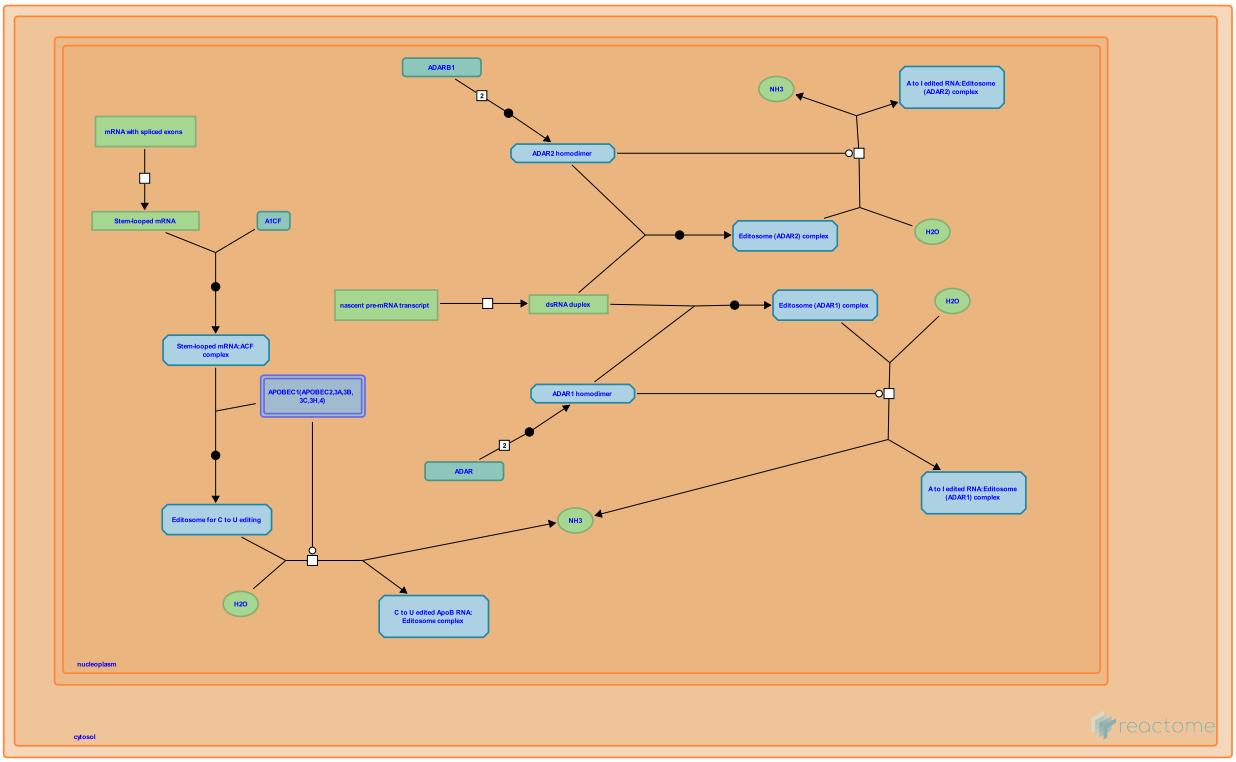
mRNA Editing



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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.
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. ↗

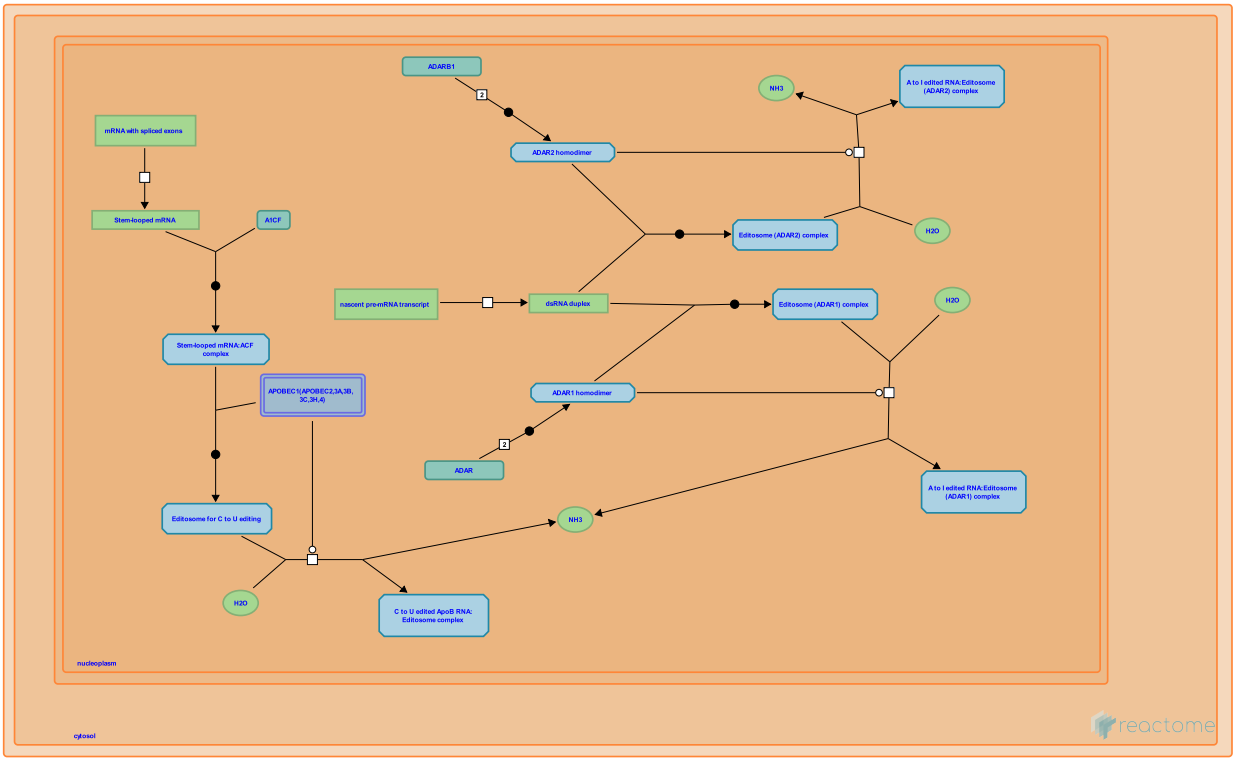
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

