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Dendritic cells in progression and pathology of HIV infection

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Abstract

Although the major targets of HIV infection are CD4+ T cells, dendritic cells (DC) represent a crucial subset in HIV infection as they influence viral transmission, target cell infection and antigen presentation of HIV antigens. DC are potent antigen presenting cells that can modulate anti-viral immune responses. Through secretion of inflammatory cytokines and interferons (IFN), DC also alter T cell proliferation and differentiation, participating in the immune dysregulation characteristic of chronic HIV infection. Their wide distribution in close proximity with the mucosal epithelia makes them one of the first cell types to encounter HIV during sexual transmission [1]. We will discuss here the multiple roles that DC play at different stages of HIV infection, emphasizing their relevance to HIV pathology and progression.

Promiscuous role of DC in HIV infection

Often described as 'Nature's adjuvant', DC display unique characteristics that can be harnessed for an efficient HIV vaccine, such as microbe sensing, secretion of anti-viral cytokines, antigen presentation, or T cell instruction through soluble and cell-associated molecules. However, their intricate interactions with CD4+ T cells can be utilized by HIV to spread and infect new target cells. Beyond viral replication, many studies in recent years have broadened the role of DC to each and every stage of HIV infection, and we discuss here the progress made in understanding DC biology in HIV infection at the molecular, cellular and population level. Although several DC subsets in different tissues are known, for the purpose of this review we will refer mainly to the myeloid CD11c+ conventional DC (cDC) and the plasmacytoid DC (pDC).

HIV capture and transmission

DC express high amounts of the HIV entry receptors CCR5 and CXCR4, as well as relatively low levels of CD4, allowing gp120 binding and attachment of HIV virions. Upon DC maturation, CCR5 is down-regulated and CXCR4 is upregulated [2]. While CD4, CXCR4 and CCR5 are considered to be the primary receptors for HIV, specific DC subsets express a number of other receptors that can bind the envelope glycoprotein gp120 [3] (Figure 1). Thus, Langerhans cells in the skin and genital epithelia express the C-type Lectin Receptor (CLR) Langerin (CD207), while conventional DC (cDC) in subepithelia and the lamina propria can bind HIV through DC-Immunoreceptor (DCIR) [4]. Other CLRs, such as

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DC-specific intercellular adhesion molecule-grabbing nonintegrin (DC-SIGN), and mannose receptor on dermal DC also bind the heavily glycosylated gp120 [3]. The DC-specific heparan sulfate proteoglycan Syndecan can also participate in gp120-mediated HIV capture [5]. The importance of each pathway for different DC subsets in vivo is not yet determined. Whereas plasmacytoid DC (pDC) express CD4 as well as the CLR BDCA-2, gp120 binding and HIV recognition by pDC is primarily through CD4-mediated endocytosis [6–8].

Env-independent modes of HIV capture have also been described, involving interactions with glycosphingolipids in the virus lipid bilayer and binding to an unknown receptor on immature or mature DC [9–11]. The lipid content of DC cell membrane is also important in mediating Env-independent viral capture. Indeed, Peroxisome proliferator-activated receptor gamma (PPARc) and liver X receptor (LXR) trigger cholesterol efflux from DC, decreasing DC-associated cholesterol content, which subsequently prevents Env-independent HIV capture [12], possibly through raft or membrane microdomains perturbation. HIV uptake is enhanced upon maturation of cDC, an effect seemingly independent of binding to the viral envelope [13]. HIV binding to DC upon cell-to cell contact needs to be more fully characterized, as it facilitates binding and stimulation at lower viral titers than free virion [7], and may affect intracellular compartmentalization and the functional outcome of the interaction. Studies in pDC demonstrate that cell-associated HIV is captured by pDC in an Env-dependent manner to trigger type I IFN [7, 14].

The fate of bound HIV virions depends on the receptor, the DC subtype, its state of maturation, and interaction with other cells. Thus, HIV binding to DC-SIGN does not lead to its full degradation, but to retention in early endosomal compartments, which may allow its delivery to uninfected T cells through an infectious synapse [15]. HIV uptake and infection in mature cDC leads to its co-localization with cholesterol enriched and tetraspanin containing compartments, and can be delivered to the cell surface via an exosomal-like pathway [9]. On the contrary, Langerin–mediated uptake by epidermal Langerhans cells directs virions to acidic compartments where virus is rapidly degraded [16]. In pDC, endocytosed HIV localizes to early endosomes to trigger type I IFN [17], whereas non-fusogenic Env-carrying HIV induced low IFN levels when cell-associated, suggesting that the virions undergo cell fusion prior to cell stimulation [14].

Sentinel DC located in mucosal tissue are one of the first cell populations encountering HIV during early infection. They probably are crucial in the establishment of successful host infection from a small viral pool, and also enhance HIV transfer to uninfected CD4 T cells. In a SIV-macaque model, pDC are recruited very early after viral challenge, presumably through CCL20 secretion by endocervical epithelial cells, and to secrete the chemoattractant CCL3 and CCL4, prompting the recruitment of target CD4+ T cells into the endocervix [18]. Furthermore, in an in vitro model, endocervical epithelial cells were shown to secrete thymic stromal lymphopoietin (TSLP) through NF-kappa B activation, which activates human cDC and induces secretion of the chemokines CCL17 and CCL22, known to attract Th2 and regulatory T cells through CCR4 [19]. TSLP-activated DC enhanced naïve CD4+ T cell proliferation and HIV infection. Vaginal tissues from SIV-infected rhesus macaques displayed high TSLP expression within 2 weeks of SIV challenge. These data suggest that mucosal DC probably play an important role in the initial stages of HIV infection.

Simian models of HIV infection have shown that the majority of initially infected or virus-carrying cells are resting CD4 T cells [20, 21], but viral carrying DC are rarely observed, and DC are poorly susceptible to HIV infection (see below). However, in vitro models have shown that DC can sequester infectious HIV for several days, and efficiently transfer intact virions to CD4+ T cells for explosive infection and viral replication [15, 22, 23]. The migratory capacity of DC, and their ability to contact many T cells at mucosal sites and in

secondary lymphoid tissues likely enhances the effect of such trans-infection. HIV trans-infection is particularly efficient upon cognate interaction with antigen-specific CD4+ T cells [24, 25], possibly resulting in the preferential infection of HIV-specific CD4+ T cells [26]. DC concentrate intact virions at the DC-T cell interface, and induce recruitment of CD4, CCR5, CXCR4 and LFA-1 in T cells to form an 'infectious synapse' [27]. DC-SIGN was originally involved in trans-infection of CD4+ T cells by monocyte-derived DC [15]. However, identification of DC-SIGN independent trans-enhancement of HIV infection [28], variable DC-SIGN expression on different DC subsets, and down-regulation of DC-SIGN upon maturation undermines the importance of this pathway. DCIR has also been shown to mediate trans-infection of CD4+ T cells [4].

