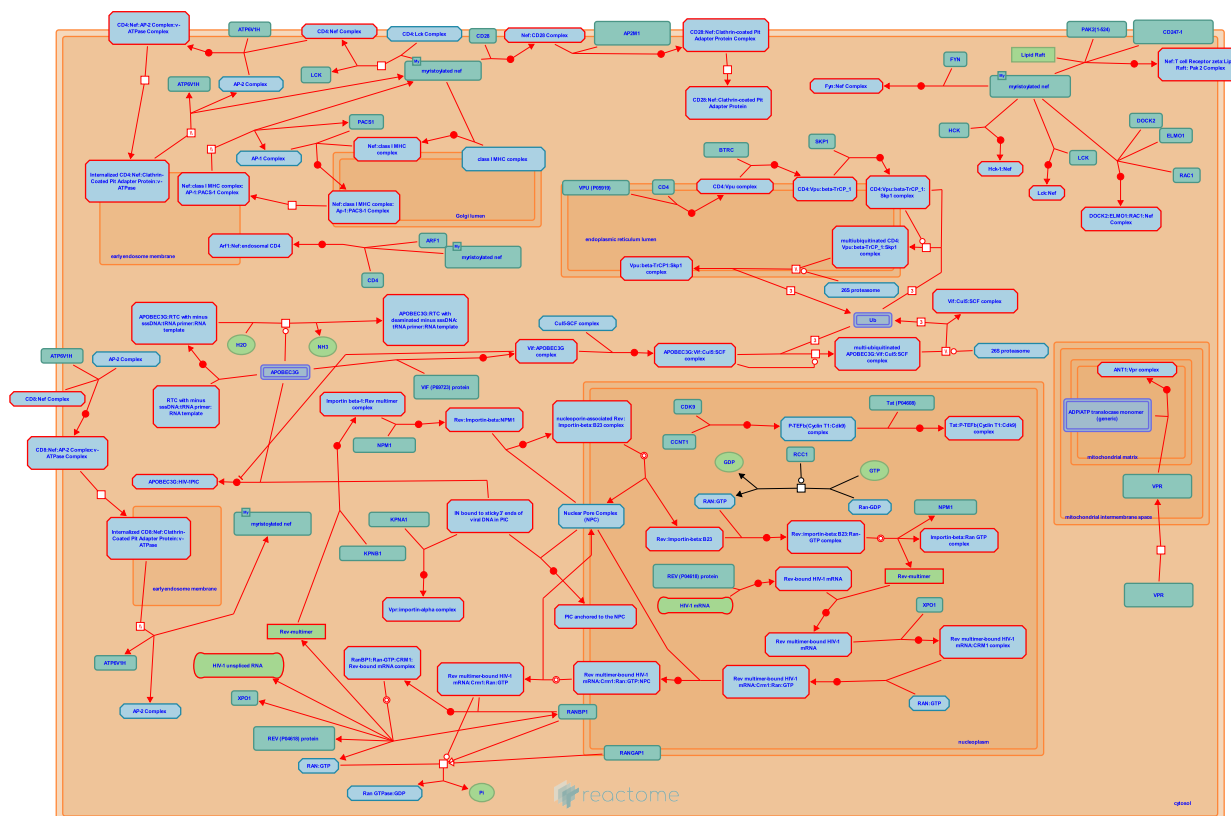


# Host Interactions of HIV factors



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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](https://reactome.org/textbook).

02/10/2024

## 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.

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## Literature references

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

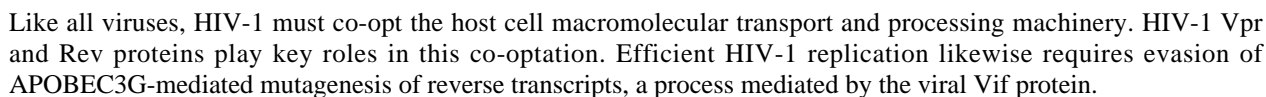
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)

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: 90

This document contains 8 pathways ([see Table of Contents](#))

