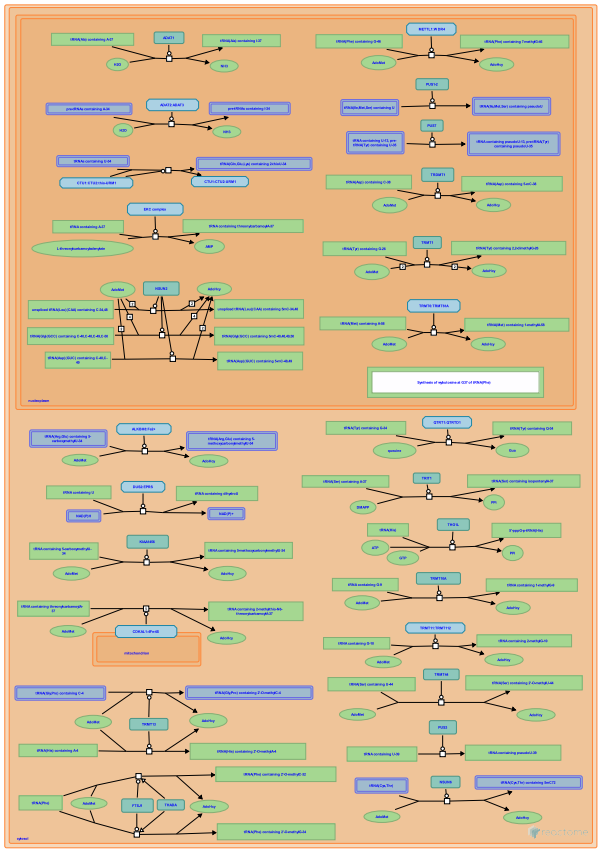
tRNA modification in the nucleus and cytosol



Alkuraya, FS., Bohnsack, MT., Jarrous, N., Levinger, L., May, B., Motorin, Y., Phizicky, EM.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

09/04/2024

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. ↗

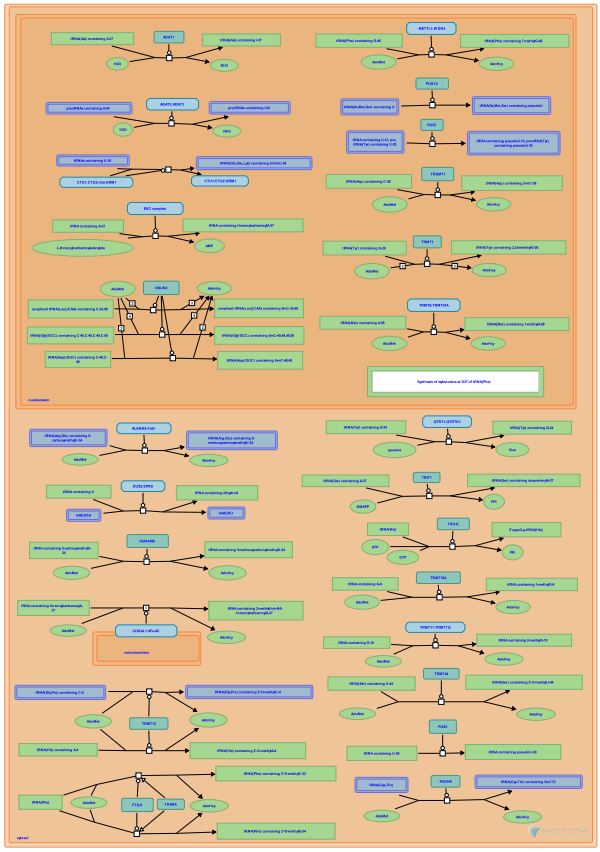
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 2 pathways and 29 reactions (see Table of Contents)

tRNA modification in the nucleus and cytosol ↗

Stable identifier: R-HSA-6782315



At least 92 distinct tRNA nucleotide base modifications have been found. The modifications are made post-transcriptionally by a large group of disparate enzymes located in the nucleus, cytosol, and mitochondria (reviewed in Boschi-Muller and Motorin 2013, Jackman and Alfonzo 2013, Gu et al. 2014, Helm and Alfonzo 2014, Li and Mason 2014). Modifications near the anticodon and near the 3' end affect interaction of the tRNA with ribosomes and tRNA synthetases, respectively, while modifications in other regions of the tRNA affect folding and stability of the tRNA (reviewed in Hou et al. 2015). Mutations in tRNA modification enzymes are associated with human diseases (reviewed in Sarin and Leidel 2014, Torres et al. 2014).

Literature references

Motorin, Y., Boschi-Muller, S. (2013). Chemistry enters nucleic acids biology: enzymatic mechanisms of RNA modification. *Biochemistry Mosc., 78*, 1392-404. ↗

Dedon, PC., Gu, C., Begley, TJ. (2014). tRNA modifications regulate translation during cellular stress. *FEBS Lett., 588*, 4287-96. ↗

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

Li, S., Mason, CE. (2014). The pivotal regulatory landscape of RNA modifications. *Annu Rev Genomics Hum Genet, 15*, 127-50. ↗

Alfonzo, JD., Jackman, JE. (2013). Transfer RNA modifications: nature's combinatorial chemistry playground. *Wiley Interdiscip Rev RNA, 4*, 35-48. ↗

Editions

2015-05-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
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2015-10-24	Reviewed	Jarrous, N.

ADAT1 deaminates adenosine-37 in tRNA(Ala) ↗

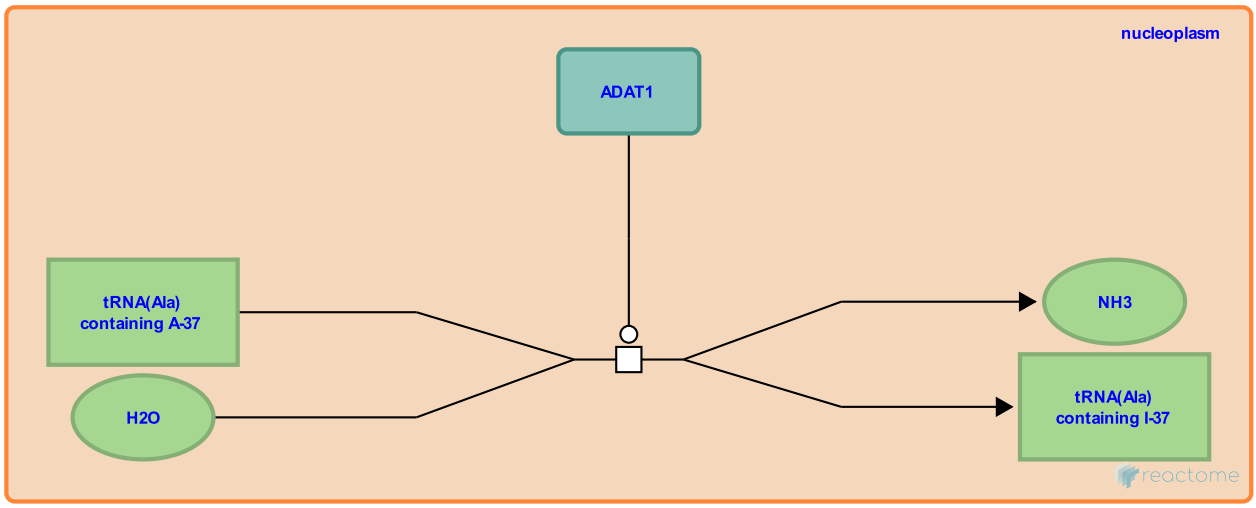
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782336

Type: transition

Compartments: nucleoplasm

Inferred from: TAD1 deaminates adenosine-37 in tRNA(Ala) yielding inosine-37 (Saccharomyces cerevisiae)



ADAT1 deaminates adenosine-37 of tRNA(Ala) yielding inosine-37, which may then be methylated to N1-methylinosine-37 (Maas et al. 1999). The homologue in Saccharomyces, Tad1p, catalyzes the same reaction, indicating the deamination of adenosine-37 is highly conserved in eukaryotes.

Literature references

Gerber, AP., Maas, S., Rich, A. (1999). Identification and characterization of a human tRNA-specific adenosine deaminase related to the ADAR family of pre-mRNA editing enzymes. *Proc. Natl. Acad. Sci. U.S.A., 96*, 8895-900. ↗

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2015-05-30	Authored, Edited	May, B.
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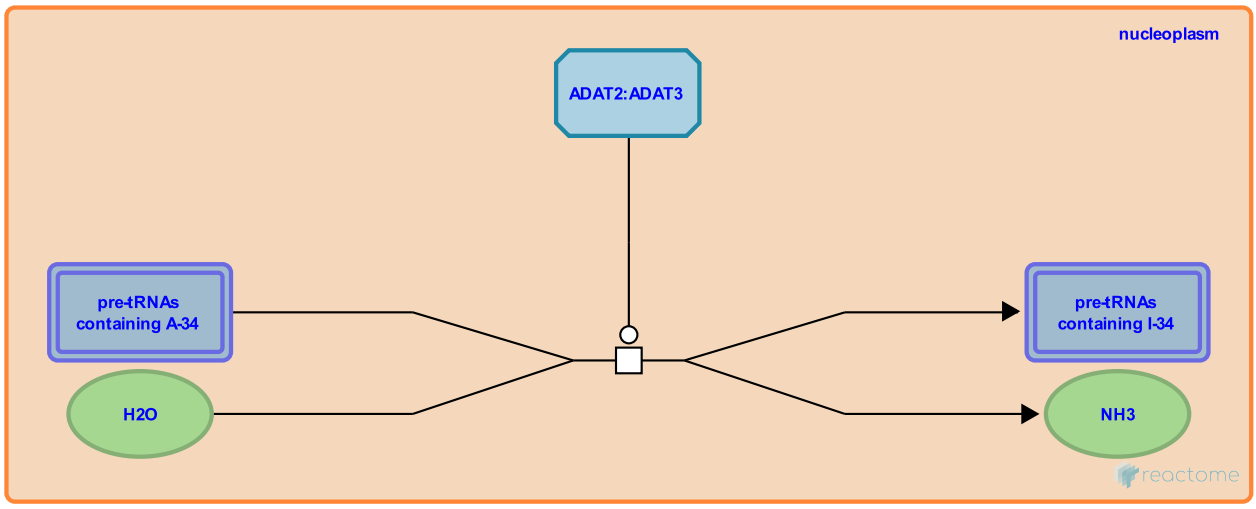
ADAT2:ADAT3 (hetADAT) deaminates adenosine-34 in tRNAs ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782311

Type: transition

Compartments: nucleoplasm



The ADAT2:ADAT3 heterodimer (hetADAT) deaminates adenosine-34 in 8 human tRNAs: tRNA(Ala-AGC), tRNA(Arg-ACG), tRNA(Ile-AAT), tRNA(leu-AAG), tRNA(Pro-AGG), tRNA(Ser-AGA), tRNA(Thr-AGT), tRNA(Val-AAC) (Torres et al. 2015). The deamination occurs in the nucleus on precursor tRNAs from which the 5' leaders and 3' trailers have not yet been cleaved. The corresponding homologues in Saccharomyces cerevisiae are Tad2p and Tad3p.

