Entry Inhibitors in HIV Therapy
Edited by Jacqueline D. Reeves and Cynthia A. Derdeyn

Attachment of human immunodeficiency virus to cells and its inhibition

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Multifaceted events regulate initial interactions between HIV-1 and target cells

The entry of enveloped viruses involves virus adsorption followed by close apposition of the viral and plasma membranes. This multistep process is initiated by specific binding interactions between glycoproteins in the viral envelope and appropriate receptors on the cell surface. In the case of HIV-1, attachment of virions to the cell surface is attributed to a high affinity interaction between envelope spike glycoproteins (Env, composed of the surface protein gp120 and the transmembrane protein gp41) and a complex made of the primary CD4 receptor and a seven-transmembrane co-receptor (e.g., CXCR4 or CCR5) (reviewed in [1]). Then a chain of dynamic events take place that enable the viral nucleocapsid to penetrate within the target cell following the destabilization of membrane microenvironment and the formation of a fusion pore.

Although it is generally accepted that HIV-1 attachment to its major cellular reservoirs (i.e., T helper cells and macrophages) occurs through the two-stage receptor-interaction pathway, there is accumulating evidence indicating that the initial attachment step is a more complex phenomenon than initially thought. Indeed it seems that adsorption of HIV-1 to the cell surface is modulated by a large variety of interactions between the viral entity and the target cell surface (reviewed in [2]). This retrovirus may also attach to some cell types by CD4-independent interactions involving highly glycosylated groups or basic residues found on gp120 and polyanionic sulfated chains or lectin-like domains on some specific cell surface receptors (reviewed in [1]). For example, heparan sulfate proteoglycans, which are expressed at high levels on different cell types, such as epithelial and endothelial cells, can interact with the envelope spike glycoprotein and serve as docking structures for HIV-1 [3]. Heparan sulfate proteoglycans such as syndecans serve as the main class of attachment receptors for HIV-1 on different cell types, e.g., macrophages and endothelial cells, and are thought to play a cardinal role in virus transmission

[4, 5]. GP120 can bind also to galactosyl ceramide and its sulfated derivative (i.e., sulfatide) [6, 7] that are found on macrophages and neural, glial and colon epithelial cells [6–8]. It can also associate with the mannose-specific macrophage endocytosis receptor (MR) [9] and other cellular lectins. In fact, the determinant role played by dendritic cells (DCs) in HIV-1 transmission might rely on specific interactions between gp120 and C-type lectins, of which the DC-specific intercellular adhesion molecule-3 (ICAM-3) grabbing nonintegrin (DC-SIGN) and DC-SIGNR (for DC-SIGN-related) are the best studied [10, 11]. These two lectins are expressed on certain DC populations and endothelial cells, respectively, and are described in more detail in this article.

HIV-1 attachment mediated by host cell proteins incorporated into the viral envelope

Incorporation of host cell surface molecules within nascent HIV-1

HIV-1, as an enveloped virus, is released by budding through the plasma membrane of the productively infected cell. In addition to its own virus-encoded envelope glycoproteins, the virus incorporates many different cellular proteins normally found on the cell surface (reviewed in [12–15]). These include major histocompatibility complex (MHC) class I and II determinants [16–19], adhesion molecules [20–23], complement regulatory proteins [24] and costimulatory molecules [25, 26], which have been found inserted in the viral envelope. The process of incorporation of host cell membrane proteins was found to be conserved among all tested HIV-1 subtypes and strains that were expanded in natural cellular reservoirs, such as mitogen-activated peripheral blood lymphocytes and human lymphoid tissue cultured *ex vivo* [27–32]. The physiological significance of this phenomenon is provided by two previous reports showing that host-encoded cell surface constituents were incorporated in plasma-derived clinical HIV-1 isolates [33, 34]. Although different host cell constituents can be found embedded within HIV-1, the incorporation process seems to be selective. For example, CD45 is the most abundant leukocyte cell surface glycoprotein [35], but is not acquired by HIV-1 [18, 36]. The CXCR4, CCR5, and CCR3 co-receptors are also excluded from HIV-1 [37]. This ability to incorporate discriminatory host antigens into mature virions has allowed two groups to demonstrate that cell-type-specific antigens can serve as markers of the cellular origin of HIV-1 replication [33, 38]. It has been estimated that between 375 and 600 HLA-DR molecules are found associated with HIV-1_{IIIB} emerging from H9 cells [39]. This observation suggests that virally embedded host HLA-DR outnumbered virus envelope (Env) glycoprotein gp120 by a factor of 8.9 to 28.6 considering that HIV-1 possesses an average of between 21 and 42 gp120 molecules per virion [40].

