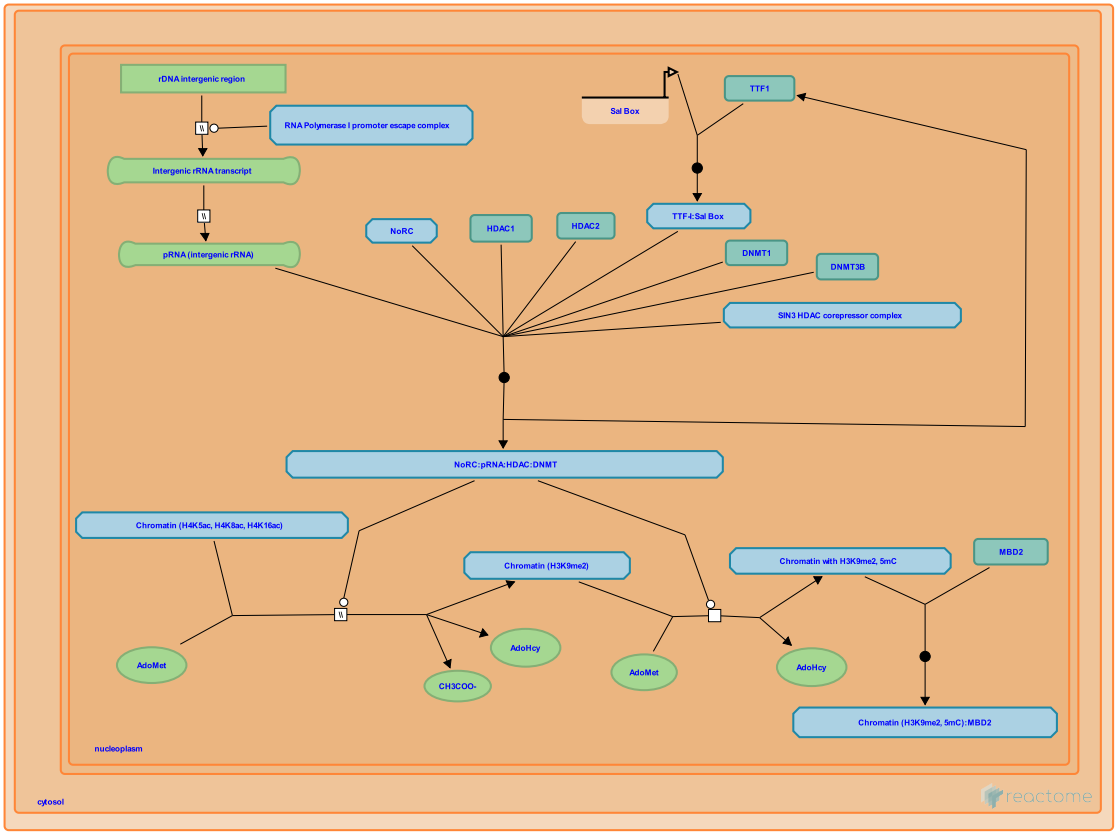
NoRC negatively regulates rRNA expression



