

# Immune Responses to HIV Gp120 that Facilitate Viral Escape

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**Abstract:** The gp160 complex of the envelope of the HIV virus and its component gp120 are essential for viral entry into the host cell. Gp120 binding to its receptor CD4 and co-receptor, CXCR4 or CCR5 is required for fusion of viral and cellular membranes. The presence of gp120 facilitates immune escape of the virus through its profound effect on the immune cells. It is a polyclonal activator of B cells, causing them to differentiate into immunoglobulin producing cells while activating the complement cascade. This results in the formation of immune complexes that are unable to kill the virus but instead shield it from the attack of other immune cells. Such HIV-1 virus that is trapped within immune complexes and is bound to the B cells *via* CD21 is more infectious than the free virion. In addition, HIV virions are trapped on the membrane of follicular dendritic cells (FDC) processes in immune complexes or through complement receptors. Thus, FDC can serve as a 'Trojan horse' and transmit the trapped virus to CD4+ T lymphocytes as they migrate through the germinal centre to the follicular mantle and paracortical areas. It was demonstrated that CXCR4-binding HIV-1 X4 gp120 causes the movement of T cells, including HIV-specific CTL, away from high concentrations of the viral protein and its expression by target cells reduces CTL efficacy *in vitro*. Therefore, apart from the essential role in viral attachment and infection of cells, gp120 possesses several properties that affect the behavior of immune cells and skew the immune response to the virus facilitating viral escape.

**Keywords:** HIV, gp120, T cells, B cells, structure, escape.

## CHEMICAL STRUCTURE OF HIV GP120

The HIV virus is about 0.1µm wide and consists of an inner, pill-shaped core containing the RNA genome protected by a capsid protein known as p24 and an outer viral membrane (see Fig. 1). HIV is a retrovirus and its RNA genome exists as a dimer with enzymes that are essential for the survival of the virus; the protease that is used to cleave viral proteins, the reverse transcriptase that transcribes the RNA back to DNA once the virus infects a host cell and the integrase that integrates the viral DNA into the host cell DNA (Fig. 1).

The viral membrane is a spherical bi-lipid layer that surrounds the inner core with an average of 14 spikes, known as gp160 complexes that the virus uses to attach itself to host cells [108]. These complexes exist as trimers of gp120 proteins, each of which is linked to a gp41 protein forming a tripod shape that anchors the gp120 proteins through the membrane (Fig. 1) [25, 59, 108].

Wyatt *et al.* identified five variable regions (loops) of the gp120 molecule interposed among more conserved regions [104]. The V1/V2 loop, classified together because of being connected by a disulfide bridge, consists of one loop of about 25 amino acids for V1 and about 45 amino acids for V2 [104]. The V3 loop, is around 30 amino acids in length [39]. Mutagenesis of the protein and investigation of the resultant gp120-CD4 interaction was conducted to further clarify the importance of each of these loops [39]. It is thought

that these loops change in structure and conformation from time to time, thereby allowing the virus to elude the immune response. This has particularly been described for the V3 loop [39, 53, 89]. While some authors describe a lack of V3-specific neutralizing antibodies in patients who develop AIDS [89], others have found that neutralizing antibodies for one strain of HIV-1 to the V3 loop could fail to neutralize another strain of the same virus and even enhance infection in a third strain [53]. These findings have identified the variable position 311 proximal to the conserved GPGR motif at the top of the V3 crown as important for viral sensitivity to neutralization or enhancement by antibodies. In addition, two small deletions on both arms of the V3 stem altered the tropism of the dual tropic 89.6P viral strain so that only CXCR4+ cells were infected. This mutation, in combination with the deletion of the V1 and V2 loops, enhanced the ability of the envelope to elicit neutralizing response [106].

