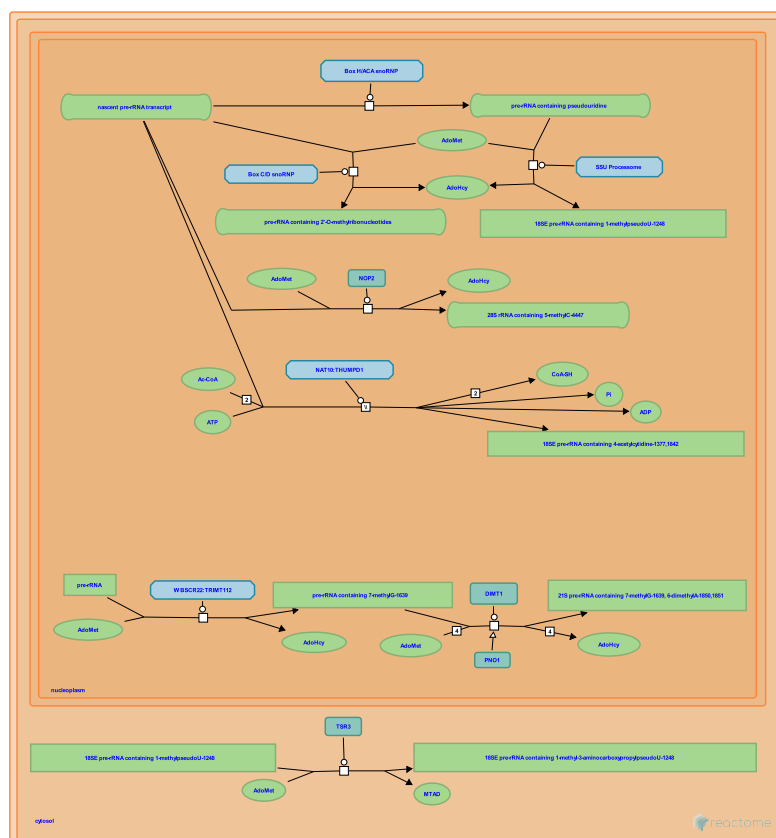


rRNA modification in the nucleus and cytosol



May, B., Sharma, S., Vincent, NG.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/faq).

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/faq).

02/05/2024

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. [↗](#)

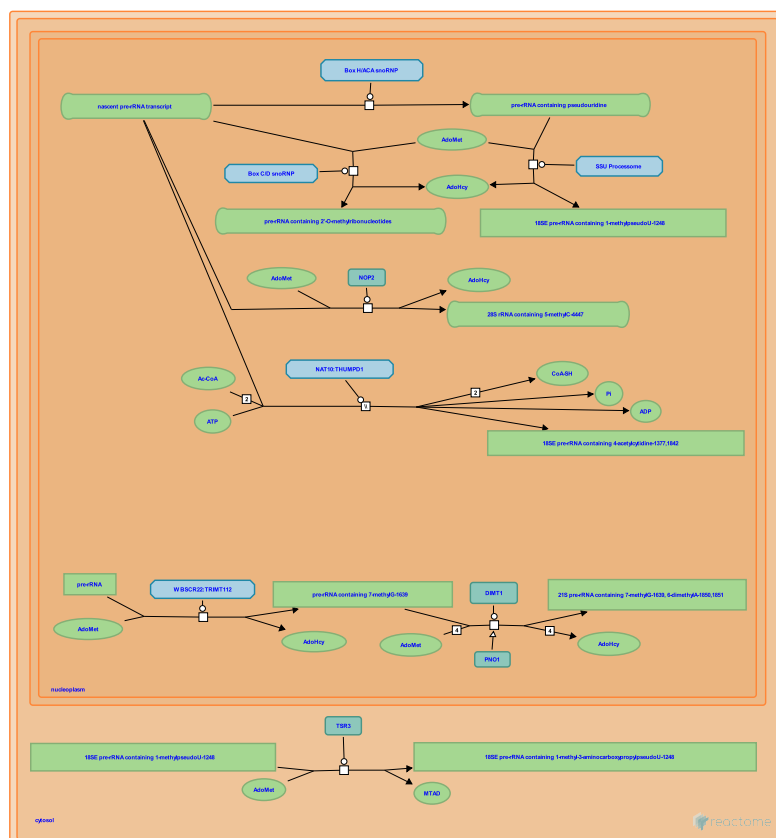
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