HIV restriction and immune recognition

Although DC can be a vehicle for trans-infection, DC are themselves poorly infected compared to T cells [29]. Several restrictions factors have been shown to block HIV replication at different stages of infection, including apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G or 3F (APOBEC3G/3F or A3G/A3F), tripartite motif-5α (TRIM-5α), bone marrow stromal cell antigen-2 (BST-2/ tetherin/ CD317) and sterile alpha motif and HD-domain containing 1 (SAMHD1). Members of the APOlipoprotein B Editing Catalytic subunit-like 3 family possess a cytidine deaminase domain. APOBEC3G is incorporated into newly-made virions, and upon infection of a new cell, it induces G to A hypermutations during reverse-transcription. APOBEC3G can significantly restrict HIV replication in DC [30]. APOBEC3G can be marked for degradation by the Viral infectivity factor (Vif) through ubiquitination and degradation by the proteasome pathway [31]. TRIM5α binds to the incoming retroviral capsid lattice and induces its disassembly before successful reverse transcription [32]. The human TRIM5α only weakly binds to HIV-1 lab strains and poorly restricts HIV in human DC, although it may more potently restrict primary isolates [33]. Tetherin is a type I IFN-inducible restriction factor that can potently block HIV-1 release in cell-to-cell transmission of HIV-1. However, it may not be able to significantly restrict virion release from DC [34]. Recently, SAMHD1 was identified as a major restriction factor in myeloid cells, blocking the post-entry replication by arresting the virus at the minus strong strand stop DNA stage [35, 36]. SAMHD1 mediates restriction activity in non-cycling cells, and functions as a deoxynucleoside triphosphate triphosphohydrolase [37, 38] that depletes the pool of intracellular deoxynucleoside triphosphates, thus inhibiting reverse transcription and complementary DNA synthesis. This model was recently challenged, as SAMHD1 restriction activity may be separable from its triphosphohydrolase activity [39]. SAMHD1 is now known to be the target of the SIV Viral protein X (Vpx) for degradation by the proteasome, and which is absent from the HIV genome. However, while Vpx delivery in moDC allows highly efficient infection by HIV, primary cDC and pDC express high levels of SAMHD1, and it does not significantly induce SAMHD1 degradation and poorly enhances HIV infection of these primary cells [40]. Type I IFN, secreted by pDC and other cells, is a potent inhibitor of or early and late stages of HIV replication [41], acting independently of SAMHD1 [42]. The IFN-induced myxovirus resistance 2 (MX2) protein was recently shown to suppress infection by multiples HIV strains through a late post-entry blockade [43]. Despite these multiple blocks to infection, HIV was shown to exploit an innate immune signaling pathway to facilitate productive infection of cDC. Uptake of HIV by DC-SIGN positive DC results in Toll-Like Receptor (TLR) 8 triggering by viral single-stranded RNA in endosomes, resulting in activation of the NF-κB subunit p65, recruitment of cyclin-dependent kinase 7 (CDK7) to the Long Terminal Repeat (LTR) of HIV. This single interaction only triggers abortive HIV transcription, whereas gp120 binding to DC-SIGN induces activation of Raf1 and phosphorylation of p65, transcription elongation factor b (p-TEFb) recruitment, which thereby facilitates full-length transcription [44].

HIV replication is severely limited in DC, but intracellular recognition of incoming or replicating HIV and subsequent immune activation seems to be blunted by host factors, possibly due to the evolutionary need to control activation by endogenous retroelements [45]. Indeed, the host exonuclease Three prime Repair Exonuclease 1 (TREX1) cleaves ssDNA derived from endogenous retroelements [46], and TREX1 deletion leads to accumulation of defective HIV viral DNA products and production of type I IFN through activation of an unknown cytoplasmic sensor, mediated by STING, TBK1 and IRF3 [47].

Vpx-induced degradation of SAMHD1, while dramatically augmenting HIV transduction of cDC [48], has been shown to trigger a potent innate immune response, characterized by expression of IFNβ and upregulation of CD80 and CD86. Immune activation depended on the interaction of cellular Cyclophilin A and de novo synthesized viral capsid protein, through an IRF3-dependent pathway [49]. The identity of the viral components responsible for activation, and the nature of intracellular sensor have not been defined at this time, but Cyclic GMP-AMP(cGAMP) Synthase (cGAS) has been proposed to function as an innate sensor of reverse-transcribed HIV DNA [50].

Viral immune recognition also occurs through a set of endosomal TLR. The response of cDC and pDC to HIV differ greatly, as pDC secrete very high amounts of IFNα in response to HIV and partially mature, while cDC secrete little if any type I IFN and do not mature. The response of pDC is mediated through TLR7 recognition of viral genomic RNA [6]. In pDC, HIV endocytosis is mediated by envelope-CD4 interaction, and leads to stable accumulation of HIV in a non-acidic early endosomal compartment [17]. The structure of the viral envelope is probably important, as soluble Env protein is rapidly delivered to acidic Lamp-1 positive compartments, unlike whole HIV virions [8]. Spatiotemporal regulation of TLR signaling, described originally for the synthetic oligonucleotides CpG type A and CpG type B [51], posits that different endosomal compartments are associated with different signaling platforms, and that nucleic acids transiting through early endosomes induce type I IFN through activation of TLR7/9 and MyD88-IRF7 recruitment. Therefore, retention of HIV into early endosomes likely explains the high levels of IFNα secreted by pDC in response to HIV. It was later shown that TLR9 is recruited to a specialized lysosome-related organelle by the action of the adapter protein-3 (AP-3), which promotes association of TRAF3 and IRF7 for induction of type I IFN, and that TLR agonists likely access this compartment from an early sorting endosome [52].

The reasons why cDC weakly respond to HIV are unclear. In contrast to pDC, they express much lower amounts of IRF7, necessary for high amounts of type I IFN production. CpG-A, a high IFN inducer in pDC that traffics to early endosomes, has been shown to rapidly reach lysosomal vesicles in cDC, preventing activation of TLRMyD88–IRF7 signaling, whereas redirecting CpG-A to early endosomes in cDC induces high amounts of IFNα [51]. Thus, a difference in the constitutive rate of endosomal maturation, or different receptor-mediated targeting of HIV between pDC and cDC may also explain the differential phenotype of pDC and cDC. For example, CLR-mediated internalization may target HIV to late endosomes/lysosomes in cDC for degradation, without significantly triggering IFN or NF-κB signaling [53]. Alternatively, HIV Env was shown to induce mTOR activation in cDC, leading to inhibition of autophagy and impaired stimulation by TLR4 and TLR8, possibly hampering HIV-mediated DC activation [54], and CLR inhibitory signaling can also antagonize TLR8-mediated activation [55].

An important consequence of HIV retention in early endosomes in pDC is a weak activation of NF-κB signaling, and only partial up-regulation of co-stimulatory molecules. On the contrary, TLR7/8 agonists like Resiquimod, or the TLR9 agonist CpG-B, as well as influenza virus, induce strong NF-κB signaling and maturation of pDC, and upregulation of

co-stimulatory and MHC molecules [17, 56]. NF-κB activation and pDC maturation seems to be correlated with a form of 'TLR tolerance', whereby previously activated pDC become refractory to further stimulation. The lack of maturation induced by HIV in pDC thus allows repetitive stimulation by HIV and continuous IFNα secretion from pDC [17], which may have important pathological consequences (see below). Whether this is an active subversion by the virus, or a consequence of receptor-mediated endocytosis and HIV trafficking to IFN-producing compartments, is not determined. Nevertheless, pDC may participate in the prolonged type I IFN secretion observed in chronic HIV infection. Recent studies have also examined IFNα secretion by pDC interacting with HIV-infected T cells. Although IFNα secretion was TLR7 dependent, viruses carrying a non-fusogenic envelope did not trigger IFNα secretion, suggesting a cytosolic intermediate stage necessary for TLR7 activation. It is thus possible that, similar to Sendai virus and Vesicular stomatitis virus, cell-associated HIV accesses the cytoplasm of pDC and is delivered to TLR7-containing endosomes through autophagy [57], although HIV Env can lead to inhibition of autophagy in DC [54]. A hybrid form of autophagy and phagocytosis, termed 'LC3-associated phagocytosis' (LAP) was also described, which was required for IFNα production by pDC in response to DNA-immune complexes independently of the adapter protein AP-3 [58]. The mechanisms of HIV trafficking in intracellular compartments, for free and cell-associated HIV, need to be better characterized to understand pDC and cDC responses to HIV.

