Chapter 2
Innate Recognition of HIV-1 Glycans: Implications for Infection, Transmission, and Immunity

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Abstract Innate immune cells such as dendritic cells (DCs), Langerhans cells (LCs), and macrophages are equipped with pattern recognition receptors that sense invading pathogens and activate immune responses. Recognition of the heavily glycosylated human immunodeficiency virus type-1 (HIV-1) envelope proteins by innate immune cells is mediated through membrane-bound C-type lectin receptors (CLRs) that interact with the carbohydrate structures. In addition, soluble lectin receptors present in tissue or blood can also bind to HIV-1 glycans. Capture of HIV-1 through CLRs is crucial for antigen presentation and induction of antiviral immunity. Strikingly, HIV-1 has evolved to exploit these innate receptors to facilitate infection as well as promote transmission to $CD4^+$ T cells. The outcome of HIV-1-glycan recognition by the host is strongly dependent on the cell type and receptors involved. Identification of the molecular mechanisms and functional results of glycan-mediated recognition of HIV-1 is essential for a better understanding of HIV-1 pathogenesis and will lead to the development of novel antiviral strategies. Here, we discuss the current knowledge on recognition of HIV-1 through innate lectin receptors and the implications for viral replication, transmission, and immunity.

Keywords HIV-1 infection • HIV-1 dissemination • Glycans • Dendritic cells • Macrophages • C-type lectins • Innate immunity

Abbreviations

BDCA	Blood dendritic cell antigen
CLR	C-type lectin receptor

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CRD	Carbohydrate recognition domain
DC	Dendritic cell
DCIR	Dendritic cell immunoreceptor
DC-SIGN	Dendritic cell-specific ICAM-3 grabbing non-integrin
GALT	Gut-associated lymphoid tissue
gp	Glycoprotein
HIV-1	Human immunodeficiency virus type-1
IFN	Interferon
IL	Interleukin
ITIM	Immunoreceptor tyrosine-based inhibitory motif
LC	Langerhans cell
LSP1	Leukocyte-specific protein 1
MBL	Mannose-binding lectin
MHC	Major histocompatibility complex
MR	Mannose receptor
NLR	NOD-like receptor
PAMP	Pathogen-associated molecular pattern
pDC	Plasmacytoid dendritic cell
PRR	Pattern recognition receptor
RLR	RIG-I-like receptor
TLR	Toll-like receptor

2.1 Introduction

Human immunodeficiency virus type-1 (HIV-1), a lentivirus that belongs to the retrovirus family, is the causing agent of AIDS. Despite progress in HIV-1 treatment strategies, HIV-1 remains a worldwide problem. The main route of HIV-1 infection is via sexual transmission, and vaginal tissue and foreskin are important entry sites of HIV-1. The progression of initial HIV-1 infection into chronic infection consists of various events, including dissemination of HIV-1 to $CD4^+$ T cells throughout the body. $CD4^+$ T cell depletion is a hallmark of HIV-1 infection and when $CD4^+$ T cell numbers decline the body becomes vulnerable to life-threatening infections as well as cancer. Innate immune cells that reside within mucosal tissues, such as dendritic cells (DCs) and macrophages, are among the first cells that encounter HIV-1. The initial interaction between HIV-1 and DCs or macrophages within the mucosa is crucial for the induction of adaptive immune responses against the virus. However, growing evidence indicates that HIV-1 subverts recognition by innate immune cells for survival and dissemination. Recent studies indicate that recognition of HIV-1 glycans by DCs and macrophages through carbohydrate-binding proteins, CLRs, plays an important role in HIV-1 replication and transmission. The immunological function of innate immune cells and their specific expression of CLRs are key elements in determining their significance and relative contributions during HIV-1 infection. In addition, several soluble lectins might also

interact with gp120 and could be involved in HIV-1 infection. In this review we discuss the current knowledge on recognition of HIV-glycans by innate receptors and the consequences of these interactions.

2.2 Innate Immunity

The innate immune system forms the first line of defense against invading pathogens. Innate immune cells such as DCs and macrophages are strategically located in epithelial tissues throughout the body, where they sample the environment for invading pathogens. To detect invading pathogens, these innate immune cells express various groups of germline-encoded pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RNA helicases (known as RIG-I-like receptors, RLRs), and CLRs (Akira et al. 2006). These PRRs recognize highly conserved pathogen-associated molecular patterns (PAMPs) expressed by a wide range of microbes such as lipids, lipoproteins, proteins, nucleic acids, and carbohydrates. When PAMPs are recognized by PRRs, intracellular signaling cascades are activated resulting in expression of genes encoding for various elements of the inflammatory response including cytokines, chemokines, and type 1 interferons (IFNs) (Blander and Sander 2012). Transcription factors such as NF-κB are key mediators in the regulation of inducible gene expression in innate immune cells (Akira et al. 2006). Various PRRs are expressed at different subcellular compartments such as at the cell surface, in endosomes, and in the cytoplasm. Expression of different PRRs enables cooperative, synergistic signaling and the induction of specific immune responses against pathogens.

DCs are professional antigen presenting cells that bridge innate and adaptive immunity by activating naive T cells in lymph nodes (Banchereau and Steinman 1998). DCs are well equipped to capture and process pathogens. Upon recognition of pathogens via their PRRs, DCs are activated and migrate to the lymph nodes to activate antigen-specific T cells (Banchereau and Steinman 1998). In order to activate antigen-specific T cells, DCs present antigens on major histocompatibility complex (MHC) molecules (Steinman and Banchereau 2007). In addition, DCs provide signals for the differentiation of $CD4^+$ T cells into distinct T helper cell subsets that are required to fight the infection (Kapsenberg 2003). For example, interleukin (IL)-12 family members and type-1 IFNs are typical mediators that are expressed by activated DCs to instruct the development of T helper 1 cells (Kadowaki et al. 2000; Salomon and Bluestone 1998; Trinchieri 2003), whereas IL-4 and OX-40 ligand are associated with T helper 2 responses (Murphy and Reiner 2002). In addition, production of IL-10 and TGF-β is associated with the induction of various types of regulatory T cells (van der Aar et al. 2011). The array of PRRs triggered by pathogens determines the expression of cytokines, co-stimulatory molecules, and other cell surface molecules by DCs (Kapsenberg 2003). Thus, pathogen recognition is central to the induction of appropriate adaptive responses. DCs are a heterogeneous population of cells, and in the mucosa different DC subsets can be distinguished. Langerhans cells (LCs) form a dense network in the upper mucosal layer, whereas

submucosal DCs reside in the underlying submucosal layer (Banchereau and Steinman 1998; Valladeau and Saeland 2005). LCs and submucosal DCs express specific PRR profiles and respond differentially to pathogens (Valladeau and Saeland 2005; van der Aar et al. 2007). Another DC subset is the plasmacytoid DC (pDC), which is abundant in blood (Ito et al. 2005).

In contrast to DCs, macrophages are resident tissue cells that do not migrate upon activation (Gordon and Taylor 2005). Macrophages are highly phagocytic and their main function is capture invading pathogens for intracellular enzymatic degradation. Upon pathogen recognition, macrophages also secrete inflammatory cytokines and chemokines to initiate local inflammation and attract other immune cells from the blood into the tissue.

2.3 HIV-1 Binding and Infection of Innate Immune Cells

The first essential step in the HIV-1 replication cycle is interaction with the host cell surface. Viral entry is dependent on the binding of the HIV-1 envelope glycoprotein gp120 with the entry receptor CD4 and co-receptors CCR5 or CXCR4 on the cell surface of host cells. DCs and macrophages in vaginal mucosa, oral mucosa, and male foreskin are among the first cells to encounter HIV-1. DCs and macrophages express CD4 and CCR5 or CXCR4 and are susceptible to HIV-1 infection (de Jong et al. 2010; Gringhuis et al. 2010; Laurence 1993). In vivo, infection of macrophages and DCs is observed soon after exposure to HIV-1 (Collins et al. 2000; Hladik et al. 2007; Hu et al. 2000; Spira et al. 1996), suggesting that these innate immune cells are early target cells for HIV-1.

HIV-1 virions interact with DCs and macrophages through entry receptors, but are also captured via PRRs. A characteristic feature of HIV-1 gp120 is its densely glycosylated surface. Approximately half of the molecular mass of gp120 consists of N-linked glycans (Barin et al. 1985). In general, complex carbohydrates are present on the variable loops of gp120 and often differ among HIV-1 isolates. In contrast, gp120 glycans of a high-mannose or hybrid character located in the less-variable regions of the protein are usually conserved among divergent HIV-1 isolates (Sanders et al. 2002). These glycans play an essential role in the proper folding of gp120 in the endoplasmic reticulum (Li et al. 1993) and protect the protein from proteolytic degradation and shield peptide epitopes from recognition by antibodies and T cells (Scanlan et al. 2007). The human immune system takes advantage of the presence of the dense glycan shield that surrounds HIV-1 which can be recognized as PAMPs by a specific family of PRRs that bind carbohydrates: the CLRs.

