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Lectin-like interactions in virus–cell recognition: human immunodeficiency virus and C-type lectin interactions

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SUMMARY

Recognition of pathogen-specific glycostructures by lectins on immune cells is an important means of host immune defence but may also be exploited by some pathogens to promote their spread. The calcium-dependent lectin dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN) is involved in human immunodeficiency virus (HIV) interactions with dendritic cells. Attachment of HIV to dendritic cells can potentiate viral infectivity for adjacent T-cells and it has been postulated that this process contributes to the dissemination of sexually transmitted virus. However, more recent research has revealed that the consequences of lectin-dependent HIV interactions with dendritic cells are diverse and can include uptake for major histocompatibility complex presentation, productive infection and transfer of virus to T-cells. In this chapter DC-SIGN and other cellular lectins known to recognize HIV are introduced, and how lectin binding might impact viral dissemination is discussed.

Keywords: Human immunodeficiency virus (HIV); Dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN); C-Type lectin; Dendritic cell; Langerin; Platelet; Dissemination; Pathogenesis

1. INTRODUCTION

Many enveloped viruses hijack the host cell glycosylation machinery to ensure appropriate carbohydrate modification of their surface proteins. The efficiency and type of glycans added to viral membrane proteins can determine recognition of viruses by cellular lectins and the humoral immune response which, in turn, can have profound consequences for viral spread and pathogenicity (Vigerust and Shepherd, 2007). Conversely, several viral glycoproteins function as lectins and employ cellular glycans for infectious entry into target cells. Most prominently, the influenza haemagglutinin binds to sialic acid present on surface structures of target cells.
(Vigerust and Shepherd, 2007) and the nature of the sialic acid linkage determines if cells are susceptible to infection by human viruses (which bind to $\alpha$-(2→6)-linked sialic acid) or avian viruses (which recognize $\alpha$-(2→3)-linked sialic acid) (see Chapter 15).

The interactions of viruses with calcium-dependent (C-type) lectins have received particular attention. This lectin family comprises membrane-bound and soluble members which can promote cell adhesion and/or sense pathogens (van Kooyk and Geijtenbeek, 2003; Ji et al., 2006; van Kooyk and Rabinovich, 2008) (see Chapter 34). One would expect that virion capture by C-type lectins invariably promotes establishment of an effective immune response. However, several lines of evidence suggest that certain viruses and non-viral pathogens specifically target C-type lectins to slip detection by the immune system (van Kooyk and Geijtenbeek, 2003). The most prominent example might be the interaction of human immunodeficiency virus (HIV) with dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN, CD209), a C-type lectin expressed at high levels on dendritic cells (DCs). Binding of HIV to DC-SIGN can potentiate viral infectivity or induce viral uptake and degradation. The molecular mechanisms underlying these processes and their consequences for HIV dissemination in and between individuals are the topic of the remainder of this review. As stated above, targeting DCs and other immune cells via DC-SIGN or related lectins is not a particular trait of HIV (Table 28.1). Thus, for example, DC-SIGN promotes DC infection, e.g. by dengue virus and measles virus, and the

| Virus                        | DC-SIGN                                      | DC-SIGNR                                      |
|------------------------------|----------------------------------------------|-----------------------------------------------|
| Human immunodeficiency virus | Curtis et al., 1992; Geijtenbeek et al., 2000b | Pöhlmann et al., 2001a; Bashirova et al., 2001; Mummidi et al., 2001 |
| Human T-cell leukemia virus  | Ceccaldi et al., 2006                         |                                               |
| Human herpes virus 8         | Rappocciolo et al., 2006a                     |                                               |
| Human cytomegalovirus        | Halary et al., 2002                           | Halary et al., 2002                           |
| Herpes simplex virus         | de Jong et al., 2008                          |                                               |
| Measles virus                | de Witte et al., 2006                         |                                               |
| Influenza virus              | Wang et al., 2008                             |                                               |
| Dengue virus                 | Navarro-Sanchez et al., 2003; Tassaneetrithep et al., 2003 | Tassaneetrithep et al., 2003 |
| West Nile virus              | Davis et al., 2006a,b                         | Davis et al., 2006a,b                         |
| Hepatitis C virus            | Gardner et al., 2003; Pöhlmann et al., 2003; Lozach et al., 2003 | Gardner et al., 2003; Pöhlmann et al., 2003; Lozach et al., 2003 |
| Sindbis virus                | Klimstra et al., 2003                         | Klimstra et al., 2003                         |
| Ebola virus                  | Alvarez et al., 2002; Simmons et al., 2003   | Alvarez et al., 2002; Simmons et al., 2003    |
| Marburg virus                | Marzi et al., 2004                            | Marzi et al., 2004                            |
| SARS-coronavirus             | Marzi et al., 2004; Yang et al., 2004         | Marzi et al., 2004; Yang et al., 2004         |
| Human coronavirus NL63       | Hofmann et al., 2006                          | Hofmann et al., 2006                          |

