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Pattern recognition receptors in HIV transmission

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Dendritic cells (DCs), Langerhans cells (LCs), and macrophages are innate immune cells that reside in genital and intestinal mucosal tissues susceptible to HIV-1 infection. These innate cells play distinct roles in initiation of HIV-1 infection and induction of anti-viral immunity. DCs are potent migratory cells that capture HIV-1 and transfer virus to $CD4^+$ T cells in the lymph nodes, whereas LCs have a protective anti-viral function, and macrophages function as viral reservoirs since they produce viruses over prolonged times. These differences are due to the different immune functions of these cells partly dependent on the expression of specific pattern recognition receptors. Expression of Toll-like receptors, C-type lectin receptors, and cell-specific machinery for antigen uptake and processing strongly influence the outcome of virus interactions.

Keywords: innate immunity, HIV transmission

INTRODUCTION

The innate immune system forms the first line of defense against invading pathogens. Innate immune cells, such as dendritic cells (DCs), Langerhans cells (LCs), and macrophages reside within mucosal tissues. The main route of HIV-1 infection is sexual transmission and therefore the interplay between the virus and innate immune cells within the mucosa plays a crucial role in initiating an effective immune response as well as dissemination of the virus. HIV-1 infects $CD4^+$ T cells within the secondary lymph nodes and innate immune cells are thought to be involved in transmitting virus to these T cells. HIV-1 infects cells upon interaction of viral envelope protein gp120 with CD4 and co-receptors, such as CCR5 or CXCR4, which initiate fusion of the virus with the cell membrane. Besides $CD4^+$ T cells, DCs, LCs, and macrophages also express CD4 and CCR5. The exact roles of the different innate immune cells upon virus entry into the host, and whether the interactions with the virus by these cells are beneficial to host or virus, are not yet clear. However, their function in HIV-1 transmission is strongly influenced by expression of pattern recognition receptors (PRRs) including C-type lectin receptors (CLRs). Extensive research during the last decade has given us more insight into the different events that follow upon HIV-1 binding to innate immune cells, which are related to cell-specific functions, receptor expression, and receptor signaling.

MUCOSAL ENTRY

Over 80% of new HIV-1 infections globally occur via sexual transmission (UNAIDS, 2010). The first barrier that HIV-1 encounters is the epithelium of the genital and intestinal tract. Epithelial cells do not express CD4 but these cells can be involved in HIV-1 transmigration albeit not efficiently. Syndecans, a specific class of heparin-sulfate proteoglycan, mediate internalization of HIV-1 through gp120 (Bobardt et al., 2007) and gp120–epithelial cell interaction decreases transepithelial resistance (Nazli et al., 2010). The latter occurs via induction of inflammatory cytokines and subsequent downregulation of junction genes, which facilitate transport of HIV-1 across the epithelial barrier. However, DCs or LCs are proposed as initial target cells of HIV-1 that mediate transfer of the virus to $CD4^+$ T cells in the draining lymph nodes, which is supported by both *ex vivo* and *in vivo* studies, (Spira et al., 1996; Hu et al., 2000; Gupta et al., 2002; Veazey et al., 2003; Hladik et al., 2007).

MUCOSAL INNATE IMMUNE CELLS

Innate immune cells residing in the mucosa express PRRs including Toll-like receptors (TLRs) and CLRs to sense pathogens and pathogenic-derived structures. Viral internalization takes place via receptor-mediated clathrin- or caveolin-dependent endocytosis, receptor-mediated phagocytosis, or through receptor-independent macropinocytosis (Trombetta and Mellman, 2005; Burgdorf and Kurts, 2008). Subsequently, uptake leads to pathogen degradation and antigen presentation to T cells to initiate immune responses (Banchereau et al., 2000; Romani et al., 2010). In addition, recognition of pathogenic structures by PRRs causes activation and maturation of the cells. Maturation leads to upregulation of costimulatory molecules to effectively present antigens and activate T cells. PRR signaling is not only required for maturation of the cells, but also induces a pathogen-tailored cytokine program that shapes specific immunity through T helper cell polarization (Banchereau et al., 2000). The extent to which maturation and activation is induced by HIV-1 is controversial. Reports on LC and DC maturation in response to HIV-1, or to other stimuli after HIV-1 exposure are contradicting, and results might be influenced by virus and cell preparations (Granelli-Piperno et al., 2004; Smed-Sorensen et al., 2004; Harman et al., 2006). Understanding of immune activation in the early events of HIV-1 infection is crucial, since activation, and maturation by HIV-1 or co-infections affects not only viral uptake and transmission, but also induction of adaptive immune responses and the presence of immune cells in the mucosa (Patterson et al., 2002; Bafica et al., 2004;