The molecular basis governing the selective incorporation of cell surface proteins within emerging HIV-1 particles is only beginning to be exposed. It

was established that the virus envelope spike glycoproteins (i.e., gp120 and gp41) are not essential to achieve insertion of ICAM-1 into HIV-1 [41]. Interestingly, ICAM-1 incorporation is governed by an intimate association between the cytoplasmic domain of ICAM-1 and the viral Gag precursor polyprotein $Pr55^{Gag}$ [42].

Involvement of virus-anchored host proteins and their ligands in the attachment process

It can be proposed that besides interactions between gp120 and multiple attachment receptors, interactions can also occur between host-derived cell surface components incorporated within emerging virions and their natural counter-ligands. This scenario has been confirmed in numerous studies where such host cell membrane molecules were found to retain their biological activity when located on the virus. For example, HLA-DR can increase HIV-1 infectivity for CD4-expressing T cells by about twofold [43], whereas ICAM-1 alone augments virus infectivity for $LFA\text{-}1^+$ target cells by up to 100-fold depending of the LFA-1 conformational state [22, 44, 45]. Activation of primary human $CD4^+$ T lymphocytes was found to result in LFA-1 clustering, an event that promotes the early events of HIV-1 replication cycle through an interaction between virus-embedded host ICAM-1 and LFA-1 clusters [46]. Confocal analyses showed that HIV-1 is concentrated in microdomains rich in LFA-1 clusters [46]. Virus entry studies including subcellular fractionation experiments with primary human $CD4^+$ T cells illustrated that the acquisition of ICAM-1 by nascent HIV-1 modified the entry route of the virus within such target cells [47]. It was established that the ICAM-1-mediated increase in virus infectivity was linked with a more productive entry process into primary $CD4^+$ T lymphocytes (i.e., cytosolic delivery of viral material) [47]. It has been reported that the higher susceptibility of memory $CD4^+$ T cells ($CD45RO^+$ subset) to HIV-1 infection is due to secondary interactions between virus-associated ICAM-1 and cell surface LFA-1 [48]. The presence of host-encoded CD28 in newly formed HIV-1 particles resulted in a close to 20-fold augmentation in virus infectivity when using target cells that express high levels of CD80 and CD86, two natural ligands of CD28 [49]. In addition, an increase in virus infectivity was also seen following insertion of host-encoded costimulatory molecules CD80 and CD86 within progeny viruses [50].

Strategies to reduce viral load by blocking interactions between virus-associated host molecules and their physiological counter-receptors

Given that attachment of HIV-1 to host cells can be modulated by the additional interactions provided by virus-anchored host cell membrane proteins, it

is thus not surprising to discover that virus susceptibility to blocking agents is affected. For example, ICAM-1-bearing virions are more resistant to antibody-mediated neutralization and this decreased sensitivity is even more dramatic when target cells expressed on their surface the activated form of LFA-1 [51, 52]. Additionally, it was reported that virions carrying host ICAM-1 on their surface are more resistant to the fusion inhibitor T-20 than are isogenic viruses lacking host ICAM-1 [53].

Although the physical presence of such host constituents on the exterior of virions might be detrimental for the infected individual, the propensity of HIV-1 to acquire numerous host cell surface components could be exploited to control viral load. Indeed, it has been shown in numerous reports that HIV-1 infectivity can be efficiently neutralized, both *in vitro* and *in vivo*, with antibodies specific for such host membrane proteins [22, 23, 26, 39, 44, 45, 54, 55]. Interestingly, it was demonstrated that HIV-1 replication is diminished upon treatment with statin compounds (e.g., lovastatin) [56], the primary drugs used in the treatment of hypercholesterolemia. The antiviral potency of lovastatin seems to be linked with its capacity to inhibit interactions between virus-associated host ICAM-1 and cell surface LFA-1. This *in vitro* work was confirmed by a proof-of-concept small-scale clinical study [57]. In this provocative study, six A1 stage HIV-1 patients not receiving combined therapy were given lovastatin for a month as their only medication. This short-term statin treatment clearly reduced serum viral RNA loads in all patients and in general increased their $CD4^+$ T cell counts. Discontinuation of treatment was followed by a rebound in viral load.