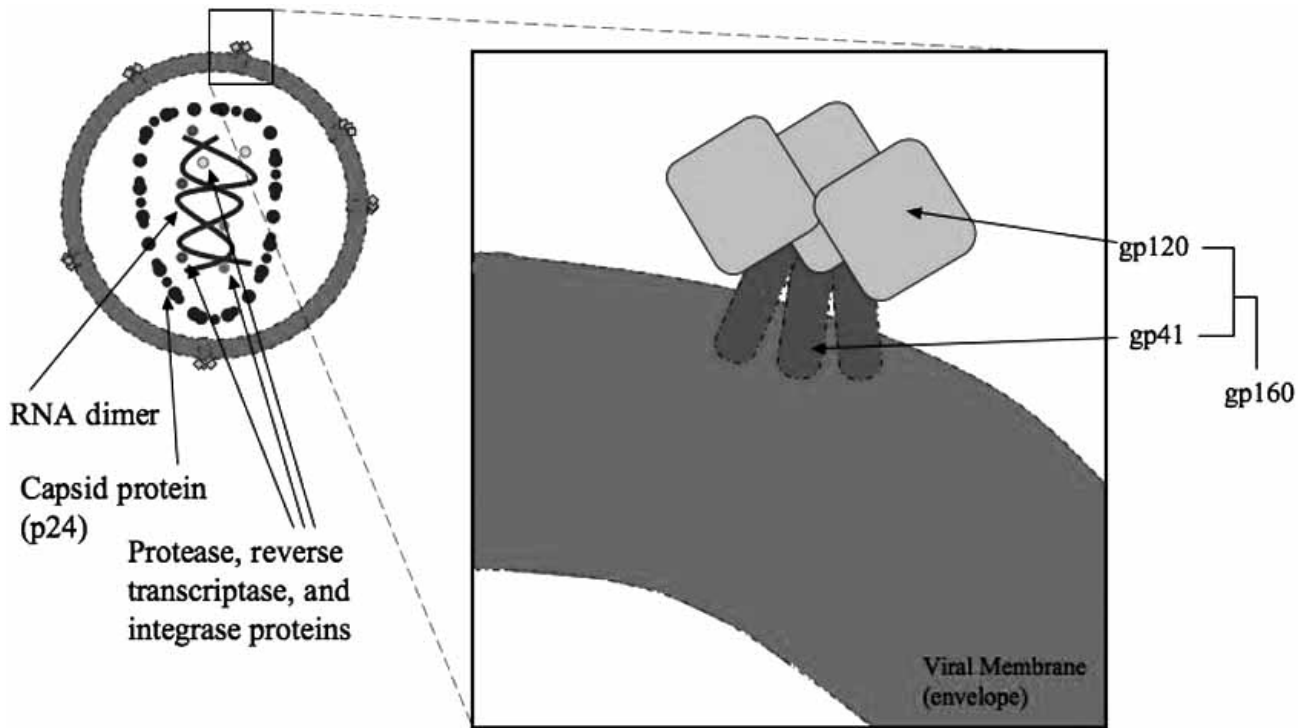
The bridging sheet is an area of the gp120 molecule that is involved in the binding of a co-receptor of CD4, the chemokine receptor CCR5 [61]. This particular region is highly conserved in all of HIV viruses and it is thought that the co-receptor affinity may be linked to viral tropism and subsequently, to pathogenesis.

As research into this area advances, it is becoming very clear that the chemical properties of the gp120 and the changes that occur in its structure might be crucial factors in allowing the virus to escape immune recognition and subsequent killing.

## THE ROLE OF GP120 IN VIRAL ENTRY

As previously mentioned, HIV gp120 is a part of a trimeric complex known as gp160, where it is associated with gp41. This complex is cleaved during transport to the surface of HIV-infected cells to form 2 fragments, gp120 and