Literature references

Camacho, N., Saint-Léger, A., Batlle, E., Filonava, L., Ribas de Pouplana, L., Torres, AG. et al. (2015). Inosine modifications in human tRNAs are incorporated at the precursor tRNA level. *Nucleic Acids Res., 43*, 5145-57. ↗

Editions

2015-05-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

ALKBH8 methylates 5-carboxymethyluridine-34 in tRNA(Arg) and tRNA(Glu) yielding 5-methoxycarbonylmethyluridine-34 ↗

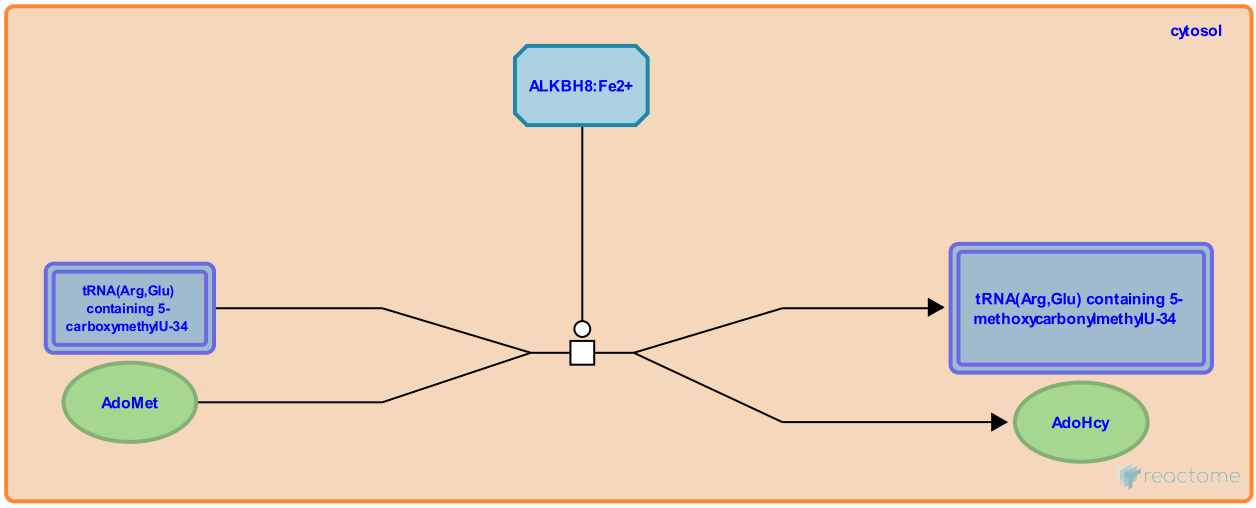
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786500

Type: transition

Compartments: cytosol

Inferred from: TRM9 methylates 5-carboxymethyluridine-34 in tRNA(Arg3) yielding 5-methoxycarbonylmethyluridine-34 (Saccharomyces cerevisiae)



ALKBH8:Fe2+ transfers a methyl group from S-adenosylmethionine (AdoMet) to 5-carboxymethyluridine-34 of tRNA, yielding 5-methoxycarbonylmethyluridine-34 (5-(2-methoxy-2-oxoethyl)uridine-34) (Fu et al. 2010, Songe-Møller et al. 2010). The corresponding homologue in Saccharomyces, Trm9p, catalyzes the same reaction.

Literature references

Dedon, PC., Chan, CT., Brophy, JA., Paules, RS., Atmore, KA., Fu, D. et al. (2010). Human AlkB homolog ABH8 Is a tRNA methyltransferase required for wobble uridine modification and DNA damage survival. *Mol. Cell. Biol., 30*, 2449-59. ↗

van den Born, E., Falnes, PØ., Kirpekar, F., Songe-Møller, L., Vågbø, CB., Kristoffersen, T. et al. (2010). Mammalian ALKBH8 possesses tRNA methyltransferase activity required for the biogenesis of multiple wobble uridine modifications implicated in translational decoding. *Mol. Cell. Biol., 30*, 1814-27. ↗

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2015-06-30	Authored, Edited	May, B.
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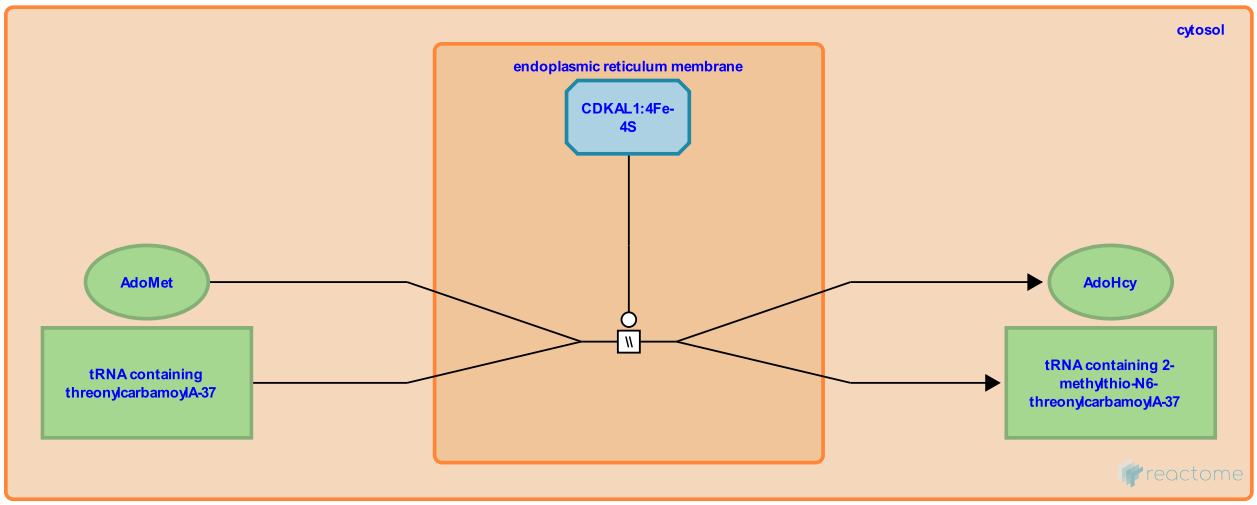
CDKAL1:4Fe-4S methylthiolates N6-threonylcarbamoyladenosine-37 in tRNA yielding 2-methylthio-N6-threonylcarbamoyladenosine-37 ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786571

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



The CDKAL1:4Fe-4S complex methylthiolates N6-threonylcarbamoyladenosine-37 in several tRNAs (Arragain et al. 2010). The source of the methyl group is S-adenosylmethionine (AdoMet). The source of the sulfur is unknown. The homologue in Bacillus subtilis, mtaB, catalyzes the same reaction (Arragain et al. 2010).
CDKAL1 is located on the cytosolic face of the endoplasmic reticulum therefore the reaction is presumed to occur in the cytosol (Brambillasca et al. 2012).

Preceded by: EKC complex threonylcarbamoylates A37 of tRNAs

Literature references

Eickelmann, P., Colombo, SF., Solimena, M., Altkrueger, A., Borgese, N., Friederich, A. et al. (2012). CDK5 regulatory subunit-associated protein 1-like 1 (CDKAL1) is a tail-anchored protein in the endoplasmic reticulum (ER) of insulinoma cells. *J. Biol. Chem., 287*, 41808-19. ↗

Wei, FY., Handelman, SK., Hunt, JF., Atta, M., Arragain, S., Tomizawa, K. et al. (2010). Identification of eukaryotic and prokaryotic methylthiotransferase for biosynthesis of 2-methylthio-N6-threonylcarbamoyladenosine in tRNA. *J. Biol. Chem., 285*, 28425-33. ↗

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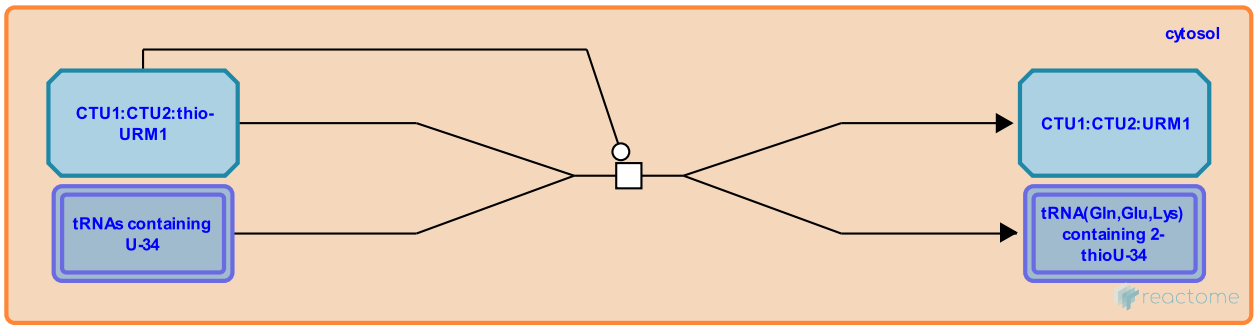
CTU1:CTU2:URM1 thiolates uridine-34 in tRNAs ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782264

Type: transition

Compartments: cytosol



The CTU1:CTU2:URM1 complex transfers a thiol group from the thiolcarboxylated C-terminus of URM1 to uridine-34 residues of tRNAs, yielding 2-thiouridine-34 (Schlieker et al. 2008). The same reaction is catalyzed by TRMU (MTU1) in mitochondria.

Literature references

Ploegh, HL., Spooner, E., Schlieker, CD., Damon, JR., Van der Veen, AG. (2008). A functional proteomics approach links the ubiquitin-related modifier Urm1 to a tRNA modification pathway. *Proc. Natl. Acad. Sci. U.S.A., 105*, 18255-60. ↗

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2015-05-30	Authored, Edited	May, B.
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2015-08-25	Reviewed	Motorin, Y.
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DUS2:EPRS reduces uridine to dihydrouridine in tRNAs ↗

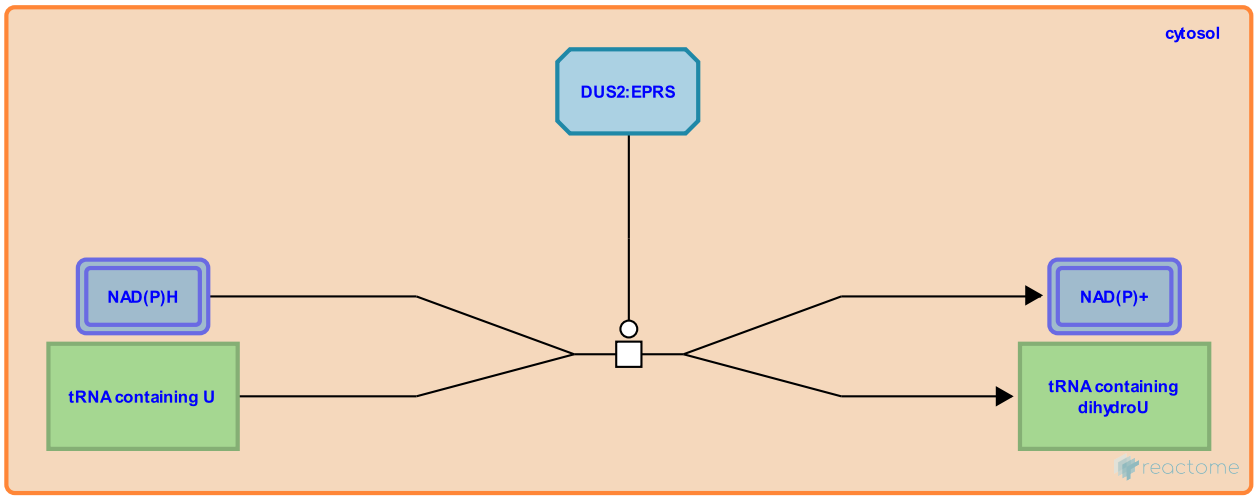
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782296

Type: transition

Compartments: cytosol

Inferred from: SMM1 (DUS2) reduces uridine-20 to dihydrouridine in tRNA(Leu) (Saccharomyces cerevisiae)



DUS2 catalyzes the reduction of the 5,6 double bond in uridine residues in the D-loop of tRNAs, yielding 5,6-dihydrouridine (Kato et al. 2005). By inference with the homolog from Saccharomyces cerevisiae, Smm1p (Dus2p), NADH or NADPH is the reducing agent.

Literature references

Daigo, Y., Nakamura, Y., Ishikawa, N., Yamabuki, T., Hayama, S., Kondo, S. et al. (2005). A novel human tRNA-dihydrouridine synthase involved in pulmonary carcinogenesis. *Cancer Res., 65*, 5638-46. ↗

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2015-05-30	Authored, Edited	May, B.
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EKC complex threonylcarbamoylates A37 of tRNAs ↗

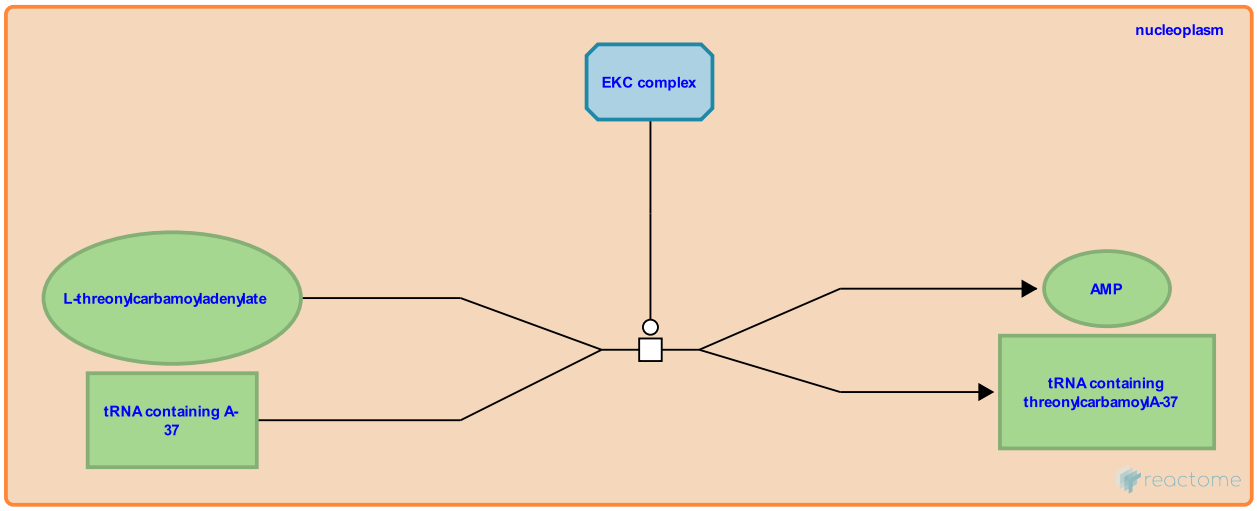
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6784494

Type: transition

Compartments: nucleoplasm

Inferred from: EKC/KEOPS complex threonylcarbamoylates adenosine-37 of tRNAs (Saccharomyces cerevisiae)



As inferred from the yeast homologs (EKC complex, KEOPS complex, BUD32:CGI121:KAE1:PCC1), the EKC complex (LAGE3:OSGEP:TP53RK:TPRKB) transfers a threonylcarbamoyl group from L-threonylcarbamoyladenylate to adenosine-37 of tRNAs, yielding threonylcarbamoyladenosine-37.

