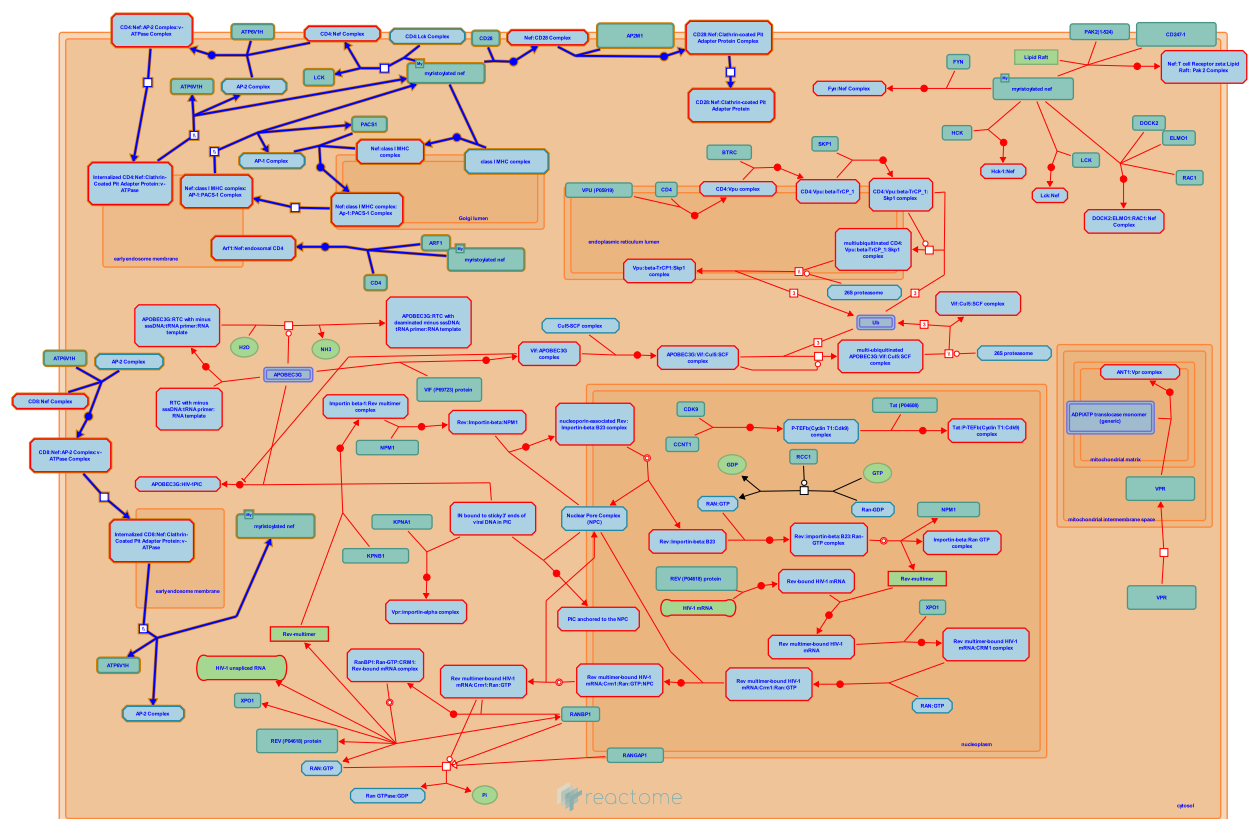


Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors



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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).

