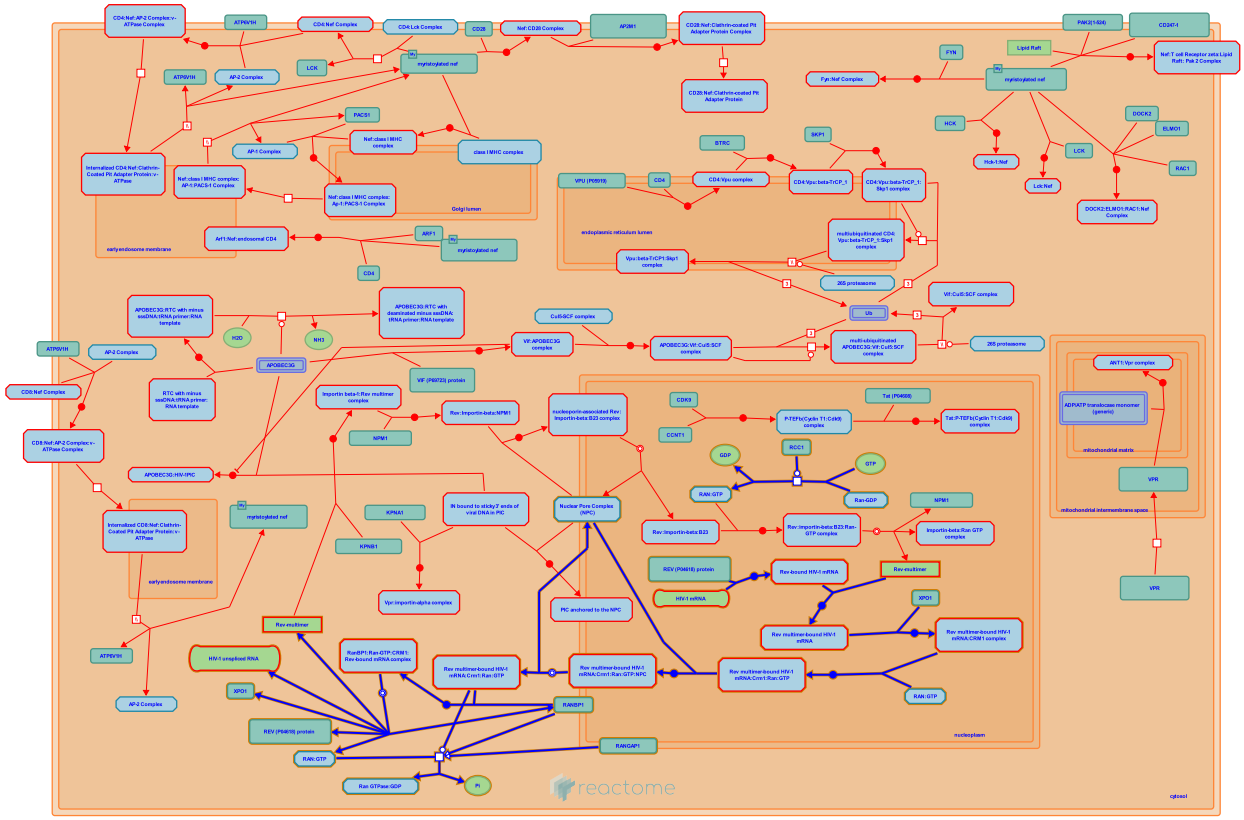
Rev-mediated nuclear export of HIV RNA



Kumar, A., Matthews, L., Rice, AP.

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

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.

