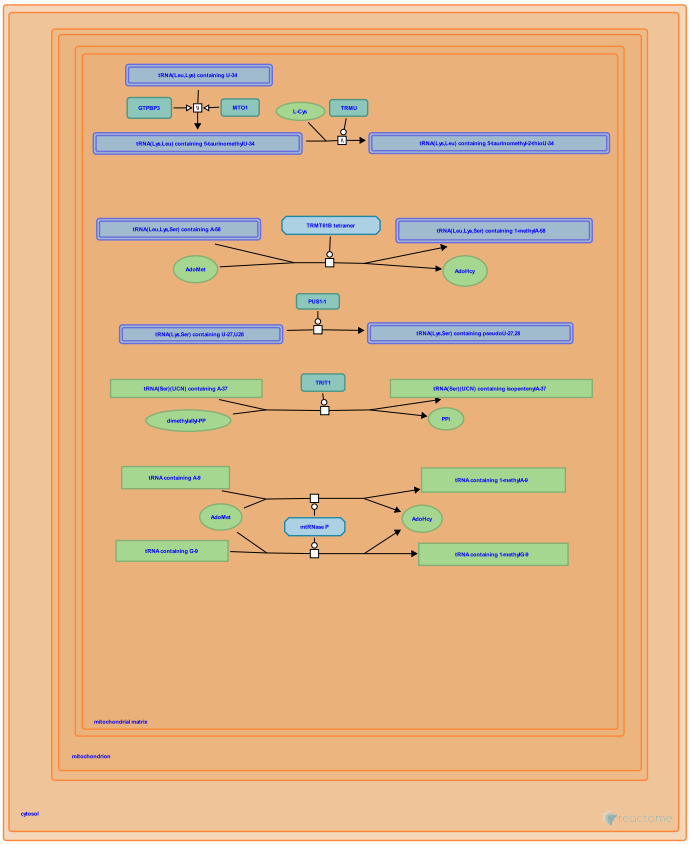
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

tRNA modification in the mitochondrion ↗

Stable identifier: R-HSA-6787450



The 22 tRNAs encoded by the mitochondrial genome are modified in the mitochondrial matrix by enzymes encoded in the nucleus and imported into mitochondria (reviewed in Suzuki et al. 2011, Salinas-Giege et al. 2015). Some enzymes such as PUS1 and TRIT1 are located in more than one compartment and modify both mitochondrial tRNAs and cytosolic tRNAs. Other enzymes such as MTO1, TRMU, and TRMT61B are exclusively mitochondrial.
Modifications near the anticodon and near the 3' end of tRNAs tend to affect interaction of the tRNA with mRNA within ribosomes and with tRNA synthetases, respectively. Modifications in other regions, typically in the "core" of the tRNA tend to affect folding and stability of the tRNA (reviewed in Hou et al. 2015). The unusual modification 5-taurinomethyl-2-thiouridine-34 in the anticodon of at least 3 tRNAs is found only in mammalian mitochondria and mutations that affect the responsible biosynthetic enzymes (GTPBP3, MTO1, TRMU) cause mitochondrial dysfunction and disease (reviewed in Torres et al. 2014).

Literature references

Giegé, P., Giege, R., Salinas-Giegé, T. (2015). tRNA biology in mitochondria. *Int J Mol Sci, 16*, 4518-59. ↗

Suzuki, T., Suzuki, T., Nagao, A. (2011). Human mitochondrial tRNAs: biogenesis, function, structural aspects, and diseases. *Annu. Rev. Genet., 45*, 299-329. ↗

Gamper, H., Hou, YM., Yang, W. (2015). Post-transcriptional modifications to tRNA--a response to the genetic code degeneracy. *RNA, 21*, 642-4. ↗

Batlle, E., Ribas de Pouplana, L., Torres, AG. (2014). Role of tRNA modifications in human diseases. *Trends Mol Med, 20*, 306-14. ↗

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GTPBP3 and MTO1 transform uridine-34 yielding 5-taurinomethyluridine-34 in tRNA