08/10/2024

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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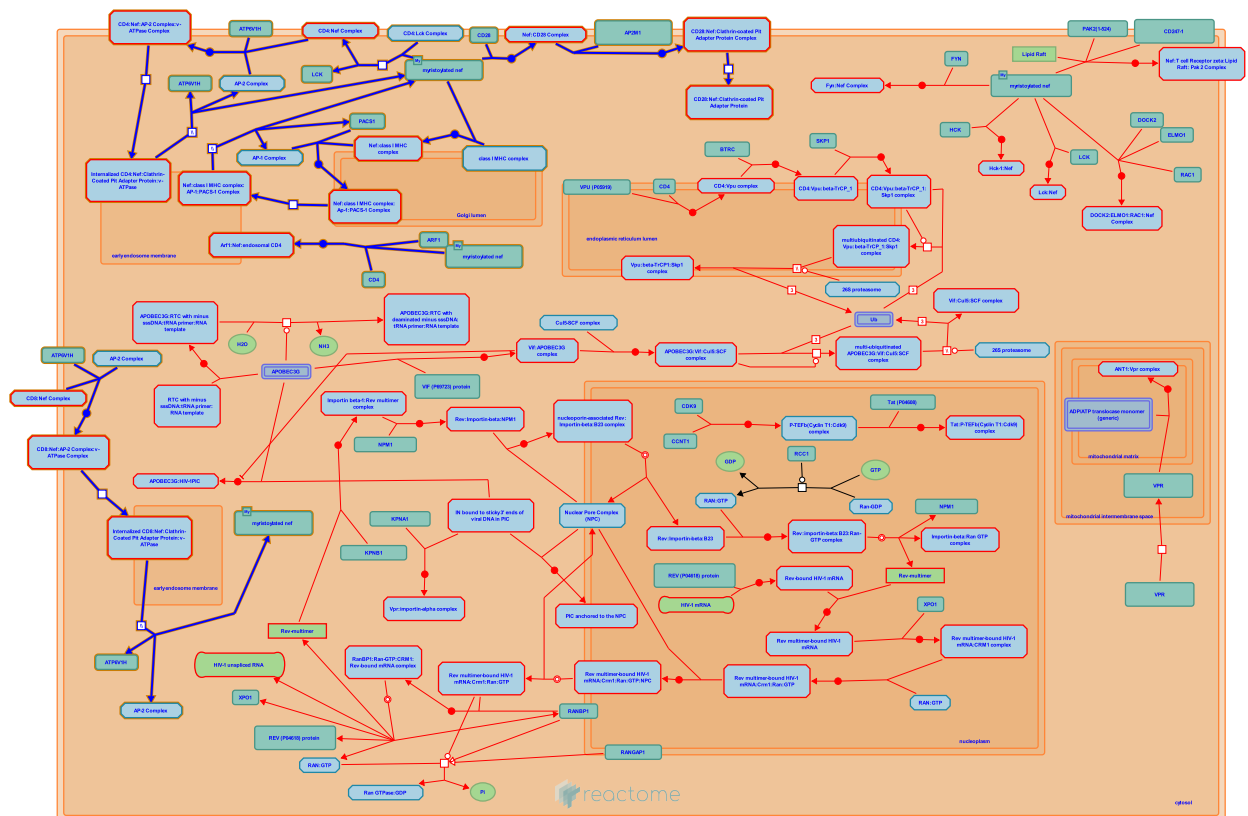
Reactome database release: 90

This document contains 5 pathways ([see Table of Contents](#))

Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors

Stable identifier: R-HSA-164938

Diseases: Human immunodeficiency virus infectious disease



The maximal virulence of HIV-1 requires Nef, a virally encoded peripheral membrane protein. Nef binds to the adaptor protein (AP) complexes of coated vesicles, inducing an expansion of the endosomal compartment and altering the surface expression of cellular proteins including CD4 and class I major histocompatibility complex. Nef affects the cell surface expression of several cellular proteins. It down-regulates CD4, CD8, CD28, and major histocompatibility complex class I and class II proteins, but upregulates the invariant chain of MHC II (CD74). To modulate cell surface receptor expression, Nef utilizes several strategies, linked to distinct regions within the Nef protein.

Since all these receptors are essential for proper functions of the immune system, modulation of their surface expression by Nef has profound effects on anti-HIV immune responses. Down-regulation of MHC I protects HIV-infected cells from host CTL response, whereas down-modulation of CD28 and CD4 probably limits the adhesion of a Nef-expressing T cell to the antigen-presenting cell, thus promoting the movement of HIV-infected cells into circulation and the spread of the virus.

