AIDS Rev. 2014;16:223-35

HIV/Dendritic Cell Interaction: Consequences in the Pathogenesis of HIV Infection

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Abstract

Dendritic cells are professional antigen-presenting cells and key elements of both innate and adaptive immunity. Tissues like skin and mucosal epithelium, more exposed to the environment, are particularly rich in dendritic cells. Given that HIV is mainly transmitted through mucosal surfaces, the cellular mechanisms governing the initial interactions between HIV and dendritic cells are crucial for establishing systemic infection in a new host.

Upon HIV/dendritic cell interaction, viral particles carried by exposed dendritic cells are transmitted to activated CD4⁺ T-cells during the antigen presentation process. Such dendritic cell/T-cell transmission of HIV plays an important role in the viral dissemination and immune dysregulation associated with HIV infection, subverting the bridge between innate and adaptive immune responses. Thus, defining how HIV interacts with dendritic cells remains a critical area of research, with downstream implications in the knowledge of pathogenic mechanisms, transmission, vaccine development, and molecular targets for therapeutic intervention. In this review we will, therefore, delve into the mechanisms involved in HIV/dendritic cell interactions that govern viral persistence, cellular trafficking, transmission and restriction, compiling the present knowledge on these subjects and attempting to postulate how some uncertain pathways may shape up and intertwine. **(AIDS Rev. 2014;16:223-35)**

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Key words

HIV. Dendritic cell. Host-pathogen interaction. Pathogenesis.

Introduction

Dendritic cells (DC) are highly heterogeneous, antigen-presenting cells (APC). Their main role is to sense invading microorganisms at the site of infection, uptake and process foreign antigens, migrate to lymph nodes, and present antigens to CD4⁺ T-cells. The interaction between DCs and T-cells (dubbed the "immunological synapse") induces strong proliferation and differentiation of naive CD4⁺ T-cells, establishing the bridge between innate and adaptive immunity[1]. Besides the initiation of adaptive immune response, precursor and immature DCs are also involved in several innate effector functions, after binding of microbial products (pathogen-associated molecular patterns) to DC's pattern recognition receptors, restricting the growth and replication of invading pathogens. Due to their role in surveillance and homeostasis, DCs populate most tissues in the body, especially the skin and mucosal epithelium, the sites that are exposed to the environment[2].

The HIV is transmitted mainly through unprotected sexual intercourse[3], defining HIV infection as being primarily a mucosal infection. Despite this and independent of the mucosal type where HIV infection originates (e.g. vaginal, uterine, foreskin, anal), the cellular mechanisms governing the initial virus/host interactions, crucial for establishing a systemic infection in a new host, remain unclear[4-6]. Many types of immune cells are present in these tissues, including DCs, which are targeted

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Table 1. Main characteristics of the different dendritic cell subsets

DC subsets		Localization	Phenotype	Function
Conventional DCs	Migratory DCs	Lymph nodes; non-lymphoid tissue; skin (dermis)	$CD11b^+$ $CD205^+$	Presentation on MHC-II
			$CD103^+$ ($CD11b^-$) $CD205^+$	Cross-presentation on MHC-I
	Lymphoid tissue-resident DCs	Lymph nodes; spleen; thymus	$CD4^+$ $CD11b^+$	Presentation on MHC-II
			$CD8\alpha^+$ $CD11b^+$	Cross-presentation on MHC-I Priming cytotoxic CD8 T-cell responses Production of IL-12 and IFN-λ
			$CD4^-CD8\alpha^-$ $CD11b^+$	Presentation on MHC-II
Plasmacytoid DCs		Lymph nodes; spleen; blood	DC-$SIGN^+$ $CD45RA^+$	High production of type I IFNs Poor antigen-presenting capacity
Langerhans cells		Skin (epidermis)	$CD205^+$ CD207 $(langerin)^+$	Migrate to lymph nodes to present antigens Tolerance induction (by presenting self antigens) Production of IL-10
Monocyte-derived DCs		Blood; non-lymphoid tissue	$CD11b^+$ $CD11c^+$ DC-$SIGN^+$	Induced by inflammation Cross-presentation Production of TNF

DC: dendritic cell; MHC: major histocompatibility complex; IL: interleukin; IFN: interferon; DC-SIGN: DC-specific ICAM3-grabbing non-integrin; TNF: tumor necrosis factor.

by HIV soon after mucosal transmission. However, HIV infection subverts normal DC biology, resulting in viral uptake, infection, and transfer to other cells (e.g. $CD4^+$ T-cells that are key players in adaptive immunity), either with or without HIV productive infection of DCs[4,5,7].

As an extraordinarily adapted pathogen, HIV encodes several proteins (e.g. Vif, Vpu, Vpx, Nef, and Vpr) that are directly involved in the regulation of HIV interactions with host cells. Not surprisingly, some of them are crucial for the infection and survival of HIV in DCs. The most recent example of this kind of viral protein is the Vpx protein, present only in HIV-2-infected cells. This protein is particularly important as it counteracts a recently characterized DC restriction factor, SAMHD1 (sterile alpha motif [SAM] and histidine/aspartic acid [HD] domain-containing protein 1), which inhibits HIV replication in DCs and has marked effects in both innate and adaptive immunity by actually preventing immune sensing[8,9].