↗

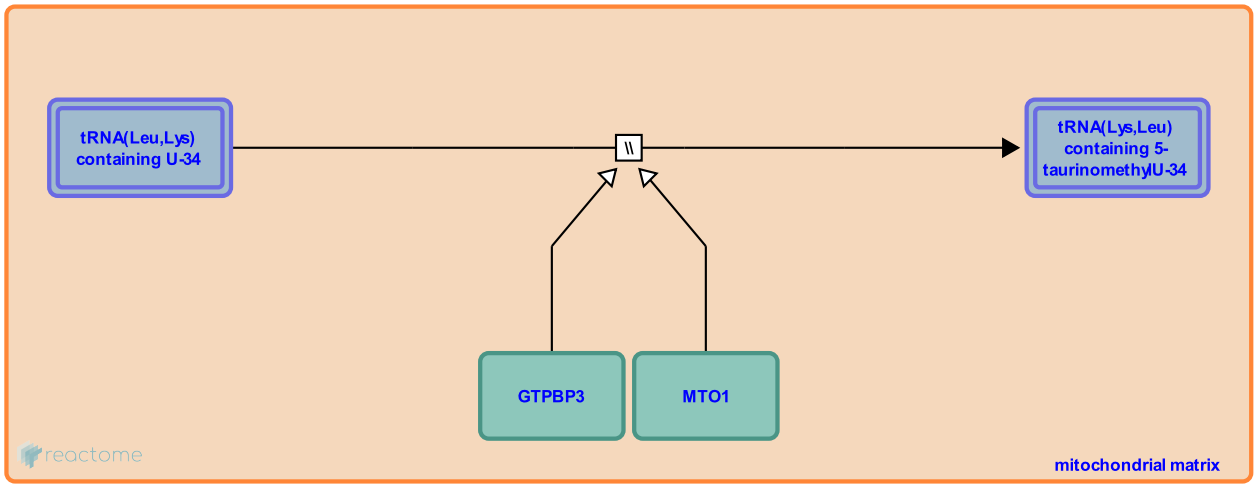
Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787403

Type: omitted

Compartments: mitochondrial matrix

Inferred from: MSS1 and MTO1 transform uridine-34 to 5-carboxymethylaminomethyluridine-34 in tRNA (Saccharomyces cerevisiae)



A conserved pathway consisting of at least GTPBP3 (MSS1 in Saccharomyces cerevisiae, MnmE in Escherichia coli) and MTO1 (MTO1 in S. cerevisiae, MnmG in E. coli) modifies the wobble nucleotide uridine-34 in mitochondrial tRNA (Asano et al. 2018). In humans a methyl group and a taurine group (2-aminoethylsulfonic acid) are conjugated to the 5 position of the uracil ring (Suzuki et al. 2002). In yeast and E. coli a methyl group and a glycine group are conjugated, yielding 5-carboxymethylaminomethyluridine. The details of the reaction mechanism are unknown. Modification of the wobble nucleotide is required for efficient and accurate translation. Mutations in constituents of the pathway cause disease symptoms characteristic of mitochondrial dysfunction: lactic acidosis, hypertrophic cardiomyopathy, respiratory chain defect, and, in association with the A1555G mutation in 12S rRNA, deafness (Ghezzi et al. 2012, Baruffini et al. 2013, Tischner et al. 2015).

Followed by: TRMU (MTO2, MTU1) transfers a sulfur atom to 5-taurinomethyluridine-34 in tRNA

Literature references

Suzuki, T., Suzuki, T., Saigo, K., Watanabe, K., Wada, T. (2002). Taurine as a constituent of mitochondrial tRNAs: new insights into the functions of taurine and human mitochondrial diseases. *EMBO J., 21*, 6581-9. ↗

Wulff, V., Hofer, A., Wenz, T., Datta, AN., Kremer, L., Tischner, C. et al. (2015). MTO1 mediates tissue specificity of OXPHOS defects via tRNA modification and translation optimization, which can be bypassed by dietary intervention. *Hum. Mol. Genet., 24*, 2247-66. ↗

