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Review

Plasma membrane signaling in HIV-1 infection ☆

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ABSTRACT

Plasma membrane is a multifunctional structure that acts as the initial barrier against infection by intracellular pathogens. The productive HIV-1 infection depends upon the initial interaction of virus and host plasma membrane. Immune cells such as CD4+ T cells and macrophages contain essential cell surface receptors and molecules such as CD4, CXCR4, CCR5 and lipid raft components that facilitate HIV-1 entry. From plasma membrane HIV-1 activates signaling pathways that prepare the grounds for viral replication. Through viral proteins HIV-1 hijacks host plasma membrane receptors such as Fas, TNFRs and DR4/DR5, which results in immune evasion and apoptosis both in infected and uninfected bystander cells. These events are hallmark in HIV-1 pathogenesis that leads towards AIDS. The interplay between HIV-1 and plasma membrane signaling has much to offer in terms of viral fitness and pathogenicity, and a better understanding of this interplay may lead to development of new therapeutic approaches. This article is part of a Special Issue entitled: Viral Membrane Proteins — Channels for Cellular Networking.

Contents

1. Introduction

HIV-1, the causative agent of AIDS (acquired immunodeficiency syndrome), belongs to the family of *Retroviridae* [1]. This family has unique enzyme called reverse transcriptase (RT) that converts viral RNA into DNA upon viral entry into the cell [2]. The genome of HIV-1 contains two identical copies of single stranded RNA molecules which encode nine open reading frames that produce 15 proteins [3]. The three major proteins are Gag, Pol and Env polyproteins. The Gag polyprotein is cleaved into the structural proteins MA (matrix), CA (capsid), and NC (nucleocapsid). The gp160 Env protein is cleaved into a surface (SU) or gp120 glycoprotein and a transmembrane (TM) gp41 glycoprotein [4]. The three pol proteins PR (protease), RT (reverse transcriptase) and IN (integrase), provide the essential enzymatic function for viral life cycle and are present within the virus particles [4]. HIV-1 encodes six additional proteins; Tat and Rev, two regulatory proteins, and additional four so called accessory proteins, Vif, Vpr, Vpu and Nef. Vif, Vpr and Nef are found in the viral particles whereas Vpu assists in virion assembly [5].

The primary cell surface receptor for HIV-1, the CD4 protein, is a member of the immunoglobulin superfamily, found on macrophages and T lymphocytes [6]. The co-receptor for HIV-1 is either CCR5 or CXCR4 that is expressed on macrophages and T cells [7–9]. CXCR4 is a α-chemokine receptor specific for the ligand stromal derived factor 1 (SDF-1 or CXCL 12). CCR5 is a beta chemokine receptor, and like

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CXCR4 it belongs to the seven transmembrane family of cell surface receptor. Its ligands are small family of molecules including MIP-1α (CCL3), MIP-1β (CCL4) and RANTES (CCL5), and variants including CCL3L1 and CCL4L1 [10,11]. All of these ligands can compete with HIV-1 and inhibits its entry [12]. Other cell surface molecules can also participate in HIV-1 binding and entry. Integrin α4β7 can bind gp120 activating LFA-1 which is involved in viral synapse formation and cell-to-cell transmission [13]. Furthermore, the host's genetics can influence the immune response to HIV-1 infection. The most important finding in this regard is the homozygosity for a 32 bp deletion in CCR5 gene, and homozygous carriers of this mutation are resistant to R5 strains of HIV-1 infection [14].

Most of HIV-1 infection occurs by sexual exposure, through blood or from mother to child [15]. Following transmission of the virus, there is a period of approximately 10 days, known as eclipse phase, before the RNA become detectable in the plasma. Study of single genome amplification and sequencing has shown that 80% of mucosally transmitted HIV-1 infections are transmitted by single virus [16–18]. At the end of eclipse phase, HIV-1 and/or HIV-1 infected cells reach the draining lymph node, where they meet activated CD4+ T cells which are target for further infection. This process is mediated by dendritic cells (DC) which bind the virus through DC-SIGN and carry it to activated CD4+ CCR5+ T cells [19]. The virus replicates and spread rapidly throughout the lymphoid tissues, particularly gut associated lymphoid tissues (GALT), where memory CD4+ T cells are present in high number [20]. Approximately, 20% of CD4+ T cells in the GALT are infected with HIV-1. Up to 60% uninfected CD4+ T cells at this sites die by activation-induced cell death, resulting in the release of apoptotic microparticles that can suppress immune function [21]. Therefore, 80% of CD4+ T cells in GALT are depleted during the first 3 weeks of infection [20,22]. In the absence of antiretroviral drugs the viral load is maintained constant by a balance between virus turn over and immune response [23,24]. Moreover, cells are latently infected and are unlikely to be removed by anti-HIV immune response or even they cannot be eliminated by HAART [25,26].

Immune activation is associated with extensive apoptosis of T cells, leading to release of apoptotic microparticles into the blood and increased expression of TNF-related apoptosis inducing ligand (TRAIL), which kill bystander cells and participates in immune suppression [21]. HIV-1 replicates in infected individuals, with a virion half-life in the plasma of less than 6 h [27]. More than 99% of viral replication occurs in activated and productively infected CD4+ T cells in peripheral blood and lymphoid tissues [28]. The combination of antiretroviral drugs from different classes in highly active antiretroviral therapy (HAART) could reduce the plasma viremia to clinically undetectable level (<40 copies per ml plasma) within two months in many patients [27,29]. However, the suppression of viral replication by HAART uncovered the existence of long-lived HIV reservoirs that occur with extremely low frequency (0.1–1 cell/10^6 lymphocytes) [30]. The current antiretroviral regimen cannot totally purge HIV-1 from these reservoirs. HAART does largely prevent the establishment of additional infected cells in the reservoirs and restrain the viral production from established reservoirs [31–33]. Discontinuation of HAART triggers a new systemic infection from these latent reservoirs [34].

