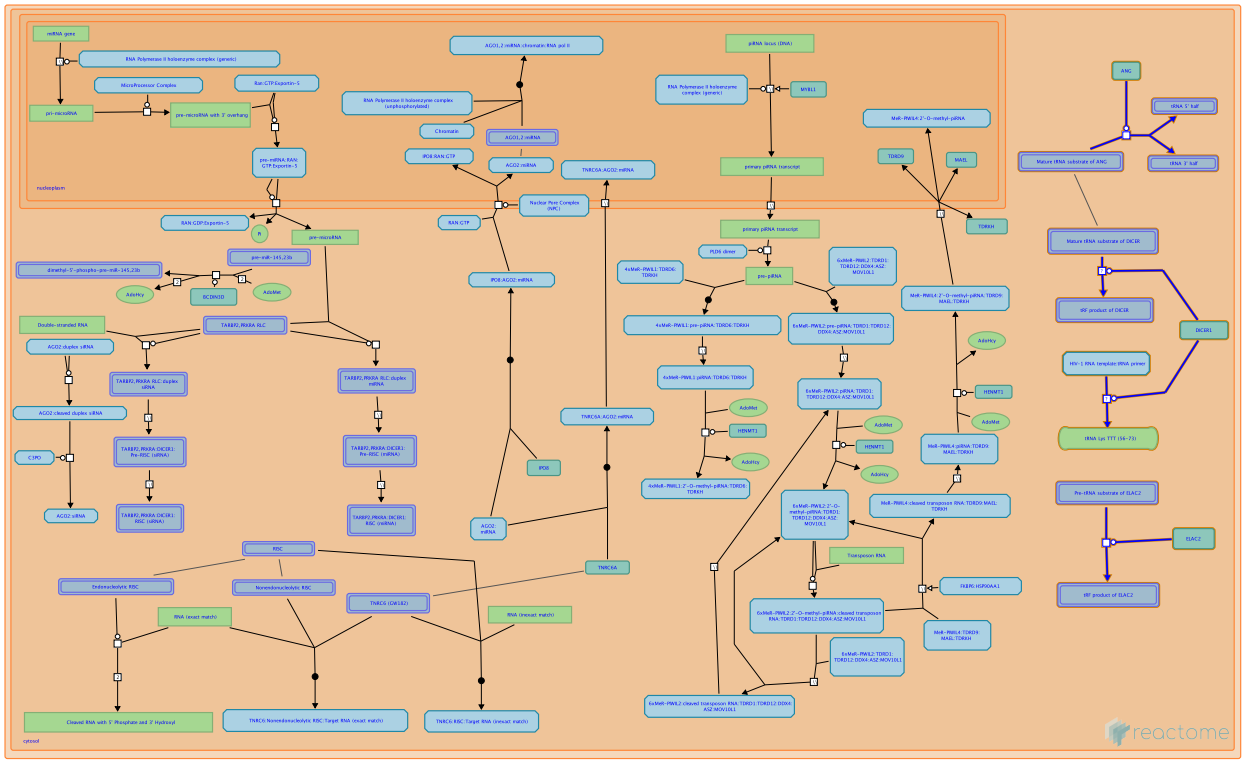
tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis



Basso, K., Dutta, A., May, B., Su, Z., Wilson, B.

