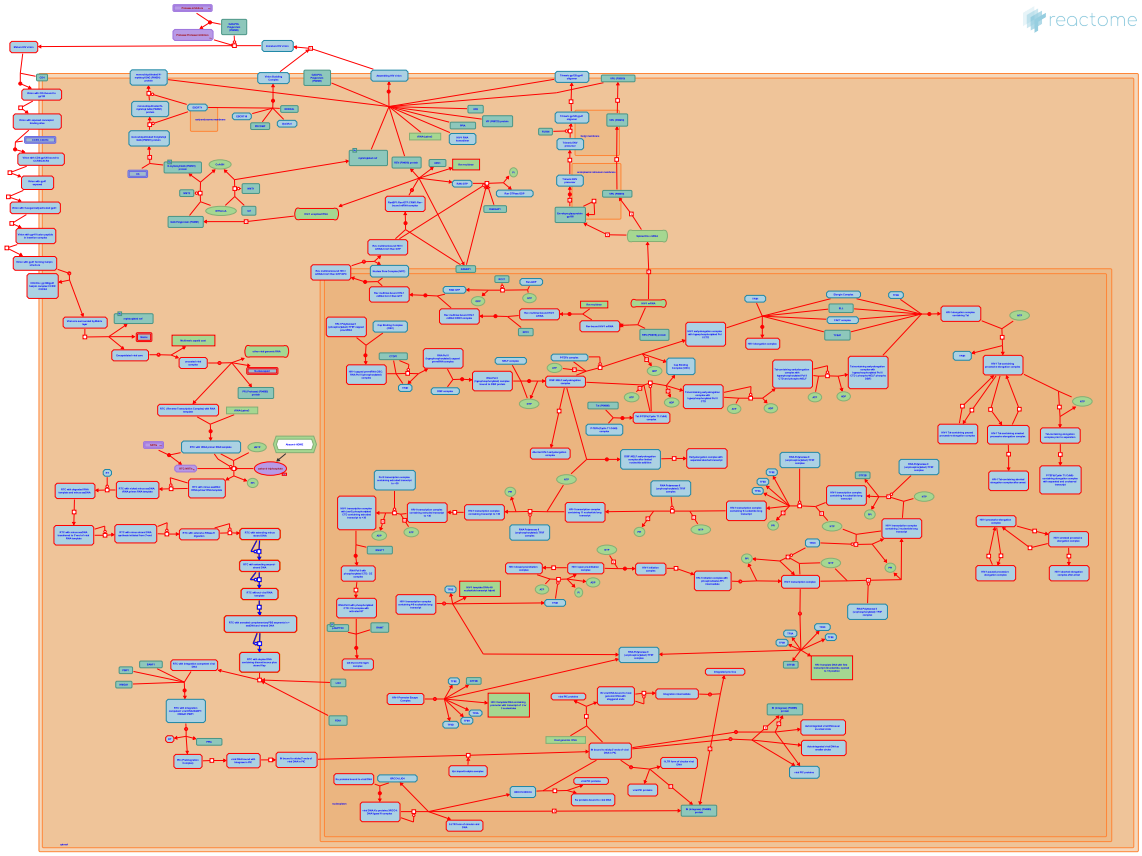
Plus-strand DNA synthesis



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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.

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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. ↗

