

ERCC6 (CSB) and EHMT2 (G9a) positively

regulate rRNA expression



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the <u>Reactome Textbook</u>.

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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.

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This document contains 1 pathway and 4 reactions (see Table of Contents)

ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression 7

Stable identifier: R-HSA-427389

Compartments: nucleoplasm



About half of the rRNA genes in the genome are actively expressed, being transcribed by RNA polymerase I (reviewed in Nemeth and Langst 2008, Bartova et al. 2010, Goodfellow and Zomerdijk 2012, Grummt and Langst 2013). As inferred from mouse, those genes that are expressed are activated by ERCC6 (also known as Cockayne Syndrome protein, CSB) which interacts with TTF-I bound to the T0 terminator region (also know as the Sal Box) of rRNA genes (Yuan et al. 2007, reviewed in Birch and Zomerdijk 2008, Grummt and Langst 2013). ERCC6 recruits the histone methyltransferase EHMT2 (also known as G9a) which dimethylates histone H3 at lysine-9 in the coding region of rRNA genes. The dimethylated lysine is bound by CBX3 (also known as Heterochromatic Protein-lgamma, HP1gamma) and increases expression of the rRNA gene. Continuing dimethylation depends on continuing transcription. Mutations in CSB result in dysregulation of RNA polymerase I transcription, which plays a role in the symptoms of Cockayne Syndrome (reviewed in Hannan et al. 2013).

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2016-02-12	Reviewed	Iben, S.

TTF-I binds to the Sal Box 🛪

Location: ERCC6 (CSB) and EHMT2 (G9a) positively regulate 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: Recruitment of ERCC6 (CSB), EHMT2 (G9a), and NuRD to the promoter of rRNA gene

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. 7

2003-07-03	Authored	Comai, L.
2014-02-18	Reviewed	Shiao, YH.
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Recruitment of ERCC6 (CSB), EHMT2 (G9a), and NuRD to the promoter of rRNA gene

7

Location: ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression

Stable identifier: R-HSA-427404

Type: binding

Compartments: nucleoplasm

Inferred from: Recruitment of CSB, G9a, and NuRD to the rRNA promoter (Homo sapiens)



Transcription Termination Factor-I (TTF-I) is a sequence-specific binding protein that binds sites 5' (Tsp and T0 sites) and 3' (T1-10 site) of rRNA genes. As inferred from mouse, when TTF-I is bound to the promoter-proximal T0 site TTF-I either recruits ERCC6 (also known as Cockayne Syndrome Protein, CSB), EHMT2 (also known as histone methyltransferase G9a), and NuRD to activate expression (Shimono et al. 2005, Lebedev et al. 2008) or recruits the Nucleolar Remodeling Complex (NoRC) to repress expression. How one is selected over the other is unknown.

CHD4 and presumably the rest of the NuRD complex is associated with bivalent domains containing H3K4me3 (active chromatin mark) and H3K27me3 (inactive chromatin mark). ERCC6 and EHMT2 appear to cooperate to regulate activation of rRNA expression with ERCC6 mediating the transition to permissive chromatin (Lebedev et al. 2008) and EHMT2 mediating the transition to active chromatin, which involves the positional shift of one nucleosome at the promoter.

Preceded by: TTF-I binds to the Sal Box

Followed by: TTF1:rRNA promoter:ERCC6:EHMT2 complex dimethylates histone H3 at lysine-9.

Literature references

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TTF1:rRNA promoter:ERCC6:EHMT2 complex dimethylates histone H3 at lysine-9. 7

Location: ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression

Stable identifier: R-HSA-427336

Type: transition

Compartments: nucleoplasm

Inferred from: Ttf-I:rRNA Promoter:Ercc6:Ehmt2 complex dimethylates histone H3 at lysine-9 (Homo sapiens)



As inferred from mouse, EHMT2 (histone methyltransferase G9a) dimethylates histone H3 at lysine-9 (H3K9me2) in the transcribed region of the rRNA gene. Dimethylation of histone H3 in the transcribed region causes increased rRNA expression, which contrasts with the repressive effect of H3K9me2 in other regions of the genome. The histone binding activity and ATPase activity of CHD4 in the NuRD complex are also needed for activation.

Preceded by: Recruitment of ERCC6 (CSB), EHMT2 (G9a), and NuRD to the promoter of rRNA gene

Followed by: CBX3 (HP1gamma) binds histone H3 dimethylated at lysine-9

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CBX3 (HP1gamma) binds histone H3 dimethylated at lysine-9 🛪

Location: ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression

Stable identifier: R-HSA-427383

Type: binding

Compartments: nucleoplasm

Inferred from: Cbx3 (HP1gamma) Binds Histone H3 dimethylated at lysine-9 (Mus musculus)



As inferred from mouse, CBX3 (Heterochromatic Protein 1gamma, HP1gamma) binds histone H3 dimethylated at lysine-9 (H3K9me2). In other regions of the genome, CBX3 can be associated with repression of transcription, however dimethylated H3 lysine-9 and CBX3 in the transcribed region of the rRNA gene are associated with enhanced expression. CBX3 bound to gene bodies can facilitate cotranscriptional processing of RNA (Smallwood et al. 2012).

Preceded by: TTF1:rRNA promoter:ERCC6:EHMT2 complex dimethylates histone H3 at lysine-9.

Literature references

Smallwood, A., Ren, B., Hon, GC., Jin, F., Henry, RE., Espinosa, JM. (2012). CBX3 regulates efficient RNA processing genome-wide. *Genome Res.*, 22, 1426-36.

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