Cells are defined by the physical presence of a lipid bilayer membrane barrier that separates the inside of a cell from extracellular medium. Extracellular hydrosoluble chemical messengers cannot cross the cell membrane, and therefore their messages must be transduced across the membrane. However, lipid soluble messenger can cross cell membranes and communicate directly with the contents of the cell by binding to intracellular receptors [35–37]. Thus, the signal transduction across the plasma membrane is important because of its fundamental role in cellular communication and regulation of cellular processes [38]. Binding of HIV-1 to plasma membrane receptors activates multiple intracellular signaling cascades [39]. This signaling requirement is important for HIV-1 to establish a latent infection of resting CD4+ T cells [39]. Plasma membrane mediated signaling events may facilitate viral infection in various immunological settings *in vivo* where cellular conditions need to be primed [40]. It means that HIV-1 exploits plasma membrane and its receptor signaling network shared among immune system to hijack signaling pathways and to facilitate HIV pathogenesis. This review describes the role of plasma membrane signaling during HIV-1 infection.

2. HIV and raft signaling

Rafts, plasma membrane lipid microdomains, are formed by glycosphingolipids, sphingomyelin and cholesterol packed in the external leaflet of plasma membrane. Rafts function as biological structures to control membrane protein–protein interactions [41–43]. Furthermore, rafts also play an important role in the immune response. Despite their role in immune activation, these host lipid microdomains are abused to target host cells by different viruses including retroviruses, measles virus and influenza. Lipid rafts are exploited by the pathogens at different stages during infection [44–47]. Lipid rafts participate to viral entry and exit, as virion assembly areas within the cell, and to the modulation of cell signaling pathways during the immune response [48]. Furthermore, specific positive signal transducer proteins such as Src family protein tyrosine kinases (Lck, LAT, Fyn) preferentially localize in lipid rafts [49,50]. A number of other proteins associated with lipid rafts are GPI (glycosylphosphatidylinositol) anchored proteins (such as CD59, CD55/DAF, CD14, CD16, CD90/Thy-1), transmembrane proteins, MHC-I and MHC-II molecules, chemokines and other cell surface receptors (such as CXCR4, CCR5, TCR, BCR, FcRs), and annexin [51,52].

Many pathogens misuse lipid rafts and lipid raft-associated proteins as entry and exit gateways [53]. Additionally to HIV, the influenza and measles viruses among others enter and bud from host cells via rafts [54,55]. HIV-1 encodes only small set of functional genes. Host cell proteins and lipids play a critical role in numerous phases of HIV life cycle. HIV-1 utilizes lipid rafts at various stages of its viral cycle such as passage through mucosal tissues, infection of host cells [56], hijacking of cellular signaling pathways for efficient viral replication and immune evasion [57], exit of host cells [58], or entrance into the vascular system of the host [59].

HIV-1 attachment and entry into the cell comprise intermolecular interactions at plasma membrane. First HIV-1 interacts with CD4 which results in conformation change in gp120 to expose chemokine receptor binding site [60]. Furthermore, the interaction of gp120-CD4 with the chemokine receptor CXCR4 or CCR5 results in gp41 conformational changes initiating membrane fusion and infection process [61,62]. The HIV entry receptors are preferentially localized in lipid rafts and lipid rafts drive gp120-gp41, CD4 and chemokine receptor into a membrane fusion process [63,64], although these findings are still discussed [65]. Additionally, glycoshingolipids (Gb3, GM1) of the host cell that are involved in gp120 interaction are found in membrane microdomains that promote HIV-1 infection [66,67]. Furthermore, c-type lectin DC-SIGN abundantly expressed on dendritic cells functions as efficient binding of gp120 [19]. DC-SIGN is distributed in well-organized microdomains on DC, and lipid rafts associated DC-SIGN molecules act as efficient docking sites for HIV-1 [68–70].

Additionally to virion-associated proteins, soluble HIV-1 proteins were shown to enter into cells via lipid rafts. HIV-1 Tat is an essential regulatory protein for viral replication and acts as a transcriptional activator of the integrated provirus [71]. Beyond, its gene regulatory capacity, soluble Tat was found to enter into the cells in a heparin-dependent manner, to traffic between cells and is present in a number of cellular fractions [72,73]. The entrance of Tat was shown to occur through caveolar endocytosis descending from lipid rafts, not by clatherin coated pit formation [74]. This entrance route might be helpful for Tat to escape lysosomal degradation, to move into Golgi apparatus, to be transported to endoplasmic reticulum (ER) and finally to be exported from ER into the cytoplasm of the cell [74]. Drugs targeting cholesterol or inhibiting glycosphingolipid synthesis were shown to prevent