The aim of this review is to summarize the current knowledge of HIV/DC interactions and their impact in the pathogenesis of HIV infection. We begin by outlining normal DC biology; next we identify and discuss the cellular mechanisms and molecular pathways involved in DC infection, in HIV survival/evasion, and in the transfer to $CD4^+$ T-cells; and finally we discuss the HIV restriction mechanisms present in DCs and the counteracting effects of viral proteins, delving into the differences between HIV-1 and HIV-2 when relevant.

Biology of dendritic cells

Dendritic cells can mainly be defined by their morphology and some key functional properties (Table 1), notably the constitutive expression of major histocompatibility (MHC) class II molecules and the capacity to stimulate and activate naive T-cells[1]. They originate from common myeloid precursor cells in the bone marrow[10,11], but are quite heterogeneous in terms of their localization, surface phenotype, and function. The development of DCs and their cellular lineage have been the target of intense research in recent years and, as a result, a current overview of DC development and homeostasis is now established.

Firstly, hematopoietic stem cells in the bone marrow differentiate into a monocyte/DC precursor, which either becomes a monocyte or a common DC precursor. Common DC precursors then differentiate

into either conventional DCs (cDC), precursors (preDC), or plasmacytoid DCs (pDC), and migrate to peripheral tissues through the systemic circulation. In both lymphoid and non-lymphoid tissues, preDCs then maturate into cDCs, while $CD14^+$ and $CD16^+$ monocytes are circulating in the blood. These blood monocytes, as well as their bone marrow counterparts, originate another subtype of DC, Langerhans cells (LC), the cells that patrol mucosal and epithelial tissues. In addition, $CD14^+$ blood monocytes can migrate to the inflamed tissue and differentiate into either migratory monocyte-derived DCs (MDDC) or macrophages, apparently depending on the inflammatory stimuli they are presented with. Therefore, four major DC subsets can be defined: cDC, LC, MDDC, and pDC.

Main differentiating features of dendritic cell subsets

Conventional DCs (cDCs) show a high phagocytic activity, and their short half-life (3-5 days) implies they are continuously replaced from their bone marrow precursors in an Fms-related tyrosine kinase 3 ligand (flt-3L)-dependent mechanism. Immature cDCs exhibit high endocytic activity and low surface expression of MHC class I and II proteins but, upon recognizing and capturing antigens, they mature and migrate to the T-cell zones of secondary lymphoid organs to trigger adaptive immunity[12,13]. This DC subset therefore encompasses both resident and migratory DCs and it is noteworthy that in the spleen, tonsil and lymph nodes, two main subsets of resident cDCs have been described: $CD1c^+$ DCs and C-type lectin domain family 9, member A $(Clec9A)^+$ $CD141^+$ DCs. Both cell types are also present in the blood, and both are highly competent at cross-presentation of pathogen antigens[12], a subject that will be addressed further on.

Langerhans cells are DCs within the epidermis and other stratified squamous epithelia. When isolated, they exhibit the classical features of DCs and express a lectin, Langerin/CD207, that is the main constituent of their characteristic and degradative Birbeck granules[1,4,5,7,14]. They differ from lymphoid tissue DCs in being flt-3L independent and macrophage colony-stimulating factor dependent, resembling tissue-resident macrophages while retaining specific cDC characteristics, especially upon activation[1,12,13].

Migratory monocyte-derived DCs, also termed inflammatory DCs, are found in human inflammatory tissues and display a phenotype distinct from macrophages and from steady-state lymphoid organ and blood DCs. They have been shown to stimulate interleukin (IL)-17 production by autologous memory $CD4^+$ T-cells and to induce T helper 17 (Th17) cell differentiation from naive $CD4^+$ T-cells by means of selective cytokine secretion[15]. Additionally, they are also capable of cross-presenting exogenous antigens on their MHC class I molecules (antigen cross-presentation)[1,12].

Plasmacytoid DCs (pDC) are found mainly in the blood and lymph nodes and their role is to provide antiviral defense, mainly through secretion of very high amounts of interferon (IFN)-α, after migrating to areas of foreign antigen exposure or inflammation. While all DCs can produce IFN-α, pDCs are able to do so upon exposure to both live and inactivated viruses because they express Toll-like receptor (TLR) 7 (TLR7) and TLR9 in vesicles membranes of the endosomal pathway[7,16]. They can also present antigen to and activate T-cells, regulating antigen presentation in a unique way, as they are able to sustain peptide/MHC II complex formation after activation, in clear contrast with other maturing DC subsets[1].

Migratory dendritic cell maturation

It is important to understand how normal DC maturation and subsequent migration are processed. Antigen capture by pattern recognition receptors, expressed at the cell surface, triggers the maturation process, leading to DC migration to draining lymph nodes, where they present antigens to T-cells and thus activate them.

Dendritic cell maturation is synonymous to altered DC function, due to changes in the surface expression of several proteins. The mature forms of all DC subsets are known to exhibit a dendritic morphology with probing processes, weak phagocytic activity, high MHC class II levels for antigen presentation, and the expression of several cell membrane receptors, some of them unique for antigen uptake and processing[1,7]. The expression of CD54 is particularly important, due to its direct involvement in the formation of immunological synapses (IS), by interacting with lymphocyte function-associated antigen 1 (LFA1) on T-cells[7]. This, while not yet completely understood, is presumed to be the main mechanism by which HIV could be transferred from DCs to T-cells, playing a critical role in the establishment and spread of HIV in the genital mucosa soon after sexual transmission[5].