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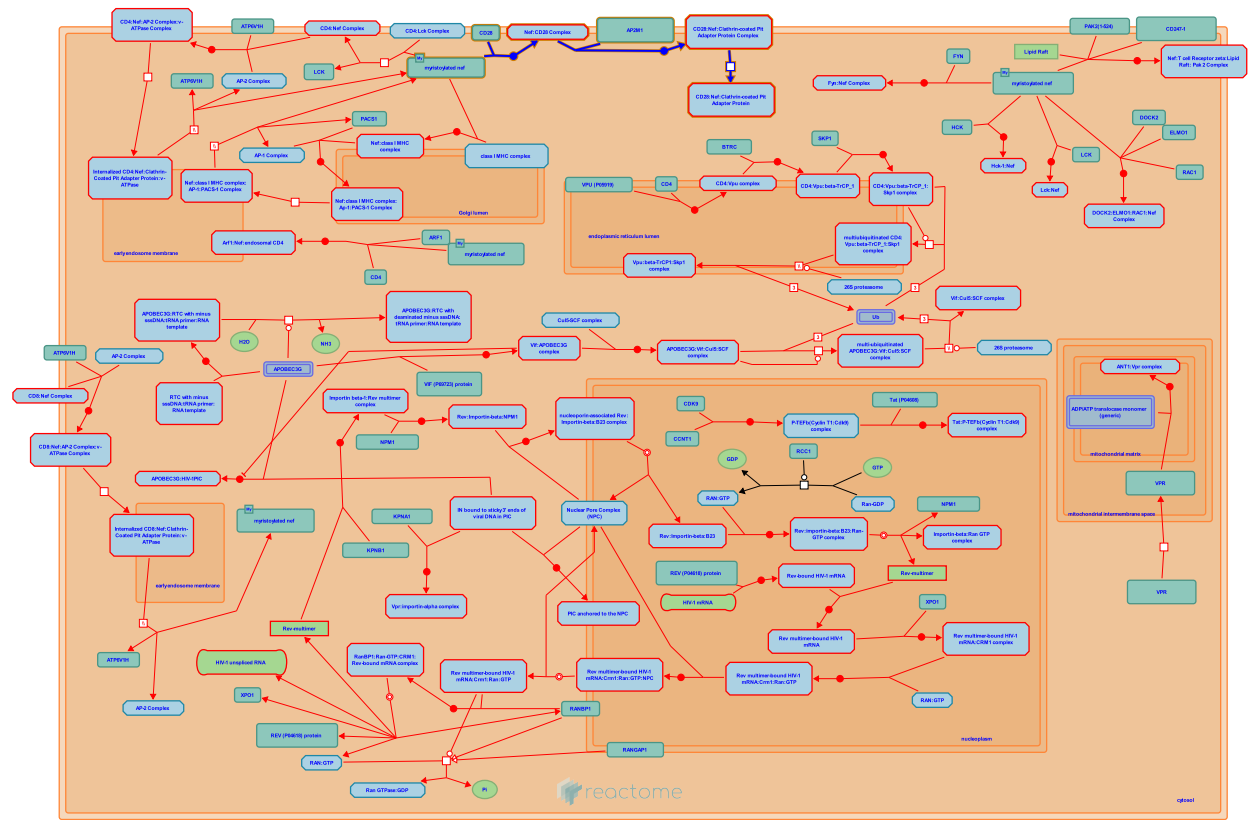
2007-07-25	Authored	Gillespie, ME.
2007-08-07	Reviewed	Skowronski, J.

Nef mediated downregulation of CD28 cell surface expression ↗

Location: Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors

Stable identifier: R-HSA-164939

Diseases: Human immunodeficiency virus infectious disease



Down-regulation of CD28 receptors involves a dileucine-based motif in the second disordered loop of Nef, which connects Nef to adaptor protein (AP) complex, which is a part of cellular endocytosis machinery. Nef induces accelerated endocytosis of CD28 via clathrin-coated pits followed by lysosomal degradation.