HIV-1 infection *in vitro* and *in vivo* demonstrating a role of raft dynamics for efficient viral entrance [75,76]. HIV-1 virions bind to and enter into the cell via lipid rafts but also bud out of the cell through lipid rafts [58]. This selective budding of HIV-1 virions allows the acquisition of specific host cells membrane associated proteins and lipids into virions that are able to deregulate antiviral immune response [77]. Furthermore, HIV Gag and envelope proteins co-localize with lipid rafts on the surface of infected cells suggesting that assembly and budding occur at membrane lipids microdomains [58,78]. Moreover, HIV-1 exploits the lipid trafficking network for efficient replication and for reaching the plasma membrane [79]. During the budding of HIV from CD4+ T cells are incorporated the host cell associated lipid localized molecules such as GPI-anchored proteins CD55 and CD59, MHC-I, MHC-II, GM1 or FcR [58,80,81]. Additionally during its budding from macrophages, HIV-1 incorporates the lipid raft associated proteins such as GPI-anchored protein CD55 and tyrosine phosphatase CD45 [82]. The tyrosine phosphatase CD45, which is specifically excluded from T-cell rafts, was found to be associated with rafts in macrophages. Therefore, rafts on macrophages display different characteristics than those on T cells [82]. This indicates that HIV-1 budding from macrophages would proceed by a different mechanism than via plasma membrane. Despite the recent advances in the understanding of HIV-1 pathogenesis, many mechanisms of viral assembly in macrophages remain to be elucidated [83,84].

Besides viral entry and budding, HIV can use raft signaling to evade recognition and killing of infected cells [57]. HIV has evolved the various ways to exploit its host, including the interruption and activation of signaling pathways in its target cell such as T cells, DC and macrophages [85–88]. HIV-1 gp120 activates MAPKs through ganglioside suggesting that lipid microdomains serve as an important factor to trigger cell signaling pathways for productive infection [89]. Pyk2 is a protein tyrosine kinase, involved in the cytoskeleton rearrangement. HIV-1 gp120 modulates the quiescent and activated T cells through MAPKs. The stimulation of primary lymphocytes with gp120 activates ERK1, ERK2 and Pyk2 in the lipid rafts (Fig. 1) [90]. Additionally, HIV-1 gp120 also activates MAPKs or focal adhesion tyrosine kinase in primary macrophages. Furthermore, gp120 inhibits B-cell chemotaxis to MCP-5 (CCL-12), MIP-3 (CCL20) and CCL-21 in a HIV coreceptor (CXCR4 and CCR5) and lipid raft dependent manner via p38 MAPK activation [91].

Nef is an abundant regulatory viral protein that is produced during early stages of the viral cycle. Nef interacts with and alters host cellular signaling pathways [92]. Nef contains several key motifs required

