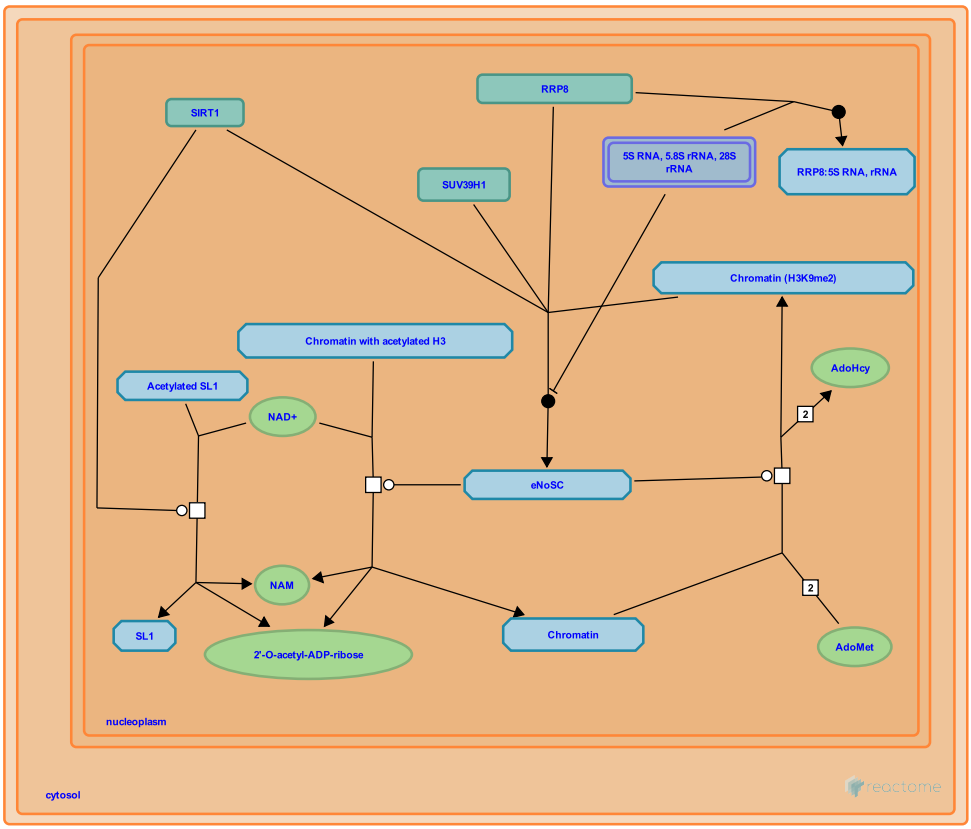
SIRT1 negatively regulates rRNA expression



Grummt, I., May, B., Voit, R.