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22/09/2024

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. ↗

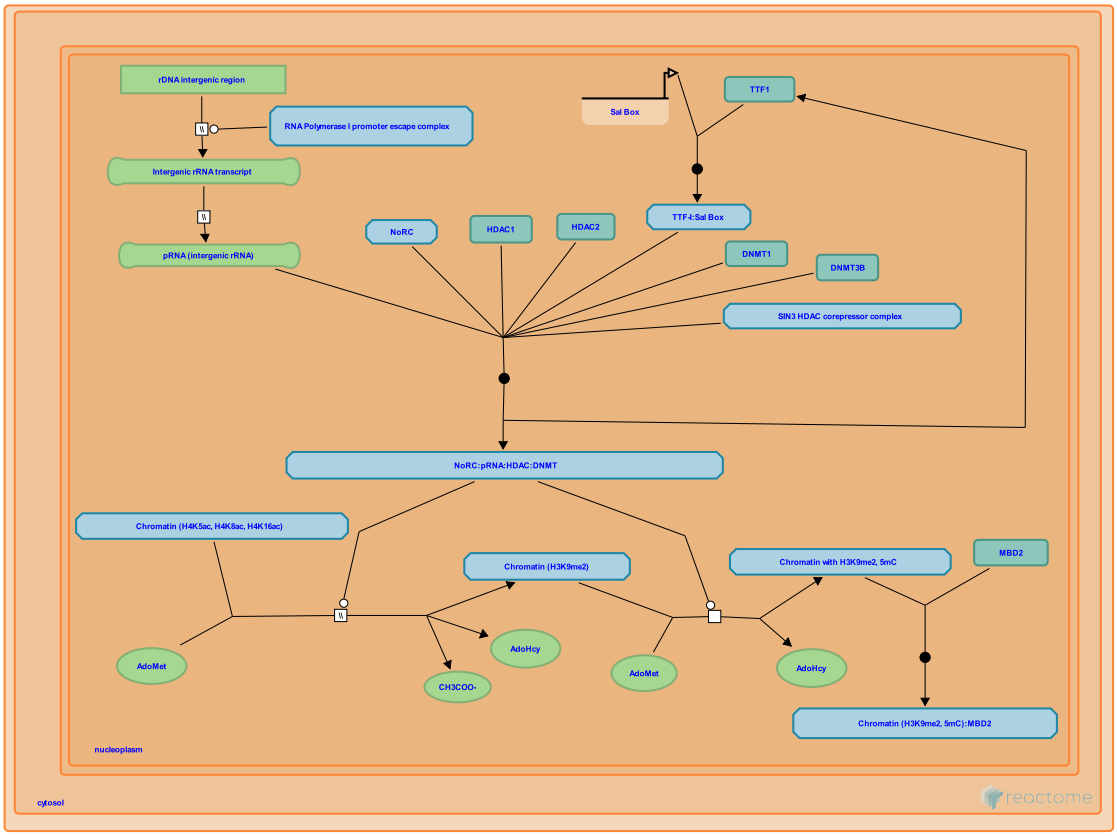
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

NoRC negatively regulates rRNA expression ↗

Stable identifier: R-HSA-427413

Compartments: nucleoplasm



The Nucleolar Remodeling Complex (NoRC) comprising TIP5 (BAZ2A) and the chromatin remodeller SNF2H (SMARCA5) silences rRNA gene (reviewed in Santoro and Grummt 2001, Grummt 2007, Preuss and Pikaard 2007, Birch and Zommerdijk 2008, McStay and Grummt 2008, Grummt and Langst 2013). The TAM domain of TIP5 (BAZ2A) binds promoter-associated RNA (pRNA) transcribed from the intergenic spacer region of rDNA. The pRNA bound by TIP5 is required to direct the complex to the main promoter of the rRNA gene possibly by triple helix formation between pRNA and the rDNA. The PHD domain of TIP5 binds histone H4 acetylated at lysine-16. Transcription Termination Factor-I (TTF-I) binds to a promoter-proximal terminator (T0 site) in the rDNA and interacts with the TIP5 subunit of NoRC. NoRC also interacts with the SIN3-HDAC complex, HDAC1, HDAC2, DNMT1, and DNMT3B. DNMT3B interacts with a triple helix formed by pRNA and the rDNA. HDAC1, DNMT1, and DNMT3B have been shown to be required for proper DNA methylation of silenced rRNA gene copies, although the catalytic activity of DNMT3B was not required.

