Negative epigenetic regulation of rRNA expression

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

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. For more information see our license.

16/07/2019
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


Reactome database release: 69

This document contains 3 pathways *(see Table of Contents)*

https://reactome.org
Negative epigenetic regulation of rRNA expression

**Stable identifier:** R-HSA-5250941

**Compartments:** nucleoplasm

Transcription of rRNA genes is controlled by epigenetic activation and repression (reviewed in McStay and Grummt 2008, Goodfellow and Zomerdijk 2012, Grummt and Längst 2013). About half of the roughly 400 rRNA genes are expressed and these have the modifications of active chromatin: unmethylated DNA and acetylated histones. Repressed genes generally have methylated DNA and histone H3 methylated at lysine-9. Regulators of repression include the eNoSC complex, SIRT1, and the NoRC complex.

SIRT1 negatively regulates rRNA expression as a subunit of the eNoSC complex, which deacetylates histone H3 and dimethylates lysine-9 of histone H3 (H3K9me2).

NoRC negatively regulates rRNA expression by shifting a nucleosome near the start of rRNA transcription into a more repressive location and recruiting Histone Deacetylase 1 and 2 (HDAC1, HDAC2) and DNA Methyltransferase 1 and 3b (DNMT1, DNMT3b).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-01-29</td>
<td>Authored, Edited</td>
<td>May, B.</td>
<td>2014-01-31</td>
<td>Reviewed</td>
<td>May, B.</td>
</tr>
</tbody>
</table>
SIRT1 negatively regulates rRNA expression

**Location:** Negative epigenetic regulation of 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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-06-22</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2014-01-21</td>
<td>Reviewed</td>
<td>Voit, R., Grummt, I.</td>
</tr>
</tbody>
</table>

https://reactome.org
NoRC negatively regulates rRNA expression

Location: Negative epigenetic regulation of rRNA expression

Stable identifier: R-HSA-427413

Compartments: nucleoplasm

The Nucleolar Remodeling Complex (NoRC) comprising TIP5 (BAZ2A) and the chromatin remodeler 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**


### Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-06-20</td>
<td>Authored</td>
<td>May, B.</td>
</tr>
<tr>
<td>2010-04-06</td>
<td>Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2014-02-18</td>
<td>Reviewed</td>
<td>Shiao, YH.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

- Negative epigenetic regulation of rRNA expression 2
  - SIRT1 negatively regulates rRNA expression 3
  - NoRC negatively regulates rRNA expression 4

Table of Contents 6