05/05/2024

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. ↗

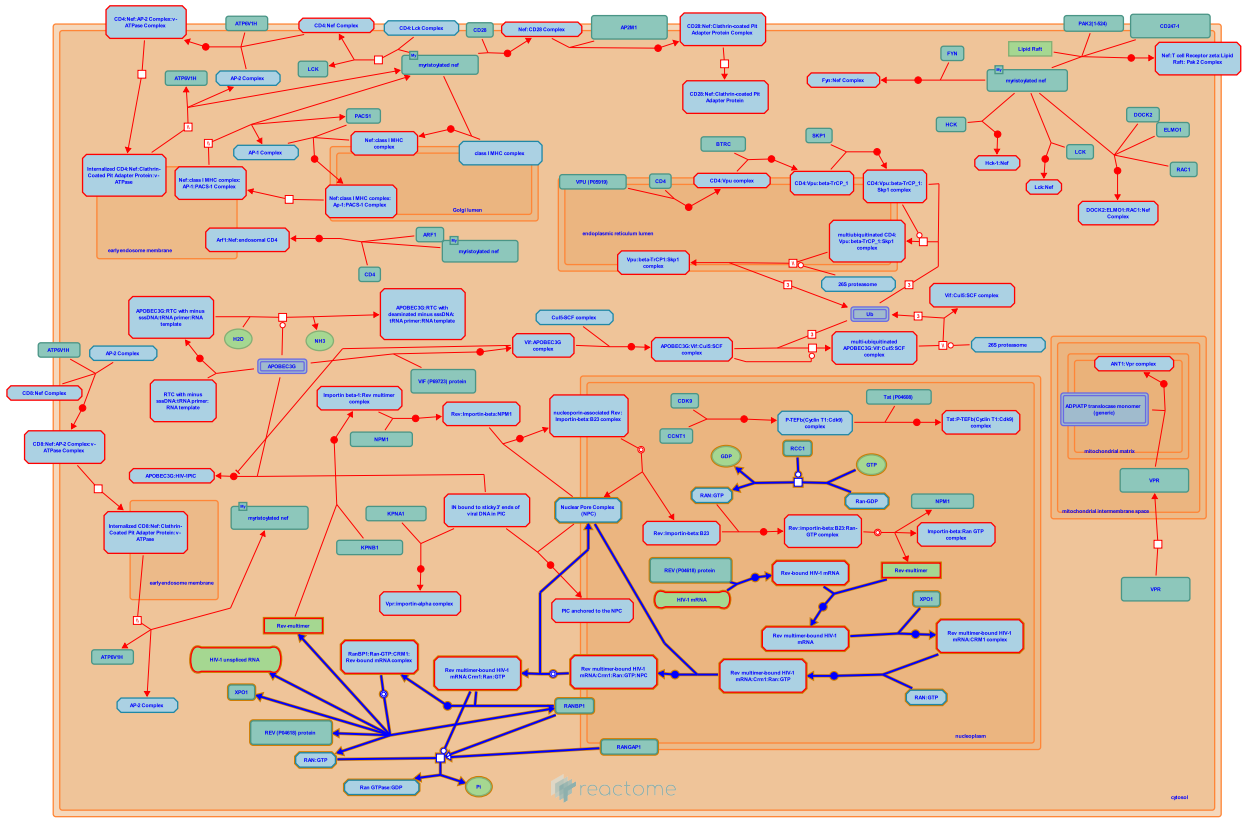
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Rev-mediated nuclear export of HIV RNA ↗

Stable identifier: R-HSA-165054

Diseases: Human immunodeficiency virus infectious disease



The HIV-1 genome contains 9 genes encoded by a single transcript. In order for the virus to replicate, unspliced, singly-spliced and fully spliced viral mRNA must be exported from the nucleus. The HIV-1 mRNA splice sites are inefficient resulting it the accumulation of a pool of incompletely spliced RNAs (Staffa and Cochrane, 1994). In the early stages of the viral life cycle, or in the absence of the viral Rev protein, completely spliced viral mRNA which encode the regulatory proteins Tat, Nef and Rev are exported from the nucleus while the incompletely spliced structural protein encoding transcripts are held within the nucleus by cellular proteins that normally function in preventing the nuclear export of cellular pre-mRNA. Export of both unspliced and partially spliced mRNA is mediated by the viral protein Rev which is recruited, along with cellular cofactors, to the Rev Response Element (RRE) within the HIV-1 mRNA sequence (Malim et al., 1990; Fischer et al., 1994). The cellular hRIP protein is essential for correct Rev-mediated export of viral RNAs to the cytoplasm (Sanchez-Velar et al., 2004; Yu et al., 2005).