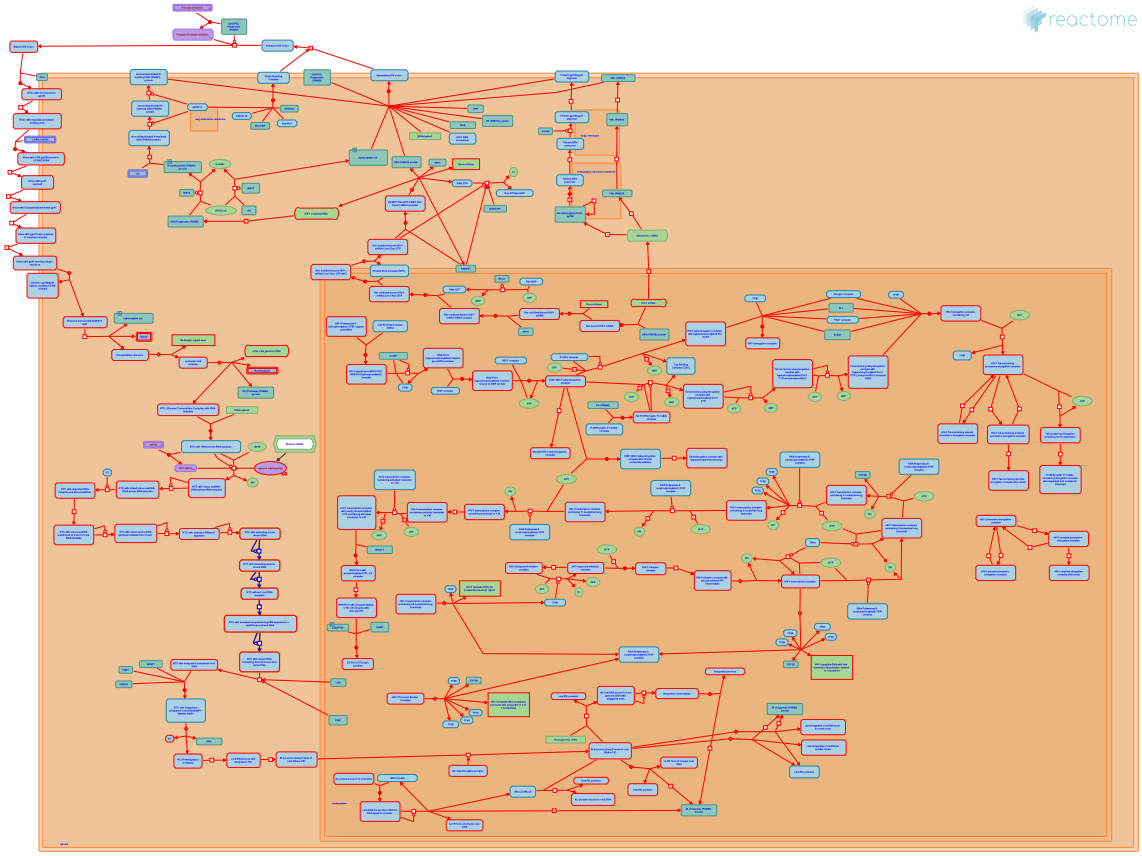
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Plus-strand DNA synthesis ↗

Stable identifier: R-HSA-164525

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



Two specific polypurine tracts (PPT sequences) in the viral RNA, one within the pol gene (central or cPPT) and one immediately preceding the U3 sequence (3' PPT), are spared from degradation during minus strand DNA synthesis and prime plus-strand synthesis. At least two discrete steps of DNA replication, removal of the PPT RNAs and the tRNA primer that initiated minus-strand synthesis, and a strand transfer lead to the synthesis of a linear duplex DNA corresponding to the full length of the HIV genomic RNA with long terminal repeat (LTR) sequences at both ends. Both DNA synthesis and RNA degradation are catalyzed by domains of the HIV-1 reverse transcriptase (RT) heterodimer. During plus-strand synthesis, Preston and colleagues observed secondary sites of plus-strand initiation at low frequency both in the cell-free system and in cultured virus-infected cells (Klarman et al., 1997).

Literature references

De Clercq, E., Anne, J., Jonckheere, H. (2000). The HIV-1 reverse transcription (RT) process as target for RT inhibitors. *Med Res Rev, 20*, 129-54. ↗

Varmus, HE., Hughes, SH., Coffin, JM. (1997). Reverse Transcriptase and the Generation of Retroviral DNA, Retroviruses. *Cold Spring Harbor Laboratory Press*, 121-160.

Editions

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3' PPT-primed initiation of plus-strand DNA synthesis ↗