III. MICROBE–HOST GLYCOSYLATED INTERACTIONS
DC-SIGN-related protein DC-SIGNR (also termed L-SIGN, CD209L) may concentrate hepatitis C virus in liver sinusoidal endothelial cells, thereby potentially promoting infection of adjacent hepatocytes (see Table 28.1). Moreover, Ebola- and Marburg virus, which induce a lethal haemor rhagic fever in humans, employ several C-type lectins for augmentation of infectivity and lectin engagement may determine the discrete cell and organ tropism observed at various stages of filovirus infection. In summary, an intricate interplay between viruses and C-type lectins impacts the balance between viral attack and host defence, as specified below for HIV, and elucidation of the underlying mechanisms can provide important insights into the pathogenesis of viral infections and may uncover attractive targets for therapy and prevention.

2. MAKING IT STICK: Env MEDIATES HIV ATTACHMENT AND ENTRY INTO HOST CELLS

Human immunodeficiency virus is the causative agent of acquired immunodeficiency syndrome (AIDS). In 2007, HIV and AIDS afflicted 33.2 million people with devastating socioeconomic consequences (Cohen et al., 2008). Interindividual spread of HIV mainly occurs via the sexual route. It is believed that capture of sexually transmitted virus by mucosal DCs (see below) is important for subsequent dissemination to lymphoid tissue (Wu and KewalRamani, 2006; Piguet and Steinman, 2007). The gut-associated lymphoid tissue is the first and the principal target of HIV infection (Veazey and Lackner, 2004). During a phase of clinical latency, virally destroyed T-cells are constantly replaced by fresh cells. However, after several years (in the absence of therapy), the capacity of the host to replenish T-cells gradually decreases and the decline in T-cell numbers is paralleled by an increasing susceptibility to opportunistic infections, which are ultimately fatal.

The HIV envelope protein (Env) allows the virus to recognize and access the host cell (Pöhlmann and Reeves, 2006). The Env protein is synthesized in the secretory pathway of infected cells. An N-terminal signal sequence earmarks nascent Env for import into the endoplasmatic reticulum, where the protein is extensively modified with N-linked mannose-rich glycans (Scanlan et al., 2007). Upon transport of Env in the Golgi apparatus, these glycans are further processed to a complex and hybrid type in a host cell-dependent fashion. However, less than half of the oligosaccharides are completely processed due to their recessed location and/or dense packaging (Scanlan et al., 2007). It has been shown that Env is also O-glycosylated (Bernstein et al., 1994), but target sites and biological relevance are largely unclear. Extensive glycosylation of surface exposed regions shields underlying epitopes from recognition by antibodies and critically contributes to immune evasion (Scanlan et al., 2007). Moreover, Env glycosylation is essential for interaction with cellular lectins, which can promote or inhibit viral spread, as discussed below.

Infectious cellular entry of HIV is initiated by Env interactions with the CD4 receptor, which is expressed on T-cells, macrophages, monocytes and DCs, all of which are susceptible to HIV (Pöhlmann and Reeves, 2006) (Figure 28.1). Binding to CD4 triggers conformational changes in the surface unit gp120, which lead to the formation and/or exposure of a co-receptor binding site. Engagement of a chemokine co-receptor, usually CCR5 or CXCR4, activates the membrane fusion machinery located in the transmembrane unit gp41 (Pöhlmann and Reeves, 2006), which undergoes a series of conformational changes resulting in the fusion of the viral and the host cell membrane (see Figure 28.1).

The interactions between Env on virions and CD4 and co-receptor on target cells are cell type-independent and indispensable for infectious entry. Consequently, they are attractive targets for therapeutic intervention (Este and Telenti, 2007). However, a constantly accumulating body
of evidence suggests that CD4- and co-receptor-independent interactions of HIV with target cells, albeit being ultimately dispensable for infectious entry, can profoundly augment infection efficiency. Thus, fragments of prostatic acidic phosphatase, which form amyloid fibrils in human semen, boost HIV infectivity by concentrating virions onto target cells (Münch et al., 2007) and attachment of HIV to DCs potentiates infectivity for adjacent T-cells (Wu and KewalRamani, 2006; Piguet and Steinman, 2007). The latter process may particularly promote dissemination of sexually transmitted HIV, because DCs might not only promote mucosal spread of HIV by facilitating infection of adjacent susceptible cells but may also ferry the virus into lymph nodes where it has ample access to target T-cells, as discussed below. It has been proposed that calcium-dependent (C-type) lectins on DCs are intimately involved in HIV capture and transfer to T-cells (Wu and KewalRamani, 2006; Piguet and Steinman, 2007). This review will introduce lectins participating in HIV capture and will discuss how lectin binding may modulate HIV spread.