Literature references

Green, MR., Fritz, CC. (1996). HIV Rev uses a conserved cellular protein export pathway for the nucleocytoplasmic transport of viral RNAs. *Curr Biol, 6*, 848-54. ↗

Cullen, BR. (1998). Retroviruses as model systems for the study of nuclear RNA export. *Virology, 249*, 203-10. ↗

Cullen, BR. (2003). Nuclear mRNA export: insights from virology. *Trends Biochem Sci, 28*, 419-24. ↗

Editions

2005-07-27	Authored	Matthews, L., Rice, AP.
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Rev molecules assemble onto the RRE RNA sequence through their ARM sequence ↗

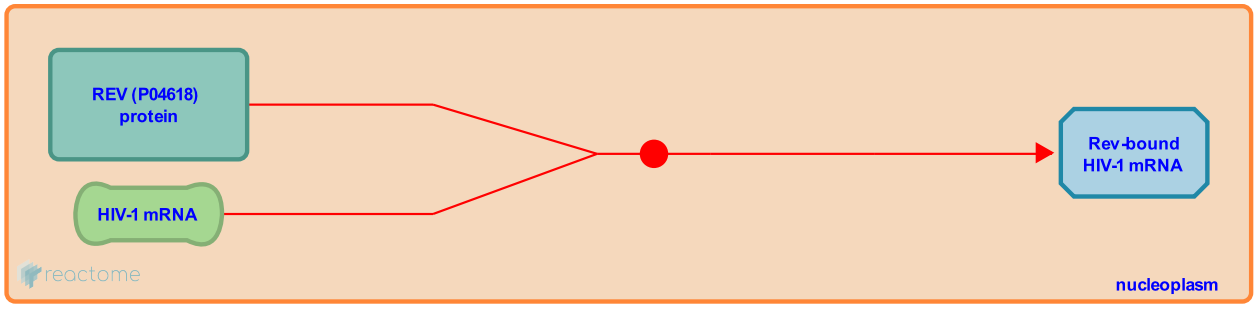
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165027

Type: binding

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



Nuclear export of the unspliced and partially spliced HIV-1 transcripts requires the association of the HIV-1 Rev protein with a cis-acting RNA sequence known as the Rev Response Element (RRE) located within the env gene. The RRE forms a stem loop structure that associates with an arginine-rich RNA binding motif (ARM) within Rev.

Followed by: Multimerization of Rev

Literature references

Green, MR., Zapp, ML. (1989). Sequence-specific RNA binding by the HIV-1 Rev protein. *Nature, 342*, 714-6. ↗

Hauber, J., McCarn, DF., Tiley, LS., Cullen, BR., Malim, MH., Rusche, JR. (1990). HIV-1 structural gene expression requires binding of the Rev trans-activator to its RNA target sequence. *Cell, 60*, 675-83. ↗

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Multimerization of Rev ↗

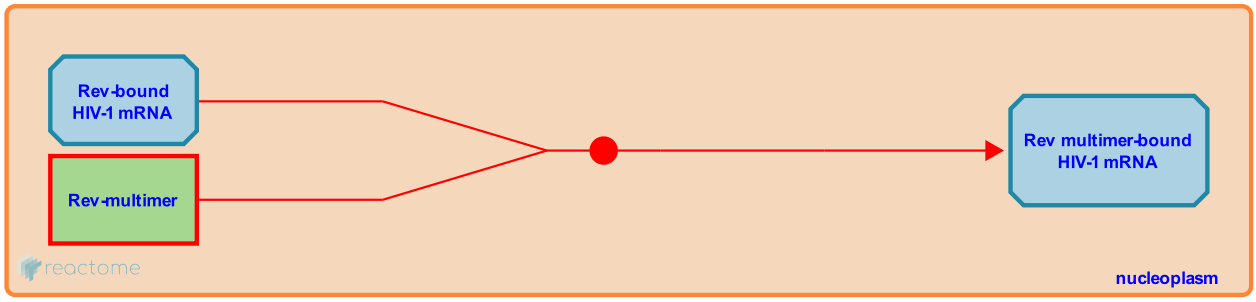
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165033

Type: binding

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



In order for Rev to function, multiple molecules must bind sequentiallly to the RRE (Malim and Cullen 1991).