Literature references

Grummt, I. (2007). Different epigenetic layers engage in complex crosstalk to define the epigenetic state of mammalian rRNA genes. *Hum Mol Genet, 16*, R21-7. ↗

Pikaard, CS., Preuss, S. (2007). rRNA gene silencing and nucleolar dominance: insights into a chromosome-scale epigenetic on/off switch. *Biochim Biophys Acta, 1769*, 383-92. ↗

Santoro, R., Grummt, I. (2001). Molecular mechanisms mediating methylation-dependent silencing of ribosomal gene transcription. *Mol Cell, 8*, 719-25. ↗

Grummt, I., McStay, B. (2008). The epigenetics of rRNA genes: from molecular to chromosome biology. *Annu Rev Cell Dev Biol, 24*, 131-57. ↗

Längst, G., Grummt, I. (2013). Epigenetic control of RNA polymerase I transcription in mammalian cells. *Biochim. Biophys. Acta, 1829*, 393-404. ↗

Editions

2009-06-19	Authored	May, B.
2010-04-06	Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

Transcription of intergenic spacer of the rRNA gene ↗

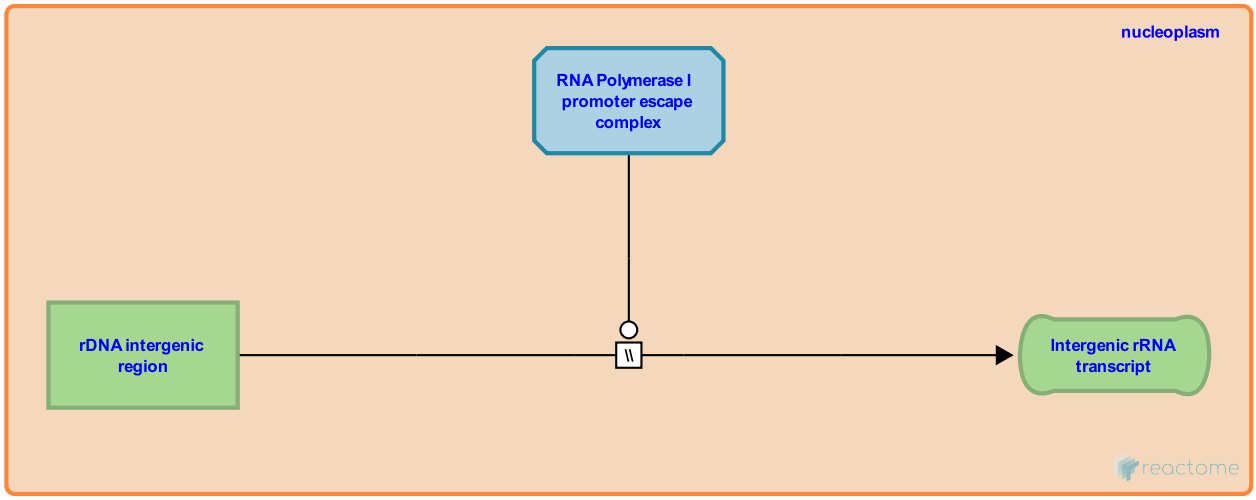
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-427366

Type: omitted

Compartments: nucleoplasm

Inferred from: Transcription of intergenic spacer of the rRNA gene (Mus musculus)



As inferred from mouse cell models, intergenic spacer regions (IGS) located between rRNA transcription units contain upstream promoters and are transcribed by RNA Polymerase I. The IGS transcripts originate approximately 2 Kb upstream of the start of rRNA transcription and proceed though the main promoter of the rRNA gene.

Followed by: Cleavage of intergenic spacer RNA to yield fragments of 150-300 nucleotides

Literature references

Alvord, WG., Gu, YD., Hwang, CJ., Anderson, LM., Kasprzak, W., Fields, JR. et al. (2009). An intergenic non-coding rRNA correlated with expression of the rRNA and frequency of an rRNA single nucleotide polymorphism in lung cancer cells. *PLoS One, 4*, e7505. ↗

