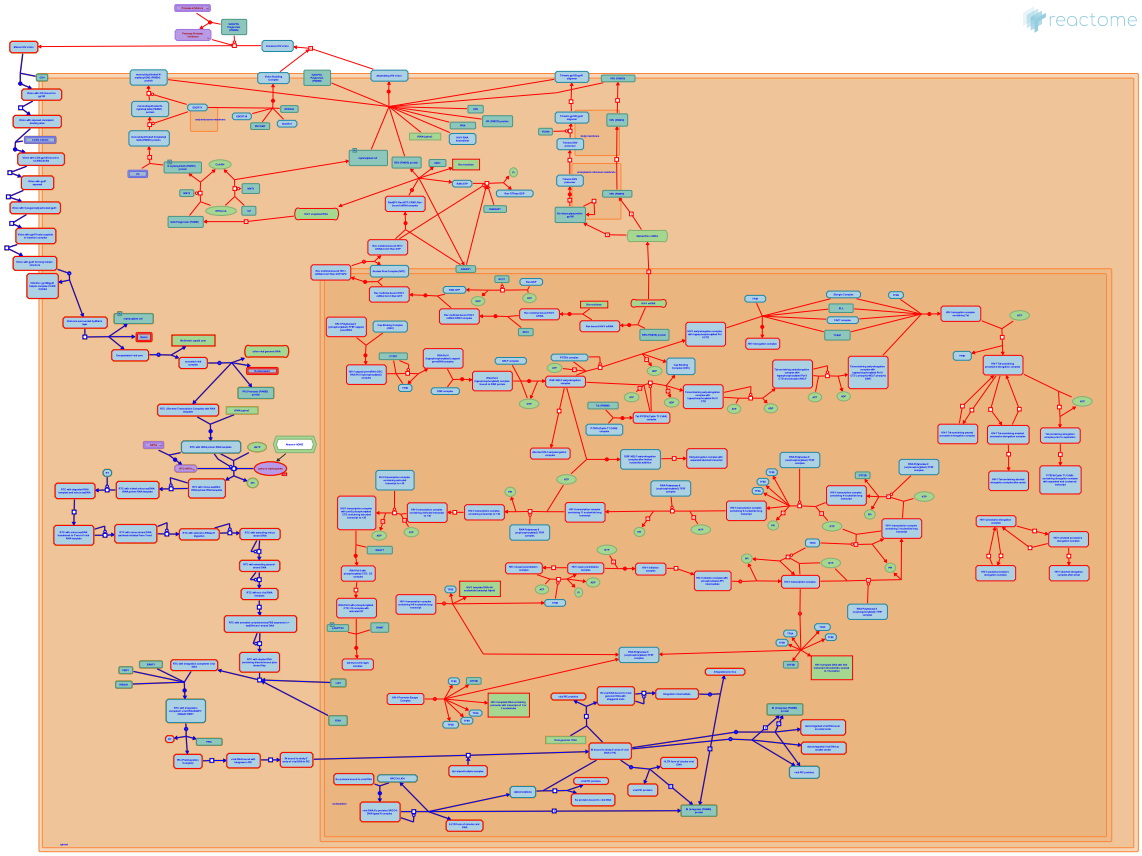
Early Phase of HIV Life Cycle



Aiken, C., Bukrinsky, M., Bushman, FD., D'Eustachio, P., Gopinathrao, G., Hughes, SH., Iordanskiy, S., Morrow, MP., Reeves, J.

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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. ↗