Tanaka, R., Yamane, Y., Goto, T., Wei, FY., Okazaki, Y., Kishita, Y. et al. (2018). Metabolic and chemical regulation of tRNA modification associated with taurine deficiency and human disease. *Nucleic Acids Res., 46*, 1565-1583. ↗

Taylor, RW., Dallabona, C., Burlina, A., Yarham, JW., Kopajtich, R., Santra, S. et al. (2013). MTO1 mutations are associated with hypertrophic cardiomyopathy and lactic acidosis and cause respiratory chain deficiency in humans and yeast. *Hum. Mutat., 34*, 1501-9. ↗

Meitinger, T., Dallabona, C., Burlina, AB., Zeviani, M., Melchionda, L., Ferrero, I. et al. (2012). Mutations of the mitochondrial-tRNA modifier MTO1 cause hypertrophic cardiomyopathy and lactic acidosis. *Am. J. Hum. Genet., 90*, 1079-87. ↗

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TRMU (MTO2, MTU1) transfers a sulfur atom to 5-taurinomethyluridine-34 in tRNA

↗

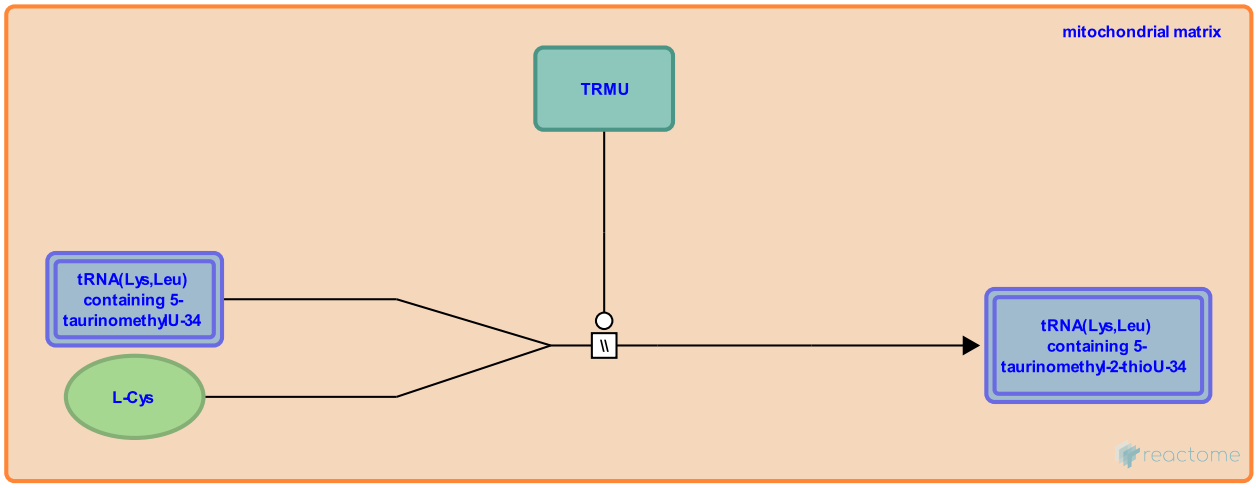
Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787447

Type: omitted

Compartments: mitochondrial matrix

Inferred from: SLM3 (MTO2, MTU1) transfers a sulfur atom to 5-carboxymethylaminomethyluridine-34 in tRNA (Saccharomyces cerevisiae)



TRMU (MTU1) transfers a sulfur atom from L-cysteine to the 2 position of 5-taurinomethyluridine-34 in tRNAs (Umeda et al. 2005, Sasarman et al. 2011). In Escherichia coli the sulfur is transferred along a relay system of proteins from L-cysteine to uridine. It is unknown if such a relay system also exists in humans. In yeast, mutations in MTU1, the homolog of TRMU act synergistically with mutations in the homologs of GTPBP3 and MTO1 to impair mitochondrial function (Umeda et al. 2005). In humans mutations in TRMU cause mitochondrial infantile liver disease (Zeharia et al. 2009, Gaignard et al. 2013), infantile respiratory chain disease (Boczonadi et al. 2013), and modify the severity of deafness associated with mutations in mitochondrial 12S rRNA (Guan et al. 2006), however abrogation of the thiouridylase function of TRMU may not be responsible for the phenotypes (Sasarman et al. 2011).