Preceded by: Rev molecules assemble onto the RRE RNA sequence through their ARM sequence

Followed by: Rev multimer-bound HIV mRNA associates with Crm1, Rev multimer-bound HIV mRNA:CRM1 complex associates with Ran:GTP

Literature references

Cullen, BR., Malim, MH. (1991). HIV-1 structural gene expression requires the binding of multiple Rev monomers to the viral RRE: implications for HIV-1 latency. *Cell, 65*, 241-8. ↗

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Rev multimer-bound HIV mRNA associates with Crm1 ↗

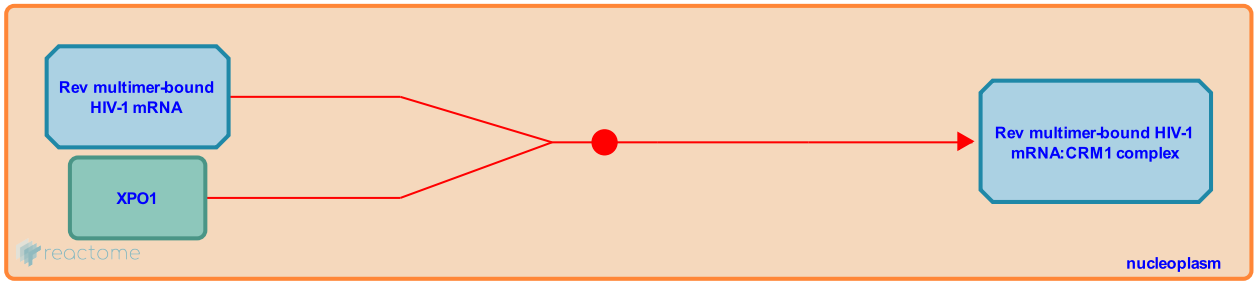
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-180885

Type: binding

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



CRM1 associates directly with Rev through the Rev nuclear export signal (NES) domain and acts as the nuclear export receptor for the Rev-RRE ribonucleoprotein complex.

Preceded by: Multimerization of Rev

Literature references

Jensen, TH., Englmeier, L., Nilsson, J., Askjaer, P., Kjems, J. (1998). The specificity of the CRM1-Rev nuclear export signal interaction is mediated by RanGTP. *J Biol Chem, 273*, 33414-22. ↗

Editions

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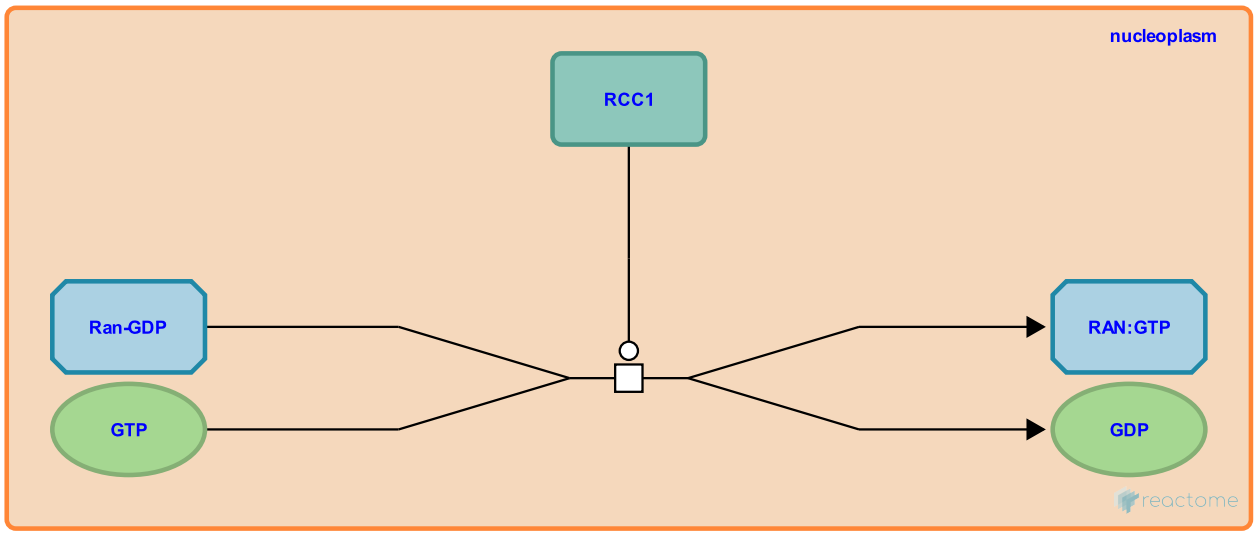
Conversion of Ran-GDP to Ran-GTP ↗

Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-180687

Type: transition

Compartments: nucleoplasm



Free, nuclear RanGTP is required for export processes out of the nucleus. RCC1 catalyses the conversion of Ran-GDP to Ran-GTP in the nucleus.