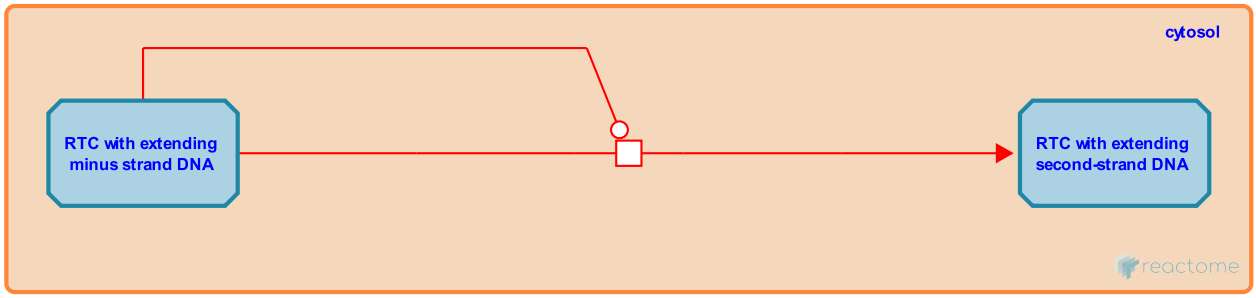
Location: Plus-strand DNA synthesis

Stable identifier: R-HSA-164513

Type: transition

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



HIV-1 genomic RNA contains a centrally located PPT (cPPT) within the pol gene that, like 3'PPT, is spared by RNase H during minus-strand DNA synthesis and persists to prime plus-strand DNA synthesis. This ribonucleotide primes the synthesis of a plus-strand DNA extending through the U3 and R regions of the HIV sequence and terminating in the PBS region (the tRNA primer-binding site). This DNA segment is known as plus-strand strong-stop DNA (+sssDNA) (Telesnitsky and Goff 1997; Pullen et al. 1993; Huber and Richardson 1990). cPPT priming is important for efficient viral replication (Alizon et al. 1992; Rausch and Le Grice 2004). Several features of cPPT priming in vivo remain to be clarified.

Followed by: RNase H-mediated digestion of tRNA, 3'PPT and cPPT RNA primers

Literature references

De Clercq, E., Anne, J., Jonckheere, H. (2000). The HIV-1 reverse transcription (RT) process as target for RT inhibitors. *Med Res Rev, 20*, 129-54. ↗

Pullen, KA., Champoux, JJ., Rattray, AJ. (1993). The sequence features important for plus strand priming by human immunodeficiency virus type 1 reverse transcriptase. *J Biol Chem, 268*, 6221-7. ↗

Huber, HE., Richardson, CC. (1990). Processing of the primer for plus strand DNA synthesis by human immunodeficiency virus 1 reverse transcriptase. *J Biol Chem, 265*, 10565-73. ↗

Varmus, HE., Hughes, SH., Coffin, JM. (1997). Reverse Transcriptase and the Generation of Retroviral DNA, Retroviruses. *Cold Spring Harbor Laboratory Press*, 121-160.

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RNase H-mediated digestion of tRNA, 3'PPT and cPPT RNA primers ↗

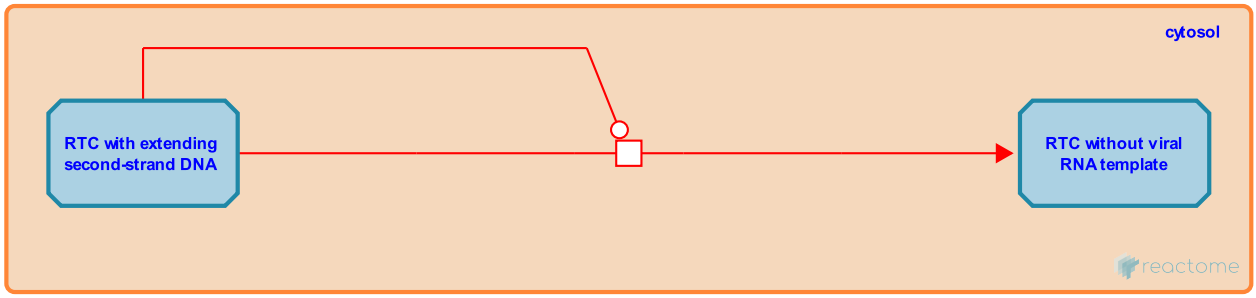
Location: Plus-strand DNA synthesis

Stable identifier: R-HSA-173769

Type: transition

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



RNase H catalyzes the precise cleavage of the bonds linking the primer tRNA attached to the minus-strand DNA, the 3' PPT RNA primer to the plus-strand strong-stop DNA, and the cPPT primer to the stretch of plus-strand DNA whose synthesis it primed. In each case, precise cleavage near the RNA-DNA junction occurs (Pullen et al. 1992). HIV-1 RT is the only reverse transcriptase that cleaves the tRNA:DNA junction so as to leave a ribo A residue from the tRNA at the 5' end of the minus strand.

While a single RT heterodimer could in principle catalyze DNA synthesis and primer RNA:DNA bond cleavage, evidence from several in vitro systems suggests that separate RT heterodimers are likely to catalyze these two reactions (Rausch and Le Grice 2004).

Preceded by: 3' PPT-primed initiation of plus-strand DNA synthesis

Followed by: Second strand transfer by annealing complementary PBS sequences

Literature references

De Clercq, E., Anne, J., Jonckheere, H. (2000). The HIV-1 reverse transcription (RT) process as target for RT inhibitors. *Med Res Rev, 20*, 129-54. ↗

Ishimoto, LK., Pullen, KA., Champoux, JJ. (1992). Incomplete removal of the RNA primer for minus-strand DNA synthesis by human immunodeficiency virus type 1 reverse transcriptase. *J Virol, 66*, 367-73. ↗

Varmus, HE., Hughes, SH., Coffin, JM. (1997). Reverse Transcriptase and the Generation of Retroviral DNA, Retroviruses. *Cold Spring Harbor Laboratory Press*, 121-160.