Editions

2009-06-19	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

Cleavage of intergenic spacer RNA to yield fragments of 150-300 nucleotides ↗

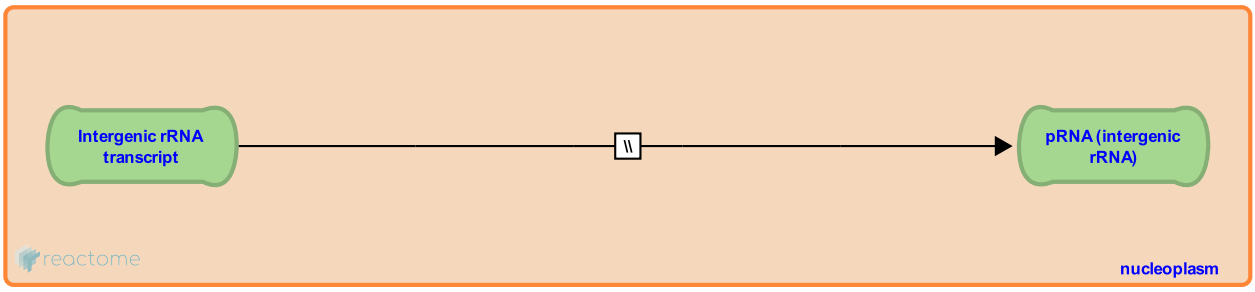
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-427394

Type: omitted

Compartments: nucleoplasm

Inferred from: Cleavage of intergenic spacer RNA to yield fragments of 150-300 nucleotides (Mus musculus)



As inferred from mouse cell models, long Intergenic Spacer RNA of about 2 Kb is cleaved to yield shorter fragments of 150-300 nucleotides. The enzyme responsible for the cleavage is unknown.

Preceded by: Transcription of intergenic spacer of the rRNA gene

Followed by: Nucleolar Remodelling Complex (NoRC) binds intergenic region of rDNA

Editions

2009-06-19	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

TTF-I binds to the Sal Box ↗

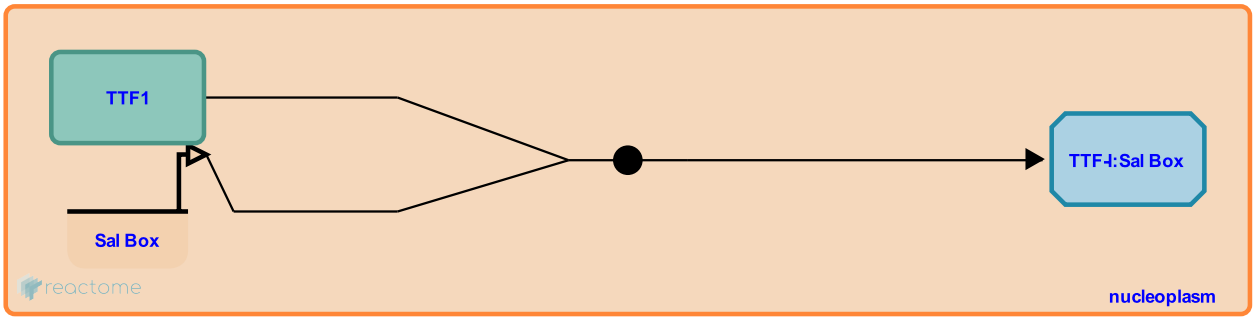
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-74987

Type: binding

Compartments: nucleoplasm

Inferred from: Ttf-I binds the T0 region (Sal Box) of the rDNA (Mus musculus)



As inferred from mouse cell models, the Transcription termination factor (TTF1, also known as TTF-1 and TTF-I) binds an 18 base pair sequence element known as the Sal Box found in multiple copies in the nontranscribed spacer downstream of the 28S rRNA coding region. This element is the termination signal for ribosomal gene transcription. Binding of TTF1 mediates the pausing of the elongating transcription complex. TTF1 has a relatively low affinity for purified DNA but binds cooperatively to chromatin. Oligomers of TTF1 interact in trans to bind adjacent intergenic regions and form loops of the rDNA. Binding of TTF1 to the Sal Box is also influenced by interaction of TTF1 with TIP5 and possibly other proteins.