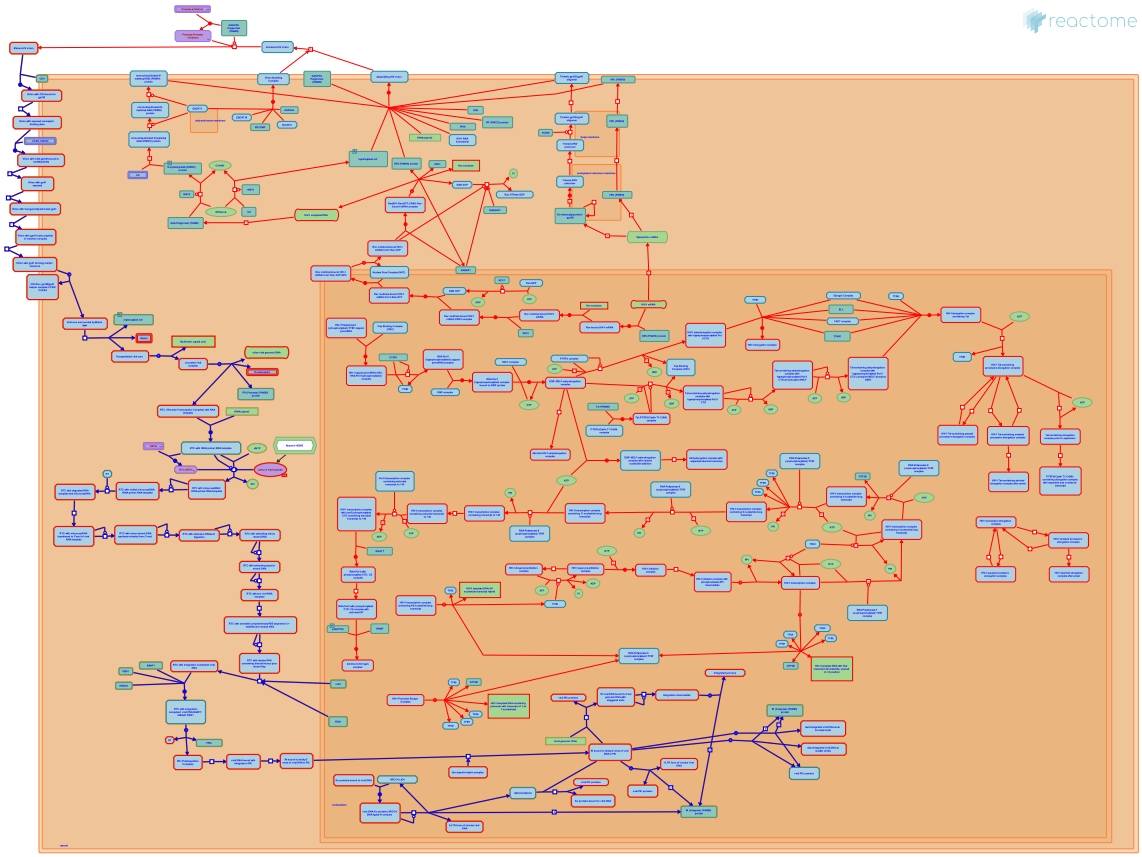
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Early Phase of HIV Life Cycle ↗

Stable identifier: R-HSA-162594

Diseases: Human immunodeficiency virus infectious disease



In the **early phase** of HIV lifecycle, an active virion binds and enters a target cell mainly by specific interactions of the viral envelope proteins with host cell surface receptors. The virion core is uncoated to expose a viral nucleoprotein complex containing RNA and viral proteins. HIV RNA genome is reverse transcribed by the viral Reverse Transcriptase to form a cDNA copy, that gets inserted into host cell DNA. The viral Integrase enzyme is vital to carry out the integration of the viral cDNA into the host genome. The host DNA repair enzymes probably repair the breaks in DNA at the sites of integration.

Literature references

Peterlin, BM., Greene, WC. (2002). Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy. *Nat Med, 8*, 673-80. ↗

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-05-16	Authored	Gopinathrao, G., D'Eustachio, P., Morrow, MP., Iordanskiy, S., Bukrinsky, M.
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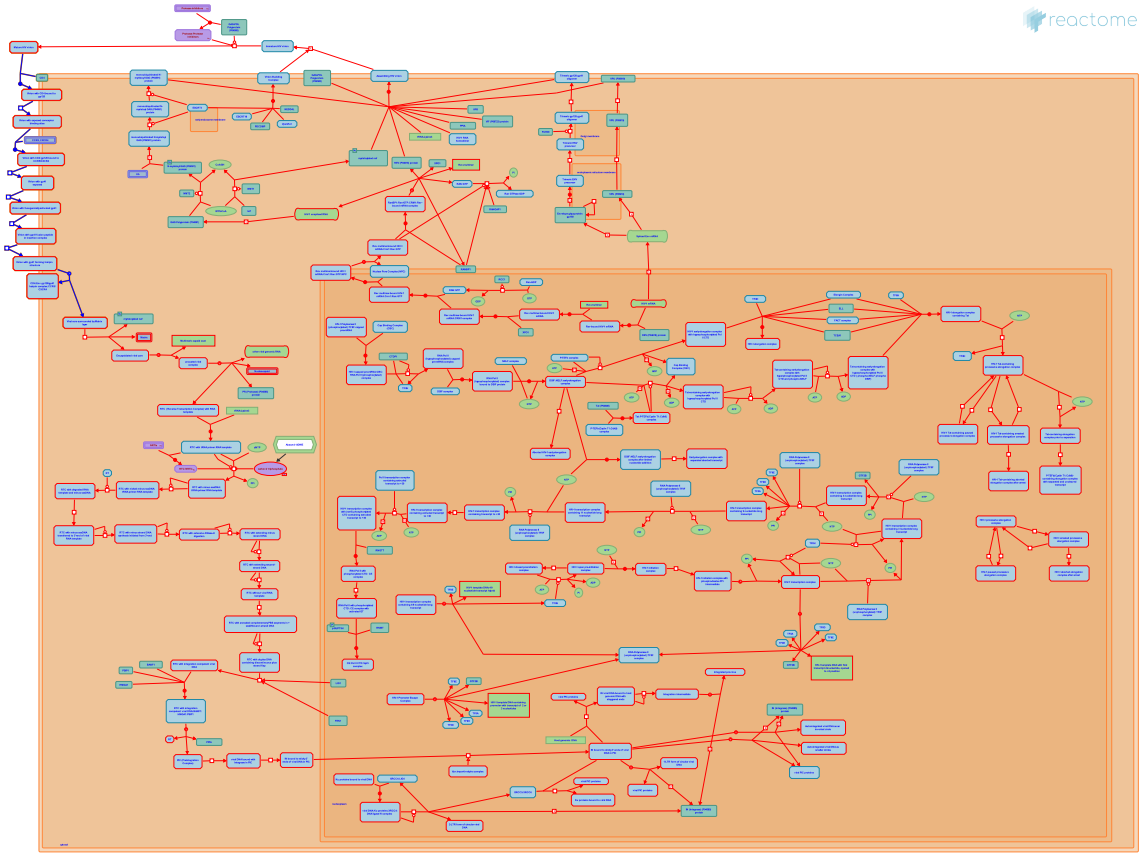
Binding and entry of HIV virion ↗

Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-173107

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



HIV enters cells by fusion at the cell surface, that results in a productive infection. The envelope (Env) protein of HIV mediates entry. Env is composed of a surface subunit, gp120, and a transmembrane subunit, gp41, which assemble as heterotrimers on the virion surface.The trimeric, surface gp120 protein (SU) on the virion engages CD4 on the host cell, inducing conformational changes that promote binding to select chemokine receptors CCR5 and CXCR4.
The sequential interplay between SU, CD4 and chemokine coreceptors prompts a conformational change in the transmembrane gp41. This coiled coil protein, assembled as a trimer on the virion membrane, springs open to project three peptide fusion domains that 'harpoon' the lipid bilayer of the target cell. A hairpin structure (also referred to as a "coiled coil bundle") is subsequently formed when the extracellular portion of gp41 collapses, and this hairpin formation promotes the fusion of virion and target cell membranes by bringing them into close proximity. Virion and target cell membrane fusion leads to the release of HIV viral cores into the cell interior.

Editions

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2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
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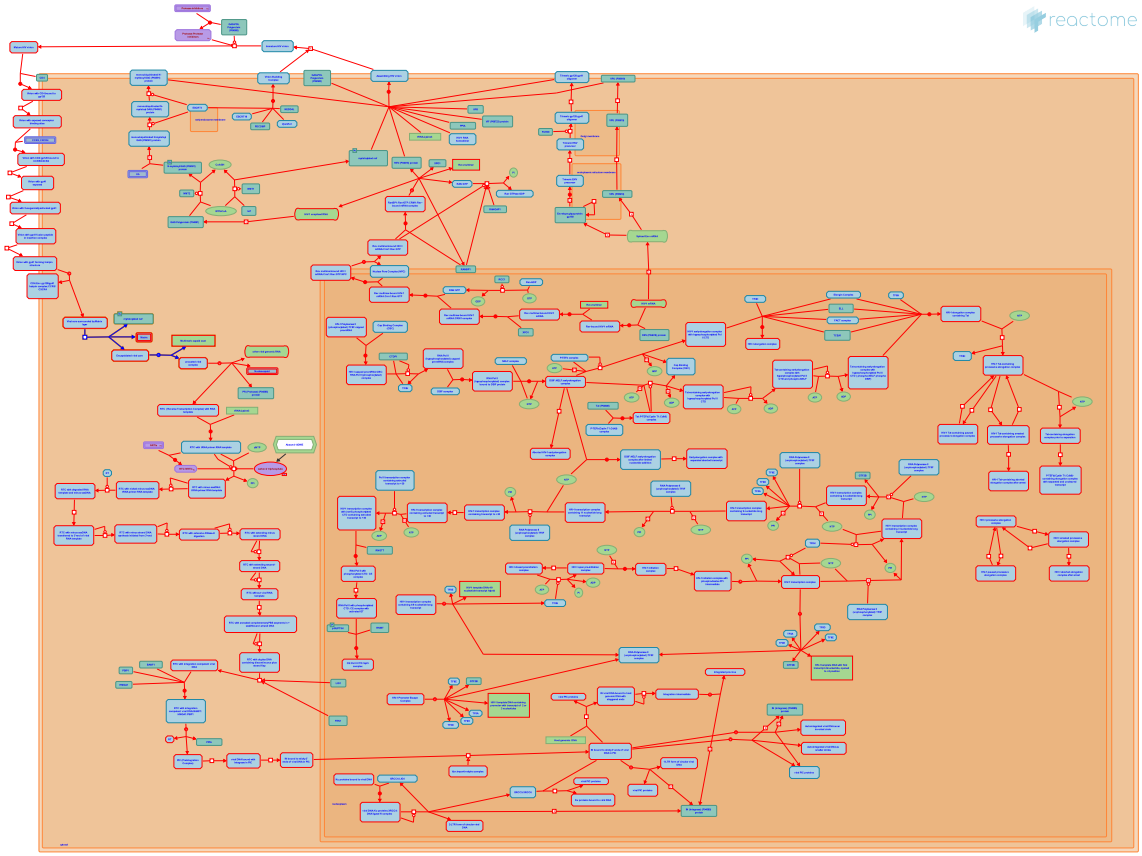
Uncoating of the HIV Virion ↗

Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-162585

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



HIV-1 uncoating is a poorly understood process. It likely involves a progressive and partial dissembly of matrix and capsid layers. While viral proteins like MA and Nef are thought to be involved, the primary cause seems to be the cytosolic pH and a simple dilution effect. Successful uncoating generates the viral reverse transcription complex, which comprises the diploid viral RNA genome, tRNALys primer, RT, IN, MA, nucleocapsid (NC), viral protein R (Vpr) and various host proteins; the reverse-transcription complex is thus liberated from the plasma membrane. It is believed that the transiting viral nucleoprotein complex associates with the elements of cytoskeleton like actin microfilaments.