rRNA modification in the nucleus and cytosol ↗

Stable identifier: R-HSA-6790901



Human ribosomal RNAs (rRNAs) contain about 200 residues that are enzymatically modified after transcription in the nucleolus (Maden and Khan 1977, Maden 1988, Maden and Hughes 1997, reviewed in Hernandez-Verdun et al. 2010, Boschi-Muller and Motorin 2013). The modified residues occur in regions of the rRNAs that are located in functionally important parts of the ribosome, notably in the A and P peptidyl transfer sites, the polypeptide exit tunnel, and intersubunit contacts (Polikanov et al. 2015, reviewed in Decatur and Fournier 2002, Chow et al. 2007, Sharma and Lafontaine 2015). The two most common modifications are pseudouridines and 2'-O-methylribonucleotides. Formation of pseudouridine from encoded uridine is catalyzed by box H/ACA small nucleolar ribonucleoprotein (snoRNP) complexes (reviewed in Hamma and Ferre-D'Amare 2010, Watkins and Bohnsack 2011, Ge and Yu 2013, Kierzek et al. 2014, Yu and Meier 2014) and methylation of the hydroxyl group of the 2' carbon is catalyzed by box C/D snoRNPs (Kiss-Laszlo et al. 1996, Lapinaite et al. 2013, reviewed in Watkins and Bohnsack 2011). The snoRNP complexes contain common sets of protein subunits and unique snoRNAs that guide each complex to its target nucleotide of the rRNA by base-pairing between the snoRNA and the rRNA (reviewed in Henras et al. 2004, Watkins and Bohnsack 2011). Other modifications of rRNA include 5-methylcytidine (reviewed in Squires and Preiss 2010), 1-methylpseudouridine, 7-methylguanosine, 6-dimethyladenosine, and 4-acetylcytidine (reviewed in Sharma and Lafontaine 2015). In yeast most modifications are introduced co-transcriptionally (Kos and Tollervy 2010, reviewed in Turowski and Tollervy 2015), however the order of modification events and pre-rRNA cleavage events is not well characterized.

Literature references

- Fournier, MJ., Decatur, WA. (2002). rRNA modifications and ribosome function. *Trends Biochem. Sci.*, 27, 344-51. ↗
- Kierzek, R., Gdaniec, Z., Turner, DH., Kierzek, E., Lisowiec, J., Malgowska, M. (2014). The contribution of pseudouridine to stabilities and structure of RNAs. *Nucleic Acids Res.*, 42, 3492-501. ↗
- Turowski, TW., Tollervy, D. (2015). Cotranscriptional events in eukaryotic ribosome synthesis. *Wiley Interdiscip Rev RNA*, 6, 129-39. ↗
- Maden, BE. (1988). Locations of methyl groups in 28 S rRNA of *Xenopus laevis* and man. Clustering in the conserved core of molecule. *J. Mol. Biol.*, 201, 289-314. ↗

Sharma, S., Lafontaine, DL. (2015). 'View From A Bridge': A New Perspective on Eukaryotic rRNA Base Modification. *Trends Biochem. Sci.*, 40, 560-75. [↗](#)

Editions

2015-08-12	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

Box C/D snoRNP methylates ribonucleotides in pre-rRNA yielding 2'-O-methylribonucleotides ↗

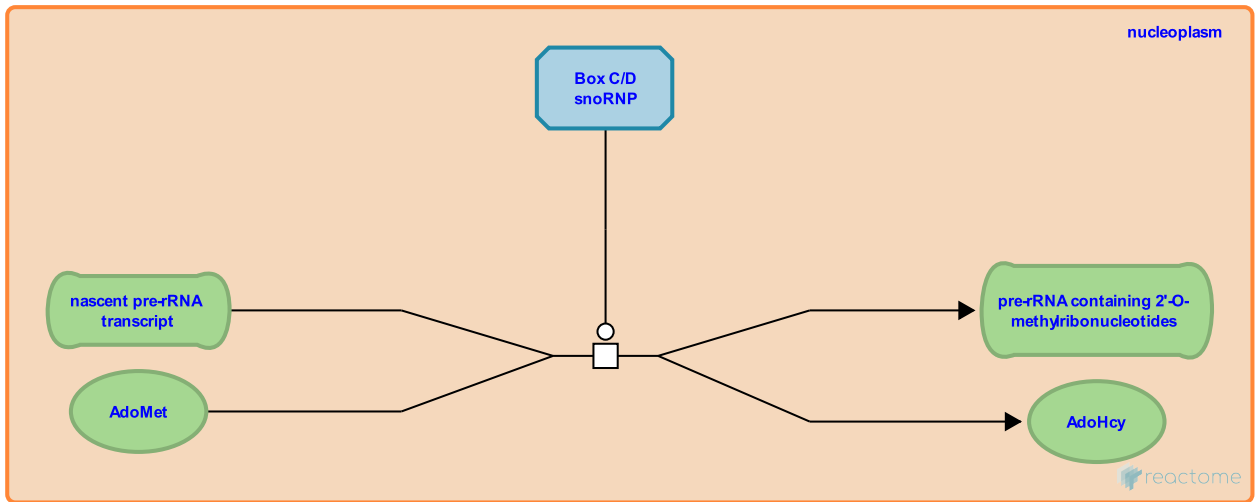
Location: rRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6790907

Type: transition

Compartments: nucleoplasm

Inferred from: Box C/D snoRNP methylates ribonucleotides in pre-rRNA (*Saccharomyces cerevisiae*)