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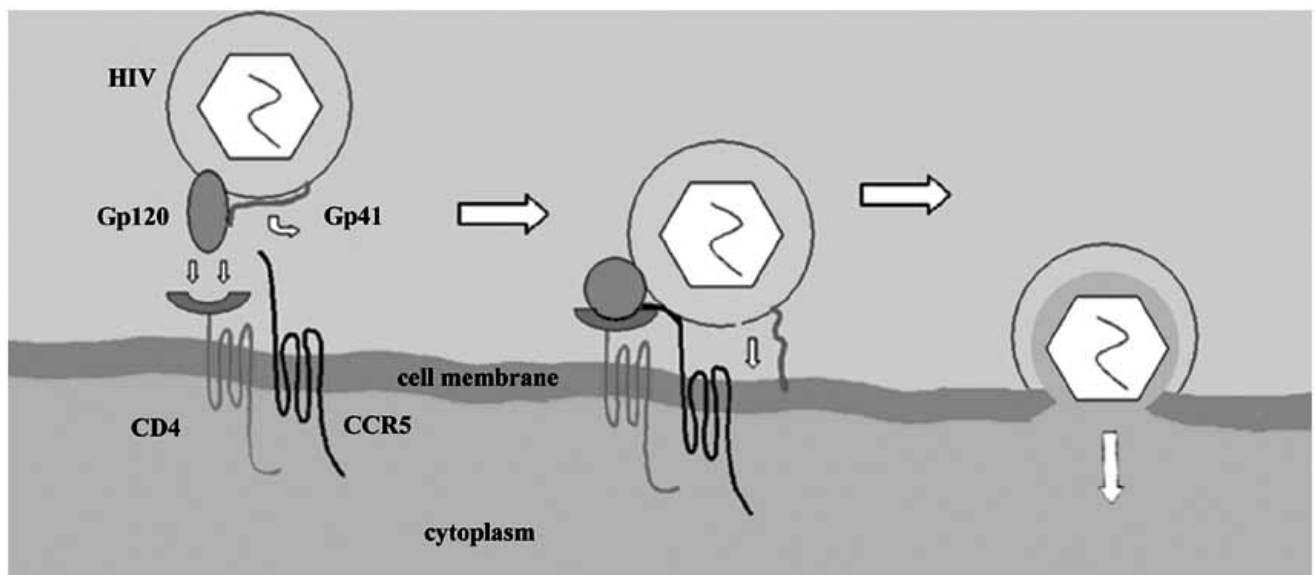
**Fig. (1).** Schematic diagram of the structure of the HIV virus. The so-called ‘spikes’ (gp160) consist of the gp120 trimers connected to the gp41 protein (augmented to the left).

gp41, which leaves gp41 in a membrane-anchored state (see Fig. 2).

The main receptor for gp120 is CD4, which is essential for virus entry [22, 51, 85]. Occasionally, CD4 negative cells can also get infected by the HIV virus [12, 40, 60, 62, 90] restricting inhibition of productive infection of CD4+ cells by certain HIV strains even by anti-CD4 monoclonal antibodies [81]. This could partially be explained in lympho-

cytes in content of their origin from CD4+ precursor cells [50] or in other cells by phenotypic mixing of the virus with human T cell leukemia viruses [63].

Gp120 binding to its receptor CD4 and a co-receptor [71] is required for fusion of viral and cellular membranes, which occurs in a multi-step process [22, 51] (see Fig. 2). The chemokine receptors CXCR4 or CCR5 function as co-receptors for HIV viral entry into the host cell [71]. During



**Fig. (2).** The process of HIV entry into the cell. Binding of gp120 to CD4 induces a conformational change in gp120 that allows for exposure of the co-receptor binding domain (left). The change also allows for the fusogenic domain of gp41 to be exposed (middle), resulting in fusion of the HIV virion membrane and T-cell membrane (right).

this process, the major function of CD4 binding to gp120 is to stimulate changes in its structure that will allow for exposure and stabilization of the co-receptor binding site [86, 96]. Clayton found that mutation of key residues in domains I or II of CD4 can eliminate or reduce binding to gp120 [17]. Wu *et al.* [102] also showed that mutant forms of the CD4 receptor had decreased affinity for gp120 compared to the normal CD4 molecule.

Early infection primarily employs CCR5 as the co-receptor whereas later infection often utilizes the co-receptor CXCR4 in most but not all individuals [15, 20, 28, 107]. The V3 loop on the gp120 molecule determines the chemokine receptor usage [18, 93]. In V3-deleted mutants, gp120 does not bind the chemokine receptor CCR5 [58, 97]. Rizzuto *et al.* used gp120 mutants to determine that a highly conserved region, adjacent to the V3 loop of gp120 is essential for CCR5 binding [82]. When CD4 undergoes binding, the variable loops V1 and V2, shift to allow exposure of residues that were otherwise protected [70]. This shift presents the necessary region for co-receptor association with CXCR4 [57, 82, 103], or CCR5 [1, 24]. On the other hand, CD4 has been shown to have little conformational change after binding gp120 [56, 57, 84]. An increase in positive charge of the third variable region of gp120 may signify a CXCR4-dominating phenotype [85]; moreover, a switch from the CCR5 to a CXCR4 phenotype is accompanied by a positive V1/V2 loop charge increase [21, 38, 100].