Followed by: CDKAL1:4Fe-4S methylthiolates N6-threonylcarbamoyladenosine-37 in tRNA yielding 2-methylthio-N6-threonylcarbamoyladenosine-37

Editions

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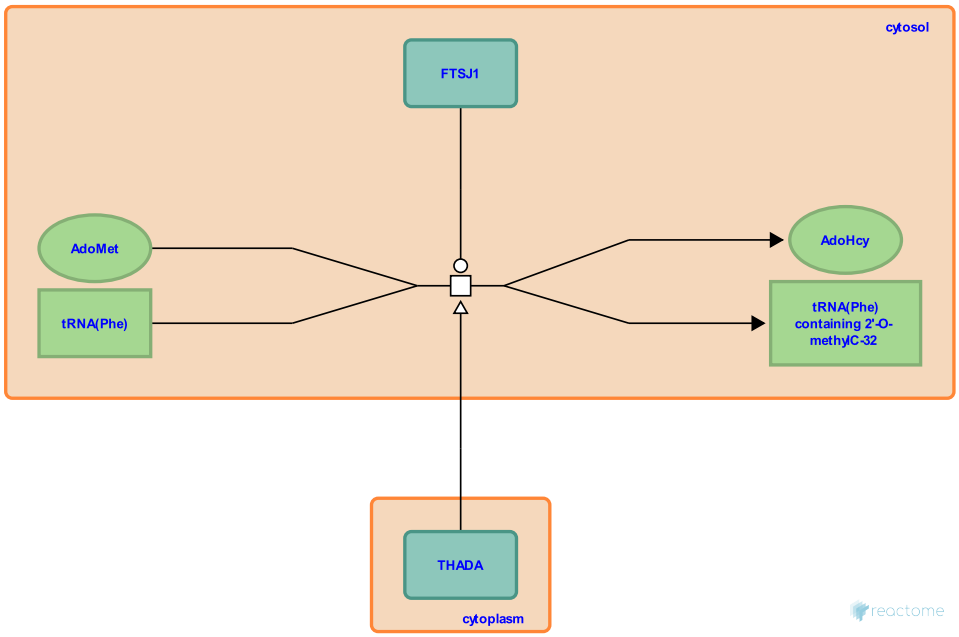
FTSJ1 2'-O-methylates cytidine-32 in tRNA(Phe) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-9024159

Type: transition

Compartments: cytosol



FTSJ1 methylates the 2'-hydroxyl group of cytidine-32 and guanosine-34 in the anticodon loop of tRNA(Phe), as well as C32 and N34 of other substrate tRNAs (Guy and Phizicky 2015a, Guy et al. 2015b). Based on the functional and sequence homology between human FTSJ1 and yeast Trm7 the reaction is inferred to occur in the cytosol. THADA is required together with FTSJ1 for the methylation reaction at C32, based on its complementation of trm732 mutants in yeast, but the function of THADA has not been directly demonstrated in human cells (Guy and Phizicky 2015a).

Literature references

Phizicky, EM., Guy, MP. (2015). Conservation of an intricate circuit for crucial modifications of the tRNAPhe anticodon loop in eukaryotes. *RNA, 21*, 61-74. ↗

Phizicky, EM., Stark, Z., Guy, MP., Hobson, L., Rose, K., Weiner, CL. et al. (2015). Defects in tRNA Anticodon Loop 2'-O-Methylation Are Implicated in Nonsyndromic X-Linked Intellectual Disability due to Mutations in FTSJ1. *Hum. Mutat., 36*, 1176-87. ↗

Editions

2016-05-09	Authored, Edited	May, B.
2016-06-20	Reviewed	Phizicky, EM.
2024-02-28	Reviewed	May, B.

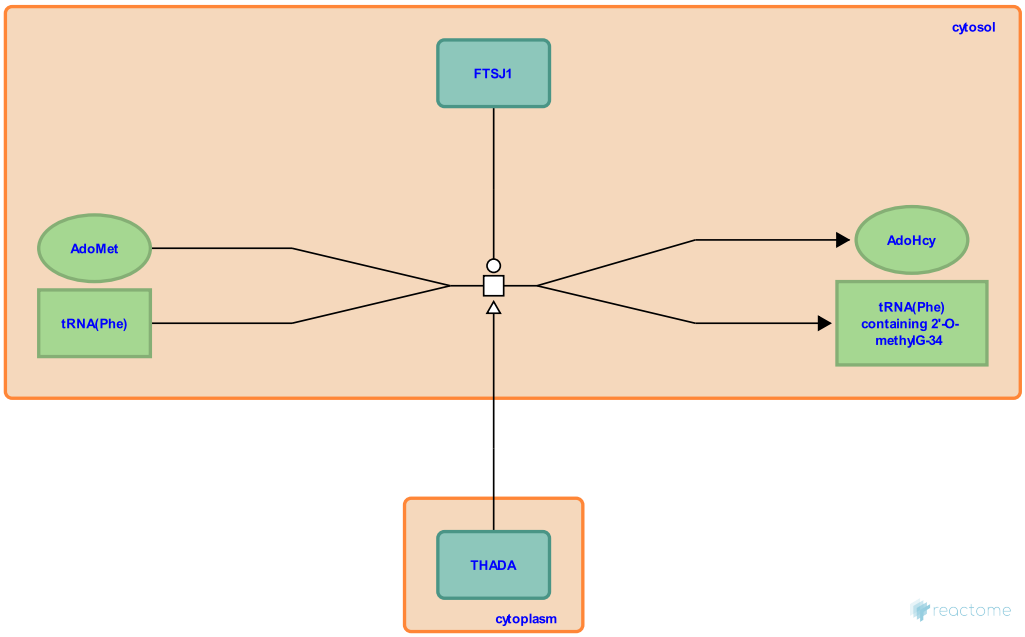
FTSJ1 2'-O-methylates guanosine-34 in tRNA(Phe) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-9024161

Type: transition

Compartments: cytosol



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Literature references

Phizicky, EM., Guy, MP. (2015). Conservation of an intricate circuit for crucial modifications of the tRNAPhe anticodon loop in eukaryotes. *RNA, 21*, 61-74. ↗

Phizicky, EM., Stark, Z., Guy, MP., Hobson, L., Rose, K., Weiner, CL. et al. (2015). Defects in tRNA Anticodon Loop 2'-O-Methylation Are Implicated in Nonsyndromic X-Linked Intellectual Disability due to Mutations in FTSJ1. *Hum. Mutat., 36*, 1176-87. ↗

Editions

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2024-02-28	Reviewed	May, B.

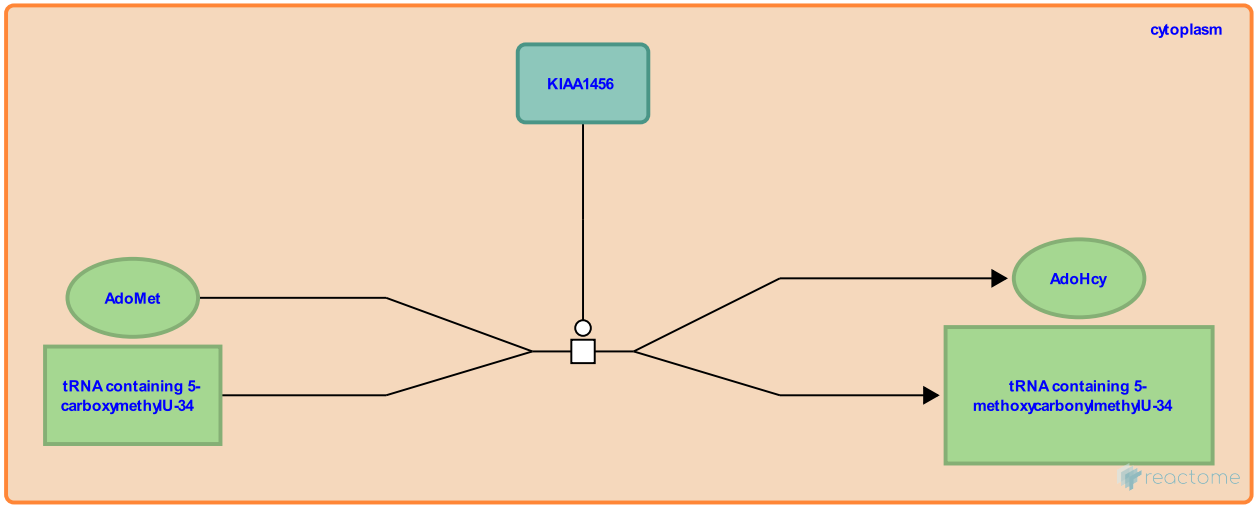
KIAA1456 (TRM9L) methylates 5-carboxymethyluridine in tRNA yielding 5-methoxy-carbonylmethyluridine ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786567

Type: transition

Compartments: cytoplasm



KIAA1456 (TRM9L, hTRM9L) transfers a methyl group from S-adenosylmethionine (AdoMet) to 5-carboxymethyluridine in tRNA, yielding 5-methoxycarbonylmethyluridine (5-(2-methoxy-2-oxoethyl)uridine) (Begley et al. 2013). The subcellular location of the reaction is unknown.

Literature references

Begley, T., Dedon, PC., Endres, L., Sosa, MS., Chan, CT., Estrada, Y. et al. (2013). A human tRNA methyltransferase 9-like protein prevents tumour growth by regulating LIN9 and HIF1-α. *EMBO Mol Med, 5*, 366-83. ↗

Editions

2015-06-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
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2015-10-24	Reviewed	Jarrous, N.

METTL1:WDR4 methylates guanosine-46 of tRNA(Phe) yielding 7-methylguanosine-46 ↗

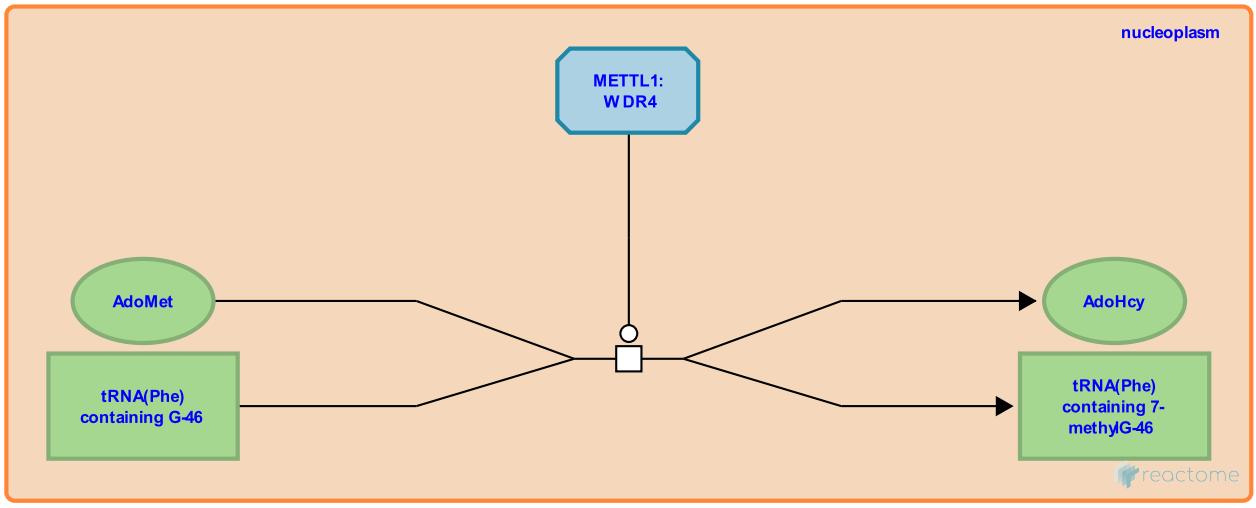
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782286

Type: transition

Compartments: nucleoplasm

Inferred from: TRM8:TRM82 methylates guanosine-46 of tRNA(Phe) yielding 7-methylguanosine-46 (Saccharomyces cerevisiae)



The METTL1:WDR4 complex transfers a methyl group from S-adenosylmethionine to guanosine-46 of tRNA(Phe), yielding 7-methylguanosine-46 (Alexandrov et al. 2002, Cartlidge et al. 2005). A homologous complex, Trm8p:Trm82p, exists in Saccharomyces cerevisiae and catalyzes the same reaction.

