Transcriptional regulation by small RNAs

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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 Reactome Textbook.

14/11/2022
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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Literature references


Reactome database release: 82

This document contains 1 pathway and 5 reactions (see Table of Contents)

https://reactome.org
Recent evidence indicates that small RNAs participate in transcriptional regulation in addition to post-transcriptional silencing. Components of the RNAi machinery (ARGONAUTE1 (AGO1, EIF2C1), AGO2 (EIF2C2), AGO3 (EIF2C3), AGO4 (EIF2C4), TNRC6A, and DICER) are observed associated with microRNAs (miRNAs) in both the cytosol and the nucleus (Robb et al. 2005, Weinmann et al. 2009, Doyle et al. 2013, Nishi et al. 2013, Gagnon et al. 2014). The AGO:miRNA complexes are imported into the nucleus by IMPORTIN-8 (IPO8, IMP8, RANBP8) and also by an unknown importin while associated with the nuclear shuttling protein TNRC6A (reviewed in Schraivogel and Meister 2014).

Within the nucleus, AGO2, TNRC6A, and DICER may associate in a complex (Gagnon et al. 2014). Nuclear AGO1 and AGO2 in complexes with small RNAs are observed to activate transcription (RNA activation, RNAa) or repress transcription (Transcriptional Gene Silencing, TGS) of genes that contain sequences matching the small RNAs (reviewed in Malecova and Morris 2010, Huang and Li 2012, Gagnon and Corey 2012, Huang and Li 2014, Salmanidis et al. 2014, Stroynowska-Czerwinska et al. 2014). TGS is associated with methylation of cytosine in DNA and methylation of histone H3 at lysine-9 and lysine-27 (Castanotto et al. 2005, Suzuki et al. 2005, Kim et al. 2006, Weinberg et al. 2006, Kim et al. 2008, reviewed in Malecova and Morris 2010, Li et al. 2014); RNAa is associated with methylation of histone H3 at lysine-4 (Huang et al. 2012, reviewed in Li et al. 2014). Small RNAs in the nucleus have also been shown to play roles in alternative splicing (Liu et al., 2012, Ameyar-Zazoua et al., 2012) and DNA damage repair (Wei et al., 2012; Francia et al., 2012). Nevertheless, elucidation of the detailed mechanisms of small RNA action requires further research.

**Literature references**


**Editions**

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Importin-8 binds AGO2:miRNA

**Location:** Transcriptional regulation by small RNAs

**Stable identifier:** R-HSA-5578712

**Type:** binding

**Compartments:** cytosol

Importin-8 (IPO8, IMP8, RANBP8) binds AGO2:miRNA complexes in the cytosol and participates in the importation of AGO2:miRNA complexes into the nucleus (Weinmann et al. 2009, Wei et al. 2014). IPO8 is also required for recruitment of AGO2:miRNA complexes to many target mRNAs in the cytosol and their efficient silencing (Weinmann et al. 2009). Moreover, other Argonautes (AGO1, AGO3, AGO4) are also observed in the nucleus (Kim et al. 2008, Weinmann et al. 2009, Ahlenstiel et al. 2012, Gagnon et al. 2014) and may be imported by the same mechanism.

**Followed by:** Importin-8 imports AGO2:miRNA into the nucleus

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Importin-8 imports AGO2:miRNA into the nucleus

**Location:** Transcriptional regulation by small RNAs

**Stable identifier:** R-HSA-5578744

**Type:** transition

**Compartments:** nuclear envelope, nucleoplasm, cytosol

The AGO2:miRNA complex is formed in the cytosol (Ohrt et al 2008) and is imported into the nucleus in a complex with Importin-8 (IPO8, Imp8, RanBP8) (Weinmann et al. 2009, Wei et al. 2014). Once in the nucleus, Imp8 in complex with the cargo interacts with RAN:GTP, causing the dissociation of Imp8 from the complex with AGO2:miRNA (Gorlich et al. 1997). Other Argonautes are also observed in the nucleus (Robb et al. 2005, Weinmann et al. 2009, Doyle et al. 2013, Ahlenstiel et al. 2012, Gagnon et al. 2014) and may be imported by the same mechanism.

**Preceded by:** Importin-8 binds AGO2:miRNA

**Followed by:** AGO1,2:small RNA complexes interact with chromatin

**Literature references**


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TNRC6A binds AGO2:miRNA

**Location:** Transcriptional regulation by small RNAs

**Stable identifier:** R-HSA-5578965

**Type:** binding

**Compartments:** cytosol

TNRC6A (GW182) is a major component of miRISC and processing bodies (P bodies or GW bodies) where transcripts are degraded (Eystathioy et al. 2003). GW182 possesses several glycine-tryptophan (GW) repeats that enable interactions with Argonaute proteins (Eulalio et al. 2009, Takimoto et al. 2009). Humans express three paralogs (TNRC6A, TNRC6B, and TNRC6C) which can each silence expression of mRNAs to which they are bound (Lazzaretti et al. 2009). In the cytosol TNRC6A binds AGO2:miRNA via three GW-repeat motifs (Landthaler et al. 2008, Takimoto et al. 2009, Nishi et al. 2013).

**Followed by:** TNRC6A:AGO2:miRNA is transported into the nucleus

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TNRC6A:AGO2:miRNA is transported into the nucleus

Location: Transcriptional regulation by small RNAs

Stable identifier: R-HSA-5578966

Type: omitted

Compartments: nucleoplasm, cytosol

TNRC6A (GW182) possesses both a nuclear localization signal (NLS) and a nuclear export signal (NES) that enable it to shuttle between the cytoplasm and the nucleus (Nishi et al. 2013). Thus the TNRC6A:AGO2:miRNA complex is transported into the nucleus by an unknown importation mechanism (Nishi et al. 2013). (TNRC6A is exported by Exportin 1.) The interaction between AGO2 and TNRC6A affects gene silencing activity in the nucleus (Nishi et al. 2013).

Preceded by: TNRC6A binds AGO2:miRNA

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AG01,2: small RNA complexes interact with chromatin

Location: Transcriptional regulation by small RNAs

Stable identifier: R-HSA-5578742

Type: binding

Compartments: nucleoplasm

Complexes containing small RNAs and AG01 or AG02 are observed within the nucleus and at the inner nuclear envelope, respectively, associated with the actin cytoskeleton (Ahlenstiel et al. 2012, Huang et al. 2013). Argonaute:miRNA complexes associate with genomic regions possessing sequences that match the miRNA, possibly via RNA transcripts tethered to chromatin (Li et al. 2006, Weinber et al. 2006, Kim et al. 2008, Place et al. 2008, Younger and Corey 2011). AG02:miRNA appears to be in complexes containing DICER and TNRC6A (Gagnon et al. 2014) and AG01 has been shown to associate with RNA polymerase II, TARBP2, and EZH2 at transcriptionally silenced promoters (Kim et al. 2006, Huang et al. 2013). AG01 also associates with RNA polymerase II at active promoters (Huang et al. 2013). Other AG0:miRNA complexes may form similar complexes.


Preceded by: Importin-8 imports AG02:miRNA into the nucleus

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