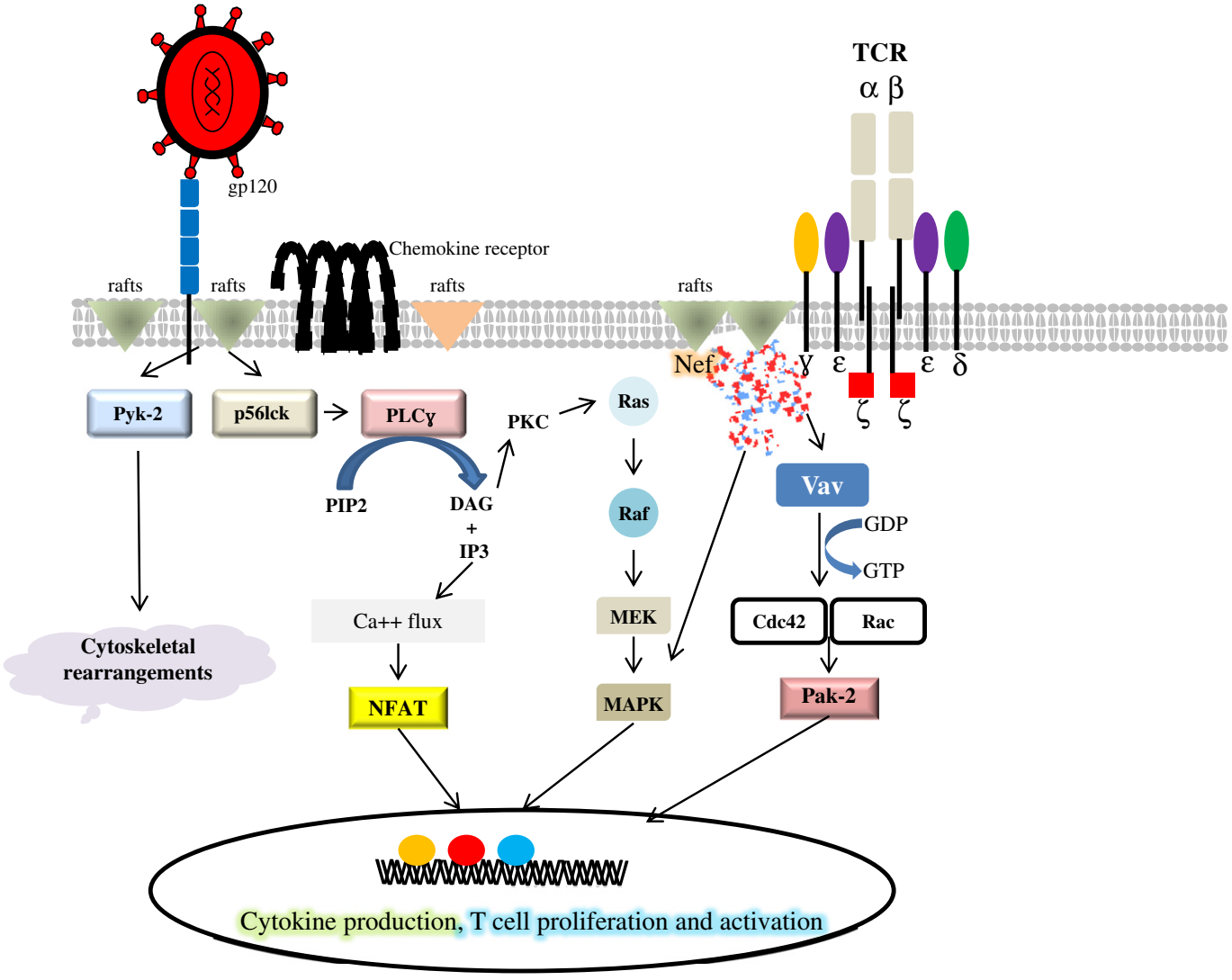

Fig. 1. A schematic overview of the signaling pathways activated by HIV-1 through lipid rafts. Binding of gp120 activates Pyk2 signaling pathways that are involved in cytoskeleton rearrangement. HIV-1 gp120 activates the lipid-associated protein Lck that then activates PLCγ that converts PIP2 into IP3 and DAG. IP3 increases calcium flux and activates NFAT signaling. DAG activates MAPK through PKC signaling. HIV-1 Nef targets TCR-associated lipid rafts and activates Pak2 signaling.

to misuse host cellular proteins [93]. The highly conserved proline rich motif (PxxP) of Nef binds to SH3 domains of a variety of raft-associated molecules including Src family kinases such as Hck, Fyn, Lck, Lyn, protein kinase C (PKC), MAPK, Pak2, TCRζ and Vav [94–96]. Furthermore, Nef activates raft-associated molecules that mediate antiapoptotic effects by phosphorylation of Bad and by inhibiting apoptosis signaling regulating kinase-1 (ASK-1) [97]. Moreover, Nef interacts with Pak-2 (p21-activated kinase 2) in the lipid rafts, which results in the activation of transcription factors such as NF- B and NFAT that leads to T-cell activation [98]. The interaction of Nef with Pak2 is mediated by cdc42 and Rac, as Nef activates these subfamilies of Rho-GTPases via Vav. This mechanism of Nef activation of Pak2 by cdc42 and Rac takes place in rafts and depends on raft integrity (Fig. 1) [99,100]. In Nef-expressing CD4 + T cells, UbcH7 (E2 ubiquitin conjugating enzyme) that is a negative regulator of T-cell signaling is absent from lipid rafts [101]. Due to the absence of UbcH7 from rafts, there is accumulation of tyrosine phosphorylated Vav, leading to increased Cdc42 activity [102]. Nef-induced Pak2 activation at the plasma membrane could be required to stably form virological synapses necessary for efficient cell-to-cell transfer of virus [103,104]. Besides the proline rich motif (PxxP), the myristoylated form of Nef activates the resting T cells by increasing the level of signaling molecules within raft [105].

3. HIV and chemokine receptor signaling

In 1996, a G-protein coupled receptor designated "fusin" was identified as the first cofactor for HIV-1 entry into CD4-positive cells [6,9,106]. The fusin was later known as CXCR4 and its natural ligand is the CXC chemokine stromal derived factor 1 (SDF1). Before the discovery of CXCR4, it was known that CC chemokines such as RANTES, MIP-1α, MIP-1β suppress HIV-1 infection [107,108]. Later on, it was confirmed that CCR5 is also a co-receptor for the entry of HIV-1 [8,109]. Chemokine receptor signaling is associated with diverse signaling pathways that mediate cell migration, transcriptional activation, cell growth and differentiation [110,111]. The binding of SDF-1 to CXCR4 activates heterotrimeric G-proteins (Gα and Gβγ). Although there are several classes of Gα, such as $G\alpha_s$, $G\alpha_{i/o}$, $G\alpha_{q/11}$ and $G\alpha_{12/13}$, the CXCR4 molecules are preferentially coupled to $G\alpha_{i/0}$ and $G\alpha_{q/11}$. $G\alpha_{q/11}$ activates phospholipase C-β (PLCβ), which catalyzes the cleavage of membrane bound phosphatidylinositol 4,5 bisphosphate (PIP2) into second messengers inositol triphosphate (IP3) and diacylglycerol (DAG). These signaling pathways lead to calcium flux and the activation of several PKC isoforms that has been shown to be important for SDF-1 induced chemotaxis [112,113]. Additionally, SDF-1 binding to CXCR4 activates $G\alpha_{i/0}$ which inhibits adenylate cyclase that in turn leads to a reduction in cAMP levels as well as the activation of phopholipases phosphodiesterase. These signaling events activate the lipid kinase PI3K via $G\alpha_{i/0}$-coupled Src family kinases as well as PI3Kγ through direct binding of Gβγ to the regulatory subunit of PI3Kγ [114,115]. SDF-1 binding to CXCR4 also stimulates guanine nucleotide exchange factors (GEFs) such as Tiam1 (T lymphoma invasion and metastasis 1) and Phosphatidylinositol 3,4,5-triphosphate dependent Rac exchanger-1 (P-Rex1) that is associated with Rho family GTPase such as Rac, Rho, Cdc42 and Ral that modulate cytoskeleton [116–118]. Moreover, SDF-1 also regulates the cytokine and growth factor driven pathways by activating JAK-STATs signaling which leads to cell proliferation and differentiation [119–121]. Finally, SDF-1 also activates Cbl/Cbl-b, which functions as an E3 ligase, regulating cell signaling through ubiquitination [122]. Altogether, SDF-1 and CXCR4 signaling pathway mediates chemotactic response for cytoskeleton rearrangement, cell polarization and migration, transcriptional activation, cell survival and proliferation.