mRNA Editing ↗

Stable identifier: R-HSA-75072

Compartments: nucleoplasm



After transcription, some RNA molecules are altered to contain bases not encoded in the genome. Most often this involves the editing or modification of one base to another, but in some organisms can involve the insertion or deletion of a base. Such editing events alter the coding properties of mRNA.
RNA editing can be generally defined as the co- or post transcriptional modification of the primary sequence of RNA from that encoded in the genome through nucleotide deletion, insertion, or base modification mechanisms.
There are two pathways of RNA editing: the substitution/conversion pathway and the insertion/deletion pathway. The insertion/deletion editing occurs in protozoans like Trypanosoma, Leishmania; in slime molds like Physarum spp., and in some viral categories like paramyxoviruses, Ebola virus etc. To date, the substitution/conversion pathway has been observed in human along with other mammals, Drosophila, and some plants. The RNA editing processes are known to create diversity in proteins involved in various pathways like lipid transport, metabolism etc. and may act as potential targets for therapeutic intervention (Smith et al., 1997).
The reaction mechanisms of cytidine and adenosine deaminases is represented below. In both these reactions, NH3 is presumed to be released:

Literature references

Emeson, RB., Gott, JM. (2001). Functions and mechanisms of RNA editing. *Annu Rev Genet, 34*, 499-531. ↗

Panigrahi, AK., Stuart, K. (2002). RNA editing: complexity and complications. *Mol Microbiol, 45*, 591-6. ↗

Editions

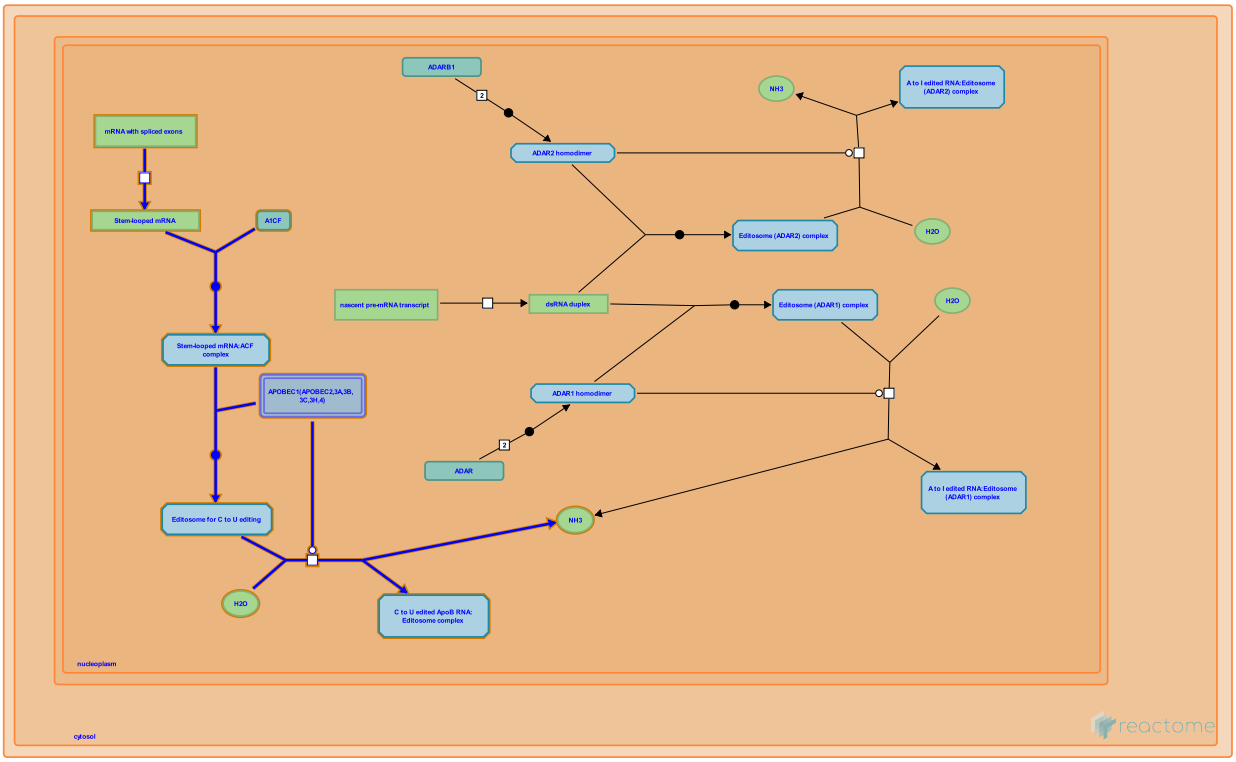
2003-08-22	Authored	Carmichael, GG.
2024-03-06	Edited	Gopinathrao, G.

