Chapter 2

Role of Dendritic Cell Subsets on HIV-Specific Immunity

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1. Introduction

DC are key regulators of immunity in view of the fact that they are involved in immune responses against infectious diseases, allergy and cancer [1, 2]. Ralph Steinman was awarded the Nobel Prize for Medicine 2011 for DC discovery in 1973 [3]. Steinman and Cohn [3] described a novel cell type in mouse spleen, which they named ´dendritic cell´ due to their tree-like shape. The major function of DC is the induction of adaptive immunity in the LN.Yet, DC can also interact with innate immune cells, for instance natural killer (NK) and NKT cells [1, 4].

Upon entry of HIV into the host, the virus has to be transported from mucosal surfaces to lymphatic tissues, where it is transmitted to its primary targets, $CD4^+$ T lymphocytes. This process is thought to be contrived by DC.

DC thereby play critical roles during HIV and SIV (simian immunodeficiency virus) infection.

The skin and mucosa are composed of two compartments, the epidermis and the dermis (skin) or stratified squamous epithelium and lamina propria (mucosa), each containing a major subset of DC - Langerhans cells (LC) reside in the suprabasal layers of the epidermis and epithelia [5], while dermal/interstitial DC are distributed throughout the connective tissue of the dermis [6, 7].

Both subsets represent immature DC that are very efficient in Ag uptake and processing. As immature DC (iDC), they reside in peripheral tissue, which they survey for invading pathogens. Upon encounter with antigen (Ag), DC mature (mDC) and migrate to the draining lymph nodes (LN). They pass through different maturation stages, which enable them to fulfill specific tasks such as the uptake, the processing and the presentation of Ag on major histocompatiblity complex (MHC) molecules to naïve T cells. In the T cell area of lymphatic

tissue the mature DC stimulate Ag-specific $CD4^+$ and $CD8^+$ T cells to proliferate and develop effector function, such as cytokine production and cytotoxic activity. Effector T cells are recruited to inflamed peripheral tissue and participate in the elimination of pathogens and infected cells. This very particular life cycle illustrates why DC are called the ´sentinels of the immune system´ [8].

In humans, different DC subsets have been identified in blood, spleen and skin, but little is known respecting resident and migratory DC in human LN. This book chapter will review the major DC subsets found in humans and their role in HIV-pathogenesis. If data are available, also the role of the viral opsonization pattern and its impact on DC interaction will be discussed.

2. DC subsets and their role in HIV infection

DC are divided into two main groups: conventional myeloid DC (cDC) and non-conventional plasmacytoid DC (pDC) (Figure 1). As recently described byDoulatov et al. (2010) [9], human multi-lymphoid progenitors can bring forth all lymphoid cell types, including monocytes, macrophages and DC. Nonetheless, most DC in steady-state emerge from a common myeloid progenitor [10]. DC areheterogenous subtypes with distinct functions, properties and localization [11]. DC progenitors migrate from the bone-marrow through the blood to lymphoid organs and peripheral tissues. There, they give rise to different cDC subsets (Figure 1). LC display an exception within the cDC group since they maintain in the epidermis independent on circulating precursors [12]. Within cDC, migratory and lymphoid-resident DC are distinguished: migratory DC travel from peripheral tissues to lymphoid organs, whereas lymphoid-resident DC populate lymphoid organs during their whole lifespan and lack the migratory function. In humans cDC comprise Langerhans Cells (LC), dermal DC ($CD103^+$ and $CD103^-$), $BDCA1^+$ (CD1c)- and $BDCA3^+$ (CD141) DC, and the recently described $CD56^+$ DC (Figure 1). They are localized in the skin, secondary lymphoid organs (spleen, tonsils) and blood. pDC develop in the bone-marrow and then they reside in lymphoid organs [13]. $HLA\text{-}DR^+CD123^+$pDC express BDCA2 and this cell subset is found in blood, secondary lymphoid organs as well as peripheral tissues, e.g. skin or lungs (Figure 1). The cDC subtypes and pDC express a different receptor repertoir and comprise distinct functions with respect to HIV spread, antiviral activity and transmission, which is reviewed below and shown in Figure 1 (Table adapted from Altfeld et al., [14]). Both cell types are resident in lymphoid tissues in the steady state, but during an inflammatory response, pDC and cDC are actively recruited to these tissues [15-17].