2.4 HIV-1 Recognition by C-Type Lectin Receptors

Lectin receptors recognize carbohydrate structures via one or more carbohydrate recognition domains (CRDs). The CLR family is classified based on the presence of a conserved structural motif in their CRDs (Drickamer 1999). Although originally

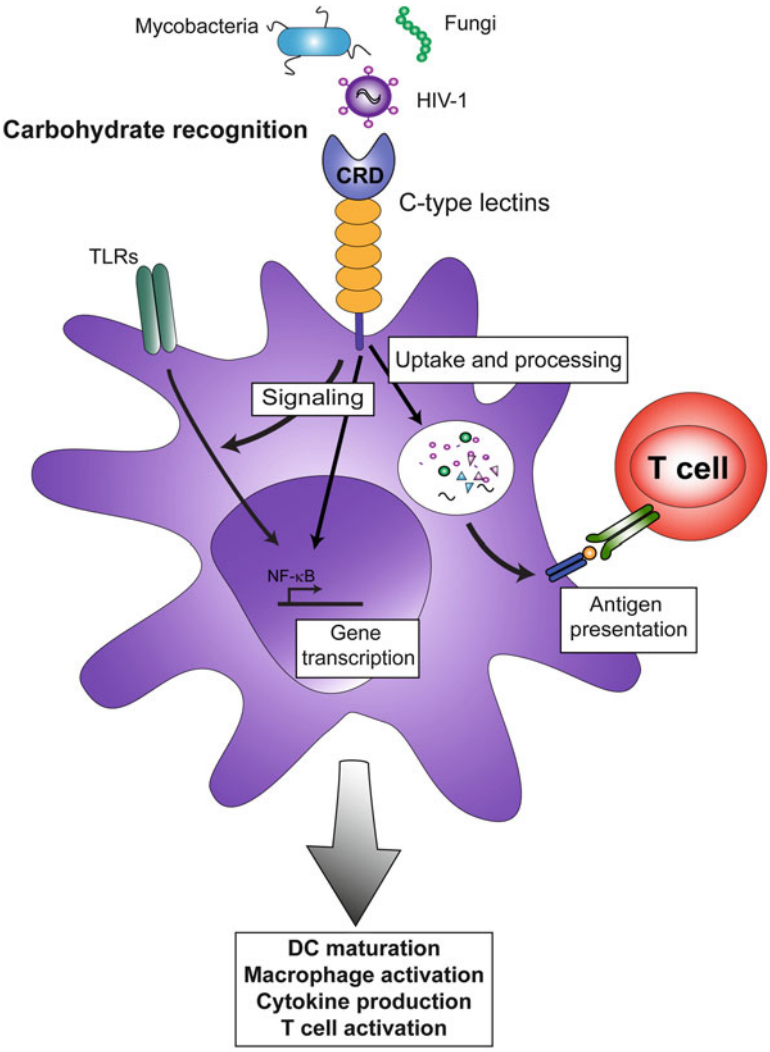

Fig. 2.1 Function of C-type lectin receptor (CLRs) in innate immunity. CLRs are pathogen recognition receptors that interact with specific glycan structures on pathogens, such as mannose, fucose, and glucan structures. CLRs expressed by DCs and macrophages mediate internalization of pathogens. Internalized pathogens are subsequently degraded or processed for antigen presentation on MHC molecules to activate specific T cells. Pathogen recognition by CLRs induces various intracellular signaling processes that lead to specific cytokine production and immunomodulation. Some CLRs modulate TLR signaling whereas other CLRs elicit signaling independently of TLR activation

the term C-type lectin referred to calcium-dependent carbohydrate recognition, the C-type lectin family now also includes proteins that do not require calcium for binding. CLRs exist both as soluble and transmembrane proteins and mediate a diverse range of functions: they are involved in a variety of cell–cell interactions but it is becoming evident that this family of receptors are important PRRs (Fig. 2.1).

Recognition of pathogens by innate immune cells through CLRs generally leads to internalization and endosomal degradation (van Kooyk and Rabinovich 2008) (Fig. 2.1). As such, C-type lectin-mediated antigen uptake is associated with efficient antigen presentation and immune stimulation by DCs (Bozzacco et al. 2007; Tacken et al. 2005). Importantly, differential CLR triggering by pathogens induces distinct immune responses through activation of distinct gene transcription profiles (Fig. 2.1). CLRs such as dectin-1 and dectin-2 directly induce gene expression by activating transcription factors belonging to the NF-κB family (Gringhuis et al. 2007, 2009b; Meyer-Wentrup et al. 2009; Rogers et al. 2005). In contrast, several CLRs, including dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) and blood dendritic cell antigen-2 (BDCA2), induce signaling pathways that modulate TLR-induced gene expression, but do not induce gene expression in the absence of signaling via other PRRs (Fig. 2.1).

CLRs induce signaling via various cellular mechanisms; BDCA2 and dectin-2 induce signaling through immunoreceptor tyrosine-based activation motif-containing adaptor molecules (Bates et al. 1999; Cao et al. 2007; Sato et al. 2006; Yamasaki et al. 2008), whereas DC-SIGN and dendritic cell immunoreceptor (DCIR) activate protein kinases or phosphatases that either directly or indirectly interact with their cytoplasmic domains (Gringhuis et al. 2007, 2009a; Rogers et al. 2005).

Different CLRs have distinct carbohydrate specificities, which are related to the amino acid sequences in their respective CRDs (Cambi et al. 2005; Robinson et al. 2006). CLRs expressed by DCs and macrophages primarily interact with pathogens through the recognition of mannose, fucose, and glucan carbohydrate structures. The HIV-1 gp120 envelope protein has a particularly high proportion of mannose structures (Sanders et al. 2002), which allows recognition of HIV-1 by mannose-recognizing CLRs. Genetic variations in genes encoding CLRs have been linked with increased or decreased risk of HIV-1 infection and disease progression (Boily-Larouche et al. 2012; Sobieszczyk et al. 2011), indicating that these receptors play an essential role during HIV-1 infection. Several CLRs recognize mannose structures expressed on gp120 including DC-SIGN (Cassol et al. 2013; Geijtenbeek et al. 2000; Kwon et al. 2002), langerin (de Jong et al. 2008; de Witte et al. 2007), the mannose receptor (MR) (Nguyen and Hildreth 2003), and BDCA2 (Martinelli et al. 2007) (Table 2.1). Recently, DCIR has also been shown to recognize gp120, however, the carbohydrate structures that are recognized remain elusive (Lambert et al. 2008, 2011). These CLRs are expressed at the cell surface of DCs and macrophages and enable recognition and capture of HIV-1 prior to infection.

HIV-1 capture by CLRs mediates internalization and degradation of the virus and results in antigen presentation for the induction of adaptive immunity (Moris et al. 2006). Moreover, internalization of HIV-1 by CLRs results in the triggering of endosomal TLRs. HIV-1-derived ssRNA can be recognized by endosomal TLR7 and TLR8 (Heil et al. 2004). In humans TLR8 seems to be an important receptor for recognition of HIV-1 and subsequent induction of immune responses; uptake of HIV-1 by DCs into endosomes triggers TLR8, via ssRNA, resulting in activation and nuclear translocation of transcription factor NF-κB (Gringhuis et al. 2010).