Literature references

Peterlin, BM., Greene, WC. (2002). Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy. *Nat Med, 8*, 673-80. ↗

Bukrinsky, M. (2004). A hard way to the nucleus. *Mol Med, 10*, 1-5. ↗

Borisy, GG., Vodicka, MA., McDonald, D., Emerman, M., Svitkina, TM., Lucero, G. et al. (2002). Visualization of the intracellular behavior of HIV in living cells. *J Cell Biol, 159*, 441-52. ↗

Lehmann-Che, J., Saib, A. (2004). Early stages of HIV replication: how to hijack cellular functions for a successful infection. *AIDS Rev, 6*, 199-207. ↗

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Formation of RTC (Reverse Transcription Complex) ↗

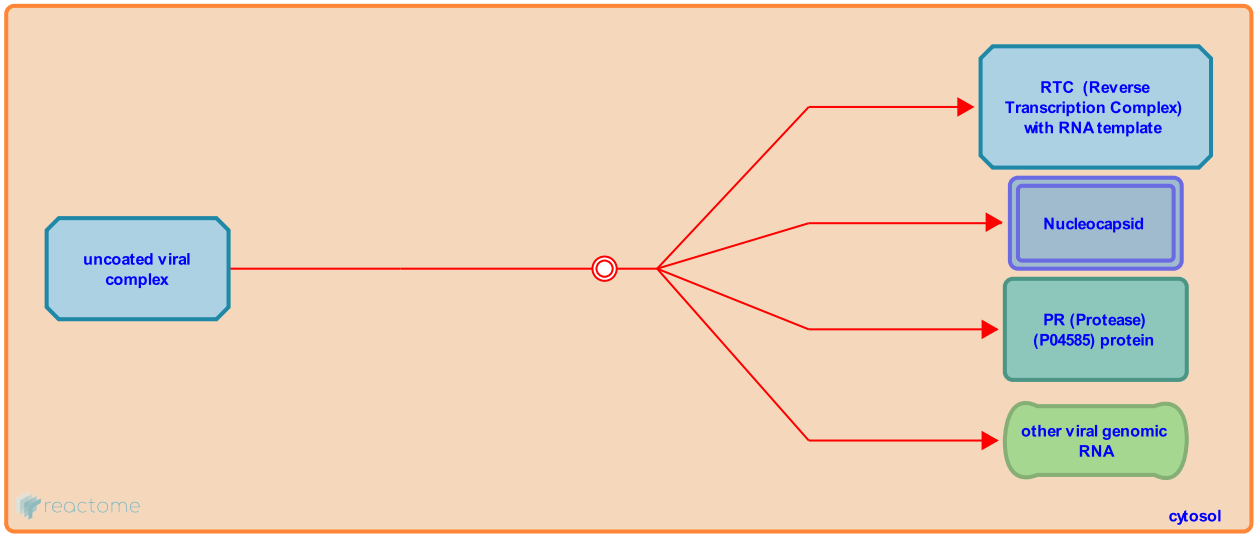
Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-173771

Type: dissociation

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



Reverse transcription complex is a transitory structure where reverse transcription takes place. Initially, it is likely identical to the RNA-protein complex found inside the virion core. Upon maturation, it may shed some HIV proteins (such as MA or Vpr) and incorporate cellular proteins (such as INI1 or PML).

Followed by: Annealing of 3'-end of unwound transfer RNA primer with genomic RNA

Literature references

Kashanchi, F., Iordanskiy, S., Berro, R., Bukrinsky, M., Altieri, M. (2006). Intracytoplasmic maturation of the human immunodeficiency virus type 1 reverse transcription complexes determines their capacity to integrate into chromatin. *Retrovirology, 3*, 4. ↗

Orenstein, J., Zhang, H., Pomerantz, RJ., Dornadula, G. (2000). Morphologic changes in human immunodeficiency virus type 1 virions secondary to intravirion reverse transcription: evidence indicating that reverse transcription may not take place within the intact viral core. *J Hum Virol, 3*, 165-72. ↗

McDonald, TL., Bukrinsky, M., Stevenson, M., Pushkarskaya, T., Sharova, N., Tarpley, WG. (1993). Association of integrase, matrix, and reverse transcriptase antigens of human immunodeficiency virus type 1 with viral nucleic acids following acute infection. *Proc Natl Acad Sci U S A, 90*, 6125-9. ↗

Fassati, A., Goff, SP. (2001). Characterization of intracellular reverse transcription complexes of human immunodeficiency virus type 1. *J Virol, 75*, 3626-35. ↗