Dendritic cells in HIV pathogenesis

Dendritic cells play an important role in HIV infection and pathogenesis (Table 2). In fact, DCs exposed to

Table 2. Major role of dendritic cell subsets during HIV infection

DC subset	Role in HIV infection
Conventional DCs	Bind to HIV and transmit the virus to T-cells in draining lymph nodes during antigen presentation
Plasmacytoid DCs	Produce type I interferons (after envelope glycoprotein binding to CD4) that inhibit viral replication and induce bystander T-cell death Induce T_{reg} cells Recruit T-cells to sites of HIV infection by producing chemokines such as CCL5 (this facilitates viral spread to activated T lymphocytes)
Langerhans cells	Internalize HIV into degradative Birbeck granules
Monocyte-derived DCs	Largely resistant to HIV-1 infection due to a block during reverse transcription (see: HIV restriction in DCs). Unknown role in trans-infection of $CD4^+$ T lymphocytes

DC: dendritic cell; T_{reg}: T regulatory.

HIV-1 help viral replication and systemic infection by two distinct mechanisms: by becoming productively infected or by transferring HIV to $CD4^+$ T-cells during IS in the absence of DC infection[17-19]. Although DCs can be infected, HIV replication is generally less productive compared with $CD4^+$ T-cells. However, extensive viral replication takes place once DCs come into contact with $CD4^+$ T-cells in lymphoid tissue[20]. HIV does this by subverting the normal biology of DCs: firstly making use of their basic cell machinery to slowly replicate while evading immune sensing; it then makes use of DC maturation and migration to draining lymph nodes in order to finally use their antigen presenting capabilities to productively infect highly susceptible T-cells within lymph nodes. This section (HIV-dendritic cell interaction: binding and internalization) will therefore discuss HIV/DC interaction and the consequences of this interaction for HIV replication and pathogenesis (Table 3). Namely, we will address the subversion of normal DC biology by HIV that leads to its evasion and survival, the dysregulation of DCs, and viral trafficking and transmission to T-cells.

HIV-dendritic cell interaction: binding and internalization

The fate of HIV varies according to the cDC receptor it initially binds to. The DC/T-cell HIV transmission occurs in two sequential phases[21-24], which correspond to the two routes of entry of HIV in DCs. The first route is via C-lectin receptor (CLR)-mediated uptake, as cDCs express DC-specific ICAM3-grabbing non-integrin (DC-SIGN), langerin and DC immunoreceptor, with the expression of these receptors varying based mainly on cDC localization and maturation[25-28]. The DC-SIGN has received much attention due to its involvement in HIV internalization as it has been largely accepted that upon binding to the HIV gp120 envelope protein, the complex is co-internalized into early endosomal compartments[25,28]. However, much controversy has surrounded the role of the endolysosomal pathway, as HIV presence within early endosomes or lysosomes has not been demonstrated. The currently accepted results rather show that, in mature cDCs, it is taken up into a single tetraspanin rich ($CD81^+$) compartment that remains connected to the extracellular space, known as a vesicular cave[24,29,30], which is involved in the infection of CD4+ T-cells[5,7,24] in a process reviewed further ahead in this text. In immature cDCs, on the other hand, a large proportion of HIV is not co-localized with CD81[24], suggesting that the virus undergoes rapid processing and transit through the early endosome, when internalized, rendering its detection quite difficult[7,29]. The fact that cDCs are able to efficiently present HIV antigens to T-cells via MHC-II further strengthens the role of the endolysosomal pathway[31-33]. The DC immunoreceptor was also recently found to bind to HIV and promote its transmission to T-cells in a similar way to DC-SIGN[34]. Finally, and in contrast to DC-SIGN-mediated internalization, HIV internalized through langerin in immature LCs is trafficked to Birbeck granules where the virus is rapidly degraded[35].

The second route of entry of HIV into cDCs is via neutral fusion of the virus envelope with the DC plasma membrane mediated by CD4/CC-chemokine receptor 5 (CCR5) or CD4/CXC-chemokine receptor 4 (CXCR4)[21,36-38]. Because cDCs express high levels of CLRs at the cell surface, HIV access to CD4/CCR5 is limited, with only less than 5% of the virus that enters via neutral fusion being able to establish productive infection in cDCs[21]. Langerhans cells, as a subset of cDCs, also express CD4 and CCR5 in their immature state, rendering them susceptible

Table 3. Description of major events in dendritic cell functions and HIV replication and pathogenesis triggered by the interaction of HIV with dendritic cells

Events during HIV/DC interaction	Consequence in DC function	Consequence in HIV replication and pathogenesis
Binding to DC-SIGN	Activation of LARG/Rho pathway allowing the formation of virologic synapse Downregulation of proinflammatory cytokines	Incomplete maturation of DCs Triggers the transcription of viral genome via NF-κB signaling Transfer from DCs to T-cell in the context of virological synapse
TLR8 activation in cDCs	Inhibition of mTOR, which negatively regulates the fusion of endosomes with autophagosomes Diminished antigen processing and presentation activities	Increased HIV survival Decreased processing and presentation of viral antigens Transfer to T-cells
Induction of IRF-1 and IRF-7 in MDDCs	Specific induction of a cluster of IFN-stimulated genes	Induction of IRF-1 and IRF-7 increase the transcription of HIV genome through binding to ISRE in LTR
Preventing IRF-3 activation in MDDCs	Prevents type I IFN production	Avoid IFN-induced immune response.
TLR7 activation in pDCs	Production of large amounts of type I IFN (particularly IFN-α) Activation of NK cell cytolytic activity Production of chemokines Facilitates adaptive immunity by promoting Th1 activation	Depletion of $CD4^+$ T-cells by apoptosis (bystander effect through induction of TRAIL) Chemokine attraction of T-cells facilitates viral spreading to neighbor cells
pDC endocytosis of HIV mediated by envelope glycoprotein-CD4 interaction	Upregulation of IDO, which prime T_{reg} cells, and consequent expression of IL-10	Impaired cDC function further blunting adaptive immune response Decrease of TH17 cells that lead to loss of gut integrity and microbial translocation