Table 2.1 Lectins of the innate immune system that interact with HIV-1

Lectin		Found on	HIV specificity	Possible role in HIV-1 infection
Transmembrane C-type lectins	DC-SIGN	DCs, macrophages	Mannose structures	Enables replication in DCs Facilitates transmission to $CD4^+$ T cells Internalizes HIV-1 for antigen presentation Modulates TLR-induced cytokine production
	DCIR	DCs	Not determined	Facilitates transmission to T cells Enhances HIV-1 replication
	Langerin	Langerhans cells	Mannose structures	Internalizes HIV-1 for degradation
	MR	Macrophages, DCs, pDCs	Mannose structures	Facilitates transmission to $CD4^+$ T cells Internalizes HIV-1 for degradation
	BDCA2	pDCs	Not determined	Suppresses IFN production in response to HIV-1
Soluble C-type lectins	MBL	In serum	Mannose structures	Opsonizes HIV-1 Inhibits DC-mediated transmission of HIV to T cells
	Surfactant protein D	Vaginal fluid, genitourinary tract, oral cavity and the gastrointestinal tract, lung fluid	Mannose structures	Neutralizes HIV-1 and inhibited direct infection of $CD4^+$ cells Enhances binding of HIV-1 to DCs Enhance DC-mediated transfer of HIV-1 to T cells
	Surfactant protein A	Vaginal fluid, genitourinary tract, oral cavity and the gastrointestinal tract, lungs	Mannose structures	Neutralizes HIV-1 and inhibits direct infection of $CD4^+$ cells Enhances binding of HIV-1 to DCs Enhances DC-mediated transfer of HIV-1 to T cells
Galectins	Galectin-1	GALT, endothelial cells, activated T cells, activated B cells, macrophages and follicular DCs	β-galactose	Enhances HIV-1 binding to $CD4^+$ cells Promotes HIV-1 infection

Inhibition of TLR7 recognition of HIV-1 did not affect NF-κB activation (Gringhuis et al. 2010), indicating that TLR8 plays a role in HIV-1 recognition. Thus, CLR-mediated recognition and uptake of HIV-1 by DCs and macrophages are important for the induction of innate and adaptive immunity against HIV-1. However, new insights indicate that HIV-1 subverts the innate recognition by CLRs to enhance transmission and replication. The outcome of HIV-1-glycan recognition depends on the CLRs and innate cells that are involved (Table 2.1 and Fig. 2.2). Expression of several lectins is confined to specific subsets of DCs, e.g., langerin is specifically expressed by LCs, while pDCs selectively express BDCA-2. Furthermore, submucosal DCs express high levels of DC-SIGN and macrophages express very high levels of MR (Gazi and Martinez-Pomares 2009). DC-SIGN, DCIR, and MR promote infection of innate immune cells as well as transmission of HIV-1 to T cells (Arrighi et al. 2004; Bates et al. 1999; Geijtenbeek et al. 2000; Nguyen and Hildreth 2003), whereas langerin seems to play a protective role against HIV-1 infection and dissemination (de Jong et al. 2008; de Witte et al. 2007). In the following sections we will discuss HIV-1 recognition by different DC subsets and macrophages via CLRs and the importance of these interactions to HIV-1 replication, HIV-1 dissemination, and in the induction of anti-viral immunity.

2.5 DC Binding of HIV-1 Enhances Infection and Transmission

DCs are potent antigen presenting cells that rapidly migrate to the lymph nodes upon pathogen recognition to activate T cells. Therefore, DCs are thought to play an important role in the early events of HIV-1 dissemination by transporting virus from the peripheral mucosa to $CD4^+$ T cell-rich lymph nodes. DCs mediate transmission of HIV-1 to $CD4^+$ T cells via two different mechanisms (Turville et al. 2004) (Fig. 2.2). Within 24 h of exposure to HIV-1, DCs transmit captured virus in the absence of productive replication, which is referred to as *in trans*-infection (Dong et al. 2007). Since DCs become infected by HIV-1 (Collins et al. 2000; de Jong et al. 2010; Gringhuis et al. 2010; Hladik et al. 2007; Hu et al. 2000; Spira et al. 1996), de novo produced viruses can also be transmitted to $CD4^+$ T cells *in cis* (Dong et al. 2007), which is more important several days after initial infection. DC-mediated infection of $CD4^+$ lymphocytes is more efficient than infection by cell-free virus (Geijtenbeek et al. 2000). DCs carrying infectious virus are detected in draining lymph nodes within hours in rhesus macaques exposed to SIV (Hu et al. 2000; Ribeiro Dos et al. 2011; Spira et al. 1996), supporting a role in HIV-1 transmission. This is further supported by observations in vivo of highly active replication of HIV-1 within lymphoid tissue in the presence of DC markers (Frankel et al. 1996, 1997; Lambert et al. 2008).

HIV-1 capture by mucosal DCs is facilitated by the C-type lectin DC-SIGN. DC-SIGN binds HIV-1 gp120 through recognition of mannose structures. DC-SIGN has a cytoplasmic domain, a transmembrane domain, a neck region, and a

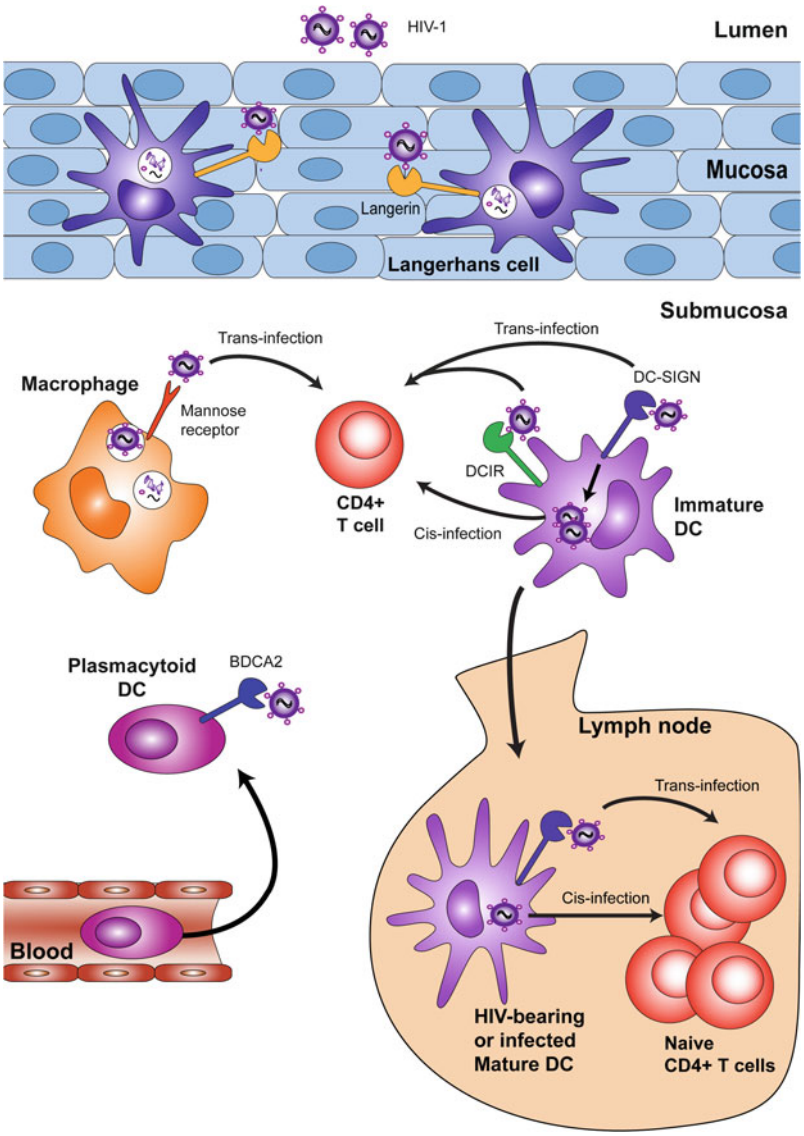

Fig. 2.2 Recognition of HIV-1 through CLR expression by different subtypes of DCs and macrophages in mucosal tissues and their role in HIV-1 dissemination. LCs in the mucosa bind HIV-1 glycans via Langerin, and promote HIV-1 capture and degradation. Submucosal DCs bind HIV-1 gp120 glycans via DC-SIGN and DCIR. Submucosal macrophages bind HIV-1 gp120 mostly via MR DC-SIGN, DCIR, and MR promote transmission of HIV-1 to $CD4^+$ T cells by DCs and macrophages, which is referred to as *in trans* transmission. Whereas macrophages mainly facilitate spreading to local T cells, DCs migrate to the lymph nodes where HIV-1 can be transmitted to large numbers of $CD4^+$ T cells. DC-SIGN signaling facilitates DC infection. Infected DCs can transmit de novo produced virus *in cis* to T cells. Internalization of HIV-1 by macrophages via MR results in viral degradation and decreases HIV-1 infectivity. The contribution of DCIR and MR in HIV-1 infection and *cis* transmission remains elusive. pDCs can bind HIV-1 via BDCA2 but the consequences of HIV-1 binding via this CLR are largely unknown

carbohydrate-binding lectin domain. The cytoplasmic domain of DC-SIGN contains motifs involved in receptor internalization and signaling (Azad et al. 2008). DC-SIGN polymorphisms have been associated with differences in HIV-1 susceptibility (Koizumi et al. 2007; Martin et al. 2004). Recent data indicate that DC-SIGN binding is the molecular basis for HIV-1 infection and transmission by DCs. Moreover, recently it was described that the C-type lectin DCIR may also be involved in HIV-1 transmission by DCs.

2.5.1 DC-SIGN Facilitates HIV-1 Transmission

Although, some studies suggest that DC-mediated transmission of HIV-1 by DCs can occur independently of DC-SIGN (Boggiano et al. 2007; Gummuluru et al. 2003), many studies indicate that DC-mediated *trans*-infection of $CD4^+$ T cells by HIV-1 is mainly facilitated via DC-SIGN (Arrighi et al. 2004; Cavrois et al. 2007; Geijtenbeek et al. 2000; Kwon et al. 2002) (Fig. 2.2).