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

02/03/2021

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. ↗

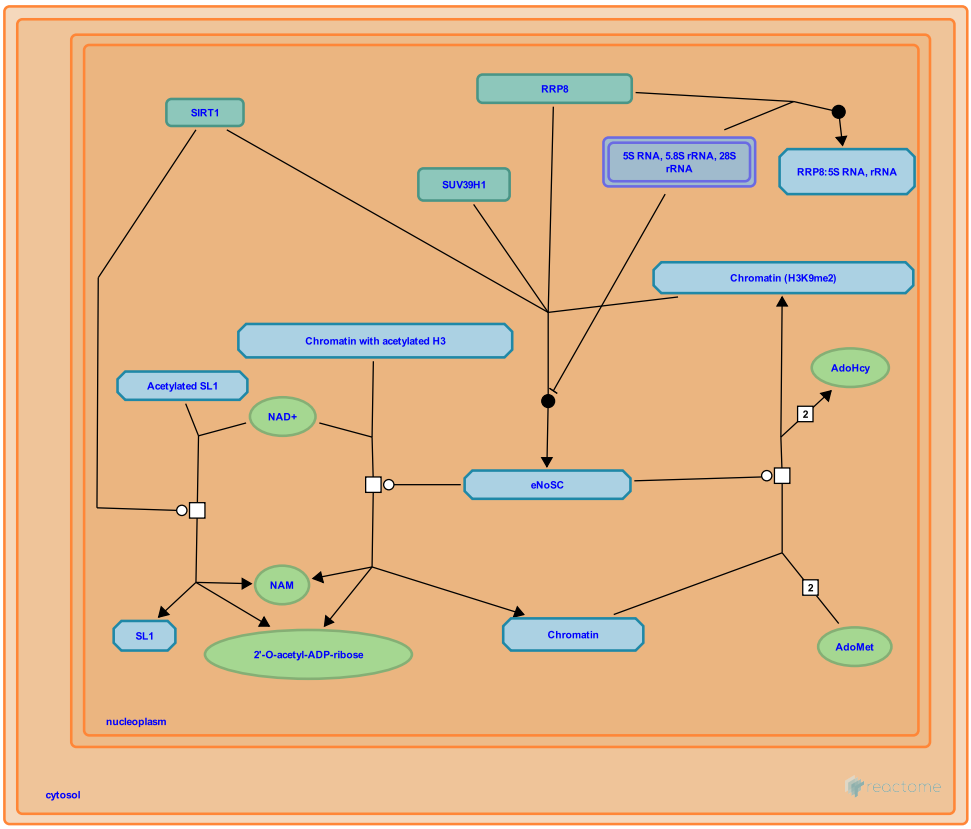
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

SIRT1 negatively regulates rRNA expression ↗

Stable identifier: R-HSA-427359

Compartments: nucleoplasm



Expression of rRNA genes is coupled to the overall metabolism of the cell by the NAD-dependent histone deacetylase SIRT1, a component of the Energy-dependent Nucleolar Silencing Complex (eNoSC) (Murayama et al. 2008, reviewed in Salminen and Kaarniranta 2009, Grummt and Voit 2010). eNoSC comprises Nucleomethylin (NML), SIRT1, and the histone methylase SUV39H1 (Murayama et al. 2008). Deacetylation and methylation of histone H3 in the chromatin of a rRNA gene by eNoSC causes reduced expression of the gene. When glucose is low, NAD is high (NADH is low), activity of SIRT1 is high, and activity of rRNA genes is reduced. It is hypothesized that eNoSC forms on a nucleosome containing dimethylated lysine-9 on histone H3 (H3K9me2) and then eNoSC deacetylates and dimethylates the adjacent nucleosome, thus catalyzing spreading of H3K9me2 throughout the gene.

Literature references

Salminen, A., Kaarniranta, K. (2009). SIRT1 regulates the ribosomal DNA locus: epigenetic candles twinkle longevity in the Christmas tree. *Biochem. Biophys. Res. Commun., 378*, 6-9. ↗

Grummt, I., Voit, R. (2010). Linking rDNA transcription to the cellular energy supply. *Cell Cycle, 9*, 225-6. ↗

Murayama, A., Ohmori, K., Fujimura, A., Minami, H., Yasuzawa-Tanaka, K., Kuroda, T. et al. (2008). Epigenetic control of rDNA loci in response to intracellular energy status. *Cell, 133*, 627-39. ↗

