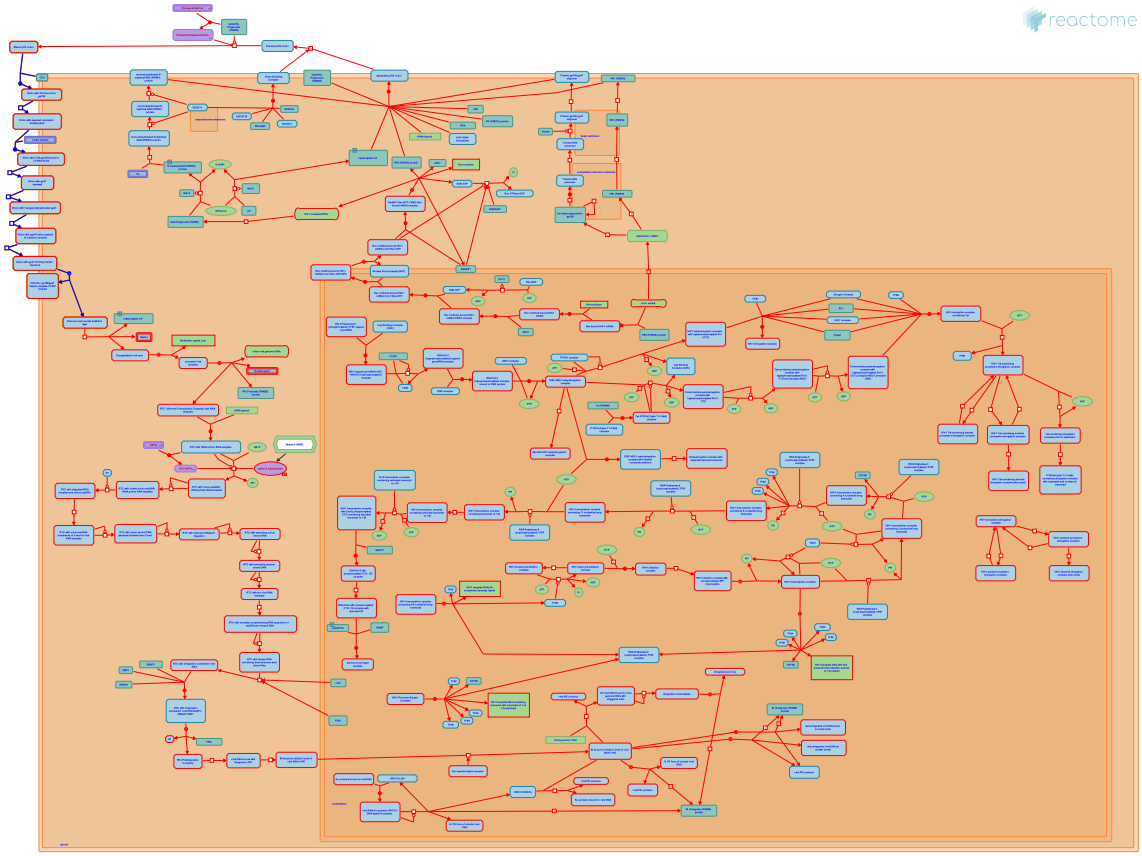
Binding and entry of HIV virion



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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.