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Annealing of 3'-end of unwound transfer RNA primer with genomic RNA ↗

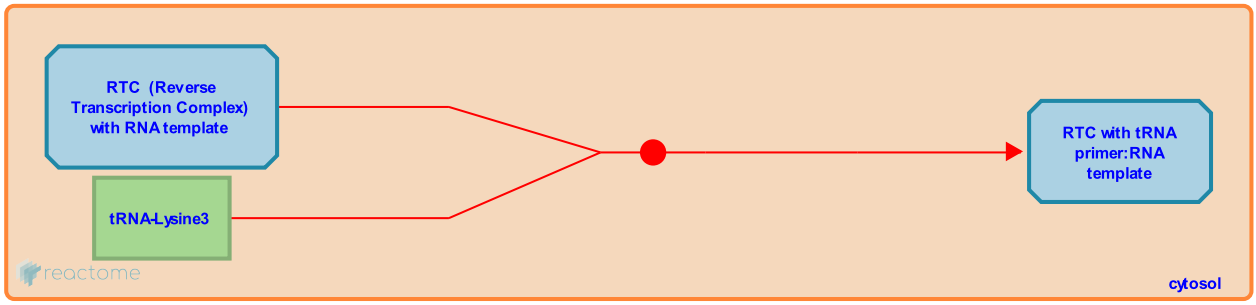
Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-164527

Type: binding

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



Retroviruses use cellular tRNAs as primers for reverse transcription of the viral genomic RNA (Mak and Kleiman 1997). The primer tRNA is selectively packaged during assembly of retrovirus particles. In the case of HIV-1, lysine tRNAs are preferentially incorporated during retroviral packaging, and lysine tRNA 3, the specific isoacceptor form that serves as a primer for reverse transcription, anneals to the PBS (primer binding site) within the U5 region of the viral genomic RNA. This association appears to be mediated by the viral reverse transcriptase (RT) protein, possibly its "thumb" and "connection" domains (Jiang et al. 1993; Mak et al. 1994; Mishima and Steitz 1995).

Preceded by: Formation of RTC (Reverse Transcription Complex)

Followed by: Reverse Transcription of HIV RNA

Literature references

Ladha, A., Jiang, M., Rovinski, B., Klein, M., Kleiman, L., Cohen, E. et al. (1993). Identification of tRNAs incorporated into wild-type and mutant human immunodeficiency virus type 1. *J Virol, 67*, 3246-53. ↗

Jiang, M., Rekosh, D., Kleiman, L., Wainberg, MA., Hammarskjold, ML., Mak, J. (1994). Role of Pr160gag-pol in mediating the selective incorporation of tRNA(Lys) into human immunodeficiency virus type 1 particles. *J Virol, 68*, 2065-72. ↗

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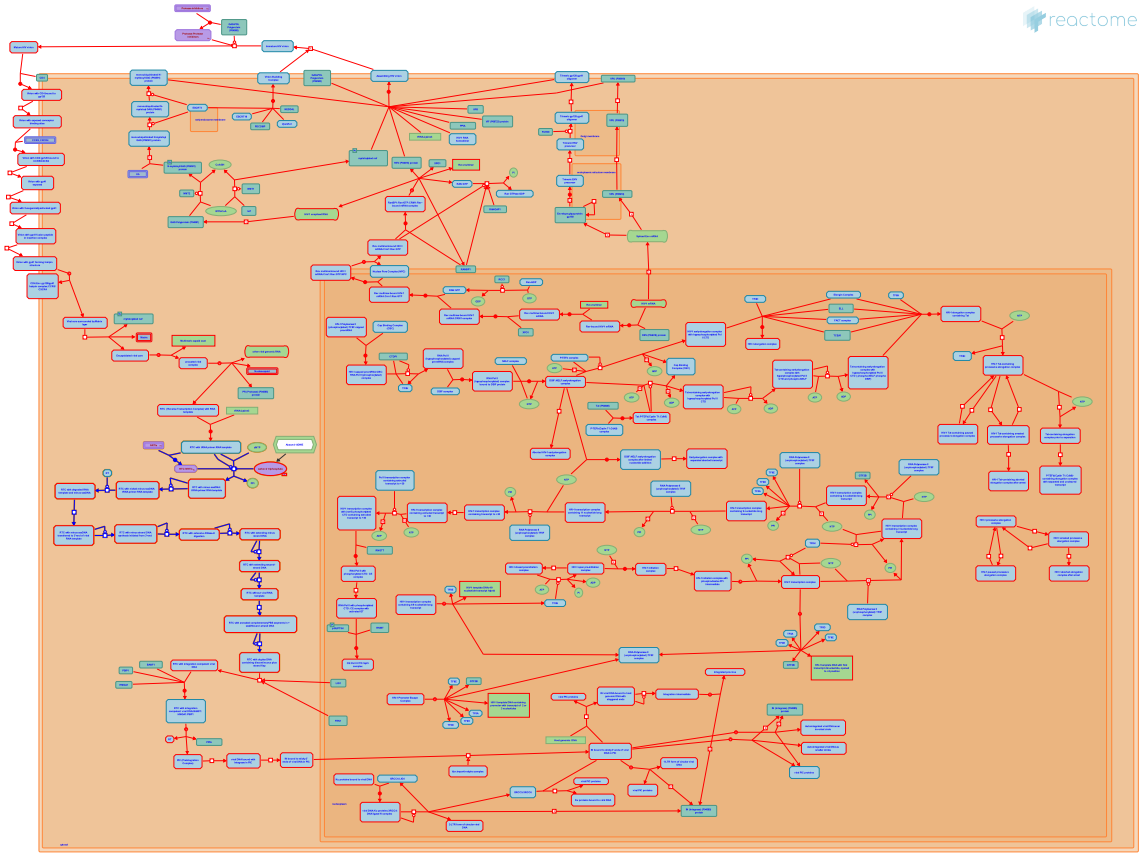
Reverse Transcription of HIV RNA ↗

Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-162589

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



The RNA genome of HIV-1, like that of other retroviruses, is reverse-transcribed (Baltimore 1970; Temin and Mizutani 1970) into double-stranded DNA, which is then integrated into a host cell chromosome and transcribed to yield both viral mRNAs and viral genomic RNAs. HIV-1 reverse transcription takes place in the cytosol of a newly infected host cell and involves multiple steps of RNA synthesis and degradation of the RNA strand of RNA:DNA duplexes mediated by the HIV-1 RT protein, as well as two template switches, to yield a DNA duplex colinear with the viral genomic RNA but with additional Long Terminal Repeat (LTR) sequence motifs at both ends (Telesnitsky and Goff 1997; Jonckheere et al. 2000).

HIV-1 RT has two catalytic activities essential for transcription of a DNA duplex copy of the viral genomic RNA: a reverse transcriptase activity and an RNase H activity. The reverse transcriptase is primer dependent and can transcribe both RNA and DNA templates in a 5'-3' direction. The RNaseH acts on the RNA strand of RNA:DNA duplexes and can catalyze both endo- and exonucleolytic cleavage of such an RNA strand. RT is a heterodimer of 66 and 51 kD polypeptides, both generated by cleavage of the HIV-1 Pol gene product: p66 contains Pol amino acid residues 599-1158; p51 contains residues 599-1038. Both active sites of the HIV-1 RT enzyme are contained in the p66 polypeptide, the polymerase activity in its aminoterminal region, and the RNase in its carboxyterminus. The p51 subunit lacks an RNaseH domain, and while its polymerase domain is intact, its conformation in the p66:p51 heterodimer occludes the active site (Hughes et al. 1996; Jacobo-Molina et al. 1993; Kohlstaedt et al. 1992; Wang et al. 1994).

The process of reverse transcription is outlined in the figure below: viral genomic RNA and primer tRNA are shown in black, "minus" strand DNA is shown in red, and "plus" strand DNA is shown in blue.

Literature references

Lentz, K., Le Grice, SF., Hughes, SH., Hostomsky, Z., Arnold, E. (1996). What is the orientation of DNA polymerases on their templates?. *J Virol, 70*, 2679-83. ↗

Rice, PA., Kohlstaedt, LA., Steitz, TA., Wang, J., Friedman, JM. (1992). Crystal structure at 3.5 A resolution of HIV-1 reverse transcriptase complexed with an inhibitor. *Science, 256*, 1783-90. ↗

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. ↗

Rice, PA., Kohlstaedt, LA., Steitz, TA., Jager, J., Smerdon, SJ., Wang, J. et al. (1994). Structural basis of asymmetry in the human immunodeficiency virus type 1 reverse transcriptase heterodimer. *Proc Natl Acad Sci U S A, 91*, 7242-6. ↗

Clark AD, Jr., Ding, J., Hughes, SH., Williams, RL., Ferris, AL., Nanni, RG. et al. (1993). Crystal structure of human immunodeficiency virus type 1 reverse transcriptase complexed with double-stranded DNA at 3.0 A resolution shows bent DNA. *Proc Natl Acad Sci U S A, 90*, 6320-4. ↗

Editions

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Removal of plus-strand flap and gap closure complete synthesis of linear duplex viral DNA ↗