DC: dendritic cell; DC-SIGN: DC-specific ICAM3-grabbing non-integrin; LARG/Rho: leukemia-associated Rho guanine nucleotide exchange factor; NF-κB: nuclear factor kappa B; TLR: toll-like receptor; mTOR: mammalian target of rapamycin; IRF: interferon regulatory factor; ISRE: interferon-stimulated response element; IFN: interferon; pDC: plasmacytoid dendritic cell; NK: natural killer; TRAIL: tumor necrosis factor (TNF)-related apoptosis-inducing ligand; IDO: indoleamine 2,3-dioxygenase; T_{reg}: T regulatory; Th: T helper; IL: interleukin; cDC: conventional dendritic cell.

to CCR5-using (R5) variants[39-41], yet activated LCs become less infectable by R5 strains, apparently due to the downregulation of CCR5 expression (reviewed[42]). Productive LC infection by HIV R5 strains must therefore take place in immature LCs or during early stages of maturation. Interestingly, immature LCs exposed to low viral concentrations can efficiently bind and take up HIV virions, but neither a productive infection nor the transfer of viral particles to T-cells occurs[35]. Instead, HIV is destroyed within Birbeck granules after virus/langerin interaction. This protective effect of LCs is inhibited in the presence of higher concentrations of HIV, leading to the transfer of internalized virus to T-cells[35], probably as a consequence of langerin-mediated uptake saturation. Additionally, a recent study showed that LCs derived from $CD34^+$ hematopoietic progenitor stem cells preferentially transfer HIV-1 to T-cells by a *cis* mechanism after productive infection took place[43].

Altogether, from the data available regarding HIV/LC interaction, it is clear that the relative importance of the different mechanisms of HIV trafficking and transmission in LCs and T-cells is far from being widely accepted.

Lastly, pDCs can capture antigen through the CLR blood dendritic cell antigen (BDCA)-2 and CD4/CCR5 but, in the case of HIV, its capture and subsequent internalization is generally mediated by interaction of the HIV gp120 envelope protein with CD4[44]. Despite their increased flexibility due to maintaining the ability to process antigens after maturation, pDCs are less efficient than myeloid DCs at endocytosing, processing and loading antigens on MHC, expressing smaller amounts of co-stimulatory molecules and MHC-II[45-47].

HIV evasion and replication in conventional dendritic cells

Interactions between HIV and cells involved in immune responses are probably connected with all aspects of HIV infection *in vivo,* including pathogenesis and immune control (Table 3). As a retrovirus, it

encodes a limited number of proteins, relying heavily on the biochemical machinery of the host cell to replicate and propagate. The way HIV evades immune sensing while replicating inside cDCs has been a subject of intense investigation and debate, and the amount of available information is immense. However, the following key points are definitely worth highlighting in order to better understand how HIV modulates the intracellular milieu of DCs in order to facilitate the infection, the persistence, and the transfer to $CD4^+$ T-cells.

A recent review[48] has expanded on how optimal priming of naive T-cells by cDCs requires optimally matured cDCs. If cDC maturation is suboptimal upon HIV antigen presentation to T-cells, a crippled immune response may result, with an expansion of antigen-specific T-cells that lack potent antiviral activity against HIV. While it has been reported that HIV partially induces cDC maturation[44,49-53], other evidence suggests that it actually inhibits such maturation[54-58]. However, it seems most reasonable to see these two opposite propositions as being two different perspectives of the same event. Indeed, the most likely scenario is that HIV/cDC interaction initially induces cDC maturation, and then HIV alters cell physiology in order to partially stifle it, leaving cDCs at the incomplete maturation state that is needed for HIV dissemination and pathogenesis.

Recent work has shown that DC-SIGN activates the leukemia-associated Rho guanine nucleotide exchange factor (LARG)/Rho pathway, which seems to be connected to viral replication in DC/T-cell co-cultures[59]. This, together with the knowledge that stimulation of DC-SIGN downregulates the expression of proinflammatory cytokines, strongly suggests that HIV uptake by DC-SIGN may be involved in achieving the partial maturation state of cDCs that is characteristic of HIV infection.

The DC-SIGN is also involved in *de novo* replication of HIV in immature cDCs along with TLR8. It targets HIV to TLR8-containing endosomal compartments, triggering the transcription of integrated HIV DNA via activation of TLR8 and subsequent nuclear factor kappa B (NF-κB) signaling. In turn, the binding of gp120 to DC-SIGN leads to rapidly accelerated fibrosarcoma proto-oncogene serine/threonine-protein kinase (RAF) 1-mediated phosphorylation of the p65 subunit of NF-κB, allowing for the elongation of HIV transcripts and thus productive transcription in infected cDCs[60,61]. Therefore, both DC-SIGN and TLR8 engagement seem to be necessary for HIV replication in cDCs.