As reviewed in Chap. 1, the composition of glycans on gp120 of different HIV-1 strains is highly heterogeneous. The particular composition of gp120 between different HIV-1 strains may play a decisive role in DC-SIGN binding and transmission efficiency. A recent study showed the importance of the composition of HIV-1 glycans for DC-SIGN-mediated transmission (van Montfort et al. 2011). Virions carrying gp120 with higher numbers of oligomannose-type glycans are more efficiently endocytosed through DC-SIGN and more proficiently processed for antigen presentation than HIV-1 containing gp120 with heterogeneous glycans. The transmission of oligomannose-enriched HIV-1 was relatively inefficient. Thus, the expression of oligomannose by HIV-1 enhances capture of DC-SIGN and transmission, but too much oligomannose negatively affects transmission by enhancing viral degradation.

Currently, the mode of DC-SIGN-mediated *trans*-infection is not completely clear. DC-SIGN-bound virions remain infectious for days allowing transmission independent of DC infection (Geijtenbeek et al. 2000; Kwon et al. 2002). It has been proposed that primarily surface-bound HIV-1 virions are transmitted by DCs and that increased capture at the surface by DC-SIGN is sufficient to enhance transmission to $CD4^+$ T cells (Cavrois et al. 2007). An LL motif in the cytoplasmic tail of DC-SIGN facilitates ligand endocytosis by DC-SIGN (Engering et al. 2002). One study showed that the LL motif in the cytoplasmic tail of DC-SIGN does not contribute to HIV-1 transmission by DC-SIGN-expressing cell lines (Burleigh et al. 2006), indicating that uptake is not required for HIV-1 *trans*-infection. In line with these findings, the HIV-1 protein Nef upregulates DC-SIGN surface expression by inhibiting its endocytosis, which results in increased *in trans*-infection of $CD4^+$ T cells (Sol-Foulon et al. 2002). Moreover, DC-SIGN-mediated uptake has been associated with degradation of HIV-1 either by targeting to the proteasome by DC-SIGN-mediated activation of leukocyte-specific protein

1 (LSP1), an F-actin-binding protein or by routing into the endosomal pathway, which negatively influenced HIV-1 transmission (Moris et al. 2004; Smith et al. 2007; van Montfort et al. 2011). In contrast, several studies indicate that intracellular vesicular transport is required to intracellular sites of DC-T cell contact, the infectious synapses, is required for transmission *in trans* (Kwon et al. 2002; McDonald et al. 2003; Yu et al. 2008). At the T cell site of the infectious synapse, CD4 molecules and co-receptors are concentrated, resulting in the establishment of a microenvironment ideally suited for HIV-1 *trans*-infection. It has been proposed that DC-SIGN-mediated uptake targets HIV-1 into specific compartments that do not belong to the classical endosomal pathway, where the virus is protected from degradation and antibody recognition (Kwon et al. 2002; Yu et al. 2008). The precise routing of internalized HIV-1 is however not clear. Garcia et al. suggested that HIV-1 is internalized into deep intracellular $CD81^+$ compartments for trafficking to the infectious synapse (Garcia et al. 2005), whereas Yu et al. proposed that HIV-1 is internalized into surface-accessible $CD81^+$ vesicles, contiguous with the plasma membrane (Yu et al. 2008). Another suggested pathway is delivery of infectious virus to the infectious synapse via intracellular endocytic vesicles known as exosomes (Wiley and Gummuluru 2006). The infectious synapse resembles the immunological synapse, but it forms independent of antigen presentation of MHC–TCR interactions (Piguet and Sattentau 2004). Notably, DC-SIGN binding by HIV-1 has been shown to be important for DC-T cell infectious synapse formation and transport of internalized HIV-1 virions to the synapse (Arrighi et al. 2004; Bennett et al. 2009; Hodges et al. 2007; Nikolic et al. 2011). Within an hour of HIV-1 exposure, the membrane of DCs starts to form extensions at the entire border of the cell. HIV-1-mediated DC-SIGN signaling leads to activation of Src kinases and downstream activation of the small GTPase Cdc42. Cdc42 activation enables actin-dependent transport of HIV-1 virions to these extensions (Nikolic et al. 2011). Additionally, DC-SIGN-mediated activation of the guanine exchange factor LARG induces cytoskeleton rearrangements that allow formation of the virological synapse (Hodges et al. 2007).

Collectively, these studies show that HIV-1 utilizes DC-SIGN to enhance transmission to $CD4^+$ T cells. Notably, DC-SIGN-mediated transmission seems to require steps beyond simple binding and sequestration of the virus. DC-SIGN signaling is subverted by HIV-1 to modulate cytoskeleton processes for uptake of HIV-1, intracellular trafficking, and for the formation of infectious synapses. Although the exact mechanisms that underlie DC-SIGN-mediated HIV-1 transmission remains to be elucidated, the trafficking of captured HIV-1 seems to be a crucial step. Factors such as glycan composition (van Montfort et al. 2011) and activation status of the DC (Frank et al. 2002; Wang et al. 2007) may be important in determining the routing of HIV-1 upon DC-SIGN binding. Whereas routing into endosomes and proteasome results in degradation of HIV-1 virions, routing of HIV-1 into specific vesicles preserves viral infectivity and mediate transmission. Further studies of the significance of the proposed transmission pathways will benefit our understanding of HIV-1 pathogenesis.

2.5.2 DC-SIGN-Mediated Signaling Is Required for Infection of DCs

DC-SIGN was shown to facilitate infection of DCs by HIV-1, and thereby transmission of *in cis* to T cells, by enhancing viral attachment and increasing exposure to entry receptors (Hijazi et al. 2011; Lekkerkerker et al. 2004) (Fig. 2.2). HIV-1 is known to only carry relatively few Env molecules and binds CD4 with relatively weak avidity (Fouts et al. 1997), and co-expression of DC-SIGN, CD4, and CCR5 in cell lines results in increased infection with HIV-1 (Lee et al. 2001; Trumpfheller et al. 2003). Importantly, signaling induced via DC-SIGN is required for HIV-1 replication in DCs (Gringhuis et al. 2010). After DNA integration in the host genome, HIV-1 depends on host and viral factors for the initiation and elongation of its transcription. Host transcription factors such as Sp1 and NF-κB are required to initiate HIV-1 transcription by RNA polymerase II (Perkins et al. 1993). HIV-1 uptake by DCs results in recognition of HIV-1 single-stranded RNA (ssRNA) by endosomal TLR8. ssRNA-induced TLR8 triggering leads to activation and nuclear translocation of NF-κB dimers containing p65 (Gringhuis et al. 2010). Induction of p65 binding to the long terminal repeat (LTR), the promoter/enhancer of HIV-1, results in subsequent recruitment of cyclin-dependent kinase 7 (CDK7) to the LTR. CDK7 then mediates phosphorylation of RNA polymerase II on Ser5 within its C-terminal domain repeats, a requirement for transcription initiation by RNA polymerase II of the integrated HIV-1 genome. However, transcription initiation upon TLR8 triggering does not lead to full-length HIV-1 transcripts (Gringhuis et al. 2009a), attenuating de novo synthesis of viral proteins. Full-length HIV-1 transcription requires additional DC-SIGN signaling for the recruitment of host transcription-elongation factors (Gringhuis et al. 2009a). The interaction of gp120 with DC-SIGN results in phosphorylation of p65 at Ser276 through Raf-1 signaling. Positive transcription elongation factor-β (pTEF-β) is then recruited to Ser276-phophorylated p65 bound at the LTR (Gringhuis et al. 2009a). pTEF-β next phosphorylates RNA polymerase II on Ser2 within its C-terminal domain repeats, thereby fully potentiating RNA polymerase II to induce transcriptional elongation and thus production of viral proteins. After generation of Tat protein, Tat is able to recruit pTEF-β to the LTR, which provides a positive feedback loop for sustained transcription of HIV-1 (Gringhuis et al. 2009a). Notably, other pathogens that can bind to DC-SIGN and induce Raf-1 activation, such as mycobacteria and fungi, can further promote HIV-1 transcription (Gringhuis et al. 2009a, 2010). Indeed, co-infection with *Mycobacterium tuberculosis* and *Candida albicans* has been shown to increase HIV-1 replication (Lawn 2004; Ranjbar et al. 2009; Toossi 2003). Thus, DC-SIGN is indispensible for HIV-1 infection of DC-SIGN$^+$ DCs. HIV-1 not only exploits binding to DC-SIGN to increase binding to the entry receptors, but also hijacks TLR8- and DC-SIGN-induced signaling for the activation of host factors that are required for replication and productive infection. Knowledge on HIV-1 replication in DCs not only provides insight on HIV-1 infection and pathogenesis, but can also be valuable for anti-HIV treatments. Although HIV-1 replication in DCs is less productive than replication in

$CD4^+$ T cells, infection of DCs may be important virus propagation and dissemination (Dong et al. 2007). Targeting specific host signaling involved in early HIV-1 replication can provide a novel antiviral strategy. Importantly, vaccines containing HIV-1 gp120 antigens to stimulate production of antibodies in vivo are being investigated. However, as observed with co-infections, gp120-induced DC-SIGN signaling may have adverse effects on antiviral efficiency by enhancing HIV-1 replication in DCs and transmission.