Followed by: Nucleolar Remodelling Complex (NoRC) binds intergenic region of rDNA

Literature references

Evers, R., Grummt, I. (1995). Molecular coevolution of mammalian ribosomal gene terminator sequences and the transcription termination factor TTF-I. *Proc Natl Acad Sci U S A, 92*, 5827-31. ↗

Editions

2003-07-03	Authored	Comai, L.
2014-02-18	Reviewed	Shiao, YH.
2016-02-12	Reviewed	Iben, S.
2024-05-24	Edited	Gillespie, ME.

Nucleolar Remodelling Complex (NoRC) binds intergenic region of rDNA ↗

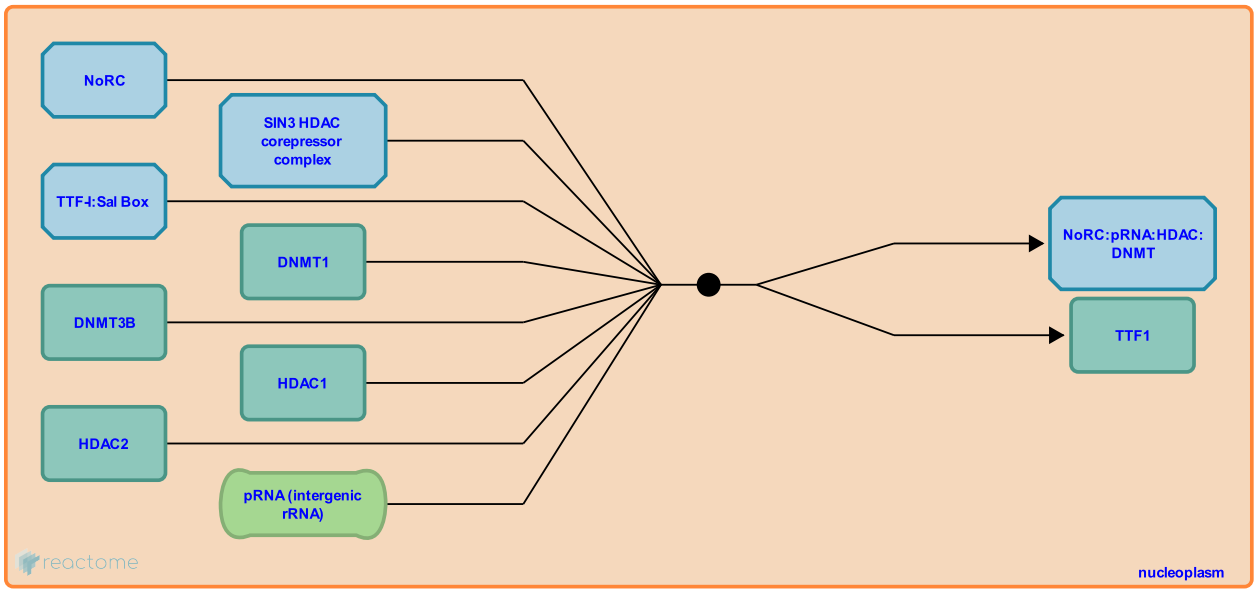
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-427409

Type: binding

Compartments: nucleoplasm

Inferred from: Nucleolar Chromatin Remodeling Complex (NoRC) binds intergenic spacer of rRNA gene (Mus musculus)