15/05/2024

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. ↗

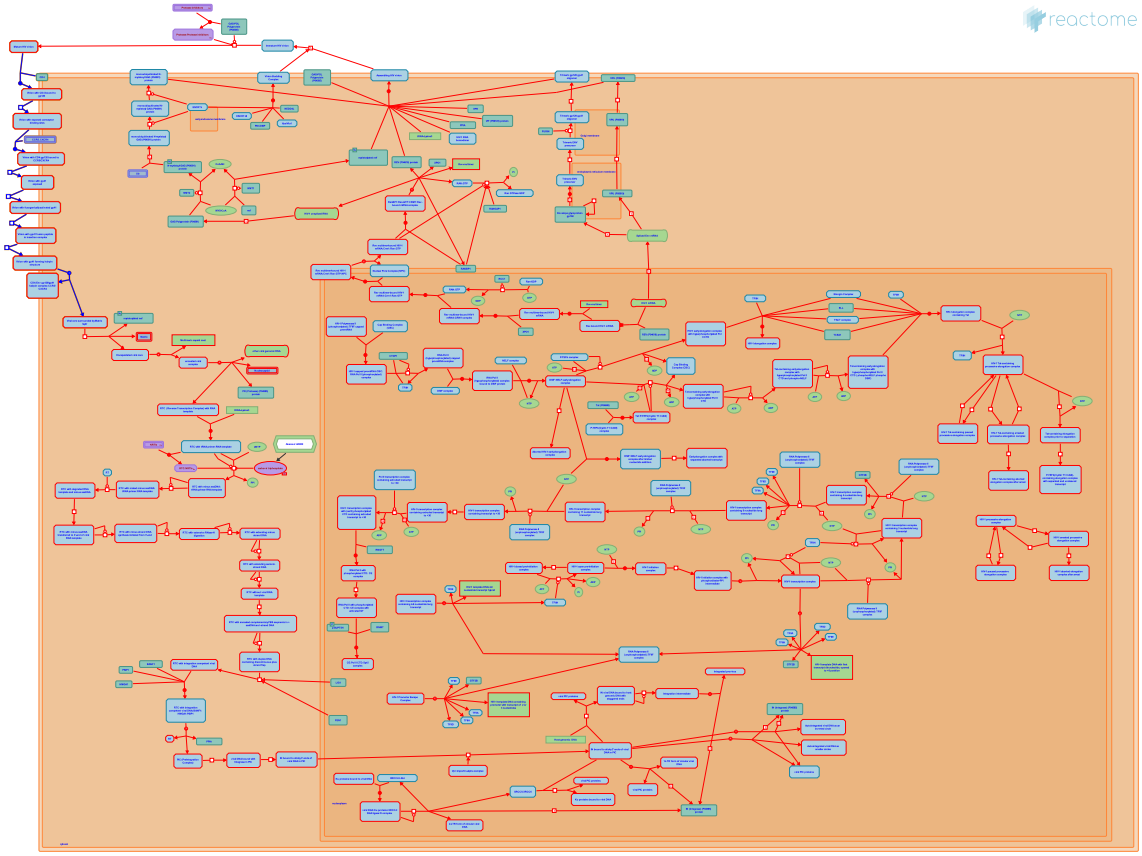
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Binding and entry of HIV virion ↗

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

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Binding of gp120 of ENV oligomer to the host CD4 ↗

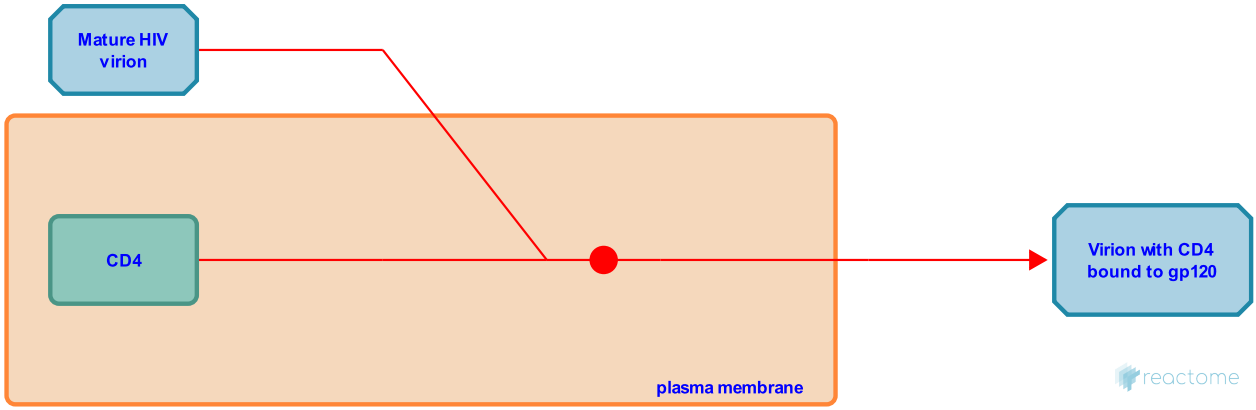
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164509

Type: binding

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



CD4, located on the host cell membrane, is the main cellular receptor for the HIV protein gp120, which aids in mediating viral entry into target cells. The initial step in this cascade of events is the binding of viral gp120 protein to its host receptor, CD4. The key binding sites in CD4 for interaction with gp120 are located in the amino-terminal part of the CD4 molecule, distal to the transmembrane domain. The gp120 protein forms an oligomer (trimer) on the viral membrane with each gp120 protein containing variable domains (known as loops) and conservative domains. The V3 loop is also often obscured by gp120 glycosylation. Crystallization studies of CD4 suggest that the molecule has two immunoglobulin like domains important for the CD4/gp120 interaction, with one of the domains (D1) playing a more prominent role. Further studies suggest the Phe 43 and Arg 59 residues of CD4 play a major role in complex formation. Crystallization of gp120 shows that the polypeptide chain is folded into two major domains (an "inner" and "outer" domain with respect to the N and C termini), with the distal end of the “outer” domain containing the V3 loop. Studies of CD4 complexed with gp120 show that CD4 is bound to gp120 in a depression which is formed at the interface between the inner and outer domains. The complex itself is held together through van der Waals forces and hydrogen bonding.