2.5.3 The Role of DCIR in HIV-1 Transmission

DC-SIGN is the most studied CLR regarding HIV-1, but other lectins have been shown to be important in viral transmission and infection. DCIR is expressed at high levels on DCs (Bates et al. 1999), and this surface molecule was recently found to promote transmission of infectious virus to $CD4^+$ T cells (Lambert et al. 2008) (Fig. 2.2). DCIR acts as an attachment factor for HIV-1 on DCs and contributes to *trans*- and *cis*-infection pathways (Lambert et al. 2008). Currently, it is unknown how HIV-1 is bound by DCIR; however, an association between the CRD of DICR and gp120 is likely to be responsible for the attachment to HIV-1 (Lambert et al. 2008, 2011). The involvement of the CRD domain of DCIR in virus capture is also indicated by reduced HIV-1 binding and transfer in the presence of a polyclonal antibody that is specific for the single CRD in the extracellular COOH-terminal end of DCIR (Lambert et al. 2008).

DCIR is the only CLR expressed on DCs containing an intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM). Recently, it was shown that DCIR-induced ITIM-associated signal transduction can enhance HIV-1 infection in DCIR-expressing cells (Lambert et al. 2011). It is still unclear by what mechanisms DCIR signaling enhances HIV-1 infection. The relative contribution of DCIR and DCIR-induced signaling during HIV-1 infection remains to be established.

2.6 A Protective Role of Langerhans Cells Against HIV-1 Through Langerin Expression

LCs are located within the top layers of the oral and anogenital mucosa and are most likely the first cells to come into contact with HIV-1 after sexual transmission (Fig. 2.2). Mucosal LCs express HIV-1 entry receptors and have been identified as early cellular targets for HIV-1 (Hladik et al. 2007; Hu et al. 2000; Patterson et al. 2002). However, infection of immature LCs is very inefficient (de Witte et al. 2007; Hladik et al. 2007). LCs do not express DC-SIGN and bind HIV-1-derived gp120 mannose glycans predominantly via langerin (de Witte et al. 2007; Turville et al. 2002). In human, langerin is exclusively expressed by LCs (Valladeau et al. 2000). HIV-1 captured by LCs through langerin is rapidly internalized (de Witte et al. 2007;

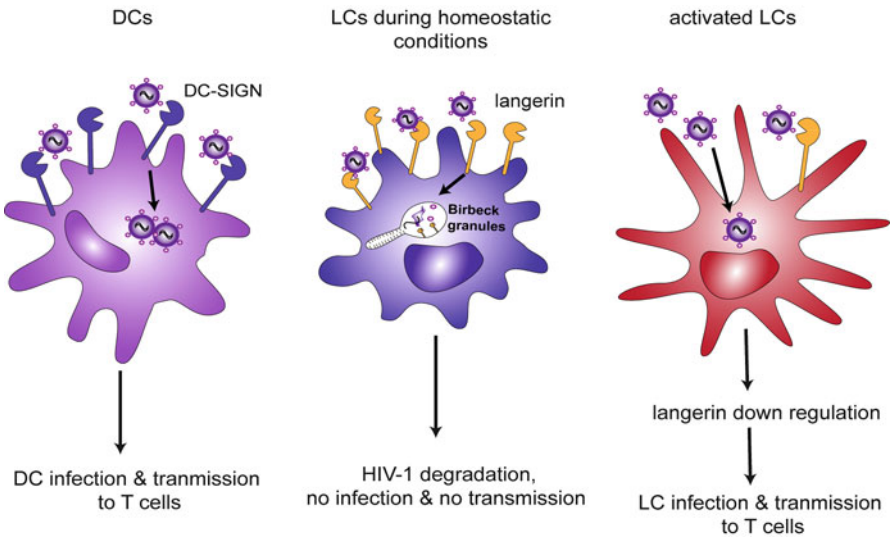

Fig. 2.3 LCs and DCs interact differently with HIV-1. DCs bind HIV-1 through DC-SIGN, which mediates HIV-1 infection of DCs and facilitates transmission to $CD4^+$ T cells. LCs interact with HIV-1 through langerin but this leads to rapid internalization of the virus into Birbeck granules. Langerin interaction with HIV-1 prevents infection and inhibition of HIV-1 transmission to T cells and results in HIV-1 degradation. LC activation by TLR agonists decreases langerin expression and results in infection of LCs by HIV-1 and consequently enhances HIV-1 transmission to T cells

Hladik et al. 2007) and directed into intracellular Birbeck granules for degradation (de Witte et al. 2007) (Fig. 2.3). Immature human LCs, which express high levels of langerin, do not become infected and also do not transmit HIV-1 to T cells (de Witte et al. 2007; Fahrbach et al. 2007). Blocking langerin by neutralizing antibodies enhances transmission of HIV-1 to T cells by LCs (de Witte et al. 2007). Thus, despite the similarity in gp120 binding, the role of langerin on LCs is very different from that of DC-SIGN on DCs (Fig. 2.3). This indicates that efficient binding of HIV-1 at the cell surface is not sufficient per se to enhance transmission and infection.

Upon LC maturation, e.g., through TLR triggering, langerin is downregulated, and in line with this observation, activated LCs are more efficiently infected and also transmit HIV-1 to T cells (de Witte et al. 2007; Fahrbach et al. 2007; Kawamura et al. 2001) (Fig. 2.3). Activation of LCs, and subsequent HIV-1 infection and transmission, can be induced for instance by TLR antagonists or co-infections. Bacteria and fungi increase replication and transmission of HIV-1 by matured LCs via induction of TNF or TLR triggering that lead to LC maturation (de Jong et al. 2008). This may partly explain the increased risk of HIV-1 infection in persons carrying other sexually transmitted diseases. Moreover, Herpes simplex virus-2 infection decreases langerin expression and thereby interferes with the protective role of LCs (de Jong et al. 2010). Although it has been reported that mature LCs can transmit HIV-1

independent of infection (Ballweber et al. 2011; de Jong et al. 2008; Hladik et al. 2007), infected LCs are more efficient in HIV-1 transmission (de Jong et al. 2008; Kawamura et al. 2001). Thus, the protective function of LCs is at least partly mediated by the recognition of langerin with HIV-1 gp120.

Langerin contains an intracellular proline-rich signaling motif (Valladeau et al. 2000) that probably functions as a docking site for signal transduction proteins (Ren et al. 1993). Association of LSP1 with langerin, similar to DC-SIGN, has been reported (Smith et al. 2007). However, currently it is unclear whether langerin signaling is involved in HIV-1 infection.

Collectively, these findings suggest that langerin expression by LCs constitutes a defense mechanism against HIV-1 invasion. However, activation of LCs breaches their innate tolerance to HIV-1. Therefore, the protective function of LCs may be particularly important during viral infection of healthy epithelium, whereas in traumatized or inflamed mucosa both LCs and DC-SIGN$^+$ submucosal DCs can be infected and/or transfer HIV-1 to activated CD4$^+$ T cells. The function of langerin needs to be further elucidated in vivo.

2.7 Recognition of HIV-1 Glycans by pDCs

The role of pDCs during HIV-1 infection is controversial. pDCs express CD4, CXCR4, and CCR5, and can become infected with HIV-1 (Fong et al. 2002; Patterson et al. 2001; Smed-Sorensen et al. 2005). Indeed, HIV-1-infected pDCs can be found in the vaginal mucosa during acute and chronic infection (Centlivre et al. 2011) and can accommodate HIV-1 replication (Reeves et al. 2012). However, whereas myeloid DCs facilitate HIV-1 transmission and increase infection of CD4$^+$ T cells, pDCs were reported to inhibit HIV-1 replication in T cells through secretion of large amounts of IFNα in response to the virus (Groot et al. 2006; Smed-Sorensen et al. 2005). Type I IFNs can inhibit replication of HIV-1 by reducing integration and reverse transcriptase activity (Hosmalin and Lebon 2006). Recent evidence suggests that IFNα production by pDC is a key factor in suppressing viral replication during acute infection, but that during chronic infection IFNα actually impairs immune functions and contributes to HIV-1 pathogenesis (Campillo-Gimenez et al. 2010; Mandl et al. 2008).