The Fibrillarin (FBL) component of Box C/D small nucleolar ribonucleoprotein complexes (snoRNPs) transfers a methyl group from s-adenosylmethionine to the 2' hydroxyl group of ribonucleotides in precursor rRNAs (pre-rRNAs) in the nucleolus (Maden and Hughes 1997, inferred from mouse homologs in Cavaille and Bachellerie 1998, and inferred from homologues in *Saccharomyces cerevisiae*). The box C/D snoRNA component of the complex guides the methylation by base pairing with 10-21 nucleotide regions of the pre-rRNA (Filippova et al. 2015, inferred from mouse homologs in Cavaille and Bachellerie 1998). The protein components of the core box C/D snoRNP are FBL (homologous to NOP1 in yeast), NOP56, NOP58, and NHP2L1 (15.5K, homologous to SNU13 of yeast) (Lyman et al. 1999, Watkins et al. 2000, Watkins et al. 2002, Schultz et al. 2006, McKeegan et al. 2007). More than 100 nucleotide positions in human rRNAs are 2'-O-methylated and the human genome encodes more than 250 box C/D snoRNAs (Lestrade and Weber 2006), which are 50-300 nucleotides in length and contain box C (RUGAGA) and box D (CUGA) elements.

Literature references

Lührmann, R., Schultz, A., Nottrott, S., Watkins, NJ. (2006). Protein-protein and protein-RNA contacts both contribute to the 15.5K-mediated assembly of the U4/U6 snRNP and the box C/D snoRNPs. *Mol. Cell. Biol.*, 26, 5146-54. ↗

Debieux, CM., Boulon, S., Watkins, NJ., Bertrand, E., McKeegan, KS. (2007). A dynamic scaffold of pre-snoRNP factors facilitates human box C/D snoRNP assembly. *Mol. Cell. Biol.*, 27, 6782-93. ↗

Weber, MJ., Lestrade, L. (2006). snoRNA-LBME-db, a comprehensive database of human H/ACA and C/D box snoRNAs. *Nucleic Acids Res.*, 34, D158-62. ↗

Lyman, SK., Gerace, L., Baserga, SJ. (1999). Human Nop5/Nop58 is a component common to the box C/D small nucleolar ribonucleoproteins. *RNA*, 5, 1597-604. ↗

Lührmann, R., Rosbash, M., Branlant, C., Charpentier, B., Wilm, M., Bachi, A. et al. (2000). A common core RNP structure shared between the small nucleolar box C/D RNPs and the spliceosomal U4 snRNP. *Cell*, 103, 457-66. ↗

Editions

2015-08-12	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

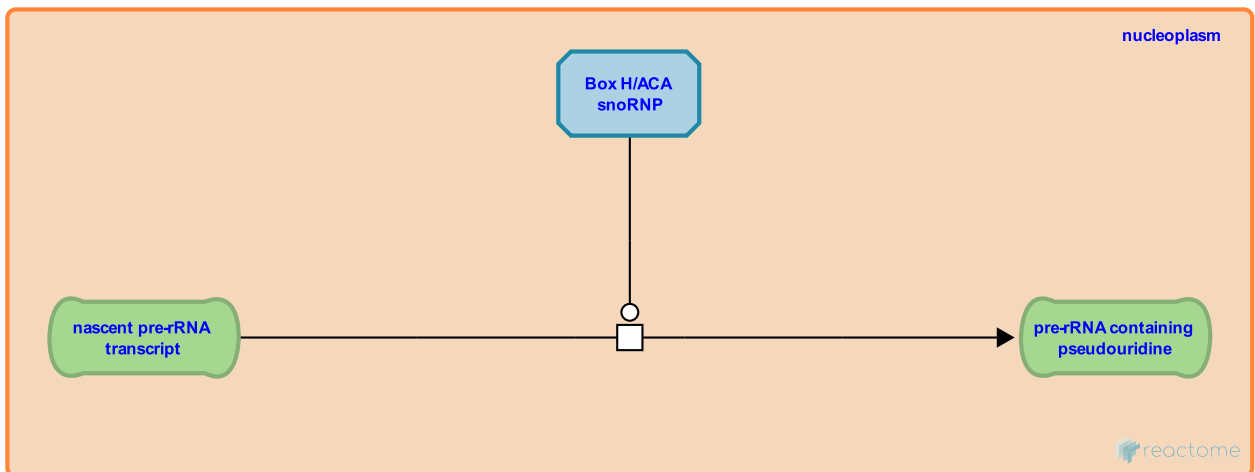
Box H/ACA snoRNP transforms uridine to pseudouridine in pre-rRNA ↗

Location: [rRNA modification in the nucleus and cytosol](#)

Stable identifier: R-HSA-6790905

Type: transition

Compartments: nucleoplasm



Box H/ACA snoRNP complexes convert uridine to pseudouridine at 97 sites in human 28S, 18S, and 5.8S rRNAs (Kiss et al. 2004, reviewed in Ge and Yu 2013). The box H/ACA snoRNA component guides the complex to specific residues of the rRNAs by base pairing between the regions of the snoRNA and the rRNA (Kiss et al. 2004, Xiao et al. 2009). The human genome encodes more than 80 box H/ACA snoRNAs (Lestrade and Weber 2006).