The fusogenic activity of HIV-1 depends on several regions [41]. Kowalski *et al.* [54] replaced specific N-terminal hydrophobic amino acids of gp41 with charged amino acids and found the syncytium formation to diminish. The consequence of this replacement was a disruption of the alpha-helical structures of fusion regions of gp41 that get inserted into CD4+ T-cell membranes [99]. CD4 binding to gp120 is thought to allow dissociation of gp120 from gp41 by the resulting conformational changes, thus exposing the fusogenic domain of gp41 [26]. Conformational changes occur in the V3 loop of gp120 after CD4 binding [86] and the V3 loop has been shown to be involved in HIV-1 penetration CD4+ T-cells and syncytium formation [23, 31]. Furthermore, the C4 domain of gp120, which is also involved in CD4 binding, interacts with the V3 loop [105]. Conformational changes could expose a masked thrombin cleavage site [46]. This would lead to cleavage of gp120 and dissociation from gp41 and thereby expose the fusogenic domain of gp41 [87]. Researchers continue to study the role of gp120 in viral entry and especially the nature of the association of the protein with the CD4 molecule and how to prevent it. However, as new data on gp120 emerge, it has become increasingly important to look into the effects that this protein has on the 'key players' of the immune response to the virus.

## HOW GP120 INFLUENCES T CELL FUNCTION

### gp120 and T Cells: Chemokines, Chemokine Receptors and HIV-1

The HIV protein gp120 has been shown to mediate chemotaxis of T cells [43, 65]. It has been demonstrated that, in contrast to CD4-dependent gp120 signaling *via* CCR5, envelope signaling through CXCR4 is CD4-independent, inducing chemotaxis of both CD4 and CD8 T cells [43]. The interaction of CXCR4 and gp120 resulted in their CD4-

independent co-internalization with both molecules translocating into early endosomes. Binding of gp120 to CXCR4 resulted in a CD4-independent phosphorylation of Pyk2 and an induction of chemotactic activity, demonstrating that this interaction has functional consequences [65]. CCR5-binding HIV-1 gp120 or so-called R5 HIV-1 gp120 induces CCR5-dependent as well as CD4-dependent intracellular signals that are involved in cell adhesion and chemotaxis [16]. These findings may be of particular interest in view of the fact that the HIV-1 gp120 molecule has been shown to dissociate from HIV-1 virions [48, 49, 73]. HIV-1 gp120 shedding has been shown to be increased in the presence of soluble CD4 (sCD4) [69]. The relevance of HIV-1 gp120 shedding *in vivo* is unknown, although a recent study by Altmeyer *et al.*, demonstrated that gp120 derived from transgenically expressed gp120/41 envelope protein could be detected in both the cytoplasm and at the plasma membrane in animal brains *in situ* [3]. Furthermore, the fact that HIV-1 gp120 itself can dysregulate immune effector cell migration may contribute to an explanation of why immunization with recombinant gp120 have been shown to date, to induce minimal neutralizing antibody and CTL responses against HIV-1 infection in humans [19, 77].

There is no clear evidence to date for the exact role that chemotactically active HIV proteins play in the pathogenesis of the retrovirus. There is speculation that HIV employs its chemotactically active proteins to attract uninfected monocytes and T-cells to a site of infection. We proposed that chemokinetically active HIV proteins, in particular HIV-1 gp120, serve as bidirectional cues for immune cells and may dysregulate immune effector cell migration. This may allow HIV-infected cells to evade the host immune response.