Editions

2009-06-22	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

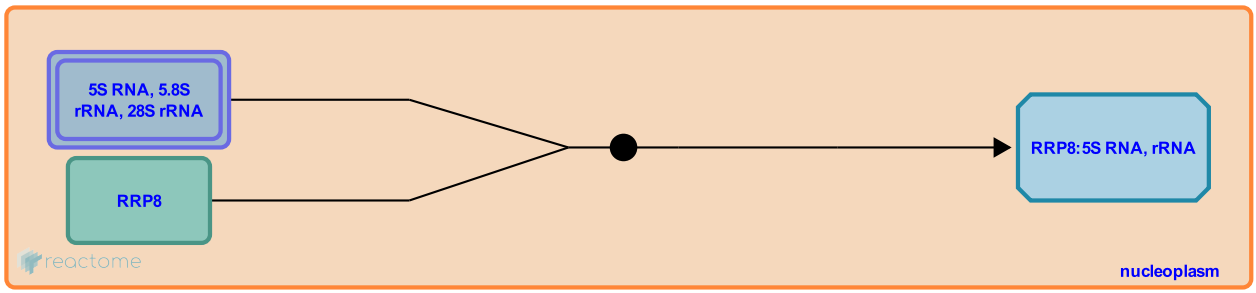
RRP8 binds RNA ↗

Location: SIRT1 negatively regulates rRNA expression

Stable identifier: R-HSA-5096488

Type: binding

Compartments: nucleoplasm



RRP8 (Nucleomethylin, NML) recruits SIRT1 to the nucleolus to form the energy-dependent Nucleolar Silencing Complex (eNoSC), which induces chromatin changes that inhibit rRNA transcription. RRP8 can bind 5S RNA (transcribed by RNA ploymerase III), 5.8S rRNA, and 28S rRNA and the bound RNA prevents RRP8 from binding SIRT1 (Yang et al. 2013). Thus the level of 5S RNA, 5.8S rRNA, and 28S rRNA in the nucleus negatively regulates the assembly of eNoSC, coupling transcriptional regulation of rRNA to epigenetic silencing of rRNA genes.

Literature references

Yang, L., Song, T., Chen, L., Kabra, N., Zheng, H., Koomen, J. et al. (2013). Regulation of SirT1-nucleomethylin binding by rRNA coordinates ribosome biogenesis with nutrient availability. *Mol. Cell. Biol., 33*, 3835-48. ↗

Editions

2013-11-10	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

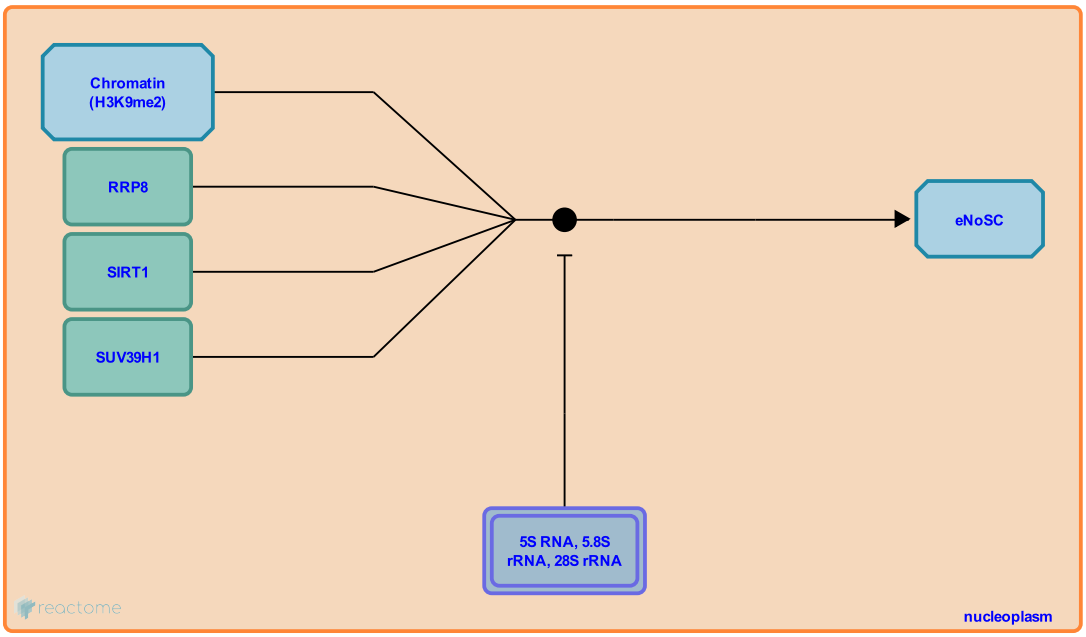
Formation of energy-dependent Nucleolar Silencing Complex (eNoSC)