Followed by: Conformational change in gp120 of Env oligomer

Literature references

Greaves, MF., Beverley, PC., Weiss, RA., Crawford, DH., Clapham, PR., Dalgleish, AG. (1984). The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature, 312*, 763-7. ↗

Sodroski, J., Hendrickson, WA., Sweet, RW., Robinson, J., Wyatt, R., Kwong, PD. (1998). Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature, 393*, 648-59. ↗

Xuong, NH., Porter, TG., Rosenberg, M., Arthos, J., Sweet, RW., Ryu, SE. et al. (1990). Crystal structure of an HIV-binding recombinant fragment of human CD4. *Nature, 348*, 419-26. ↗

Hercend, T., Gruest, J., Champagne, E., Klatzmann, D., Gluckman, JC., Guetard, D. et al. (1984). T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature, 312*, 767-8. ↗

Cort, SP., McDougal, JS., Sligh, JM., Nicholson, JK., Kennedy, MS., Mawle, A. (1986). Binding of HTLV-III/LAV to T4+ T cells by a complex of the 110K viral protein and the T4 molecule. *Science, 231*, 382-5. ↗

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Conformational change in gp120 of Env oligomer ↗

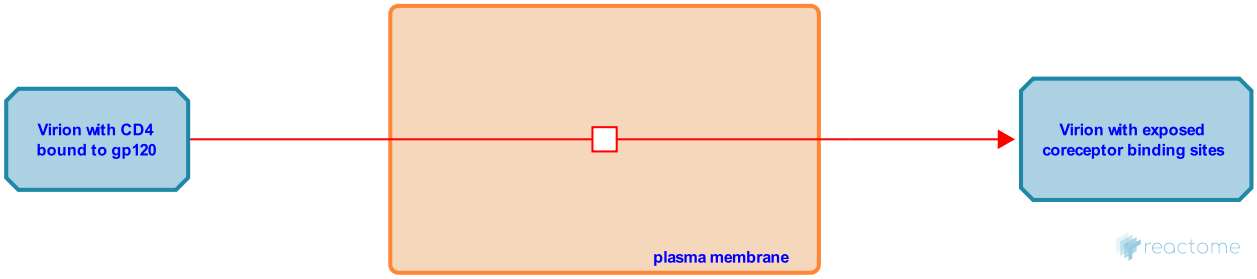
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164510

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



HIV-1 infection of target cells depends on the sequential interaction of the gp120 glycoprotein with the cellular CD4 receptor as well as members of the chemokine receptor family, such as CCR5. Upon interaction with the cellular CD4 receptor, gp120 undergoes a conformation change which allows interaction with these chemokine receptors to occur. Studies indicate that upon binding to CD4, this conformational change results in a repositioning of V1 and V2 loops of gp120, and exposes or forms the "bridging sheet domain" epitopes, which are then available for co-receptor (chemokine receptor) binding along with other domains of gp120. These epitopes are recognized by 17b, a member of a class of antibodies that recognize CD4-induced (CD4i) epitopes (Kwong et al., 1998, Rizzuto et al., 1998, Zhang et al., 1999).

Preceded by: Binding of gp120 of ENV oligomer to the host CD4

Followed by: CD4:gp120 binds to chemokine co-receptor CCR5/CXCR4

Literature references

Capon, DJ., Gregory, T., Berman, P., Shimasaki, C., Fennie, C., Lasky, LA. et al. (1987). Delineation of a region of the human immunodeficiency virus type 1 gp120 glycoprotein critical for interaction with the CD4 receptor. *Cell, 50*, 975-85. ↗

Sodroski, J., Hendrickson, WA., Sweet, RW., Robinson, J., Wyatt, R., Kwong, PD. (1998). Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature, 393*, 648-59. ↗