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

01/09/2021

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. ↗

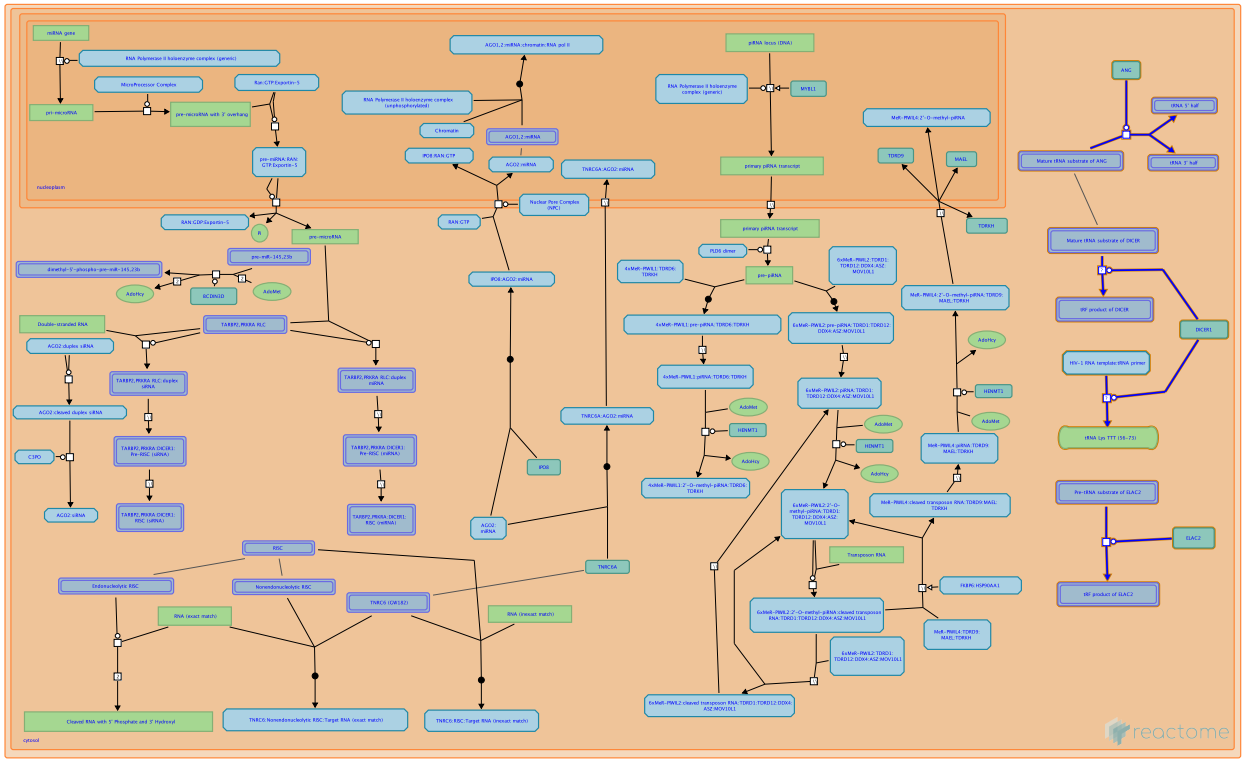
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis ↗

Stable identifier: R-HSA-9708296



Defined fragments of tRNAs, termed tRNA‐derived small RNAs (tsRNAs), have been observed in particular cell types and in response to biological conditions such as exposure to sex hormone or stresses such as hypoxia, starvation, oxidative stress, and virus infection (reviewed in Keam and Hutvagner 2015, Kumar et al. 2016, Oberbauer and Schaefer 2018, Park et al. 2020, Su et al. 2020, Xie et al. 2020, Zhu et al. 2020). Rather than being the random products of tRNA degradation, tsRNAs appear to be the specific products of ribonucleases. Two categories of tRNA‐derived small RNAs (tsRNAs) have been described: (1) longer (31‐40nt) tsRNAs known as tRNA halves or stress‐induced tsRNAs (tiRNAs) that are produced by single cleavage of tRNAs within or near the anticodon and (2) shorter (15‐30 nt) tsRNAs termed tRNA-related fragments (tRFs) that result from cleavage closer to the 5' or 3' end of the tRNA. tRF-3s are derived from the 3' region of the tRNA, approximately the region from the T loop to the 3' terminus. tRF-5s are derived from the 5' region of the tRNA, approximately the region from the D loop to the 5' terminus. tRF2‐type tRFs (also called internal tRFs) are derived from the central region of the tRNA, approximately the region between the D loop and the T loop and containing the anticodon. tRF-1s, also known as Type II tRFs or 3'U tRFs, are the 3' trailers of particular tRNAs that persist after processing.