DC dynamics and dysfunction

Owing to the important role of DC at many stages of HIV infection, it is crucial to examine the dynamics and functionality of DC populations during acute and chronic infections. Both cDC and pDC display reduced frequencies in the blood very early after infection, a reduction which persists in chronic infection [59, 60]. Even acute patients under antiretroviral treatment had lower circulating DC numbers. Furthermore, DC frequencies were inversely correlated with plasma viral load [59, 60]. Due to the poor DC infectivity, it is unlikely that infection by itself explains the reduced DC frequencies. pDC and cDC numbers may be reduced due to the acute and chronic type I IFN secreted upon HIV infection, as IFNα can impair cDC differentiation [61], and type I IFN has been shown to negatively regulate pDC numbers in vivo [62]. However, increased numbers of DC have been observed in secondary lymphoid organs of infected patients [63–65]. HIV can directly induce partial maturation of pDC and CCR7 up-regulation [66], and cytokine or pathogen-induced maturation of cDC could also induce their migration to secondary lymphoid organs. In experimental SIV infection, DC in blood, lymph nodes and inflamed mucosa can be monitored closely during the course of infection [67]. During acute pathogenic SIVmac infection of rhesus macaques, pDC are massively recruited to inflamed lymph nodes, where they undergo significant cell death [68], suggesting that peripheral lymph nodes and possibly inflamed mucosa function as 'sinks' for recruited DC. The significance of this observation is highlighted by the fact that cDC from macaques with progressive, but not stable, disease, display early chemokine-mediated recruitment to lymph nodes. cDC do not however accumulate in lymph nodes due to high rates of apoptosis, and this early influx to lymph nodes results in loss of cDC in the blood of animals with progressive disease at viral set point [69]. These studies highlight the complex dynamics of DC mobilization and suggest that it plays an important role to influence the long-term pathogenicity of the infection.

Activation of DC from HIV+ subjects ex-vivo has been evaluated, but results are seemingly contradictory. Early experiments showed that normal DC infected by HIV, or DC from seropositive patients stimulated lower autologous or allogeneic T cell responses [70, 71]. Furthermore, both cDC and pDC from chronically infected individuals were somewhat less responsive to TLR7/8 stimulation, as measured by maturation marker upregulation and

IFNα secretion [72]. On the contrary, recent studies showed that cDC and pDC from acute HIV patients [59], or normal DC infected by HIV [29], mature normally in response to TLR7/8 agonists. In the former study, DC from HIV patients tended to induce stronger allogeneic T cells responses than DC from healthy donors, and cDC secreted higher amounts of cytokines and chemokines upon TLR stimulation. pDC showed blunted IFNα responses early after infection but increased secretion at later stages. The sampling kinetics may thus affect the ex-vivo monitoring of DC function, as the early cytokine storm, migration of DC to secondary lymphoid organs or microbial products derived from microbial translocation in the gut could all impact the composition and phenotype of DC sampled.

Acute HIV infection is characterized by a systemic increase in inflammatory cytokines, acute-phase reactants and high levels of viral replication [73]. In addition, viral replication is linked to T cell death, either via infection or through indirect mechanisms [74–76], leading to the appearance of apoptotic microparticles in the plasma [73]. This immunologically active milieu can potently affect DC function. Indeed, acute and chronic HIV patients' plasma dramatically inhibited the secretion of IL12, TNFα and IL-6 upon stimulation by TLR2, TLR3, TLR4 or TLR7/8 agonists, and subsequently impaired Th1 priming by cDC and NK cell activation [77, 78]. The suppression was partially mediated by apoptotic microparticles binding to the hyaluronate receptor CD44 on DC. Inhibition of DC function paralleled viral ramp-up, but was likely not mediated by direct interaction with the virus. Indeed, lab strains, founder strains or virus derived from HIV infected CD4+ T cells were unable to inhibit DC responsiveness to TLR stimulation [77, 78]. Soluble factors in the infected plasma could also potently suppress DC function. In chronically infected patients, circulating microbial products could contribute to DC tolerization, but LPS was not responsible for DC suppression [78]. The nature of the circulating immunosuppressive factors thus remains to be determined. Although suppression of innate responses by HIV virus was not observed in the above-mentioned studies, it was noted in a different setting that HIV virions could activate the mTOR pathway in cDC, leading to autophagy exhaustion and impaired innate immune signaling in response to LPS [54].

The latter study also demonstrated that autophagy regulates HIV antigen processing and presentation to HIV-specific CD4+ T cells. Inhibition of autophagy by HIV could thus impair MHC-II restricted HIV antigen presentation. The mechanisms of HIV uptake, in particular the endocytic receptors triggered, likely affect viral antigen presentation. Presentation of HIV antigens by cDC to CD4+ and CD8 T cell clones were found to be independent of DC-SIGN, DEC-205 and mannose receptor, although mannan could block MHC-I presentation at high concentrations [79]. MHC-I presentation was also dependent on viral fusion through CD4/co-receptor interaction. Others found DC-SIGN to be involved in MHC-I presentation by primary cDC [80]. In fact, the glycation of HIV Env modifies its affinity for DC-SIGN, its uptake by cDC, HIV antigen presentation and HIV trans-infection [81]. Cross-presentation of HIV antigens has been demonstrated both by cDC [82] and by pDC [83]. In the latter case, pDC could cross-present HIV antigens from apoptotic cells as efficiently as cDC. The CD141+ BDCA3+ CLEC9A+ human DC subset, the equivalent of the murine CD8α [84], may be important for cross-presentation of HIV antigens in vivo [85]. How HIV antigen presentation is regulated in vivo, and how it contributes to the development of CD8+ cytotoxic and CD4+ T cell responses at different stages of the infection require further investigation. Despite obvious differences, persistent viral infections in animal models may provide clues to the role of different DC subsets for HIV antigen presentation [86]. Alternatively, HIV infection and dynamics of immune regulation could be tested in humanized mice models that mimic viral progression as well as CD4+ T cell loss [87].

DC and immunopathology

Chronic immune activation is a hallmark of progressive HIV infection, and markers of CD4+ and CD8+ T cell activation (e.g. Ki67+, CD38, HLA-DR expression) correlate better with disease progression than viremia [88]. Chronic immune activation persists even under antiretroviral therapy, and contributes to infection-associated co-morbidities [89]. One of the major contributors to immune activation is probably microbial translocation across the epithelial lining of the gastrointestinal tract [90], inducing DC activation through innate microbial sensing, and imbalance of mucosal DC populations. Thus, damage to the colonic epithelial barrier in SIV infection of rhesus macaques is associated with loss of mucosal CD103+ DC and IL-17 and IL-22 secreting lymphocytes [91]. pDC accumulate in the gut mucosa and associated lymphoid tissue and contribute to immune activation by secreting inflammatory cytokines [92, 93]. In addition to their role at mucosal surfaces, systemic cytokine secretion by DC, and in particular type I IFN, likely plays a major role in disease progression (Figure 2). High plasma titers of type I IFN in acute and chronic infection correlate with disease progression [94], and lymphoid tissue of progressors express higher levels of IFNα [95]. Transcriptional profiling of pathogenic and non-pathogenic infection in non-human primates showed that progressive infection is characterized by a persistent and systemic IFN response signature, in contrary to non-progressive infections, where IFN signature subsides quickly, despite high levels of viral replication [96, 97]. In humans, type I IFN may contribute to T cell exhaustion during the chronic phase of the disease. IFN can induce TNF-related apoptosis-inducing ligand (TRAIL) and Death Receptor 5 on CD4+ T cells, directly contributing to T cell apoptosis [98]. Inflammatory cytokines and type I IFN can limit thymic output [99], enhance bystander T cell proliferation [100] and inhibit telomerase activity in human T cells [101]. IFN-induced hyperproliferation may drive memory T cell exhaustion over time [102]. Importantly, prolonged type I IFN signaling in chronic viral infection induces the expression of inhibitory surface molecules (PD-L1) on DC, secretion of suppressive cytokines (IL-10), and decreased IFNγ secretion by antiviral CD4+ T cells. Blockade of type I IFN signaling helped resolve persistent infection [103, 104]. Inhibitory co-stimulatory molecules on DC may also contribute to establishment of viral latency in infected CD4+ T cells [105]. The contribution of different DC subsets and other cells to prolonged IFN secretion during HIV infection is unknown, but continuous stimulation of pDC by HIV [17], or cDC by gut microbes, may play an important role. In this respect, pathogenic SIV infections are associated with increased enteric viral infections [106] and expansions of pathogenic bacterial populations in the gut [107], likely contributing to intestinal mucosa damage and systemic activation through microbial translocation. Whereas pDCs have been considered a major source of type I IFN, recent data indicates that blocking pDC-mediated IFN with TLR7/9 inhibitors does not significantly reduce IFN in the serum, viral load, or immune activation during acute SIV infection of rhesus macaques [108]. Although the role of pDC-derived IFN during chronic infection is unknown, these studies highlight the need to better define IFN producing cells in the course of acute and chronic viral infection.