3. PROMOTION OF HIV CAPTURE, TRANS-INFECTION AND DISSEMINATION BY DC-SIGN – THE PARADIGM REVISITED

Dendritic cells are divided into different subsets, which can be of myeloid and lymphoid origin, and are intimately involved in innate responses, tolerance induction and adaptive immunity (Liu, 2001). Langerhans cells and dermal DCs line the major surfaces of the human body and are uniquely equipped to recognize, take up and process antigen. Upon acquisition of antigen, both dendritic cell types migrate into lymphoid tissue and undergo a process termed maturation, during which expression of the antigen capture machinery is downregulated while production of factors required for antigen presentation is upregulated. In lymphoid tissues, mature DCs present antigen to T-cells and, due to their unique capability to stimulate naïve T-cells, are intimately involved in the induction of adaptive responses (Banchereau and Steinman, 1998).
Cell culture studies undertaken in the early 1990s indicated that DCs, despite their key role in the immune system, might promote HIV spread. Thus, it was demonstrated that HIV-exposed DCs could catalyse efficient infection of T-cells, apparently without being productively infected (Cameron et al., 1992; Pope et al., 1994). A possible interpretation of these findings was the existence of a so far unidentified factor on DCs which captures HIV and facilitates transmission of the virus to adjacent susceptible cells, a process termed “infection in trans”. Two reports by Geijtenbeek and colleagues, which showed that the C-type lectin DC-SIGN is expressed on DCs and promotes HIV trans-infection, supported this concept (Geijtenbeek et al., 2000a,b) (Table 28.2). Much effort has subsequently been devoted to the definition of the DC-SIGN/HIV interface and to the analysis of the molecular mechanisms underlying DC-SIGN-facilitated HIV trans-infection.

Sequence comparison and functional analysis of DC-SIGN defined the following domain structure: an N-terminal cytoplasmic domain, a transmembrane region, a repeat (also termed neck) region consisting of 7.5 repeats of a 23 amino acid comprising sequence and a C-type lectin domain. The C-type lectin domain, whose atomic structure has been determined (Feinberg et al., 2001; Guo et al., 2004), recognizes mannose- and fucose-containing glycans and is responsible for DC-SIGN binding to appropriately glycosylated ligands like the HIV Env protein, as discussed below. While monomers of the carbohydrate recognition domain (CRD) bind to ligands, DC-SIGN tetramerization, which is mainly driven by the repeat region, is required for high avidity binding (Mitchell et al., 2001; Feinberg et al., 2005; Snyder et al., 2005). Recognition of ligands by DC-SIGN is solely carbohydrate-dependent (Lin et al., 2003; Snyder et al., 2005), albeit evidence to the contrary has been reported.

| Lectin               | Tissue                        | Cell type                                      | Gp120 binding | HIV trans-infection | HIV-degradation |
|----------------------|-------------------------------|------------------------------------------------|----------------|---------------------|----------------|
| DC-SIGN (CD209)      | Mucosa, dermis, lymph node, spleen, bone marrow, placenta, lung | Dendritic cell, megakaryocyte, macrophage | Yes            | Yes                 | Yes            |
| DC-SIGNR (CD209L, L-SIGN) | Liver, lymph node, lung, intestine, placenta, bone marrow | Sinusoidal and capillary endothelial cell, alveolar cell | Yes            | Yes                 | ?              |
| Langerin (CD207)     | Mucosa, dermis                | Langerhans cell                                | Yes            | No                  | Yes            |
| LSECtin              | Liver, lymph node, bone marrow | Sinusoidal endothelial cells                   | Yes            | No                  | ?              |
| CLEC-2               | Bone marrow, liver            | Megakaryocyte, platelet, sinusoidal endothelial cell | No             | Yes                 | ?              |

aSee text for references.
(Geijtenbeek et al., 2002) and this has two important consequences. First, ligands which do not exhibit appreciable amino acid sequence homology but display appropriate glycans in an adequate spatial configuration can be recognized by DC-SIGN. Indeed, a wide spectrum of viral and non-viral pathogens with glycosylated surface structures has been found to interact with DC-SIGN and, for many, it has been suggested that targeting DCs via DC-SIGN might promote their spread (Khoo et al., 2008). Second, due to the cell type-dependent nature of glycosylation, the cellular background used for generation of HIV and other pathogens will profoundly impact the interaction with DC-SIGN. For example, the Env protein of HIV produced in T-cells is efficiently modified with high-mannose glycans and the respective viruses are robustly transmitted to target cells in a DC-SIGN-dependent manner (Lin et al., 2003). In contrast, incorporation of mannose-rich glycans and trans-infection driven by DC-SIGN is inefficient if viruses are generated in macrophages (Lin et al., 2003). The cell type used for pathogen amplification thus needs to be taken into account when evaluating the potential in vivo relevance of DC-SIGN interactions with pathogens observed in vitro.