### gp120 and T Cells: HIV-1 Infection, Immune Control and Immune Evasion

HIV-1 establishes a chronic infection in humans that the host immune system fails to eradicate. This virus exploits various mechanisms in order to evade the immune system including the infection and killing of HIV-specific helper cells, and the maintenance of a latent state and mutation of its immunogenic envelope protein [2, 10, 37, 78]. Studies of the immune control of HIV-1 have recently been focused on the role of HIV-specific CD8+ CTLs and HIV-specific CD4+ T-cell help in containing HIV infection [10, 37]. There is an increasing evidence from the studies of long-term non-progressors that HIV-1-specific cytotoxic T cell (CTL) activity correlates with protection from progression to AIDS [7, 35, 52, 79]. These findings in HIV-infected individuals were definitively supported by *in vivo* studies of macaques whose CD8+ T-cells had been depleted using a monoclonal antibody. CD8+ T-cell depleted macaques showed significantly increased levels of viral load following primary challenge with SIV-1 [88]. Conversely, viral load declined with the subsequent reappearance of CD8+ T-cells in the periphery and lymph nodes [45, 88]. In addition to the induction of a CTL response, HIV-1 clearly induces strong helper cell responses. This HIV-1 specific help, specifically related to Gag specific T-helper cells, was recently defined as being critical for the control of viremia in cross-sectional studies of HIV-infected individuals [47]. However, HIV-1 specific help in general may be reduced in magnitude in patients with chronic progressive HIV-disease [29].

Despite HIV-specific CTLs and HIV-1 specific help, the vast majority of HIV-infected individuals fail to control their viremia in the long term. The issue of how much immune pressure is exerted against HIV-1 by these immune effector cells *in vivo* is currently being examined [8, 11, 36, 75]. Initial studies suggest that CTL responses *in vivo* may not be maximally functional and that CTLs *in vivo* may in fact be unresponsive. This mismatch between *in vitro* activity of CTLs and *in vivo* evidence of effector T-cell function was exemplified by an adoptive transfer study in which autologous gag-specific CTLs were infused into HIV-infected individuals. CTLs co-localized with HIV-infected cells but no sustained reduction in HIV infected cells was seen [94]. The failure of CTLs to contain HIV *in vivo* has been explained by a lack of adequate T-cell help, HLA class I homozygosity and the loss of HIV-specific CTLs over time due to a number of mechanisms including macrophage induction of apoptosis and tolerization to antigen by B-cells [11, 36]. A further study examined the persistence of specific CTL clones in primary infection [75]. The authors demonstrated that HIV-specific T-cell clones that were present at the time of acute infection rapidly disappeared. This finding was explained by the concept of high-dose tolerance or clonal exhaustion. The results of a recent study of the distribution of virus-specific CTL in blood and lymph in primarily HIV infected individuals suggest an alternative mechanism. Clonotype specific PCR and the analysis of activated HIV-specific CTL *in vivo* demonstrated that CTLs preferentially accumulated in the blood whereas HIV infected cells were predominantly localized to the lymph nodes [75]. The authors suggested that HIV-specific immune effector cells may fail to migrate to those areas in which HIV proliferation is high as in the lymph nodes into the peripheral blood, where low levels of HIV replication take place by as yet an unknown mechanism [74].

Other subtle effects of HIV-1 on the localization of specific subpopulations of HIV-specific T-cells to the peripheral blood and lymph node have been detected. Brodie *et al.*, examined the localization of adoptively transferred *in vitro* expanded gag specific CTLs in three HIV-infected patients without detectable HIV-specific T-helper responses [11]. They demonstrated the localization of adoptively transferred CTLs to parafollicular areas containing productively infected T-cells at a single time point following a second infusion of CTLs. However, the CTLs were not found within the follicular dendritic cell network that contained free virions. The localization of CTLs in the peripheral blood declined over 14 days and was undetectable by 28 days. This decline in peripheral blood CTLs was associated with a rebound in HIV-infected cells and was attributed to a failure of HIV-specific helper responses to support lymph node CTLs. The ultimate fate of the CTLs that were localized to the lymph node was not examined in this study. It is clear from the presented data that the percentage of peripheral blood CD4<sup>+</sup> T-cells expressing HIV gag continued to rise in all three patients following the single time point at which lymph node biopsy was performed despite the co-localization of CTLs to parafollicular areas of lymph nodes.