In most cases the enzymes responsible for the cleavages are not yet known, however several ribonucleases involved in cleavage of tRNA have been identified: the secreted and endocytosed ribonuclease A family members angiogenin (ANG) and RNase 1; the interferon-induced ribonucleases RNase L, Schlafen 11 (SLFN11) and Schlafen13 (SLFN13 or RNase S13); the cytosolic ribonuclease III‐like (double strand RNA‐specific) enzyme DICER1; and the RNA processing enzyme ELAC2. ANG is secreted, binds receptors on cell membranes, is endocytosed, and translocates to the nucleus. ANG cleaves within the anticodon loop to produce tRNA halves and the cleavage is thought to occur while ANG is transiently located in the cytosol (Lee and Vallee 1989, Saxena et al. 1992, Fu et al. 2009, Yamasaki et al. 2009, Emara et al. 2010, Ivanov et al. 2011). Cleavage by ANG is observed in response to cellular stresses such as starvation (Fu et al. 2009, Yamasaki et al. 2009, Emara et al. 2010, Ivanov et al. 2011). However, ANG knockout cells continue to produce stress-induced tRNA halves, suggesting that other enzymes are also involved in pro-

ducing the halves (Su et al. 2019). Similar to ANG as an RNase A member, the secreted endoribonuclease RNase 1 cleaves tRNAs at the anticodon loop in the extracellular space (Nechooshtan et al. 2020).

Interferon-induced RNases can also cleave tRNAs. RNase L is responsive to double stranded RNAs and cleaves at the tRNA anticodon loop (Donovan et al. 2017). Schlafen family members SLFN11 and SLFN13 can also cleave tRNAs (Li et al. 2018, Yang et al. 2018).

DICER1 cleaves double‐stranded regions of tRNAs near the 5' terminus or 3' terminus to produce short tRFs (Cole et al. 2009, Yeung et al. 2009, Maute et al. 2013, Hasler et al. 2016). The mechanism that dissociates the double‐stranded products of DICER1 to yield single‐stranded tRFs may be the same as that for miRNAs, but this has not yet been demonstrated. Furthermore, the bulk of the short tRFs is still detected in DICER1-null cells (Kumar 2014, Kuscu & Kumar et al. 2018), suggesting other unknown factors are involved in their biogenesis. ELAC2 in the cytosol cleaves the 3' trailers of precursors of tRNA Ser TGA, tRNA Ser GTC, and tRNA Asp GTC, and tRNA Asp GTC (Lee et al. 2009). The trailers (also called tRF-1s) then persist in the cytosol (Kumar et al. 2014).

Literature references

Keam, SP., Hutvagner, G. (2015). tRNA-Derived Fragments (tRFs): Emerging New Roles for an Ancient RNA in the Regulation of Gene Expression. *Life (Basel), 5*, 1638-51.

Yamasaki, S., Ivanov, P., Hu, GF., Anderson, P. (2009). Angiogenin cleaves tRNA and promotes stress-induced translational repression. *J Cell Biol, 185*, 35-42.

Hasler, D., Lehmann, G., Murakawa, Y., Klironomos, F., Jakob, L., Grässer, FA. et al. (2016). The Lupus Autoantigen La Prevents Mis-channeling of tRNA Fragments into the Human MicroRNA Pathway. *Mol Cell, 63*, 110-24.

Zhu, P., Yu, J., Zhou, P. (2020). Role of tRNA-derived fragments in cancer: novel diagnostic and therapeutic targets tRFs in cancer. *Am J Cancer Res, 10*, 393-402.

Su, Z., Wilson, B., Kumar, P., Dutta, A. (2020). Noncanonical Roles of tRNAs: tRNA Fragments and Beyond. *Annu Rev Genet, 54*, 47-69.

Editions

2020-11-27	Authored, Edited	May, B.
2021-02-13	Reviewed	Basso, K.
2021-02-20	Reviewed	Dutta, A., Wilson, B., Su, Z.