Turville et al., 2004). Although it is unclear how direct activation by HIV-1 occurs, HIV-1 modulates adaptive immunity induced by other stimuli through interactions with DC-SIGN (Gringhuis et al., 2009).

In the female genital tract, mucosal tissue consists of a single layer of endocervical columnar epithelium or squamous epithelium of vagina and ectocervix. Although some studies report slightly different expression patterns of widely used markers, in general LCs – defined by expression of CD1a and Langerin – are present within the epithelium. Intraepithelial and beneath this layer in the submucosa, CD11c+ DCs, CD68+ macrophages, and $CD4^+$ T cells, are localized (Geijtenbeek et al., 2000; Hladik et al., 2007; Hirbod et al., 2009, 2011). Also in the intestinal tract, foreskin, and rectum, DC, LCs, and macrophages are present (Geijtenbeek et al., 2000; Patterson et al., 2002; Gurney et al., 2005; Ribeiro Dos Santos et al., 2011).

Dendritic cells, LCs, and macrophages have their specific function in the immune system. Macrophages continually display phagocytic activity and are prone to initiate local inflammation and persist in the tissue (Cassol et al., 2010). DCs on the other hand are equipped to rapidly migrate to the lymph nodes, and therefore have a bridging function between innate and adaptive immunity (Banchereau et al., 2000). LCs belong to the DC family and are thought to have an important function to maintain mucosal homeostasis (von Bubnoff et al., 2004; Chu et al., 2011). It is not clear whether LCs are as efficient in their antigen presenting functions as DC, since compared to conventional DCs, these cells have slower migratory capacities (Villadangos and Heath, 2005; Romani et al., 2010). Innate immune cells express CD4 and coreceptors, required for HIV-1 infection, as well as PRRs that sense viruses to initiate immune activation. These include TLRs to recognize viral nucleic acids and CLRs that besides sensing can also function as viral attachment receptors. Furthermore, besides CLRs, syndecans can also function as attachments receptor on innate immune cells (Saphire et al., 2001; de Witte et al., 2007a).

PATTERN RECOGNITION RECEPTORS IN HIV-1 INFECTION

Infected DCs, LCs, and macrophages have been observed shortly after sexual transmission (Spira et al., 1996; Collins et al., 2000; Hu et al., 2000; Patterson et al., 2002; Hladik et al., 2007), strongly suggesting that these innate immune cells are an initial target for HIV-1. In addition to entry receptors, infection of innate immune cells is influenced by expression of CLRs and TLRs via internalization and/or immune activation. Whereas fusion of HIV-1 depends on CD4 and coreceptors, internalization and uptake depends on CLRs. CLRs recognize glycosylated structures via conserved carbohydrate recognition domains (Cambi et al., 2005; Robinson et al., 2006) and the heavily glycosylated HIV-1 envelope glycoprotein gp120 is recognized by mannose-specific CLRs such as dendritic cell specific ICAM-3 grabbing non-integrin (DC-SIGN), LC-specific Langerin, and the mannose receptor (MR). A recent study suggests that gp120 is also recognized by DC Immunoreceptor (DCIR) but the carbohydrate structures recognized are not clear (Lambert et al., 2008). MR, DC-SIGN, and DCIR are expressed by specific macrophage and DC subsets (Turville et al., 2001, 2002; Lambert et al., 2008). Langerin is specific for LCs in humans (Valladeau et al., 1999). In mice, a Langerin expressing DC subset has been identified, but its human homolog is not yet clear (Ginhoux et al., 2007) DC-SIGN, MR, and DCIR promote infection of innate immune cells but also transmission of HIV-1 to target T cells, while Langerin prevents infection through viral degradation (de Witte et al., 2008; van der Vlist et al., 2011). Therefore, expression of specific CLRs influences infection and HIV-1 internalization and at least partly determines the role of the innate immune cells in HIV-1 transmission.

