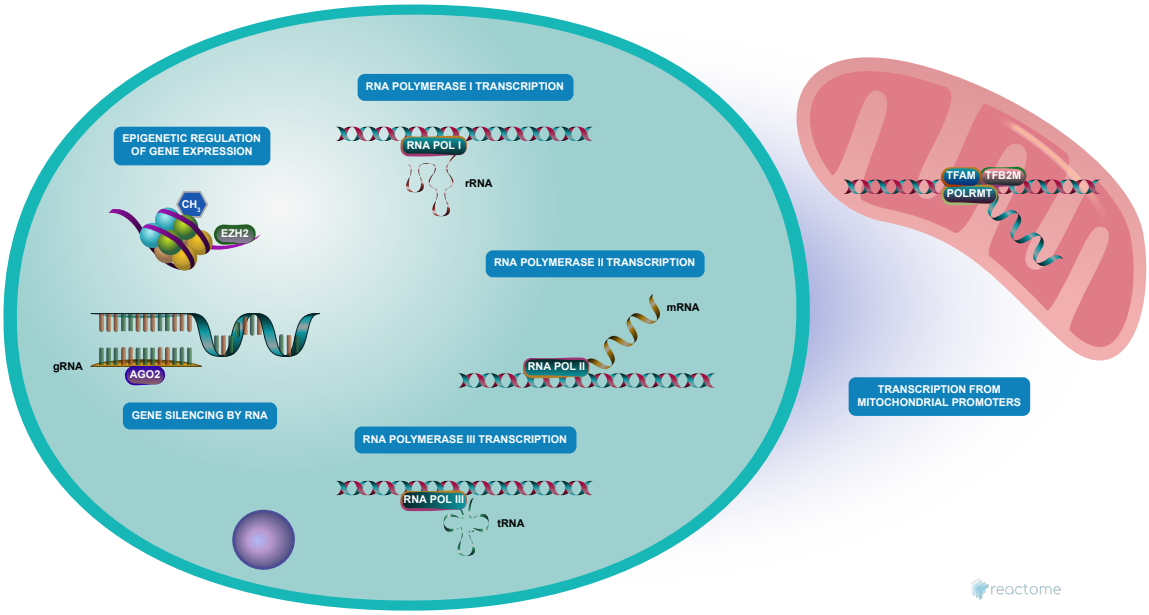
Gene expression (Transcription)



Cantatore, P., Caudy, M., Comai, L., Conaway, JW., Conaway, RC., D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Gustafsson, CM., Hannon, GJ., Hernandez, N., Hu, P., Joshi-Tope, G., Karginov, F., Kornblihtt, AR., Larsson, NG., Matthews, L., May, B., Paule, M., Proudfoot, NJ., Reinberg, D., Timmers, HTM., Willis, I., Zhao, X.

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

07/05/2024

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. ↗

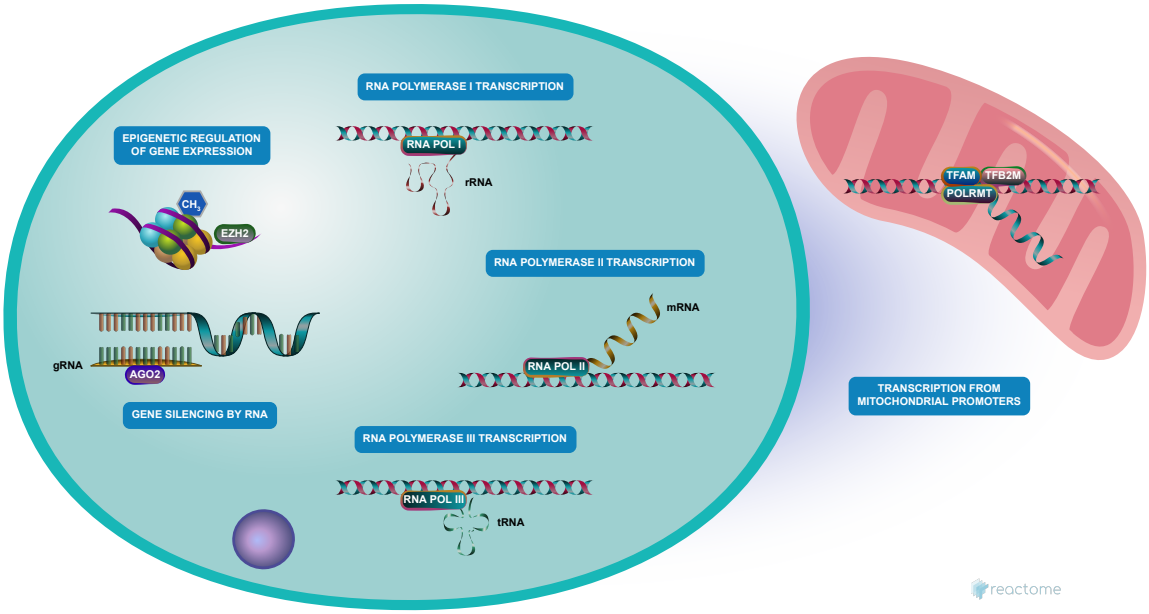
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 7 pathways (see Table of Contents)