Followed by: Rev multimer-bound HIV mRNA:CRM1 complex associates with Ran:GTP

Literature references

Bischoff, FR., Ponstingl, H., Kempf, T., Krebber, H., Hermes, I. (1995). Human RanGTPase-activating protein RanGAP1 is a homologue of yeast Rna1p involved in mRNA processing and transport. *Proc Natl Acad Sci U S A, 92*, 1749-53. ↗

Bischoff, FR., Ponstingl, H. (1991). Catalysis of guanine nucleotide exchange on Ran by the mitotic regulator RCC1. *Nature, 354*, 80-2. ↗

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Rev multimer-bound HIV mRNA:CRM1 complex associates with Ran:GTP

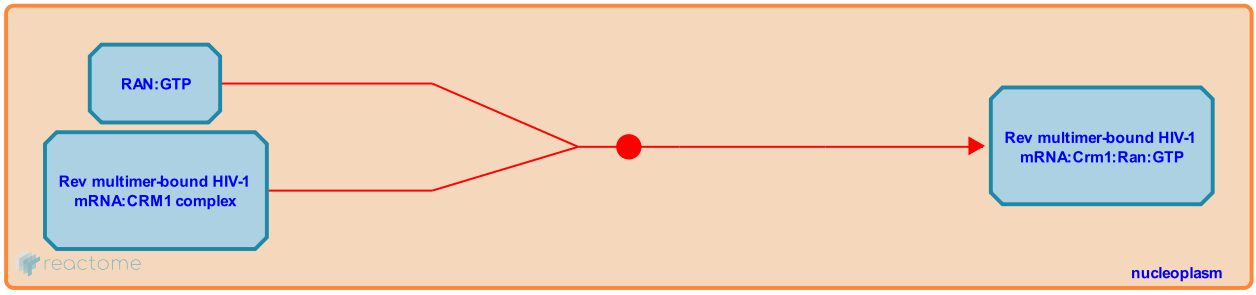
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165034

Type: binding

Compartments: nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



RanGTP binds to a preformed Rev-CRM1 complex.

Preceded by: Conversion of Ran-GDP to Ran-GTP, Multimerization of Rev

Followed by: Rev multimer-bound HIV mRNA:Crm1:Ran:GTP complex associates with the NPC

Literature references

Jensen, TH., Englmeier, L., Nilsson, J., Askjaer, P., Kjems, J. (1998). The specificity of the CRM1-Rev nuclear export signal interaction is mediated by RanGTP. *J Biol Chem, 273*, 33414-22.

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Rev multimer-bound HIV mRNA:Crm1:Ran:GTP complex associates with the NPC ↗

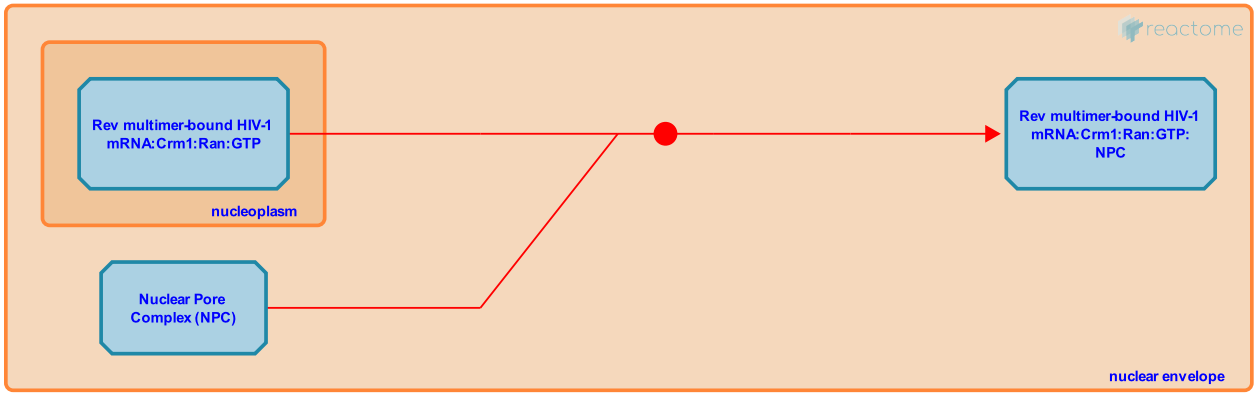
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165043

Type: binding

Compartments: nuclear envelope, nucleoplasm

Diseases: Human immunodeficiency virus infectious disease



The Rev multimer-bound HIV-1 mRNA:Crm1:Ran:GTP complex associates with the NPC (Askjaer et al. 1998; Daugherty et al. 2010).