The deregulation of regulatory T cells (Treg) and Th17 cells in blood and mucosal tissues of HIV infected patients may participate in the breakdown of the mucosal barrier and microbial translocation [109], as bacterial translocation is not observed in non-pathogenic infection in which Th17 function is maintained. Depletion of Th17 and increased numbers of Treg in lymphoid tissues is a characteristic of progressive SIV infection [109]. On the contrary, increased Treg numbers are found in the secondary lymphoid tissues of chronically infected individuals [110]. Th17 depletion may be the result of direct HIV infection, but DC have also been shown to play a role in regulating Th17/Treg ratios. Type I IFN constrains the development of Th17 cells [111]. IFN and TLR signaling can also induce the expression of immune-regulatory enzymes in DC. For example, the enzyme indoleamine 2,3 dioxygenase

(IDO) regulating tryptophan catabolism, plays a role in regulating proliferation of activated T cells, but can also enhance the differentiation and activation of Treg [112]. IDO expression by cDC is augmented in HIV patients with progressive disease and is associated with deregulated Th17/ Treg populations [113], whereas in acute SIV infection, pDC accumulate in secondary lymphoid organs in parallel with increased viremia and augmented IDO activity [114]. pDC activated by HIV and other TLR agonists can express IDO and induce the generation of Treg from naïve CD4+ T cells, through activation of the non-canonical NF-κB pathway by HIV in pDC [115, 116], and IDO+ pDC can regulate interconversion of Th17 and Treg under inflammatory conditions [117, 118]. Mouse models of pDC depletion showed that pDC contribute to Treg maintenance in the small intestine, and pDC depleted mice display increased number of Th17 in the lamina propria, confirming the importance of pDC in regulating Th17/ Treg ratios in the gastrointestinal tract [119].

Consequences for HIV prevention and therapy

As described above, DC contribute to HIV infection and pathogenesis through multiple mechanisms, from initial recruitment of target cells, systemic cytokine secretion to alteration of T cell dynamics, and blocking or modulating these DC-initiated pathogenic pathways could be beneficial. Immuno-modulatory microbicides can prevent DC and T cell recruitment during the initial stage of infection. Thus, glycerol monolaurate blocked pDC and T cell recruitment through inhibition of CCL20 secretion by endocervical epithelial cells, enabling protection against high dose SIV challenge [18]. Continuous DC activation and cytokine secretion can potentially be targeted through TLR blockers, such as chloroquine [120] or inhibitory oligonucleotides [108]. Alternatively, neutralization of inflammatory cytokines, e.g. TNFα, have been used with beneficial effects on HIV/AIDS symptoms [121]. Type I IFN blockade also represents an important strategy, due to its major pathogenic role, and has been shown to enhance anti-viral immune responses and viral clearance in models of chronic viral infection [103, 104]. DC are very potent antigen presenting cells and ideal candidate for cell-based vaccines. Autologous DC pulsed with autologous heat-inactivated HIV induced decreased viral set points and enhanced anti-HIV T cell responses after antiretroviral therapy interruption in a small cohort of patients [122]. DC vaccination may be enhanced by blockade of immune checkpoints, such as PD1. PD1 is a marker of T cell exhaustion during chronic viral infections [123], and its blockade in chronically SIV infected macaques decreased the expression of IFN-stimulated genes, while also augmenting immunity to gut-resident pathogenic bacteria [124]. Restoration of gut immunity and normalized Th17/ Treg ratio would be highly beneficial, and segmented filamentous bacteria or their products could potentially be used to stimulate intestinal CD103+ DC to secrete IL-23 and augment Th17 responses against enteric pathogens [125].

Concluding remarks

Remarkable advances have been made in the past years, relating DC dynamics and function to the pathological features of HIV infection. Although much remains to be investigated, it is clear that DC play an essential role in viral transmission, chronic immune activation, T cell dysregulation and exhaustion characteristic of advanced disease. Dissection of the molecular pathways through which DC interact with HIV and with other immune cells will provide targets for therapeutic intervention. Recent successes in prophylactic vaccination against HIV can certainly provide information as to how DC can be harnessed to mount a protective, rather than dysfunctional, anti-HIV immune response. Information gathered from human patients, non-human primate and mouse models will help define rational strategies to uncouple the beneficial and detrimental roles of DC in HIV infection.

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REFERENCES

1. Miller CJ. Host and viral factors influencing heterosexual HIV transmission. Reviews of reproduction. 1998; 3:42–51. [PubMed: 9509988]
2. Sallusto F, et al. Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. European journal of immunology. 1998; 28:2760–2769. [PubMed: 9754563]
3. Turville SG, et al. Diversity of receptors binding HIV on dendritic cell subsets. Nat Immunol. 2002; 3:975–983. [PubMed: 12352970]
4. Lambert AA, et al. The C-type lectin surface receptor DCIR acts as a new attachment factor for HIV-1 in dendritic cells and contributes to trans- and cis-infection pathways. Blood. 2008; 112:1299–1307. [PubMed: 18541725]
5. de Witte L, et al. Syndecan-3 is a dendritic cell-specific attachment receptor for HIV-1. Proc Natl Acad Sci U S A. 2007; 104:19464–19469. [PubMed: 18040049]
6. Beignon AS, et al. Endocytosis of HIV-1 activates plasmacytoid dendritic cells via Toll-like receptor-viral RNA interactions. J Clin Invest. 2005; 115:3265–3275. [PubMed: 16224540]
7. Schmidt B, et al. HIV-infected cells are major inducers of plasmacytoid dendritic cell interferon production, maturation, and migration. Virology. 2005; 343:256–266. [PubMed: 16278001]
8. Sandgren KJ, et al. Human Plasmacytoid Dendritic Cells Efficiently Capture HIV-1 Envelope Glycoproteins via CD4 for Antigen Presentation. J Immunol. 2013; 191:60–69. [PubMed: 23729440]
9. Izquierdo-Useros N, et al. Capture and transfer of HIV-1 particles by mature dendritic cells converges with the exosome-dissemination pathway. Blood. 2009; 113:2732–2741. [PubMed: 18945959]
10. Hatch SC, et al. Glycosphingolipid composition of human immunodeficiency virus type 1 (HIV-1) particles is a crucial determinant for dendritic cell-mediated HIV-1 trans-infection. J Virol. 2009; 83:3496–3506. [PubMed: 19193785]
11. Gummuluru S, et al. Binding of human immunodeficiency virus type 1 to immature dendritic cells can occur independently of DC-SIGN and mannose binding C-type lectin receptors via a cholesterol-dependent pathway. J Virol. 2003; 77:12865–12874. [PubMed: 14610207]
12. Hanley TM, et al. PPARgamma and LXR signaling inhibit dendritic cell-mediated HIV-1 capture and trans-infection. PLoS pathogens. 2010; 6:e1000981. [PubMed: 20617179]
13. Izquierdo-Useros N, et al. Maturation of blood-derived dendritic cells enhances human immunodeficiency virus type 1 capture and transmission. J Virol. 2007; 81:7559–7570. [PubMed: 17475656]
14. Lepelley A, et al. Innate sensing of HIV-infected cells. PLoS pathogens. 2011; 7:e1001284. [PubMed: 21379343]
15. Geijtenbeek TB, et al. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell. 2000; 100:587–597. [PubMed: 10721995]
16. de Witte L, et al. Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat Med. 2007; 13:367–371. [PubMed: 17334373]
17. O'Brien M, et al. Spatiotemporal trafficking of HIV in human plasmacytoid dendritic cells defines a persistently IFN-alpha-producing and partially matured phenotype. J Clin Invest. 2011; 121:1088–1101. [PubMed: 21339641]
18. Li Q, et al. Glycerol monolaurate prevents mucosal SIV transmission. Nature. 2009; 458:1034–1038. [PubMed: 19262509]
19. Fontenot D, et al. TSLP production by epithelial cells exposed to immunodeficiency virus triggers DC-mediated mucosal infection of CD4+ T cells. Proc Natl Acad Sci U S A. 2009; 106:16776–16781. [PubMed: 19805372]