**Diseases:** Human immunodeficiency virus infectious disease



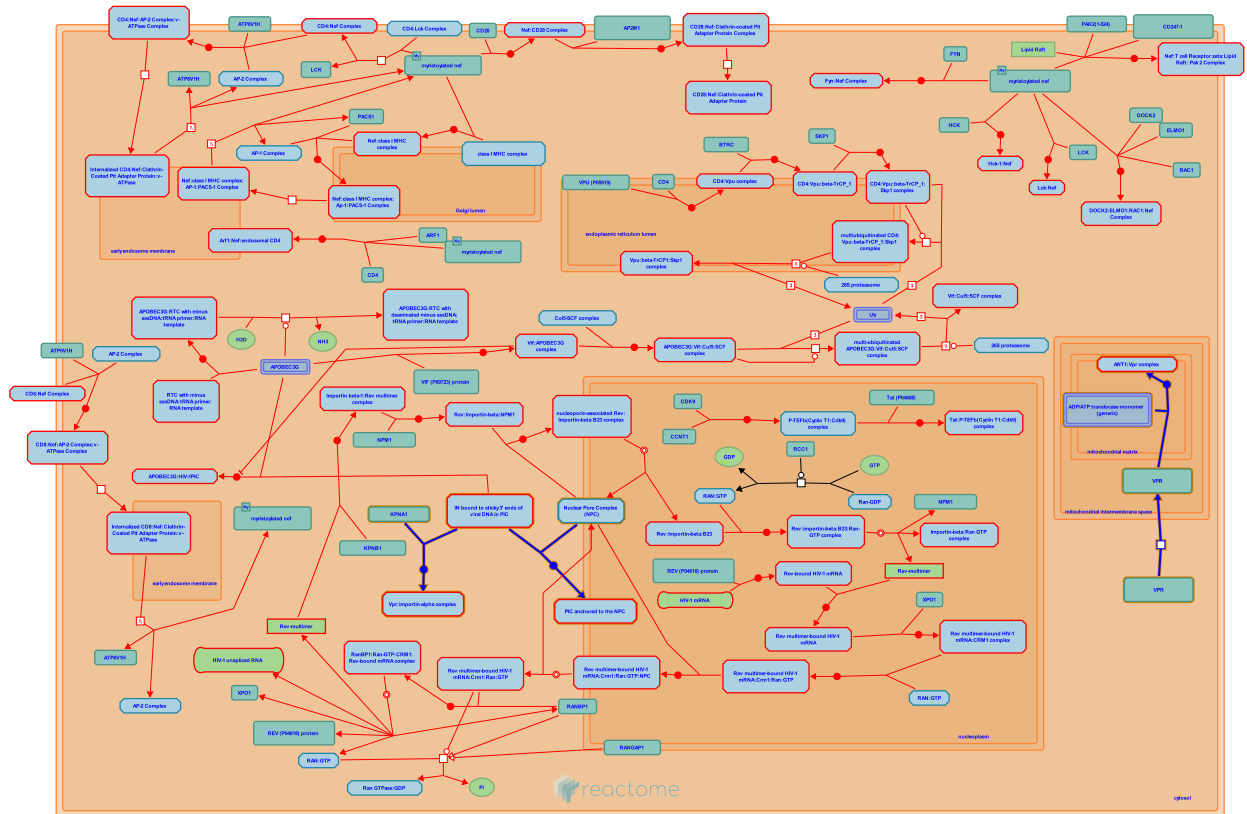
## Benarous, R., Zhao, RY., Peterlin, BM.

## Interactions of Vpr with host cellular proteins ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-176033

**Diseases:** Human immunodeficiency virus infectious disease



Vpr has been implicated in multiple processes during HIV-1 replication, including nuclear import of the pre-integration complex (PIC)(Heinzinger et al., 1994), apoptosis (Stewart et al., 1997) and induction of cell cycle G2/M arrest (He et al., 1995; Re et al., 1995; Zhao et al., 1996).

Interactions between Vpr and host nucleoporins (importin) appear to facilitate the nuclear import of the PIC (Popov et al., 1998; Vodicka et al., 1998) while interactions between Vpr the adenine nucleotide transporter (ANT) protein at the inner mitochondrial membrane may contribute to release of apoptosis factors by promoting permeabilization of the mitochondrial outer membrane (Jacotot et al., 2000).

Vpr induces cell cycle G2/M arrest by promoting hyperphosphorylation of Cdk1/Cdc2 (Re et al., 1995; Zhao et al., 1996). However, it is unclear which protein(s) Vpr interacts with to cause this effect. For recent reviews, see, (Li et al., 2005; Zhao, Bukrinsky, and Elder, 2005). Progression of cells from G2 phase of the cell cycle to mitosis is a tightly regulated cellular process that requires activation of the Cdk1/Cdc2 kinase, which determines onset of mitosis in all eukaryotic cells. The activity of Cdk1/Cdc2 is regulated in part by the phosphorylation status of tyrosine 15 (Tyr15) on Cdk1/Cdc2, which is phosphorylated by Wee1 kinase during late G2 and is rapidly dephosphorylated by the Cdc25 tyrosine phosphatase to trigger entry into mitosis. These Cdk1/Cdc2 regulators are the downstream targets of two well-characterized G2/M checkpoint pathways which prevent cells from entering mitosis when cellular DNA is damaged or when DNA replication is inhibited. It is clear that Vpr induces cell cycle G2/M arrest by promoting Tyr15 phosphorylation of Cdk1/Cdc2 both in human and fission yeast cells (Elder et al., 2000; Re et al., 1995; Zhao et al., 1996), which modulates host cell cycle machinery to benefit viral survival or replication. Although some aspects of Vpr-induced G2/M arrest resembles induction of host cellular checkpoints, increasing evidence suggests that Vpr induces cell cycle G2 arrest through a mechanism that is to some extent different from the classic G2/M checkpoints. One the unique features distinguishing Vpr-induced G2 arrest from the classic checkpoints is the role of phosphatase 2A (PP2A) in Vpr-induced G2 arrest (Elder, Benko, and Zhao, 2002; Elder et al., 2001; Masuda et al., 2000). Interestingly, PP2A is targeted by a number of other viral proteins including SV40 small T antigen, polyomavirus T antigen, HTLV Tax and adenovirus E4orf4. Thus an in-depth understanding of the molecular mechanisms underlying Vpr-induced G2 arrest will provide additional insights into the basic biology of cell cycle G2/M regulation and into the biological significance of this effect during host-pathogen interactions.