HIV-1 attachment mediated by cellular lectins

HIV-1 capture by cellular lectins: Targets for microbicides

The prevention of HIV-1 infection by microbicides, topically applied inhibitors that block access of sexually transmitted HIV-1 to the host system, is an attractive strategy [58]. Understanding which cell types are first targeted by sexually transmitted HIV-1 and how these cells interact with HIV-1 is key to the generation of effective microbicides. Several studies suggest that DCs, professional antigen-presenting cells, might be intimately involved in the early local and subsequent systemic spread of sexually transmitted HIV-1 [59]. Langerhans DCs in the top layer of the anogenital mucosa are probably the first cells exposed to sexually transmitted HIV-1. Mucosal macrophages and submucosal DCs might subsequently get into contact with virus crossing the mucosal barrier via local breaches or with progeny virions generated by infected Langerhans cells. DCs and macrophages express CD4 and chemokine receptors, and are thus permissive to HIV-1 infection, albeit infection of DCs is often relatively inefficient and depends on the subpopulation analyzed [59]. It has been proposed, however, that mere attachment of HIV-1 to mucosa asso-

ciated DCs might be sufficient to promote HIV-1 spread, since these motile cells might ferry bound virus into lymphoid tissue, the major compartment of HIV-1 replication, as part of their migratory and antigen-presenting functions within the immune system [10]. Several cellular lectins have been implicated in virus attachment to DCs, macrophages and other cell types relevant to HIV-1 spread. Here, we discuss the role of the lectins DC-SIGN, DC-SIGNR, MR and langerin in HIV-1 infection and introduce strategies to inhibit HIV-1 interactions with these molecules.

DC-SIGN and HIV-1: Uptake, processing and MHC presentation versus transmission

DC-SIGN has initially been identified as a gp120-binding calcium-dependent lectin expressed in placental tissue [60]. The lectin has been "rediscovered" in 2000 when Geijtenbeek and colleagues [10] showed that DC-SIGN is expressed on DCs and is involved in HIV-1 binding and subsequent transfer of the virus to T cells, the latter process presumably involving DC-SIGN-dependent endocytosis and conservation of infectious HIV-1 in a low pH compartment [61]. DC-SIGN seemed to mainly account for the ability of DCs to promote HIV-1 infection of cocultured T cells, and it was proposed that DCs might function as Trojan horses, which take up HIV-1 via DC-SIGN and transport the virus into lymphoid tissue [10, 62]. Geijtenbeek and coworkers also provided evidence that DC-SIGN interacts with ICAM-2 on endothelial cells [63] and ICAM-3 on T cells [64], and proposed that these interactions contribute to extravasation of DCs from blood vessels into tissues and to the close contact between DCs and T cells required for efficient antigen presentation, respectively. Thus, a scenario emerged in which DC-SIGN was involved in DC functions critical for the establishment of an effective immune response and simultaneously allowed HIV-1 to misuse DCs to ensure its spread in the host.

A critical contribution of DC-SIGN to DC interactions with T cells/endothelial cells or HIV-1 has subsequently been challenged. It was reported that DC-SIGN or the related protein DC-SIGNR bind to ICAMs with submicromolar affinities similar to that observed for nonspecific cellular proteins [65], suggesting that ICAM recognition might not account for a potential role of DC-SIGN in cell-cell interactions. It was also documented that HIV-1 capture by DCs does either not dependent on DC-SIGN [66, 67] or that the contribution of DC-SIGN is relatively modest with other factors playing an important role [68–71]. In fact, Truville and colleagues [72] provided evidence that different DCs bind to HIV-1 gp120 via different lectins or via CD4, as discussed below. Moreover, it has been demonstrated that transformed cells frequently used to assess DC-SIGN function were not THP-1 monocytes, as reported [10], but most likely Raji B-cells [73], and that these cells as well as monocyte-derived DCs were permissive to infection by HIV-1 [74–76]. The latter observation suggests that the ability of DC-SIGN-expressing cells to

maintain HIV-1 infectious over prolonged time is most likely due to productive infection of these cells [74–76]. Indeed, DC-SIGN-dependent HIV-1 transmission is probably a short-lived process (Fig. 1), which is only observed a few hours after the DC-SIGN-positive, HIV-1-exposed cells make contact with target cells. Mainly, HIV-1 might be endocytosed and processed for MHC presentation ([77, 78], Fig. 1). Finally, two reports indicate that DC-SIGN might not be a good marker for DCs *in vivo* [68, 79], with DC-SIGN-positive cells in lymphoid tissue being of macrophage origin [68]. How these results relate to a series of previous studies demonstrating DC-SIGN expression on tissue DCs [10, 80, 81] is currently unclear.