How does binding of HIV Env to DC-SIGN facilitate infection of adjacent target cells? A straightforward explanation could be that DC-SIGN tethers virions on the cell surface and thereby increases the chance of virus transfer to susceptible cells, once virus-loaded cells and target cells make random contacts. However, several studies indicated that DC-SIGN-mediated trans-infection may be more complex. For one, analyses of mutant lectins revealed that HIV binding and transmission are dissociable functions, indicating that mere concentration of virions on target cells is insufficient for DC-SIGN-dependent trans-infection (Baribaud et al., 2001; Pöhlmann et al., 2001c). In addition, Geijtenbeek and colleagues reported that binding of HIV to a DC-SIGN-expressing cell line conserves viral infectivity over several days (Geijtenbeek et al., 2000b), a remarkable finding, considering that infectivity of cell free virus is lost within hours. Finally, Kwon and co-workers provided evidence that DC-SIGN-dependent trans-infection involves DC-SIGN-driven uptake of virions into low pH compartments, where infectivity is preserved and from which virus is regurgitated upon contact of virus-containing cells with T-cells (Kwon et al., 2002). Cumulatively, these observations fitted with a model suggesting that DCs in the submucosa, which express high levels of DC-SIGN, may take up sexually transmitted HIV in a DC-SIGN-dependent fashion and might subsequently transport HIV into lymph nodes, where the virus could be transferred to T-cells (Geijtenbeek et al., 2000b). In such a scenario, DC-SIGN-expressing DCs would act as Trojan horses which shield the virus from the immune system by conserving particles in intracellular vesicles and which promote HIV dissemination due to their natural capability to migrate into lymphoid tissues, the major target sites of HIV infection. However, several key aspects of the “Trojan horse model” have subsequently been challenged, as discussed below.

3.1. Several receptors contribute to HIV capture by dendritic cells

Geijtenbeek and colleagues demonstrated that anti-DC-SIGN antibodies and the mannose-polymer mannann profoundly inhibited HIV interactions with DC-SIGN-positive cell lines (Geijtenbeek et al., 2000b). Reduction of HIV trans-infection by monocyte-derived DCs (MDDCs) was also observed but inhibition was less robust compared to experiments with cell lines (Geijtenbeek et al., 2000b). These studies have subsequently been repeated by several groups and a wide spectrum of effects was observed, ranging from DC-SIGN being responsible for the vast majority of dendritic cell-mediated HIV trans-infection to DC-SIGN not being involved in
this process at all (Baribaud et al., 2002; Wu et al., 2002a,b; Trumpfheller et al., 2003; Gummuluru et al., 2003; Arrighi et al., 2004b; Granelli-Piperno et al., 2005; van Montfort et al., 2007; Boggiano et al., 2007). The reasons for these discrepancies are unclear but may involve usage of different viruses and virus producer cells as well as different DCs. In fact, Turville and colleagues showed that different types of DCs bind HIV Env via different receptors, with both CD4 and C-type lectins contributing to Env capture (Turville et al., 2002). A recent study complemented these findings by demonstrating that CD4 expression negatively regulates DC-SIGN-mediated trans-infection, with viruses exposed to cells co-expressing CD4 and DC-SIGN being mainly sorted into late endosomal compartments (Wang et al., 2007). Finally, variable trans-infection results may have been due to the ability of some DCs to support HIV infection, as discussed below.