2.1. cDC

2.1.1. LC and HIV

LC survey the basal and suprabasal layers of the stratified squamous epithelium of the skin and oral and ano-genital mucosa for invading pathogens [18-21]. Due to their ideal

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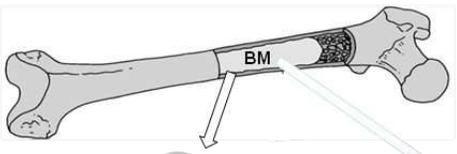

C-type lectin expression	Langerin	Langerin DEC-205	DC-SIGN DEC-205	DEC205	CLEC9A	n.d.	BDCA-2
	LC	CD103⁺ Dermal DC	CD103⁻	BDCA1⁺	Blood DC BDCA3⁺	CD56⁺	pDC
TLR expression	TLR2,3,5	TLR2,3,4,5	TLR2,3,4,5	TLR2,3,4,7,8	TLR2,3,8	n.d.	TLR7,9
Cytokine production	IL-1β, IL-6, IL-8, IL-12, IL-15, IL-23					IL-1β, IL-6	IFNα, IFNβ, IL-6, TNF
Function	•Prime Ag-specific T cells and B cells •NK cell activation by IL-12					• CD56⁺ γδ T cell activation • NK cell activation	• Treg induction • Plasma cell induction • NK cell activation by IFNs
Role in HIV infection	Degradation of HIV in Birbeck granules	HIV shuttle and transfer	HIV shuttle and transfer	Unknown	Unknown	Unknown	• Production of type I IFN: antiviral and induction of bystander T cell death • Induction of Treg cells by HIV-induced IDO up-regulation • Recruitment of T cells to sites of HIV-infection, thus facilitating viral spread
Pathology during HIV infection	•Reduced frequency in peripheral blood •Conflicting results respecting dysfunction and functionality						• Reduced frequency in peripheral blood • Conflicting results respecting dysfunction and functionality

Figure 1. DC-subsets and functions during HIV-infection (Table adapted from *Altfeld et al., 2011*; CD56⁺ DC added). HIV co-localizes with Langerin in LC to high extend as shown by confocal microscopic analyses (co-localization: yellow). CD1a⁺ LC were isolated from human skin, incubated with HIV for 2 hrs, fixed and permeabilized with Cytofix/-perm (BD Biosciences). The cells were then stained using an anti-human Langerin-PE mAb (red, Dendritics) and the anti-HIV-Ab KC57-FITC ((green, Beckman Coulter). The nucleus was stained using DRAQ5™ (blue, Invitrogen) (*Posch et al., unpublished*).

localization in mucosal tissues and their long dendrites to efficiently capture Ag, they comprise the first line defense against mucosal infections. After Ag acquisition, LC start to mature, as represented by up-regulation of co-stimulatory molecules (CD80, CD86, CD40), MHC class I and II molecules, CD83 and CCR7 and down-regulation of Langerin and E-cadherin [22].

Due to CCR7 up-regulation, the mature LC migrate to the LN along a CCL19 and CCL21-leu (leucine isoform of CCL21) gradient to efficiently prime T cells there [23]. Beside initiating an effective adaptive immune response, LC were illustrated by DeWitte et al. [24, 25] to also have important functions with respect to innate immune responses. Beside a specific set of TLRs (TLR2, 3, 5) and high expression of CD1a, LC express Langerin and contain Birbeck granules that might be crucial to their innate function [21, 26-29] (Figure 1). The C-type lectin Langerin interacts with non-opsonized HIV-1 (Figure 2) and other pathogens such as fungi and bacteria, via fucose or mannose residues. Thereby degradation of HIV-1 in Birbeck granules is promoted and HIV-1 dissemination is limited [24].