Preceded by: GTPBP3 and MTO1 transform uridine-34 yielding 5-taurinomethyluridine-34 in tRNA

Literature references

Garrido, G., Shohat, M., Guan, MX., Li, R., del Castillo, I., Gallo-Teran, J. et al. (2006). Mutation in TRMU related to transfer RNA modification modulates the phenotypic expression of the deafness-associated mitochondrial 12S ribosomal RNA mutations. *Am. J. Hum. Genet., 79*, 291-302. ↗

Ohya, Y., Suzuki, T., Suzuki, T., Umeda, N., Shindo, H., Yukawa, M. et al. (2005). Mitochondria-specific RNA-modifying enzymes responsible for the biosynthesis of the wobble base in mitochondrial tRNAs. Implications for the molecular pathogenesis of human mitochondrial diseases. *J. Biol. Chem., 280*, 1613-24. ↗

Gomez-Duran, A., Tulinius, M., Schara, U., Pyle, A., Horvath, R., Chinnery, PF. et al. (2013). Altered 2-thiouridylation impairs mitochondrial translation in reversible infantile respiratory chain deficiency. *Hum. Mol. Genet., 22*, 4602-15. ↗

Antonicka, H., Horvath, R., Sasarman, F., Shoubridge, EA. (2011). The 2-thiouridylase function of the human MTU1 (TRMU) enzyme is dispensable for mitochondrial translation. *Hum. Mol. Genet., 20*, 4634-43. ↗

Elpeleg, O., Pappo, O., Beinat, M., Marom, D., Karicheva, O., Rötig, A. et al. (2009). Acute infantile liver failure due to mutations in the TRMU gene. *Am. J. Hum. Genet., 85*, 401-7. ↗

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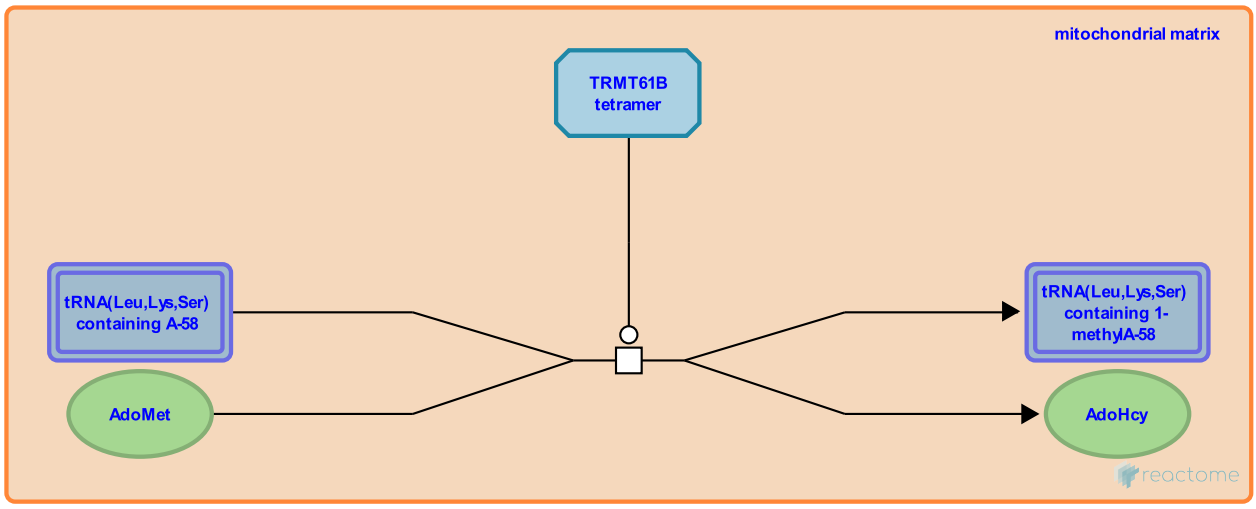
TRMT61B methylates adenosine-58 in tRNA yielding 1-methyladenosine-58 ↗

Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787525

Type: transition

Compartments: mitochondrial matrix



A TRMT61B oligomer, probably a tetramer, transfers a methyl group from S-adenosylmethionine to the (N)1 position of adenosine-58 in 3 mitochondrial tRNAs (tRNA(Leu)(UUR), tRNA(Lys), tRNA(Ser(UCN)) (Chujo and Suzuki 2012).

Literature references

Suzuki, T., Chujo, T. (2012). Trmt61B is a methyltransferase responsible for 1-methyladenosine at position 58 of human mitochondrial tRNAs. *RNA, 18*, 2269-76. ↗

Editions

2015-07-13	Authored, Edited	May, B.
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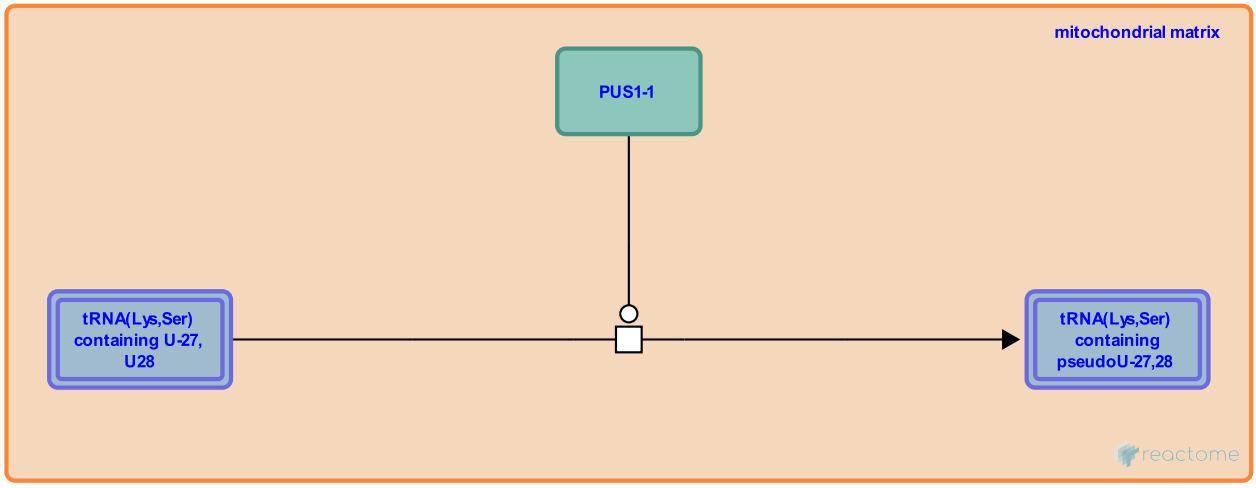
PUS1 isoform 1 transforms uridine-27, uridine-28 yielding pseudouridine in tRNA(Lys,Ser)

Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787566

Type: transition

Compartments: mitochondrial matrix



PUS1-1, the longer isoform of PUS1 located in the mitochondrion (Fernandez-Vizarra et al. 2007), converts uridine-27 and uridine-28 to pseudouridine residues in the anticodon stems of mitochondrial tRNA(Lys)(UUU) and tRNA(Ser)(UGA) (Patton et al. 2005, Fernandez-Vizarra et al. 2007, Sibert et al. 2008, Sibert and Patton 2012). Isomerization of uracil to pseudouridine creates an extra hydrogen bond donor and increases base stacking, acting to rigidify the RNA structure (reviewed in Charette and Gray 2000). As inferred from yeast Pus1p, PUS1 may also convert uridine to pseudouridine in other tRNAs and pre-tRNAs. Mutations in PUS1 cause mitochondrial myopathy and sideroblastic anemia (MLSA) (Bykhovskaya et al. 2004, Patton et al. 2005, Fernandez-Vizarra et al. 2007)

Literature references

Bykhovskaya, Y., Casas, K., Inbal, A., Fischel-Ghodsian, N., Mengesha, E. (2004). Missense mutation in pseudouridine synthase 1 (PUS1) causes mitochondrial myopathy and sideroblastic anemia (MLASA). *Am. J. Hum. Genet., 74*, 1303-8.