As inferred from mouse cell models, the Nucleolar Remodeling Complex (NoRC) comprises TIP5 (BAZ2A) and the chromatin remodeller SNF2H (SMARCA5). The TAM domain of TIP5 (BAZ2A) binds promoter-associated RNA (pRNA) transcribed from the intergenic spacer region of rDNA (Anosova et al. 2015). Binding is not sequence-specific but depends on the secondary structure of the RNA. The pRNA bound by TIP5 is required to direct the complex to the main promoter of the rRNA gene possibly by triple helix formation between pRNA and the rDNA. The PHD domain of TIP5 binds histone H4 acetylated at lysine-16. Transcription Termination Factor-I (TTF-I) binds to a promoter-proximal terminator (T0 site) in the rDNA and interacts with the TIP5 subunit of NoRC. NoRC also interacts with the SIN3-HDAC complex, HDAC1, HDAC2, DNMT1, and DNMT3B. DNMT3B interacts with a triple helix formed by pRNA and the rDNA. HDAC1 and DNMT1 have been shown to be required for proper DNA methylation of silenced rRNA gene copies (Espada et al. 2007).

Preceded by: TTF-I binds to the Sal Box, Cleavage of intergenic spacer RNA to yield fragments of 150-300 nucleotides

Followed by: NoRC:HDAC:DNMT deacetylates histone H4 and methylates histone H3

Literature references

Sattler, M., Anosova, I., Melnik, S., Grummt, I., Kateb, F., Tripsianes, K. (2015). A novel RNA binding surface of the TAM domain of TIP5/BAZ2A mediates epigenetic regulation of rRNA genes. *Nucleic Acids Res., 43*, 5208-20. ↗

Längst, G., Fraga, MF., Villar-Garea, A., Esteller, M., Santoro, R., Ballestar, E. et al. (2007). Epigenetic disruption of ribosomal RNA genes and nucleolar architecture in DNA methyltransferase 1 (Dnmt1) deficient cells. *Nucleic Acids Res, 35*, 2191-8. ↗

Editions

2009-06-19	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

NoRC:HDAC:DNMT deacetylates histone H4 and methylates histone H3 ↗

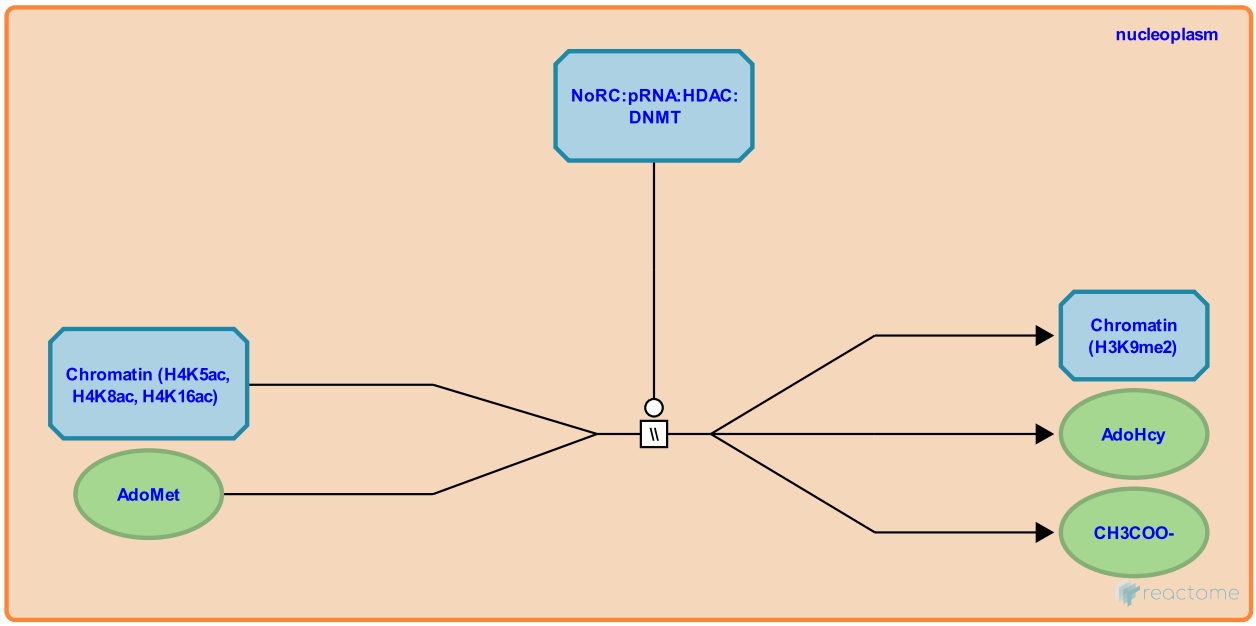
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-433672