Literature references

Cartlidge, RA., Phizicky, EM., Alexandrov, A., Cohen, P., Peggie, M., Knebel, A. (2005). The tRNA methylase METTL1 is phosphorylated and inactivated by PKB and RSK in vitro and in cells. *EMBO J., 24*, 1696-705. ↗

Phizicky, EM., Martzen, MR., Alexandrov, A. (2002). Two proteins that form a complex are required for 7-methylguanosine modification of yeast tRNA. *RNA, 8*, 1253-66. ↗

Editions

2015-06-06	Authored, Edited	May, B.
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NSUN2 methylates cytidine-34, cytidine-48 of unspliced tRNA(Leu)(CAA) ↗

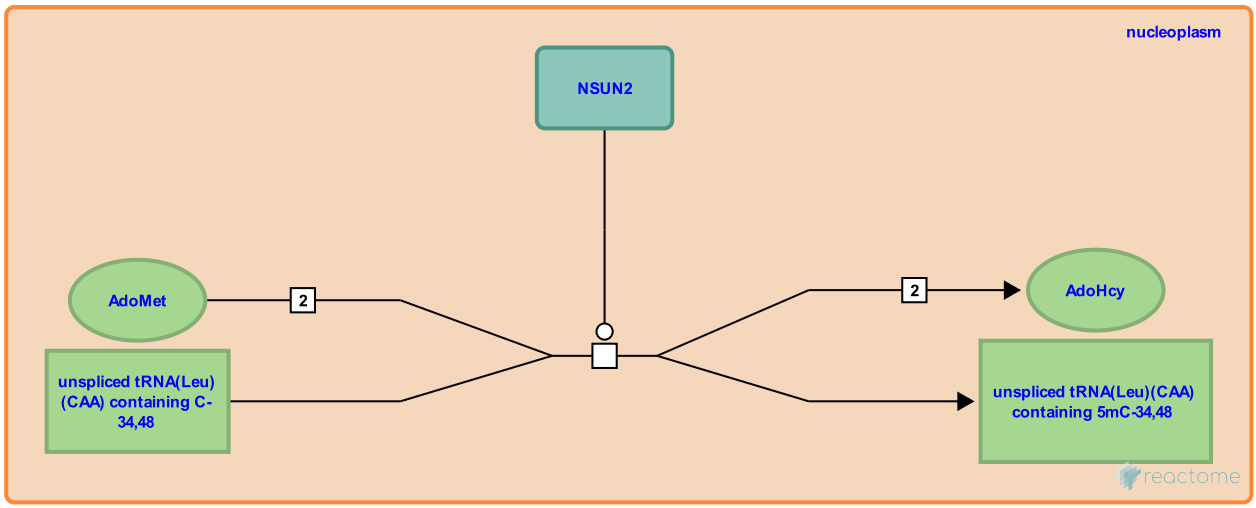
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782388

Type: transition

Compartments: nucleoplasm

Inferred from: NCL1 (TRM4) methylates cytidine-34 of unspliced tRNA(Leu) yielding 5-methylcytidine-34 (Saccharomyces cerevisiae)



NSUN2 transfers a methyl group from S-adenosylmethionine to the 5 positions of cytidine-34 and cytidine-48 in tRNA(Leu)(CAA) (Brzezicha et al. 2006, Auxilien et al. 2012, Squires et al. 2012, Khoddami and Cairns 2013). Methylation of cytidine-34 occurs on the uspliced precursor tRNA(Leu)(CAA) (Brzezicha et al. 2006, Auxilien et al. 2012); methylation of cytidine-48 occurs on either the spliced or unspliced tRNA(Leu)(CAA) (Auxilien et al. 2012).

Literature references

Auxilien, S., Golinelli-Pimpaneau, B., Guérineau, V., Szweykowska-Kulińska, Z. (2012). The human tRNA m (5) C methyltransferase Misu is multisite-specific. *RNA Biol, 9*, 1331-8. ↗

Cairns, BR., Khoddami, V. (2013). Identification of direct targets and modified bases of RNA cytosine methyltransferases. *Nat. Biotechnol., 31*, 458-64. ↗

Humphreys, DT., Patel, HR., Squires, JE., Preiss, T., Sibbritt, T., Nousch, M. et al. (2012). Widespread occurrence of 5-methylcytosine in human coding and non-coding RNA. *Nucleic Acids Res., 40*, 5023-33. ↗

Brzezicha, B., Schmidt, M., Jarmolowski, A., Szweykowska-Kulinska, Z., Makalowska, I., Pienkowska, J. (2006). Identification of human tRNA:m5C methyltransferase catalysing intron-dependent m5C formation in the first position of the anticodon of the pre-tRNA Leu (CAA). *Nucleic Acids Res., 34*, 6034-43. ↗

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2015-10-24	Reviewed	Jarrous, N.

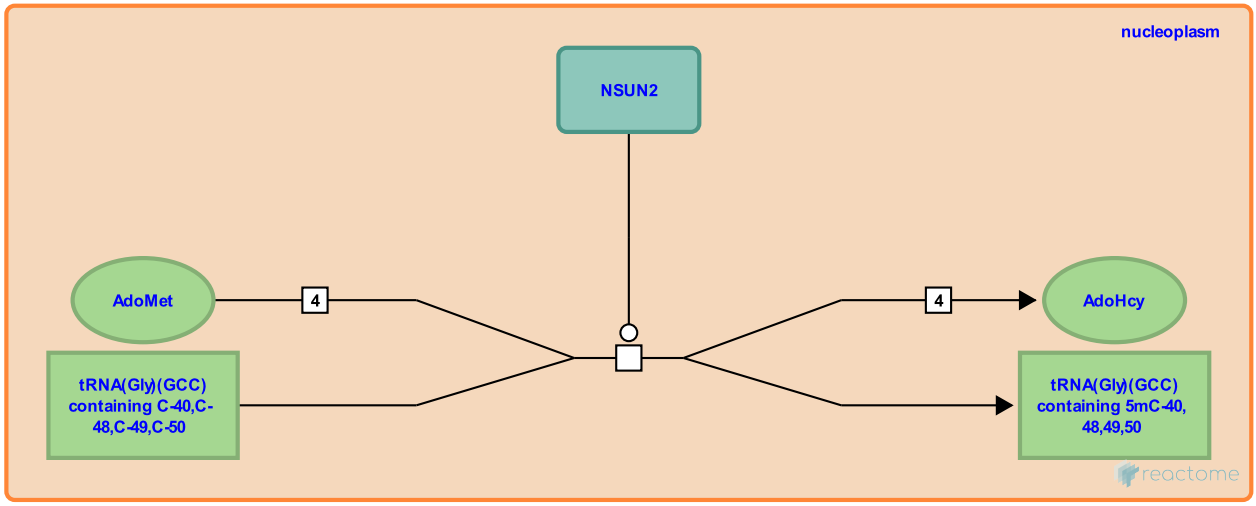
NSUN2 methylates cytidine-40, cytidine-48, cytidine-49, cytidine-50 of tRNA(GLY)(GCC)

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6785438

Type: transition

Compartments: nucleoplasm



NSUN2 transfers methyl groups from S-adenosylmethionine to the 5 positions of cytidine-40, cytidine-48, cytidine-49, and cytidine-50 of tRNA(Gly)(GCC) (Auxilien et al. 2012, Khoddami and Cairns 2013).

Literature references

Auxilien, S., Golinelli-Pimpaneau, B., Guérineau, V., Szweykowska-Kulińska, Z. (2012). The human tRNA m (5) C methyltransferase Misu is multisite-specific. *RNA Biol, 9*, 1331-8.

Cairns, BR., Khoddami, V. (2013). Identification of direct targets and modified bases of RNA cytosine methyltransferases. *Nat. Biotechnol., 31*, 458-64.

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2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

NSUN2 methylates cytidine-48 and cytidine-49 of tRNA(Asp)(GUC)

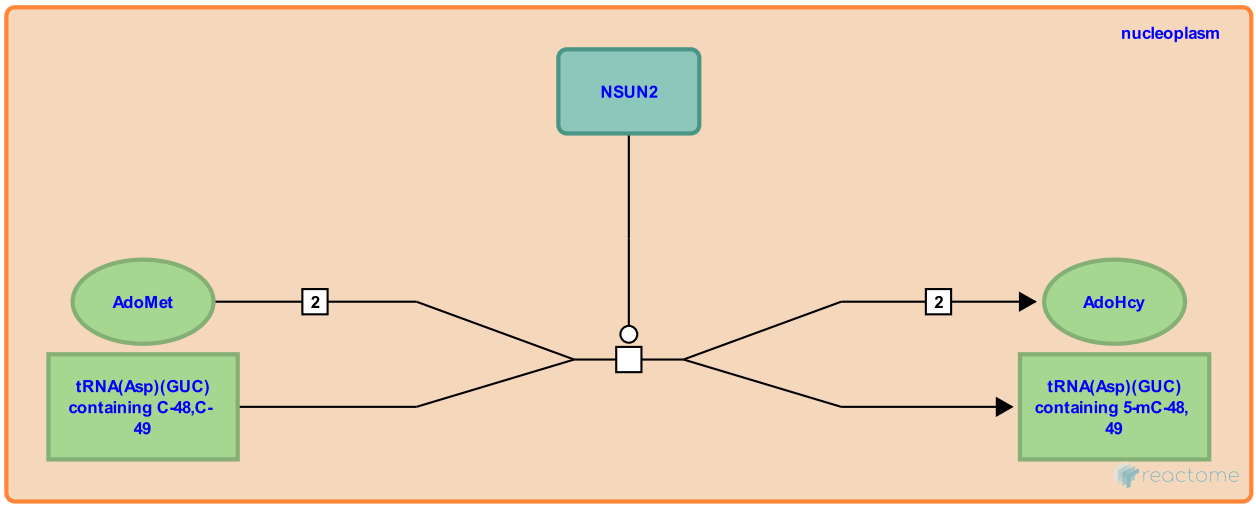
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6785409

Type: transition

Compartments: nucleoplasm

Inferred from: NCL1 (TRM4) methylates cytidine-49 of tRNA(Asp) yielding 5-methylcytidine-46 (Saccharomyces cerevisiae)



NSUN2 transfers methyl groups from S-adenosylmethionine to the 5 positions of cytidine-48 and cytidine-49 of tRNA(Asp)(GUC) (Squires et al. 2012, Khoddami et al. 2013).

Literature references

Cairns, BR., Khoddami, V. (2013). Identification of direct targets and modified bases of RNA cytosine methyltransferases. *Nat. Biotechnol., 31*, 458-64.

Humphreys, DT., Patel, HR., Squires, JE., Preiss, T., Sibbritt, T., Nousch, M. et al. (2012). Widespread occurrence of 5-methylcytosine in human coding and non-coding RNA. *Nucleic Acids Res., 40*, 5023-33.