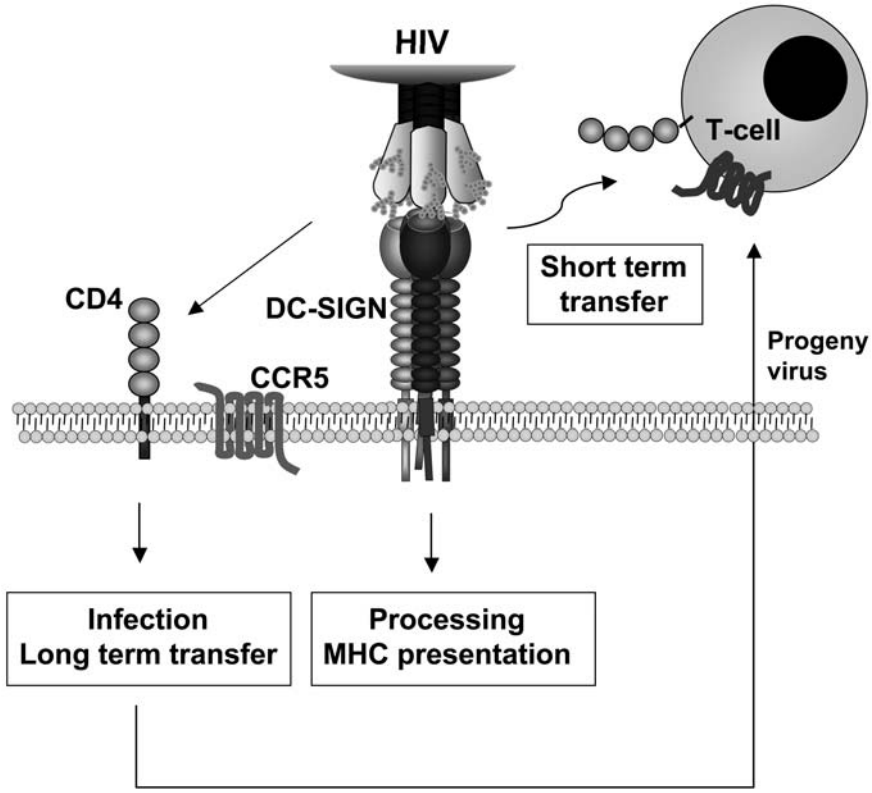

Figure 1. HIV-1 interactions with DC-SIGN on dendritic cells (DCs). DC-SIGN is expressed at high levels on DCs and binds to carbohydrates present on the surface of the heavily glycosylated HIV-1 envelope protein. Binding of HIV-1 to DC-SIGN-positive DCs can have multiple consequences. During a relatively short time window (hours) bound virus can be transferred to adjacent susceptible cells ("short-term transfer"). Certain HIV-1 isolates can also productively infect DCs via CD4 and a chemokine coreceptor. Prior engagement of DC-SIGN might augment infectious entry. Progeny virions produced from infected DCs can then be efficiently transmitted to cocultured T cells over a prolonged time period (days, "long-term transfer"). Finally, HIV-1 captured by DC-SIGN can be endocytosed and processed for MHC presentation.

Can a significant contribution of DC-SIGN to DC interactions with HIV-1, and thus to sexual transmission of HIV-1, be disregarded in the light of these results? Probably not, since several studies also provide evidence for a role of DC-SIGN in HIV-1 capture and transmission by DCs. For example, Arrighi and colleagues [82] demonstrated that siRNA-mediated down-modulation of DC-SIGN diminishes HIV-1 capture by DCs. The contribution of DC-SIGN to this process might be due to an involvement of this lectin in the formation of an infectious synapse [83], a microenvironment established between HIV-1-bearing cells and target cells, which promotes efficient transfer of infectious virions [84]. Interestingly, DC-SIGN did not contribute to HIV-1 infection of target cells in cervical explants but, together with CD4, was mainly responsible for HIV-1 uptake by migratory cells present in these explants [85], suggesting that in HIV-1-infected individuals DC-SIGN might indeed contribute to HIV-1 dissemination by motile cells expressing this lectin. In this regard, it is noteworthy that platelets have been shown to express DC-SIGN and to capture HIV-1 in a largely DC-SIGN-dependent manner [86, 87]. These cells might bind HIV-1 via DC-SIGN once the virus has reached the blood stream and might promote its dissemination in the host system. Similarly, a recent report suggests that a subset of B cells expresses DC-SIGN and facilitates HIV-1 transmission to T cells in a DC-SIGN-dependent manner [88]. Finally, two groups found that certain polymorphisms in the DC-SIGN gene are associated with decreased risk of HIV-1 infection [89, 90], highlighting that DC-SIGN might modulate important events leading to the establishment of HIV-1 infection. Thus, further research is needed to clarify the role of DC-SIGN in HIV-1 infection and to evaluate whether this protein is a potential target for microbicides.