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Second strand transfer by annealing complementary PBS sequences ↗

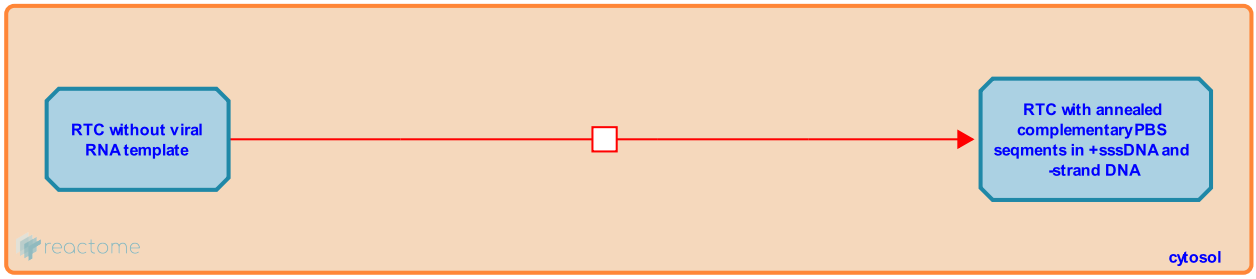
Location: Plus-strand DNA synthesis

Stable identifier: R-HSA-164512

Type: transition

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



With the removal of all viral genomic RNA and tRNA, the PBS sequence at the 3' end of the plus-strand strong-stop DNA (+sssDNA) is free to pair with the complementary PBS sequence at the 3' end of the minus-strand DNA, to generate a circular structure (Telesnitsky and Goff 1997).

Preceded by: RNase H-mediated digestion of tRNA, 3'PPT and cPPT RNA primers

Followed by: Synthesis of full-length duplex viral DNA with a discontinuous plus strand

Literature references

De Clercq, E., Anne, J., Jonckheere, H. (2000). The HIV-1 reverse transcription (RT) process as target for RT inhibitors. *Med Res Rev, 20*, 129-54. ↗

Varmus, HE., Hughes, SH., Coffin, JM. (1997). Reverse Transcriptase and the Generation of Retroviral DNA, Retroviruses. *Cold Spring Harbor Laboratory Press*, 121-160.

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Synthesis of full-length duplex viral DNA with a discontinuous plus strand ↗

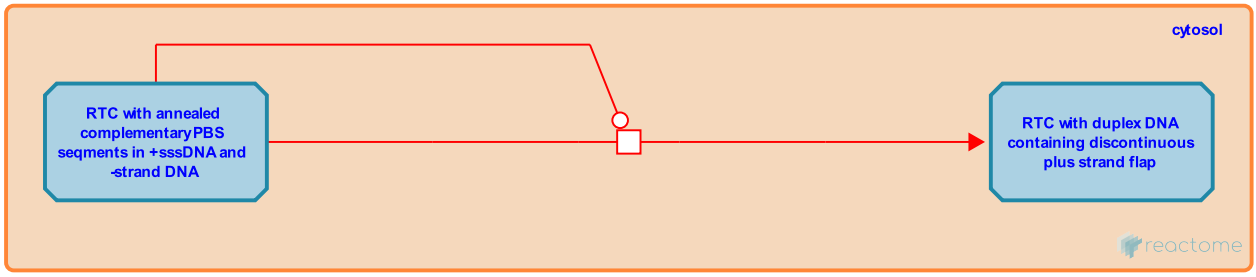
Location: Plus-strand DNA synthesis

Stable identifier: R-HSA-164505

Type: transition

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



After the second jump, elongation of the plus and minus strands continues. The elongation process requires strand displacement, which RT can mediate, at least in vitro (Huber et al. 1989; Hottiger et al. 1994; Rausch and Le Grice 2004). The final product is a blunt-ended linear duplex DNA with a discontinuity in its "plus" strand at the site of the cPPT sequence motif.

Preceded by: Second strand transfer by annealing complementary PBS sequences

Literature references

De Clercq, E., Anne, J., Jonckheere, H. (2000). The HIV-1 reverse transcription (RT) process as target for RT inhibitors. *Med Res Rev, 20*, 129-54. ↗

Varmus, HE., Hughes, SH., Coffin, JM. (1997). Reverse Transcriptase and the Generation of Retroviral DNA, Retroviruses. *Cold Spring Harbor Laboratory Press*, 121-160.

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