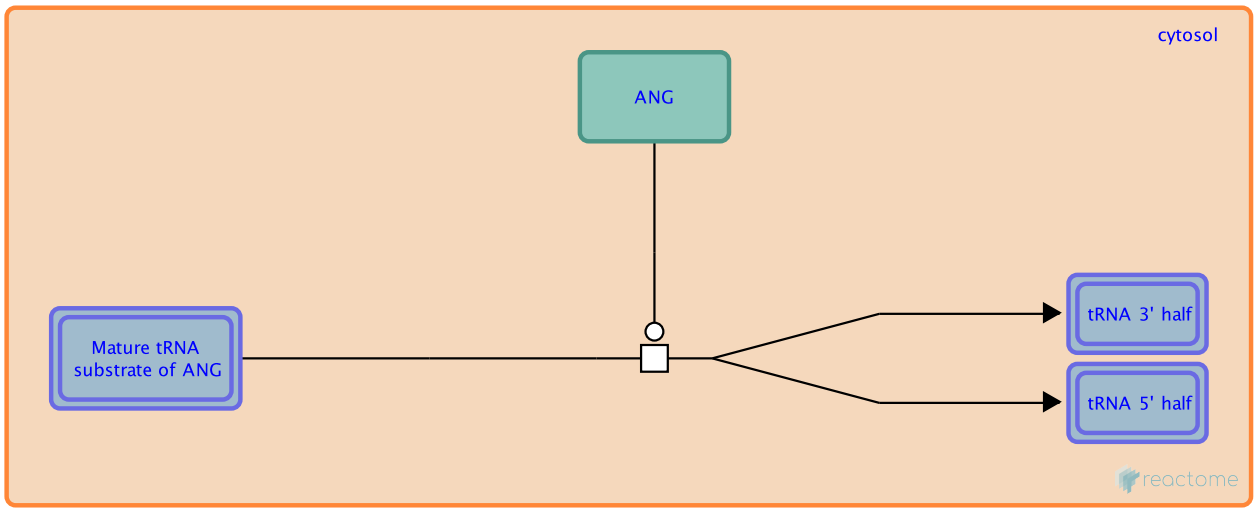
ANG cleaves tRNA to yield tRNA halves ↗

Location: tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis

Stable identifier: R-HSA-9708327

Type: transition

Compartments: cytosol



Angiogenin (ANG) cleaves within or near the anticodon of specific tRNAs including but not limited to: tRNA Arg ACG (Fu et al. 2009), tRNA Arg CCG (Fu et al. 2009), tRNA Glu CTC (Fu et al. 2009), tRNA Gly CCC (Fu et al. 2009), tRNA Gly GCC (Fu et al. 2009), tRNA Met CAT (Fu et al. 2009, Su et al. 2019), tRNA Pro AGG (Yamasaki et al. 2009), tRNA Pro TGG (Yamasaki et al. 2009), tRNA Val AAC (Fu et al. 2009), tRNA Ala AGC (Su et al. 2019), tRNA Ala CGC (Su et al. 2019), tRNA Ala TGC (Su et al. 2019), tRNA Asp GTC (Su et al. 2019), tRNA Glu TTC (Su et al. 2019), tRNA His GTG (Su et al. 2019), tRNA Leu CAG (Su et al. 2019), tRNA Leu TAG (Su et al. 2019), tRNA Lys TTT (Su et al. 2019), tRNA Ser GCT (Su et al. 2019), tRNA Ser CGA (Su et al. 2019), tRNA Val CAC (Su et al. 2019), tRNA Val TAC (Su et al. 2019) (also Lee and Vallee 1989, Saxena et al. 1992, Emara et al. 2010, Ivanov et al. 2011). The products are a 5' fragment of about 30-35 nt and a 3' fragment of about 40 nt known as tRNA halves or stress-induced tRNA fragments (tiRNAs) (Emara et al. 2010). As a result of ANG cleavage, the 5' tRNA halves contain 5' monophosphates (Emara et al. 2010) and 3' cyclic monophosphates (Shigematsu et al. 2018), while the 3' tRNA halves contain 5' hydroxyl groups (Shigematsu et al., 2018). ANG cleaves tRNA in response to biological conditions such as exposure to sex hormones and stresses such as starvation, oxidative stress, and virus infection (Fu et al. 2009, Emara et al. 2010, Ivanov et al. 2011, Wang et al. 2013, Honda et al. 2015, Selitsky et al. 2015), but several tRNA halves are still produced after stress in ANG knockout cells (Su et al. 2020). The 5' tiRNAs inhibit translation by displacing eIF4F from the m(7)G caps of mRNAs (Emara et al. 2010, Ivanov et al. 2011). The 3' tiRNAs protect cells against stress-induced apoptosis by interacting with cytochrome C (inferred from mouse homologs in Saikia et al, 2014). The products of ANG have modifications present on mature tRNAs (Drino et al. 2020); therefore, the cleavage is believed to occur in the cytosol (Yamasaki et al. 2009, reviewed in Lyons et al. 2018) perhaps as ANG is translocated from receptors on the plasma membrane through the cytosol to the nucleus.