DC-SIGNR polymorphisms and susceptibility to HIV-1 infection

DC-SIGNR [11], also termed L-SIGN (for liver SIGN) [91], shares 77% sequence identity with DC-SIGN and is expressed by sinusoidal endothelial cells in liver (LSECs) and in lymph nodes, alveolar macrophages [92] and enterocytes of the small intestine [93]. Moreover, DC-SIGNR transcripts have been detected at sites of mucosal HIV-1 transmission [94]. DC-SIGNR, like DC-SIGN, binds to high-mannose carbohydrates and captures HIV-1, HIV-2 and simian immunodeficiency virus [11, 91]. Binding to ICAM proteins has also been demonstrated [91]. However, the natural function of DC-SIGNR is currently unclear. Expression of DC-SIGNR in lymph node sinusoids might concentrate HIV-1 in this compartment, while DC-SIGNR on LSECs might promote infection of this cell type, which was shown to be permissive *in vitro* [95] and *in vivo* [96, 97]. LSECs might therefore constantly release progeny virus into the blood stream, thereby promoting HIV-1 spread.

DC-SIGN and DC-SIGNR are both organized into a N-terminal intracellular domain, a transmembrane domain, a neck region containing 7.5 repeats of

a 23-amino acid-comprising sequence and a C-terminal lectin domain. In contrast to the neck domain of DC-SIGN, which is highly conserved among individuals, the neck domain of DC-SIGNR is polymorphic. While 7.5 repeats are most often found and are considered wild type (wt), alleles with 5.5 and 6.5 repeats are also frequent (28.9% and 12.2%, respectively, in the Caucasian population [91]). The impact of polymorphisms in the DC-SIGNR neck region on susceptibility to HIV-1 infection has been analyzed by two studies. Lichterfeld and colleagues [98] found no significant differences in DC-SIGNR allele distribution between HIV-1-infected individuals and healthy controls. Also, no correlation between DC-SIGNR allele frequency and course of HIV-1 disease was observed [98]. In contrast, Liu and colleagues [99] found that the 7/7 genotype was significantly less frequent in high-risk HIV-1-seronegative individuals compared to HIV-1-seropositive individuals, while the 5/7 genotype was associated with some protection against HIV-1 infection. It is currently unclear, however, how such a protective effect can be explained on the molecular level. Thus, DC-SIGNR variants with 5 and 6 repeats were found to form stable homo-oligomers [100] and to augment HIV-1 infection [101] with similar efficiency as the wt protein. Also, coexpression of DC-SIGNR alleles with 5 and 7 repeats allowed formation of stable hetero-oligomers and did not result in decreased HIV-1 interactions when compared to controls expressing the 7/7 allele combination [101]. A linkage between DC-SIGNR polymorphisms and alterations in unrelated genes determining susceptibility to HIV-1 infection can therefore at present not be excluded.

MR and langerin mediate HIV-1 gp120 binding to DC subsets

The observation that DCs can bind to HIV-1 independently of DC-SIGN raised the question whether related lectins might be involved. A detailed analysis of gp120 interactions with different DC subsets revealed that MR on dermal DCs might contribute to gp120 capture by these cells [72]. MR is an endocytic receptor that harbors multiple lectin domains and recognizes ligands bearing mannose, fucose or *N*-acetylglucosamine (GlcNac) [102]. The lectin is expressed on DCs, macrophages and some endothelial cells [102] and might contribute to capture of HIV-1 virions by these cells. In fact, it has been demonstrated that an MR-specific antibody can reduce HIV-1 attachment to macrophages [103]. Langerin contains a single carbohydrate recognition domain specific for mannose, fucose and GlcNac and is expressed exclusively by Langerhans cells [104, 105]. Expression of langerin triggers formation of Birbeck granules, which are part of the endosomal recycling machinery of Langerhans cells [106, 107]. The lectin might function as an antigen uptake receptor that releases ligands upon exposure to low pH in endosomal compartments [105]. While Langerin recognizes HIV-1 gp120, it needs to be determined whether it contributes to infection of Langerhans cells, which are sus-

ceptible to HIV-1 in culture and in patients [108, 109], or to transmission of HIV-1 from Langerhans cells to adjacent target cells.