Gene expression (Transcription) ↗

Stable identifier: R-HSA-74160



Gene expression encompasses transcription and translation and the regulation of these processes. RNA Polymerase I Transcription produces the large preribosomal RNA transcript (45S pre-rRNA) that is processed to yield 18S rRNA, 28S rRNA, and 5.8S rRNA, accounting for about half the RNA in a cell. RNA Polymerase II transcription produces messenger RNAs (mRNA) as well as a subset of non-coding RNAs including many small nucleolar RNAs (snRNA) and microRNAs (miRNA). RNA Polymerase III Transcription produces transfer RNAs (tRNA), 5S RNA, 7SL RNA, and U6 snRNA. Transcription from mitochondrial promoters is performed by the mitochondrial RNA polymerase, POLRMT, to yield long transcripts from each DNA strand that are processed to yield 12S rRNA, 16S rRNA, tRNAs, and a few RNAs encoding components of the electron transport chain. Regulation of gene expression can be divided into epigenetic regulation, transcriptional regulation, and post-transcription regulation (comprising translational efficiency and RNA stability). Epigenetic regulation of gene expression is the result of heritable chemical modifications to DNA and DNA-binding proteins such as histones. Epigenetic changes result in altered chromatin complexes that influence transcription. Gene Silencing by RNA mostly occurs post-transcriptionally but can also affect transcription. Small RNAs originating from the genome (miRNAs) or from exogenous RNA (siRNAs) are processed and transferred to the RNA-induced silencing complex (RISC), which interacts with complementary RNA to cause cleavage, translational inhibition, or transcriptional inhibition.

Editions

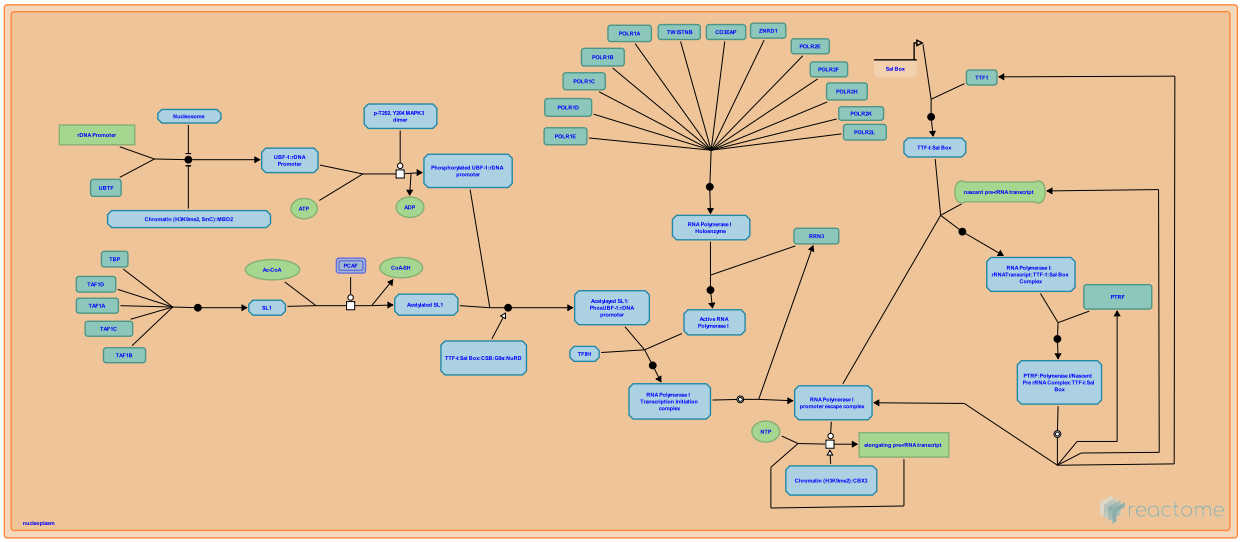
2003-09-11	Authored	Proudfoot, NJ., Comai, L., Hernandez, N., Reinberg, D., Timmers, HTM., Conaway, RC. et al.
2008-12-03	Authored	Proudfoot, NJ., Kornblihtt, AR., D'Eustachio, P., Caudy, M.
2016-12-29	Revised	D'Eustachio, P.
2024-03-06	Edited	Joshi-Tope, G.
2024-03-06	Reviewed	Paule, M., Zhao, X., Willis, I.

