The multiple facets of HIV attachment to dendritic cell lectins

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Summary
Entry of enveloped viruses into host cells depends on the interactions of viral surface proteins with cell surface receptors. Many enveloped viruses maximize the efficiency of receptor engagement by first binding to attachment-promoting factors, which concentrate virions on target cells and thus increase the likelihood of subsequent receptor engagement. Cellular lectins can recognize glycans on viral surface proteins and mediate viral uptake into immune cells for subsequent antigen presentation. Paradoxically, many viral and non-viral pathogens target lectins to attach to immune cells and to subvert cellular functions to promote their spread. Thus, it has been proposed that attachment of HIV to the dendritic cell lectin DC-SIGN enables the virus to hijack cellular transport processes to ensure its transmission to adjacent T cells. However, recent studies show that the consequences of viral capture by immune cell lectins can be diverse, and can entail negative and positive regulation of viral spread. Here, we will describe key concepts proposed for the role of lectins in HIV attachment to host cells, and we will discuss recent findings in this rapidly evolving area of research.

Viruses need to access host cells to propagate and spread. The plasma membrane constitutes a physical barrier to infection, and enveloped viruses evolved specialized surface proteins (also termed envelope- or glyco-proteins) to overcome this obstacle. These proteins mediate binding of viruses to host cells and subsequent fusion of the viral and a limiting host cell membrane, which allows the delivery of viral nucleic acid and protein into the host cell cytoplasm (Harrison, 2008). The first essential step in the entry cascade is the cognate binding of viral envelope proteins to components of the host cell surface, termed viral receptors (Harrison, 2008). Receptor binding can limit infection efficiency, for example when receptor expression levels and/or receptor affinity of the viral envelope protein are low (Bannert et al., 2000). To circumvent this limitation, viruses can also engage cellular attachment factors, which promote viral binding to the cell surface and thus increase the possibility of successful receptor engagement and infectious entry. For instance, HIV can incorporate cellular proteins into its envelope, which interact with binding partners on target cells and thereby augment viral attachment and entry (Cantin et al., 2005).

Dendritic cells are professional antigen presenting cells, which can initiate primary and stimulate memory immune responses. Immature dendritic cells are particularly adept in antigen capture, while mature dendritic cells efficiently present antigen to T cells. The major dendritic cell subsets in human blood are myeloid and plasmacytoid dendritic cells, which can produce high amounts of IL-12 and IFN-α respectively (Wu and KewalRamani, 2006). Dendritic cells of myeloid origin also line body surfaces and attachment of HIV to these cells in the anogenital mucosa might play a prominent role in the sexual transmission of HIV, the major route of viral spread, as discussed below. Initial evidence for an important role of myeloid dendritic cells in HIV transmission came from cell culture studies demonstrating that mature, myeloid dendritic cells isolated from blood boost HIV infection of cocultured T cells without becoming infected (trans-infection) (Cameron et al., 1992). Subsequent studies extended these findings to monocyte-derived immature and mature dendritic cells (reviewed by Wu and KewalRamani, 2006), model systems for myeloid dendritic cells in blood and tissues. A molecular basis for HIV trans-infection by immature dendritic cells was provided by Geijtenbeek and colleagues, who showed that these cells express the lectin DC-SIGN (for dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin), and that DC-SIGN binds to glycans on HIV
Env and facilitates trans-infection of adjacent T cells (Geijtenbeek et al., 2000). Based on these findings, and taking into account the natural ability of dendritic cells to migrate from the periphery into lymphoid tissue, it was proposed that sexually transmitted HIV hijacks submucosal dendritic cells via DC-SIGN to promote its dissemination, a concept referred to as the Trojan horse model (Geijtenbeek et al., 2000). Reports that other viruses and non-viral pathogens exploit DC-SIGN on dendritic cells to augment their spread (Table 1) suggested that the Trojan horse model might be paradigmatic for the host invasion by a broad spectrum of pathogens. Recent work challenged important features of this model, but also demonstrated new mechanisms how pathogens can target DC-SIGN to propagate.

In the present review, we will introduce potential consequences of HIV interactions with DC-SIGN and other immune cell lectins and we will discuss recent developments in the field. Our focus will be on HIV, since important mechanisms underlying DC-SIGN-dependent augmentation of pathogen spread have been established with this virus, and apply to other viruses as well.