Editions

2015-06-27	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

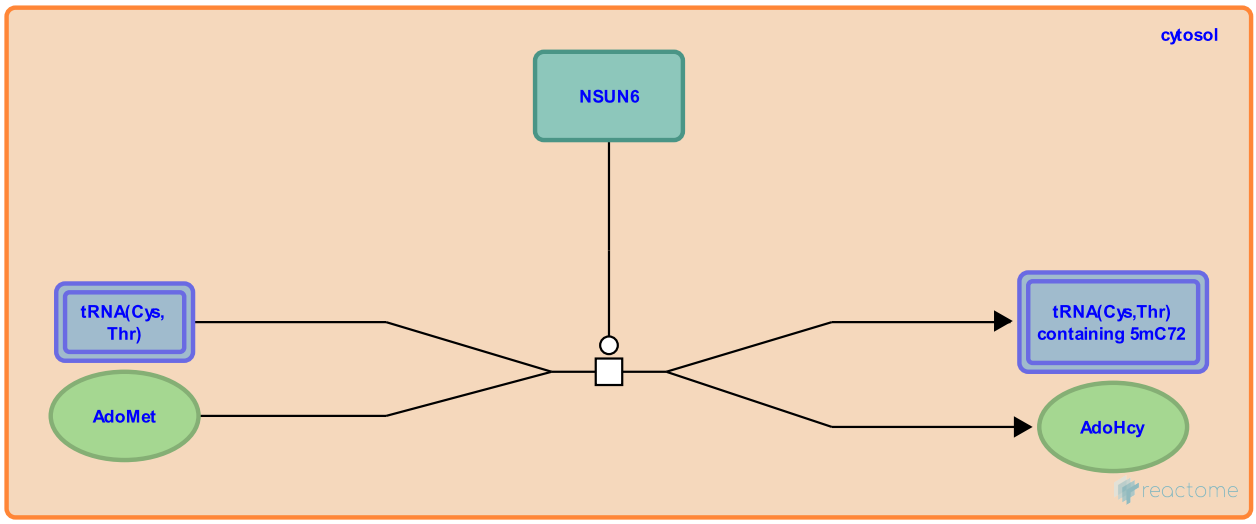
NSUN6 methylates cytidine-72 in tRNA(Cys) and tRNA(Thr) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-8932765

Type: transition

Compartments: cytosol



NSUN6 methylates position 5 of the cytosine ring of cytidine-72 in the acceptor stem of tRNA(Cys) and tRNA(Thr) (Haag et al. 2015). As the reaction occurs in the cytoplasm and requires the 3' CCA on the tRNA substrates, it is believed to occur late in tRNA biogenesis

Literature references

Warda, AS., Günnigmann, MA., Haag, S., Kretschmer, J., Höbartner, C., Bohnsack, MT. (2015). NSUN6 is a human RNA methyltransferase that catalyzes formation of m5C72 in specific tRNAs. *RNA, 21*, 1532-43. ↗

Editions

2016-07-28	Authored, Edited	May, B.
2016-08-10	Reviewed	Bohnsack, MT.

PUS1 isoform 2 transforms uridine residues to pseudouridine in the anticodon stems of tRNAs ↗

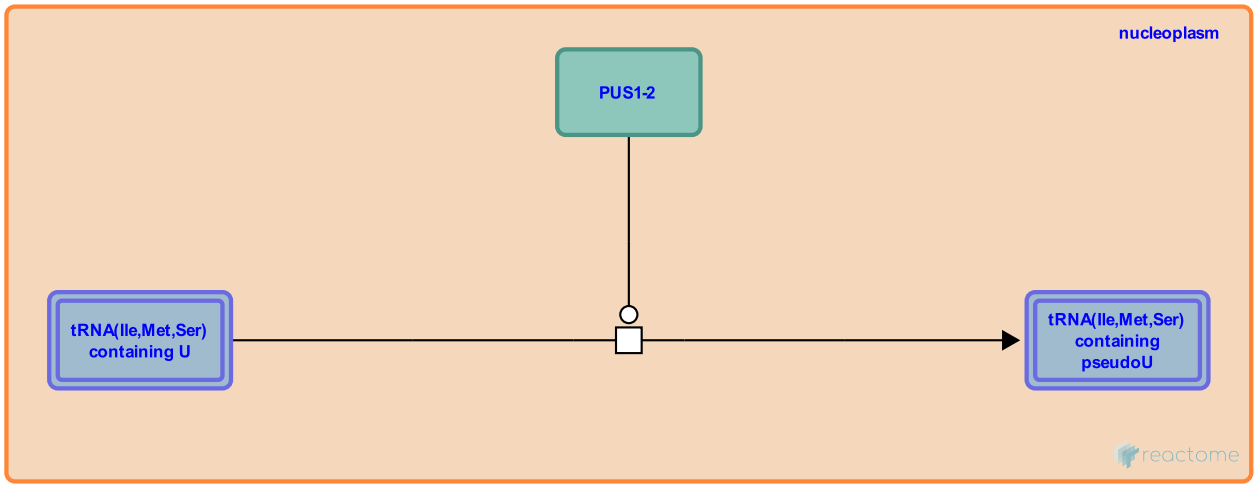
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782381

Type: transition

Compartments: nucleoplasm

Inferred from: PUS1 transforms uridine residues to pseudouridine in unspliced tRNA(Ile,Tyr) (Saccharomyces cerevisiae)



The shorter isoform of PUS1, PUS1-2, converts uridine to pseudouridine in the anticodon stem of tRNAs in the nucleus (Fernandez-Vizarra et al. 2007, Sibert et al. 2008). The longer isoform of PUS1 (PUS1-1) is present in mitochondria; a shorter isoform of PUS1 (PUS1-2) possessing a different N-terminus is present in the nucleus (Fernandez-Vizarra et al. 2007). In contrast, the yeast Saccharomyces cerevisiae has 2 genes: PUS1 which encodes the nuclear enzyme and PUS2 which encodes the mitochodrial enzyme. PUS1 and its substrates are conserved from yeast to humans. Like the yeast homologue, Pus1p, human PUS1 may also act on additional tRNAs, pre-tRNAs, and U2 snRNA. Mutations in PUS1 cause mitochondrial myopathy and sideroblastic anemia (MLASA) (Bykhovskaya et al. 2004, 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. ↗

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. ↗

Editions

2015-06-06	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

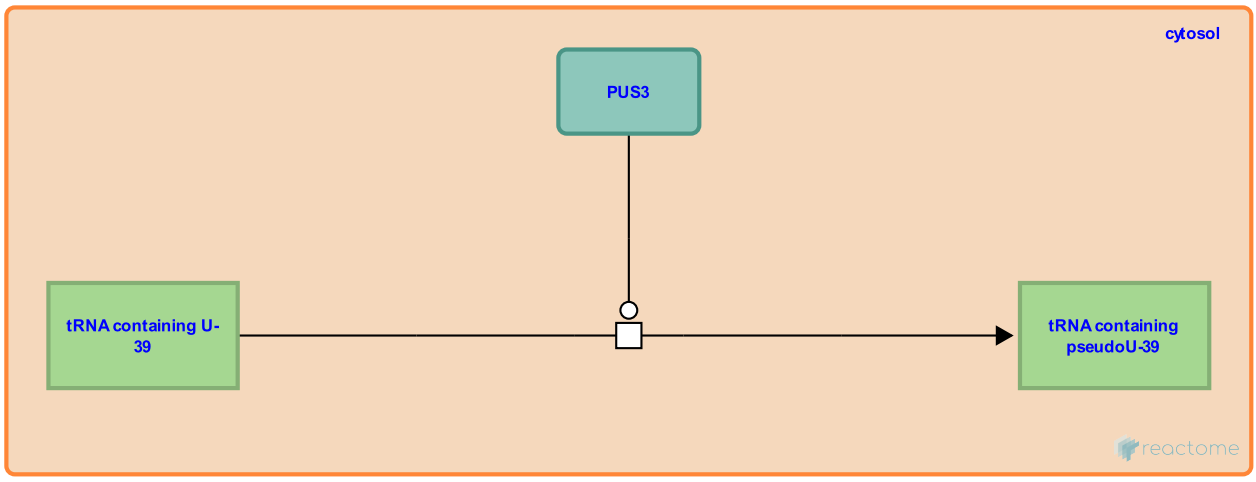
PUS3 transforms uridine-39 to pseudouridine-39 in tRNA ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-8870289

Type: transition

Compartments: cytosol



PUS3 catalyzes the modification (isomerization) of uridine to pseudouridine at nucleotides 38 and 39 in the anticodon loops of tRNAs (Shaheen et al. 2016). Homologues of PUS3 in mouse (Chen and Patton 2000) and yeast (Lecointe et al. 1998) catalyze the same reaction, and both the PUS3 gene family and the modification are highly conserved. Deletion of DEG1 encoding Pus3p in budding yeast (Saccharomyces cerevisiae) causes slow growth (Lecointe et al. 1998) while a truncating mutation in human PUS3 causes a reduction in pseudouridines 38 and 39 with consequent intellectual disability (Shaheen et al. 2016).

Literature references

Grosjean, H., Lecointe, F., Sauer, A., Motorin, Y., Simos, G., Hurt, EC. (1998). Characterization of yeast protein Deg1 as pseudouridine synthase (Pus3) catalyzing the formation of psi 38 and psi 39 in tRNA anticodon loop. *J. Biol. Chem., 273*, 1316-23. ↗

Phizicky, EM., Faqeih, E., Alobeid, E., Han, L., Ewida, N., Shaheen, R. et al. (2016). A homozygous truncating mutation in PUS3 expands the role of tRNA modification in normal cognition. *Hum. Genet.*. ↗

Patton, JR., Chen, J. (2000). Pseudouridine synthase 3 from mouse modifies the anticodon loop of tRNA. *Biochemistry, 39*, 12723-30. ↗

Editions

2016-05-07	Authored, Edited	May, B.
2016-06-20	Reviewed	Alkuraya, FS., Phizicky, EM.

PUS7 transforms uridine to pseudouridine in tRNAs ↗

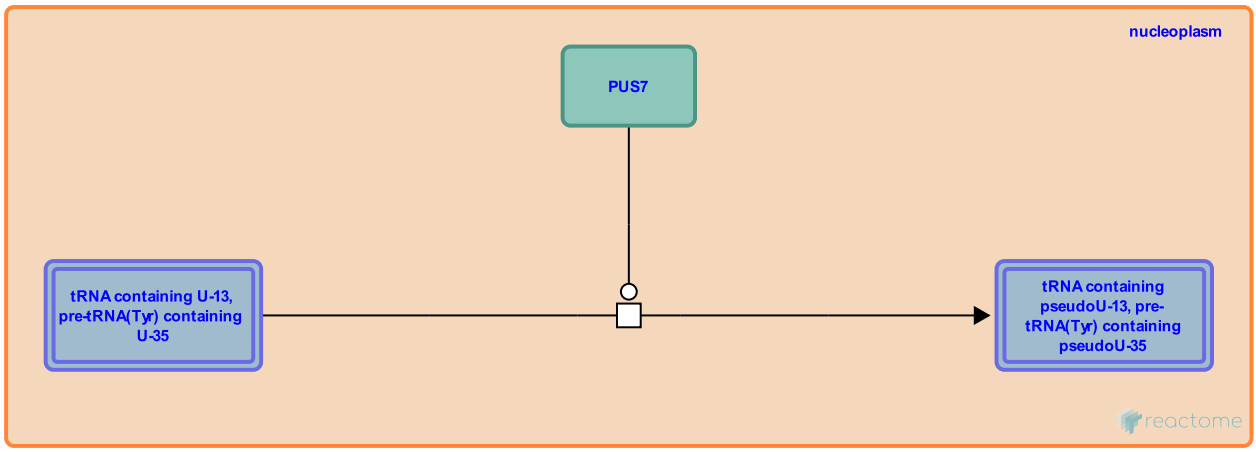
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786583

Type: transition

Compartments: nucleoplasm

Inferred from: PUS7 transforms uridine to pseudouridine at nucleotide 13 of tRNA (Saccharomyces cerevisiae)



As inferred from the homologue in Saccharmyces cerivisiae, PUS7 converts uridine to pseudouridine at nucleotide 13 of cytoplasmic tRNA and at nucleotide 35 of unspliced tRNA(Tyr). PUS7 also synthesizes pseudouridine in U2 snRNA and in pre-tRNA(Tyr). Pus7p is a nuclear protein according to global analysis of protein locations in yeast.