20. Zhang ZQ, et al. Roles of substrate availability and infection of resting and activated CD4+ T cells in transmission and acute simian immunodeficiency virus infection. Proc Natl Acad Sci U S A. 2004; 101:5640–5645. [PubMed: 15064398]
21. Miller CJ, et al. Propagation and dissemination of infection after vaginal transmission of simian immunodeficiency virus. J Virol. 2005; 79:9217–9227. [PubMed: 15994816]
22. Cameron PU, et al. Dendritic cells exposed to human immunodeficiency virus type-1 transmit a vigorous cytopathic infection to CD4+ T cells. Science. 1992; 257:383–387. [PubMed: 1352913]
23. Pope M, et al. Conjugates of dendritic cells and memory T lymphocytes from skin facilitate productive infection with HIV-1. Cell. 1994; 78:389–398. [PubMed: 7914836]
24. Lore K, et al. Myeloid and plasmacytoid dendritic cells transfer HIV-1 preferentially to antigen-specific CD4+ T cells. J Exp Med. 2005; 201:2023–2033. [PubMed: 15967828]
25. Weissman D, et al. The efficiency of acute infection of CD4+ T cells is markedly enhanced in the setting of antigen-specific immune activation. J Exp Med. 1996; 183:687–692. [PubMed: 8627183]
26. Douek DC, et al. HIV preferentially infects HIV-specific CD4+ T cells. Nature. 2002; 417:95–98. [PubMed: 11986671]
27. McDonald D, et al. Recruitment of HIV and its receptors to dendritic cell-T cell junctions. Science. 2003; 300:1295–1297. [PubMed: 12730499]
28. Boggiano C, et al. Dendritic cell-mediated trans-enhancement of human immunodeficiency virus type 1 infectivity is independent of DC-SIGN. J Virol. 2007; 81:2519–2523. [PubMed: 17182696]
29. Smed-Sorensen A, et al. Differential susceptibility to human immunodeficiency virus type 1 infection of myeloid and plasmacytoid dendritic cells. J Virol. 2005; 79:8861–8869. [PubMed: 15994779]
30. Pion M, et al. APOBEC3G/3F mediates intrinsic resistance of monocyte-derived dendritic cells to HIV-1 infection. J Exp Med. 2006; 203:2887–2893. [PubMed: 17145955]
31. Sheehy AM, et al. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. Nat Med. 2003; 9:1404–1407. [PubMed: 14528300]
32. Grutter MG, Luban J. TRIM5 structure, HIV-1 capsid recognition, and innate immune signaling. Current opinion in virology. 2012; 2:142–150. [PubMed: 22482711]
33. Battivelli E, et al. Modulation of TRIM5alpha activity in human cells by alternatively spliced TRIM5 isoforms. J Virol. 2011; 85:7828–7835. [PubMed: 21632761]
34. Coleman CM, et al. Tetherin does not significantly restrict dendritic cell-mediated HIV-1 transmission and its expression is upregulated by newly synthesized HIV-1 Nef. Retrovirology. 2011; 8:26. [PubMed: 21504576]
35. Hrecka K, et al. Vpx relieves inhibition of HIV-1 infection of macrophages mediated by the SAMHD1 protein. Nature. 2011; 474:658–661. [PubMed: 21720370]
36. Laguette N, et al. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. Nature. 2011; 474:654–657. [PubMed: 21613998]
37. Goldstone DC, et al. HIV-1 restriction factor SAMHD1 is a deoxynucleoside triphosphate triphosphohydrolase. Nature. 2011; 480:379–382. [PubMed: 22056990]
38. Lahouassa H, et al. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat Immunol. 2012; 13:223–228. [PubMed: 22327569]
39. White TE, et al. The retroviral restriction ability of SAMHD1, but not its deoxynucleotide triphosphohydrolase activity, is regulated by phosphorylation. Cell host & microbe. 2013; 13:441–451. [PubMed: 23601106]
40. Bloch N, et al. HIV-1 Infection of Plasmacytoid and Myeloid Dendritic Cells is Restricted by High Levels of SAMHD1 that Cannot be Counteracted by Vpx. AIDS Res Hum Retroviruses. 2013
41. Meylan PR, et al. Mechanisms for the inhibition of HIV replication by interferons-alpha, -beta, and -gamma in primary human macrophages. Virology. 1993; 193:138–148. [PubMed: 7679856]
42. Goujon C, et al. Evidence for IFNalpha-induced, SAMHD1-independent inhibitors of early HIV-1 infection. Retrovirology. 2013; 10:23. [PubMed: 23442224]

43. Goujon C, et al. Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection. Nature. 2013
44. Gringhuis SI, et al. HIV-1 exploits innate signaling by TLR8 and DC-SIGN for productive infection of dendritic cells. Nat Immunol. 2010; 11:419–426. [PubMed: 20364151]
45. Iwasaki A. Innate immune recognition of HIV-1. Immunity. 2012; 37:389–398. [PubMed: 22999945]
46. Stetson DB, et al. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell. 2008; 134:587–598. [PubMed: 18724932]
47. Yan N, et al. The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. Nat Immunol. 2010; 11:1005–1013. [PubMed: 20871604]
48. Goujon C, et al. With a little help from a friend: increasing HIV transduction of monocyte-derived dendritic cells with virion-like particles of SIV(MAC). Gene therapy. 2006; 13:991–994. [PubMed: 16525481]
49. Manel N, et al. A cryptic sensor for HIV-1 activates antiviral innate immunity in dendritic cells. Nature. 2010; 467:214–217. [PubMed: 20829794]
50. Gao D, et al. Cyclic GMP-AMP Synthase Is an Innate Immune Sensor of HIV and Other Retroviruses. Science. 2013
51. Honda K, et al. Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. Nature. 2005; 434:1035–1040. [PubMed: 15815647]
52. Sasai M, et al. Bifurcation of Toll-like receptor 9 signaling by adaptor protein 3. Science. 2010; 329:1530–1534. [PubMed: 20847273]
53. van Kooyk Y, Geijtenbeek TB. DC-SIGN: escape mechanism for pathogens. Nat Rev Immunol. 2003; 3:697–709. [PubMed: 12949494]
54. Blanchet FP, et al. Human immunodeficiency virus-1 inhibition of immunoamphisomes in dendritic cells impairs early innate and adaptive immune responses. Immunity. 2010; 32:654–669. [PubMed: 20451412]
55. Meyer-Wentrup F, et al. DCIR is endocytosed into human dendritic cells and inhibits TLR8-mediated cytokine production. J Leukoc Biol. 2009; 85:518–525. [PubMed: 19028959]
56. Kerkmann M, et al. Activation with CpG-A and CpG-B oligonucleotides reveals two distinct regulatory pathways of type I IFN synthesis in human plasmacytoid dendritic cells. J Immunol. 2003; 170:4465–4474. [PubMed: 12707322]
57. Lee HK, et al. Autophagy-dependent viral recognition by plasmacytoid dendritic cells. Science. 2007; 315:1398–1401. [PubMed: 17272685]
58. Henault J, et al. Noncanonical autophagy is required for type I interferon secretion in response to DNA-immune complexes. Immunity. 2012; 37:986–997. [PubMed: 23219390]
59. Sabado RL, et al. Evidence of dysregulation of dendritic cells in primary HIV infection. Blood. 2010; 116:3839–3852. [PubMed: 20693428]
60. Donaghy H, et al. Dysfunction and infection of freshly isolated blood myeloid and plasmacytoid dendritic cells in patients infected with HIV-1. Blood. 2003; 101:4505–4511. [PubMed: 12576311]
61. Kodama A, et al. Impairment of in vitro generation of monocyte-derived human dendritic cells by inactivated human immunodeficiency virus-1: Involvement of type I interferon produced from plasmacytoid dendritc cells. Human immunology. 2010; 71:541–550. [PubMed: 20206223]
62. Swiecki M, et al. Type I interferon negatively controls plasmacytoid dendritic cell numbers in vivo. J Exp Med. 2011; 208:2367–2374. [PubMed: 22084408]
63. Dillon SM, et al. Plasmacytoid and myeloid dendritic cells with a partial activation phenotype accumulate in lymphoid tissue during asymptomatic chronic HIV-1 infection. Journal of acquired immune deficiency syndromes. 2008; 48:1–12. [PubMed: 18300699]
64. Lehmann C, et al. Plasmacytoid dendritic cells accumulate and secrete interferon alpha in lymph nodes of HIV-1 patients. PLoS One. 2010; 5:e11110. [PubMed: 20559432]
65. Nascimbeni M, et al. Plasmacytoid dendritic cells accumulate in spleens from chronically HIV-infected patients but barely participate in interferon-alpha expression. Blood. 2009; 113:6112–6119. [PubMed: 19366987]