Toll-like receptors comprise a family of plasma membrane and intracellular receptors. DCs and macrophages express a variety of TLRs (TLR1-8 and TLR10) to recognize bacterial and viral ligands (Kawai and Akira, 2011). Regarding HIV-1 recognition, HIV-1-derived ssRNA is sensed by TLR7/8 (Heil et al., 2004), although a recent study shows that infection of DCs triggers TLR8 but not TLR7 (Gringhuis et al., 2010), suggesting that TLR8 might be more important in HIV-1 sensing. LCs mainly express TLRs for recognition of viral products and lack TLR4. However, expression of TLR7/8 by LCs is debated (Flacher et al., 2006; van der Aar et al., 2007). Most TLRs are constitutively expressed in the genital mucosa but expression is tightly regulated, and both TLR2 and TLR4 seem restricted to the upper parts of the tract (Pioli et al., 2004; Fazeli et al., 2005), suggesting that the site of mucosal transmission might influence immune activation. TLR activation leads to innate immune activation as well as adaptive immune responses. Antiviral TLRs specifically induce production of interferons that interfere with virus replication (Bowie and Unterholzner, 2008; Ogawa et al., 2009). As a consequence, TLR4 signaling in DCs and macrophages decreases infection of the cells (Kornbluth et al., 1989; Thibault et al., 2009; Wang et al., 2011), whereas signaling via TLRs has also been shown to promote HIV-1 infection in innate cells directly through signaling and promoting HIV-1 transcription or indirect through cytokine induction (**Table 1**; Bafica et al., 2004; Gringhuis et al., 2010; Herbein et al., 2010). However, the effect of TLR triggering on HIV-1 infection as well as the effect of infection on PRR function depends on the innate immune cell a well as the receptor. Thus, TLR expression on innate immune cells and pathogen-driven TLR activation in the mucosa affects HIV-1 transmission.

Besides CLRs and TLRs, cytoplasmic tripartite motif-containing protein 5α (TRIM5α) acts as a PRR in myeloid cells. Retrovirus restriction factor TRIM5α interacts with the HIV-1 capsid (Stremlau et al., 2004), accelerates uncoating of the virus and thereby prevents reverse-transcriptase (Stremlau et al., 2006). However, recently another function of TRIM5α was described. HIV-1 capsid interaction with TRIM5α generates ubiquitin chains that activate the TAK1 kinase complex and subsequenlty activate transcription factors NFκB and AP-1 (Pertel et al., 2011). Notably, TRIM5α constitutively promotes innate immune signaling and sensing of retroviral capsids increases inflammatory gene transcription as well as retroviral restriction activity. Thus, TRIM5α can act as a PRR and activate innate signaling in response to retroviral infection. The importance in HIV-1 infection and sensing needs to be investigated.

LANGERHANS CELLS

Due to their localization in the epithelium LCs are the first cells to encounter HIV-1 and therefore regarded as "primary gatekeepers"

Table 1 | Examples of PRR-mediated effects on HIV infection in innate immune cells.