mRNA Editing: C to U Conversion ↗

Location: mRNA Editing

Stable identifier: R-HSA-72200

Compartments: nucleoplasm



The best characterized case of C to U editing is in the intestinal apolipoprotein B transcript, where the editing event creates a premature translation stop codon and consequently leads to a shorter form of the protein. In the liver, C to U editing is important in the expression of specific isoforms of the apolipoprotein B enzyme. ApoB mRNA editing is a posttranscriptional, nuclear process that can be initiated after splicing, at the time of polyadenylation and is completed by the time pre-mRNA matures fully (reviewed by Blanc and Davidson, 2003).
This editing event is a simple hydrolytic cytidine deamination to uridine, and is carried out by the Apobec-1 enzyme, along with the Apobec-1 complementing factor, ACF. The editing of apo-B mRNA involves the site-specific deamination of (C6666 to U), which converts codon 2153 from a glutamine codon, CAA, to a premature stop codon, UAA. As ACF is distributed in a variety of tissues, and these genes contain multiple family members, it is possible that editing events in additional targets will be found.
The cis-acting regulatory elements for C to U editing include: 22 nt editing site within ApoB mRNA, 5' tripartite motif with an enhancer element adjacent to the target cytidine, a spacer element and mooring sequence both 3' to the cytidine (reviewed by Smith et al., 1997).

Literature references

Smith, HC., Dance, GS., Sowden, MP., Wedekind, JE. (2003). Messenger RNA editing in mammals: new members of the APOBEC family seeking roles in the family business. *Trends Genet, 19*, 207-16. ↗

Davidson, NO., Blanc, V. (2003). C-to-U RNA editing: mechanisms leading to genetic diversity. *J Biol Chem, 278*, 1395-8. ↗

Emeson, RB., Gott, JM. (2001). Functions and mechanisms of RNA editing. *Annu Rev Genet, 34*, 499-531. ↗