Preceded by: Rev multimer-bound HIV mRNA:CRM1 complex associates with Ran:GTP

Followed by: Translocation of nuclear RNA transport complex to cytoplasm

Literature references

Jensen, TH., Englmeier, L., Nilsson, J., Askjaer, P., Kjems, J. (1998). The specificity of the CRM1-Rev nuclear export signal interaction is mediated by RanGTP. *J Biol Chem, 273*, 33414-22. ↗

Daugherty, MD., Liu, B., Frankel, AD. (2010). Structural basis for cooperative RNA binding and export complex assembly by HIV Rev. *Nat. Struct. Mol. Biol., 17*, 1337-42. ↗

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2007-02-01	Reviewed	Kumar, A.

Translocation of nuclear RNA transport complex to cytoplasm ↗

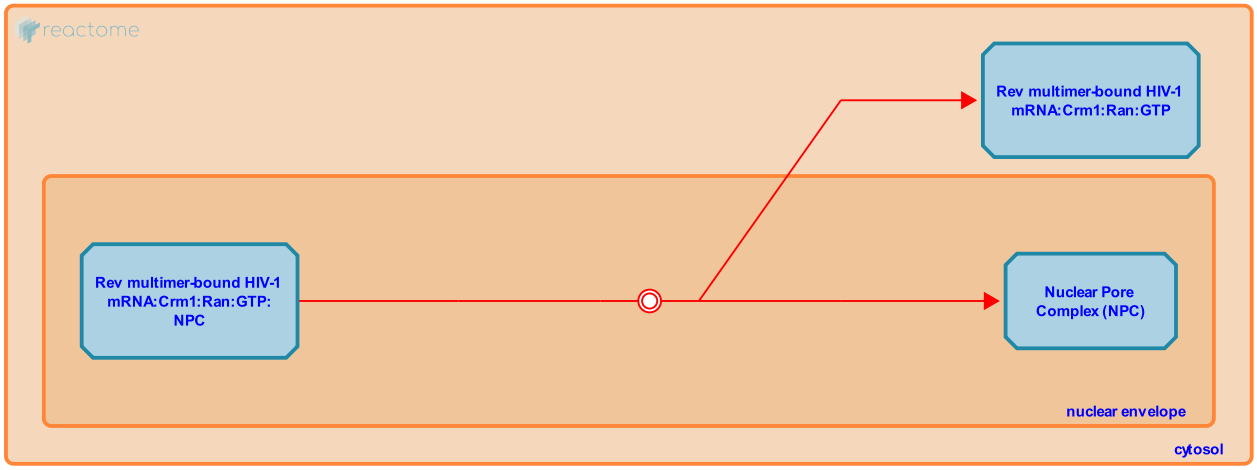
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165047

Type: dissociation

Compartments: nuclear envelope, cytosol

Diseases: Human immunodeficiency virus infectious disease



Crm1 is a nucleocytoplasmic transport factor that is believed to interact with nucleoporins facilitating docking of the RRE-Rev-CRM1-RanGTP complex to the nuclear pore and the translocation of the complex across the nuclear pore complex (see Cullen 1998) Crm1 has been found in complex with two such nucleoporins, CAN/Nup214 and Nup88 which have been shown to be components of the human nuclear pore complex (Fornerod et al., 1997).

Preceded by: Rev multimer-bound HIV mRNA:Crm1:Ran:GTP complex associates with the NPC

Followed by: Hydrolysis of Ran:GTP to Ran:GDP, Association of RanBP1 with Ran-GTP:CRM1:Rev:mRNA complex

Literature references

Malim, MH., Meyer, BE. (1994). The HIV-1 Rev trans-activator shuttles between the nucleus and the cytoplasm. *Genes Dev, 8*, 1538-47. ↗

Yi, R., Cullen, BR., Bogerd, HP. (2002). Recruitment of the Crm1 nuclear export factor is sufficient to induce cytoplasmic expression of incompletely spliced human immunodeficiency virus mRNAs. *J Virol, 76*, 2036-42. ↗