Sodroski, J., Chaiken, I., Canziani, G., Zhang, W., Hendrickson, W., Sweet, R. et al. (1999). Conformational changes of gp120 in epitopes near the CCR5 binding site are induced by CD4 and a CD4 miniprotein mimetic. *Biochemistry, 38*, 9405-16. ↗

Sodroski, J., Potz, J., Dayton, A., Goh, WC., Basiripour, L., Kowalski, M. et al. (1987). Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1. *Science, 237*, 1351-5. ↗

Sodroski, J., Thali, M., Sun, Y., Robinson, J., Gershoni, J., Sullivan, N. et al. (1998). CD4-Induced conformational changes in the human immunodeficiency virus type 1 gp120 glycoprotein: consequences for virus entry and neutralization. *J Virol, 72*, 4694-703. ↗

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

CD4:gp120 binds to chemokine co-receptor CCR5/CXCR4 ↗

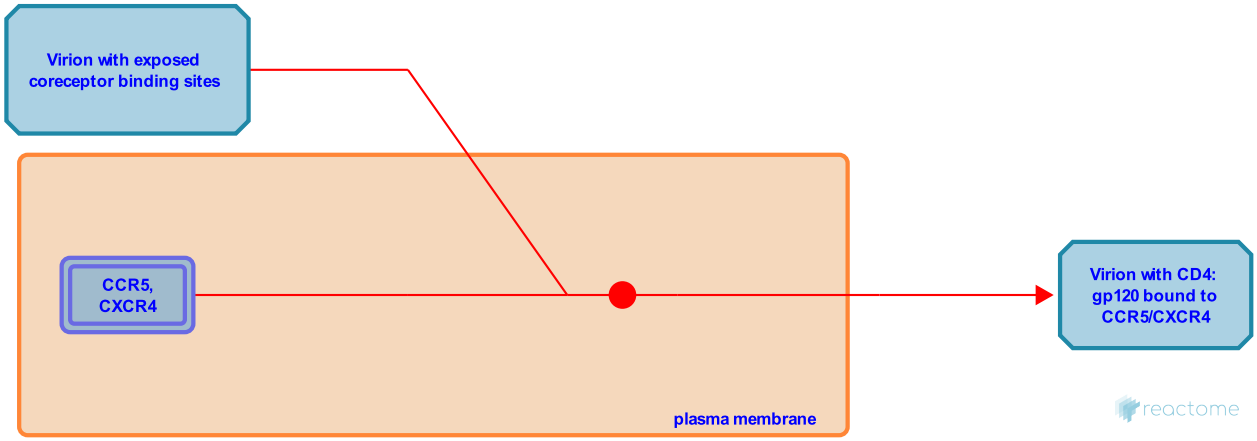
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164507

Type: binding

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



Once the viral gp120 protein has bound to cellular CD4, its bridging sheet region becomes exposed/formed as a result of conformation changes in the V1 and V2 loops as well as a conformational change in the gp120 core domain. Once this region is exposed, it is free to bind the HIV co-receptors CCR5 or CXCR4 (also known as chemokine receptors). Different viruses use different co-receptors (CCR5 or CXCR4) for entry, and many studies investigated the structural determinants of interaction between gp120 and the co-receptor.
Studies of CCR5 binding by gp120 revealed that active regions in the second extracellular loop (ECL2), the N-terminal extracellular domain (specifically the NYYTSE motif) and at the junction between the fifth transmembrane domain and third cytoplasmic loop of the receptor are important for viral attachment and subsequent fusion. The N-terminal region likely interacts with the core of gp120 (bridging sheet and adjacent regions) and the base of V3, while ECL2 may be important for interacting with the tip of V3. The transmembrane 5 / cytoplasmic loop 3 junction of CCR5 has been shown to influence the conformation of the receptor which allows for subsequent binding of gp120 (Wang et al.,1999). Deletion of the V3 loop in gp120 abolished Env interaction with co-receptor without affecting the binding of soluble gp120 to CD4, underscoring the importance of this loop in chemokine receptor, but not CD4, binding. Furthermore, the V3 loop is a major determinant of coreceptor specificity, with amino acid at positions 11 and 25 being partly predictive of CCR5 or CXCR4 use. Single amino acid changes in V3 can alter coreceptor use, however sequences outside of V3 can also contribute to coreceptor specificity.