Followed by: [EMG1 of the SSU processome methylates pseudouridine-1248 of 18S rRNA yielding N\(1\)-methylpseudouridine-1248](#)

Literature references

Schattner, P., Yang, C., Yu, YT., Xiao, M. (2009). Functionality and substrate specificity of human box H/ACA guide RNAs. *RNA*, 15, 176-86. ↗

Weber, MJ., Lestrade, L. (2006). snoRNA-LBME-db, a comprehensive database of human H/ACA and C/D box snoRNAs. *Nucleic Acids Res.*, 34, D158-62. ↗

Kiss, AM., Kiss, T., Bertrand, E., Jády, BE. (2004). Human box H/ACA pseudouridylation guide RNA machinery. *Mol. Cell. Biol.*, 24, 5797-807. ↗

Yu, YT., Ge, J. (2013). RNA pseudouridylation: new insights into an old modification. *Trends Biochem. Sci.*, 38, 210-8. ↗

Editions

2015-08-12	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

NOP2 (NSUN1) methylates cytidine-4447 of 28S rRNA yielding 5-methylcytidine-4447



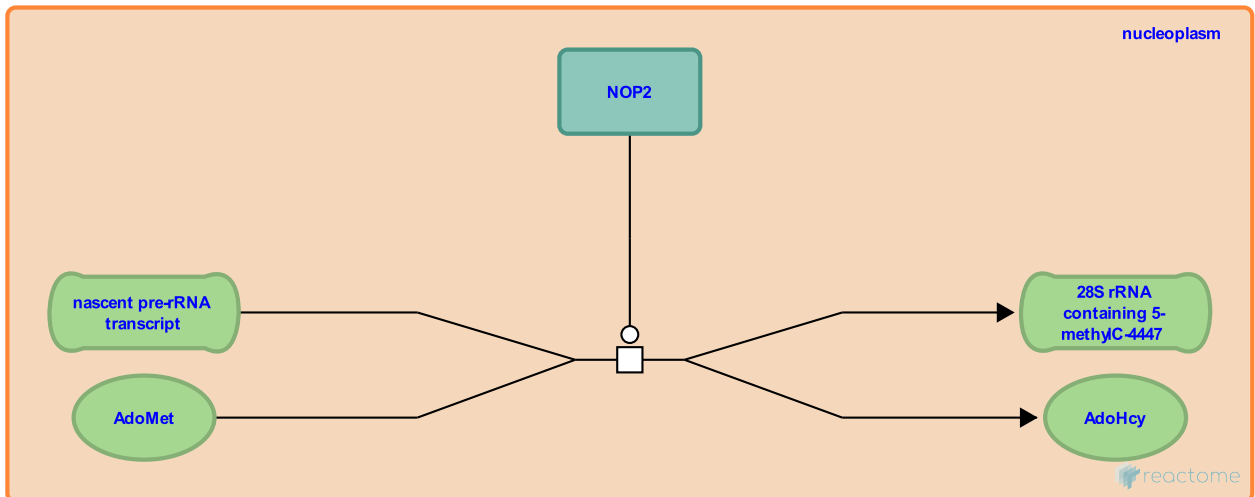
Location: rRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6790944

Type: transition

Compartments: nucleoplasm

Inferred from: NOP2 methylates cytosine-2870 of 25S rRNA yielding 5-methylcytosine-2870 (*Saccharomyces cerevisiae*)



NOP2 methylates the carbon at the 5th position of the cytosine ring at cytidine-4447 in 28S rRNA (Bourgeois et al. 2015). NOP2 also has a role in rRNA processing that is independent of its methylase activity.

Literature references

Schaefer, M., Ney, M., Kellner, S., Motorin, Y., Aigueperse, C., Bourgeois, G. et al. (2015). Eukaryotic rRNA Modification by Yeast 5-Methylcytosine-Methyltransferases and Human Proliferation-Associated Antigen p120. *PLoS ONE*, 10, e0133321. [↗](#)

Editions

2015-08-15	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

EMG1 of the SSU processome methylates pseudouridine-1248 of 18S rRNA yielding N(1)-methylpseudouridine-1248 ↗

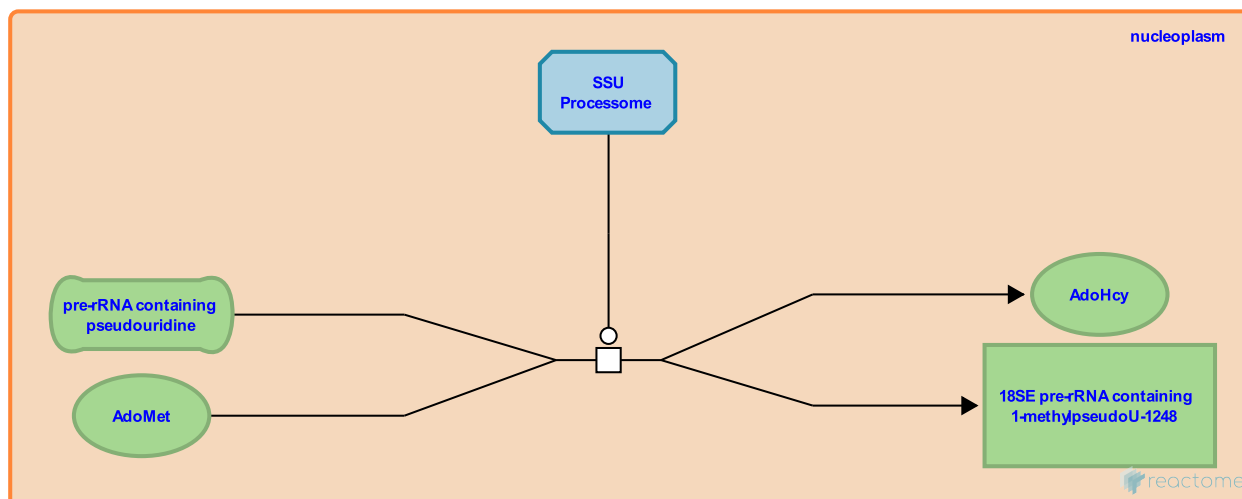
Location: [rRNA modification in the nucleus and cytosol](#)