In a process that is likely chronologically preceded by TLR8 activation by HIV, or otherwise dependent on the receptor used for viral entry, HIV seems to prevent its own autophagy-mediated degradation. This happens via the inhibition of mammalian target of rapamycin, which negatively regulates the fusion of endosomes with autophagosomes[62]. This loss of lysosomal fusion, in turn, may interfere with MHC-II-associated antigen presentation and also lead to a documented decrease in expression of cathepsin B, C, S, and Z, alongside increased expression of cathepsin L. The net effect is largely diminished cathepsin activity in HIV-infected cDCs, resulting in increased HIV survival and transfer to T-cells, but decreased processing and presentation of viral antigens while the virus continues to replicate at a slow pace[55,63,64].

Complementing this, HIV has also been shown, by a recent study[65], to induce a distinct subset of IFN-stimulated genes in MDDCs, without detectable type I or II IFN production. According to this study, the direct stimulation of this specific IFN-stimulated gene subset in HIV-infected MDDCs seems to suggest direct viral modulation to enable functional transfer to T-cells. The expression of all these IFN-stimulated genes is driven by IFN regulatory factor (IRF)-1, which is initially and persistently upregulated by the virus in infected MDDCs in order to aid its own replication through binding to an IFN-stimulated response element (ISRE) in HIV long terminal repeat (LTR). Its two inhibitors, IRF-2 and IRF-8 are transiently upregulated as well, and this combination is argued to provide an early replication stimulus to the initially taken-up HIV, while restricting viral replication enough to retain host cell integrity until it reaches T-cells. These data further suggest that the early and sustained induction of IRF-7 may have an important role in stimulating HIV replication as it is one of the main inducers of type I IFNs in most cell types and yet, in MDDCs, its upregulation by HIV does not induce type I IFN production.

Additionally and very importantly, HIV seems to inhibit IFN production and thus largely cripple immune response by preventing activation of IRF-3, one of the main inducers of type I IFN production. This was shown to take place not through Vpr- and Vpu-mediated ubiquitination, as happens in T-cells, but through Vpr-dependent inhibition of IRF-3 translocation to the nucleus where it would act[65].

Concerning cDC restriction factors (Table 4), there are differences worth noting between HIV-1 and HIV-2. For HIV-1, the accessory proteins Vif and Vpu counter the restriction factors catalytic polypeptide-like apolipoprotein B mRNA editing enzyme (APOBEC) and tetherin, respectively. The APOBEC inhibits HIV infection[66]

Table 4. Intracellular restriction factors affecting HIV replication and viral proteins that counteract these factors

Cellular restriction factor	Mechanism of action	Counteracting viral factor	HIV evasion mechanism
SAMHD1	Depletes intracellular pool of deoxynucleoside triphosphates. Impairs reverse transcription and thus productive infection in DC	Vpx (only present in HIV-2).	Vpx targets SAMHD1 for proteasome degradation, facilitating HIV replication by promoting synthesis of viral DNA
BST2/tetherin	Inhibits viral release from the membrane of virus producer cells. Trapped virions are probably endocytosed and degraded in lysosomes	Vpu (only present in HIV-1). Transmembrane envelope glycoprotein (HIV-2).	Vpu reduces the level of tetherin at cell surface, either by sequestering it in the trans-Golgi network, or by causing its internalization
TRIM5α	Targets the incoming HIV capsid protein and triggers premature viral uncoating. Results in inhibition of reverse transcription and nuclear import. Not effective in human cells. Restricts host range of HIV-1	TRIM5α does not inhibit retroviruses isolated from the same host species.	
APOBEC3G	Cytidine deaminase; Induces alterations in the nucleotide sequence through cytidine deamination, converting cytidines to uridines (C to U) or deoxycytidines (dC) to deoxyuridines (dU)	Vif	Vif inhibits the packaging of APOBEC3G in virus producer cells by functioning as an adaptor molecule that links a cullin-5-based E3 ubiquitin ligase complex with APOBEC3G, leading to polyubiquitination and targeting APOBEC3G and 3F to proteasome degradation

DC: dendritic cell.

by inducing hypermutations in the nascent viral DNA during reverse transcription, while tetherin blocks viral release from the infected cell[67]. HIV-2 expresses an additional protein, Vpx, which facilitates HIV replication by promoting synthesis of viral DNA[68] and causing the destruction of restriction factor SAMHD1, which may actually work against the progression of HIV infection. This restriction factor is active against not only HIV-2 but also HIV-1, and its role as well as that of Vpx will be explored in detail in the next section of this review.

Plasmacytoid dendritic cell response and dysregulation

In contrast to myeloid DCs, pDCs efficiently and rapidly detect HIV mainly through TLR7, leading to the production of large amounts of type I IFNs, particularly IFN-α, independently of productive infection[69]. This cytokine normally activates natural killer (NK) cell cytolytic activity (making pDCs mediators of innate immunity), restricts viral replication in other potential host cells, and facilitates adaptive immunity by promoting type 1 helper T-cell (Th1) activation[70,71].