3.2. DC-SIGN – not specific for dendritic cells?

Most studies on DC-SIGN function used a THP cell line engineered to express DC-SIGN. The THP cells are of monocytic origin and can be differentiated into macrophages upon phorbol myristate acetate treatment. Consequently, these cells may mirror some aspects of MDDCs. However, Wu and colleagues discovered that the THP cells widely used for DC-SIGN expression were indeed of B-cell origin and are most likely identical to Raji B-cells (the cell line is now termed B-THP) (Wu et al., 2004a). In fact, analysis of true THP-DC-SIGN cells revealed that these cells are not able to mediate HIV trans-infection with appreciable efficiency (Wu et al., 2004a). The reason for the cell type-dependence of DC-SIGN-driven HIV trans-infection is at present unclear. It has been noted that trans-infection requires cell-to-cell contact and can be diminished by contact of transmitting cells with certain cell types (Wu et al., 2004b). Yet, the factors governing trans-infection efficiency remain to be elucidated on a molecular level. Of note, misidentification of DC-SIGN-expressing cells might also have occurred upon analysis of human and macaque tissue sections. Thus, initial studies indicated that DC-SIGN is a marker for DCs and that DC-SIGN-positive DCs are found in lymph nodes (Wu and KewalRamani, 2006; Piguet and Steinman, 2007). In contrast to this view, Granelli-Piperno and colleagues provided evidence that DC-SIGN-positive cells in normal lymph nodes are almost exclusively of macrophage origin (Granelli-Piperno et al., 2005). Similarly, DC-SIGN-positive macrophages were detected in rheumatoid arthritis synovium (van Lent et al., 2003), in the lung (Soilleux et al., 2002) and in lesions of leprosy patients (Krutzik et al., 2005). A potential misidentification of DC-SIGN-positive macrophages as DCs in lymph nodes and maybe in other tissues would have important implications for the contribution of DC-SIGN to HIV transmission, considering that macrophages but not DCs are readily susceptible to infection by CCR5-tropic viruses. A more detailed characterization of the nature of the DC-SIGN-positive cells in tissues, particularly in the anogenital mucosa, may therefore be required.

3.3. Enhancement of viral infectivity by DC-SIGN – trans-infection versus productive infection of transmitting cells

Analyses of DC-SIGN-mediated HIV trans-infection were based on the assumption that neither the commonly used B-THP DC-SIGN cell line nor MDDCs were susceptible to productive HIV infection. As it turned out, both assumptions were wrong. Nobile and colleagues demonstrate that B-THP cells are susceptible to infection by CXC4-tropic HIV (Nobile et al., 2005), most likely due to expression of CXC4
and low levels of CD4. Thus, the reported DC-SIGN-mediated preservation of HIV infectivity by B-THP cells (Geijtenbeek et al., 2000b; Kwon et al., 2002) may have been due to release of infectious progeny viruses from transmitting cells and not to transfer of captured HIV. Notably, analogous observations were made with MDDCs. Thus, it is now established that both immature and mature DCs are susceptible to productive infection with CCR5-using viruses (albeit with different efficiencies) and that, apart from receptor expression, restriction by APOBEC3G mainly regulates susceptibility of DCs to HIV infection (Wu and KewalRamani, 2006; Piguet and Steinman, 2007). In the light of these observations, the consequences of HIV interactions with DCs were re-analysed. These studies revealed that input virus is transmitted only during a short-time window (hours) after HIV exposure of DCs, while all subsequent transmission events (days) are due to release of progeny viruses (Figure 28.2), suggesting that DCs might not be capable of storing infectious HIV over prolonged time periods (Turville et al., 2004; Nobile et al., 2005; Burleigh et al., 2006).

It was proposed that DC-SIGN-driven uptake of HIV into acidic intracellular vesicles is a prerequisite to efficient trans-infection and the LL motif in the cytoplasmic domain of DC-SIGN has been shown to facilitate DC-SIGN internalization upon ligand uptake (Kwon et al., 2002; Engering et al., 2002). However, subsequent studies could not confirm a role for intracellular acidic pH or DC-SIGN internalization in trans-infection (Nobile et al., 2005; Burleigh et al., 2006). In fact, the vast majority of virus internalized by DCs was found to be processed for major histocompatibility complex (MHC) presentation (Moris et al., 2004, 2006), while mainly particles located at the surface of DCs were transferred to T-cells (Cavrois et al., 2007), albeit the latter finding is controversial (Piguet and Steinman, 2007) (see Figure 28.2). Internalization and conservation of infectious HIV particles by different types of DCs therefore warrants further assessment.