## Literature references

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## Editions

2006-05-15	Authored, Edited	Matthews, L.
2006-07-12	Reviewed	Zhao, RY.

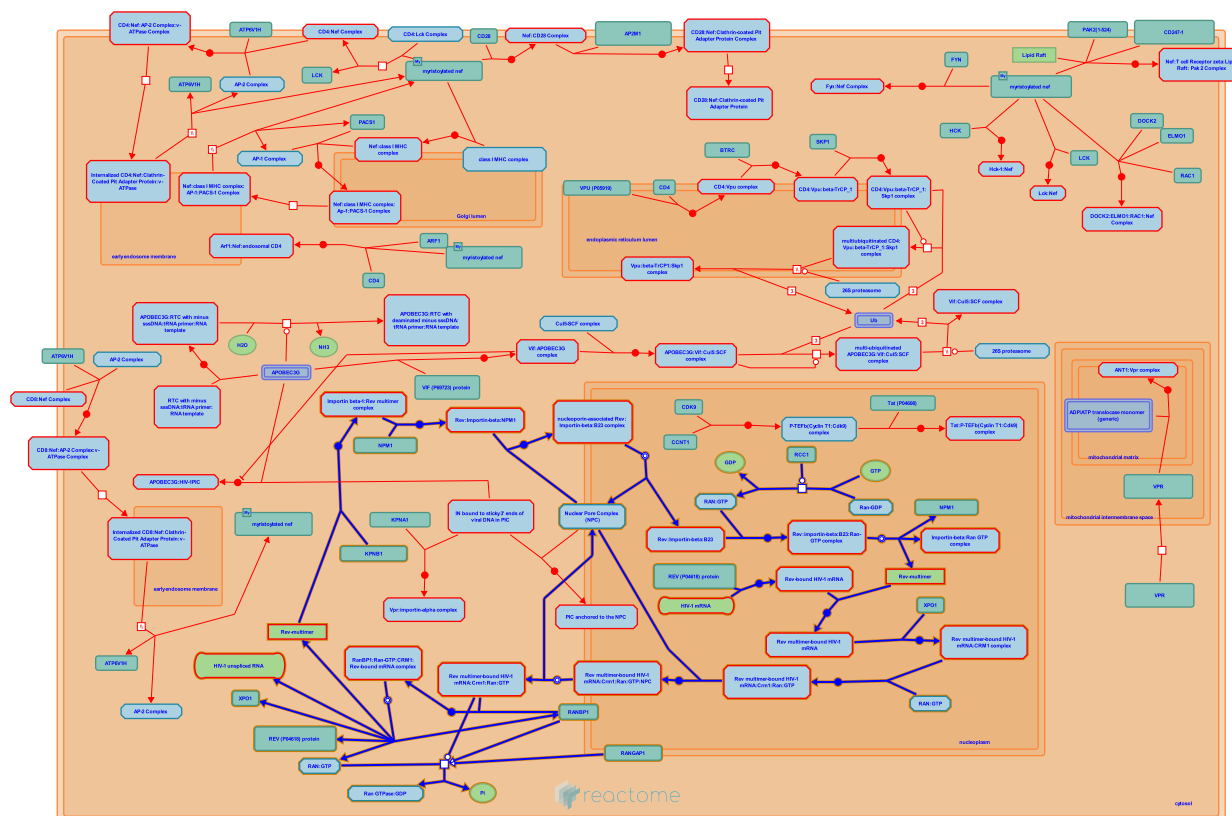
# Interactions of Rev with host cellular proteins ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-177243

**Compartments:** nucleoplasm

**Diseases:** Human immunodeficiency virus infectious disease



In order to facilitate the transport of incompletely spliced HIV-1 transcripts, Rev shuttles between the cytoplasm and nucleus using host cell transport mechanisms (reviewed in Li et al. 2005). Nuclear import appears to be achieved by the association of Rev with importin-beta and B23 and docking at the nuclear pore through interactions between importin-beta and nucleoporins. The dissociation of Rev with the import machinery and the subsequent export of Rev-associated HIV-1 mRNA complex requires Ran-GTP. Ran GTP associates with importin-beta, displacing its cargo. Crm1 associates with the Rev:RNA complex and Ran:GTP and 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. In the cytoplasm, RanBP1 associates with Ran-GTP causing the Crm1-Rev-Ran-GTP complex to disassemble. The Ran GAP protein promotes the hydrolysis of RanGTP to Ran GDP. The activities of Ran GAP in the cytoplasm and Ran-GEF, which converts Ran-GDP to Ran-GTP in the nucleus, produce a gradient of Ran-GTP/GDP required for this shuttling of Rev and other cellular transport proteins.