Sibert, BS., Patton, JR., Fischel-Ghodsian, N. (2008). Partial activity is seen with many substitutions of highly conserved active site residues in human Pseudouridine synthase 1. *RNA, 14*, 1895-906.

Sibert, BS., Patton, JR. (2012). Pseudouridine synthase 1: a site-specific synthase without strict sequence recognition requirements. *Nucleic Acids Res., 40*, 2107-18.

Valente, L., Fernandez-Vizarra, E., Berardinelli, A., Zeviani, M., Tiranti, V. (2007). Nonsense mutation in pseudouridylate synthase 1 (PUS1) in two brothers affected by myopathy, lactic acidosis and sideroblastic anaemia (MLASA). *J. Med. Genet., 44*, 173-80.

Charette, M., Gray, MW. (2000). Pseudouridine in RNA: what, where, how, and why. *IUBMB Life, 49*, 341-51.

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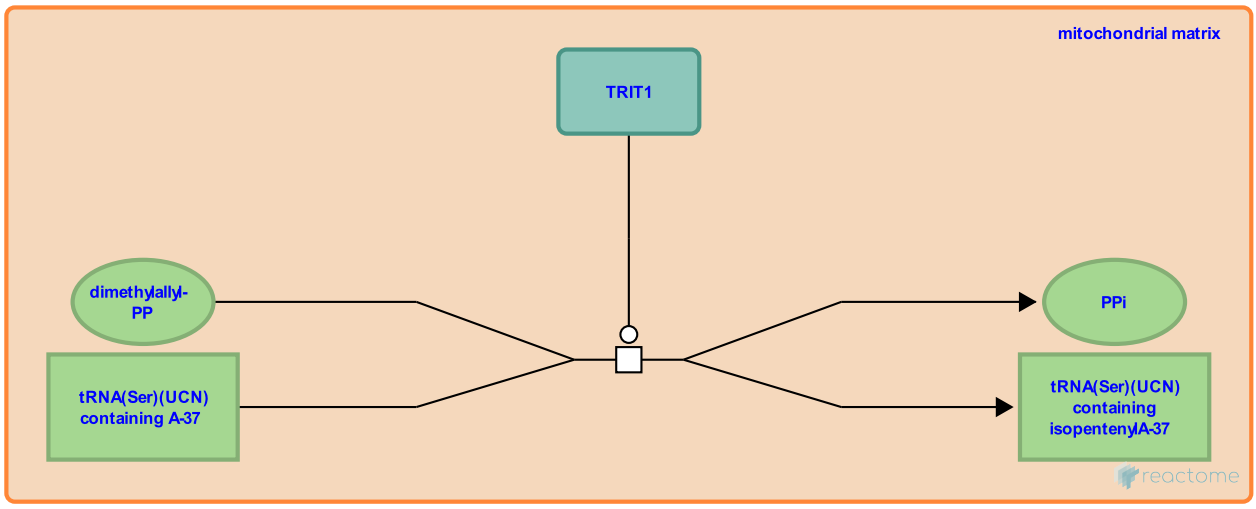
TRIT1 transfers dimethylallyl group to adenosine-37 of tRNA(Ser)

Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787567

Type: transition

Compartments: mitochondrial matrix



TRIT1 transfers a dimethylallyl group (isopentenyl group) from dimethylallyl diphosphate to the N6 position of adenosine-37 in mitochondrial tRNA(Ser,UCN), yielding N6-dimethylallyladenosine-37 (N6-isopentenyladenosine-37) (Lamichhane et al. 2013, Yarham et al. 2014). TRIT1 modifies both cytosolic and mitochondrial tRNAs and a mutation in TRIT1 causes defects in mitochondrial protein synthesis and respiration (Yarham et al. 2014).