Type: omitted

Compartments: nucleoplasm

Inferred from: NoRC:intergenic spacer:Hdac:Dnmt complex deacetylates histone H4 and dimethylates lysine-9 of histone H3 in main promoter of the rRNA gene (Mus musculus)



As inferred from mouse cell models, histones in silenced rRNA gene copies are deacetylated by HDAC1 (and possibly HDAC2), which is part of the SIN3-HDAC complex bound to NoRC. The PHD domain of the TIP5 (BAZ2A) component of NoRC binds acetylated lysine-16 of histone H4. The residues of histone H4 that are deacetylatd are lysine-5, lysine-8, and lysine-12.
In the main promoters of silenced rRNA gene copies, histone H3 is methylated on lysine-9 (H3K9) by an unknown histone methyltransferase. H3K9 methylation is still observed when deacetylation is inhibited, therefore histone methylation does not depend on deacetylation. However histone deacetylation is required for DNA methylation. Significantly more dimethylation than trimethylation is observed.

Preceded by: Nucleolar Remodelling Complex (NoRC) binds intergenic region of rDNA

Followed by: NoRC:HDAC:DNMT methylates cytosine of the rRNA genes

Editions

2009-06-19	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

NoRC:HDAC:DNMT methylates cytosine of the rRNA genes ↗

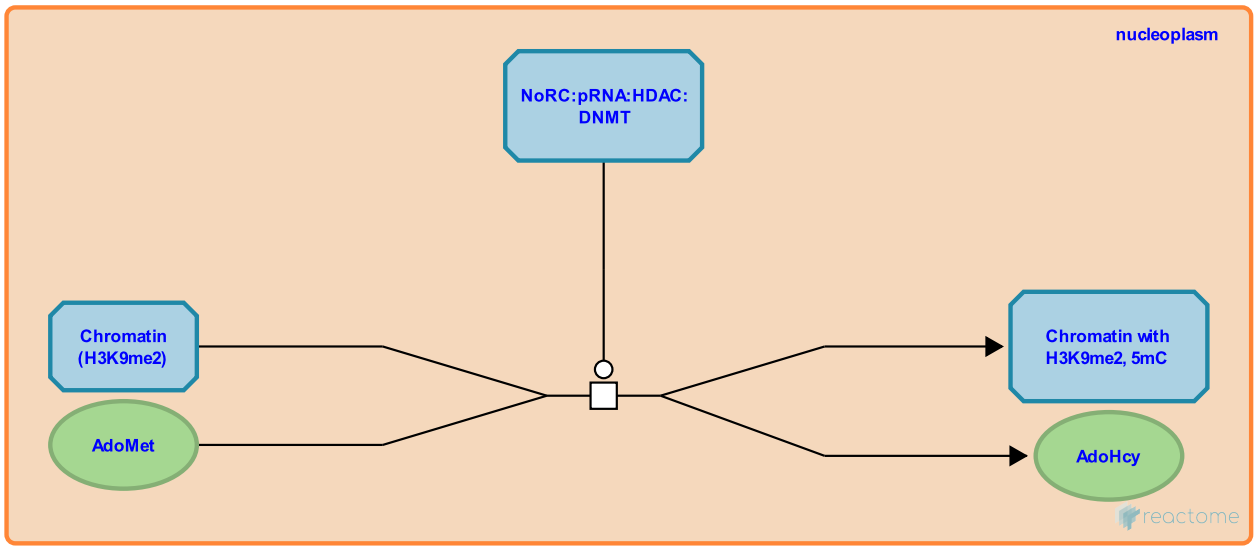
Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-5227490