## 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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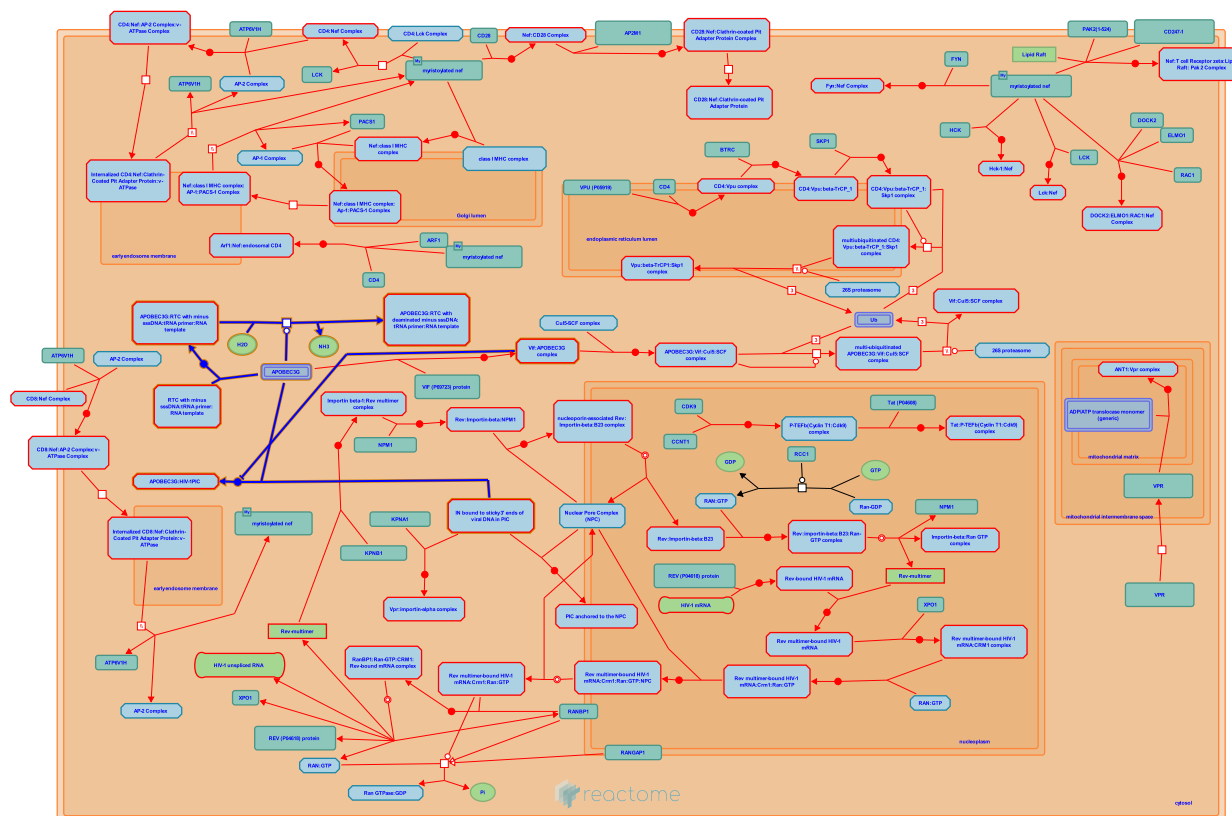
2005-07-27	Authored	Matthews, L., Rice, AP.
2006-03-24	Edited	Matthews, L.
2007-02-01	Reviewed	Kumar, A.

# APOBEC3G mediated resistance to HIV-1 infection ↗

**Location:** Host Interactions of HIV factors

**Stable identifier:** R-HSA-180689

**Diseases:** Human immunodeficiency virus infectious disease



Representatives of the apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 (APOBEC3) family provide innate resistance to exogenous and endogenous retroviruses (see Cullen 2006 for a recent review). Humans and other primates encode a cluster of seven different cytidine deaminases with APOBEC3G, APOBEC3F and APOBEC3B having some anti HIV-1 activity. Our understanding is most complete for APOBEC3G which has been described first and the reactions described herein will focus on this representative enzyme.

APOBEC3G is a cytoplasmic protein which strongly restricts replication of Vif deficient HIV-1 (Sheehy 2002). It is expressed in cell populations that are susceptible to HIV infection (e.g., T-lymphocytes and macrophages). In the producer cell, APOBEC3G is incorporated into budding HIV-1 particles through an interaction with HIV-1 gag nucleocapsid (NC) protein in a RNA-dependent fashion.