66. Fonteneau JF, et al. Human immunodeficiency virus type 1 activates plasmacytoid dendritic cells and concomitantly induces the bystander maturation of myeloid dendritic cells. J Virol. 2004; 78:5223–5232. [PubMed: 15113904]

67. Wonderlich ER, et al. Dissecting the role of dendritic cells in simian immunodeficiency virus infection and AIDS. Immunologic research. 2011; 50:228–234. [PubMed: 21717075]

68. Brown KN, et al. Rapid influx and death of plasmacytoid dendritic cells in lymph nodes mediate depletion in acute simian immunodeficiency virus infection. PLoS pathogens. 2009; 5:e1000413. [PubMed: 19424421]

69. Wijewardana V, et al. Early myeloid dendritic cell dysregulation is predictive of disease progression in simian immunodeficiency virus infection. PLoS pathogens. 2010; 6:e1001235. [PubMed: 21203477]

70. Macatonia SE, et al. Suppression of immune responses by dendritic cells infected with HIV. Immunology. 1989; 67:285–289. [PubMed: 2788124]

71. Roberts M, et al. Dendritic cells from HIV-1 infected individuals show reduced capacity to stimulate autologous T-cell proliferation. Immunology letters. 1994; 43:39–43. [PubMed: 7737688]

72. Martinson JA, et al. Dendritic cells from HIV-1 infected individuals are less responsive to toll-like receptor (TLR) ligands. Cellular immunology. 2007; 250:75–84. [PubMed: 18334250]

73. McMichael AJ, et al. The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol. 2010; 10:11–23. [PubMed: 20010788]

74. Doitsh G, et al. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. Cell. 2010; 143:789–801. [PubMed: 21111238]

75. Cooper A, et al. HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. Nature. 2013; 498:376–379. [PubMed: 23739328]

76. Finkel TH, et al. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. Nat Med. 1995; 1:129–134. [PubMed: 7585008]

77. Frleta D, et al. HIV-1 infection-induced apoptotic microparticles inhibit human DCs via CD44. J Clin Invest. 2012; 122:4685–4697. [PubMed: 23160198]

78. Miller EA, et al. Plasma factors during chronic HIV-1 infection impair IL-12 secretion by myeloid dendritic cells via a virus-independent pathway. Journal of acquired immune deficiency syndromes. 2012; 61:535–544. [PubMed: 22902724]

79. Sabado RL, et al. Pathways utilized by dendritic cells for binding, uptake, processing and presentation of antigens derived from HIV-1. European journal of immunology. 2007; 37:1752–1763. [PubMed: 17534864]

80. Moris A, et al. DC-SIGN promotes exogenous MHC-I-restricted HIV-1 antigen presentation. Blood. 2004; 103:2648–2654. [PubMed: 14576049]

81. van Montfort T, et al. HIV-1 N-glycan composition governs a balance between dendritic cell-mediated viral transmission and antigen presentation. J Immunol. 2011; 187:4676–4685. [PubMed: 21957147]

82. Buseyne F, et al. MHC-I-restricted presentation of HIV-1 virion antigens without viral replication. Nat Med. 2001; 7:344–349. [PubMed: 11231634]

83. Hoeffel G, et al. Antigen crosspresentation by human plasmacytoid dendritic cells. Immunity. 2007; 27:481–492. [PubMed: 17869134]

84. Poulin LF, et al. Characterization of human DNGR-1+ BDCA3+ leukocytes as putative equivalents of mouse CD8alpha+ dendritic cells. J Exp Med. 2010; 207:1261–1271. [PubMed: 20479117]

85. Radford KJ, Caminschi I. New generation of dendritic cell vaccines. Human vaccines & immunotherapeutics. 2013:9. [PubMed: 23570049]

86. Ng CT, et al. Networking at the Level of Host Immunity: Immune Cell Interactions during Persistent Viral Infections. Cell host & microbe. 2013; 13:652–664. [PubMed: 23768490]