RNA Polymerase I Transcription ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-73864

Compartments: nucleolus



RNA polymerase (Pol) I (one of three eukaryotic nuclear RNA polymerases) is devoted to the transcription of the ribosomal DNA genes, which are found in multiple arrayed copies in every eukaryotic cell. These genes encode for the large ribosomal RNA precursor, which is then processed into the three largest subunits of the ribosomal RNA, the 18S, 28S, and 5.8S RNAs. In human cells the rDNA gene clusters are localized on the short arm of the five pairs of the acrocentric chromosomes. The rRNA promoter has two essential and specially spaced sequences: a CORE element and an upstream control element (UCE, also called UPE). The CORE element of the human promoter overlaps with the transcription start site, extending from 20 to 45, and is required for specific initiation of transcription.
The polymerase is a multisubunit complex, composed of two large subunits (the most conserved portions include the catalytic site that shares similarity with other eukaryotic and bacterial multisubunit RNA polymerases) and a number of smaller subunits. Under a number of experimental conditions the core is competent to mediate ribonucleic acid synthesis, in vivo however, it requires additional factors to select the appropriate template. In humans the RNA transcript (45S) is approximately 13,000 nucleotides long. Before leaving the nucleus as assembled ribosomal particles, the 45S rRNA is cleaved to give one copy each of the 28S rRNA, the 18S rRNA, and the 5.8S rRNA. Equal quantities of the three rRNAs are produced by initially transcribing them as one transcript.

Literature references

Comai, L. (2004). Mechanism of RNA polymerase I transcription. *Adv. Protein Chem., 67*, 123-55. ↗

Editions

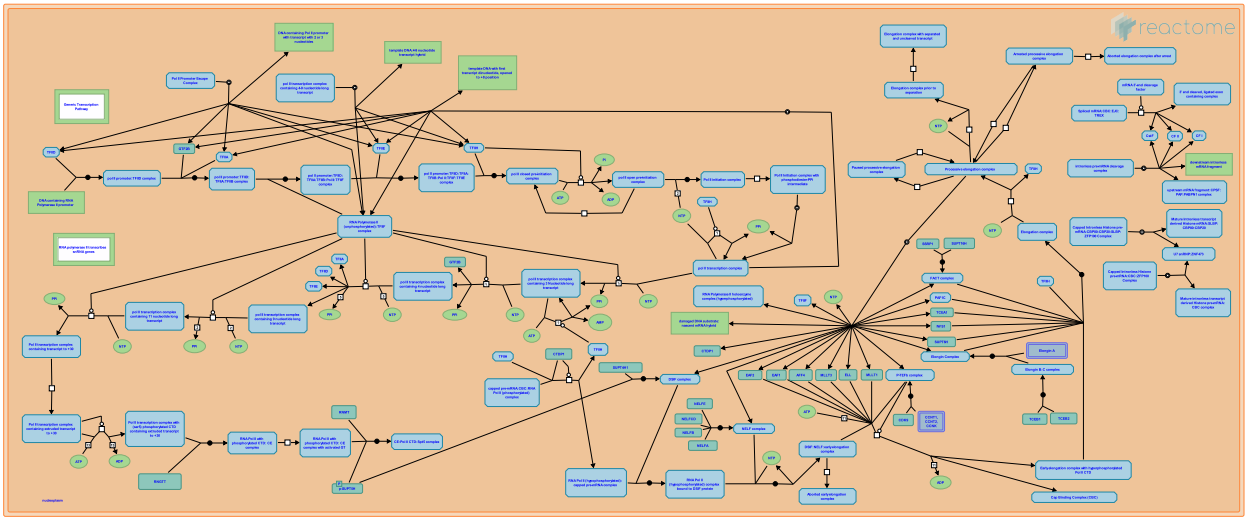
2003-07-03	Authored	Comai, L.
2024-03-06	Edited	Gillespie, ME.
2024-03-06	Reviewed	Paule, M., Zhao, X.