Preceded by: Conformational change in gp120 of Env oligomer

Followed by: Conformational changes in gp120 exposes gp41

Literature references

Sodroski, J., Hendrickson, WA., Sweet, RW., Robinson, J., Wyatt, R., Kwong, PD. (1998). Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature, 393*, 648-59. ↗

Sodroski, J., Hendrickson, WA., Rizzuto, CD., Sun, Y., Hernandez-Ramos, N., Kwong, PD. et al. (1998). A conserved HIV gp120 glycoprotein structure involved in chemokine receptor binding. *Science, 280*, 1949-53. ↗

Schweickart, V., Sun, Y., Lee, B., Murray, JL., Wang, Z., Zhang, T. et al. (1999). CCR5 HIV-1 coreceptor activity. Role of cooperativity between residues in N-terminal extracellular and intracellular domains. *J Biol Chem, 274*, 28413-9 . ↗

Sodroski, J., Rollins, B., Sun, Y., Choe, H., Wu, L., Gerard, C. et al. (1996). The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell, 85*, 1135-48. ↗

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Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Conformational changes in gp120 exposes gp41 ↗

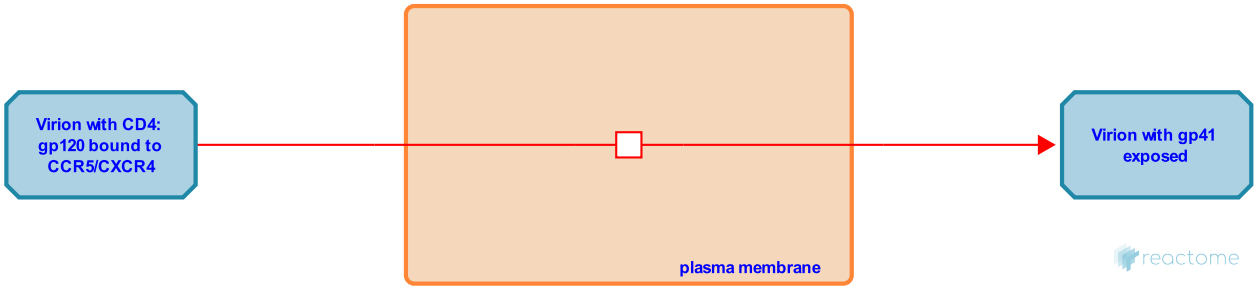
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164500

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



The HIV protein known as gp41 is a transmembrane protein which is considered the major mediator of fusion of extracellular virions to the target cells in the host. HIV gp120 and gp41 proteins form non-covalently linked oligomers on the surface of virions. The gp41 subunit of the oligomer is anchored in the viral membrane and contains a non-polar fusion peptide at its N-terminus. Upon CD4 and receptor binding, gp120 undergoes a second conformation change. The conformation change exposes gp41 which continues to mediate fusion of the viral envelope with the host plasma membrane. Electron microscopy and circular dichroism measurements of the gp41 protein suggest a rod-like conformation with a high alpha-helical content. Although some studies suggest that gp41must dissociate from gp120 in order to cause fusion between HIV envelope and the target cell plasma membrane, evidence on this point is not conclusive.

Preceded by: CD4:gp120 binds to chemokine co-receptor CCR5/CXCR4

Followed by: Fusogenic activation of gp41

Literature references

Sodroski, J., Potz, J., Dayton, A., Goh, WC., Basiripour, L., Kowalski, M. et al. (1987). Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1. *Science, 237*, 1351-5. ↗

Wong-Staal, F., Bosch, ML., Earl, PL., Picciafuoco, S., Franchini, G., Fargnoli, K. et al. (1989). Identification of the fusion peptide of primate immunodeficiency viruses. *Science, 244*, 694-7. ↗

Calder, LJ., Moss, B., Earl, PL., Weissenhorn, W., Skehel, JJ., Aliprandis, E. et al. (1996). The ectodomain of HIV-1 env subunit gp41 forms a soluble, alpha-helical, rod-like oligomer in the absence of gp120 and the N-terminal fusion peptide. *EMBO J, 15*, 1507-14. ↗

Kim, PS., Carr, CM. (1993). A spring-loaded mechanism for the conformational change of influenza hemagglutinin. *Cell, 73*, 823-32. ↗

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Fusogenic activation of gp41 ↗