Pathogen	Cell type	Effect on HIV infection	Receptors involved	References
Mycobacterium tuberculosis	Macrophage	Increased replication, transmission, LTR activation	TLR2	Zhang et al. (1995), Mancino et al. (1997)
Neisseria gonorrhoeae	DC	Increased entry/replication	TLR2	Zhang et al. (2005)
	LC	Increased transmission	TLR1/2	de Jong et al. (2008)
Lactobacillus acidophilus	Macrophage	Increased infection	TLR2	Ahmed et al. (2010)
Leishmania donovani	Macrophage	Increased replication	TLR2	Bernier et al. (1995)
Candida albicans	LC	Increased transmission	TLR1/2	de Jong et al. (2008)
Escherichia coli	Macrophage	Reduced infection	TLR4	Ahmed et al. (2010)
Staphylococcus aureus	DC	Reduced infection	TLR4	Ogawa et al. (2009)
	LC	Increased infection		
Salmonella typhimurium	DC	Reduced infection	TLR4	Ogawa et al. (2009)
	LC	No effect		
Herpes simplex virus-2	LC	Increased infection, transmission	Langerin	de Jong et al. (2010)
LIGANDS				
Pam3Cysk4, LTA	DC	Increased transmission	TLR2	Thibault et al. (2009)
LPS	DC, macrophage	Reduced infection/transmission, replication	TLR4	Kornbluth et al. (1989), Thibault et al. (2009), Wang et al. (2011)
Interferon	Macrophage	Reduced infection, replication	TLR3	Kornbluth et al. (1989), Ahmed et al. (2010)

(Kawamura et al., 2003). Infected mucosal LCs have been identified as early target cells in foreskin and vagina (Hu et al., 2000; Patterson et al., 2002; Hladik et al., 2007). However, although HIV-1 is very rapidly internalized by these cells, infection of immature LCs is very inefficient (de Witte et al., 2007b; Hladik et al., 2007; Ballweber et al., 2011). LCs bind gp120 predominantly through the CLR Langerin (Turville et al., 2002; de Witte et al., 2007b). Notably, HIV-1 virions captured by Langerin are directed to birbeck granules for degradation (de Witte et al., 2007b). As a consequence, immature LCs do not promote T cell infection (de Witte et al., 2007b; Fahrbach et al., 2007) (**Figure 1**). The outcome of LC interaction with HIV-1 is mainly determined by their activation status. In contrast to immature LCs, activated LCs transmit HIV-1 to T cells (de Witte et al., 2007b; Fahrbach et al., 2007). Transmission by LCs to T cells is considered to be dependent on LC infection, since infected LCs effectively transmit HIV-1 to T cells (Reece et al., 1998; Kawamura et al., 2000; Sivard et al., 2004; de Jong et al., 2008), although it has been reported that LCs are able to transfer virus to T cells independent of infection (Hladik et al., 2007; de Jong et al., 2008; Ballweber et al., 2011).

Langerhans cell activation, and subsequently enhanced infection as well as transmission is induced by co-infections, and explains partly the increased risk of HIV-1 infection in persons carrying other sexually transmitted diseases. Gram+ bacteria, *Candida albicans*, and *Neisseria gonorrhea* enhance capture, replication, and transmission via induction of TNF-α or modulation of the interferon response as a result of TLR1/TLR2 binding (de Jong et al., 2008; Ogawa et al., 2009). On another level, Herpes Simplex Virus-2 interferes with the protective role of Langerin by competing for receptor binding and decreasing expression levels (de Jong et al., 2010). Thus, immune activation is a critical determinant in susceptibility to HIV-1.

Immature LCs have a protective role in infection, which drastically changes upon cell maturation as mature LCs effectively transfer HIV-1. Because of the striking differences between immature and activated LCs in virus degradation and transmission respectively, LCs play a pivotal role in HIV-1 transmission.

DENDRITIC CELLS

Infected DCs and DC-T cell conjugates have been observed soon after infection in vaginal and rectal tissue. Within hours upon exposure, HIV-1 infected cells were detected in draining lymph nodes (Spira et al., 1996; Hu et al., 2000; Ribeiro Dos Santos et al., 2011). DCs are the most potent APCs, capable of rapid migration to the lymph nodes to present antigens to T cells and therefore it has been proposed that DCs migrate to the lymph node where they transfer HIV-1 to T cells (**Figure 1**).

Dendritic cells binding and internalization of HIV-1 is mainly facilitated by DC-SIGN and DC-SIGN-bound virions remain infectious for days allowing transmission independent of infection, supporting a role for DCs in viral transport (Geijtenbeek et al., 2000; Kwon et al., 2002). However, DCs are also infected by HIV-1. The importance of direct infection compared to HIV-1 capture depends on the time scale. Whereas DC-SIGN-captured virus can be transmitted for several days, Turville et al. (2004) have shown that after two days DC infection becomes more important in HIV-1 transmission. Furthermore, DC infection might lead to the formation of HIV-1 reservoirs as has been shown for macrophages (Coleman and Wu, 2009). Both immature and mature DCs internalize HIV-1 and facilitate trans-infection.