RNA Polymerase II Transcription ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-73857

Compartments: nucleoplasm



RNA polymerase II (Pol II) is the central enzyme that catalyses DNA- directed mRNA synthesis during the transcription of protein-coding genes. Pol II consists of a 10-subunit catalytic core, which alone is capable of elongating the RNA transcript, and a complex of two subunits, Rpb4/7, that is required for transcription initiation.
The transcription cycle is divided in three major phases: initiation, elongation, and termination. Transcription initiation include promoter DNA binding, DNA melting, and initial synthesis of short RNA transcripts. The transition from initiation to elongation, is referred to as promoter escape and leads to a stable elongation complex that is characterized by an open DNA region or transcription bubble. The bubble contains the DNA-RNA hybrid, a heteroduplex of eight to nine base pairs. The growing 3-end of the RNA is engaged with the polymerase complex active site. Ultimately transcription terminates and Pol II dissocitates from the template.

Literature references

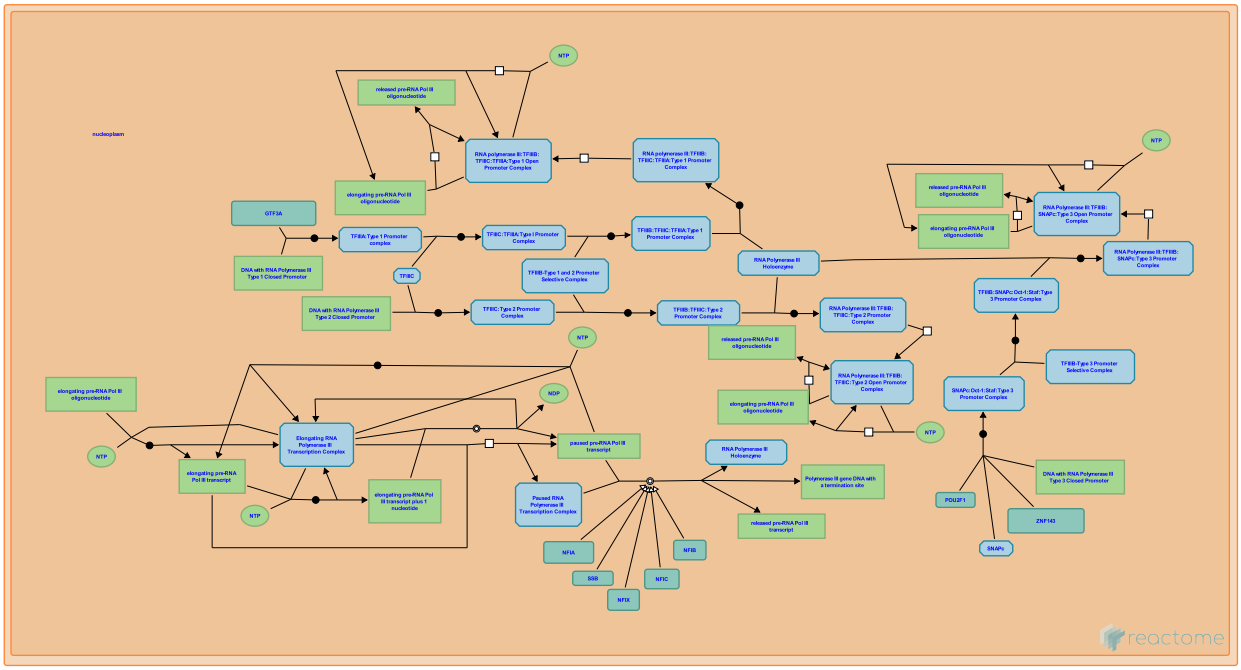
Cramer, P. (2004). Structure and function of RNA polymerase II. *Adv. Protein Chem., 67*, 1-42. ↗