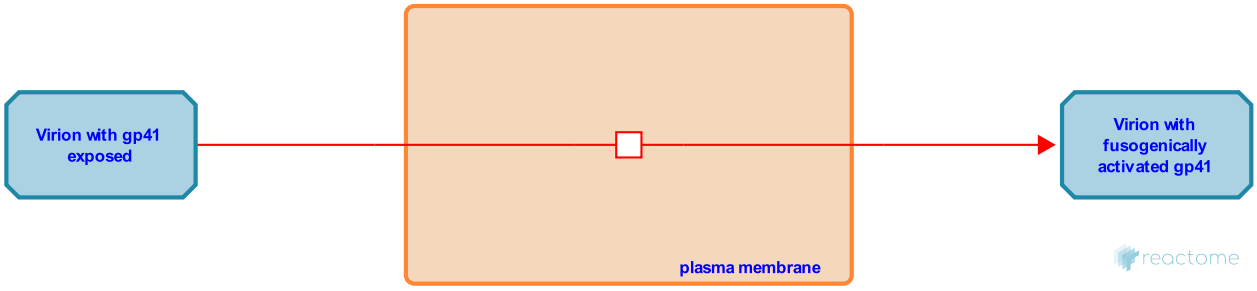
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164515

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



Fusion of HIV with target cell plasma membranes is mediated largely by the gp41 glycoprotein. This glycoprotein contains a stretch of strongly hydrophobic amino acids flanked by a series of polar amino acids at its N terminus. Subsequent to the second conformation change in gp120, the N-terminal fusion peptide of gp41 adopts a position which brings it into close proximity with the target cell plasma membrane. As gp41 is found in trimers within the viral membrane, the resulting structure of this conformational change is often referred to as a “prong”, in which three N-terminal peptides extend towards the target cell plasma membrane. The process of fusion begins at this time, with the N-terminus of gp41 inserting itself into the membrane of the target cell.

Preceded by: Conformational changes in gp120 exposes gp41

Followed by: Insertion of gp41 fusion peptide into the target membrane

Literature references

Risser, R., Freed, EO., Myers, DJ. (1990). Characterization of the fusion domain of the human immunodeficiency virus type 1 envelope glycoprotein gp41. *Proc Natl Acad Sci U S A, 87*, 4650-4. ↗

Sodroski, J., Thali, M., Bergeron, L., Repke, H., Helseth, E., Cao, J. (1993). Effects of amino acid changes in the extracellular domain of the human immunodeficiency virus type 1 gp41 envelope glycoprotein. *J Virol, 67*, 2747-55. ↗

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Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Insertion of gp41 fusion peptide into the target membrane ↗

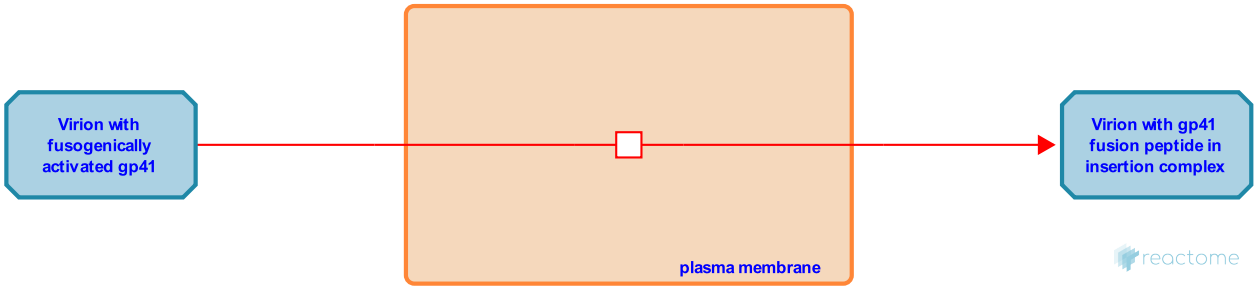
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164521

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



Insertion of the N-terminal fusion peptide of the HIV gp41 protein is the first step in the fusion of viral and target cell membranes. Substitutions of polar amino acids at residues 2, 9, 15 and 26 of the N terminus of this peptide completely eliminated its ability to cause fusion, implicating these residues in gp41's role in insertion and fusion. Studies have also shown that mutations in a stretch of residues from 36-64(568 to 596 of ENV protein) caused gp41 to become partially or completely defective in mediating membrane fusion, suggesting that conformation of the peptide is important for proper insertion and fusion to occur.