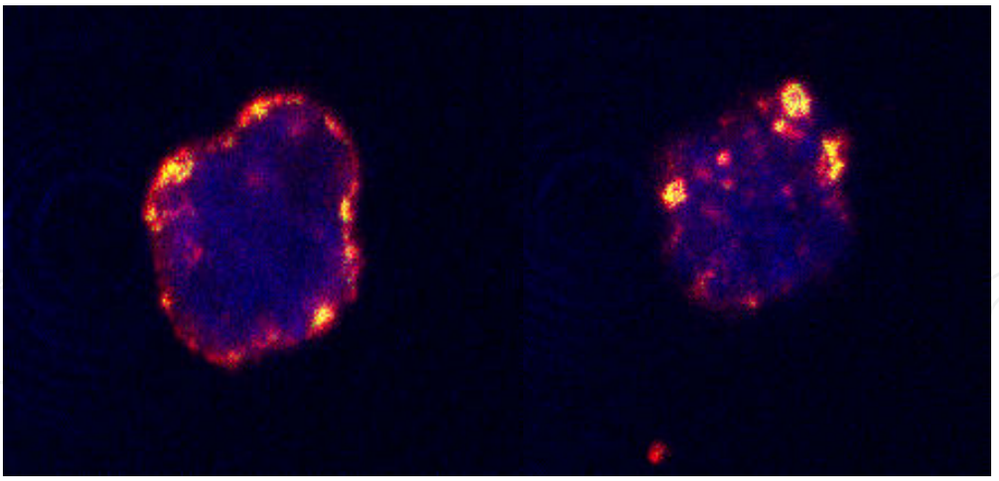

Figure 2. Co-localization of HIV and Langerin on CD1a$^+$ Langerhans Cells isolated from human skin

Early investigations of HIV-LC interactions illustrated that LC are productively infected by HIV and that they efficiently transmit the virus to T cells [30-32]. These results suggested that HIV take advantage of the antigen-capturing properties of LC to reach the T cell zone in the lymphatic tissues and via this route, HIV can establish a productive infection of the host. However, *in vivo* only low percentages of LC are infected and despite abundant expression of the primary HIV-receptor CD4 and the chemokine co-receptor CCR5, high HIV-1 concentrations are required to infect LC *in vitro* [31, 32]. As shown by Wu and KewalRemani [33] the percentages to acquire HIV-1 after heterosexual contact with an HIV-positive individual are between 0.01 to 0.1%, which might be due to a restriction by LC.

Engagement of Langerin trimers on the surface of LC induces formation of Birbeck granules, which are part of the endosomal recycling system and uniquely found in LC (Figure 3, lower right panel) [34]. Upon capture of mycobacterial lipoproteins by Langerin, these were exposed to CD1a molecules in Birbeck granules [35], which suggests that Birbeck granule formation displays a non-classical antigen processing pathway [20]. Also HIV-1 attaches to Langerin on LC and is subsequently routed to Birbeck granules, which points to a role of the granules with respect to degradation of viruses.

Studies by Gejitenbeek´s laboratory [24] showed that under homeostatic conditions, Langerin expressed on LC and acts as restriction factor for HIV infection. They demonstrated that, if HIV-gp120 attaches to Langerin, the viral particle is internalized and subsequently degraded in Birbeck granules. Thus, LC are protected from infection with incoming, non-opsonized HIV particles and HIV-1 is not disseminated throughout the host [24]. The rapid internalization of HIV-1 into LC by Langerin impedes interactions and subsequent fusion with CD4 and CCR5 and also prevents transmission to the main target cells of the virus, CD4$^+$ T cells. Thereby, Langerin acts as a protective anti-HIV barrier during the first steps of HIV-1 infection, if the virus is non-opsonized and if sexually transmitted pathogens are lacking.

As demonstrated, if the host system is facing other sexually transmitted infections, the anti-HIV-1-barrier of LC is abrogated and HIV-1 transfer to susceptible $CD4^+$ T cells is promoted [20, 36, 37]. Pathogens, such as Candida or Neisseria, directly interact with Langerin and compete with HIV-1-binding. Additional factors explaining the by-passing of the anti-HIV-1-barrier function of Langerin are that:

- by high viral loads the receptor becomes saturated,
- infections, e.g. Herpes simplex virus infection, down-regulate Langerin surface expression [20],
- the HIV-1 entry receptors CD4 and CCR5 are up-regulated during additional sexually transmitted infections [37],
- or the antiviral function of Langerin is reverted by inflammation-induced TNF-α (tumor-necrosis-factor α) production due to Candida albicans or Neisseria gonorrhoea [36].

These observations allow to conclude that during acute co-infection the anti-viral function of LC is significantly decreased.