While HIV mutes type I IFN production in cDCs as previously detailed, it stimulates it tremendously in the case of pDCs[72]. It has been previously postulated[73-75] that this rampant type I IFN production may lead to generalized $CD4^+$ T-cell loss, mainly by inducing rapid $CD4^+$ T-cell expression of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). This effectively transforms pDCs into IFN-producing killer pDCs that may well contribute to bystander $CD4^+$ T-cell death through their cytotoxic activity[16,73,75]. Furthermore, and in support of this hypothesis, evidence shows that pDCs produce T-cell-attracting chemokines that may facilitate viral spread to neighboring T-cells, similar to what happens in simian immunodeficiency virus[76,77].

Finally, HIV-exposed pDCs prime regulatory T (T_{reg}) cells due to upregulated expression of indoleamine 2,3-dioxygenase (IDO), which is driven by gp120/CD4 mediated endocytosis of HIV. This could impair cDC function due to T_{reg} expression of IL-10 and also block effector T-cell activation, further blunting adaptive immunity in the process[4,78,79]. In turn, promotion of T_{reg} cell responses by pDCs may cause the decrease in

Th17 cells that occurs during HIV infection[80], which is thought to lead to the loss of gut integrity and microbial translocation in patients with HIV[81].

All of the above indicates that the dysregulation of pDCs may indeed have a predominant role in the immunopathogenesis of HIV infection. In agreement with this notion, research has already shown that preservation of pDC function may be one of the key players in the effective viremia control of so-called "elite controllers" (EC)[16]. The next section will discuss this topic in more detail.

Viral trafficking and transmission to T-cells

As previously mentioned, HIV can be transferred to T-cells in two distinct phases: *trans*-infection and *cis*-infection[21,82].

First phase transfer, also dubbed *trans*-infection, takes place if the DC comes into contact with a T-cell within the first hours of infection, probably in the submucosa, and decreases with time. This occurs as a result of the vesicular caves mentioned earlier in this review, which are relocated along with their viral contents at the DC/T-cell contact zone, in this case dubbed a virological synapse[23,83], whereupon they are released in order to infect $CD4^+$ T-cells in their vicinity. According to a recent review[7], DC-SIGN has been shown to be involved in the formation of virological synapses through the activation of the LARG/Rho signaling pathway upon binding to HIV.

Trans-infection ceases after roughly 24 hours, at which point all the remaining virions have been destroyed by the DCs, possibly by acidic proteolysis in late endosomes, and no further transfer of virus to T-cells is observed[21,29,84].

Second-phase transfer, or *cis*-infection, begins approximately 48 hours post-infection, taking place mostly in lymph nodes. During *cis*-infection, newly synthesized virions bud off from the plasma membrane of productively infected DCs and the amount of HIV transferred increases with time. This occurs as a result of increasing *de novo* viral synthesis, which is derived from the small percentage of virions that initially entered via neutral fusion with the DC membrane, mainly through CD4/CCR5-mediated entry as previously described in this work.

Although HIV replication is limited in DCs, *cis*-infection is required for long-term transfer to $CD4^+$ T-cells, allowing HIV to replicate to a much greater extent in antigen-specific $CD4^+$ T-cells, its prime target[85-88]. It is assumed that the close contact between DCs and T-cells during the formation of the IS supports the *in vivo* transfer of HIV to $CD4^+$ T-cells[85,89], though the precise molecular mechanism involved in the actual transfer has yet to be clarified. One of the most debated aspects of cell-to-cell transfer of HIV is the influence of BST2/tetherin expression. This cellular antiviral factor inhibits HIV release from infected cells by anchoring budding viral particles at the cell membrane and is antagonized by HIV-1 Vpu protein[67,90]. Accordingly, BST2/tetherin favors the accumulation of virus particle on the cell membrane, whereas the interaction of Vpu with BST2/tetherin promotes virion release. Several reports have addressed the question of whether BST2/tetherin assists or inhibits HIV transmission from DC to T-cell during IS. However, in most cases, the experimental conditions used may be less than ideal, favoring *trans*- rather than *cis*-infection, and thus warrants further investigation in the physiological function of BST2/tetherin in the context of the antigen-mediated IS[5].

Regarding cross-presentation of HIV by human DC subsets, most findings are still quite hypothetical and heavily based in murine models that may not reflect the complex network observed in the human host (as reviewed[12]). Nevertheless, pDCs and some cDC subsets (namely, $Clec9A^+CD141^+$ DCs and $CD1c^+$ DCs) have been shown to be intrinsically capable of cross-presentation of antigens to T-cells[91]. Another study[92] has also shown that HIV Gag protein is efficiently cross-presented to T-cells when antibody-targeted towards the DEC-205 receptor in Flt3 ligand-mobilized murine $CD8^+$ DCs.

HIV restriction in dendritic cells

Intracellular restriction factors are key players in host defense against viral infections (Table 4). Some of these cell-intrinsic factors were identified as effective barriers to HIV infection in certain cell types (e.g. Trim5α, cyclophilin A, APOPEC3G, BST2/Tetherin, SAMHD1), inhibiting or slowing down viral infection and dissemination, thus providing the host with a first line of defense against this infection. However, as an extraordinarily adapted pathogen, HIV has evolved in order to subvert, evade, or antagonize some of these cellular antiviral proteins, mainly through the action of some viral accessory proteins (e.g. Vif, Vpu, Vpx). *Per se,* both cell restriction factors and viral counterparts are potential targets for therapeutic intervention and thus further investigation may be necessary and desirable.