Literature references

Fu, H., Feng, J., Liu, Q., Sun, F., Tie, Y., Zhu, J. et al. (2009). Stress induces tRNA cleavage by angiogenin in mammalian cells. *FEBS Lett, 583*, 437-42. ↗

Yamasaki, S., Ivanov, P., Hu, GF., Anderson, P. (2009). Angiogenin cleaves tRNA and promotes stress-induced translational repression. *J Cell Biol, 185*, 35-42. ↗

Emara, MM., Ivanov, P., Hickman, T., Dawra, N., Tisdale, S., Kedersha, N. et al. (2010). Angiogenin-induced tRNA-derived stress-induced RNAs promote stress-induced stress granule assembly. *J Biol Chem, 285*, 10959-68. ↗

Lee, FS., Vallee, BL. (1989). Characterization of ribonucleolytic activity of angiogenin towards tRNA. *Biochem Biophys Res Commun, 161*, 121-6. ↗

Saxena, SK., Rybak, SM., Davey, RT., Youle, RJ., Ackerman, EJ. (1992). Angiogenin is a cytotoxic, tRNA-specific ribonuclease in the RNase A superfamily. *J Biol Chem, 267*, 21982-6. ↗

Editions

2020-11-27	Authored, Edited	May, B.
2021-02-13	Reviewed	Basso, K.
2021-02-20	Reviewed	Dutta, A., Wilson, B., Su, Z.

DICER1 cleaves tRNA ↗

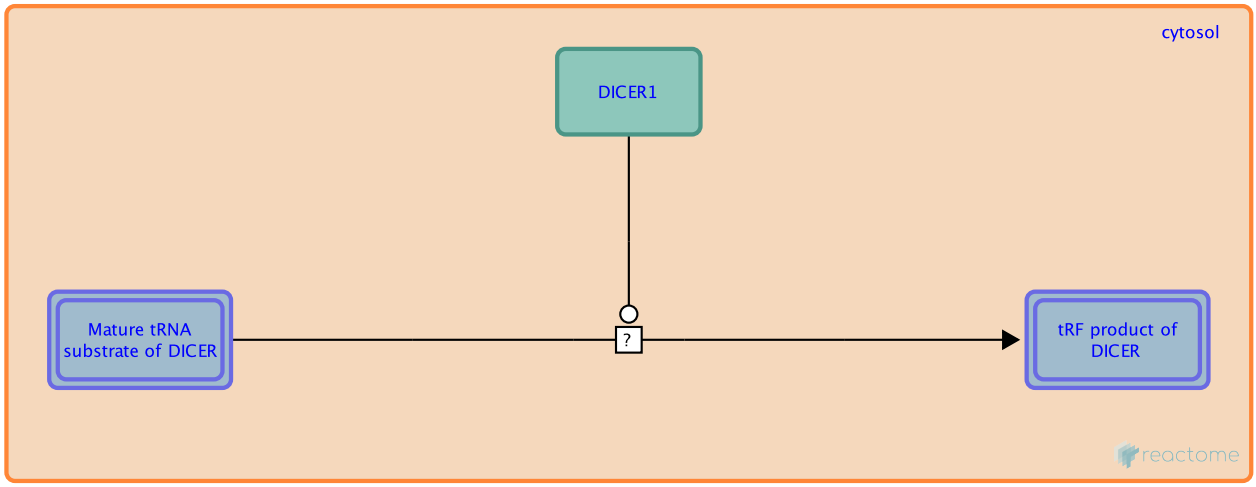
Location: tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis

Stable identifier: R-HSA-9708292

Type: uncertain

Compartments: cytosol

Inferred from: Dicer1 cleaves tRNA Ile TAT to yield miR-1983 (Mus musculus)



DICER1 cleaves: tRNA Gln CTG in the D-loop, releasing a 19 nt fragment from the 5' end of the tRNA (Cole et al. 2009); tRNA Gly GCC, releasing a 22 nt fragment, tRF-3b (tRF-3027b), from the 3' end of the tRNA (Maute et al. 2013); precursor tRNA Ile TAT, releasing a 21 nt fragment, known as sRNA-Ile or miR-1983, from the 3' end of the tRNA (Hasler et al. 2016, and inferred from mouse homologs). Most tRFs are thought to arise in a DICER1 independent manner, however, as deletion of DICER1 does not significantly alter tRF expression (Kumar et al. 2014, Kuscu and Kumar et al. 2018).