3.4. Contribution of DC-SIGN to formation of infectious synapses

Transmission of HIV from DCs to T-cells occurs most efficiently at sites of intimate cell-to-cell contact. Thus, DCs were shown to accumulate internalized HIV particles at the site of contact to T-cells which, in turn, concentrate CD4 and coreceptor at the cell–cell interface (McDonald et al., 2003; Garcia et al., 2005). As a consequence, a
At first sight there is no obvious connection between HIV and platelets, except that thrombocytopenia is frequently observed in HIV/AIDS patients. A closer look, however, reveals several links. For one, HIV productively infects megakaryocytes and this process is potentially promoted by DC-SIGN (Scaradavou, 2002). Moreover, an association between platelet counts and viral load/disease progression has been reported (Rieg et al., 2007) and, most importantly, a substantial fraction of HIV in the blood of infected individuals has been found to be associated with platelets (Lee et al., 1998). The molecular mechanism behind HIV binding to platelets has recently been uncovered, when two groups independently demonstrated that platelets, or at least a substantial fraction of these cell fragments, express DC-SIGN and capture HIV via this receptor (Boukour et al., 2006; Chaipan et al., 2006). Platelets exposed to HIV were found to promote trans-infection of T-cells in a DC-SIGN-dependent fashion (Chaipan et al., 2006). However, a fraction of the bound virus may also be degraded since both intact and inactivated particles were detected in platelets and were localized to anatomically distinct compartments (Boukour et al., 2006). Therefore, the consequences of HIV capture by platelets for HIV infectivity require further assessment. Besides DC-SIGN, the C-type lectin-like receptor 2 (CLEC-2) contributed to HIV capture by platelets, by interacting with one or more cellular factors incorporated into the viral envelope upon release of progeny particles from infected cells (Chaipan et al., 2006). Identification of the responsible factor(s) may yield further insights into the interplay between HIV and platelets. In summary, platelets express HIV attachment factors and, simply because of their high concentration in human blood, are likely to modulate viral spread. A quantitative analysis of HIV binding to permissive and non-permissive blood cells, including platelets, the investigation of lectin expression levels on platelets of healthy and HIV-infected individuals and the correlation of the data with...
viral load and disease progression might help to clarify the role of platelets in HIV spread.

Infection of B-cells is normally inefficient in HIV/AIDS patients but these cells may be able to transfer the virus to T-cells (De Milito, 2004). This capability has been linked to DC-SIGN expression (Rappocciolo et al., 2006b), which was detected on a subset of B-cells from blood and tonsils (Rappocciolo et al., 2006b; He et al., 2006), albeit these data are not undisputed (Geijtenbeek et al., 2000a). Expression of DC-SIGN was enhanced by treatment of cells with IL-4 and CD40L and was found to be responsible for trans-infection of T-cells with CXCR4- and CCR5-tropic viruses (Rappocciolo et al., 2006b). Notably, DC-SIGN on B-cells may not only promote HIV infection but compromise the humoral immune response of the infected host. Thus, it has been shown that binding of HIV Env to C-type lectins, particularly DC-SIGN, on a subset of B-cells induces class switch DNA recombination in these cells, which is further enhanced by IL-4 and IL-10 (He et al., 2006). This phenomenon may explain why hyperactivation of B-cells is frequently seen in HIV/AIDS patients and leads to production of non-protective antibodies with specificity for HIV Env or irrelevant specificity.

5. IMPACT OF DC-SIGN POLYMORPHISMS ON THE SUSCEPTIBILITY TO HIV INFECTION

The neck region of the DC-SIGN-related protein DC-SIGNR (also termed L-SIGN, CD209L) is highly polymorphic and polymorphisms may affect the risk of HIV infection, as discussed below. In contrast, the DC-SIGN neck region was found to be rarely polymorphic when patients in US-based cohorts were analysed (Liu et al., 2004a). Nevertheless, polymorphisms were detected more often in multiple exposed seronegative individuals compared to HIV-infected patients (Liu et al., 2004a). These findings were extended by a subsequent study showing that polymorphisms in the DC-SIGN neck region are more frequent in the Chinese population compared to the US or the worldwide population and are associated with reduced risk of HIV infection (Zhang et al., 2008). Albeit independent analyses reached different conclusions (Wichukhinda et al., 2007; Rathore et al., 2008b), the above discussed studies indicate that variations in the neck region impact DC-SIGN interactions with HIV, but the molecular basis for this finding is not entirely clear. Engineered alterations in the number and configuration of repeat units in the neck region, as well as N-glycosylation of the N-terminal repeat unit, can impact DC-SIGN multimerization and carbohydrate binding (Feinberg et al., 2005; Serrano-Gomez et al., 2008). Polymorphic DC-SIGN variants analysed in one study retained the ability to form homo-oligomers but did not multimerize appreciably with wild-type DC-SIGN (Serrano-Gomez et al., 2008), suggesting that cells from heterozygous individuals might express less (or less stable) DC-SIGN homo-oligomers on the cell surface. However, it remains to be proven that such a reduction in wild-type DC-SIGN homo-oligomers indeed impacts the interaction with pathogens. The observation that at least MDDCs express DC-SIGN copy numbers in excess of these required for highly efficient HIV trans-infection by cells lines (Pohlmann et al., 2001b; Baribaud et al., 2002) suggests that this may not be the case. In fact, transient co-expression of wild-type DC-SIGNR with DC-SIGNR neck region variants did not reduce HIV trans-infection compared to cells expressing wild-type DC-SIGNR alone (Gramberg et al., 2006).