Literature references

Shohdy, N., Swigut, T., Skowronski, J. (2001). Mechanism for down-regulation of CD28 by Nef. *EMBO J*, 20, 1593-604. ↗

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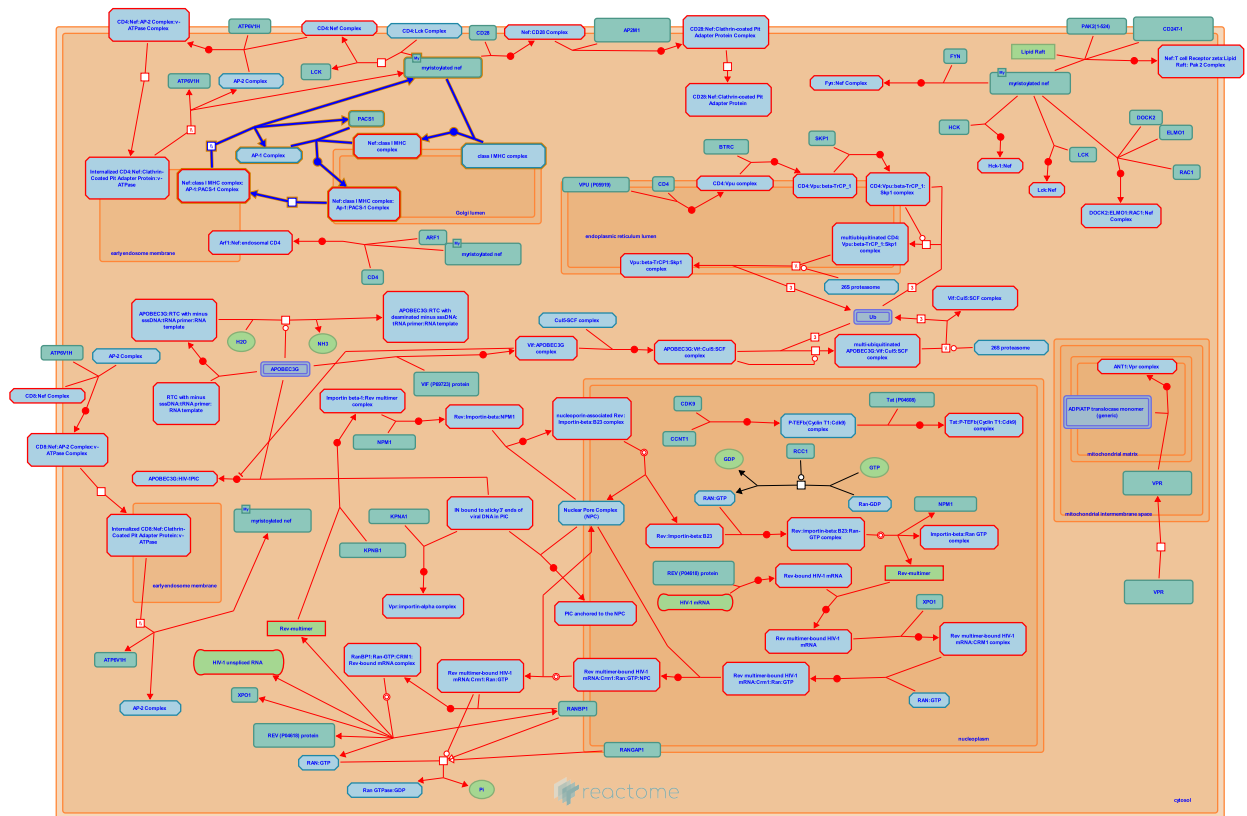
2007-07-25	Authored	Gillespie, ME.
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Nef mediated downregulation of MHC class I complex cell surface expression ↗

Location: Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors

Stable identifier: R-HSA-164940

Diseases: Human immunodeficiency virus infectious disease



Down-regulation of MHC class I involves Nef-mediated connection in the endosomes between MHC-I's cytoplasmic tail and the phosphofurin acidic cluster sorting protein-1 (PACS-1)-dependent protein-sorting pathway. Down-regulation of MHC I protects HIV-infected cells from host CTL response.