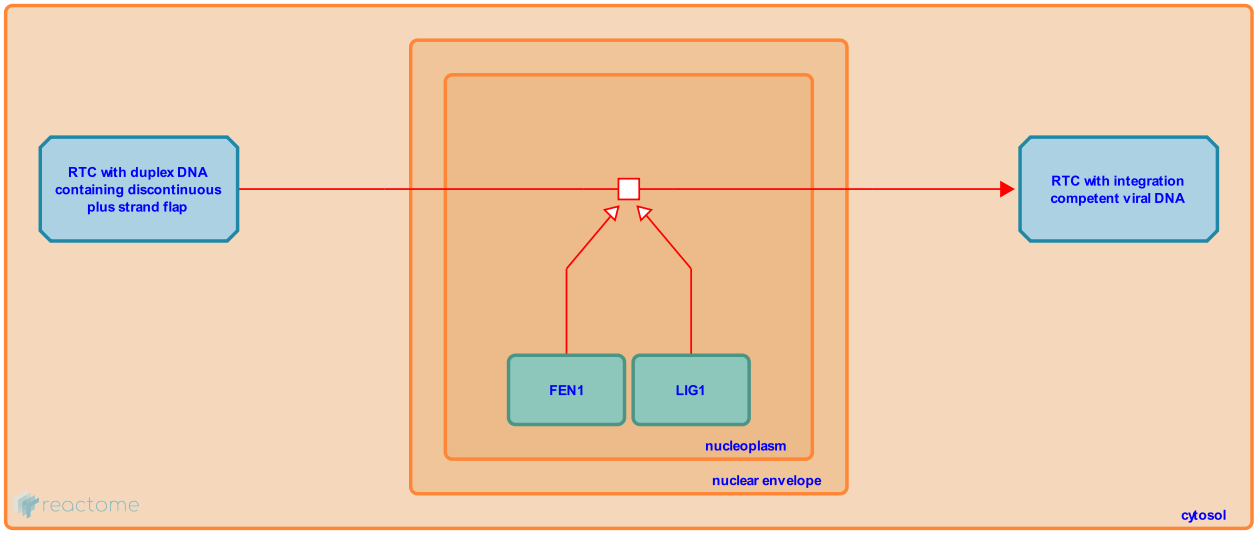
Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-182876

Type: transition

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



The fate of the discontinuous viral DNA duplex synthesized in the cytosol of an infected cell by HIV-1 reverse transcriptase is not entirely clear. Studies of some viral systems suggest that this discontinuous structure is required for passage of the viral duplex DNA into the nucleus while there are evidence contrary to this observation. Studies in vitro indicate that human nuclear flap endonuclease and DNA ligase can remove the flap and seal the plus-strand discontinuity in HIV-1 DNA (Miller et al. 1995; Rausch and Le Grice 2004; Rumbaugh et al. 1998), although role of flap is not yet clear.

Literature references

Le Grice, SF., Rausch, JW. (2004). 'Binding, bending and bonding': polypurine tract-primed initiation of plus-strand DNA synthesis in human immunodeficiency virus. *Int J Biochem Cell Biol, 36*, 1752-66. ↗

Fuentes, GM., Bambara, RA., Rumbaugh, JA. (1998). Processing of an HIV replication intermediate by the human DNA replication enzyme FEN1. *J Biol Chem, 273*, 28740-5. ↗

Wang, B., Bushman, FD., Miller, MD. (1995). Human immunodeficiency virus type 1 preintegration complexes containing discontinuous plus strands are competent to integrate in vitro. *J Virol, 69*, 3938-44. ↗

Editions

2006-05-19	Authored	Gopinathrao, G., D'Eustachio, P.
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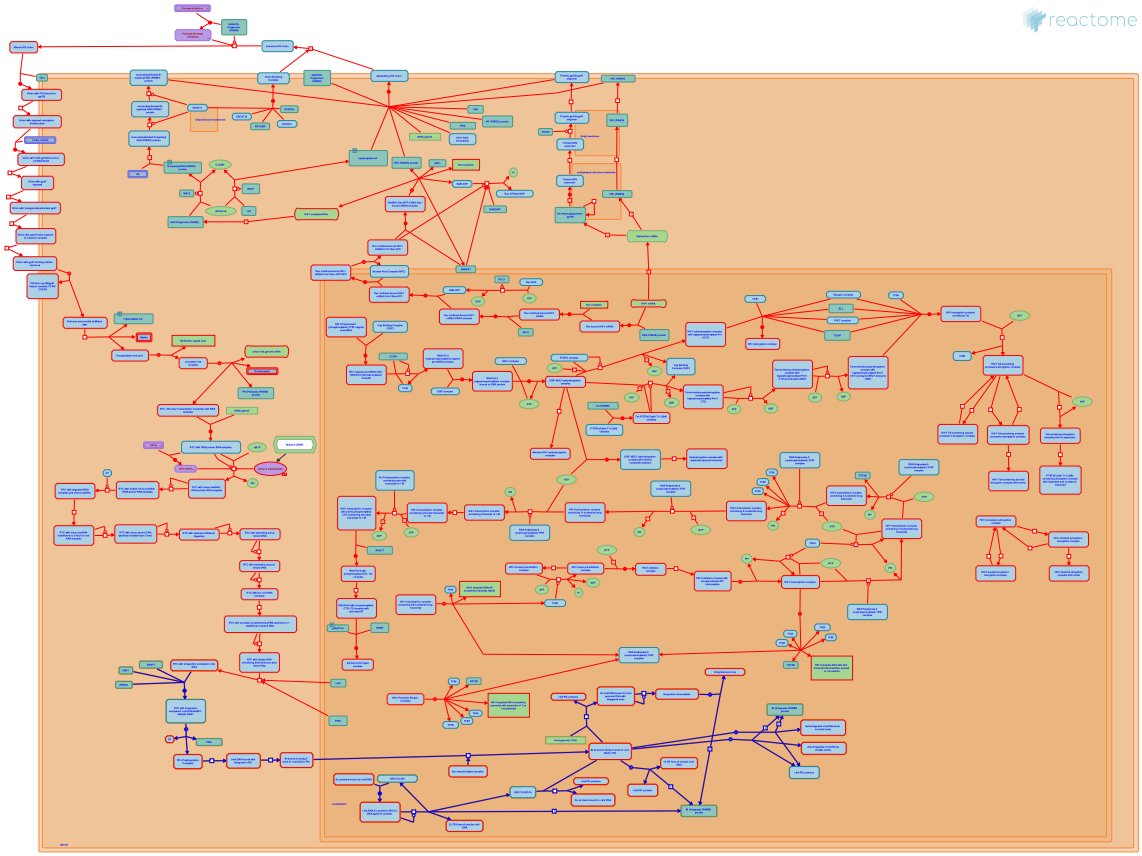
Integration of provirus ↗