Binding of HIV-1 to pDCs was thought to be only mediated by binding to CD4 (Schmidt et al. 2005), but recent studies indicate that HIV-1 is also bound by pDCs through interaction of gp120 glycans with BDCA2 (Martinelli et al. 2007) (Table 2.1 and Fig. 2.2). BDCA2 is exclusively expressed on human pDCs (Dzionek et al. 2000). In addition to BDCA2, pDCs also express low levels of MR, which also binds to high-mannose oligosaccharides of HIV-1 gp120 (Nguyen and Hildreth 2003). Currently, it is unknown whether CLR recognition of HIV-1 plays a role in HIV-1 replication or transmission, but there are indications that CLR-mediated binding of HIV-1 is important for IFNα production by pDCs. The actual induction of IFNα production in response to HIV-1 occurs via triggering of endosomal TLR9

or TLR7 by internalized virions (Martinelli et al. 2007; O'Brien et al. 2011). Recognition of viral envelopes by MR was shown to be important for HIV-1 internalization by pDC (Milone and Fitzgerald-Bocarsly 1998) and blocking MR inhibited HIV-1-induced IFNα production by pDCs (Milone and Fitzgerald-Bocarsly 1998), indicating that internalization of HIV-1 via MR is required for TLR triggering and IFN production. In contrast, although anti-BDCA2 antibodies are rapidly internalized by pDCs (Dzionek et al. 2001), binding of gp-120 via BDCA-2 was shown to suppress IFN-α/β production (Dzionek et al. 2001). Recent studies indicate that BDCA-2 induces signaling that interferes with TLR9 activation (Martinelli et al. 2007). Thus, HIV-1 may hijack recognition via BDCA2 to suppress immunity. Several groups have suggested that type I IFN production by blood pDCs is attenuated during both acute and chronic infection (Kamga et al. 2005; Sachdeva et al. 2008), whereas others have indicated that circulating pDCs in patients with HIV show a normal or increased type I IFN response (Lehmann et al. 2008). Additional studies will be necessary to understand the consequences of gp120-glycan recognition by pDCs during HIV-1 infection.

2.8 Recognition of HIV-1 by Macrophages Through MR and DC-SIGN

Macrophages express the receptors required for HIV-1 entry and are susceptible to HIV-1 infection (Verani et al. 2005). Infected macrophages are detected in the female genital tract soon after exposure to HIV-1 (Collins et al. 2000). Thus, similar to DCs, macrophages in the submucosa can be early cellular targets for HIV-1. The main function of macrophages is to trap and degrade invading pathogens (Gordon and Taylor 2005). Because macrophages do not migrate after activation, their role in HIV-1 dissemination is thought to be less prominent than for DCs. However, macrophages may play an important role in local HIV-1 dissemination (Meltzer et al. 1990) (Table 2.1 and Fig. 2.2). Macrophages produce cytokines and chemokines that attract T cells and locally interact with activated T cells for regulation of adaptive immunity (Gordon 2003). It was shown that macrophages can transmit newly synthesized virus to $CD4^+$ T cells (Carr et al. 1999; Carter and Ehrlich 2008), but can also mediate infection of T cells in the absence of de novo virus production (Sharova et al. 2005). Virus assembly in macrophages occurs in $CD81^+$ cytoplasmic vesicles, which exhibit the characteristics of multivesicular bodies or late endosomes. Virions in these cytoplasmic vesicles were shown to retain infectivity for time intervals up to 6 weeks (Sharova et al. 2005). Notably, HIV-infected macrophages are relatively resistant to cytopathic effects of the virus and are thought to serve as an important reservoir during chronic infection.

Macrophages express high levels of MR and the interaction of HIV-1 glycans with this CLR accounts for a large part of the binding capacity (Nguyen and

Hildreth 2003; Trujillo et al. 2007). However, HIV-1 binding to MR does not lead to productive infection (Trujillo et al. 2007). Recently an alternative internalization route of HIV-1 by macrophages was described that leads to productive infection (Carter et al. 2011). Whether CLRs are involved in this pathway is currently unknown. Several studies indicate that MR facilitates HIV-1 transmission by macrophages (Table 2.1 and Fig. 2.2). In vitro transmission of HIV-1 by macrophages to T cells is reduced upon blocking MR binding (Nguyen and Hildreth 2003). No transmission was observed beyond 24 h after virus binding by macrophages. Thus, unlike HIV-1 binding to DC-SIGN, MR-bound HIV-1 has only a slightly lower half-life compared to free virus (Nguyen and Hildreth 2003). Rapid internalization of HIV-1 by MR and subsequent degradation via the clathrin-dependent lysosomal pathway probably accounts for the decrease in viral longevity (Nguyen and Hildreth 2003).

In addition to MR, certain macrophage subsets also express DC-SIGN. DC-SIGN expression has been reported on subsets of macrophages in lung and placenta in vivo (Gurney et al. 2005; Soilleux et al. 2001) and on macrophages in breast milk (Satomi et al. 2005). DC-SIGN expression by macrophages is induced in vitro by IL-4 or IL-13 stimulation (Cassol et al. 2013; Chehimi et al. 2003). This upregulation of DC-SIGN is associated with enhanced HIV-1 infection and transmission of virus to $CD4^+$ T cells by macrophages (Cassol et al. 2013), indicating that DC-$SIGN^+$ macrophages could play an important role in HIV-1 replication and dissemination. However, the relative contribution of DC-$SIGN^-$ versus DC-$SIGN^+$ macrophages to HIV-1 dissemination in vivo remains unknown.

Currently it is unknown whether CLR-induced signaling is involved in HIV-1 infection and transmission by macrophages. Macrophages transmit HIV-1 across virological synapses (Carr et al. 1999; Groot et al. 2008; Sharova et al. 2005) and similar to DCs, CLR signaling may be involved in these processes.

In conclusion, HIV-1 binding by macrophages through CLRs may play a pivotal role in local transmission and propagation of HIV-1. Therefore, therapeutic strategies that interfere with CLR–HIV-1 interactions on macrophages may be clinical relevant to prevent persistent HIV-1 infection.

2.9 The Role of Transmembrane CLRs in Induction of Adaptive Immunity Against HIV-1

An important function of DCs is linking innate recognition of pathogens with adaptive immunity. DCs are the principal initiators of naive and memory T cell responses. In addition to their role in HIV-1 infection and transmission, CLRs are involved in HIV-1 uptake and antigen presentation by DCs (Fig. 2.1). Therefore, in this section we will discuss innate HIV-glycan recognition by CLRs in relation to induction of specific T cell responses.

2.9.1 CLRs Involved in HIV-1 Antigen Presentation

DCs present HIV-1-derived antigens to both $CD4^+$ and $CD8^+$ T cells. During acute HIV-1 infection, strong T cell responses against HIV-1 proteins such as Nef, Tat, Vpr, Gag, and Env are observed (Fortis and Poli 2005; Granelli-Piperno et al. 2004; Moris et al. 2004). DC-SIGN mediates uptake of HIV-1 by DCs and plays an important role in presentation of HIV-1 antigens to T cells. The majority of virions internalized via DC-SIGN are routed into the endosomal pathway for antigen presentation (Moris et al. 2006). In the endosomes, pathogens are processed and loaded onto MHC-II molecules for presentation to $CD4^+$ T cells (Moris et al. 2006). It was shown that blocking DC-SIGN leads to a reduction of HIV-1-specific $CD4^+$ T cell activation. DCs can also crosspresent internalized HIV-1 particles to $CD8^+$ T cells (Buseyne et al. 2001); expression of DC-SIGN has been shown to enhance MHC-I-mediated HIV-1 presentation, probably by facilitating uptake (Moris et al. 2004). Activation of HIV-1-specific $CD8^+$ T cells was shown to be dependent on proteasome-dependent processing (Moris et al. 2004). As mentioned above, DC-SIGN-mediated activation of LSP1 targets internalized HIV-1 to the proteasome (Smith et al. 2007), which may therefore be essential for $CD8^+$ T cell activation. These studies show that capture of HIV-1 through DC-SIGN is important for the induction of adaptive immunity against the virus. Other CLRs, such as MR, have also been suggested to be involved in HIV-1 internalization and targeting into endosomes (Turville et al. 2004), and may also play a role in antigen presentation of HIV-1.

Little is known about the induction of cytokines and T cell responses by LCs after interaction with HIV-1. It is not known whether LCs are able to present HIV-1 antigens to $CD4^+$ T cells, or crosspresent HIV-1 antigens to $CD8^+$ T cells. For measles virus, it has been shown that LCs efficiently process captured virus for MHC class II presentation to $CD4^+$ T cells, but virus uptake does not lead to crosspresentation (van der Vlist et al. 2011). These data suggest that internalization pathways might dictate the ability of antigen presentation by different DC subsets.