Within the newly infected cell (= target cell), virus-associated APOBEC3G regulates the infectivity of HIV-1 by deaminating cytidine to uracil in the minus-strand viral DNA intermediate during reverse transcription. Deamination results in the induction of G-to-A hypermutations in the plus-strand viral DNA which subsequently can either be integrated as a non-functional provirus or degraded before integration.

## Literature references

Cullen, BR. (2006). Role and mechanism of action of the APOBEC3 family of antiretroviral resistance factors. *J Virol*, 80, 1067-76. ↗

## Editions

2006-06-08	Authored	Mathews, L.
2007-01-30	Edited	Mathews, L.
2007-01-31	Reviewed	Simon, V., Mulder, L.

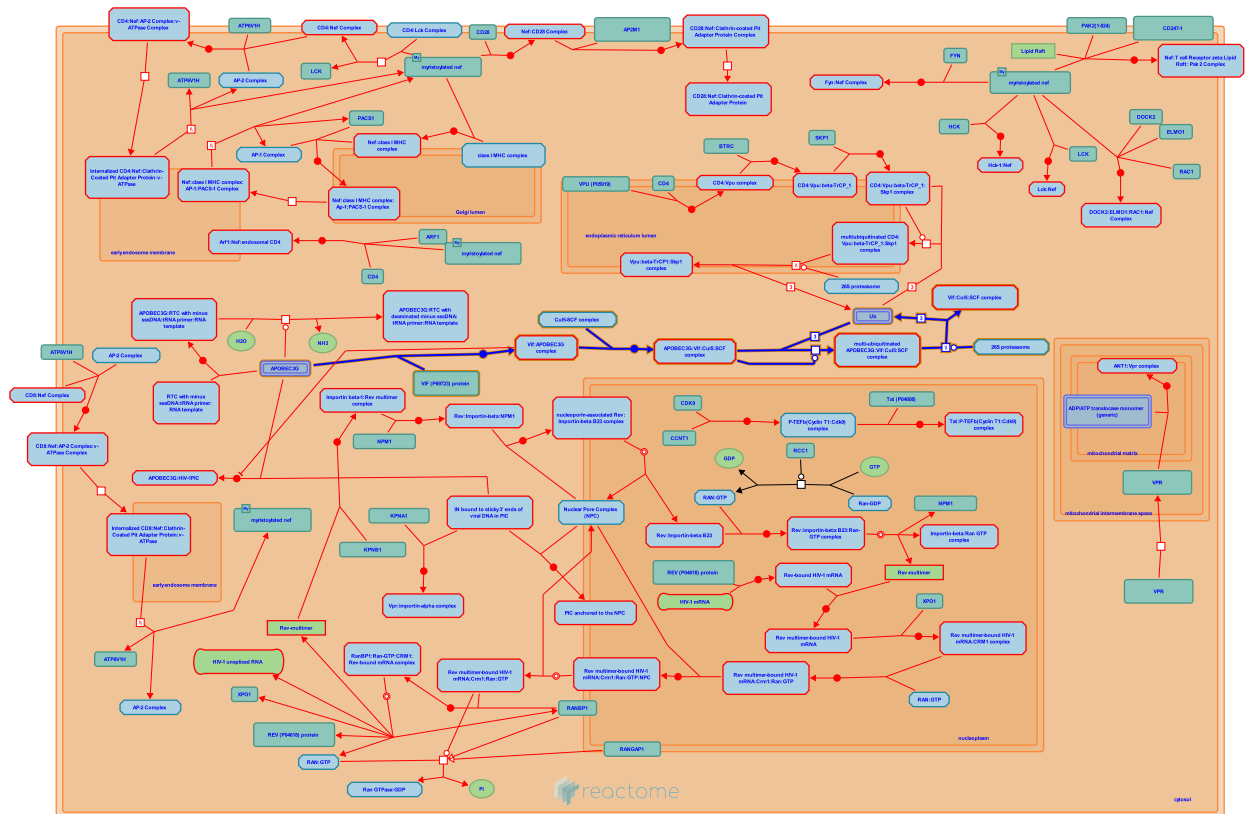
## Vif-mediated degradation of APOBEC3G ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-180585

**Compartments:** cytosol

**Diseases:** Human immunodeficiency virus infectious disease



The HIV-1 accessory protein Vif (Viral infectivity factor) is required for the efficient infection of primary cell populations (e.g., lymphocytes and macrophages) and 'non-permissive' cell lines. Vif neutralises the host DNA editing enzyme, APOBEC3G, in the producer cell. Indeed, in the absence of a functional Vif, APOBEC3G is selectively incorporated into the budding virions and in the next cycle of infection leads to the deamination of deoxycytidines (dC) within the minus-strand cDNA during reverse transcription (Sheehy et al 2003; Li et al., 2005 ; Stopak et al. 2003).