RNA Polymerase III Transcription ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-74158

Compartments: nucleoplasm



RNA polymerase III is one of three types of nuclear RNA polymerases present in eucaryotic cells. About 10% of the total transcription in dividing cells can be attributed to its activity. It synthesizes an eclectic collection of catalytic or structural RNA molecules, some of which are involved in protein synthesis, pre-mRNA splicing, tRNA processing, and the control of RNA polymerase II elongation, whereas some others have still unknown functions. Like other RNA polymerases, RNA polymerase III cannot recognize its target promoters directly. Instead it is recruited to specific promoter sequences through the help of transcription factors. There are three basic types of RNA polymerase III promoters, called types 1, 2, and 3(Geiduschek and Kassavetis, 1992). Although in vivo, RNA polymerase III may be recruited to these promoters as part of a large complex (holo RNA polymerase III) containing the polymerase and its initiation factors (Wang et al., 1997), in vitro the reaction can be divided into several steps. First, the promoter elements are recognized by DNA binding factors, which then recruit a factor known as TFIIIB. TFIIIB itself then directly contacts RNA polymerase III. In human cells but not in *S. cerevisiae*, there are at least two versions of TFIIIB. One contains TBP, Bdp1, and Brf1 (Brf1-TFIIIB), and the other TBP, Bdp1, and Brf2 (Brf2-TFIIIB) (Schramm et al., 2000; Teichmann et al., 2000).

Literature references

Yamamoto, KR., McKnight, SL. (1992). RNA polymerase III Transcription Complexes, Transcriptional Regulation. *Cold Spring Harbor Laboratory Press*, 247-280.

Luo, T., Wang, Z., Roeder, RG. (1997). Identification of an autonomously initiating RNA polymerase III holoenzyme containing a novel factor that is selectively inactivated during protein synthesis inhibition. *Genes Dev, 11*, 2371-82. ↗

Wang, Z., Teichmann, M., Roeder, RG. (2000). A stable complex of a novel transcription factor IIB- related factor, human TFIIIB50, and associated proteins mediate selective transcription by RNA polymerase III of genes with upstream promoter elements. *Proc Natl Acad Sci U S A, 97*, 14200-5. ↗

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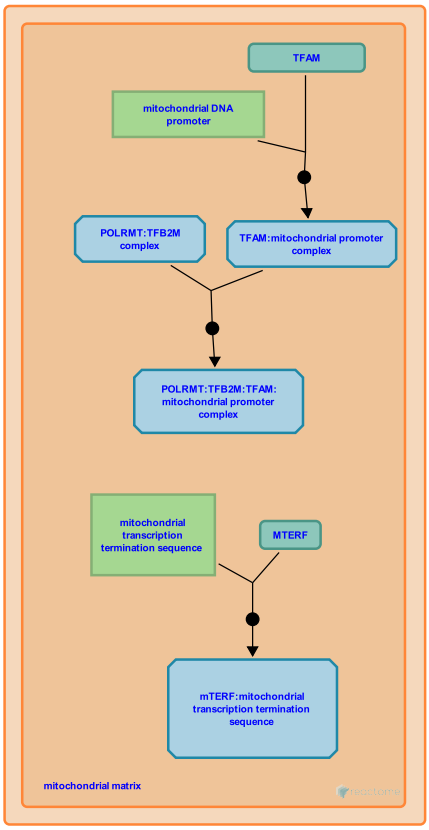
Editions

2003-09-11	Authored	Hernandez, N.
2024-03-06	Edited	Joshi-Tope, G.