DC-SIGN on dendritic cells and HIV trans-infection: progress and pitfalls

DC-SIGN is expressed by monocyte-derived dendritic cells (MDDCs) and by dendritic cells in mucosal and lymphoid tissues, although concerns have been raised that DC-SIGN-positive cells found in some tissues might indeed be macrophages (Granelli-Piperno et al., 2005; Gurney et al., 2005). In addition, expression of DC-SIGN outside the macrophage/dendritic cell lineage has been noted; for instance a subset of B cells expresses DC-SIGN (Rappocciolo et al., 2006a). DC-SIGN is a type II transmembrane protein, in which the following domains have been identified: a cytoplasmic domain, a transmembrane domain, a neck-region and a lectin domain. The cytoplasmic domain contains motifs involved in receptor internalization and signalling, while the neck region facilitates DC-SIGN tetramerization, which is required for high-affinity ligand binding (Serrano-Gomez et al., 2008; Tabarani et al., 2009). Finally, the lectin domain, which requires calcium for its structural integrity (C-type), binds to high-mannose and fucose residues on pathogens and cellular proteins (Guo et al., 2004).

Trans-infection was reported to depend on DC-SIGN-mediated binding and cellular uptake of HIV into dendritic cells (Geijtenbeek et al., 2000; Kwon et al., 2002), followed by intracellular transport of virions to sites of dendritic cell–T cell contact, termed infectious synapses (McDonald et al., 2003) (Fig. 1). At the T cell site of the infectious synapse CD4 and coreceptor are concentrated (McDonald et al., 2003), resulting in the establishment of a microenvironment ideally suited for HIV trans-infection. Collectively, these results suggest that HIV exploits...
mechanisms normally used for antigen presentation by dendritic cells to increase its infectivity for adjacent T cells. In the following, we will review recent work examining key features of this concept.

Sticky and sweet: several lectins mediate HIV binding to dendritic cells

Initial work suggested that DC-SIGN was required for efficient MDDC-mediated HIV trans-infection (Geijtenbeek et al., 2000). Albeit this finding is controversial (Gummuluru et al., 2003; Boggiano et al., 2007), a number of reports indicate that blockade of DC-SIGN by either antibodies, carbohydrates (Baribaud et al., 2002; Wu et al., 2002; Wang et al., 2007a) or RNAi (Arrighi et al., 2004a,b) indeed diminishes HIV trans-infection (Gumey et al., 2005). In addition, DC-SIGN promotes HIV dissemination by migratory cells from cervical explants (Hu et al., 2004). However, the indicated role of DC-SIGN in HIV trans-infection by dendritic cells is not universal. Thus, different types of dendritic cells employ different C-type lectins, DC-SIGN, mannose receptor (MR) and langerin, as well as CD4 for binding to HIV Env, and dendritic cell maturation shifts Env capture from lectins to CD4 (Turville et al., 2002). Accordingly, DC-SIGN is believed to contribute to HIV trans-infection mediated by immature but not by mature dendritic cells (Izquierdo-Useros et al., 2007; Wang et al., 2007a), although one study reached a different conclusion (Baribaud et al., 2002), and coexpression of CD4 was found to diminish DC-SIGN-mediated trans-infection, possibly by facilitating uptake and transport of HIV into late endosomal compartments (Wang et al., 2007b). The list of lectins involved in HIV attachment to dendritic cells was recently expanded to include the C-type lectin DCIR (dendritic cell immunoreceptor), but the relative contributions of DC-SIGN and DCIR to HIV trans-infection remain to be established (Lambert et al., 2008). Finally, HIV attachment to dendritic cells can also proceed in a lectin- and CD4-independent fashion (de Witte et al., 2007a; Hatch et al., 2009; Izquierdo-Useros et al., 2009). Thus, dendritic cells have multiple means to capture HIV, and the prevalent mode of
viral binding depends on the origin and the maturation status of the cells.

**DC-SIGN-dependent HIV uptake and trafficking in dendritic cells: degradation versus trans-infection**

Kwon and colleagues found that HIV transfer to T cells by DC-SIGN-positive cells was dependent on lectin-mediated viral internalization into low pH compartments (Kwon et al., 2002), in which viral infectivity was preserved (Geijtenbeek et al., 2000; Kwon et al., 2002) (Fig. 1). An LL motif in the cytoplasmic tail of DC-SIGN facilitates ligand endocytosis by DC-SIGN (Engering et al., 2002). However, a contribution of the LL motif to HIV transmission by DC-SIGN expressing cell lines was not observed by a subsequent study (Burleigh et al., 2006), and the role of a low pH compartment in HIV trans-infection has been questioned (Nobile et al., 2005; Wang et al., 2007a). The former observation is in agreement with work demonstrating that DC-SIGN contributes to HIV uptake into dendritic cells, but targets the majority of internalized virions for degradation and MHC presentation (Moris et al., 2004; 2006) (Fig. 1). The identification of LSP1 as a cellular binding partner of the cytoplasmic tail of DC-SIGN further supports such a scenario (Smith et al., 2007). Thus, normal expression of LSP1 diverts HIV into the proteasome of dendritic cells, while LSP1 knockdown increases trans-infection (Smith et al., 2007).