Stable identifier: R-HSA-6790906

Type: transition

Compartments: nucleoplasm

Inferred from: [EMG1 of the SSU processome methylates pseudouridine-1191 of 18S rRNA yielding N\(1\)-methylpseudouridine-1191 \(Saccharomyces cerevisiae\)](#)



EMG1 (NEP1) methylates a pseudouridine residue in precursor rRNA (pre-rRNA) to yield N(1)-methylpseudouridine (Wurm et al. 2010 and inferred from the yeast homolog) in the nucleolus (Eschrich et al. 2002). Following further modification and nucleolytic processing, the N(1)-methylpseudouridine residue will become N1-methyl-N3-(3-amino-3-carboxypropyl) pseudouridine-1248 of the 18S rRNA. A mutation in EMG1 causes Bowen-Conradi Syndrome, which is characterized by growth retardation, microcephaly, severe psychomotor delay, and minor external abnormalities (Armistead et al. 2009). As inferred from the yeast homolog, EMG1 is a component of the small subunit processome (SSU processome) a large complex of proteins that binds the 5' region of pre-rRNA, processes and modifies the 18S rRNA, and assists the assembly of the small ribosomal subunit.

Preceded by: [Box H/ACA snoRNP transforms uridine to pseudouridine in pre-rRNA](#)

Followed by: [TSR3 transfers aminocarboxypropyl group from S-adenosylmethionine to N\(1\)-methylpseudouridine-1248 of 18SE rRNA yielding N\(1\)-methyl-N\(3\)-aminocarboxypropylpseudouridine-1248](#)

Literature references

- Triggs-Raine, B., Cattini, PA., Wrogemann, K., Meyer, B., Greenberg, CR., Khatkar, S. et al. (2009). Mutation of a gene essential for ribosome biogenesis, EMG1, causes Bowen-Conradi syndrome. *Am. J. Hum. Genet.*, 84, 728-39. ↗
- Kötter, P., Eschrich, D., Buchhaupt, M., Entian, KD. (2002). Nep1p (Emg1p), a novel protein conserved in eukaryotes and archaea, is involved in ribosome biogenesis. *Curr. Genet.*, 40, 326-38. ↗
- Kötter, P., Held, M., Wurm, JP., Bahr, U., Wöhnert, J., Engels, JW. et al. (2010). The ribosome assembly factor Nep1 responsible for Bowen-Conradi syndrome is a pseudouridine-N1-specific methyltransferase. *Nucleic Acids Res.*, 38, 2387-98. ↗

Editions

2015-08-15	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

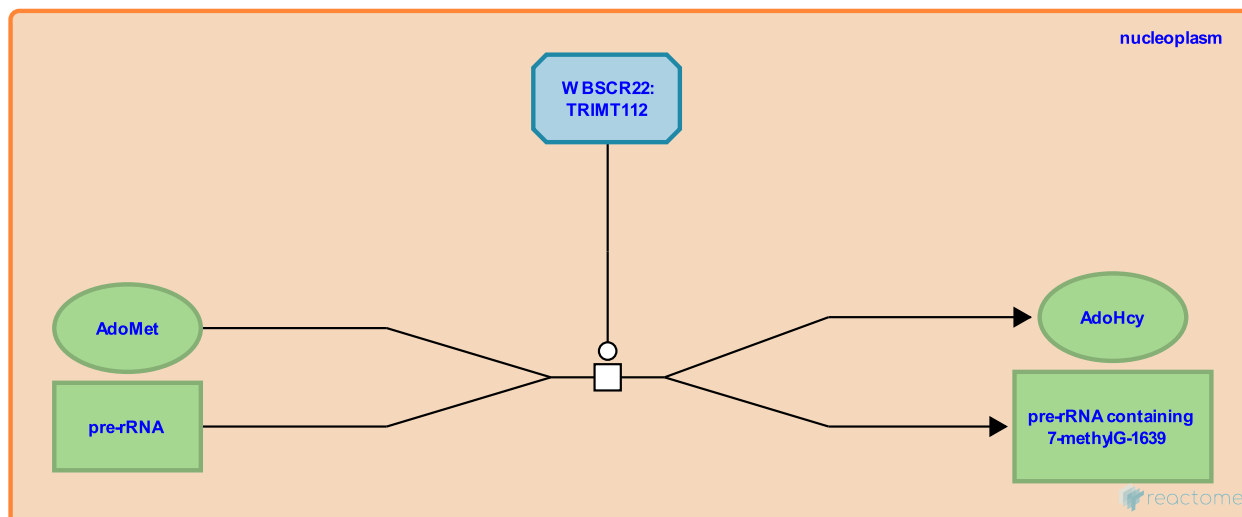
WBSCR22:TRMT112 methylates guanosine-1639 of 18S rRNA yielding 7-methyl-guanosine-1639 ↗