Deamination changes cytosine to uracil and thus results in G to A transitions and stop codons in the provirus. The aberrant cDNAs produced in the infected cell can either be integrated in form of non-functional proviruses or degraded. Vif counteracts the antiviral activity of APOBEC3G by associating directly with it and promoting its polyubiquitination and degradation by the 26S proteasome.

Vif binds APOBEC3G and recruits it into an E3 ubiquitin-enzyme complex composed by the cytoplasmic proteins Cullin5, Rbx1, ElonginC and ElonginB (Yu et al., 2003) . Thus, in the presence of Vif, APOBEC3G incorporation into the virion is minimal.

## Literature references

Uchiyama, T., Takaori-Kondo, A., Miyauchi, Y., Iwai, K., Kobayashi, M. (2005). Ubiquitination of APOBEC3G by an HIV-1 Vif-Cullin5-Elongin B-Elongin C complex is essential for Vif function. *J Biol Chem*, 280, 18573-8. ↗

Yu, XF., Luo, K., Kong, W., Mao, P., Liu, B., Yu, X. et al. (2003). Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex. *Science*, 302, 1056-60. ↗

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## Editions

2006-05-16	Authored	Matthews, L.
2007-01-30	Edited	Matthews, L.
2007-01-31	Reviewed	Simon, V., Mulder, L.

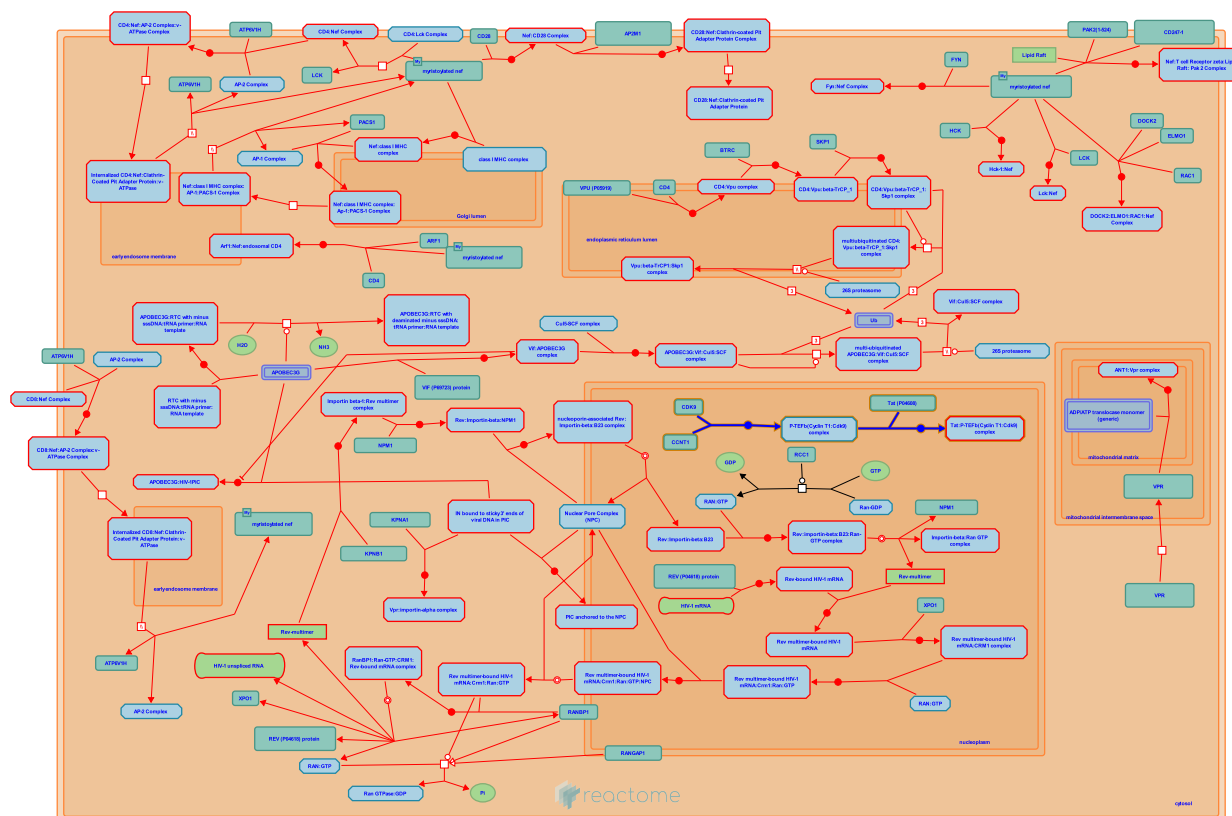
# Interactions of Tat with host cellular proteins ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-176034

**Compartments:** nucleoplasm

**Diseases:** Human immunodeficiency virus infectious disease



The elongation of HIV-1 mRNA depends upon the interaction of Tat with the host P-TEFb complex (Hermann and Rice, 1995; Wei et al., 1998).