Regardless of the role of DC-SIGN, it is undisputed that HIV is efficiently taken up into dendritic cells and important differences between immature and mature dendritic cells have been noted (Frank et al., 2002; Wang et al., 2007a). Thus, virions taken up into mature dendritic cells accumulate in large endocytic compartments, which resemble structures seen in macrophages upon HIV uptake by macrophagocytosis (Wang et al., 2007a). In comparison, virions associated with immature dendritic cells are mostly found close to the cell surface, with only a few virions being present in intracellular vesicles, which exhibit a clathrin-coat (Wang et al., 2007a). Notably, the ability to traffic HIV into deep intracellular compartments was found to correlate with protection of virus from proteases, and inhibitors of intracellular trafficking and cytoskeleton integrity were shown to inhibit trans-infection (Wang et al., 2007a; 2008b), in agreement with the proposal that HIV traffics intracellularly, via a tetraspandin-sorting pathway, to infectious synapses (Garcia et al., 2005). In contrast, a separate study postulated that virions reach infectious synapses exclusively by transport on the cell surface instead of travelling along intracellular routes (Cavrois et al., 2007). In agreement with this scenario, it was reported that HIV is routed towards the infectious synapse in a surface accessible, intracellular compartment (Yu et al., 2008). Irrespective of the route of HIV trafficking, there is ample evidence that HIV capture does not preserve viral infectivity (Turville et al., 2004; Nobile et al., 2005; Burleigh et al., 2006; Wang et al., 2007a), with the initially postulated conservation of viral infectivity likely being due to productive infection of the transmitting cells (Nobile et al., 2005; Burleigh et al., 2006).

Collectively, HIV trans-infection driven by dendritic cells is short lived (hours) and DC-SIGN on immature dendritic cells contributes to this process in at least two ways: DC-SIGN promotes capture and potentially uptake of virions subsequently transferred to T cells. In addition, DC-SIGN seems to stimulate the formation of infectious synapses by a so far incompletely understood mechanism (Arrighi et al., 2004a).

**DC-SIGN signals dendritic cells to transmit HIV**

Recent studies revealed a novel facet of HIV interactions with DC-SIGN on dendritic cells, the modulation of the immune response. It was demonstrated that binding of HIV to MDDCs induces ERK-dependent signal transduction, which correlates with production of the immunosuppressive cytokine IL-10 and compromised maturation of dendritic cells (Shan et al., 2007). These effects were dependent on appropriate Env glycosylation and on C-type lectin expression, and a role of DC-SIGN was postulated (Shan et al., 2007). Removal of mannos-rich glycans from Env improved immunogenicity of the protein (Banerjee et al., 2009), further pointing towards a role of mannos-specific lectins in immune responses shaped by dendritic cells. In agreement with these findings, HIV binding to DC-SIGN on dendritic cells was demonstrated to induce signalling via the Rho guanine nucleotide–exchange factor LARG and the small GTPase RhoA, which results in aberrant dendritic cell maturation (Hodges et al., 2007). Thus, the cells fail to upregulate CD86 and MHC II but readily form infectious synapses with T cells (Hodges et al., 2007), indicating that HIV signalling via DC-SIGN compromises the immune function of dendritic cells and simultaneously primes the cells for trans-infection. A separate study showed that binding of HIV to DC-SIGN induces signals via a multi-protein complex, including the kinase Raf-1, which modulates TLR-induced cytokine production by regulating acetylation of the NF κB subunit p65 (Gringhuis et al., 2007). Interestingly, activation of Raf-1 was dependent on LARG and RhoA and on the carbohydrate profile of the pathogen bound to DC-SIGN. Thus, HIV and *Mycobacterium tuberculosis*, which bind to DC-SIGN via high-mannose residues, activated Raf-1 signalling and induced production of a cytokine profile different from that triggered by *Helicobacter pylori*, which was due to recognition of fucose containing structures and did not involve Raf-1 activation (Gringhuis et al.,...
Finally, signalling via TLR8 and DC-SIGN was required for NFκB-dependent recruitment of the transcription factor pTEF-b to the viral promoter, and thus for the generation of full-length HIV transcripts in dendritic cells – a prerequisite for productive infection (Gringhuis et al., 2010) (Fig. 2). However, HIV infection of dendritic cells is inefficient compared with T cells and macrophages (reviewed by Wu and KewalRamani, 2006), and a contribution of this mechanism to viral spread in vivo remains to be established. In sum, DC-SIGN has signalling capacity, which can be exploited by pathogens to modulate immune responses and to establish productive infection of dendritic cells and adjacent target cells.

Langerin on langerhans cells: a roadblock to HIV transmission?

