Small interfering RNA (siRNA) biogenesis

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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.

29/12/2022

https://reactome.org
**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: 83

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

https://reactome.org
Small interfering RNA (siRNA) biogenesis

Stable identifier: R-HSA-426486

Compartments: cytosol

Small interfering RNAs (siRNAs) are 21-25 nucleotide single-stranded RNAs produced by cleavage of longer double-stranded RNAs by the enzyme DICER1 within the RISC loading complex containing DICER1, an Argonaute protein, and either TARBP2 or PRKRA (PACT). Typically the long double-stranded substrates originate from viruses or repetitive elements in the genome and the two strands of the substrate are exactly complementary.

After cleavage by DICER1 the 21-25 nucleotide double-stranded product is loaded into an Argonaute protein (humans contain 4 Argonautes) and rendered single-stranded by a mechanism that is not well characterized.

siRNA-loaded AGO2 is predominantly located at the cytosolic face of the rough endoplasmic reticulum and has also been observed in the nucleus.

Literature references


**Dicer cleaves double-stranded RNA to yield double-stranded siRNA**

**Location:** Small interfering RNA (siRNA) biogenesis

**Stable identifier:** R-HSA-426464

**Type:** transition

**Compartments:** cytosol

Double stranded RNA binds the RISC loading complex and DICER1, an RNase III component of the complex, cleaves double-stranded RNAs to yield short double-stranded RNAs of 21-25 nucleotides, duplex siRNAs (small interfering RNAs). SiRNAs are similar to microRNAs (miRNAs) in their final structure but differ from miRNAs in their source: siRNAs are produced from long double stranded RNAs that originate from viruses, transposable elements, centromeric repeats and other repetitive structures.

The RLC as originally characterized contains DICER1, AGO2, and TARBP2 (TRBP). Alternative RLCs appear to contain other Argonaute proteins (AGO1, AGO3, AGO4) rather than AGO2 and PRKRA rather than TARBP2. Diffusion activity of TARBP2 and PRKRA along duplex RNA may enhance processing by DICER1.

**Followed by:** Duplex siRNA is loaded into Argonaute

**Literature references**

Ching, YP., Kok, KH., Jin, DY., Ng, MH. (2007). Human TRBP and PACT directly interact with each other and associate with dicer to facilitate the production of small interfering RNA. *J. Biol. Chem.*, 282, 17649-57.


**Editions**

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https://reactome.org
Duplex siRNA is loaded into Argonaute

Location: Small interfering RNA (siRNA) biogenesis

Stable identifier: R-HSA-2106625

Type: omitted

Compartments: cytosol

Following cleavage the duplex siRNA reoriented on DICER1 and then transferred from DICER1 to an Argonaute protein (AGO1, AGO2, AGO3, or AGO4) within the RISC loading complex (RLC).

Preceded by: Dicer cleaves double-stranded RNA to yield double-stranded siRNA

Followed by: C3PO hydrolyzes cleaved passenger strand, Removal of siRNA passenger strand, AGO2 cleaves passenger strand of duplex siRNA

Literature references


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Removal of siRNA passenger strand

Location: Small interfering RNA (siRNA) biogenesis

Stable identifier: R-HSA-2106615

Type: omitted

Compartments: cytosol

The short double-stranded RNA passed from DICER1 to an Argonaute protein is rendered single-stranded by removal and loss of the passenger strand through a mechanism that is not well characterized. All Argonautes (AGO1 (EIF2C1), AGO2 (EIF2C2), AGO3 (EIF2C3), AGO4 (EIF2C4)) can remove the passenger strand without cleaving it. AGO2 (EIF2C2) possesses endonucleolytic activity and cleaves the passenger strand of siRNAs, which facilitates removal of the passenger strand but is not required (Matranga et al. 2005). RNA helicase A associated with the RISC loading complex can also facilitate removal of the passenger strand.

The mechanism that selects which strand is retained as the guide RNA is not well understood in humans. Overhanging nucleotides and strength of base-pairing at each end of the input duplex are observed to influence strand selection.

Argonaute proteins loaded with miRNAs or siRNAs are predominantly located in association with TARBP2 or PRKRA at the cytosolic face of the rough endoplasmic reticulum in cultured cells.

Preceded by: Duplex siRNA is loaded into Argonaute

Literature references


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AGO2 cleaves passenger strand of duplex siRNA

**Location:** Small interfering RNA (siRNA) biogenesis

**Stable identifier:** R-HSA-9023912

**Type:** transition

**Compartments:** cytosol

C3PO appears to act as a nuclease that hydrolyzes the passenger strand after cleavage by AGO2. C3PO could also be part of a DICER1-independent pathway for loading AGO2. AGO2 of humans may contain either miRNAs or siRNAs.

The mechanism that selects which strand is retained as the guide RNA is not well understood in humans. Overhanging nucleotides and strength of base-pairing at each end of the input duplex are observed to influence strand selection.

**Preceded by:** Duplex siRNA is loaded into Argonaute

**Literature references**


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C3PO hydrolyzes cleaved passenger strand

**Location:** Small interfering RNA (siRNA) biogenesis

**Stable identifier:** R-HSA-9023909

**Type:** transition

**Compartments:** cytosol

C3PO appears to act as a nuclease that hydrolyzes the passenger strand after cleavage by AGO2. C3PO could also be part of a DICER1-independent pathway for loading AGO2. AGO2 of humans may contain either miRNAs or siRNAs.

The mechanism that selects which strand is retained as the guide RNA is not well understood in humans. Overhanging nucleotides and strength of base-pairing at each end of the input duplex are observed to influence strand selection.

**Preceded by:** Duplex siRNA is loaded into Argonaute

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