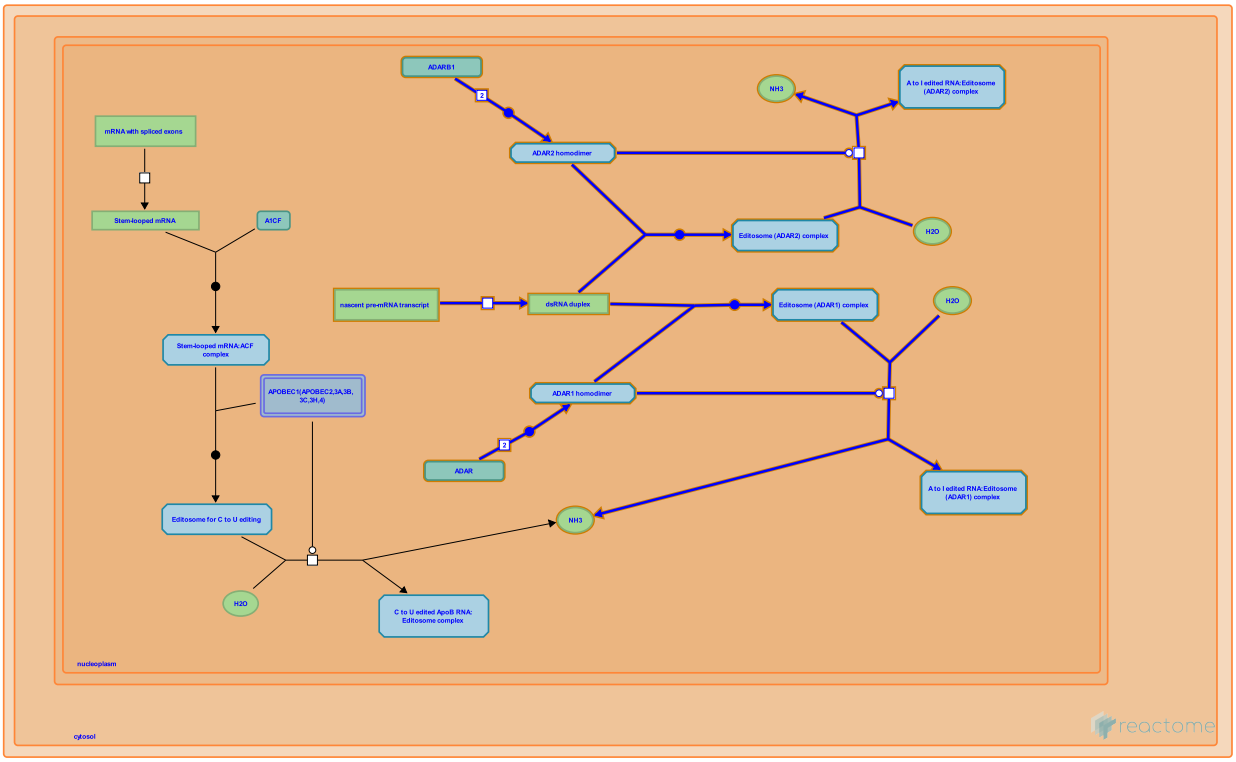
Anant, S., Navaratnam, N., Scott, J., Chester, A. (2000). RNA editing: cytidine to uridine conversion in apolipoprotein B mRNA. *Biochim Biophys Acta, 1494*, 1-13. ↗

mRNA Editing: A to I Conversion ↗

Location: mRNA Editing

Stable identifier: R-HSA-75064

Compartments: nucleoplasm



In humans the deamination of adenosines to inosines is the most common editing event. It is particularly prevalent in the brain, where it leads to amino acid changes that affect the conductance of several ion channels. Inosines are recognized by the translation machinery as if they were guanosines.
ADARs (Adenosine Deaminases Acting on RNA) modify pre-mRNA, acting as single peptides and recognize structural determinants in the RNA. To date 3 members of this deaminase family are known: ADAR 1, ADAR 2, and ADAR 3 that share a common modular domain structure. ADAR 1 and 2 contain a catalytic deaminase domain, a double-stranded RNA binding domain and exhibit RNA editing activity. ADAR1 activity is found in various mammalian tissues with the highest concentration in brain.
An increasing number of mammalian genes have been found to undergo deamination by ADARs. Deamination by editing in pre-mRNAs encoding subunits of ionotropic glutamate receptors (GluRs) is another well studied example. An editing event at the Q/R site of the GluR2 (GluRB) subunit of AMPA receptors converts a Gln codon CAG to an Arg codon CIG rendering the heteromeric receptor impermeable to Ca 2+ ions. Another example is the editing of 5-HT2C subtype serotonin receptor mRNA resulting in receptor isoforms with reduced G-protein coupling efficiency (reviewed by Gerber and Keller, 2001).
In mice, the editosomes with ADAR proteins require some cis-acting elements like an intronic 'editing-site complementary sequence (ECS)'. Although evolutionarily conserved, the actual role of ECS is not yet elucidated in humans. The editing complex can be generally represented as:

Literature references

Keller, W., Gerber, AP. (2001). RNA editing by base deamination: more enzymes, more targets, new mysteries. *Trends Biochem Sci, 26*, 376-84. ↗

Pomerantz, SC., McCloskey, JA., Crain, PF., Polson, AG., Bass, BL. (1992). The mechanism of adenosine to inosine conversion by the double-stranded RNA unwinding/modifying activity: a high-performance liquid chromatography-mass spectrometry analysis. *Biochemistry, 30*, 11507-14. ↗

Bass, BL. (2002). RNA editing by adenosine deaminases that act on RNA. *Annu Rev Biochem, 71*, 817-46. ↗

Davidson, NO., Blanc, V. (2003). C-to-U RNA editing: mechanisms leading to genetic diversity. *J Biol Chem, 278*, 1395-8. ↗

Higuchi, M., Herb, A., Sprengel, R., Maas, S., Seeburg, PH., Melcher, T. (1997). RED2, a brain-specific member of the RNA-specific adenosine deaminase family. *J Biol Chem, 271*, 31795-8. ↗

Editions

2003-08-22	Authored	Carmichael, GG.

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