Editions

2015-06-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

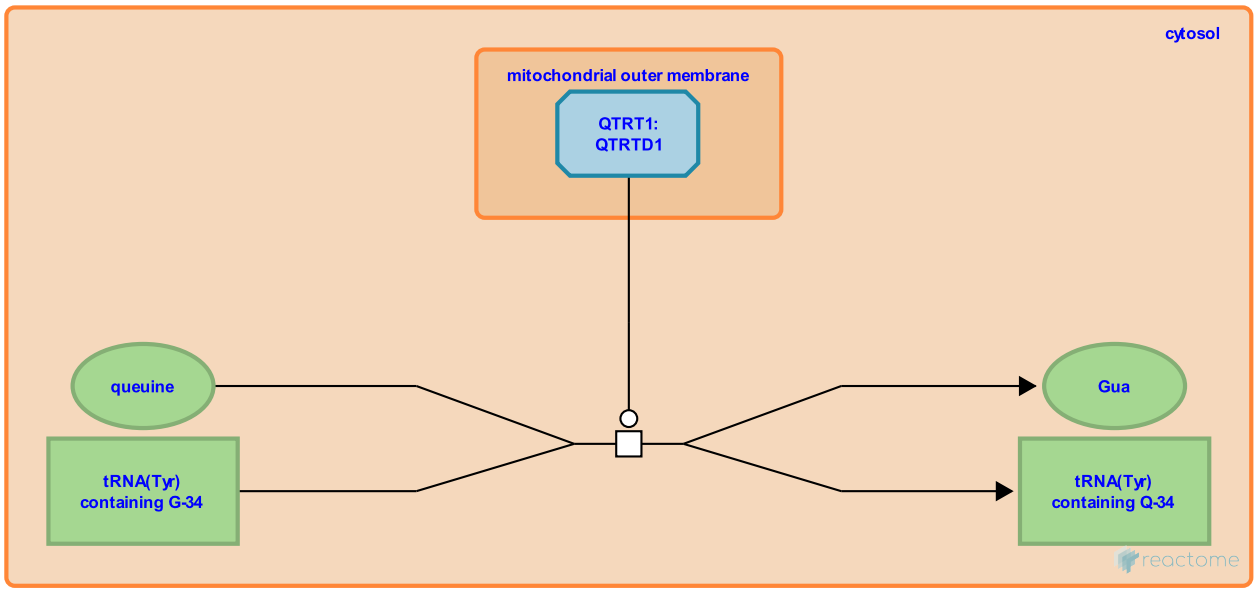
QTRT1:QTRTD1 exchange guanine for queuosine at guanosine-34 of tRNA(Tyr) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782443

Type: transition

Compartments: cytosol, mitochondrial outer membrane



The transglycosylase complex QTRT1:QTRTD1 exchanges guanine for queuine at nucleotide 34 of tRNA(Tyr) (Chen et al. 2010, Chen et al. 2011). The QTRT1 subunit is responsible for the transglycosylase activity. Eukaryotes are unable to synthesize queuine and must obtain it from dietary sources or symbiotic gut flora. As inferred from the mouse homologs, QTRT1:QTRTD1 associates with the outer mitochondrial membrane (Boland et al. 2009). The homologous enzyme in Escherichia coli is tgt.

Literature references

Kittendorf, JD., Goodenough-Lashua, DM., Garcia, GA., Brooks, AF., Chen, YC., Showalter, HD. (2011). Evolution of eukaryal tRNA-guanine transglycosylase: insight gained from the heterocyclic substrate recognition by the wild-type and mutant human and Escherichia coli tRNA-guanine transglycosylases. *Nucleic Acids Res., 39*, 2834-44. ↗

Stachura, SV., Garcia, GA., Kelly, VP., Chen, YC. (2010). Characterization of the human tRNA-guanine transglycosylase: confirmation of the heterodimeric subunit structure. *RNA, 16*, 958-68. ↗

Nishimura, S., Boland, C., Hayes, P., Kelly, VP., Santa-Maria, I. (2009). Queuosine formation in eukaryotic tRNA occurs via a mitochondria-localized heteromeric transglycosylase. *J. Biol. Chem., 284*, 18218-27. ↗

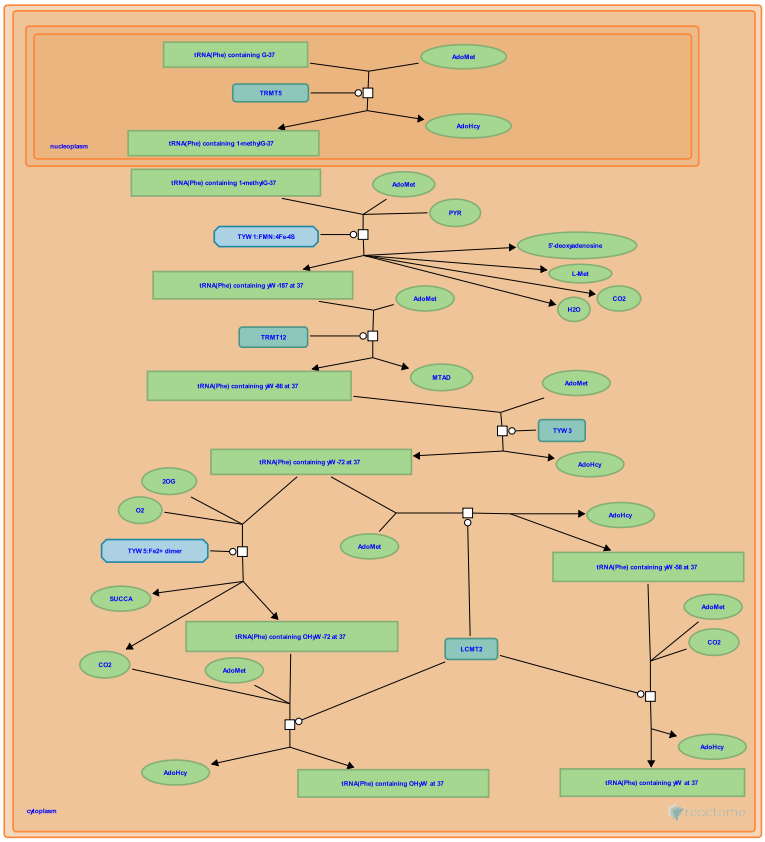
Editions

2015-06-07	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

Synthesis of wybutosine at G37 of tRNA(Phe) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782861



Derivatives of wyosine are tricyclic bases found at nucleotide 37 of tRNA(Phe) in eukaryotes. The pathway of wybutosine synthesis begins with a templated guanosine residue and proceeds through 6 steps catalyzed by 5 enzymes: N1 methylation of guanosine, condensation of 1-methylguanosine with pyruvate to yield 4-demethylwyosine, addition of an aminocarboxypropyl group to yield yW-86, methylation of yW-86 to yield yW-72, methylation of yW-72 to yield yW-58, and methoxycarbonylation of yW-58 to yield wybutosine (reviewed in Young and Bandarian 2013, Perche-Letuvée et al. 2014). Wybutosine may further be modified by hydroxylation and methylation. Wyosine derivatives at position 37 of tRNAs participate in translational fidelity by stabilizing codon-anticodon pairing (Konevega et al. 2004) and preventing frameshifting (Waas et al. 2007).

Literature references

Perche-Letuvée, P., Molle, T., Atta, M., Mulliez, E., Forouhar, F. (2014). Wybutosine biosynthesis: structural and mechanistic overview. *RNA Biol, 11*, 1508-18. ↗

Rodnina, MV., Semenkov, YP., Wintermeyer, W., Konevega, AL., Makhno, VI., Katunin, VI. et al. (2004). Purine bases at position 37 of tRNA stabilize codon-anticodon interaction in the ribosomal A site by stacking and Mg2+-dependent interactions. *RNA, 10*, 90-101. ↗

Schimmel, P., Hanan, M., Waas, WF., Druzina, Z. (2007). Role of a tRNA base modification and its precursors in frameshifting in eukaryotes. *J. Biol. Chem., 282*, 26026-34. ↗

Bandarian, V., Young, AP. (2013). Radical mediated ring formation in the biosynthesis of the hypermodified tRNA base wybutosine. *Curr Opin Chem Biol, 17*, 613-8. ↗

Editions

2015-06-08	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

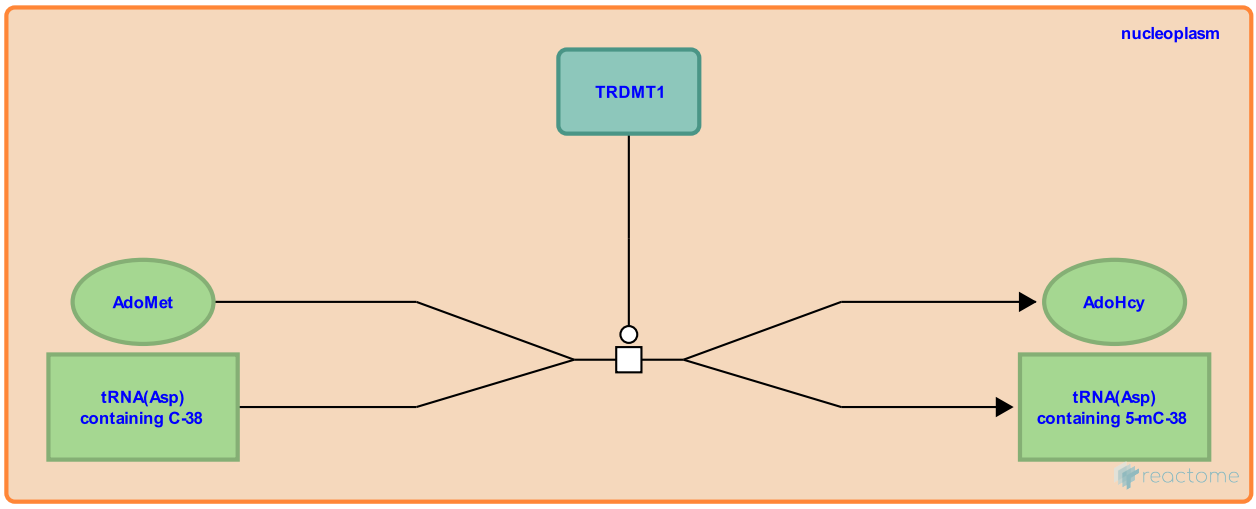
TRDMT1 (DNMT2) methylates cytidine-38 of tRNA(Asp) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782419

Type: transition

Compartments: nucleoplasm



TRDMT1 (DNMT2) transfers a methyl group from S-adenosylmethionine to the 5 position of cytidine-38 of tRNA(Asp) (Goll et al. 2006, Jurkowski et al. 2008, Jurkowski et al. 2012). TRDMT1 uses a similar mechanism to DNA methyltransferases (DNMT1, DNMT3A, DNMT3B) (Jurkowski et al. 2008).

Literature references

Maggert, KA., Golic, KG., Yoder, JA., Kirpekar, F., Hsieh, CL., Zhang, X. et al. (2006). Methylation of tRNAAsp by the DNA methyltransferase homolog Dnmt2. *Science, 311*, 395-8. ↗

Nellen, W., Phalke, S., Jurkowski, TP., Reuter, G., Helm, M., Jeltsch, A. et al. (2008). Human DNMT2 methylates tRNA(Asp) molecules using a DNA methyltransferase-like catalytic mechanism. *RNA, 14*, 1663-70. ↗

Shanmugam, R., Jurkowski, TP., Helm, M., Jeltsch, A. (2012). Mapping the tRNA binding site on the surface of human DNMT2 methyltransferase. *Biochemistry, 51*, 4438-44. ↗

Editions

2015-06-07	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

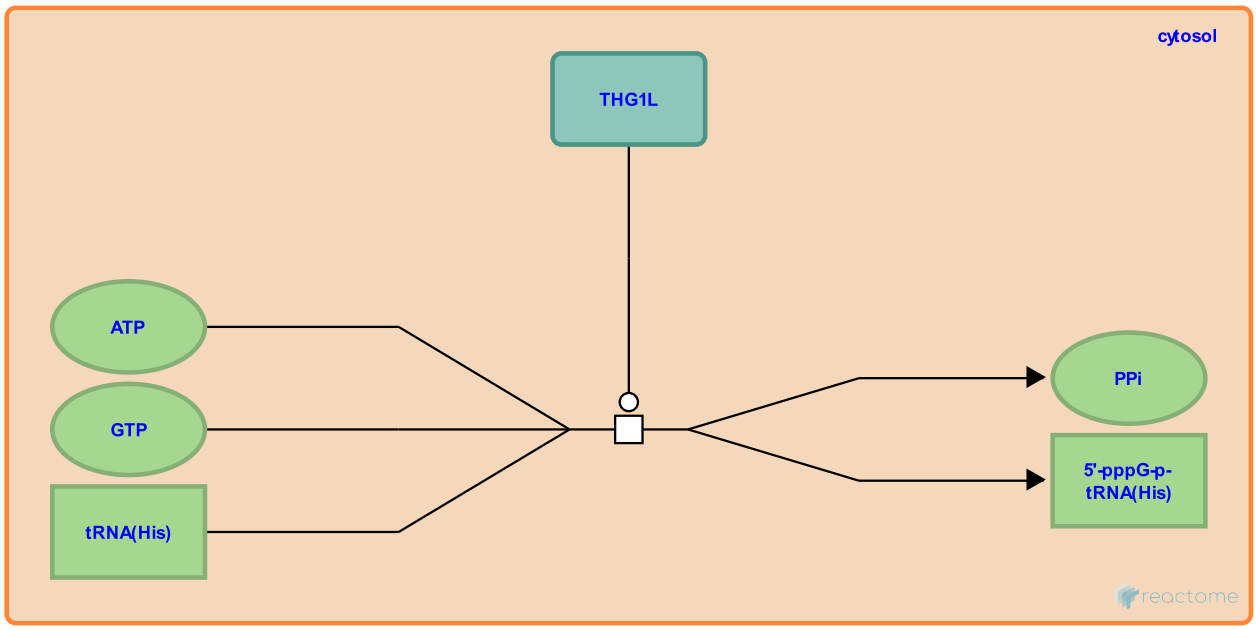
THG1L transfers GMP to 5' end of tRNA(His) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782434

Type: transition

Compartments: cytosol



THG1L (THG1) adds a guanosine triphosphate residue to the 5' end of tRNA(His), a 3'-5' addition that contrasts with the usual 5'-3' directionality of nucleotide polymerases (Hyde et al. 2010).