Preceded by: Fusogenic activation of gp41

Followed by: N and C terminal heptad repeat helices of gp41 form six-helix bundle

Literature references

Jiang, S., Lin, K., Neurath, AR., Strick, N. (1993). Inhibition of HIV-1 infection by a fusion domain binding peptide from the HIV-1 envelope glycoprotein GP41. *Biochem Biophys Res Commun, 195*, 533-8. ↗

Oas, T., Matthews, T., Bolognesi, D., Wild, C., McDanal, C. (1992). A synthetic peptide inhibitor of human immunodeficiency virus replication: correlation between solution structure and viral inhibition. *Proc Natl Acad Sci U S A , 89*, 10537-41. ↗

Risser, R., Freed, EO., Myers, DJ. (1990). Characterization of the fusion domain of the human immunodeficiency virus type 1 envelope glycoprotein gp41. *Proc Natl Acad Sci U S A, 87*, 4650-4. ↗

Sodroski, J., Thali, M., Bergeron, L., Repke, H., Helseth, E., Cao, J. (1993). Effects of amino acid changes in the extracellular domain of the human immunodeficiency virus type 1 gp41 envelope glycoprotein. *J Virol, 67*, 2747-55. ↗

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

N and C terminal heptad repeat helices of gp41 form six-helix bundle ↗

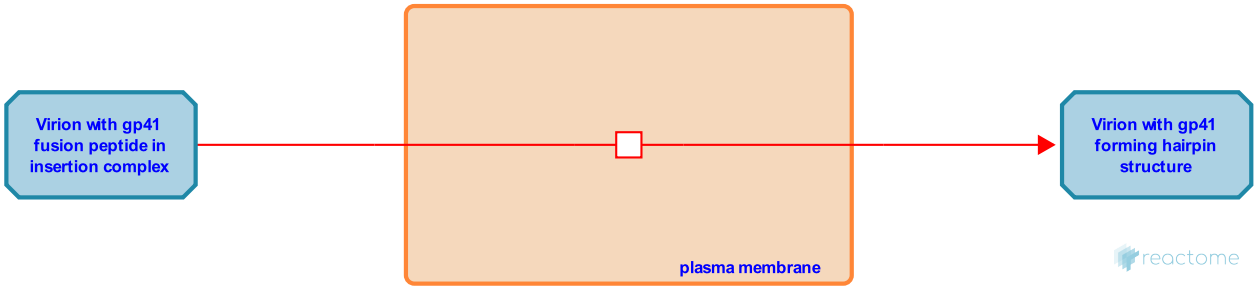
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164508

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



The gp41 glycoprotein contains N- and C-terminal heptad repeats, which form a stable six-helical bundle. This six-helix bundle represents a fusion-active gp41 core, and its conformation is critical for membrane fusion. Among the interactions necessary for the six helix bundle conformation is the formation of a salt bridge between the Asp632 residue in the C-terminal heptad repeat and the Lys574 terminal in the N-terminal coiled-coil. Disruption of this interaction has been found to lead to destabilization of the six helix bundle formation, with a subsequent severe reduction in viral fusion activity. Also, the N-terminal heptad repeat alone was found to be important in viral fusion, as removal or truncation of this repeat reduced the fusion activity of the peptide even when the adjacent, full length N-terminal fusion peptide was in place. The bundle itself is formed during the fusion process, prior to pore formation but after insertion of the gp41 fusion peptide into the target cell membrane. Upon insertion of the fusion peptide, the three N-terminal helices of gp41 adjacent to the target cell membrane and three C-terminal helices adjacent to the viral membrane undergo a conformational change which brings them into close proximity with one another, creating a six-helix bundle and leading to eventual fusion.

Preceded by: Insertion of gp41 fusion peptide into the target membrane

Followed by: Fusion of viral membrane with host cell membrane

Literature references

Gallo, SA., Blumenthal, R., Puri, A. (2001). HIV-1 gp41 six-helix bundle formation occurs rapidly after the engagement of gp120 by CXCR4 in the HIV-1 Env-mediated fusion process. *Biochemistry, 40*, 12231-6. ↗

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Dubay, JW., Hunter, E., Roberts, SJ., Brody, B. (1992). Mutations in the leucine zipper of the human immunodeficiency virus type 1 transmembrane glycoprotein affect fusion and infectivity. *J Virol, 66*, 4748-56. ↗

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Liu, S., Jiang, S., Debnath, AK., He, Y. (n.d.). Formation of a Salt Bridge between the N- and C-terminal Heptad Repeats of HIV-1 gp41 Is Critical for Stabilization of 6-Helix Bundle and Virus Fusion. Retrieved from http://www.retroconference.org/2004/cd/Abstract/295.htm

Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Fusion of viral membrane with host cell membrane ↗