Type: transition

Compartments: nucleoplasm

Inferred from: NoRC:intergenic spacer:Hdac:Dnmt complex methylates cytosine in the rRNA genes (Mus musculus)



From research with human cells (Espada et al. 2007) and inferences from mouse cell models, cytosine residues in the main promoter of silenced rRNA gene copiess are methylated by DNMT1 and DNMT3B. DNMT3B directly binds a triple helix formed by pRNA and the main promoter of rDNA. The methylated cytosines prevent binding of the UBF transcription factor, thus preventing transcription of silenced rRNA gene copies. Histone deacetylation is required for DNA methylation.

Preceded by: NoRC:HDAC:DNMT deacetylates histone H4 and methylates histone H3

Followed by: MBD2 binds methylcytosine in chromatin

Literature references

Längst, G., Fraga, MF., Villar-Garea, A., Esteller, M., Santoro, R., Ballestar, E. et al. (2007). Epigenetic disruption of ribosomal RNA genes and nucleolar architecture in DNA methyltransferase 1 (Dnmt1) deficient cells. *Nucleic Acids Res, 35*, 2191-8. ↗

Editions

2014-01-09	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

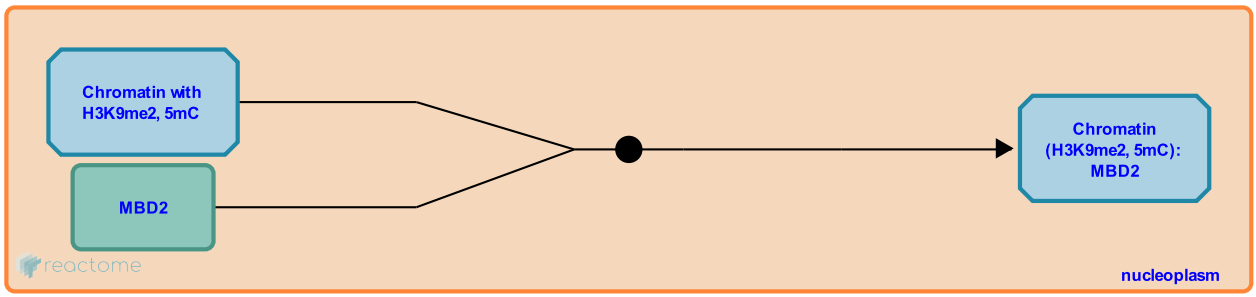
MBD2 binds methylcytosine in chromatin ↗

Location: NoRC negatively regulates rRNA expression

Stable identifier: R-HSA-427337

Type: binding

Compartments: nucleoplasm



Methyl Binding Domain protein 2 (MBD2) binds 5-methylcytosine residues in DNA (Ng et al. 1999) and may recruit further silencing complexes. MBD2 has been shown to specifically bind 5-methylcytosine in the promoters of rRNA gene copies to reduce promoter activity (Ghoshal et al. 2004).

Preceded by: NoRC:HDAC:DNMT methylates cytosine of the rRNA genes

Literature references

Erdjument-Bromage, H., Zhang, Y., Ng, HH., Reinberg, D., Bird, A., Turner, BM. et al. (1999). MBD2 is a transcriptional repressor belonging to the MeCP1 histone deacetylase complex. *Nat. Genet., 23*, 58-61. ↗

Majumder, S., Bai, S., Ghoshal, K., Motiwala, T., Sharma, SM., Datta, J. et al. (2004). Role of human ribosomal RNA (rRNA) promoter methylation and of methyl-CpG-binding protein MBD2 in the suppression of rRNA gene expression. *J Biol Chem, 279*, 6783-93. ↗

Editions

2009-06-19	Authored, Edited	May, B.
2014-02-18	Reviewed	Shiao, YH.

Table of Contents