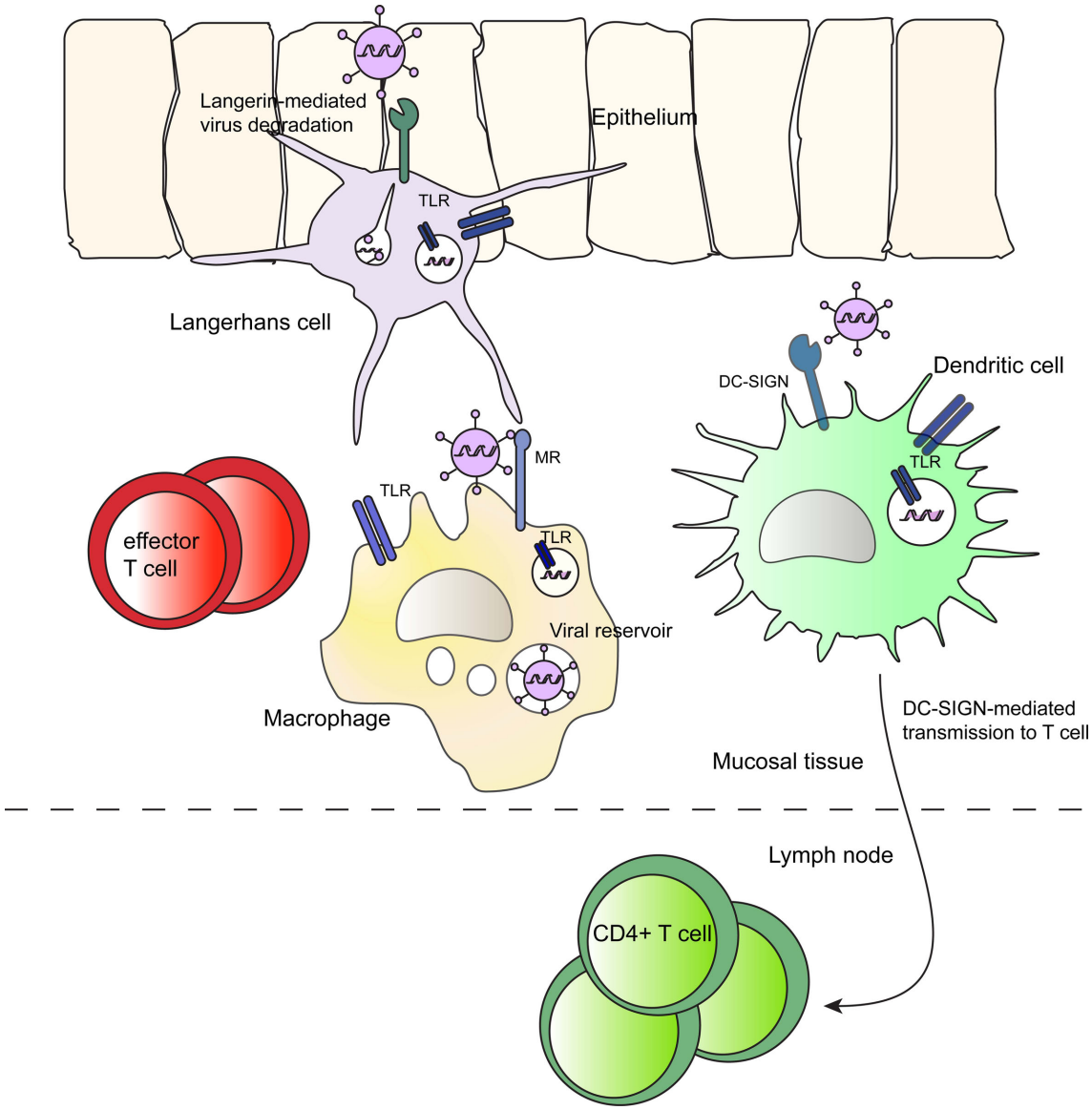

FIGURE 1 | The role of innate immune cells in HIV-1 infection largely depends on PRR expression. Innate immune cells reside in mucosal and submucosal tissue. DCs internalize HIV-1 and migrate to the lymph node to transfer virus to $CD4^+$ T cells and this process is mediated by DC-SIGN. Immature LCs express Langerin, which promotes viral degradation in Birbeck granules. Macrophages take up HIV-1 via MR, but are most important as an HIV-1 reservoir. All three innate immune cells in addition express various TLRs on the cell surface and in endosomes to sense pathogenic-derived antigens. Subsequent TLR signaling influences HIV-1 infection and immune activation.

Immature DCs capture HIV-1 more efficiently and infection is higher, whereas mature DCs most efficiently transfer virus to T cells (Turville et al., 2004; Yu et al., 2008). In addition to promoting viral transfer, virus capture through DC-SIGN favors infection of DCs since DC-SIGN colocalizes with CD4 and CCR5 and thereby promotes binding to the fusion receptors (Lee et al., 2001). Strikingly, DC-SIGN signaling is also crucial for initiation of HIV-1 transcription. Notably, other pathogens that interact with DC-SIGN also induce DC-SIGN signaling and thereby enhance HIV-1 transcription (Gringhuis et al., 2010). In addition to internalization, DC-SIGN ligation and T cell contact induce formation of a virological synapse to which HIV-1-containing vesicles are rapidly recruited for transfer (McDonald et al., 2003; Arrighi et al., 2004; Turville et al., 2004). Although the virological synapse is reminiscent of immunological synapse it forms independent of antigen presentation or MHC–TCR interactions (Piguet and Sattentau, 2004). Different models have been proposed regarding how HIV-1 in DCs is protected from degradation and whether the virus is internalized upon DC-SIGN binding and if so, to what compartments it is directed to enable transfer to T cells. It has been proposed that the majority of transferred virus is retained surface-bound (Cavrois et al., 2007), but most studies support a model in