## Literature references

Rice, AP., Herrmann, CH. (1995). Lentivirus Tat proteins specifically associate with a cellular protein kinase, TAK, that hyperphosphorylates the carboxyl-terminal domain of the large subunit of RNA polymerase II: candidate for a Tat cofactor. *J Virol*, 69, 1612-20. ↗

Wei, P., Jones, KA., Fang, SM., Fischer, WH., Garber, ME. (1998). A novel CDK9-associated C-type cyclin interacts directly with HIV-1 Tat and mediates its high-affinity, loop-specific binding to TAR RNA. *Cell*, 92, 451-62. ↗

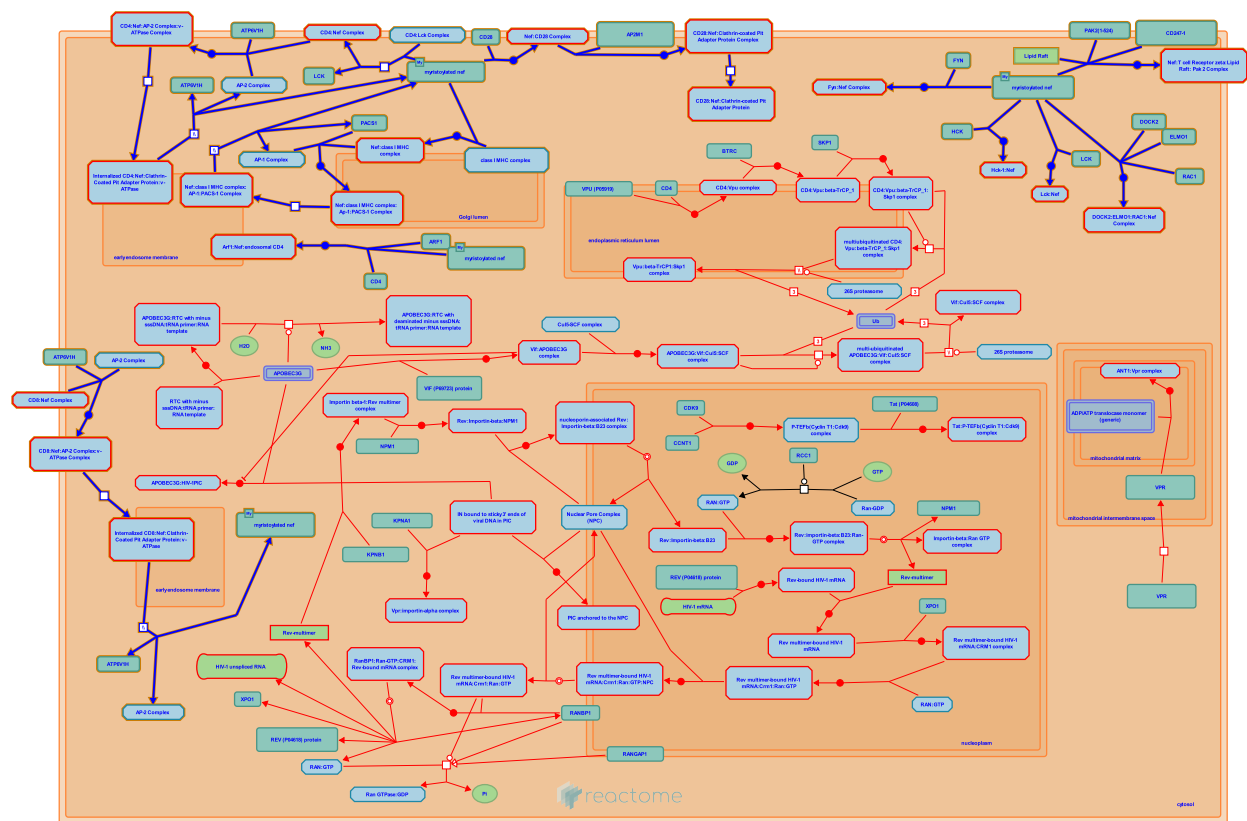
## Editions

2005-07-27	Authored	Matthews, L., Rice, AP.
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# The role of Nef in HIV-1 replication and disease pathogenesis ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-164952



The HIV-1 Nef protein is a 27-kDa myristoylated protein that is abundantly produced during the early phase of viral replication cycle. It is highly conserved in all primate lentiviruses, suggesting that its function is essential for survival of these pathogens. The protein name "Nef" was derived from early reports of its negative effect on viral replication, thus 'negative factor' or Nef. Subsequently it has been demonstrated that Nef plays an important role in several steps of HIV replication. In addition, it appears to be a critical pathogenic factor, as Nef-deficient SIV and HIV are significantly less pathogenic than the wild-type viruses, whereas Nef-transgenic mice show many features characteristic to HIV disease.

The role of Nef in HIV-1 replication and disease pathogenesis is determined by at least four independent activities of this protein. Nef affects the cell surface expression of several cellular proteins, interferes with cellular signal transduction pathways, enhances virion infectivity and viral replication, and regulates cholesterol trafficking in HIV-infected cells.