Location: SIRT1 negatively regulates rRNA expression

Stable identifier: R-HSA-427528

Type: binding

Compartments: nucleoplasm



RRP8 (Nucleomethylin, NML), SIRT1, and SUV39H1 form the energy-dependent Nucleolar Silencing Complex (eNoSC) at inactive rRNA genes (Murayama et al. 2008). RRP8 is constitutively located in the nucleolus (Yang et al. 2013), binds histone H3 dimethylated at lysine-9 (Murayama et al. 2008) and appears to recruit SIRT1 from the nucleoplasm to the nucleolus (Yang et al. 2013). The eNoSC binds chromatin throughout the rRNA transcription unit. SIRT1 may deacetylate and, hence, activate SUV39H1 but this has not yet been shown at rDNA. Abrogation of any member of eNoSC interferes with binding of the other members of the complex. The eNoSC complex appears to cause spreading of heterochromatin at rDNA.

Followed by: eNoSC deacetylates histone H3

Literature references

Murayama, A., Ohmori, K., Fujimura, A., Minami, H., Yasuzawa-Tanaka, K., Kuroda, T. et al. (2008). Epigenetic control of rDNA loci in response to intracellular energy status. *Cell, 133*, 627-39.

Yang, L., Song, T., Chen, L., Kabra, N., Zheng, H., Koomen, J. et al. (2013). Regulation of SirT1-nucleomethylin binding by rRNA coordinates ribosome biogenesis with nutrient availability. *Mol. Cell. Biol., 33*, 3835-48.