Binding of HIV to its chemokine receptor (CCR5, CXCR4) has also been shown to trigger the activation of Pyk2, Erk1/2, PI3K, Akt and NFAT (Fig. 2) [123–126]. Furthermore, gp120 binding to chemokine receptor mediates chemotaxis, cytoskeleton rearrangement, and the activation of cofilin (actin depolarization factor) to increase the cortical actin dynamics in resting CD4 + T cells [127]. After the discovery of HIV-1 coreceptors, the involvement of chemokine signaling in HIV-1 infection was thoroughly studied [9]. In a series of experiments, by using PTX and CCR5 mutants, no involvement of chemokine signaling in HIV infection and pathogenesis was shown [128,129]. Later on, a significant number of studies have demonstrated that the chemokine receptor signaling might be important for viral replication. For example, pretreatment of macrophages or CD4 + T cells with CC-chemokines was found to enhance HIV replication [130,131]. Similarly, stimulation of CD4 + T cells from HIV infected subjects with gp120 can induce HIV replication [132]. In addition, the replication of some HIV-1 isolates in macaque cells were blocked at a step after entry and reverse transcription but prior to nuclear import of preintegration complex, but this block could be relieved by the expression of HIV-1 coreceptors in macaque cells [133]. It was shown that three to nine amino acid changes in the envelope of SIVmac293 conferred to the virus the ability to replicate 100 to 1000 times more efficiently in macrophages [134]. Broad spectrum chemokine inhibitors (BSCIs) which block chemokine induced chemotaxis in range of leukocytes, irrespective of the chemokine used [135,136], inhibit HIV-1 infection without blocking gp120/CCR5 interaction [137]. These results suggest the involvement of coreceptor signaling in post entry steps.

Chemokine receptor signaling plays an important role for the establishment of latent infection in resting CD4 + T cells [138]. This absolute requirement of chemokine signaling is even required in resting T cells exposed to certain cytokines such as IL-2 or IL-7 [139]. In fact, the static cortical actin in resting CD4 + T cells represents a unique barrier for viral post entry migration. HIV-1 gp120 utilizes $G\alpha_{i/o}$-dependent signaling from chemokine receptor CXCR4 to activate cofilin (actin

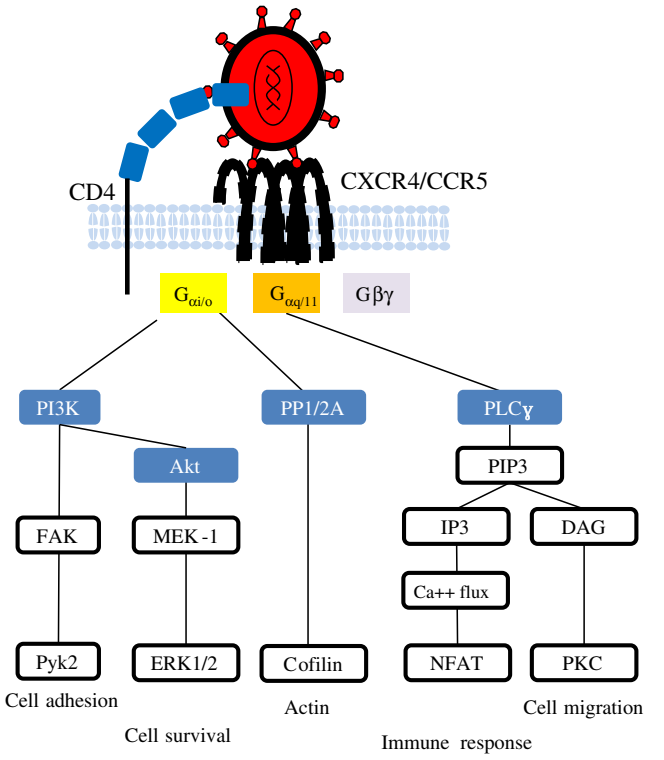

Fig. 2. Activation of chemokine receptors signaling in HIV-1 infection. HIV-1 gp120 ligation to chemokine receptors (CXCR4) activates G protein and multiple downstream signaling pathways. Gαi/o activates PI3K which stimulates downstream targets such as Akt, mitogen/extracellular signal regulated kinase (MEK) and extracellular signal regulated kinases (ERKs). PI3K also triggers the phosphorylation of focal adhesion complex component such as proline rich tyrosine kinase (Pyk-2). Cytoskeleton arrangement occurs through interplay between protein phosphatases and cofilin. Gαq/11 activates PLCγ which hydrolyzes PIP3 into IP3 and DAG which triggers calcium flux and activation of PKC signaling pathway.

depolymerizing factor) to overcome this restriction. This unique requirement of coreceptor signaling can be observed in resting CD4+ T cells, since in activated T cells cofilin is constitutively active to facilitate cell cycle driven actin remodeling that renders CXCR4 signaling unnecessary [127]. Chemokine signaling also activates rapid actin polymerization. This process may be important for capping of CD4 with CCR5 or CXCR4 and also for efficient synthesis of viral DNA [127,140]. This early actin polymerization may be involved in assembling large numbers of CD4 and CCR5 or CXCR4 molecules at plasma membrane to facilitate gp120 binding and viral entry [141]. In addition, CCR5 signaling has also been shown to trigger unique signaling cascades that activate kinases and nuclear transcription factors [126,142,143]. It has been reported that R5 envelopes induce the expression of genes belonging to MAPK and genes regulating cell cycle [143]. Additionally the R5 envelope also activates NFAT and induces its translocation into the nucleus that likely enhances viral transcription from LTR promoter [144].