2.9.2 Modulation of Cytokine Production by DC-SIGN

T cell polarization by DCs is a hallmark of adaptive immunity and is required for effective eradication of distinct pathogens. The type of T cell responses induced by DCs is determined by the expression of cell surface molecules and by the cytokine profile expressed upon activation by inducible gene expression (de Jong et al. 2002; Kapsenberg 2003). As explained above, DC-SIGN cannot induce gene expression by itself. However, DC-SIGN facilitates recognition of HIV-1 by other PRRs. DC-SIGN-mediated HIV-1 uptake results in degradation of HIV-1 and subsequent recognition of HIV-1 single-stranded RNA (ssRNA) by endosomal TLR8. ssRNA-induced TLR8 triggering leads to activation and nuclear translocation of NF-κB dimers containing p65 (Gringhuis et al. 2010). In addition

DC-SIGN-mediated HIV-1 replication results in the production of molecules that can be detected by cytoplasmic PRRs including viral DNA by RIG-1 (Solis et al. 2011) and retroviral capsid by tripartite motif containing protein 5α (TRIM5α) (Stremlau et al. 2006). However, the extent to which recognition of these HIV-1-derived products induce DC activation is controversial. Upon HIV-1 infection of DCs, co-stimulatory molecules are only modestly upregulated (Granelli-Piperno et al. 2004; Lore et al. 2002). Other reports suggest that HIV-1 replication in myeloid DCs stimulates partial maturation and migration, which may enhance the transport and subsequent transfer of HIV-1 to $CD4^+$ T cells in the submucosa or lymph nodes (Harman et al. 2006).

Importantly, DC-SIGN binding by HIV-1 can shape TLR-induced immune responses (Gringhuis et al. 2009a). Signaling by DC-SIGN alone does not lead to NF-κB translocation into the nucleus, but enhances activation of certain NF-κB subunits via posttranslational modifications (Gringhuis et al. 2009a). Mannose-induced DC-SIGN signaling activates the serine/threonine protein kinase Raf-1 which induces phosphorylation of NF-κB subunit p65 at Ser276 (Gringhuis et al. 2007). This allows subsequent acetylation of p65 at different lysine residues (Gringhuis et al. 2007, 2009a). Acetylation of p65 prolongs and increases transcriptional activity of p65 as well as nuclear localization, which enhances transcription of pro-inflammatory cytokines such as IL-6 and IL-12. Thus, DC-SIGN triggering modifies signaling induced by other PRRs such as TLRs, which enhances production of specific cytokines (Gringhuis et al. 2009a). These data suggest that HIV-1 glycan recognition via DC-SIGN affects T cell polarization. However, the effects on adaptive immunity in vivo remain largely unknown. Enhancement of IL-12 and IL-6 may result in the induction of T helper 1 cells. However, reduced DC maturation and release of anti-inflammatory cytokine IL-10 during HIV-1 infection may dampen the induction of effective immunity and render DCs more prone for induction of regulatory T cells (van der Aar et al. 2011). Indeed, co-culturing in vitro of infected DCs with autologous T cells has been associated with the induction of T cells that produce high amounts of IL-10 (Granelli-Piperno et al. 2004).

Currently it is unclear whether specific T cell polarization by HIV-1-derived glycans is beneficial for the host or virus. A better understanding of the implications of HIV-1-induced polarization of T cells in the progression of HIV-1 infection would be instrumental in the development of antiviral vaccines.

2.10 HIV-1 Glycan Interaction with Soluble Lectins

In addition to the cellular C-type lectins discussed above, soluble lectins present in blood and tissue can also recognize carbohydrate structures. Several collectins and galectin-1 have recently been suggested to directly bind to gp120 with different functional results (Table 2.1). In this section we discuss recognition of gp120 by these soluble lectins.

2.10.1 HIV-Glycan Binding by Collectins

Collectins are part of the C-type lectin family and consist of collagen-like domain and one Ca^{2+}-dependent carbohydrate-binding domain (Litvack and Palaniyar 2010). Through the formation of a trimeric unit and additional oligomerization, collectins have a high avidity for repeated carbohydrate structures (Litvack and Palaniyar 2010). Several members of the collectin family bind to mannosylated carbohydrates present on HIV-1 gp120 envelope protein, including mannose-binding lectin (MBL), surfactant protein D, and surfactant protein A (Ezekowitz et al. 1989; Gaiha et al. 2008; Hart et al. 2002, 2003; Meschi et al. 2005; Saifuddin et al. 2000).

MBL is primarily synthesized by the liver and secreted into the blood, and mediates several innate immune functions including opsonization of microbes, internalization of microbes through interaction with collagen receptors on phagocytic cells, initiation of the lectin complement pathway, and direct neutralization (Jack and Turner 2003). Several studies have clearly shown that efficiently MBL binds various HIV-1 strains via high mannose carbohydrates on gp120 (Hart et al. 2002). HIV-1 particles that lack gp120 do not bind MBL, supporting that gp120 mediates the interaction between whole virus and MBL (Saifuddin et al. 2000).

MBL was reported to neutralize a cell line-adapted HIV-1 strain at concentrations found in serum of most donors (Ezekowitz et al. 1989). However, later studies showed that MBL only mediates low levels of neutralization (<20 %) of infection in peripheral blood monocytes by primary HIV-1 isolates and cell line-adapted HIV-1 (Hart et al. 2003; Ying et al. 2004). Although these studies suggest that MBL does not efficiently neutralize HIV-1 in vivo, it may mediate other important antiviral functions. In contrast to its low neutralization activity, MBL efficiently opsonizes HIV-1 for uptake by monocytic cells (Ying et al. 2004), which may consequently affect virus eradication as well as antigen processing and presentation of HIV-1 antigens to T cells by DCs. In addition, MBL inhibits DC-mediated transmission of HIV to T cells by blocking the interaction between HIV and DC-SIGN in vitro (Spear et al. 2003). As explained above, the interaction between HIV-1 and DCs can facilitate dissemination of virus from peripheral sites to lymphoid tissues. Therefore, blocking the interaction between HIV and DC-SIGN by MBL may be beneficial for the host.

The level of serum MBL increases during the acute phase of HIV-1 infection (Thiel et al. 1992), however, the functional consequences of increased MBL activity during HIV-1 infection remain to be elucidated. The level of MBL in human sera varies due to polymorphic variations in the coding or promoter sequences of the protein. Several studies indicate that there is an association between low levels of MBL and an increased susceptibility to HIV infection (Boniotto et al. 2000; Garred et al. 1997; Pastinen et al. 1998). Whether low levels of MBL are associated with higher rates of disease progression or mortality after infection is unclear (Garred et al. 1997; McBride et al. 1998). Further studies are needed to define the in vivo contribution of MBL to clearance and destruction of HIV-1.

Recently, the surfactant protein D and surfactant protein A were also shown to efficiently bind the mannose structures of HIV-1 gp120 (Gaiha et al. 2008; Madsen et al. 2013; Meschi et al. 2005). Importantly, both surfactant protein A and D are present at HIV-1 entry sites, including in vaginal fluid, the genitourinary tract, the oral cavity, and the gastrointestinal tract (Madsen et al. 2000). The presence of these surfactant proteins at these important sites for HIV entry and their capacity to bind HIV-1 suggests that they play an immunological role during HIV-1 infections in vivo. In contrast to MBL, surfactant protein A and D efficiently neutralize HIV-1 in vitro and effectively inhibit direct infection of $CD4^+$ cells (Gaiha et al. 2008; Madsen et al. 2013; Meschi et al. 2005). Surfactant proteins are known to mediate opsonization and phagocytosis of pathogens by innate cells (Wright 2005). Both surfactant protein A and D enhance binding of HIV-1 to DCs and DC-mediated transfer of HIV-1 to T cells (Gaiha et al. 2008; Madsen et al. 2013; Meschi et al. 2005). The role of the surfactant proteins in HIV-1 internalization and antigen presentation by DCs has not yet been investigated.

In conclusion, these studies indicate that soluble CLRs, similar to transmembrane CLRs, collectins may have multifaceted effects during HIV-1 infection. However, the impact of HIV-1 recognition by collectins in vivo and the possible use as therapeutic agents need to be further investigated.