Approaches to inhibit HIV-1 interactions with cellular lectins

Lectin-dependent HIV-1 attachment to cells can be prevented by interfering with lectin expression or by targeting domains in the lectin required for efficient ligand recognition. Alternatively, carbohydrate structures in HIV-1-gp120, which are recognized by relevant lectins, are targets for intervention. Down-modulation of lectin expression can be achieved by specific siRNA [82, 110] and by sanglifehrin A [111], an immunosuppressant that diminishes C-type lectin expression on DCs. However, issues with delivery (siRNA) and possible unwanted side effects (sanglifehrin A) need to be addressed. Several inhibitors that impede the interaction of DC-SIGN with HIV-1 or other viruses have been described. A synthetic, branched molecule that presents 32 mannose residues on its surface has been shown to inhibit HIV-1-gp120 binding to DC-SIGN [112] and to block DC-SIGN interactions with reporter viruses bearing the Ebola virus glycoprotein [113], a well-established DC-SIGN ligand [114, 115]. The antiviral activity of comparable molecules bearing sialic acid, the structure recognized by influenza hemagglutinin, has also been demonstrated in a mouse model for influenza infection [116], underlining the feasibility of this approach. The inhibitory substances used to target lectin-mediated HIV-1 attachment must not necessarily be of synthetic origin, since bovine lactoferrin [117] and a substance in human milk which harbors Lewis X carbohydrates [118] were shown to bind to DC-SIGN and to inhibit HIV-1 transmission by DCs. Similarly, a DC-SIGN inhibitory activity was identified in human cervicovaginal lavage fluid [119]. These natural substances might modulate the risk of HIV-1 transmission and merit further investigation. Finally, inhibition of ligand binding to lectins can be achieved by monoclonal antibodies, and a variety of DC-SIGN- or DC-SIGNR-specific monoclonal antibodies that inhibit pathogen interactions with these lectins have been generated [68, 69, 71, 120].

While several lectins expressed at the cell surface can mediate HIV-1 attachment, soluble human-, plant- and bacteria-derived lectins can be employed to inhibit this process. Thus, mannose-binding lectin (MBL), a soluble lectin that is involved in innate immunity and is known to bind to HIV-1-gp120 [121], inhibits DC-SIGN-dependent HIV-1 transmission to target cells, probably by competing with DC-SIGN for binding sites in HIV-1-gp120 [122]. A similar observation was reported for Ebola virus [123], validating that lectins with overlapping carbohydrate specificity can compete for binding sites in gp120, which can result in reduction of viral attachment. In fact, soluble lectins were shown to be effective against HIV-1 transfer by DCs and direct infection of DCs [124], highlighting that lectins applied within a microbicide formulation might help to block HIV-1 infection upon sexual transmission. A promising

candidate microbicide is Cyanovirin N, a mannose-specific lectin obtained from the Cyanobacterium *Nostoc ellipsosporum* [125]. CV-N binds to the HIV-1-gp120 protein and inhibits HIV-1 interactions with DCs *in vitro* [124] and, when applied topically, infection of macaques with a simian/human immunodeficiency hybrid virus upon vaginal and rectal challenge [126, 127].

Concluding remarks

A more complete understanding of the possible contribution of virus-associated host proteins to the HIV-1 life cycle is crucial because it might lead to the development of alternative approaches for the treatment of HIV-1 infection and/or the design of an efficient vaccine strategy. Interestingly, a therapeutic or vaccine strategy targeted at virus-associated host cell surface proteins might circumvent problems due to the great genetic variability displayed by HIV-1. Elucidation of the molecular mechanisms underlying HIV-1 capture by cellular lectins and assessment of the contribution of this process to HIV-1 dissemination in and between individuals might help to define novel strategies for preventive or therapeutic intervention. Moreover, lectins on DCs can be used as tools to target HIV-1 antigens to these important antigen-presenting cells [128–131], which might facilitate the generation of an effective HIV-1 vaccine.

Acknowledgements
We acknowledge numerous contributions from various laboratories whose references were not cited in this review due to space limitations. The work presented in this review is supported by grants to M.J.T. from the Canadian Institutes of Health Research HIV/AIDS Research Program (HOP-14438) and by grants from the Deutsche Forschungsgemeinschaft to S.P. (SFB466, GK 1071). M.J.T. is the recipient of the Canada Research Chair in Human Immuno-Retrovirology (senior level).

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