Literature references

Taylor, RW., Griffin, H., Yarham, JW., He, L., Santibanez-Koref, M., Chinnery, PF. et al. (2014). Defective i6A37 modification of mitochondrial and cytosolic tRNAs results from pathogenic mutations in TRIT1 and its substrate tRNA. *PLoS Genet., 10*, e1004424.

Maraia, RJ., Mattijssen, S., Lamichhane, TN. (2013). Human cells have a limited set of tRNA anticodon loop substrates of the tRNA isopentenyltransferase TRIT1 tumor suppressor. *Mol. Cell. Biol., 33*, 4900-8.

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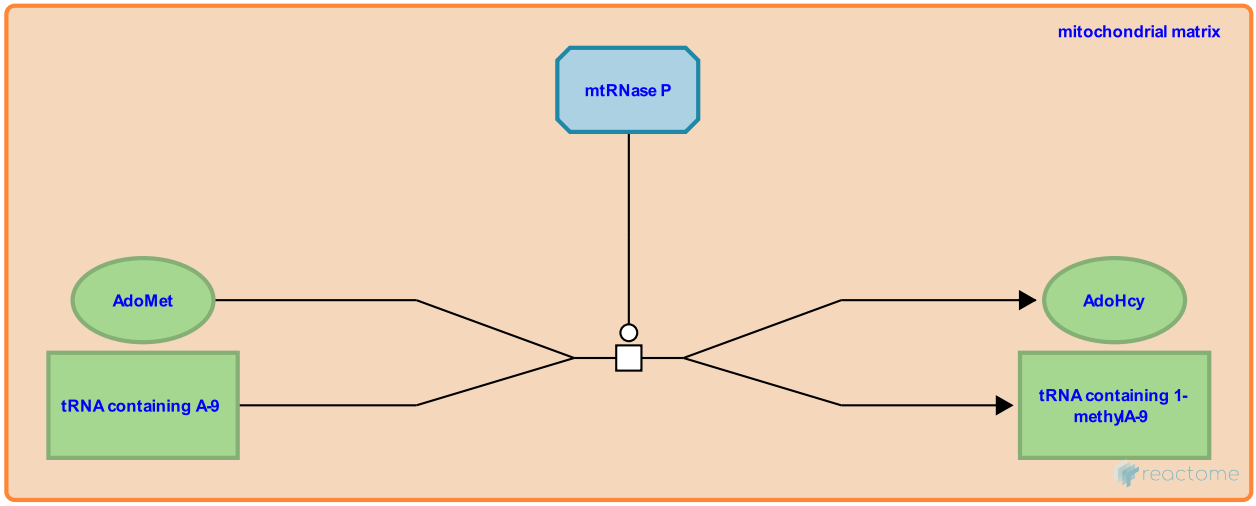
TRMT10C:HSD17B10 (TRMT10C:SDR5C1) methylates adenosine-9 in tRNA yielding 1-methyladenosine-9

Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787594

Type: transition

Compartments: mitochondrial matrix



TRMT10C of TRMT10C:HSD17B10 (TRMT10C:SDR5C1), a subcomplex of the mitochondrial RNase P complex, methylates the 1 position of adenosine-9 in mitochondrial tRNAs (Vilardo et al. 2012). 14 of 22 mitochondrial tRNAs have an A9 residue. Methylation of A9 appears to be important for correct folding of tRNA (Helm et al. 1998). Mutations in the HSD17B10 (SDR5C1) dehydrogenase subunit of RNase P impair dehydrogenation, tRNA methylation, and tRNA processing, causing HSD10 disease, which is characterized by progressive neurodegeneration and cardiomyopathy (Vilardo and Rossmanith 2015).

Literature references

Degoul, F., Florentz, C., Giegé, R., Brulé, H., Cepanec, C., Helm, M. et al. (1998). The presence of modified nucleotides is required for cloverleaf folding of a human mitochondrial tRNA. *Nucleic Acids Res., 26*, 1636-43.