2.10.2 HIV-Glycan Binding by Galectin-1

Another receptor involved in HIV-1-glycan recognition is galectin-1. Galectin-1 is not a CLR, but is a member of the galectin family. Galectins are synthesized and stored in the cytoplasmic compartment and are either passively released by dying cells or actively secreted by inflammatory activated cells upon pathogen-driven activation (Hughes 1999). The galectin family is defined by conserved peptide sequence elements in the CRD consisting of approximately130 amino acids (Barondes et al. 1994) and recognize a galactose residue linked to an adjacent carbohydrate in the β configuration (called β-galactoside) (Barondes et al. 1994; Rabinovich et al. 2002). β-galactosides are often found in N-linked "complex glycans," which are also present on the HIV-1 envelope protein. Only galectin-1 (out of 15 galectins discovered so far) has been reported to bind to HIV-1 particles. This binding can be inhibited by the β-galactoside containing lactose, but not by mannose, suggesting that galectin-1 recognizes HIV-1 through β-galactoside residues expressed on the envelope proteins (Mercier et al. 2008; Ouellet et al. 2005; St-Pierre et al. 2011). In vitro, galectin-1 enhances HIV-1 binding to $CD4^+$ susceptible cells and promotes infection of various HIV-1 variants (Mercier et al. 2008; Ouellet et al. 2005; St-Pierre et al. 2011). Recent studies indicate that the CD4 glycoprotein is one of the host ligands of galectin-1 and that galecin-1 facilitates HIV-1 infection through direct cross-linking of gp120 and CD4 (St-Pierre et al. 2011). Moreover, galectin-1 also increases HIV-1 infectivity in macrophages, most likely by facilitating capture and HIV-1 entry (Mercier et al. 2008). These studies indicate that recognition of

complex glycans by galectins is exploited by HIV-1 to facilitate transmission or replication of HIV-1. Galectin-1 is expressed by many different cells including gut-associated lymphoid tissue (GALT), endothelial cells, activated T cells, macrophages, and by follicular DCs in the lymphoid tissues (Baum et al. 1995; Blaser et al. 1998; Ouellet et al. 2005; Rabinovich et al. 1996, 2002). Thus, in vivo galectin-1 is present at important sites for HIV-1 transmission and replication and may play an important role during HIV-1 infection.

2.11 Future Directions and Concluding Remarks

Glycan recognition plays a pivotal role in innate recognition of HIV-1 by different immune cells. DCs and macrophages express various CLRs that recognize carbohydrate structures expressed by gp120. The extent and diversity of glycosylation of the envelope protein gp120 allows recognition by various CLRs on different subtypes of DCs and macrophages (Table 2.1 and Fig. 2.2). In this review, we have discussed the distinct roles of DC-SIGN, langerin, DCIR, BDCA2, MR, and soluble lectins during HIV-1 infection. CLRs such DC-SIGN and MR facilitate HIV-1 uptake and are involved in antigen presentation and the activation of T cell responses against HIV-1. Although CLR-mediated recognition is required for the induction of appropriate immune responses, HIV-1 has evolved to exploit CLR-mediated recognition to promote infection and transmission. It is clear that the outcome of HIV–CLR interactions is dependent on the cells and the CLRs involved (Table 2.1, Figs. 2.2 and 2.3). Whereas langerin on LCs has a protective function, DC-SIGN, MR, and DCIR on DCs and macrophages enhance HIV-1 infection and transmission, indicating that the integrity of the mucosa, and thereby the type of cell that is encountered will have a major impact on the final outcome of HIV-1 infection.

DCs and macrophages appear to play an important role in HIV-1 dissemination. However, their exact role in the onset of HIV-1 infection remains unclear. As explained above, DCs and macrophages reside in the tissues where HIV-1 enters the body and are proposed as the initial target cells for HIV-1 that mediate viral propagation and transfer of the virus to $CD4^+$ T cells in the draining lymph nodes. Indeed, infected macrophages and DCs can be observed soon after exposure to HIV-1 (Collins et al. 2000; Hladik et al. 2007; Hu et al. 2000; Spira et al. 1996). However, in contrast to the traditional view of HIV-1 infection, characterized by a slow decline of $CD4^+$ T cells from circulation, recent studies indicate that extensive infection and removal of local $CD4^+$ T cells in GALT occurs within the first month of infection (Haase 2010), indicating that $CD4^+$ T cells may be the initial cell type infected at the portal of entry. On the other hand, recent studies indicate that during sexual transmission only few HIV-1 particles penetrate across genital epithelial layers to reach the mucosa-associated lymphoid tissues and the GALT that are rich in HIV-1-susceptible $CD4^+$ T cells (Haase 2010). HIV-1 particles that penetrate genital epithelia have to interact rapidly with susceptible cells or with cells expressing alternative receptors, since cell-free HIV-1 virions become inactive in a relatively

short period of time (Haase 2010). Thus, viral attachment is a rate-limiting step during virus entry. Therefore, binding of HIV-1 to DCs and macrophages in the mucosa through CLRs may be essential for crossing the epithelial layer. In accordance to this, cell-free HIV-1 does not efficiently pass genital epithelial cells (Bobardt et al. 2007; Steinman et al. 2003), and evidence suggests that more-efficient binding of envelope gp120 to DC-SIGN is correlated to enhanced mucosal transmissibility of HIV-1 (Lue et al. 2002). Further investigation in vivo will be necessary to elucidate the exact role of DCs and macrophages at the early stages of HIV-1 infection.

The interaction of HIV-1 with CLRs is an attractive potential target for the design of therapeutic agents. Carbohydrate-binding agents or lectins that bind to mannose-rich glycans can reduce or even abrogate HIV-1 transmission and infection (Alexandre et al. 2012; Anderluh et al. 2012). Structural mimics of mannose-based oligo- and polysaccharides have been designed and proved to inhibit HIV-1 CLR interactions (Anderluh et al. 2012). Various lectins isolated from plants or prokaryotes have been shown to be efficient inhibitors of DC-SIGN-mediated transfer of HIV-1 to PBMC (Alexandre et al. 2012). As such, these lectins may be useful in blocking early events in HIV-1 transmission in mucosal tissues. The application of lectins as therapeutic agents is further discussed in detail by Koharudin and Gronenborn in Chap. 7.

DC-SIGN-based bifunctional proteins may also be useful to prevent infection by blocking virus entry into the host target cells and block virus transmission from virus-infected cells to non-infected cells. CD4-DC-SIGN fusion proteins were reported to have enhanced avidity to gp120 and efficiently inhibited HIV-1 infection *in trans* via a DC-SIGN-expressing cell line and primary human DCs in vitro (Du et al. 2012). Given that DC-SIGN binding to gp120 increases exposure of the CD4-binding site and that the soluble forms of CD4 and DC-SIGN occur in vivo, further improvement of these fusion proteins may render them potentially useful in antiviral therapeutics.

Since some mannose-binding CLRs can have a protective function during HIV-1 infection, selective CLR targeting may be preferable. Because of its well-investigated effects on HIV-1 replication and transmission, DC-SIGN is currently the main CLR of interest in the design of therapeutic agents against HIV-1. In vitro studies have demonstrated that DC-SIGN antagonists block effectively the transmission of HIV-1 infection (Anderluh et al. 2012). Recently, multivalent dendrimeric compounds based on Lewis-type antigens that bind DC-SIGN with high selectivity and avidity have been designed (Garcia-Vallejo et al. 2013). These compounds effectively blocked gp120 binding to DC-SIGN and, consequently, HIV transmission to $CD4^+$ T cells (Garcia-Vallejo et al. 2013). Thus, Lewis-type glycodendrimers could be a new therapeutic agent for the prevention of HIV-1 transmission. In addition to DC-SIGN, galectin-1 also facilitates HIV-1 replication and transmission. Several highly specific galectin-1 antagonists have been developed, which may also be a new class of therapeutic agents against HIV-1 (St-Pierre et al. 2012).

Although therapeutic agents that inhibit lectin–HIV-1 interactions are promising, their use has not been validated in vivo yet. The role of CLRs in the induction of

adaptive immunity against HIV-1 should be taken into consideration during the development of new therapeutic strategies. CLRs such as DC-SIGN and MR are crucial for antigen uptake, presentation, and T cell activation. It should therefore be carefully monitored whether agents that prevent lectin binding of HIV-1 do not compromise our natural defence system.

Another therapeutic approach is the induction of efficient anti-HIV T cell responses to promote HIV-1 eradication by targeting HIV-1 antigens to specific CLRs. For instance, targeting antigens to DEC205 has been shown to greatly facilitate antigen presentation (Bonifaz et al. 2004). Moreover, currently it remains largely unknown how HIV-1-induced cytokine profiles influence immunity and pathogenesis. Specific T cell skewing by using adjuvants and triggering specific receptors could be beneficial in the treatment HIV-1 infection.

In conclusion, over the past decades much progress has been made in identifying CLRs on innate immune cells that bind HIV-1 glycans and on obtaining knowledge about their role during HIV-1 infection. Elucidating in more detail the cellular effects of HIV-1 interactions with CLRs and the consequences for HIV-1 replication and immunity will contribute to a better understanding of HIV-1 pathogenesis and more efficient strategies for HIV-1 eradication.

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