SAMHD1, dendritic cells and Vpx: differences between HIV-1 and -2

SAMHD1, a recently characterized cell-type specific restriction factor, is not counteracted by HIV-1[9,93]. While the antiviral activity of other restriction factors is saturable, SAMHD1 is not, with it remaining operative during HIV-1 intracellular spread thanks to its mechanism of action[94,95]: in HIV-1-infected DCs, it depletes the intracellular pool of deoxynucleoside triphosphates, thus impairing HIV-1 reverse transcription, productive infection and, consequently, productive cell-to-cell transmission[93,94]. This results in a lower viral replication in DCs, which may enable HIV-1 avoidance of a recently described cryptic viral sensor that would otherwise trigger IFN-mediated antiviral immunity[96,97]. This could eventually favor generalized $CD4^+$ T-cell depletion[4,96]. Therefore, while SAMHD1 effectively renders DCs less permissive to HIV-1 infection, it seems to be somewhat paradoxically responsible for the HIV-1 evasion of immune sensing and subsequent poor priming of adaptive immunity, as discussed in the previous section.

HIV-2 brings in a new and interesting element: Vpx, an accessory protein that is believed to have originated by duplication of the common *vpr* gene present in primate lentiviruses[98], possibly to compensate for a theorized low HIV-2 RT affinity for deoxynucleoside triphosphates[8,99]. This accessory protein antagonizes the effect of SAMHD1 by targeting it for proteasome degradation[9,68,93,100], rendering HIV-2-infected cells much more permissive to productive infection and viral replication than they would otherwise be, and allowing faster accumulation of full length viral DNA[100]. This has been shown to have a widely positive DC-specific effect in the innate immune sensing of HIV infection[8,97,100,101] and it may be related to the lower viral load and slower progression to AIDS that is characteristic of HIV-2 infection compared to HIV-1[102]. In the next section we will look into the HIV-2 model in more detail.

These immunologically positive effects of Vpx are not limited to HIV-2, with data showing that MDDCs infected with HIV-1 produced type I IFN and upregulated CD86 only in the presence of Vpx[8]. These findings further suggest that HIV-1, by avoiding efficient productive infection of MDDCs through preservation of SAMHD1, may also control the array of presented or cross-presented viral antigens, resulting in qualitatively or quantitatively minor $CD8^+$ and $CD4^+$ responses[8,101,103], in line with what was referred to in the previous section.

Indeed, individuals with low SAMHD1 activity or silenced SAMHD1 present an enhanced immune response to HIV-1 infection, as previously hypothesised[93,97] and demonstrated[8]. Accordingly, data shows that silencing of SAMHD1 significantly enhances HIV-1 intercellular transmission, albeit less efficiently than the addition of Vpx to MDDCs. It also seems possible that Vpx exerts additional SAMHD1-independent effects to facilitate infection[8,99], making this an area with vast potential for not only deepening the understanding of DC cell biology, but also for the development of vectors aiming the genetic modification of MDDCs with strong potential in gene therapy[104].

Plasmacytoid dendritic cells in elite controllers

HIV elite controllers (EC) are a rare group of HIV-1 infected patients who are able to maintain high $CD4^+$ T-cell counts and undetectable viral loads in the absence of antiretroviral therapy (ART), despite a prolonged course of infection[105]. The mechanisms behind this rare, spontaneous HIV viremia control have been studied and can hopefully help in the design of a therapeutic vaccine against HIV, with results suggesting that the quantitative and qualitative (alternatively, numerical and functional) preservation of pDCs are some of the most important factors to be considered and further investigated[16].

Indeed, when comparing EC pDCs to ART-naive viremic subjects with high viral load pDCs, it was found that EC pDCs are largely superior antiviral agents. Their IFN-α production is drastically higher, their capability to induce the apoptosis of HIV-infected T-cells is maintained, and they also preserve homogeneous surface expression of CD4, which is necessary for efficient pDC activation by HIV and seems to be gradually internalized in viral load as a result of continuous exposure to the virus[16].

These results emphasize the importance of innate immunity in HIV pathogenesis, and underline how important and helpful a deeper understanding of pDC mechanisms may be for future HIV therapy design.

Dendritic cell/natural killer cell crosstalk

Natural killer cells promote antiviral immunity through the production of proinflammatory cytokines and by lysing infected cells[106-108]. In addition, they interact with T-cells and DCs to shape the magnitude and quality of adaptive immune responses[106,109,110].

In addition to their own antiviral functions, NK cells can also modulate DC function in order to regulate antiviral immunity. Crosstalk between NK cells and DCs results in activation of both cell types, with DCs upregulating NK cell effector functions and NK cells inducing further maturation of DCs. Both cytokine production and cell-cell interactions have been shown to be involved in this process: DCs are activated by HIV-1 and secrete proinflammatory cytokines, including IL-12, IL-15, and type I IFN, promoting NK cell proliferation and cytotoxicity. Activated NK cells secrete IFN-γ, which promotes DC maturation and Th1-type immune responses. Furthermore, NK cells can eliminate immature DCs in a process called editing, promoting the induction of adaptive T -cell immunity.

Data suggests that both NK cell-mediated DC editing and DC-NK crosstalk are disrupted during HIV-1 infection, due to the functional impairment of DCs and NK cells alike[111]. The precise mechanisms by which this happens are yet to be fully understood. In agreement with this, a recent review[4] underlines how further research in this field of interest may provide new targets for HIV therapeutic modulation and vaccine design; indeed, the development of DC-based vaccine strategies that elicit HIV-specific NK cell responses and stimulate the production of memory cells may be crucial for the success of future vaccines.