Experimental data from our laboratory show that the gp120 protein of HIV deregulates immune effector cell migration [9]. It was demonstrated that CXCR4-binding HIV-1 X4 gp120 causes the movement of T cells, including HIV-

specific CTL, away from high concentrations of the viral protein. This migratory response is CD4 independent and inhibited by anti-CXCR4 antibodies and pertussis toxin. Additionally, the expression of X4 gp120 by target cells reduces CTL efficacy in an *in vitro* system designed to account for the effect of cell migration on the ability of CTL to kill their target cells. Recombinant X4 gp120 also significantly reduced antigen-specific T-cell infiltration at a site of antigen challenge *in vivo*. The repellent activity of HIV-1 gp120 on immune cells *in vitro* and *in vivo* was shown to be dependent on the V2 and V3 loops of HIV-1 gp120. These data suggest that the active movement of T cells away from CXCR4-binding HIV-1 gp120, which we previously termed fuge-taxis, may provide a novel mechanism by which HIV-1 evades challenge by immune effector cells *in vivo* [9]. This novel mechanism may contribute to an explanation of why the HIV-specific immune response or adoptive transfer of targeted HIV-specific immune effector cells *in vivo* fails to significantly diminish viral load in the peripheral blood or in tissues in HIV infected individuals. Further studies examining this phenomenon in depth on animal models of disease are ongoing.

### GP120 ALSO AFFECTS B CELLS

Increased B cell activation is a characteristic feature of the HIV-infection. This is manifested by polyclonal B cell activation [67], elevated immunoglobulins in sera, presence of circulating immunocomplexes and the presence of autoantibodies. The number of spontaneously immunoglobulin secreting cells also increases. B cell immunodeficiency occurs and responses to immunization with polysaccharide and protein antigens are impaired [4]. It has been shown that impaired B cell responses to antigens are due to the dysfunction of T cell-dependent B cell proliferation. HIV gp120-treated T cells fail to provide adequate help to B cells because of the interference of T-B cell contact-dependent interaction and the inhibition of cytokine secretion by T cells [14].

The B cell dysfunction in HIV infection is also characterized by impairment of isotype switching [6, 72]. In fact, it was recently described that the negative factor protein of HIV (Nef) suppresses immunoglobulin class-switch DNA recombination by inducing I $\kappa$ B $\alpha$  and SOCS proteins that block CD154 and cytokine signaling *via* NF- $\kappa$ B and STAT. Consequently, HIV-1 could evade the T-cell dependent class switching in bystander B cells to protective IgG and IgA-producing cells and in such a way avoid neutralization and clearance [80].

In addition, the carboxy terminus of the gp41 region (amino acids 739-863) has been shown to be able to induce polyclonal activation of normal B cells, causing them to differentiate into immunoglobulin-secreting cells [13]. Furthermore, binding of gp120 to the VH3 domain of surface IgM on B cells was shown to cause T cell-independent B cell differentiation suggesting a role for gp120 as B cell superantigen [5].

B cells are also a potential reservoir of infection. It has been demonstrated that the heavily glycosylated and partly sialylated envelope proteins gp120 and gp41 bind to cells expressing the complement receptor CR2 (CD21). The binding requires activation of the alternative complement pathway and in the absence of CD4, it does not result in cell in-

fection [68]. A recent study demonstrated that lymphoid tissue and peripheral blood-derived B cells of HIV-1 infected viremic patients carry replication-competent virus on their surface [66]. The mechanism of binding was found to involve binding of HIV-containing immune complexes to the CD21 on the surface of the B cells [66]. Such HIV-1 virus that is trapped within the immune complexes and bound to the B cells is more infectious than the free virion [44]. Furthermore, another study had shown that B cells deliver a potent CD86/CD28 costimulatory signal that induces T cell proliferation and simultaneously enhances HIV-1 replication [55].

Multiple research groups continue to investigate the influence of gp120 on B cell function and B-T cell interaction.