87. Brehm MA, et al. Humanized mice for the study of infectious diseases. Current opinion in immunology. 2013

88. Hazenberg MD, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. Aids. 2003; 17:1881–1888. [PubMed: 12960820]
89. Baker JV, Duprez D. Biomarkers and HIV-associated cardiovascular disease. Current opinion in HIV and AIDS. 2010; 5:511–516. [PubMed: 20978394]
90. Klatt NR, et al. Microbial translocation, immune activation, and HIV disease. Trends in microbiology. 2013; 21:6–13. [PubMed: 23062765]
91. Klatt NR, et al. Loss of mucosal CD103+ DCs and IL-17+ and IL-22+ lymphocytes is associated with mucosal damage in SIV infection. Mucosal immunology. 2012; 5:646–657. [PubMed: 22643849]
92. Kwa S, et al. Plasmacytoid dendritic cells are recruited to the colorectum and contribute to immune activation during pathogenic SIV infection in rhesus macaques. Blood. 2011; 118:2763–2773. [PubMed: 21693759]
93. Reeves RK, et al. SIV infection induces accumulation of plasmacytoid dendritic cells in the gut mucosa. The Journal of infectious diseases. 2012; 206:1462–1468. [PubMed: 22711907]
94. von Sydow M, et al. Interferon-alpha and tumor necrosis factor-alpha in serum of patients in various stages of HIV-1 infection. AIDS Res Hum Retroviruses. 1991; 7:375–380. [PubMed: 1906289]
95. Herbeuval JP, et al. Differential expression of IFN-alpha and TRAIL/DR5 in lymphoid tissue of progressor versus nonprogressor HIV-1-infected patients. Proc Natl Acad Sci U S A. 2006; 103:7000–7005. [PubMed: 16632604]
96. Bosinger SE, et al. Global genomic analysis reveals rapid control of a robust innate response in SIV-infected sooty mangabeys. J Clin Invest. 2009; 119:3556–3572. [PubMed: 19959874]
97. Jacquelin B, et al. Nonpathogenic SIV infection of African green monkeys induces a strong but rapidly controlled type I IFN response. J Clin Invest. 2009; 119:3544–3555. [PubMed: 19959873]
98. Herbeuval JP, et al. CD4+ T-cell death induced by infectious and noninfectious HIV-1: role of type 1 interferon-dependent, TRAIL/DR5-mediated apoptosis. Blood. 2005; 106:3524–3531. [PubMed: 16046522]
99. Demoulins T, et al. Reversible blockade of thymic output: an inherent part of TLR ligand-mediated immune response. J Immunol. 2008; 181:6757–6769. [PubMed: 18981093]
100. Tough DF, et al. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. Science. 1996; 272:1947–1950. [PubMed: 8658169]
101. Reed JR, et al. Telomere erosion in memory T cells induced by telomerase inhibition at the site of antigenic challenge in vivo. J Exp Med. 2004; 199:1433–1443. [PubMed: 15148341]
102. Sedaghat AR, et al. Chronic CD4+ T-cell activation and depletion in human immunodeficiency virus type 1 infection: type I interferon-mediated disruption of T-cell dynamics. J Virol. 2008; 82:1870–1883. [PubMed: 18077723]
103. Wilson EB, et al. Blockade of chronic type I interferon signaling to control persistent LCMV infection. Science. 2013; 340:202–207. [PubMed: 23580528]
104. Teijaro JR, et al. Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science. 2013; 340:207–211. [PubMed: 23580529]
105. Kulpa DA, et al. The immunological synapse: the gateway to the HIV reservoir. Immunological reviews. 2013; 254:305–325. [PubMed: 23772628]
106. Handley SA, et al. Pathogenic simian immunodeficiency virus infection is associated with expansion of the enteric virome. Cell. 2012; 151:253–266. [PubMed: 23063120]
107. Moeller AH, et al. SIV-Induced Instability of the Chimpanzee Gut Microbiome. Cell host & microbe. 2013; 14:340–345. [PubMed: 24034619]
108. Kader M, et al. Blocking TLR7- and TLR9-mediated IFN-alpha Production by Plasmacytoid Dendritic Cells Does Not Diminish Immune Activation in Early SIV Infection. PLoS pathogens. 2013; 9:e1003530. [PubMed: 23935491]
109. Favre D, et al. Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection. PLoS pathogens. 2009; 5:e1000295. [PubMed: 19214220]
110. Boasso A, et al. Do regulatory T-cells play a role in AIDS pathogenesis? AIDS reviews. 2006; 8:141–147. [PubMed: 17078484]

111. Guo B, et al. The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. J Clin Invest. 2008; 118:1680–1690. [PubMed: 18382764]

112. Munn DH, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity. 2005; 22:633–642. [PubMed: 15894280]

113. Favre D, et al. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Science translational medicine. 2010; 2 32ra36.

114. Malleret B, et al. Primary infection with simian immunodeficiency virus: plasmacytoid dendritic cell homing to lymph nodes, type I interferon, and immune suppression. Blood. 2008; 112:4598–4608. [PubMed: 18787223]

115. Manches O, et al. HIV-activated human plasmacytoid DCs induce Tregs through an indoleamine 2,3-dioxygenase-dependent mechanism. J Clin Invest. 2008; 118:3431–3439. [PubMed: 18776940]

116. Manches O, et al. Activation of the noncanonical NF-kappaB pathway by HIV controls a dendritic cell immunoregulatory phenotype. Proc Natl Acad Sci U S A. 2012; 109:14122–14127. [PubMed: 22879398]

117. Baban B, et al. IDO activates regulatory T cells and blocks their conversion into Th17-like T cells. J Immunol. 2009; 183:2475–2483. [PubMed: 19635913]

118. Sharma MD, et al. Indoleamine 2,3-dioxygenase controls conversion of Foxp3+ Tregs to TH17-like cells in tumor-draining lymph nodes. Blood. 2009; 113:6102–6111. [PubMed: 19366986]

119. Takagi H, et al. Plasmacytoid dendritic cells are crucial for the initiation of inflammation and T cell immunity in vivo. Immunity. 2011; 35:958–971. [PubMed: 22177923]

120. d'Ettorre G, et al. HIV-associated immune activation: from bench to bedside. AIDS Res Hum Retroviruses. 2011; 27:355–364. [PubMed: 21309730]

121. Ting PT, Koo JY. Use of etanercept in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. International journal of dermatology. 2006; 45:689–692. [PubMed: 16796629]

122. Garcia F, et al. A dendritic cell-based vaccine elicits T cell responses associated with control of HIV-1 replication. Science translational medicine. 2013; 5 166ra162.

123. Barber DL, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature. 2006; 439:682–687. [PubMed: 16382236]

124. Dyavar Shetty R, et al. PD-1 blockade during chronic SIV infection reduces hyperimmune activation and microbial translocation in rhesus macaques. J Clin Invest. 2012; 122:1712–1716. [PubMed: 22523065]

125. Ivanov II, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009; 139:485–498. [PubMed: 19836068]

Highlights

- HIV poorly infects DC, but DC efficiently trans-infect CD4+ T cells.
- DC may help the initial HIV infection and spreading through chemokine secretion
- Activation of pDC by HIV involves IFNα secretion, but cDC are poorly activated
- DC frequencies and innate functions are altered during acute and chronic infection
- Chronic DC stimulation contributes to T cell exhaustion