4. HIV and CD4 receptor signaling

The CD4 molecule plays a very important role in the development and activation of T cells. It increases the affinity of TCR for the peptide of MHC-II molecules and transduces the signal through associated tyrosine kinase $p56^{lck}$ [145–147]. The CD4 molecule consists of an N-terminal extracellular portion, a transmembrane part and a short cytoplasmic tail. The extracellular portion of CD4 molecule consists of four domains (D1–D4) with an Ig-like structure and is involved in the interaction with class II molecules of the MHC and other ligands [145,148,149]. The cytoplasmic portion of CD4 is involved in cell signaling and the palmitoylation sequences in the juxtatransmembrane region of CD4 act as raft targeting motifs [150]. CD4 is required for efficient recruitment of the TCR to lipid microdomains [151]. Furthermore, CD4 has been shown to be required for MHC clustering and efficient Lck recruitment to the immunological synapse [152].

Binding of HIV-1 to CD4 is necessary but not sufficient for productive infection [153]. The interaction of gp120 with CD4 and subsequently with CXCR4 or CCR5 is crucial to initiate cell fusion [154]. After binding to CD4, HIV-1 develops conformation change in gp120 that enables it to bind to the chemokine receptors [155,156]. HIV-1 gp120 binding to the CD4 molecule induces rapid tyrosine phosphorylation of Src kinase $p56^{lck}$ that inhibits the binding and chemotaxis of CD4+ T cells in response to SDF-1α by downregulating CXCR4 [157]. A significant reduction in HIV-1 replication has been observed in cells expressing a truncated cytoplasmic domain of CD4 that resulted from the inability of the receptor to associate with $p56^{lck}$ and to stimulate nuclear translocation of NF- B [158]. These results indicate that the CD4-associated tyrosine kinase Lck is critical in the transduction of signals that favor T-cell activation. Through its SH2 and SH3 domains Lck interacts with various downstream targets such as LckBP, PLC-γ, MAPK, Zap-70 and PI3K [159–162]. The interaction of gp120 to CD4 has been shown to induce the production of IL-6, IL-10, IFN-γ, TNF-α, and to up-regulate the expression of the Fas antigen [163–165]. Therefore, the modulation of signaling pathways by binding of HIV-1 or gp120 to the CD4 receptor may have important consequences for HIV-1 induced pathogenicity [166–169].

The binding of purified virions of HIV-1 or gp120 to CD4 receptor results in tyrosine phosphorylation that activates Lck and Raf signaling pathways through a Ras-independent signaling [170]. Additionally, the binding of HIV-1 on CD4 molecules activates MEK/ERK signaling pathways and also stimulates the expression of a number of transcription factors such as AP1, NF- B, and C/EBP. The activation of these signaling pathways is independent of HIV-1 binding to the chemokine receptors and can be induced in CD4+ T cells by both T-cell tropic and macrophage-tropic HIV-1 variants [171]. Therefore the increased expression of inflammatory genes by gp120 activation contributes significantly to enhanced HIV-1 replication as well as deregulation of the immune system.

HIV-1 gp120 binds to the CD4 molecule and stimulates LFA-1 in active conformation that allows binding to ICAM-1 with high affinity [172]. LFA-1 and ICAM-1 are incorporated into the envelope of virions budding from activated CD4+ T cells that support productive viral replication [173,174]. Furthermore, HIV virions exhibiting ICAM-1 are more infectious than ICAM-1-negative virions [175,176]. Therefore, activation of LFA-1 on target and infected CD4+ T cells enhances the HIV-1 infectivity and transmission [172]. The ability of gp120 to activate LFA-1 through CD4 has been further evidenced by increased sensitivity of quiescent T cells upon interaction with surface bound gp120 to LtxA. LtxA is a bacterial leukotoxin that preferentially kills leukocytes bearing the active form of LFA-1 [177]. The binding of gp120 to CD4 is crucial for LFA-1 activation as the disruption of gp120 and CD4 interaction prevented the cell contact with ICAM-1 and nullifies the enhanced susceptibility of cells to LtxA [178].

5. Signaling from plasma membrane and HIV pathogenesis

HIV infection results in the progressive decline in CD4+ T cells and, subsequently, CD8+ T cells. Daily loss of CD4+ T cells has been estimated between 3.5×10^7 and 2×10^9 cells during HIV infection [179,180]. HIV-1 induces the reduction in immune cells by various mechanisms. First, the T-cell generation is impaired during HIV-1 infection which results in fewer healthy T cells being released into the peripheral bloodstream [181]. Second, HIV induced immune activation leads to programmed cell death. Third, HIV-1 and its proteins can induce a more specific signal to immune cells and directly cause their apoptosis [182,183]. HIV-1 triggers apoptosis of uninfected bystander CD4+ and CD8+ T cells [168]. HIV-1 proteins modulate signaling pathways through the plasma membrane, resulting in T lymphocytes depletion (Fig. 3). The lymphocyte apoptosis is highly regulated and is dependent on the expression of a family of ligands and receptors such as Fas/FasL, TNF/TNFR, TRAIL/DR4/5. These plasma membrane receptors are increased during HIV-1 infection and correlated inversely with CD4+ T-cell number [184–187]. FasL is present on uninfected macrophages and its expression is enhanced in HIV-1 infected macrophages resulting in selective killing of uninfected CD4+ T cells [188].