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Editions

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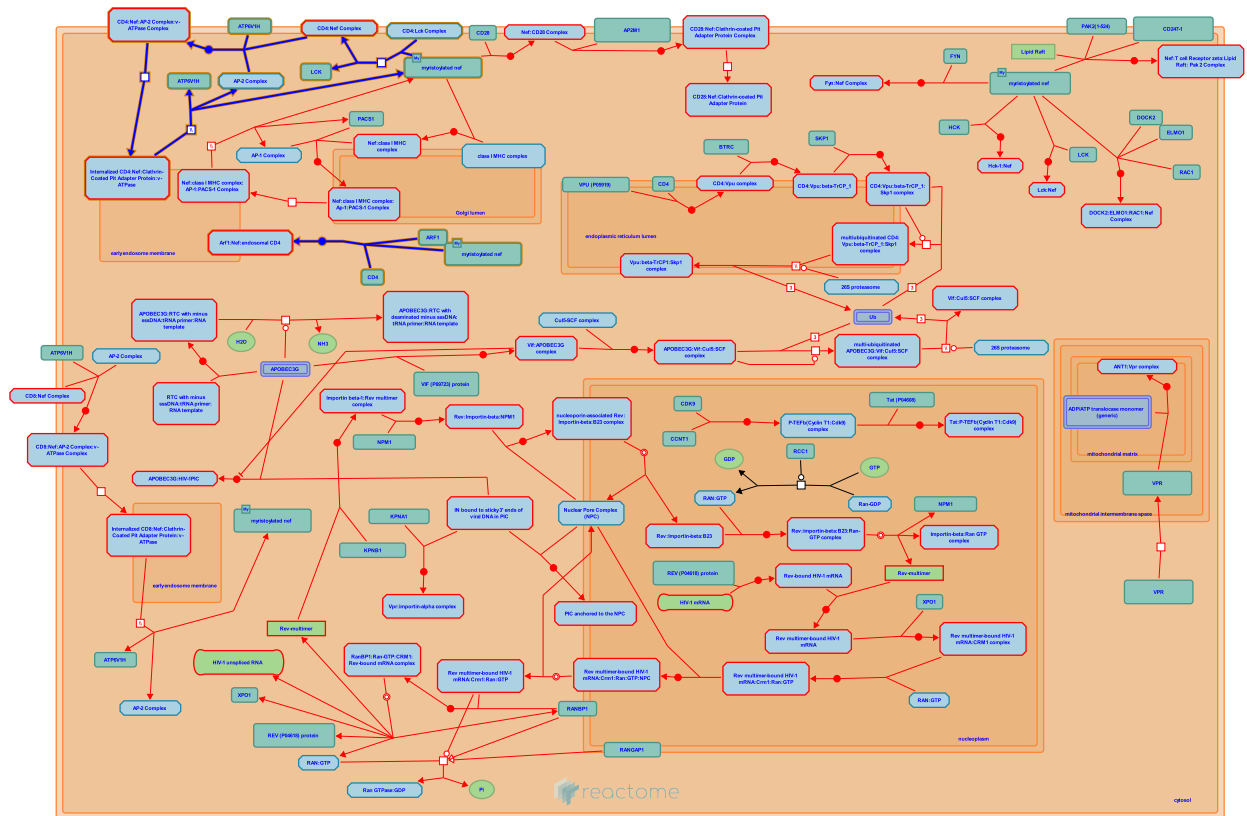
Skowronski, J.

Nef Mediated CD4 Down-regulation ↗

Location: Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors

Stable identifier: R-HSA-167590

Diseases: Human immunodeficiency virus infectious disease



The presence of Nef accelerates endocytosis and lysosomal degradation of the transmembrane glycoprotein CD4. CD4 has its own internalization motif, though this motif is normally concealed by CD4 interaction with Lck, a tyrosine kinase. Nef is known to disrupt this interaction and then facilitate a cascade of protein interactions that ultimately result in the degradation of internalized CD4 protein. The final set of protein interactions that direct Nef to the beta-subunit of the COPI coatamers are at this time unclear.

A benefit for the virus from CD4 down-modulation is abolition of interaction between the receptor and the Env protein of the budding virus, which likely increases HIV release from infected cell as well as infectivity of viral particles.