Langerhans cells are located in the top layer of the mucosa and are most likely the first cell type to come in contact with sexually transmitted HIV. Langerhans cells are DC-SIGN-negative but express CD4 and the C-type lectin langerin (Soilleux and Coleman, 2001). Pioneer work by de Witte and colleagues provided evidence that langerin constitutes a defence mechanism against HIV invasion (de Witte et al., 2007b). Thus, langerin binds to Env and targets bound virions into Birbeck granules, an intracellular compartment specific to Langerhans cells, where the virus is degraded (de Witte et al., 2007b). Counter-intuitively, however, C-type lectins were reported to play a minor role in HIV entry into vaginal Langerhans cells (Hladik et al., 2007), and examination of skin explants inoculated with HIV indicated HIV infection of Langerhans cells, but not other types of dendritic cells, and transfer of virus from Langerhans cells to T cells (Kawamura et al., 2008). The latter observations suggest that infection of Langerhans cells might be an important early event in HIV transmission. Such a scenario can be reconciled with the findings of de Witte and colleagues, when taking into account that the barrier imposed by
langerin can be overcome by high doses of virus (de Witte et al., 2007b) and that TNF-α, produced upon genital coinfections, like candida albicans, might increase permissiveness of Langerhans cells to HIV infection (de Jong et al., 2008b) – hypotheses that should be tested in animal models.

**DC-SIGN: target for many viruses**

DC-SIGN is targeted by different viruses which all contain envelope proteins with an appropriate glycan signature. Three major consequences of viral engagement of DC-SIGN have been described: first, DC-SIGN can function as a bona fide entry receptor. In this case, expression of DC-SIGN is sufficient to render cells susceptible to infection. Such a scenario has been suggested, e.g. for dendritic cell infection by human herpesvirus 8 (HHV-8) (Rappocciolo et al., 2008), the causative agent of Kaposi sarcoma and for Ebolavirus infection of T cells (Alvarez et al., 2002). However, it is technically challenging to discriminate between entry mediated solely by DC-SIGN (receptor function) and entry augmented by DC-SIGN but facilitated by a coexpressed receptor, a process termed cis-infection (Lee et al., 2001). In fact, DC-SIGN most likely functions as an attachment factor in the context of Ebolavirus entry into lymphoid cells (Marzi et al., 2007). Second, DC-SIGN might augment cis-infection, as described above. DC-SIGN-driven cis-infection has been established for dengue virus infection of dendritic cells, which are important early targets of this pathogen (Lozach et al., 2005). Polymorphisms in the DC-SIGN gene were shown to impact disease development, suggesting that cis-infection might facilitate viral spread in patients (Sakuntabhai et al., 2005). Third, DC-SIGN can promote trans-infection of target cells. While this route has first been established for HIV, trans-infection of several viruses by DC-SIGN has been demonstrated, including Measles virus (de Witte et al., 2008) and Ebolavirus (Alvarez et al., 2002), and might promote transmission of these pathogens. Whether DC-SIGN engagement by viruses other than HIV also modulates cytokine release and thus impacts the establishment of an immune response remains to be determined.

**Conclusions**

Detailed information on the processes ensuing exposure of anogenital mucosa to sexually transmitted HIV is indispensable to understand viral dissemination and pathogenesis and to develop effective antiviral strategies. There is continued and well founded belief that dendritic cells play an important role in the establishment of HIV infection. However, the idea of the role of DC-SIGN in HIV interactions with dendritic cells has changed considerably (Fig. 1). It has become clear that dendritic cells have several means to bind and transfer HIV to cells, with C-type lectins being one of them. In addition, an appreciable protection of HIV from antiviral agents upon attachment to dendritic cells is under discussion, and the concept of long-term storage and subsequent regurgitation of infectious HIV by dendritic cells had to be abandoned. On the other hand, DC-SIGN-mediated HIV trans-infection, although found to be a short-lived process, and cis-infection might promote viral amplification in the genital mucosal, which could be critical for the establishment of the primary infection. Conversely, langerin on Langerhans cells was discovered to target HIV for degradation, suggesting a barrier function of this lectin. Finally, intriguing new findings revealed a signalling capacity of DC-SIGN (and other lectins), which is exploited by HIV to compromise immune defences and to promote its spread. Vaccine development should therefore encompass the optimization of the glycan profiles of candidate substances, and new strategies for immunotherapy can be envisioned. Ultimately, key concepts need to be evaluated in improved cell culture systems and animal models for sexual transmission of HIV. An important but often overlooked parameter determining outcome and significance of such experiments is the source of the virus. Glycosylation of HIV depends on the producer cell type, and viruses generated in macrophages are unlikely to be detected efficiently by C-type lectins on mucosal dendritic cells (Lin et al., 2003). Consequently, these viruses might overcome the mucosal barrier with different efficiency and potentially by employing different strategies compared with viruses generated in T cells – and similar considerations apply to most if not all other DC-SIGN ligands.

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