which HIV-1 is internalized into compartments that do not belong to the classical endosomal/lysosomal pathway. Here the virus is protected from lysosomes and neutralizing antibodies (Kwon et al., 2002; McDonald et al., 2003; Turville et al., 2004). Slightly different models have been proposed where HIV-1 induces specific surface-accessible CD81+ vesicles, contiguous with the plasma membrane to protect the virus from lysosomal degradation (Yu et al., 2008). Furthermore, it has been suggested that HIV-1 makes use of the exosome pathway to be secreted for transmission (Wiley and Gummuluru, 2006), which is supported by suggestion that HIV-1 particles contain similar proteins and lipids as exosomes (Gould et al., 2003). Exploitation of the exosome pathway by HIV-1 for transfer to T cells has also been proposed to occur independent of gp120 and CLRs (Izquierdo-Useros et al., 2009). Notably, the exosome pathways contain tetraspanin proteins, such as CD81, also found in HIV-1-containing multivesicular bodies, which might be involved in exosome production and might explain presence of HIV-1 in exosomes.

Over the last few years, some underlying mechanisms of DC-SIGN signaling, and how these events affect transmission, have become clear. DC-SIGN–HIV-1 interaction leads to recruitment of Guanine exchange factor (GEF) LARG and RhoA to the DC-SIGN signalosome and in turn activation of kinase Raf-1. Through Raf-1 activation, DCs shape adaptive immune responses to HIV-1 (Gringhuis et al., 2009). However, Raf-1 activation by HIV-1 is also required for HIV-1 replication in DCs (Gringhuis et al., 2010). Multiple studies focused on how proteins involved in DC-SIGN signaling affect internalization and synapse formation by influencing motility or arrangement of the cytoskeleton. Specifically, DC-SIGN-mediated activation of LARG induces cytoskeleton rearrangements that are important for the formation of the virological synapse (Hodges et al., 2007), whereas DC-SIGN activation of Rho-GTPase cdc42 is crucial for the induction of membrane extensions and recruitment of virus to the synapse (Nikolic et al., 2011). Scaffolding protein LSP1, part of the DC-SIGN signalosome, is proposed to mediate transfer to the proteasome for degradation and thus has a negative role for transmission (Smith et al., 2007). LSP1 is involved in chemotaxis of DCs, but LSP1-induced cell motility is also facilitated by gp120–CCR5 interaction (Anand et al., 2009), indicating multiple HIV-1 receptors might be involved in transmission events.