HIV-2 infection as a natural long-term non-progressive infection

Almost all the data included in this review was derived from studies using HIV-1 as a model. However, HIV-2 is a lentivirus that shows decreased pathogenic abilities in humans, reflected by a slower rate of disease progression with a longer asymptomatic period and lower levels of viremia (recently reviewed[112]). In fact, several studies[113-115] showed that, in general, HIV-2-infected individuals could be defined as long-term non-progressors (referred earlier in these review) as also described for a small percentage of HIV-1 infections[105].

Several factors (e.g. virologic and immunologic) should account for a best-fitted host response that ultimately enables the control and confinement of HIV-2 pathogenic potential. A recent report even suggested an apparent protective effect of a preexisting infection by HIV-2, resulting in a slower rate of HIV-1 disease progression[116]. The mechanisms underlying this control are still poorly understood, but surely result from a combination of distinct features involving the virus, its replication, and the interaction with host cells, resulting in a better preserved equilibrium between HIV-2 replication and host immune response when compared to HIV-1 infection.

One of the factors that account for this attenuated course of infection should be the way HIV-2 envelope glycoproteins interact with host-cell receptors[117]. The identification of HIV-2 isolates that are able to infect cells in the absence of CD4[118,119], the promiscuous use of chemokine receptors as coreceptors for viral entry[120-124], and the identification of primary HIV-2 isolates unable to use the two major coreceptors (i.e. CCR5 and CXCR4)[125,126] are notorious examples of the heterogeneous mechanisms by which HIV-2 interacts with and infects target cells.

The attenuated *in vivo* phenotype of HIV-2 is followed by a decreased capacity to spread within the human population. Compared to HIV-1, HIV-2 has a lower transmission rate[127,128], not only as a consequence of the lower viremia observed in HIV-2-infected individuals, but also related to hypothetical additional vulnerabilities during mucosal transmission. In fact, data are still missing regarding the initial interaction of HIV-2 with cells present at mucosal and submucosal tissues, e.g. LCs, other DCs, macrophages and T lymphocytes. Important clues will certainly emerge from studies addressing: (i) the engagement of cellular receptors, including (but not limited to) DC-SIGN, CD4 and chemokine receptors; (ii) the interplay with cellular restriction factors (e.g. BST2/tetherin, SAMHD1); (iii) the interactions with endolysosomal antigen-degradative mechanisms dictating the fate of endocytosed viral particles. This knowledge will certainly help in understanding how the human host is able to control an exogenous lentiviral infection, reducing the immune dysregulation that in general is associated with HIV-1 infection.

Conclusion

The pathogenesis of HIV infection is a highly complex network of interconnected processes. It likely borrows much of its complexity from the co-evolution with several mammalian species that this and other lentiviruses have enjoyed over an unknown, but rather long expanse of time. This makes the understanding of HIV pathogenesis quite synergic with a more profound understanding of human cell biology and immunology.

Throughout this review, important research targets have been pointed out – some more specific than others. However, a common element to all of them is their

potential usefulness in the design of new strategies for HIV vaccination. This prevention strategy continues to be seen as ideal in the pursuit of successful therapeutic modulation of HIV infection, and some of the many potential targets pinpointed in recent years are already showing promise. For example, adjuvants and vaccine vectors that target cDCs and pDCs simultaneously could trigger adaptive immune responses and limit the induction of T_{reg} cells in order to control viral entry through the mucosa as well as through direct inoculation in the blood stream. Another possible approach is vaccination with a pseudotyped, integrase-deficient HIV construct as a highly efficient immunogen to prime DCs and memory T-cells.

An overwhelmingly large percentage of these targets are, indeed, directly related to different DC subsets. This denotes how important it is to regularly consolidate the knowledge that is unearthed on their interactions with HIV, which define themselves as a critical network of processes taking place during all stages of HIV infection. With that in mind, it is increasingly clear how well adapted this virus is to the human host and how the most successful treatment/prevention strategies will likely derive from the modulation of human cell functions rather than acting directly upon viral mechanisms.

Incidentally, this review has also shown that some mechanisms and molecular pathways still need to be understood to a much better extent than they currently are before any conclusive steps can be taken. It showcases just how much has been discovered regarding DCs and their role in HIV infection in recent years, and at the same time, how feeble this knowledge can be. As pointed out in previous sections, it is quite likely that the experimental conditions being used in some studies are suboptimal and are therefore hindering more objective and decisive progress in this field. Particularly, murine MDDCs have been widely used *in vitro* in many studies cited in this review, yet research has also shown that such models may indeed present considerable differences to human MDDCs *in vivo*. This highlights one of the problems in studying the events of host-HIV interactions during and soon after HIV transmission: the lack of a suitable *in vivo* model.

In general, and across the different DC subsets as well as NK cells, more *in vivo* studies are needed in order to apply this basic knowledge to the direct or indirect manipulation of DCs, during the right time frames, with the final goal of developing a functional vaccine.

Acknowledgements

This work was supported by grants from *Fundação para a Ciência e Tecnologia and Ministério da Saúde de Portugal* (FCT grant: VIH/SAU/0006/2011).

We are especially grateful to Elsa Anes for helpful and stimulating discussions and for critical reading of the manuscript.

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