HIV-1 induces apoptosis through several proteins belonging to the TNF ligand superfamily, such as TNFα, FasL and TRAIL. Soluble and membrane-bound Fas and FasL levels are increased in HIV infection. During HIV-1 infection, the Fas expression is increased in T lymphocytes (CD4+ and CD8+) while FasL expression is increased on monocytes, macrophages and natural killer cells both in peripheral blood circulation and lymph nodes [189,190]. HIV-1 infected cells are more susceptible to Fas mediated apoptosis *in vitro* as compared to uninfected cells. However, a lot of studies suggest that the infected cells do not make up the majority of apoptotic cells *in vivo* [188,191]. Most of apoptotic cell death involves uninfected cells in lymphoid tissues of HIV-infected patients. TNFα is an inflammatory cytokine, secreted by activated macrophages and lymphocytes, and induces diverse functions including inflammation and apoptosis [192]. TNFα binds to its receptors TNFR1 and TNFR2 on the plasma membrane and modulates the host immunity [193]. HIV-1 proteins target TNFR signaling pathways, modulating gene expression and T-cell apoptosis which results in immune suppression and formation of viral reservoirs during HIV-1 infection [194]. TRAIL is a member of the TNF ligand superfamily that mediates apoptosis of CD4+ T cells in HIV-1 infection through its interaction with its death inducing receptors, DR4 and DR5, on infected cells as well as on bystander cells. During HIV-1 infection, the expression of TRAIL and DR5 is increased as compared to uninfected cells [195]. Furthermore, HIV-1 infection of macrophages increases the expression of TRAIL, which can then trigger apoptosis in bystander T cells [196].

The HIV-1 envelope glycoprotein binds to the CD4 receptor and signals through it without changing its conformation. After binding of gp120 to CD4 molecule, it activates PKC, and results in decreased FLIP