Literature references

Hyde, SJ., Eberley, WA., Eckenroth, BE., Heintz, NH., Doublié, S., Jackman, JE. et al. (2010). tRNA(His) guanylyl-transferase (THG1), a unique 3'-5' nucleotidyl transferase, shares unexpected structural homology with canonical 5'-3' DNA polymerases. *Proc. Natl. Acad. Sci. U.S.A., 107*, 20305-10. ↗

Editions

2015-06-07	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRIT1 transfers dimethylallyl group to adenosine-37 of tRNAs ↗

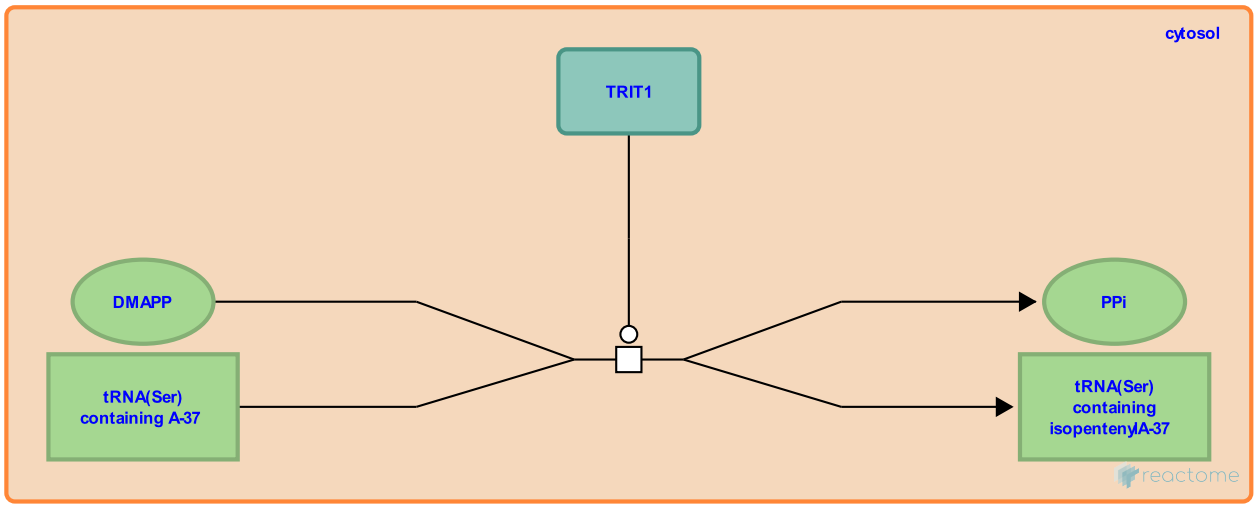
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6784462

Type: transition

Compartments: cytosol

Inferred from: MOD5 transfers dimethylallyl group to adenosine-37 of tRNA(Ser) (Saccharomyces cerevisiae)



TRIT1 transfers a dimethylallyl group (isopentenyl group) from dimethylallyl diphosphate to the N6 position of adenosine-37 in tRNA(Ser), yielding N6-dimethylallyladenosine-37 (N6-isopentenyladenosine-37) (Golovko et al. 2000, Spinola et al. 2005, Lamichhane et al. 2013, Yarham et al. 2014, Smaldino et al. 2015). TRIT1 modifies both cytosolic and mitochondrial tRNAs and a mutation in TRIT1 causes mitochondrial respiratory defects (Yarham et al. 2014). Expression of TRIT1 is down-regulated in lung adenocarcinomas compared with normal tissue (Spinola et al. 2005). The homologue in Saccharomyces cerevisiae, MOD5, catalyzes the same reaction.

Literature references

Pignatiello, C., Spinola, M., Paroni, R., Galvan, A., Nicander, B., Conti, B. et al. (2005). Identification and functional characterization of the candidate tumor suppressor gene TRIT1 in human lung cancer. *Oncogene, 24*, 5502-9. ↗

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. ↗

Engelke, DR., Smaldino, PJ., Hopper, AK., Pratt-Hyatt, M., Read, DF. (2015). The cytoplasmic and nuclear populations of the eukaryote tRNA-isopentenyl transferase have distinct functions with implications in human cancer. *Gene, 556*, 13-8. ↗

Golovko, A., Hjälm, G., Nicander, B., Sitbon, F. (2000). Cloning of a human tRNA isopentenyl transferase. *Gene, 258*, 85-93. ↗

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. ↗

Editions

2015-06-20	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

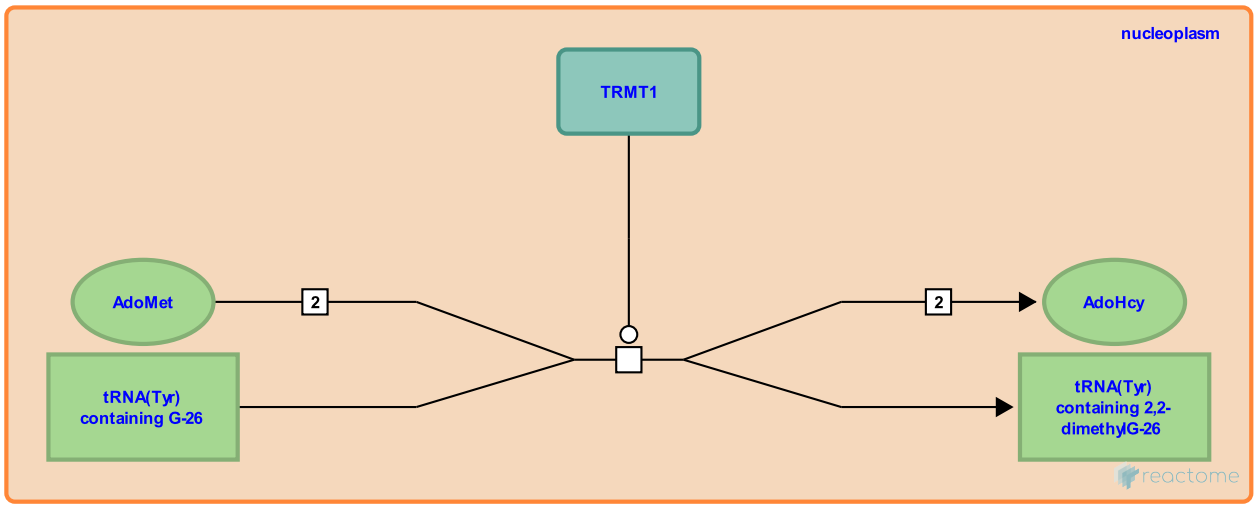
TRMT1 (hTRM1) dimethylates guanosine-26 of tRNA(Tyr) ↗

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6782416

Type: transition

Compartments: nucleoplasm



TRMT1 (hTRM1) transfers two methyl groups from two molecules of S-adenosylmethionine to the 2 position of guanosine-26 of tRNA(Tyr), yielding 2-dimethylguanosine (Liu and Straby 2000). TRMT1 can dimethylate both spliced and unspliced tRNA (Liu and Straby 2000).

Literature references

Strâby, KB., Liu, J. (2000). The human tRNA(m(2)(2)G(26))dimethyltransferase: functional expression and characterization of a cloned hTRM1 gene. *Nucleic Acids Res., 28*, 3445-51. ↗

Editions

2015-06-07	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRMT10A methylates guanosine-9 in tRNA ↗

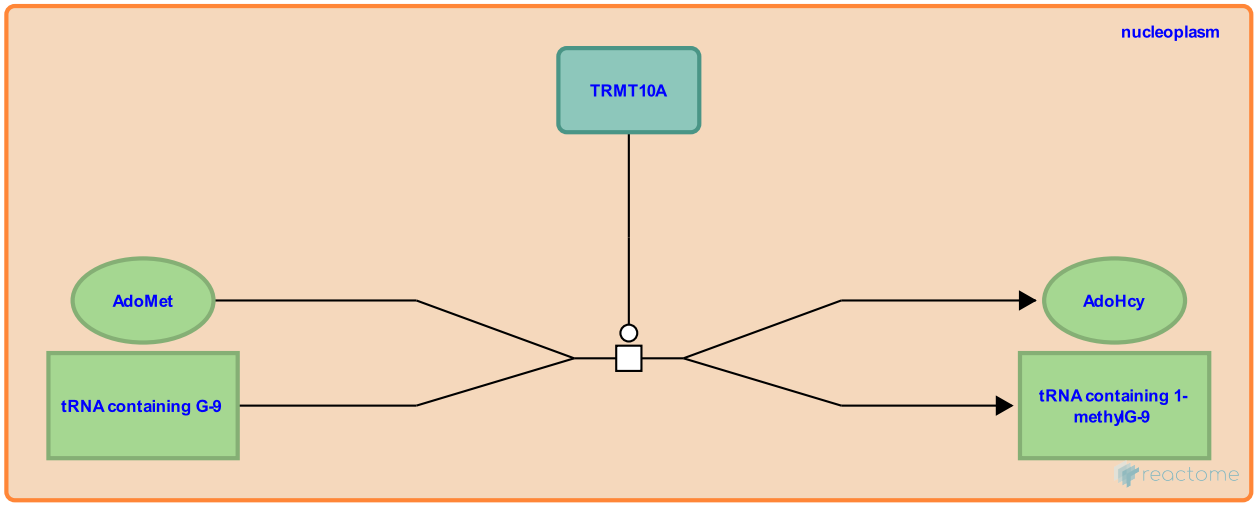
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786621

Type: transition

Compartments: nucleoplasm

Inferred from: TRM10 methylates guanosine-9 in tRNA (Saccharomyces cerevisiae)



As inferred from the homologue in Saccharomyces cerevisiae, TRMT10A methylates the 1 position of guanosine at nucleotide 9 of tRNAs. TRMT10A is located in the nucleus (Igoillo-Esteve et al. 2013). A nonsense mutation in TRMT10A causes diabetes and microcephaly (Igoillo-Esteve et al. 2013).

Literature references

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. ↗

Julier, C., Drielsma, A., Hattersley, AT., Vanderhaeghen, P., Pirson, I., Abdulkarim, B. et al. (2013). tRNA methyltransferase homolog gene TRMT10A mutation in young onset diabetes and primary microcephaly in humans. *PLoS Genet., 9*, e1003888. ↗

Editions

2015-06-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRMT11:TRMT112 methylates guanosine-10 in tRNA ↗

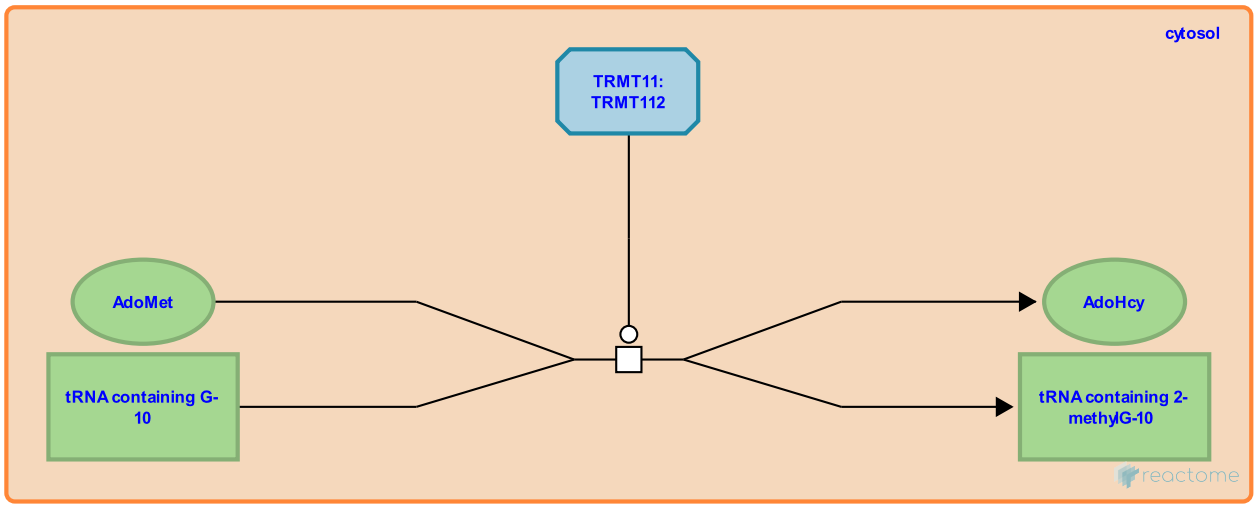
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6786501

Type: transition

Compartments: cytosol

Inferred from: TRM11:TRM112 methylates guanosine-10 in tRNA yielding N(2)-methylguanosine-10 (Saccharomyces cerevisiae)



As inferred from homologues in Saccharomyces cerevisiae, TRMT11 (catalytic subunit) and TRMT112 (zinc-binding subunit) form a complex which methylates the 2 position of guanosine-10 in tRNA (Purushothaman et al. 2005).