Transcription from mitochondrial promoters ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-75944



Thirteen of the ~80 different proteins present in the respiratory chain of human mitochondria are encoded by the mitochondrial genome (mtDNA). The circular mtDNA, which is present in 1000 to 10000 copies in the human cell, also encodes for 2 ribosomal RNAs, and 22 transfer RNAs. The double-stranded mitochondrial genome lacks introns and the longer non-coding region contains the control elements for transcription and replication of mtDNA (Shadel and Clayton, 1997). The two mtDNA strands are referred to as the heavy (H-strand) and the light (L-strand) due to their differing G+T content. In human cells, each strand contains one single promoter for transcriptional initiation, the light-strand promoter (LSP) or the heavy-strand promoter (HSP). Transcription from the mitochondrial promoters produce polycistronic precursor RNA encompassing all the genetic information encoded in each of the specific strands. The primary transcripts are processed to produce the individual tRNA and mRNA molecules (Clayton, 1991; Ojala et al., 1981). There is likely a second initiation site for heavy strand transcription, which produces RNAs spanning the rDNA region. The resulting transcript including the genes for the two mitochondrial rRNAs and ends at the boundary between the 16 S rRNA and the tRNALeu(UUR) genes (Montoya et al., 1982; Montoya et al.,1983; Christianson and Clayton 1986). The existence of such a separate transcription unit may explain why the steady-state levels of rRNAs are much higher than the steady state levels of mRNAs.

Literature references

Attardi, G., Montoya, J., Gaines, GL. (1983). The pattern of transcription of the human mitochondrial rRNA genes reveals two overlapping transcription units. *Cell, 34*, 151-9. ↗

Attardi, G., Montoya, J., Rabinowitz, M., Christianson, T., Levens, D. (1982). Identification of initiation sites for heavy-strand and light-strand transcription in human mitochondrial DNA. *Proc Natl Acad Sci U S A, 79*, 7195-9. ↗

Shadel, GS. (1997). Mitochondrial DNA maintenance in vertebrates. *Annu Rev Biochem, 66*, 409-35. ↗

Christianson, TW. (1986). In vitro transcription of human mitochondrial DNA: accurate termination requires a region of DNA sequence that can function bidirectionally. *Proc Natl Acad Sci U S A, 83*, 6277-81. ↗

Attardi, G., Montoya, J., Ojala, D. (1981). tRNA punctuation model of RNA processing in human mitochondria. *Nature , 290*, 470-4. ↗

Editions

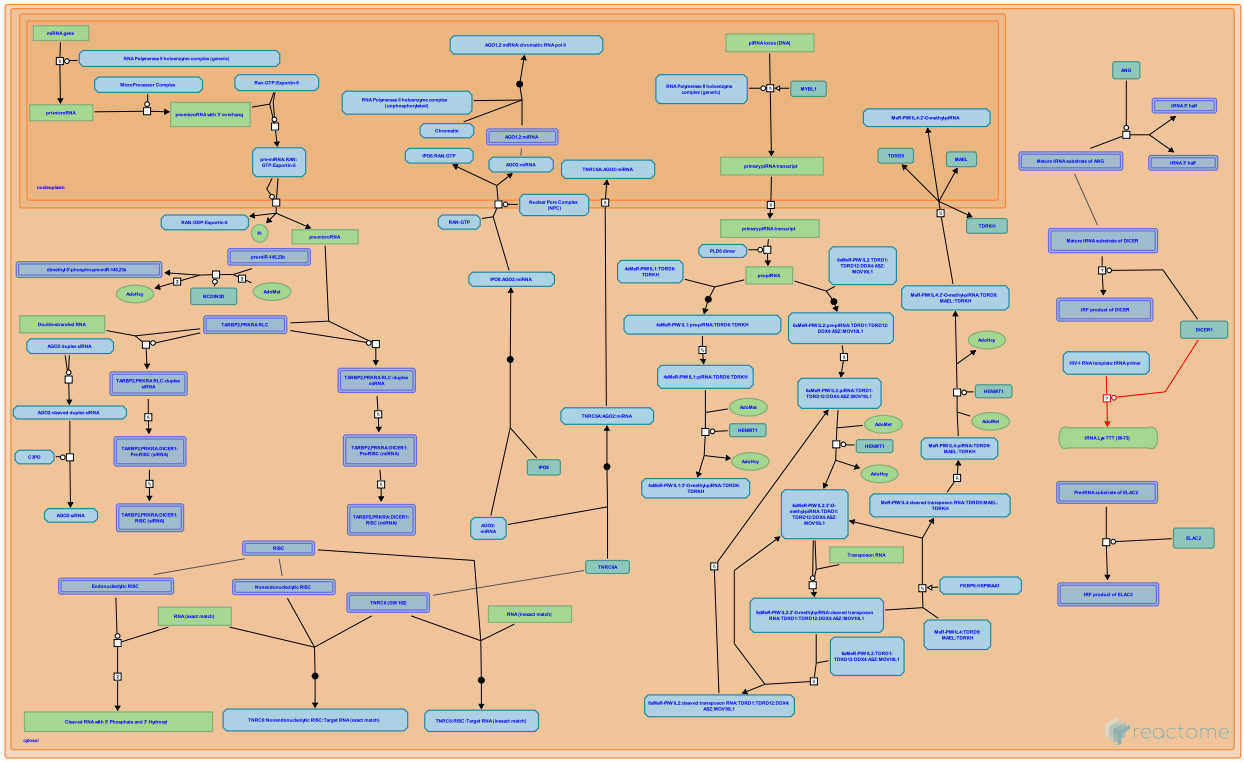
2005-04-26	Authored	Gustafsson, CM.
2024-03-06	Reviewed	Cantatore, P.
2024-03-06	Edited	Matthews, L.