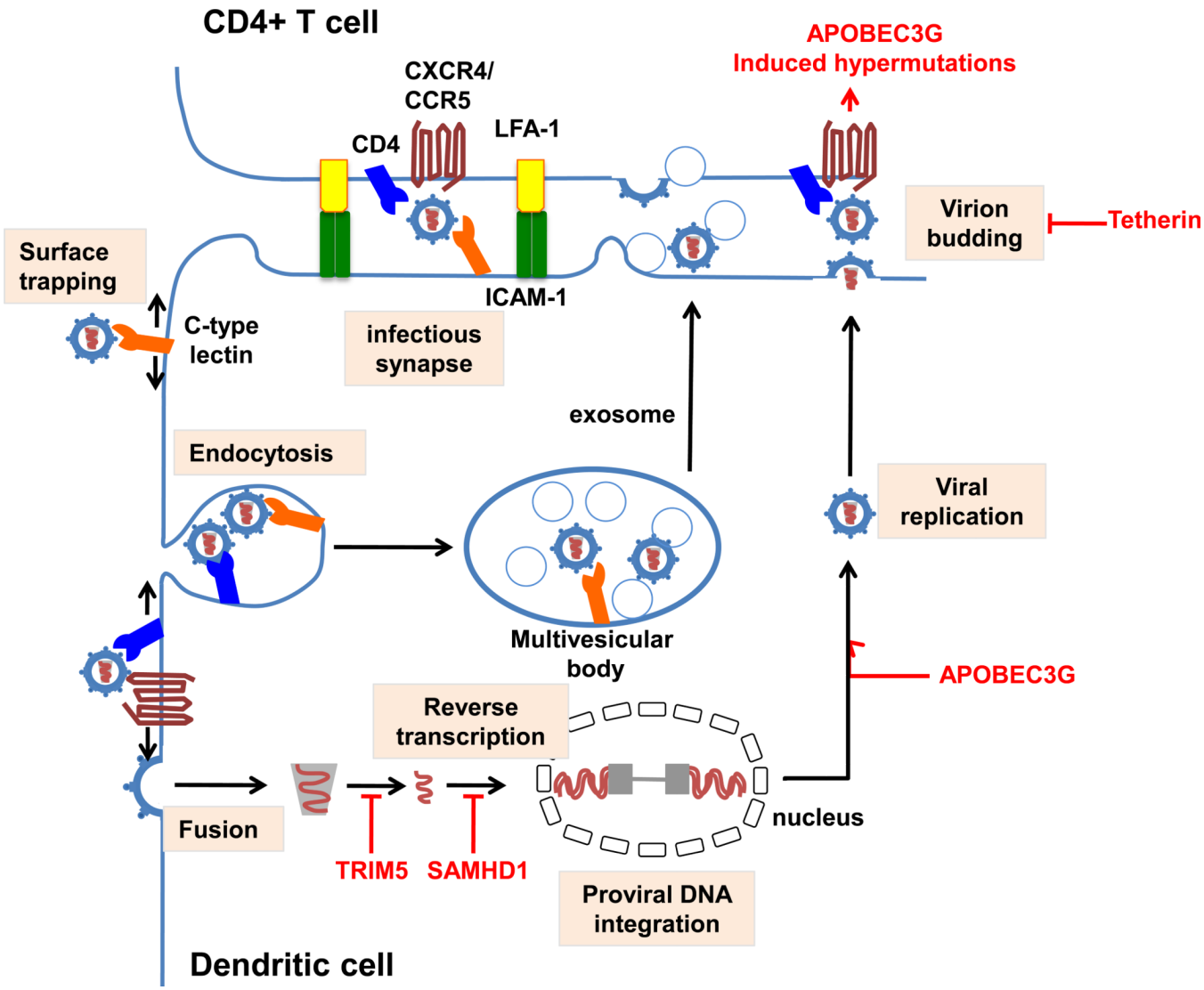

Figure 1. HIV infection and trans-infection by DC

HIV binding to CD4 and CXCR4 or CCR5 allows infection of DC through fusion with the cell membrane. However, several restrictions factors (red) prevent efficient infection of DC, acting at different stages. TRIM5α binds to the incoming viral capsid to perturb its timely disassembly. SAMHD1 very potently blocks HIV infection, potentially through depletion of deoxynucleotides necessary for successful reverse transcription. APOBEC3G is incorporated into newly made virions, and induces hypermutations in newly infected cells during reverse transcription. Tetherin prevents viral budding and release. Type I IFN signaling secreted by pDC can potentiate HIV restriction (not depicted). Despite low infectivity, DC can participate to CD4+ T cells trans-infection. HIV attachment to DC through C-type lectins, such as DC-SIGN, can lead to endocytosis and storage of intact virions, or to its retention on the cell surface. HIV into multivesicular bodies can be delivered through an exocytic route that converges with the exosome dissemination pathway. Alternatively, virions trapped on the surface of DC can be directly transmitted to target T cells. The efficiency of trans-infection is highly augmented by the formation of an ‘infectious synapse’, which concentrate virions and HIV receptors in a limited intercellular region. The interaction between the adhesion molecules (LFA-1, ICAM-1) help stabilize the

infectious synapse. Newly formed virions from infected DC can also bud to be released in the infectious synapse and binding to HIV receptors on CD4+ T cells.

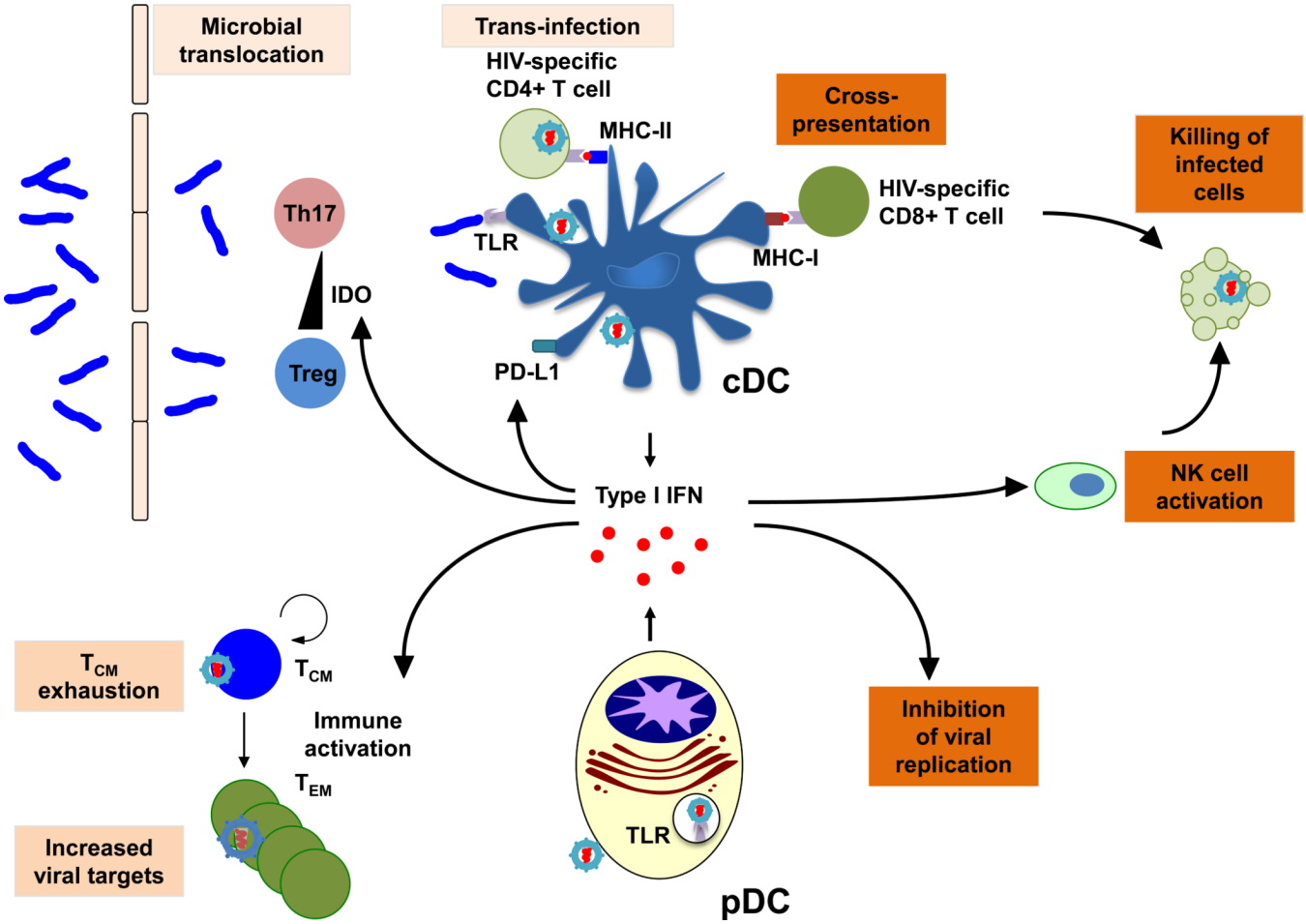

Figure 2. Conflicting role of DC in HIV infection

cDC and pDC both contribute to elimination of HIV infected cells, but at the same time participate to the immunopathology of HIV infection. cDC and potentially pDC, can cross-present HIV antigens to CD8+ T cells, leading to the differentiation of cytotoxic T cells. DC and NK cell cross-talk, through the secretion of inflammatory cytokines or type I IFN, can stimulate NK cell activation and elimination of HIV-infected cells. Type I IFN also acts directly on infected cells to trigger cell-intrinsic antiviral pathways, or can induce TRAIL-induced apoptosis through TRAIL expression on CD4+ T cells (not depicted). On the other hand, DC play an active role in the pathological immune activation observed in chronic HIV infection. In addition to trans-infection, inflammatory cytokines and type I IFN contribute to alteration of Th17 and Treg frequencies in the gut, in part through expression of immunoregulatory enzyme (indoleamine 2,3 dioxygenase is depicted here), facilitating microbial translocation and chronic stimulation of Toll-like receptors or other pattern-recognition receptors by viral or bacterial products. Persistent inflammatory cytokines and IFN secretion can also augment central memory CD4+ T cell (T_{CM}) proliferation and differentiation, leading to exhaustion of the CD4+ T cell pool, while at the same time generating increased target cell numbers for HIV infection. Type I IFN also induces the expression of immunosuppressive molecules (PDL-1) at the surface of DC, leading to diminished anti-viral immune responses.