Editions

2015-06-30	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

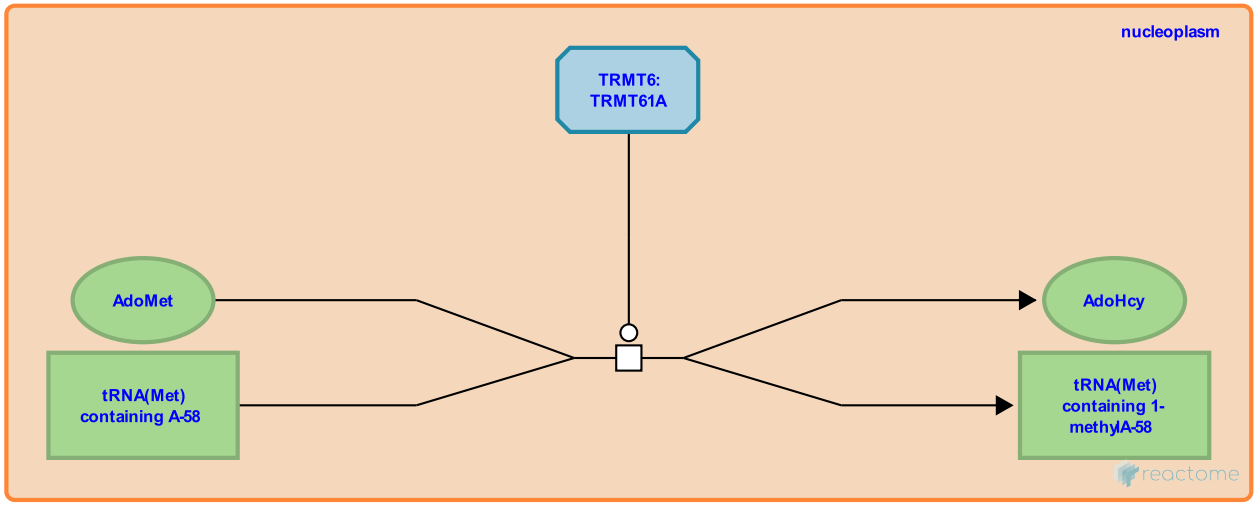
TRMT6:TRMT61A methylate adenosine yielding 1-methyladenosine at nucleotide 58 of tRNA(Met)

Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6783492

Type: transition

Compartments: nucleoplasm



The TRMT6:TRMT61A complex transfers a methyl group from S-adenosylmethionine to the 1 position of adenosine-58 of tRNA(Met) (Ozanick et al. 2005). Based on the location of the homologous complex (GCD10:GCD14) in yeast (Anderson et al. 1998), methylation by the TRMT6:TRMT61A complex is inferred to occur in the nucleus.

Literature references

Krecic, A., Ozanick, S., Anderson, JT., Andersland, J. (2005). The bipartite structure of the tRNA m1A58 methyltransferase from S. cerevisiae is conserved in humans. *RNA, 11*, 1281-90.

Anderson, J., Cuesta, R., Phan, L., Hinnebusch, AG., Björk, GR., Carlson, BA. et al. (1998). The essential Gcd10p-Gcd14p nuclear complex is required for 1-methyladenosine modification and maturation of initiator methionyl-tRNA. *Genes Dev., 12*, 3650-62.

Editions

2015-06-15	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRMT13 2'-O-methylates cytidine-4 in tRNA ↗

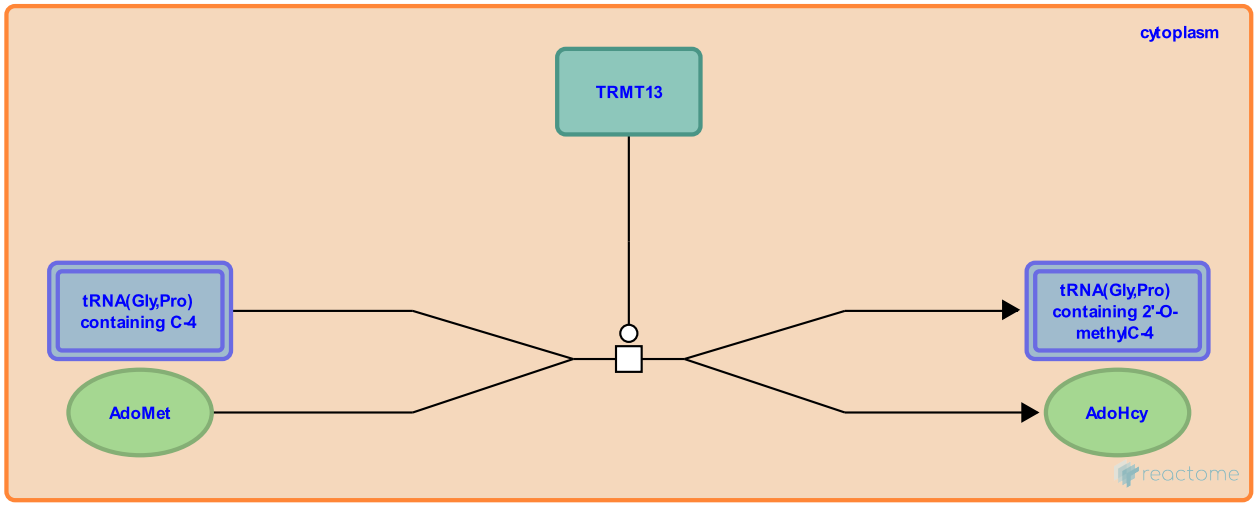
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6788684

Type: transition

Compartments: cytoplasm

Inferred from: TRM13 2'-O-methylates cytidine-4 in tRNA (Saccharomyces cerevisiae)



As inferred from the yeast homolog, TRMT13 methylates the 2' hydroxyl group of cytidine-4 in the acceptor stems of tRNA(Gly) and tRNA(Pro). The subcellular location of the reaction is unknown. Yeast lacking TRM13 do not have an obvious growth defect.

Editions

2015-07-23	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRMT13 2'-O-methylates adenosine-4 in tRNA ↗

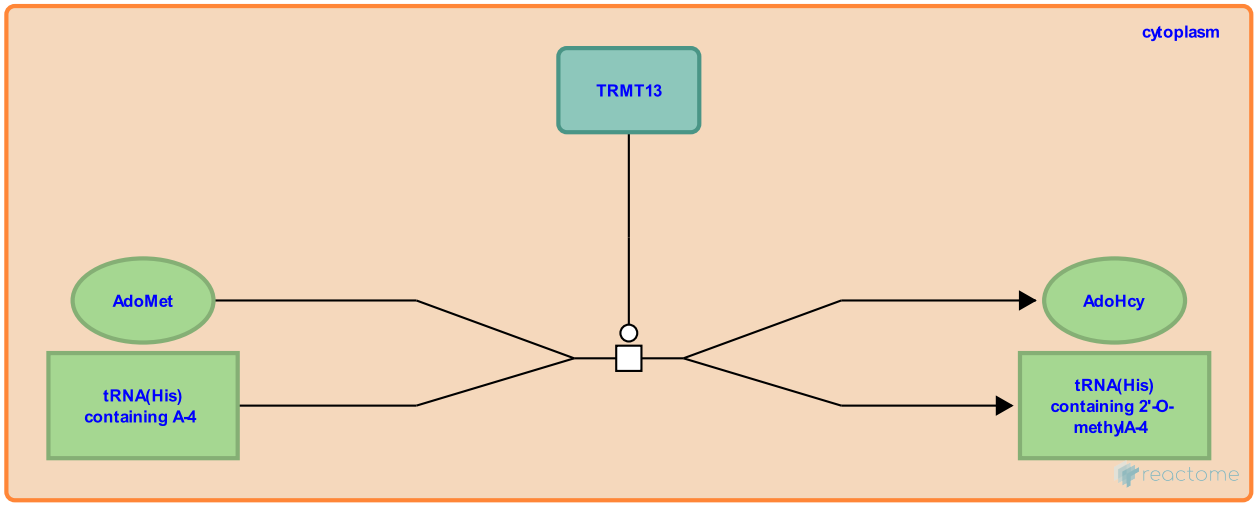
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6788668

Type: transition

Compartments: cytoplasm

Inferred from: TRM13 2'-O-methylates adenosine-4 in tRNA (Saccharomyces cerevisiae)



As inferred from the yeast homolog, TRMT13 methylates the 2' hydroxyl group of adenosine-4 in the acceptor stems of tRNA(His). The subcellular location of the reaction is unknown. Yeast lacking TRM13 do not have an obvious growth defect.

Editions

2015-07-23	Authored, Edited	May, B.
2015-08-11	Reviewed	Levinger, L.
2015-08-25	Reviewed	Motorin, Y.
2015-10-24	Reviewed	Jarrous, N.

TRMT44 2'-O-methylates uridine-44 in tRNA(Ser) ↗

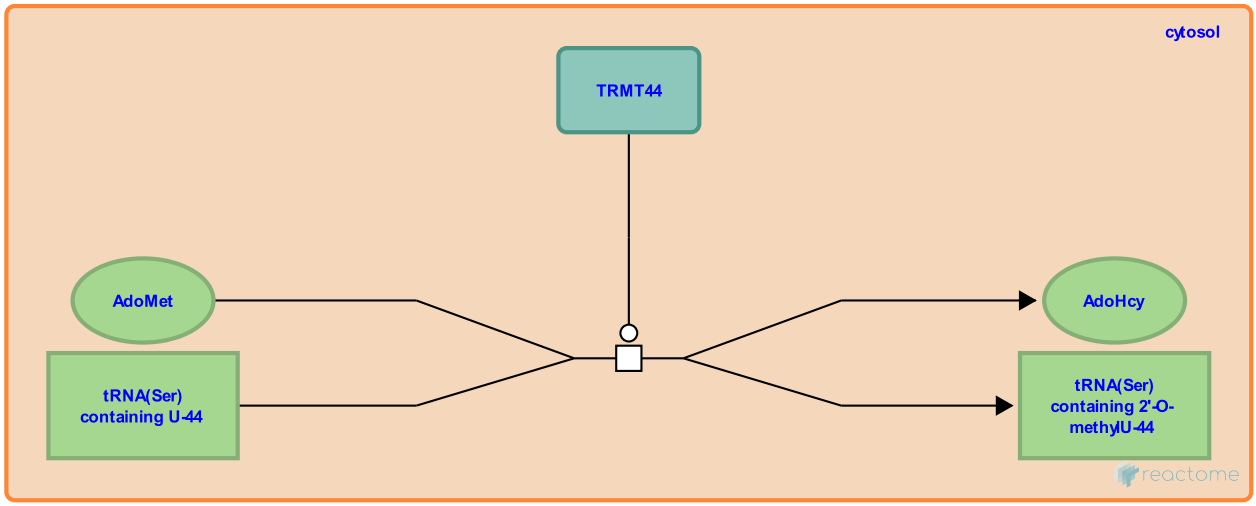
Location: tRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6788707

Type: transition

Compartments: cytosol

Inferred from: TRM44 2'-O-methylates uridine-44 in tRNA(Ser) (Saccharomyces cerevisiae)



As inferred from the yeast homolog, TRMT44 methylates the 2' hydroxyl group of uridine-44 in tRNA(Ser). In yeast 2'-O-methyluridine-44 together with N(4)-acetylcytidine appears to be required to maintain abundance of tRNA(Ser).

Editions

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