Gene Silencing by RNA ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-211000

Compartments: nuclear envelope, nucleoplasm, cytosol



In this module, the biology of various types of regulatory non-coding RNAs are described. Biogenesis and functions of small interfering RNAs (siRNAs) and microRNAs (miRNAs) are annotated. Biogenesis of PIWI-interacting small RNAs (piRNAs) and tRNA-derived small RNAs (tsRNAs) are also annotated.

Literature references

Liu, J., Hannon, GJ., Parker, R., Valencia-Sanchez, MA. (2006). Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes Dev, 20*, 515-24. ↗

Tomari, Y., Zamore, PD. (2005). Perspective: machines for RNAi. *Genes Dev, 19*, 517-29. ↗

Joshua-Tor, L., Ipsaro, JJ. (2015). From guide to target: molecular insights into eukaryotic RNA-interference machinery. *Nat. Struct. Mol. Biol., 22*, 20-8. ↗

Carthew, RW., Sontheimer, EJ. (2009). Origins and Mechanisms of miRNAs and siRNAs. *Cell, 136*, 642-55. ↗

Ketting, RF. (2011). microRNA Biogenesis and Function : An overview. *Adv Exp Med Biol, 700*, 1-14. ↗

Editions

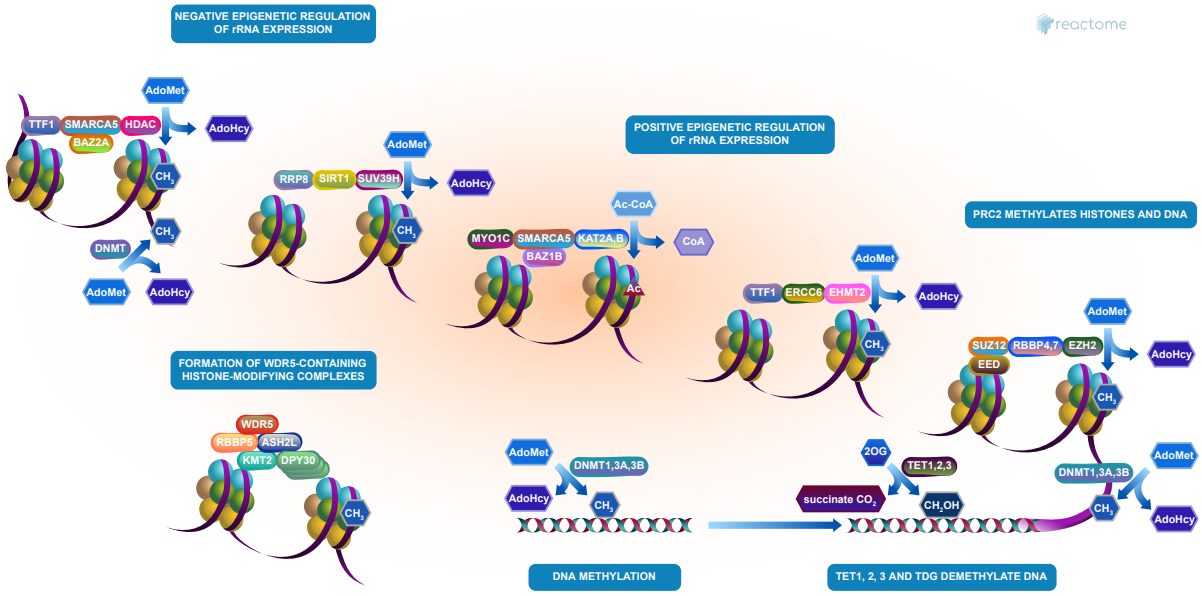
2008-01-23	Authored	Gopinathrao, G.
2008-02-08	Reviewed	Hannon, GJ., Karginov, F.
2009-06-10	Edited	May, B.

Epigenetic regulation of gene expression ↗

Location: Gene expression (Transcription)

Stable identifier: R-HSA-212165

Compartments: nucleoplasm



Epigenetic processes regulate gene expression by modulating the frequency, rate, or extent of gene expression in a mitotically or meiotically heritable way that does not entail a change in the DNA sequence. Originally the definition applied only to heritability across generations but later also encompassed the heritable changes that occur during cellular differentiation within one organism.
Molecular analysis shows epigenetic changes comprise covalent modifications, such as methylation and acetylation, to DNA and histones. RNA interference has been implicated in the initiation of some epigenetic changes, for example transcriptional silencing of transposons. Proteins which bind to the modified DNA and histones are then responsible for repressing transcription and for maintaining the epigenetic modifications during cell division.