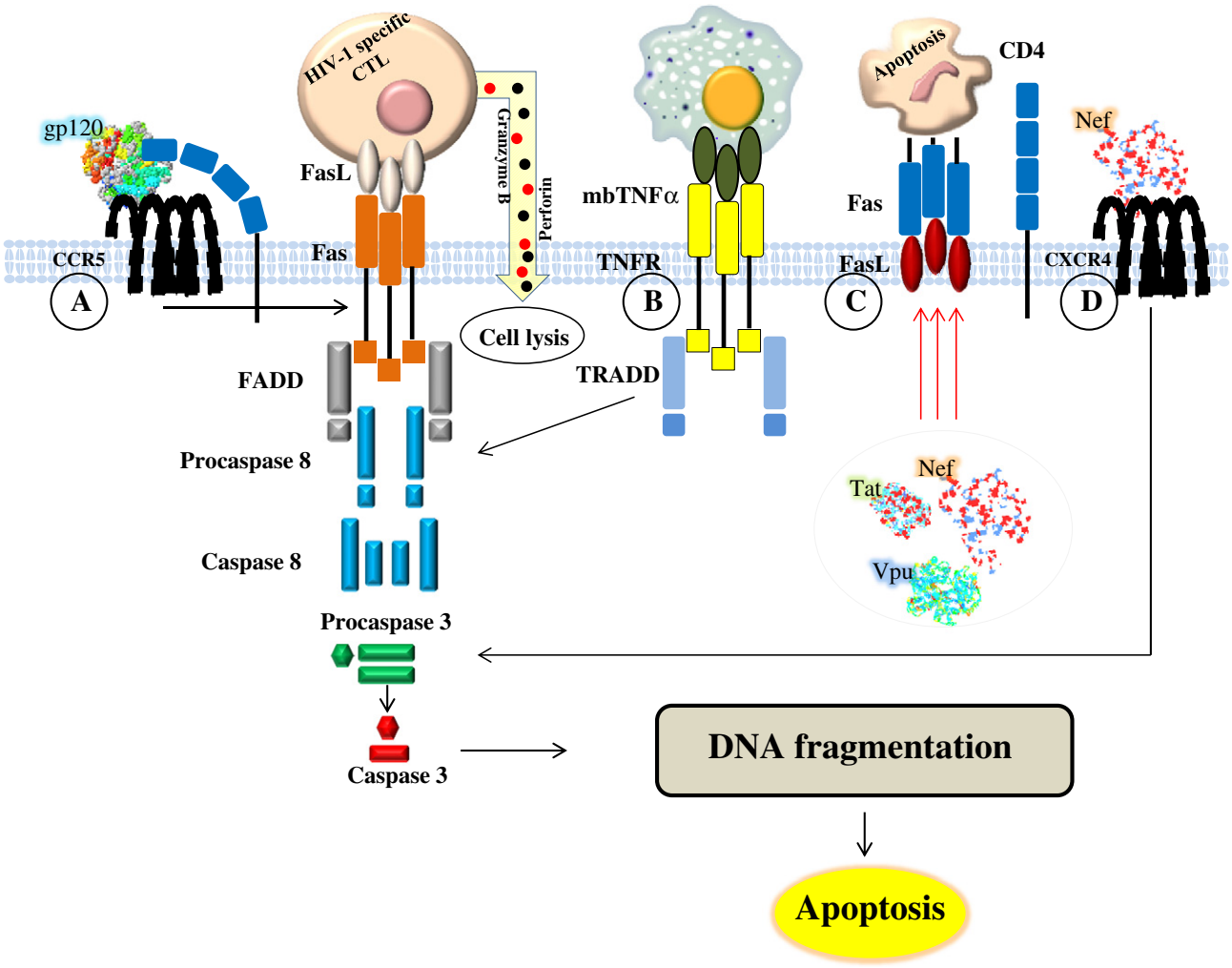

Fig. 3. Plasma membrane receptors and T-cell apoptosis. A) HIV-1 gp120 binds to CCR5 or CD4 receptors, and activates the signaling pathways that upregulate Fas expression that increases the susceptibility of T cells to Fas-mediated apoptosis. B) Apoptosis occurs in T cells in contact with macrophages as a result of membrane-bound TNFα and TNFR interaction, and activation of caspase activity. C) HIV-1 viral proteins (Nef, Tat and Vpu) upregulate FasL and send apoptotic signals to the attacking CTLs. D) Extracellular Nef binds to CXCR4 surface receptors and induces apoptosis.

levels that increase the CD4+ T cells susceptibility to Fas-mediated apoptosis [166,197,198]. This CD4-dependent Fas susceptibility requires CD4 signaling, since deleting the CD4 cytoplasmic tail inhibits the Fas-mediated apoptotic response [199,200]. Furthermore, mutations in the binding region of gp120 to CD4 also inhibit CD4+ T cell apoptosis [201]. Moreover, gp120 also binds to CCR5 without first binding to the CD4 molecule, and also makes the CD4+ T cells susceptible to Fas mediating killing [202,203]. However, CXCR4 activation by gp120 causes Fas-independent and caspase-independent CD4+ T cell death [203,204]. The death signal through CXCR4 is independent of G protein signaling [205]. Interestingly, the binding of R5 gp120 to CD8+ T cells does not trigger cell death while binding of X4 gp120 to CXCR4 receptors expressed on CD8+ T cells causes a rapid caspase independent cell death, despite the equal expression of CCR5 and CXCR4 on the cell surface [203]. HIV-1 gp120 also induces apoptosis in non-immune cells as CXCR4 is expressed on a number of cells. Particularly, CXCR4 is expressed on the cell surface of human neurons. The X4 gp120 binds and signals through the neuronal CXCR4, and causes a direct caspase independent cellular apoptosis [206,207]. Furthermore, human hepatocytes also express CXCR4 on the cell surface and undergo caspase independent apoptosis when gp120 binds to hepatocytes via CXCR4 [208]. Thus, the chemokine-mediated apoptosis as a result of HIV envelope gp120 signaling may explain the occurrence of neurological disorders and liver-related diseases during the course of HIV-1 infection. In addition, HIV-1 gp120 ligation of CXCR4 on macrophages induces the upregulation of membrane-bound TNFα. This up-regulation of membrane-bound TNFα induces apoptosis through binding to TNFR2 in CD8+ T cells which favors T-cell depletion [209].

During HIV-1 infection, the extracellular Tat protein is released in the stromal microenvironment of infected cells that can be efficiently taken up by most of cell types [72]. In uninfected cells, Tat favors the transmission of both R5 and R4 HIV by inducing the expression of chemokine receptors CCR5 and CXCR4 [210,211]. Additionally, exogenous Tat upregulates the production of TRAIL in macrophages *in vitro* [212,213], which may induce TRAIL-dependent apoptosis of bystander CD4+ T cells *in vivo*. Moreover, gp120 and Tat can synergize with FasL expression leading to TCR-induced apoptosis [214]. The HIV-1 accessory protein Vpu down-regulates the CD4 receptor and allows efficient budding of newly produced virions, and the Vpr protein increases the susceptibility of Jurkat T cells to Fas-mediated apoptosis [215]. Finally, Nef is a viral regulatory protein that is expressed abundantly in the early stages of viral replication. Nef-expressing T cells have been demonstrated to upregulate the Fas and FasL, and to display increased PD-1 expression, and thereby undergo apoptosis through both caspase-dependent and -independent mechanisms [216–218]. However, Nef can also prevent the Fas- and TNF-receptor-mediated

apoptosis via interaction with the apoptosis signal regulating kinase-1 (ASK-1) [97].

6. Conclusion

All the important steps of the HIV-1 life cycle i.e. entry, assembly, budding, induction of signal transduction and subsequent cell activation are taking place at the plasma membrane. Furthermore, numerous cellular proteins that are essential for HIV-1 propagation are either concentrated in membrane microdomains or recruited to plasma membrane during the virological synapse. HIV-1 and its proteins hijack the plasma membrane receptors and the lipid microdomains to efficiently enter into host cells and to optimize viral replication. A better understanding of the signaling mechanisms resulting from the interaction of HIV-1 with the plasma membrane holds the key to unlock part of the mystery of HIV-mediated cell death and pathogenesis, and will lead to new therapeutic approaches in the future.

Conflict of interest

The authors declare no conflict of interest.

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