DC-SIGN is the most studied CLR regarding HIV-1 due to its special role in promoting infection and transmission, but other CLRs expressed by DCs, including DCIR and MR, have been demonstrated to interact with HIV-1. Although not much known about the function of DCIR in DCs, and no specific ligands have been described, binding of HIV-1 to DCIR enhances infection of DCs and transmission tot T cells (Lambert et al., 2008). DCIR is the only CLR expressed on DCs containing an intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM), and this intracellular part is required for its effect on infection (Lambert et al., 2008, 2011). MR has been suggested to internalize and traffic virus to endosomes and lysosomes upon binding gp120 (Turville et al., 2004). Thus MR interaction might promote degradation and MHCII Ag presentation in DCs. Capture via DC-SIGN has also been proposed to promote antigen presentation, both in the context of MHCI, following fusion and proteosomal degradation, or MHCII via a pathway independent of productive infection (Moris et al., 2004, 2006). Thus, DC-SIGN, but also other CLRs are involved in uptake of HIV-1 leading to transmission or antigen presentation.

Similar to macrophages, involvement of TLRs can be detrimental for DC infection. Although both TLR2 and TLR4 ligands enhance entry, only TLR2 ligands, such as *Neisseria gonorrhoeae*, enhance infection, and transmission of DCs through signaling (Zhang et al., 2005), whereas TLR4 triggering decreases due to interferon induction and TLR5 TLR7/9 have no effect (Thibault et al., 2009). Strikingly, although HIV-1 RNA efficiently activates plasmacytoid DCs through TLR7 and TLR9, it does not activate conventional DCs through TLR7 and TLR8 (Beignon et al., 2005). Recent data show that TLR8 triggering and NF-κB activation is required for HIV-1 infection in DCs (Gringhuis et al., 2010), suggesting that HIV-1 additional signals are required for activation in DCs.

Dendritic cells express several CLRs that promote infection and viral transfer to T cells. Virus interaction with DC-SIGN induces internalization into specific vesicles and formation of a virological synapse to facilitate transmission. DCs therefore have an important role in virus dissemination.

MACROPHAGES

Infected macrophages are detected in the female genital tract soon after exposure to HIV-1 (Collins et al., 2000). However, compared to DCs and LCs, macrophages do not seem to be important in initiation of infection, since they do not have a clear protective or HIV-1 transmitting function.

Uptake of HIV-1 by macrophages can occur dependent or independent of CLR binding. Uptake has been shown to occur by macropinocytosis, leading to degradation of many particles in lysosomes (Marechal et al., 2001). An additional receptor-mediated phagocytosis pathway was described, which is induced by interaction with MR, accounting for a large part of HIV-1 binding (Nguyen and Hildreth, 2003). Virus–MR interactions lead to degradation via clathrin-dependent lysosomal pathway and antigen presentation whereas the interactions do not promote infection (Trujillo et al., 2007). Besides its role in antigen presentation, MR is also involved in HIV-1 transmission (Nguyen and Hildreth, 2003). In contrast to DC-SIGN, MR-mediated uptake does not lead to protection of HIV-1, supporting a function in antigen degradation and presentation similar to its role in DCs (Nguyen and Hildreth, 2003). Recently a novel uptake route, an alternative macropinocytosis pathway, has been described. This entry route, independent of caveolin, clathrin and PI3K, but dependent on actin, Rho family GTPases, and dynamin leads to infection by HIV-1. How this pathway is induced and whether MR is involved is not known (Carter et al., 2010).