During differentiation, patterns of gene expression are established by polycomb complexes PRC1 and PRC2. PRC2 methylates histones and DNA to produce the initial marks of repression: trimethylated lysine-27 on histone H3 (H3K27me3) and 5-methylcytosine in DNA. PRC2, through its component EZH2 or, in some complexes, EZH1 trimethylates lysine-27 of histone H3. The H3K27me3 produced by PRC2 is bound by the Polycomb subunit of PRC1. PRC1 ubiquitinates histone H2A and maintains repression.
PRC2 and other epigenetic systems modulate gene expression through DNA methyation, the transfer of a methyl group from S-adenosylmethionine to the 5 position of cytosine in DNA by a family of DNA methyltransferases (DNMTs): DNMT1, DNMT3A, and DNMT3B.
In the reverse process TET1,2,3 and TDG demethylate DNA through the oxidation of the methyl group of 5-methylcytosine by TET enzymes and the excision of the oxidized product (5-formylcytosine or 5-carboxylcytosine) by TDG.
Ribosomal RNA (rRNA) genes are activated and deactivated according to the metabolic requirements of the cell. Positive epigenetic regulation of rRNA expression occurs through chromatin modifications produced by activators such as ERCC6 (CSB), the B-WICH complex, and histone acetylases such as KAT2B (PCAF). Negative epigenetic regulation of rRNA expression occurs through chromatin modifications produced by repressors such as the eNoSC complex, SIRT1, and the NoRC complex.

WDR5 is a component of six histone methyltransferases and three histone acetyltransferases involved in epigenetic regulation of gene expression (reviewed in Guarnaccia and Tansey 2018).

Literature references

Tansey, WP., Guarnaccia, AD. (2018). Moonlighting with WDR5: A Cellular Multitasker. *J Clin Med, 7*. ↗

Bird, A., Jaenisch, R. (2003). Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat. Genet., 33*, 245-54. ↗

Editions

2008-02-09	Authored, Edited	Gopinathrao, G., May, B.
2009-07-06	Edited	May, B.
2014-02-26	Reviewed	Matthews, L.

Table of Contents