The role of Nef in HIV-1 replication and disease pathogenesis

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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**


Reactome database release: 71

This document contains 3 pathways (see Table of Contents)

https://reactome.org
The role of Nef in HIV-1 replication and disease pathogenesis

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


Editions

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Nef interferes with cellular signal transduction pathways in a number of ways. Nef is associated with lipid rafts through its amino-terminal myristoylation and a proline-rich SH3-binding domain. These cholesterol-rich membrane microdomains appear to concentrate potent signaling mediators. Nef was found to complex with and activate serine/threonine protein kinase PAK-2, which may contribute to activation of infected cells. In vitro, HIV-infected T cells produce enhanced levels of interleukin-2 during activation. When expressed in macrophages, Nef intersects the CD40L signaling pathway inducing secretion of chemokines and other factors that attract resting T cells and promote their infection by HIV.

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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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