The polymorphism 336G in the DC-SIGN promoter reduces promoter activity by altering a binding site for the transcription factor SP1 and impacts the risk of acquiring dengue fever but not dengue haemorrhagic fever (Sakuntabhai
Notably, individuals carrying the polymorphism $-$336C were found to be more susceptible to HIV infection by the parenteral route while susceptibility to sexually transmitted HIV was not affected (Martin et al., 2004). This finding suggests that DC-SIGN-positive cells impact HIV spread if the virus directly enters the blood stream. In this scenario, high DC-SIGN expression levels seem to be beneficial for the host, provided that the $-$336G and $-$336C polymorphisms are identical.

6. LAGERIN ON LANGERHANS CELLS – BARRIER AGAINST HIV TRANSMISSION?

Langerhans cells in the top layer of the mucosal epithelium are among the very first cell types to be exposed to sexually transmitted HIV. It is, therefore, conceivable that HIV interactions with these cells might impact transmission efficiency. Indeed, Langerhans cells, which constitutively express CD4 but not DC-SIGN (Soilleux and Coleman, 2001), were shown to be permissive in *in vitro* and *ex vivo* systems and were found to be infected in HIV-positive individuals (Kawamura et al., 2005). Also, Langerhans cells were among the first cell types infected after intravaginal challenge of macaques (Hu et al., 2000), albeit independent studies reached different conclusions (Spira et al., 1996; Zhang et al., 1999). However, experimental infection of Langerhans cells is typically inefficient and mostly limited to CCR5-tropic viruses, probably due to absence or low expression of CXCR4 on immature Langerhans cells (Kawamura et al., 2005). Hence, it has been speculated that low susceptibility of Langerhans cells to HIV infection might account for the infrequent transmission of HIV upon sexual encounters (Kawamura et al., 2005).

Recently, a molecular mechanism has been identified by which susceptibility of Langerhans cells to HIV infection may be regulated. De Witte and colleagues demonstrated that langerin, a Langerhans cell-specific C-type lectin previously identified as a gp120 binding partner (Turville et al., 2002), promotes HIV uptake by cell lines expressing exogenous langerin and by Langerhans cells (de Witte et al., 2007) (see Table 28.2). Virus captured by langerin is transported to Birbeck granules, a Langerhans cell-specific intracellular compartment, where virions are degraded (de Witte et al., 2007). Since HIV Env may preferentially bind to langerin compared to CD4 (Turville et al., 2002), one can envision that langerin constitutes a powerful barrier against acquisition of HIV infection by the mucosal route. On the other hand, it has been reported that langerin-expressing 293 cells bind to soluble gp120 but not to HIV particles (Gramberg et al., 2008) and it can be speculated that particularly high langerin expression levels might be required for virus capture while reduced levels may be sufficient for gp120 binding. More importantly, however, it has recently been demonstrated that Langerhans cells were responsible for the vast majority of HIV dissemination driven by emigrants of infected human skin explants (Kawamura et al., 2008). Dissemination was dependent on availability of CCR5 but not C-type lectins and, out of three dendritic cell subsets analysed, only Langerhans cells were found to be infected (Kawamura et al., 2008). The potency of langerin as a potential barrier against sexually transmitted HIV therefore requires further assessment.

7. DC-SIGNR AND LSECtin – CONSEQUENCES OF HIV CAPTURE BY VASCULAR ENDOTHELIAL CELLS

Shortly after the discovery of DC-SIGN as an HIV binding factor on DCs, a related molecule, termed DC-SIGNR, has been discovered (Bashirova et al., 2001; Pöhlmann et al., 2001a;
The role of C-type lectins in HIV infection