Editions

2009-06-22	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

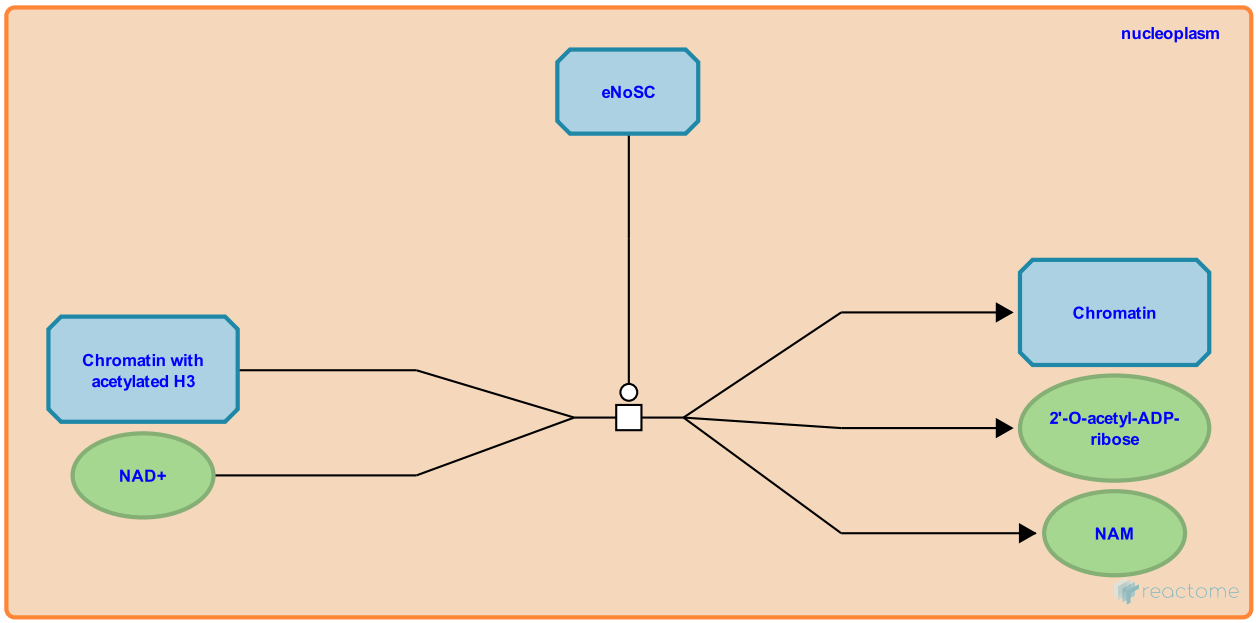
eNoSC deacetylates histone H3 ↗

Location: SIRT1 negatively regulates rRNA expression

Stable identifier: R-HSA-427514

Type: transition

Compartments: nucleoplasm



The Sirtuin-1 (SIRT1) component of eNoSC deacetylates histone H3 at lysine-9 (Vaquero et al. 2004, Murayama et al. 2008). The reaction uses nicotinamide adenine dinucleotide (NAD) as the acceptor of the acetyl group and generates nicotinamide and 1-O-acetyl-ADP-ribose as products (Vaquero et al. 2004). The use of NAD links the reaction to the overall energy balance of the cell. Cells exposed to high glucose have a greater NADH:NAD ratio and therefore lower activity of eNoSC (Murayama et al. 2008). Low glucose produces higher NAD and higher activity of eNoSC.

Preceded by: Formation of energy-dependent Nucleolar Silencing Complex (eNoSC)

Followed by: eNoSC dimethylates histone H3 at lysine-9

Literature references

Murayama, A., Ohmori, K., Fujimura, A., Minami, H., Yasuzawa-Tanaka, K., Kuroda, T. et al. (2008). Epigenetic control of rDNA loci in response to intracellular energy status. *Cell, 133*, 627-39. ↗

Vaquero, A., Scher, M., Lee, D., Erdjument-Bromage, H., Tempst, P., Reinberg, D. (2004). Human SirT1 interacts with histone H1 and promotes formation of facultative heterochromatin. *Mol. Cell, 16*, 93-105. ↗

Editions

2009-06-22	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

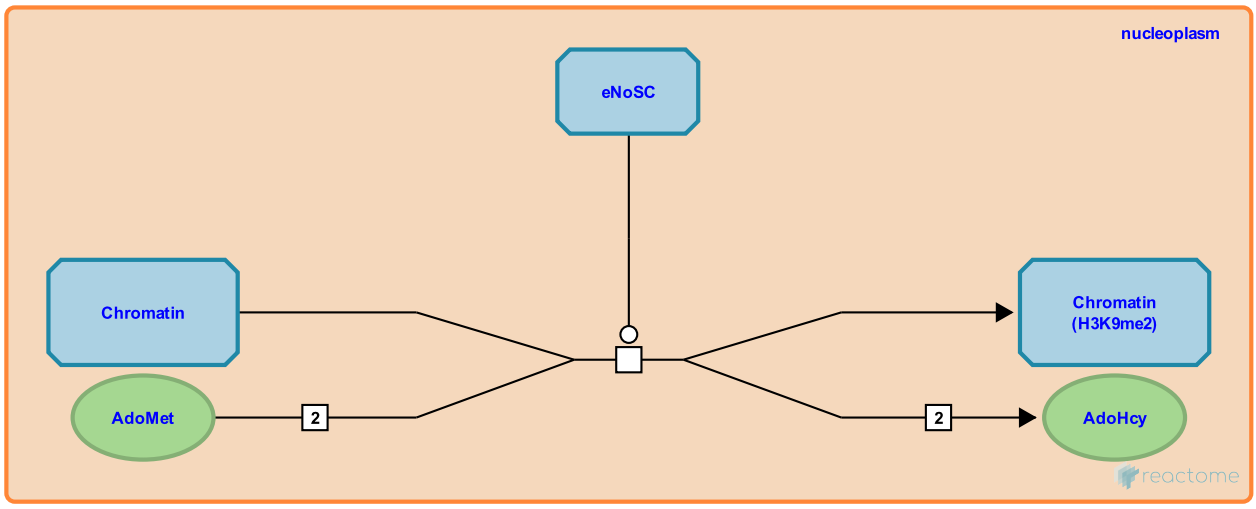
eNoSC dimethylates histone H3 at lysine-9 ↗

Location: SIRT1 negatively regulates rRNA expression

Stable identifier: R-HSA-427527

Type: transition

Compartments: nucleoplasm



The SUV39H1 component of eNoSC dimethylates histone H3 at lysine-9 (Murayama et al. 2008). The reaction depends on the prior deacetylation reaction catalyzed by the SIRT1 component of eNoSC. Histone H3 dimethylated at lysine-9 inhibits expression of rRNA genes.