Since macrophages do not migrate after activation, their function in initial dissemination of HIV-1 to T cells is limited. However infected macrophages are an important HIV-1 reservoir, and very capable of infecting T cells over a prolonged time period. Within multivesicular bodies, *de novo* produced virus can persist and retain infectious for weeks to infect T cells (Carr et al., 1999; Sharova et al., 2005) (**Figure 1**). Stored virus from the CD81+ compartments can be transmitted in a regulated way to T cells

via transient synapse formation (Deneka et al., 2007; Groot et al., 2008). Similarly, the exosome pathway might be involved, since exosomes are derived from multivesicular bodies (Denzer et al., 2000). Thus, macrophages as reservoirs might facilitate infection of other cells including T cells but also DCs in mucosal tissues. It is however unclear whether a reservoir role for macrophages is relevant in mucosal tissue direct after sexual transmission since the replication capacity of transmitted/founder virus in macrophages is lower compared to HIV strains used in most *in vitro* studies (Ochsenbauer et al., 2012).

Macrophage activation by TLR ligands influences HIV-1 infection. Interferon-inducing ligands or pathogens that trigger TLR3 TLR4, TLR7/8 have been shown to impair replication (Kornbluth et al., 1989; Wang et al., 2011), while infection with pathogens that trigger TLR2 increase virus production (e.g., *M. tuberculosis*) or do not affect infection (Mancino et al., 1997; Bafica et al., 2003; Ahmed et al., 2010). This suggests that depending on the pathogen, co-infections increase, or protect from HIV-1 replication in macrophages in the mucosa.

Macrophages seem to function as reservoirs for HIV-1 and therefore are able to transmit virus to T cells or DCs residing in mucosal tissues. As opposed to DCs, HIV-1 capture leads also to degradation and Ag presentation and therefore HIV-1 infection of macrophages is a major factor in their role as HIV-1 reservoir.

FUTURE DIRECTIONS AND CONCLUDING REMARKS

Innate immune cells reside in the tissues where HIV-1 enters the body. Their capacity to capture and digest pathogens, and subsequently interact with T cells, contributes to mechanisms of viral transfer to $CD4^+$ T cells. Cell-specific CLRs mediate HIV-1 degradation, antigen processing, or in the case of DC-SIGN protection of HIV-1. Multiple HIV-1 binding CLRs and PRR-induced pathways influence dissemination or degradation by innate immune cells and dominance of one particular pathway will depend on activation status of the innate immune cell. Our knowledge of mechanisms underlying these events has improved greatly, but some important questions remain and might be crucial to answer before effective prevention methods can be developed. For example, the reason why sexual transmission of HIV-1 is restricted to R5 strains remains to be elucidated. DCs are infected with and transmit both X4 and R5 strains, and mucosal T cells express both coreceptors (Geijtenbeek et al., 2000; Kwon et al., 2002; Veazey et al., 2003). LCs are primarily infected with R5 virus, although X4 transmission has been observed as well, indicating the need for additional research on this topic (Sivard et al., 2004; de Jong and Geijtenbeek, 2009). Secondly, non-human primate studies provide a valuable tool for *in vivo* pathogenesis studies and drug testing. Although the SIV infection in macaques is similar to HIV infection in humans, differences in disease progression and host factors must be kept in mind (Sina et al., 2010; Van Rompay, 2012). The importance of the described mechanisms *in vivo* is another point of debate. Contradicting findings can be explained by the use of different experimental setups, *ex vivo* models or use of specific differentiation methods for DCs, LCs, or macrophages. In addition, the *in vivo* plasticity of the phenotype and function of innate immune cells makes it difficult to translate all results to the *in vivo* situation (Geissmann et al., 2010; Galli et al., 2011). Still, an important role for CLR in HIV-1 transmission *in vivo* is illustrated by a recent finding that expression of Langerin, DC-SIGN, and MR, but not HLA-DR, is significantly higher in mucosa of a high-risk population (Hirbod et al., 2009). But whether this increased expression is protective or detrimental for the host cannot be answered.

During the last years, the focus of HIV-1 transmission research has shifted toward a more immunological approach. Elucidating intracellular signaling and cellular effects following HIV-1 interaction will contribute to a better understanding of the first events upon sexual transmission.

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