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Association of RanBP1 with Ran-GTP:CRM1:Rev:mRNA complex ↗

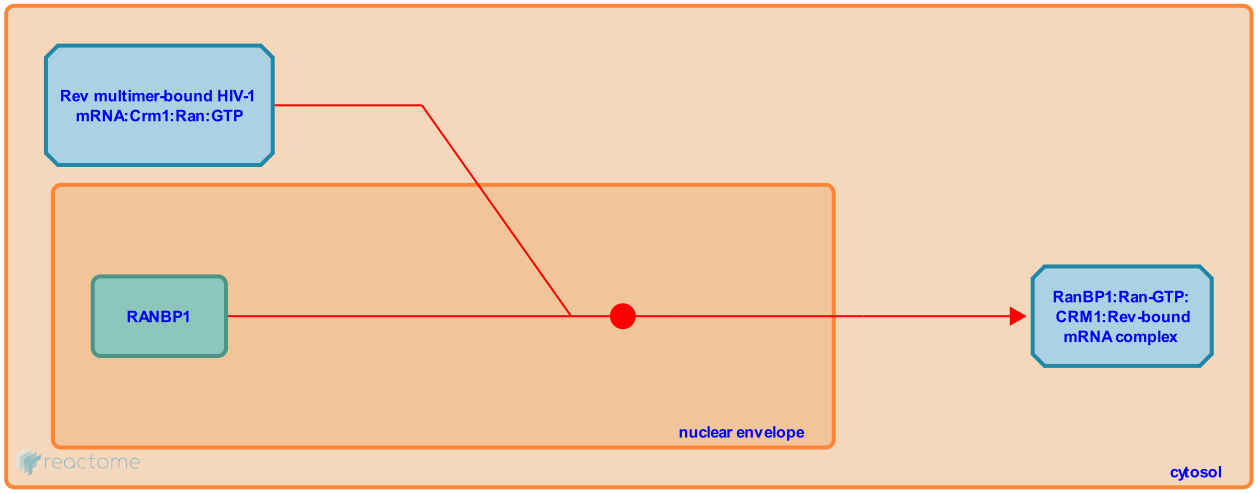
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-180739

Type: binding

Compartments: nuclear envelope, cytosol

Diseases: Human immunodeficiency virus infectious disease



Upon translocation to the cytoplasm, RanBP1 associates with Ran-GTP in the Rev-CRM1-Ran-GTP complex.

Preceded by: Translocation of nuclear RNA transport complex to cytoplasm

Followed by: Release of the HIV mRNA and Crm1 from Rev in the cytoplasm

Literature references

Green, MR., Fritz, CC. (1996). HIV Rev uses a conserved cellular protein export pathway for the nucleocytoplasmic transport of viral RNAs. *Curr Biol, 6*, 848-54. ↗

Editions

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Release of the HIV mRNA and Crm1 from Rev in the cytoplasm ↗

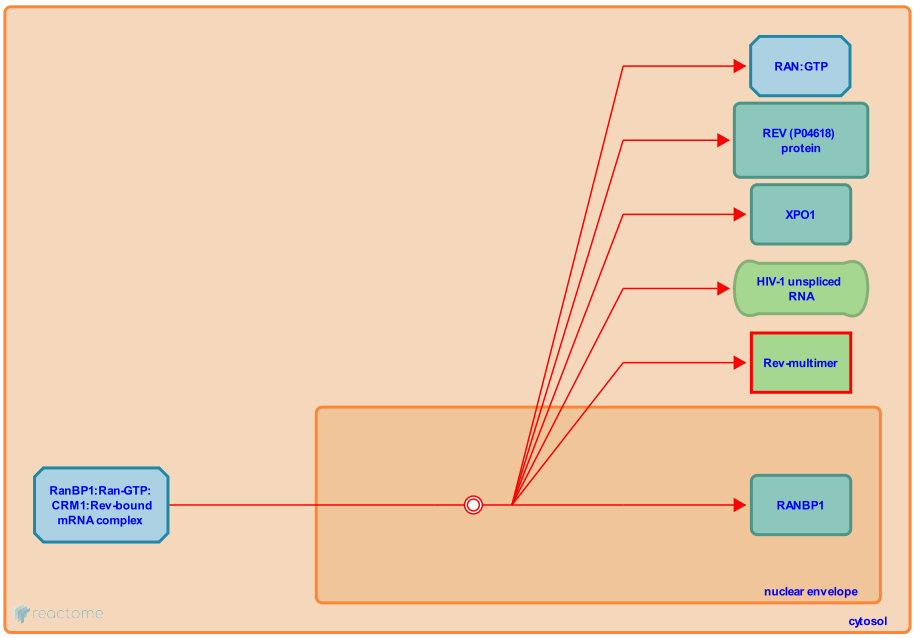
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165028