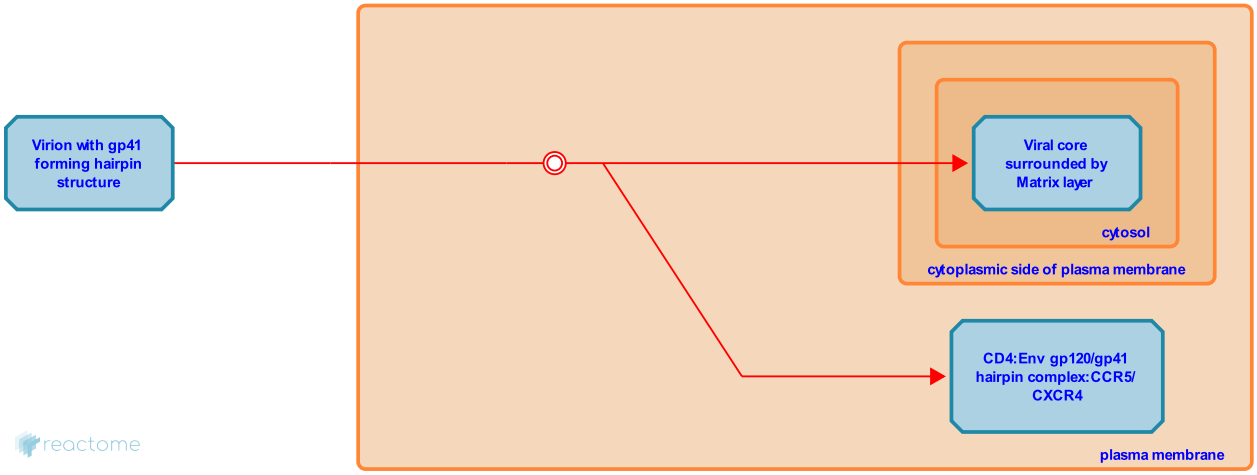
Location: Binding and entry of HIV virion

Stable identifier: R-HSA-164524

Type: dissociation

Compartments: plasma membrane, cytosol

Diseases: Human immunodeficiency virus infectious disease



With the transition of gp41 into the six-helix bundle, fusion of the viral and target cell membranes begins to take place. The specifics of fusion are not completely clear, but it is understood that fusion proceeds after insertion of the gp41 fusion peptide, which results in curvature of viral and target cell membranes. This results in a state of hemi-fusion, where only the outer lipid bilayers of each membrane are fused, whereas membrane leaflets that are distal with respect to the intermembrane gap remain separate at this stage. Hemi-fusion allows the exchange of lipids between the contacting leaflets, whereas the exchange of aqueous content between the virus and the cell remains blocked. The next step in fusion is the merger of the distal leaflets, leading to the formation of a nascent fusion pore, which leads to mixing of viral and cellular contents. Studies of fusion of Influenza virus suggested that multiple hairpin structures may form a narrow fusion pore which subsequently expands to a larger opening. In the case of HIV, this larger opening allows for passage of the Matrix-surrounded viral core out of the virus and into the host cell cytoplasm.

Preceded by: N and C terminal heptad repeat helices of gp41 form six-helix bundle

Literature references

Sodroski, J., Potz, J., Dayton, A., Goh, WC., Basiripour, L., Kowalski, M. et al. (1987). Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1. *Science, 237*, 1351-5. ↗

Luciw, PA., Long, EM., Chackerian, B., Overbaugh, J. (1997). Human immunodeficiency virus type 1 coreceptors participate in postentry stages in the virus replication cycle and function in simian immunodeficiency virus infection. *J Virol, 71*, 3932-9. ↗

Heckel, C., Meyer, S., Teufel, M., Luhrmann, R., Rautmann, G., Fischer, U. (1994). Evidence that HIV-1 Rev directly promotes the nuclear export of unspliced. *EMBO J, 13*, 4105-12. ↗

Weissenhorn, W., Skehel, JJ., Strassmaier, T., Ferrer, M., Schreiber, SL., Oprian, D. et al. (1999). Selection of gp41-mediated HIV-1 cell entry inhibitors from biased combinatorial libraries of non-natural binding elements. *Nat Struct Biol, 6*, 953-60. ↗

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Editions

2006-02-17	Edited	Gopinathrao, G.
2006-03-08	Authored	Morrow, MP., Bukrinsky, M.
2006-06-12	Reviewed	Reeves, J.

Table of Contents