Literature references

Cole, C., Sobala, A., Lu, C., Thatcher, SR., Bowman, A., Brown, JW. et al. (2009). Filtering of deep sequencing data reveals the existence of abundant Dicer-dependent small RNAs derived from tRNAs. *RNA, 15*, 2147-60. ↗

Maute, RL., Schneider, C., Sumazin, P., Holmes, A., Califano, A., Basso, K. et al. (2013). tRNA-derived microRNA modulates proliferation and the DNA damage response and is down-regulated in B cell lymphoma. *Proc Natl Acad Sci U S A, 110*, 1404-9. ↗

Hasler, D., Lehmann, G., Murakawa, Y., Klironomos, F., Jakob, L., Grässer, FA. et al. (2016). The Lupus Autoantigen La Prevents Mis-channeling of tRNA Fragments into the Human MicroRNA Pathway. *Mol Cell, 63*, 110-24. ↗

Kumar, P., Anaya, J., Mudunuri, SB., Dutta, A. (2014). Meta-analysis of tRNA derived RNA fragments reveals that they are evolutionarily conserved and associate with AGO proteins to recognize specific RNA targets. *BMC Biol, 12*, 78. ↗

Kuscu, C., Kumar, P., Kiran, M., Su, Z., Malik, A., Dutta, A. (2018). tRNA fragments (tRFs) guide Ago to regulate gene expression post-transcriptionally in a Dicer-independent manner. *RNA, 24*, 1093-1105. ↗

Editions

2020-11-27	Authored, Edited	May, B.
2021-02-13	Reviewed	Basso, K.
2021-02-20	Reviewed	Dutta, A., Wilson, B., Su, Z.

DICER1 cleaves tRNA Lys TTT 3 in tRNA:HIV RNA hybrid ↗

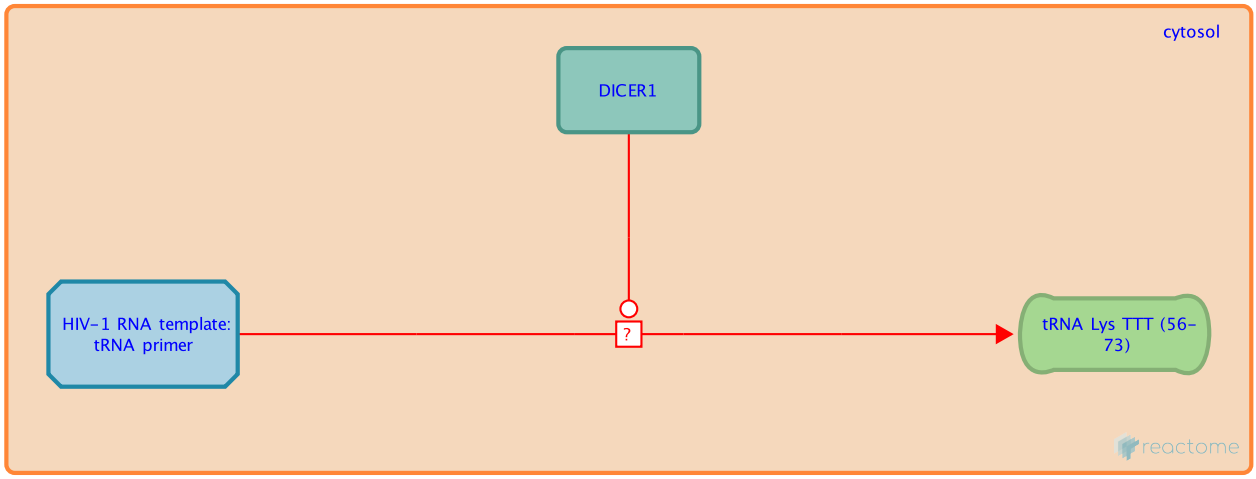
Location: tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis

Stable identifier: R-HSA-9708408

Type: uncertain

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



DICER1 cleaves the double-stranded RNA hybrid formed by the primer binding site (PBS) of HIV genomic RNA and tRNA Lys UUU, the tRNA that primes reverse transcription of the HIV genome. The products are a tsRNA, PBSncRNA, that is 18 nt of the 3' end of tRNA Lys UUU and an uncharacterized fragment of the HIV genome (Yeung et al. 2009).