Mummidi et al., 2001). The domain organization and carbohydrate specificity of DC-SIGNR is similar to that of DC-SIGN, albeit DC-SIGNR seems to exhibit exclusive specificity for high-mannose carbohydrates (Guo et al., 2004) and both lectins interact with much the same ligands. However, DC-SIGNR but not DC-SIGN augments infectious entry of West Nile virus with high efficiency and binding of virions to DC-SIGNR seems to depend on recognition of complex carbohydrates (Davis et al., 2006a,b). Despite similarities in structure and ligand specificity, DC-SIGN and DC-SIGNR differ in their expression patterns, with DC-SIGNR being expressed by liver and lymph node sinusoidal endothelial cells, placental macrophages and alveolar type II cells (Bashirova et al., 2001; Pöhlmann et al., 2001a; Jeffers et al., 2004; Gramberg et al., 2008) (see Table 28.2). On liver and lymph node sinusoidal endothelial cells, DC-SIGNR is co-expressed with the related C-type lectin LSECtin, which binds to soluble gp120 (Liu et al., 2004b; Gramberg et al., 2008). In addition, liver sinusoidal endothelial cells (LSECs) also express the HIV attachment factor CLEC-2 (Chaipan et al., 2006). Despite the expression of various attachment factors, a role for these endothelial cells in HIV infection is not obvious. However, evidence has been reported that LSECs are permissive to HIV infection in vitro (Steffan et al., 1992) and possibly in vivo. In addition, DC-SIGNR-mediated binding of soluble gp120 and Ebola glycoprotein to LSECs (Dakappagari et al., 2006) and facilitated hepatitis C virus transmission by LSECs (Lai et al., 2006), suggesting that DC-SIGNR on these cells may promote cis- and trans-infection of HIV and other pathogens. Cis-infection might result in constant virus release into the blood stream by infected LSECs, while LSEC-dependent trans-infection might promote HIV spread to T-cells in the blood or to susceptible Kupffer cells in the liver. It is at present unclear to what degree LSECtin contributes to HIV interactions with LSECs, since expression of this lectin on cell lines promotes binding of soluble gp120 but does not facilitate HIV capture and trans-infection (Gramberg et al., 2008). The reasons for this defect remain to be identified.

In contrast to DC-SIGN, the repeat region of DC-SIGNR is highly polymorphic and several studies assessed whether polymorphisms impact the risk of HIV infection (Lichterfeld et al., 2003; Liu et al., 2006; Wichukchinda et al., 2007; Rathore et al., 2008a). Overall, the results suggest that heterozygosity for DC-SIGNR may be associated with reduced risk of HIV infection, while homozygosity for the wild-type variant may increase the risk of acquiring the virus (Liu et al., 2006; Wichukchinda et al., 2007). Notably, one study observed these associations only in females (Wichukchinda et al., 2007), indicating that DC-SIGNR differentially impacts HIV susceptibility of females and males, an observation that deserves further investigation. How can a lectin expressed in liver and lymph node sinusoids impact the risk of acquiring HIV? Importantly, HIV present in low amounts in the blood may be concentrated in lymph nodes in a DC-SIGNR-dependent fashion. Moreover, DC-SIGNR transcripts were detected at sites of mucosal transmission (Liu et al., 2005), suggesting the DC-SIGNR may be involved in the very early events in HIV transmission.

8. CONCLUSIONS

Cellular lectins can modulate HIV infection in cell culture. DC-SIGN on DCs may impact dissemination of sexually transmitted HIV. However, the consequences of HIV interactions with DC-SIGN on DCs are more diverse than were initially appreciated. The majority of virus seems to be degraded for MHC presentation while a minor portion can be transmitted to T-cells. Transmission does not seem to require transport of virions into acidic intracellular compartments and may not involve preservation of viral infectivity by the transmitting cells. Whether the short-time window during
which bound virus can be transmitted to T-cells in a DC-SIGN-dependent fashion is sufficient to impact spread of sexually transmitted HIV is at present unclear. The observation that virus-loaded DCs are detectable in lymph nodes of vaginally challenged macaques as early as 30 minutes post challenge argues that trans-infection could indeed impact dissemination (Kawamura et al., 2005). The contribution of DC-SIGN to HIV transmission by DCs is still a matter of debate. It is becoming clear, however, that a contribution of DC-SIGN to dendritic cell-mediated HIV trans-infection might be at least in part due to the lectins’ involvement in the formation of infectious synapses (Hodges et al., 2007), specialized microenvironments that serve as conduits for HIV transfer to T-cells. Finally, langerin-dependent HIV degradation and interference of DC-SIGN with antibody-mediated HIV and simian immunodeficiency virus (SIV) neutralization are novel and so far little explored functions, which highlight the multiple consequences of HIV binding to cellular lectins. Future research areas and open questions for investigation are listed in the Research Focus Box.

**RESEARCH FOCUS BOX**

- Determination of whether HIV internalization into DCs is required for viral transmission to T-cells via the infectious synapse.
- Detailed analyses of the nature of the DC-SIGN-positive cells found in vivo: DC versus macrophage phenotype.
- Does DC-SIGN on platelets and B-cells promote viral spread in vivo or is bound virus mainly degraded?
- Does DC-SIGN promote SIV dissemination in the SIV-macaque model?
- Does DC-derived langerin block mucosal transmission of SIV in the macaque model?
- Role of the vascular endothelium in HIV dissemination?

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III. MICROBE–HOST GLYOSYLATED INTERACTIONS
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