Location: rRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6790982

Type: transition

Compartments: nucleoplasm



The WBSCR22:TRMT112 complex, homolog of the Bud23:Trm112 complex in yeast (Ounap et al. 2013), methylates guanosine-1639 of 18S rRNA at the N(7) position of the guanine base (Haag et al. 2015, Zorbas et al. 2015). The WBSCR22:TRMT112 complex but not its methylase activity is required for efficient processing of precursor rRNA at site 2 and site 3 (Haag et al. 2015, Zorbas et al. 2015). Hemizygosity at the region containing WBSCR22 causes Williams-Beuren syndrome (Doll and Grzeschik 2001).

Followed by: [DIMIT1 dimethylates adenosine-1850,1851 of 18S rRNA yielding 6-dimethyladenosine-1850,1851](#)

Literature references

- Nicolas, E., Huvelle, E., Zorbas, C., Heurgué-Hamard, V., Wacheul, L., Lafontaine, DL. (2015). The human 18S rRNA base methyltransferases DIMIT1L and WBSCR22-TRMT112 but not rRNA modification are required for ribosome biogenesis. *Mol. Biol. Cell*, 26, 2080-95. ↗
- Kurg, A., Kurg, R., Öunap, K., Käsper, L. (2013). The human WBSCR22 protein is involved in the biogenesis of the 40S ribosomal subunits in mammalian cells. *PLoS ONE*, 8, e75686. ↗
- Haag, S., Kretschmer, J., Bohnsack, MT. (2015). WBSCR22/Merm1 is required for late nuclear pre-ribosomal RNA processing and mediates N7-methylation of G1639 in human 18S rRNA. *RNA*, 21, 180-7. ↗
- Grzeschik, KH., Doll, A. (2001). Characterization of two novel genes, WBSCR20 and WBSCR22, deleted in Williams-Beuren syndrome. *Cytogenet. Cell Genet.*, 95, 20-7. ↗

Editions

2015-08-15	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

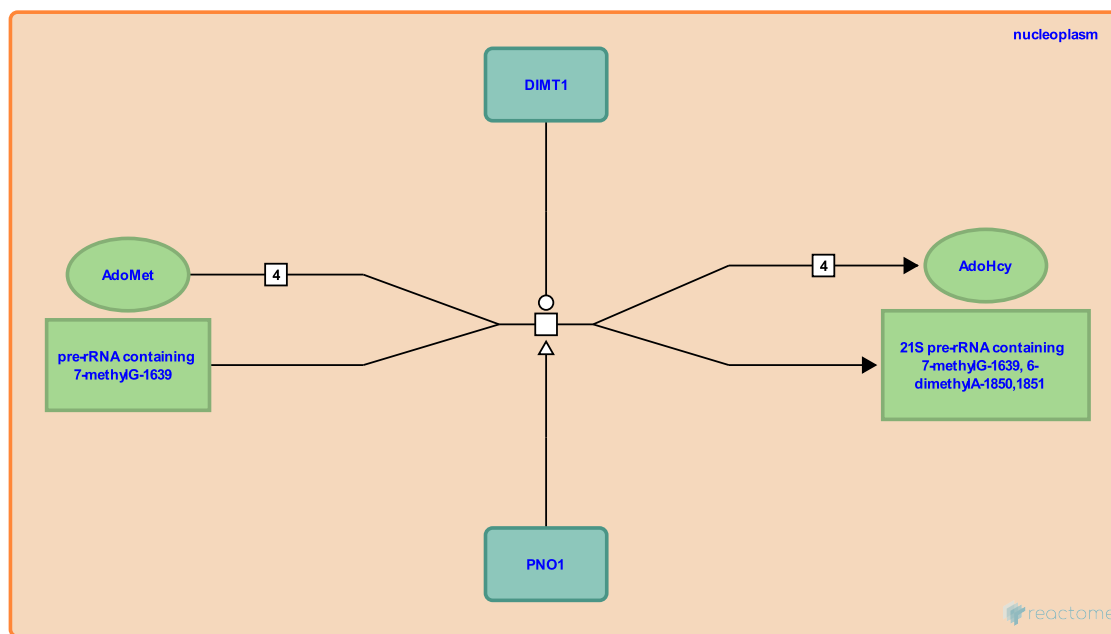
DIMT1 dimethylates adenosine-1850,1851 of 18S rRNA yielding 6-dimethyladenosine-1850,1851 ↗

Location: rRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6790994

Type: transition

Compartments: nucleoplasm



DIMT1 (DIMT1L) dimethylates the N(6) position of adenosine-1850 and adenosine-1851 of a precursor to 18S rRNA in the nucleolus (Zorbas et al. 2015). Dimethylation is observed on the 21S precursor and therefore occurs at this stage of rRNA processing or prior. Dimethylation of adenosine residues appears to occur after N(7)-methylation of guanosine-1639 by WBSCR22:TRMT112 (Zorbas et al. 2015). PNO1 is required for the methylation activity of DIMT1 (Zorbas et al. 2015). DIMT1 protein but not DIMT1 methylase activity is also required for efficient concomitant cleavage of 47S precursor rRNA at site A0 and site 1 (Zorbas et al. 2015).