Preceded by: eNoSC deacetylates histone H3

Literature references

Murayama, A., Ohmori, K., Fujimura, A., Minami, H., Yasuzawa-Tanaka, K., Kuroda, T. et al. (2008). Epigenetic control of rDNA loci in response to intracellular energy status. *Cell, 133*, 627-39. ↗

Editions

2009-06-22	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

SIRT1 deacetylates TAF1B in SL1 complex ↗

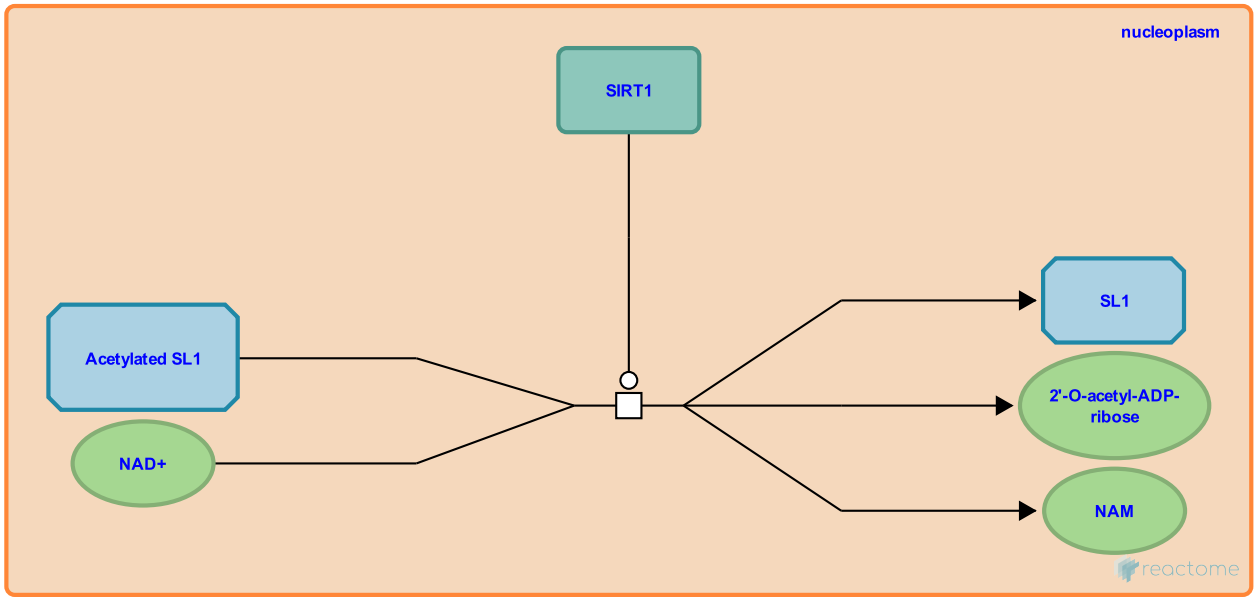
Location: SIRT1 negatively regulates rRNA expression

Stable identifier: R-HSA-5211239

Type: transition

Compartments: nucleoplasm

Inferred from: Sirt1 deacetylates Taf1b in SL1 complex (Mus musculus)



As inferred from mouse, SIRT1, an NAD+ dependent deacetylase, deacetylates the TAF1B (TAF(1)68) subunit of the SL1 complex. Deacetylation of TAF1B inhibits transcription of rRNA genes.

Editions

2013-11-15	Authored, Edited	May, B.
2014-01-21	Reviewed	Voit, R., Grummt, I.

Table of Contents