## Literature references

Zhao, RY., Bukrinsky, M., Pauza, CD., Li, HS., Li, L. (2005). Roles of HIV-1 auxiliary proteins in viral pathogenesis and host-pathogen interactions. *Cell Res*, 15, 923-34. ↗

## Editions

2007-07-25	Authored	Gillespie, ME.
2007-08-07	Reviewed	Skowronski, J.

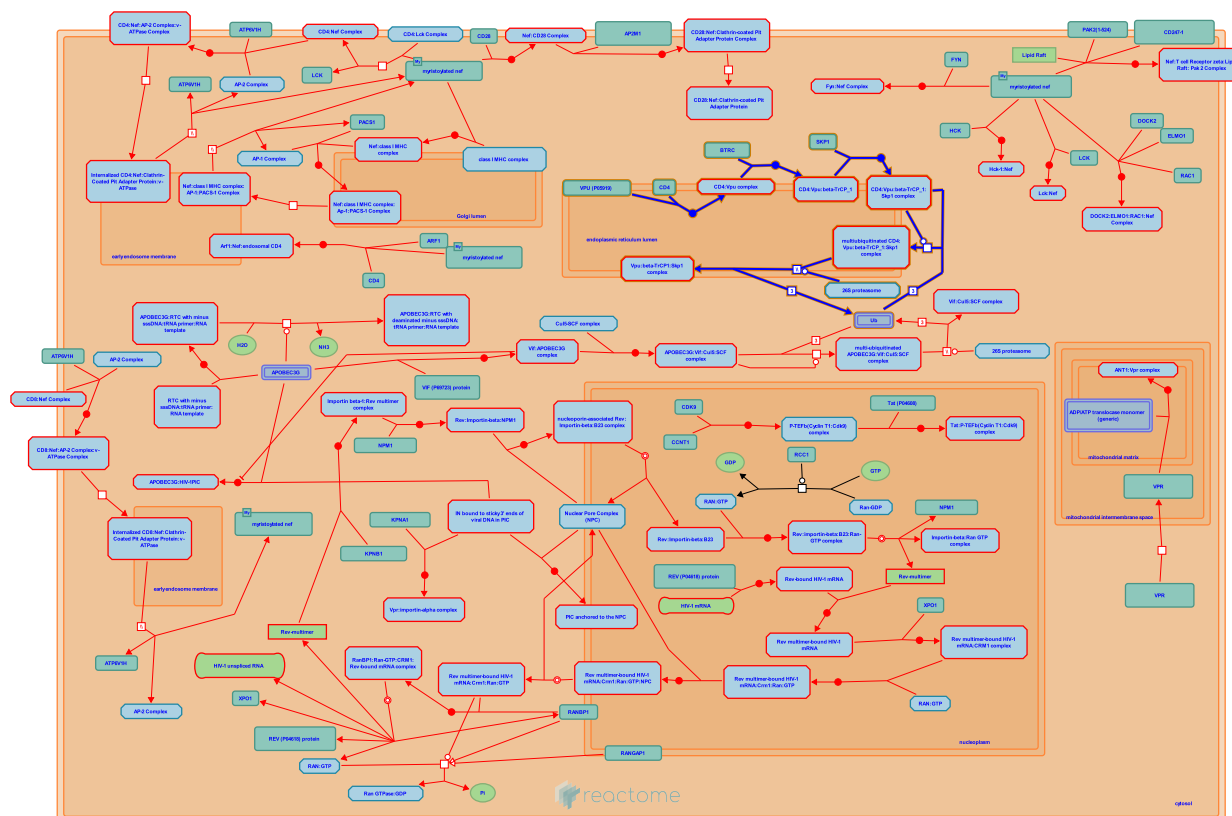
## Vpu mediated degradation of CD4 ↗

**Location:** [Host Interactions of HIV factors](#)

**Stable identifier:** R-HSA-180534

**Compartments:** cytosol

**Diseases:** Human immunodeficiency virus infectious disease



The HIV-1 Vpu protein promotes the degradation of the CD4 receptor by recruiting an SCF like ubiquitination complex that promotes CD4 degradation. Vpu links beta-TrCP to CD4 at the ER membrane through interactions with beta-TrCP and the cytoplasmic tail of CD4. The SKP1 component of the SCF complex is then recruited to the Vpu:beta-TrCP:CD4 promoting ubiquitination and subsequent proteasome-mediated degradation of CD4 (reviewed in Li et al., 2005). Vpu has also been shown to also increases progeny virus secretion from infected cells. Although the precise role of Vpu in this process is not yet known, it may affect ion conductive membrane pore formation and/or interference with TASK-1, an acid-sensitive K<sup>+</sup> channel that inhibits virion release in some cells (see references in Li et al., 2005).

## Literature references

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## Editions

2006-05-15

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Matthews, L.

2006-09-21

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Benarous, R.

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