Preceded by: WBSCR22:TRMT112 methylates guanosine-1639 of 18S rRNA yielding 7-methylguanosine-1639

Literature references

Nicolas, E., Huvelle, E., Zorbas, C., Heurgué-Hamard, V., Wacheul, L., Lafontaine, DL. (2015). The human 18S rRNA base methyltransferases DIMT1L and WBSCR22-TRMT112 but not rRNA modification are required for ribosome biogenesis. *Mol. Biol. Cell*, 26, 2080-95. ↗

Editions

2015-08-15	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

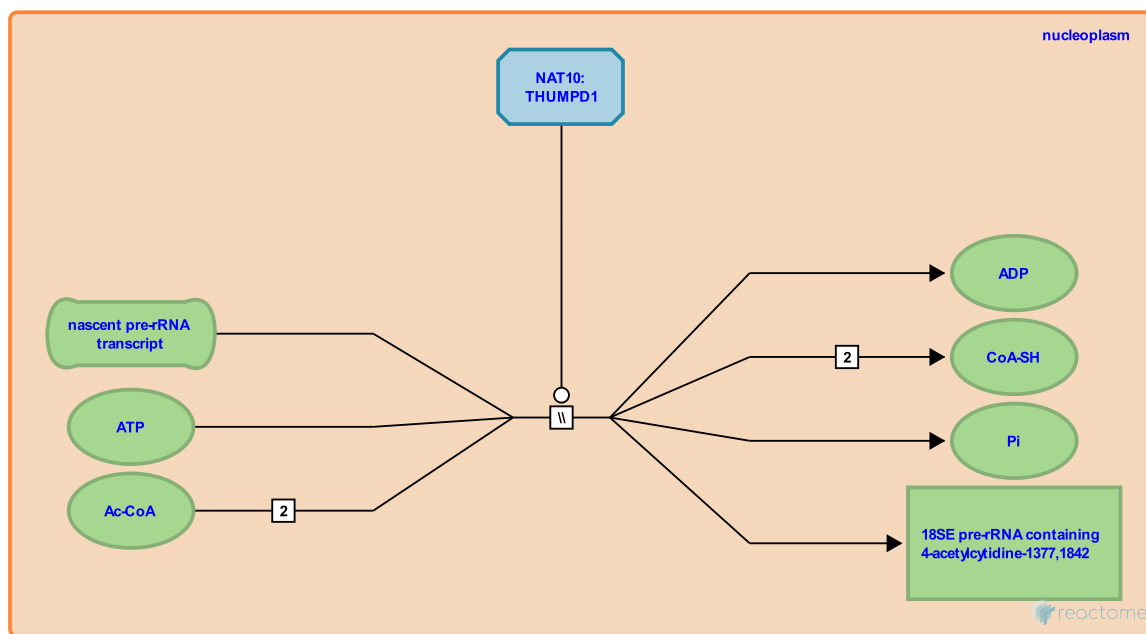
NAT10 acetylates cytidine-1337 and cytidine-1842 of 18S rRNA yielding 4-acetylcytidine-1377 and 4-acetylcytidine-1842 ↗

Location: rRNA modification in the nucleus and cytosol

Stable identifier: R-HSA-6790987

Type: omitted

Compartments: nucleoplasm, cytosol



NAT10 transfers an acetyl group from acetyl coenzyme A to the N4 positions of the residues that will become cytidine 1337 and cytidine-1842 in 18S rRNA (Ito et al. 2014, Sharma et al. 2015). (The point at which NAT10 acts during rRNA nucleolytic processing is unknown.) NAT10 also hydrolyzes ATP, presumably to provide helicase activity for the reaction (Ito et al. 2014, Sharma et al. 2015). NAT10 in a complex with THUMPD1 also acetylates tRNAs, however THUMPD1 is not required for acetylation of rRNA (Sharma et al. 2015).

Literature references

- Suzuki, T., Tanaka, Y., Suzuki, T., Ito, S., Suzuki, T., Kawauchi, H. et al. (2014). Human NAT10 is an ATP-dependent RNA acetyltransferase responsible for N4-acetylcytidine formation in 18 S ribosomal RNA (rRNA). *J. Biol. Chem.*, 289, 35724-30. ↗
- Kötter, P., Sharma, S., Watzinger, P., Langhendries, JL., Entian, KD., Lafontaine, DL. (2015). Yeast Kre33 and human NAT10 are conserved 18S rRNA cytosine acetyltransferases that modify tRNAs assisted by the adaptor Tan1/THUMPD1. *Nucleic Acids Res.*, 43, 2242-58. ↗

Editions

2015-08-15	Authored, Edited	May, B.
2016-01-30	Reviewed	Vincent, NG.
2016-02-12	Reviewed	Sharma, S.