Literature references

Yeung, ML., Bennasser, Y., Watashi, K., Le, SY., Houzet, L., Jeang, KT. (2009). Pyrosequencing of small non-coding RNAs in HIV-1 infected cells: evidence for the processing of a viral-cellular double-stranded RNA hybrid. *Nucleic Acids Res, 37*, 6575-86. ↗

Editions

2020-11-29	Authored, Edited	May, B.
2021-02-13	Reviewed	Basso, K.
2021-02-20	Reviewed	Dutta, A., Wilson, B., Su, Z.

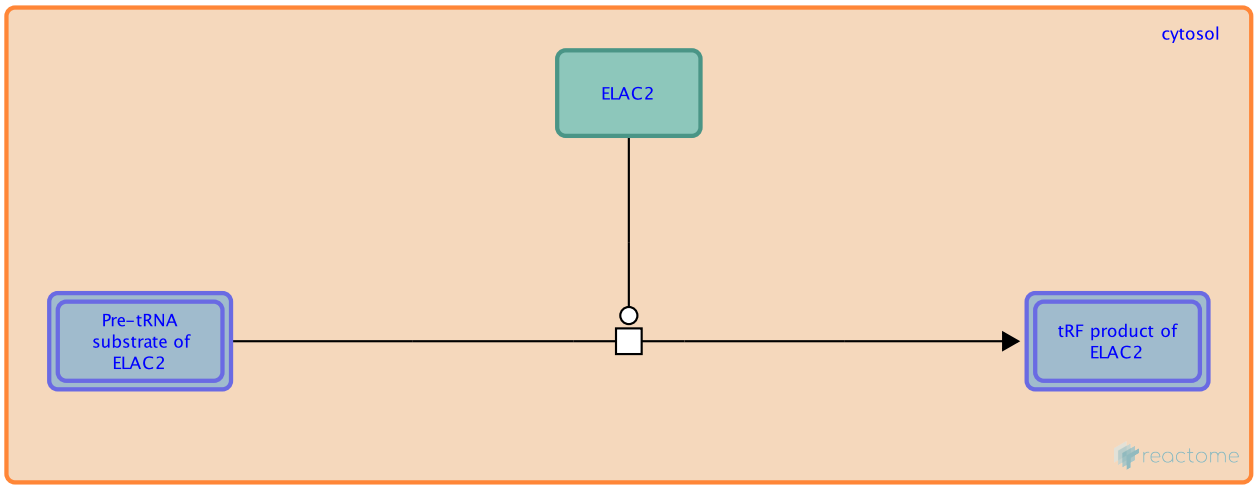
ELAC2 cleaves pre-tRNA to yield 3' trailer (type II tRF or tRF-1) ↗

Location: tRNA-derived small RNA (tsRNA or tRNA-related fragment, tRF) biogenesis

Stable identifier: R-HSA-9708812

Type: transition

Compartments: cytosol



ELAC2, the cytosolic ribonuclease responsible for tRNA maturation, cleaves pre-tRNA Ser TGA to create the 3' end of the mature tRNA and a downstream fragment, tRF-1001, which persists in the cytosol (Lee et al. 2009). ELAC2 is also thought to release tRF-1002 from pre-tRNA Asp GTC, tRF-1003 from pre-tRNA Ser GCT, and tRF-1004 from pre-tRNA Asp GTC.

Literature references

Lee, YS., Shibata, Y., Malhotra, A., Dutta, A. (2009). A novel class of small RNAs: tRNA-derived RNA fragments (tRFs). *Genes Dev, 23*, 2639-49. ↗

Editions

2020-11-29	Authored, Edited	May, B.
2021-02-13	Reviewed	Basso, K.
2021-02-20	Reviewed	Dutta, A., Wilson, B., Su, Z.

Table of Contents