Type: dissociation

Compartments: nuclear envelope, cytosol

Diseases: Human immunodeficiency virus infectious disease



The association of RanBp1 with RanGTP:CRM1:Rev promotes disassembly of the complex and release of the Rev:RNA cargo (Mahboobi et al. 2015).

Preceded by: Association of RanBP1 with Ran-GTP:CRM1:Rev:mRNA complex

Followed by: Hydrolysis of Ran:GTP to Ran:GDP

Literature references

Mahboobi, SH., Javanpour, AA., Mofrad, MR. (2015). The interaction of RNA helicase DDX3 with HIV-1 Rev-CRM1-RanGTP complex during the HIV replication cycle. *PLoS ONE, 10*, e0112969. ↗

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Hydrolysis of Ran:GTP to Ran:GDP ↗

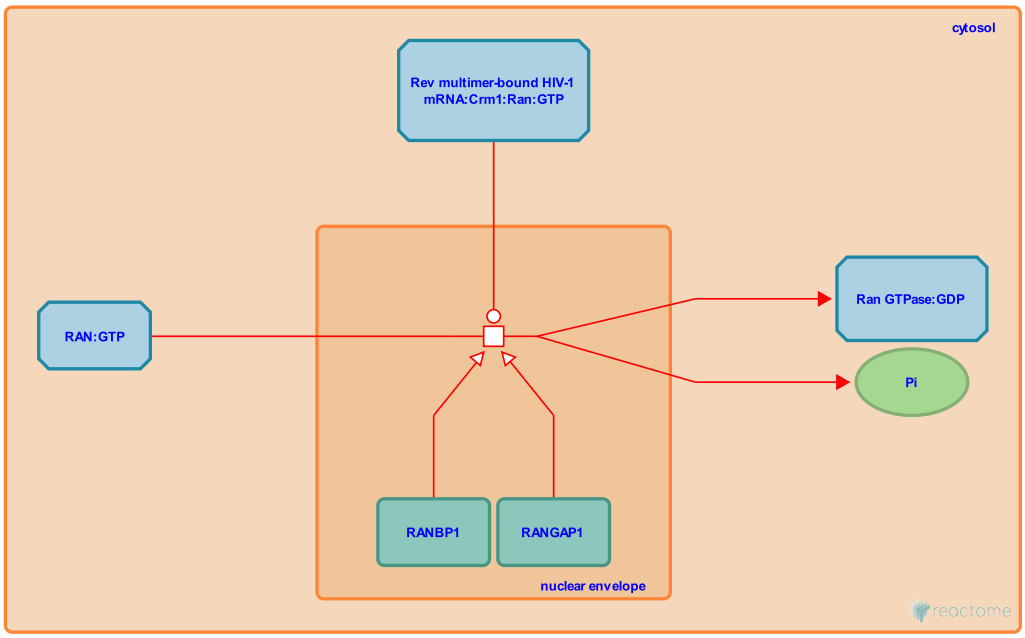
Location: Rev-mediated nuclear export of HIV RNA

Stable identifier: R-HSA-165055

Type: transition

Compartments: nuclear envelope, cytosol

Diseases: Human immunodeficiency virus infectious disease



Ran-GAP, a Ran-specific GTPase-activating protein converts Ran-GTP to Ran-GDP, producing a Ran-GTP gradient across the nuclear membrane.

Preceded by: Release of the HIV mRNA and Crm1 from Rev in the cytoplasm, Translocation of nuclear RNA transport complex to cytoplasm

Literature references

Bischoff, FR., Ponstingl, H., Kempf, T., Krebber, H., Hermes, I. (1995). Human RanGTPase-activating protein RanGAP1 is a homologue of yeast Rna1p involved in mRNA processing and transport. *Proc Natl Acad Sci U S A, 92*, 1749-53. ↗

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