Taschner, A., Vilardo, E., Rossmanith, W., Holzmann, J., Buzet, A., Nachbagauer, C. (2012). A subcomplex of human mitochondrial RNase P is a bifunctional methyltransferase--extensive moonlighting in mitochondrial tRNA biogenesis. *Nucleic Acids Res., 40*, 11583-93.

Vilardo, E., Rossmanith, W. (2015). Molecular insights into HSD10 disease: impact of SDR5C1 mutations on the human mitochondrial RNase P complex. *Nucleic Acids Res., 43*, 5112-9.

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2015-11-07	Reviewed	Powell, CA.

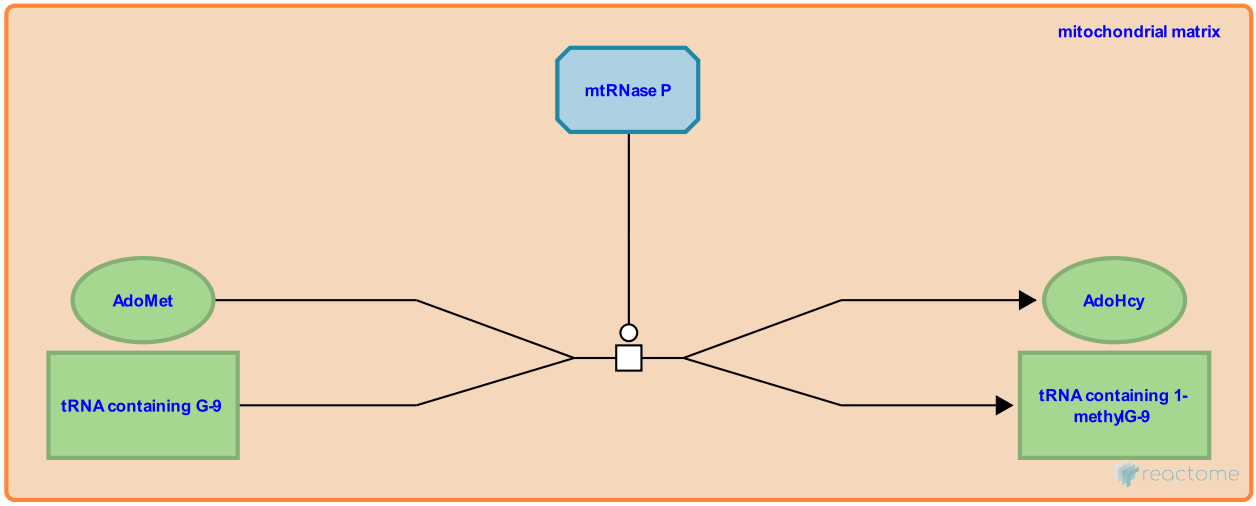
TRMT10C:HSD17B10 (TRMT10C:SDR5C1) of mitochondrial RNase P methylates guanosine-9 in tRNA yielding 1-methylguanosine-9

Location: tRNA modification in the mitochondrion

Stable identifier: R-HSA-6787591

Type: transition

Compartments: mitochondrial matrix



TRMT10C in TRMT10C:HSD17B10 (TRMT10C:SDR5C1), a subcomplex of the mitochondrial RNase P complex, methylates the 1 position of guanosine-9 in mitochondrial tRNAs (Vilardo et al. 2012). 5 of 22 mitochondrial tRNAs have a G9 residue. Methylation of G9 appears to be important for correct folding of tRNA. Mutations in the SDR5C1 dehydrogenase subunit of RNase P impair dehydrogenation, tRNA methylation, and tRNA processing, causing HSD10 disease, which is characterized by progressive neurodegeneration and cardiomyopathy (Vilardo and Rossmanith 2015).

Literature references

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Vilardo, E., Rossmanith, W. (2015). Molecular insights into HSD10 disease: impact of SDR5C1 mutations on the human mitochondrial RNase P complex. *Nucleic Acids Res., 43*, 5112-9.

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