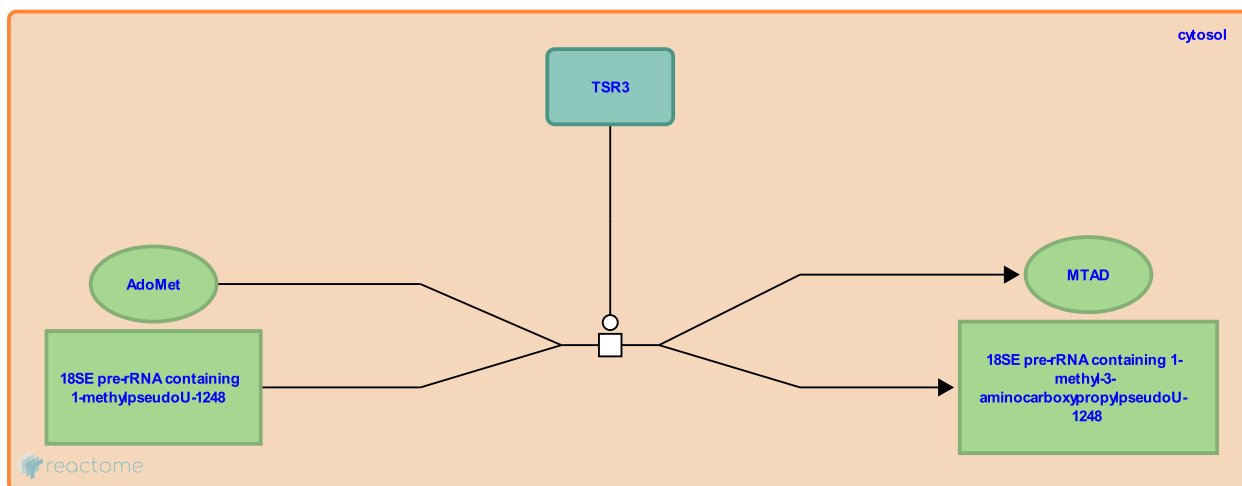
TSR3 transfers aminocarboxypropyl group from S-adenosylmethionine to N(1)-methylpseudouridine-1248 of 18SE rRNA yielding N(1)-methyl-N(3)-aminocarboxypropylpseudouridine-1248 ↗

Location: [rRNA modification in the nucleus and cytosol](#)

Stable identifier: R-HSA-8868783

Type: transition

Compartments: cytosol



In the cytoplasm TSR3 transfers an aminocarboxypropyl group from S-adenosylmethionine (AdoMet) to the N(3) position of N(1)-methylpseudouridine at nucleotide 1248 of 18S rRNA yielding N(1)-methyl-N(3)-aminocarboxypropylpseudouridine-1248 (Meyer et al. 2016). Prior to this reaction, the SNORA13 or ACA13 H/ACA snoRNP (homologue of the snR35 snoRNP in yeast) in the nucleus converts uridine-1248 to pseudouridine-1248 and the EMG1 component of the small subunit processome in the nucleus methylates the N(1) position of pseudouridine-1248. The 18SE precursor of 18S rRNA containing N(1)-methylpseudouridine is then exported to the cytosol as part of the 40S pre-ribosomal subunit. TSR3 is believed to act on the 18SE precursor rather than the mature 18S rRNA because interference with the activity of TSR3 results in an accumulation of 18SE precursor (Meyer et al. 2016).

Preceded by: [EMG1 of the SSU processome methylates pseudouridine-1248 of 18S rRNA yielding N\(1\)-methylpseudouridine-1248](#)

Literature references

Kötter, P., Wurm, JP., Wöhnert, J., Pogoryelov, D., Sharma, S., Immer, C. et al. (2016). Ribosome biogenesis factor Tsr3 is the aminocarboxypropyl transferase responsible for 18S rRNA hypermodification in yeast and humans. *Nucleic Acids Res.* ↗

Editions

2016-04-25	Authored, Edited	May, B.
2016-04-30	Reviewed	Sharma, S.

Table of Contents

Introduction	1
❏ rRNA modification in the nucleus and cytosol	2
➤ Box C/D snoRNP methylates ribonucleotides in pre-rRNA yielding 2'-O-methylribonucleotides	4
➤ Box H/ACA snoRNP transforms uridine to pseudouridine in pre-rRNA	5
➤ NOP2 (NSUN1) methylates cytidine-4447 of 28S rRNA yielding 5-methylcytidine-4447	6
➤ EMG1 of the SSU processome methylates pseudouridine-1248 of 18S rRNA yielding N(1)-methyl-pseudouridine-1248	7
➤ WBSR22:TRMT112 methylates guanosine-1639 of 18S rRNA yielding 7-methylguanosine-1639	8
➤ DIMT1 dimethylates adenosine-1850,1851 of 18S rRNA yielding 6-dimethyladenosine-1850,1851	9
❏ NAT10 acetylates cytidine-1337 and cytidine-1842 of 18S rRNA yielding 4-acetylcytidine-1337 and 4-acetylcytidine-1842	10
➤ TSR3 transfers aminocarboxypropyl group from S-adenosylmethionine to N(1)-methylpseudouridine-1248 of 18S rRNA yielding N(1)-methyl-N(3)-aminocarboxypropylpseudouridine-1248	11
Table of Contents	12