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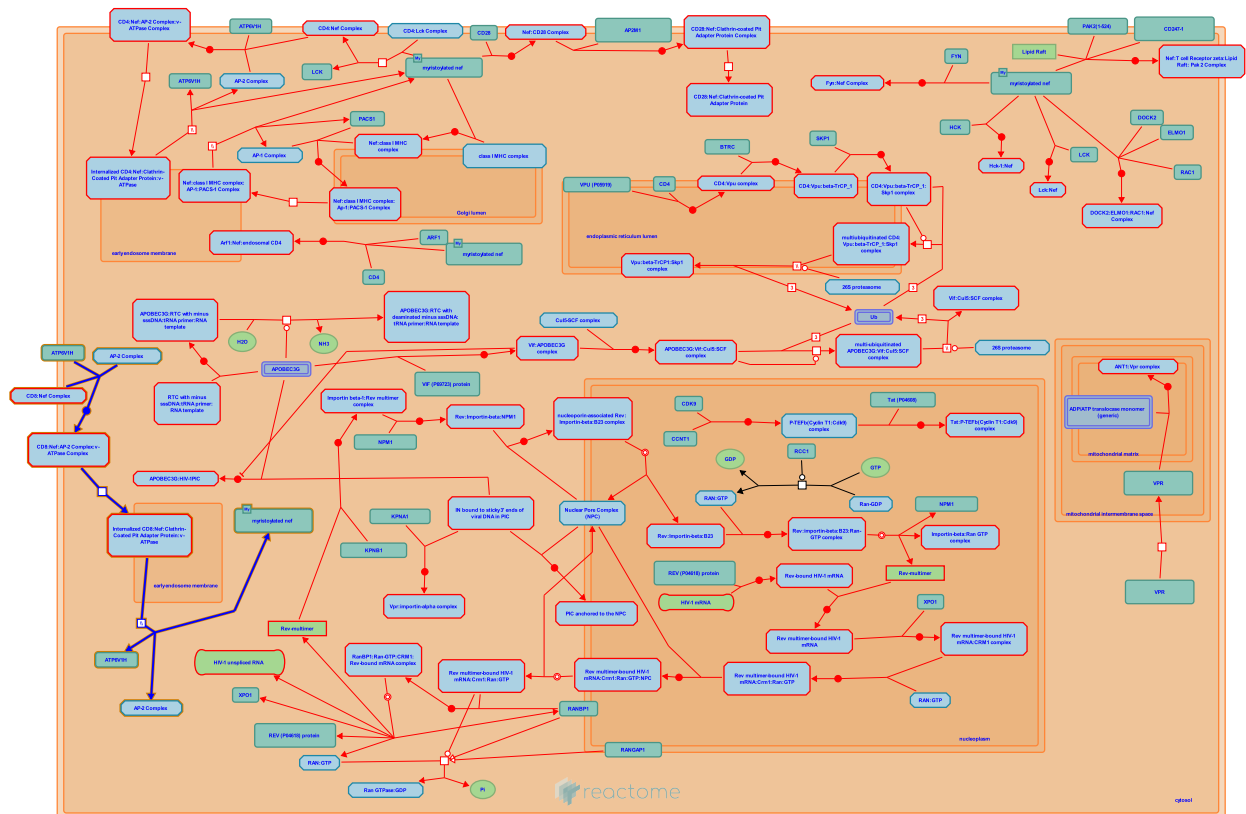
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Nef Mediated CD8 Down-regulation ↗

Location: Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adaptors

Stable identifier: R-HSA-182218

Diseases: Human immunodeficiency virus infectious disease



Human immunodeficiency virus (HIV) Nef is a membrane-associated protein decreasing surface expression of CD4, CD28, and major histocompatibility complex class I on infected cells. Nef also strongly down-modulates surface expression of the beta-chain of the CD8alpha-beta receptor by accelerated endocytosis, while CD8 alpha-chain expression is less affected. Mutational analysis of the cytoplasmic tail of the CD8 beta-chain indicates that an FMK amino acid motif is critical for the Nef-induced endocytosis. Although independent of CD4, endocytosis of the CD8 beta-chain is abrogated by the same mutations in Nef that affect CD4 down-regulation, suggesting common molecular interactions. The ability to down-regulate the human CD8 beta-chain was conserved in HIV-1, HIV-2, and simian immunodeficiency virus SIVmac239 Nef and required an intact AP-2 complex.

Literature references

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Skowronski, J.

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