Location: Early Phase of HIV Life Cycle

Stable identifier: R-HSA-162592

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



For retroviral DNA to direct production of progeny virions it must become covalently integrated into the host cell chromosome (reviewed in Coffin et al. 1997; Hansen et al. 1998). Analyses of mutants have identified the viral integrase coding region (part of the retroviral pol gene) as essential for the integration process (Donehower 1988; Donehower and Varmus 1984; Panganiban and Temin 1984; Quinn and Grandgenett 1988; Schwartzberg et al. 1984). Also essential are regions at the ends of the viral long terminal repeats (LTRs) that serve as recognition sites for integrase protein (Colicelli and Goff 1985, 1988; Panganiban and Temin 1983).

The viral genomic RNA is reverse transcribed to form a linear double-stranded DNA molecule, the precursor to the integrated provirus (Brown et al. 1987, 1989; Fujiwara and Mizuuchi 1988). The provirus is colinear with unintegrated linear viral DNA (Dhar et al. 1980; Hughes et al. 1978) but differs from the reverse transcription product in that it is missing two bases from each end (Hughes et al. 1981). Flanking the integrated HIV provirus are direct repeats of the cellular DNA that are 5 base pairs in length (Vincent et al. 1990). This duplication of cellular sequences flanking the viral DNA is generated as a consequence of the integration mechanism (Coffin et al., 1997).

Linear viral DNA is found in a complex with proteins in the cytoplasm of infected cells. These complexes (termed "preintegration complexes", PICs) can be isolated and have been shown to mediate integration of viral DNA into target DNA in vitro (Bowerman et al. 1989; Brown et al. 1987; Ellison et al. 1990; Farnet and Haseltine 1990, 1991).

The development of in vitro assays with purified integrase has allowed its enzymatic functions to be elucidated. The provirus is formed by two reactions catalyzed by the viral integrase: terminal cleavage and strand transfer. Studies with purified integrase have shown that it is sufficient for both 3' end cleavage (Bushman and Craigie 1991; Craigie et al. 1990; Katzman et al. 1989; Sherman and Fyfe 1990) and joining of the viral DNA to the cellular chromosome or naked target DNA (Bushman et al. 1990; Craigie et al. 1990; Katz et al. 1990). HIV integrase catalyze the removal of two bases from the 3' end of each viral DNA strand, leaving recessed 3' hydroxyl groups (Brown et al. 1989; Fujiwara and Mizuuchi 1988; Roth et al. 1989; Sherman and Fyfe 1990). This terminal cleavage reaction is required

for proper integration. It may allow the virus to create a standard end from viral DNA termini that can be heterogeneous due to the terminal transferase activity of reverse transcriptase (Miller et al. 1997; Patel and Preston 1994). In addition, the terminal cleavage step is coupled to the formation of a stable integrase-DNA complex (Ellison and Brown 1994; Vink et al. 1994). Following terminal cleavage, a recessed hydroxyl is exposed that immediately follows a CA dinucleotide. More internal LTR sites are also important for integration (Balakrishnan and Jonsson 1997; Bushman and Craigie 1990; Leavitt et al. 1992). After end processing, integrase catalyzes the covalent attachment of hydroxyl groups at the viral DNA termini to protruding 5' phosphoryl ends of the host cell DNA (Brown et al. 1987; Brown et al. 1989; Fujiwara and Mizuuchi 1988). The DNA cleavage and joining reactions involved in integration are shown in the figure below. Both the viral DNA 3' end cleavage and strand transfer reactions are mediated by single-step transesterification chemistry as shown by stereochemical analysis of reaction products (Engelman et al. 1991). Biochemical analysis of purified integrase revealed that it requires a divalent metal - either Mg2+ or Mn2+ - to carry out reactions with model substrates, that probably mediate the reaction chemistry (Bushman and Craigie 1991; Craigie et al. 1990; Katzman et al. 1989; Sherman and Fyfe 1990; Gao et al. 2004).

Literature references

Bushman, FD., Lewinski, MK. (2005). Retroviral DNA integration--mechanism and consequences. *Adv Genet, 55*, 147-81. ↗

Editions

2006-05-19	Authored, Edited	Gopinathrao, G., D'Eustachio, P.
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Table of Contents