### DENDRITIC CELLS AND GP120: HOW THE NORMAL PROCESS OF ANTIGEN PRESENTATION ENHANCES HIV INFECTION

Immature dendritic cells (DCs) residing at mucosal surfaces of the rectum, uterus, cervix and skin are the first cells targeted by HIV infection. These DCs bind the HIV virus *via* interaction of the gp120 protein with a DC-specific C-type lectin, DC-SIGN [33]. Mucosal DC of the uterus and rectum express high levels of DC-SIGN and coexpress CD4 but do not express CCR5 [32]. DC-SIGN might therefore play a crucial role in mediating binding of the HIV virus to DC *via* a gp120-DC-SIGN interaction. The virus might then exploit the migratory capacity of these activated DC to reach CD4+CCR5+ T cell-rich lymphoid tissues and mediate efficient infection of permissive cells [32]. In addition to DC-SIGN, HIV-1 gp120 binding to at least two more C-type lectin receptors was observed; mannose receptor on immature DC and langerin on Langerhans cells [98]. When these cells migrated out of mucosal sites and skin, pattern of binding changed from predominantly C-type lectin receptor to CD4-dependent [98].

In the early stages of HIV infection, germinal centers serve as important reservoirs of free virus in the interstitial spaces and this reservoir disappears as the germinal centers involute with advancing disease [30]. Follicular dendritic cells (FDCs) are found in germinal centers of all secondary lymphoid tissues, where they trap and retain antigens in the form of immune complexes formed with specific antibodies and complement proteins [64]. It has been previously described that the HIV virions are trapped on the membrane of the FDC processes in immune complexes or through complement receptors [27]. The FDC-trapped virus remained infectious *in vivo* at all time points examined over a period of 9 months and for at least 25 days *in vitro*, while virus without FDC lost infectivity in only a few days in *in vitro* conditions [91]. FDCs maintain virus infectivity in a dose-dependent manner and both virus-specific antibody and FDC-Fcγ receptors are needed for this activity [92]. Therefore, not only did FDCs facilitate the HIV infection in the presence of an active humoral immune response but they also provided a sanctuary in which the replication-competent virus persists for a long time in order to reignite infection when conditions are permissible. At the same time, most of the cells infected with HIV in lymph nodes were identified as CD4+ T cells. That led to the hypothesis that, similar to other lentiviral infections, FDCs serve as 'Trojan horse' [76]

and transmit the trapped virus to CD4+ T lymphocytes as they migrate through the germinal center to the follicular mantle and paracortical areas [27].

Overall, the overwhelming experimental evidence presented above points out that the role of gp120 envelope protein in HIV infection is much more complex than previously thought. It has been described long time ago that some sera from HIV-1 seropositive individuals and animals immunized by HIV-1 mediates enhancement of virus infection [42, 83, 95], *via* Fc-mediated enhancement of the bound antibody with Fc receptor bearing cells or *via* the complement CR2 receptor [83]. This activity was later attributed to the variability of the V3 loop of the gp120 protein [53]. In addition, an increase in positive charge of the V1/V2 loop is accompanied with a switch from CCR5 to CXCR4 receptor use for viral entry, a phenotype that occurs in late infection [21, 38, 100]. In short, variability of the loops has often been pointed out as one of the major factors that allow the virus to escape the immune response. Furthermore, a recent study found an occurrence of resistant strains of the HIV virus in the presence of neutralizing antibodies that was attributed to a changing 'glycan shield'-selected changes in N-linked glycosylation that are located throughout the envelope and prevent binding of neutralizing antibody [101]. In addition, it was recently pointed out that enhanced macrophage (M)-tropism of R5 HIV-1 observed in disease progression, results from adaptive viral evolution selecting for HIV-1 variants that have increased ability to utilize relatively low levels of CD4 and CCR5 expressed on macrophages. The evidence also suggests that these late-emerging, R5 viral strains have reduced sensitivity to entry inhibitors, and increased ability to cause CD4+ T-lymphocyte loss as reviewed in [34].

Here we reviewed immune responses to the envelope protein in order to show that even without the mutations in the virus (or prior to it), the gp120 protein elicits immune responses that contribute to the viral escape. In other words, gp120 has a deleterious effect on the three main players of the immune response: the primary antigen presenting cell-dendritic cell, B cells and T cells. In fact, it would appear that gp120, through its fugitactic activity for T cells, the polyclonal activation of B cells that leads to the formation of a protective coating of complement complexes and through its binding and persistence on FDC processes shields the HIV virus from destruction by the immune mechanisms of the body. The extent and the exact mechanisms by which this occurs are yet to be dissected.

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