Not only acute co-infection, but also opsonization of HIV with either complement fragments or specific Abs might result in reduction or abolishment of the anti-viral function mediated by Langerin (*Wilflingseder and Posch, unpublished data*). Upon entry of viruses into the body, immediate non-specific immune responses are triggered and within a short time the innate immune system is completely activated. During acute infection multiple humoral and cellular players, including cytokines, complement, acute-phase proteins, DC, macrophages, and natural killer (NK) cells, that co-operate to generate an efficient defense against infection, are activated. HIV-1 spontaneously triggers the complement system also in absence of specific Abs by interactions of gp41 with C1q [38-41]. Due to regulators of complement activation (RCAs) in the viral surface, HIV-1 is very efficiently protected against virolysis, which normally occurs due to MAC (membrane attack complex) formation and destruction of pathogens or infected cells. The incorporation of RCAs in the viral surface acts as protection mechanism and results in opsonization of HIV-1 with complement C3 fragments at the very initial steps following viral entry. After seroconversion, when HIV-1-specific Abs are established, the virus additionally is opsonized with specific IgGs. The different coating patterns of the virus change the receptor used on DC due to the density of complement fragments or Abs on the viral surface [42]. The C-type lectin-virus interaction becomes rather unimportant if the virus is opsonized and is substituted by complement or Fc receptor-virus interactions as already demonstrated using dermal DC [42]. After LC incubation using complement-opsonized HIV-1, we found that not only sexually transmitted diseases abrogate the antiviral barrier mediated via Langerin but also opsonization of HIV-1 (*Wilflingseder and Posch, unpublished data*).

In summary, during acute co-infection or by opsonization with complement fragments or Abs, the anti-viral function of LC is significantly reduced due to competition for Langerin or different receptor utilization. This facilitates HIV-1 infection of LC via CD4 and CCR5, intra-

cellular uptake of the virus (Figure 3) and promotion of HIV-1 transfer to its targets, $CD4^+$ T cells.

On the other hand LC were implicated in establishment of infection due to their location in the foreskin and due to compelling evidence that male circumcision efficiently reduces the risk to become infected with HIV-1 [43]. It was furthermore shown *in vivo* in highly HIV-1-exposed but (IgG) seronegative individuals, that gp41-specific IgA Abs efficiently blocked transfer of sexually transmitted HIV-1 [44-46]. A very recent study by Tudor et al. [46] illustrated that monomeric 2F5 IgA2 bound to gp41 MPER (membrane proximal external region) and free virus with greater efficiency than IgG1 and interferred with the initial HIV-1 transmission via Langerhans Cells. 2F5 IgA2 and IgG1 monomers blocked HIV-1 transcytosis in monostratified or multilayered epithelia as well as in rectal tissue [46, 47]. These Abs decreased infection of $CD4^+$ T cells and transfer from LC to autologous $CD4^+$ T cells [46]. The 2F5 IgA2 monomer inhibited virus transcytosis and $CD4^+$ T cell infection more efficiently, while the 2F5 IgG1 monomer was superior in blocking the LC-$CD4^+$ T cell transmission. A synergistic effect of both, 2F5 IgA2 and IgG1, was observed with respect to LC-$CD4^+$ T cell transmission and decrease of $CD4^+$ T cell infection [46].

2.1.2. Dermal DC and HIV

Along with LC, HIV-1 firstly attaches to dermal (interstitial) DC upon entry at mucosal surfaces (Figure 1). Dermal DC are underlying the epithelium, do not contain Birbeck granules and express heterogenous amounts of CD1a [48].

Interstitial DC are localized in the dermis and oral, vaginal and colonic lamina propria [6, 49-52]. They are characterized by the expression of CD11c, high expression of various C-type lectin receptors (Langerin on $CD103^+$ DC, DC-SIGN on $CD103^-$ DC, DEC-205 on both subsets), TLR2, 3, 4 and 5 and they secrete various cytokines upon pathogenic stimulation (Figure 1). Since there are only 2 studies available on human $CD103^+$ DC and SIV [53, 54], the following chapter refers to $CD103^-$, DC-$SIGN^+$ dermal DC.

In vitro experiments showed that DC efficiently capture HIV-1 or SIV, independent on the maturation status of the cells (Figure 3 and [55]) and subsequently transfer the virus to $CD4^+$ T cells, which initiates a vigorous infection [41, 42, 56, 57]. These experiments imply that *in vivo* HIV exploits DC at mucosal sites as shuttles to $CD4^+$ T cells in the LN, but the exact events with respect to virus spread from mucosal sites to LN have not been enlightened yet. Thereby, DC seem to play a significant role in the spread of infection as well as in the induction of antiviral immunity.

As shown in Figure 3, dermal DC (left panel) and LC (right panel), which emigrated from whole skin explants, take up variable amounts of HIV-1 particles. As demonstrated by Frank et al. [55], human and macaque DC interacted similarly with SIV and ample amounts of virus were captured by DC. Transmission electron microscopic analyses revealed that iDC, which are endocytically highly active, captured few viral particles near the periphery of the membrane, while mDC, which down-regulate the endocytic capacity, retained high

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amounts of virions in large vesicular compartments deeper within DC [55]. This points to a diverse entry and handling of virions within iDC and mDC.

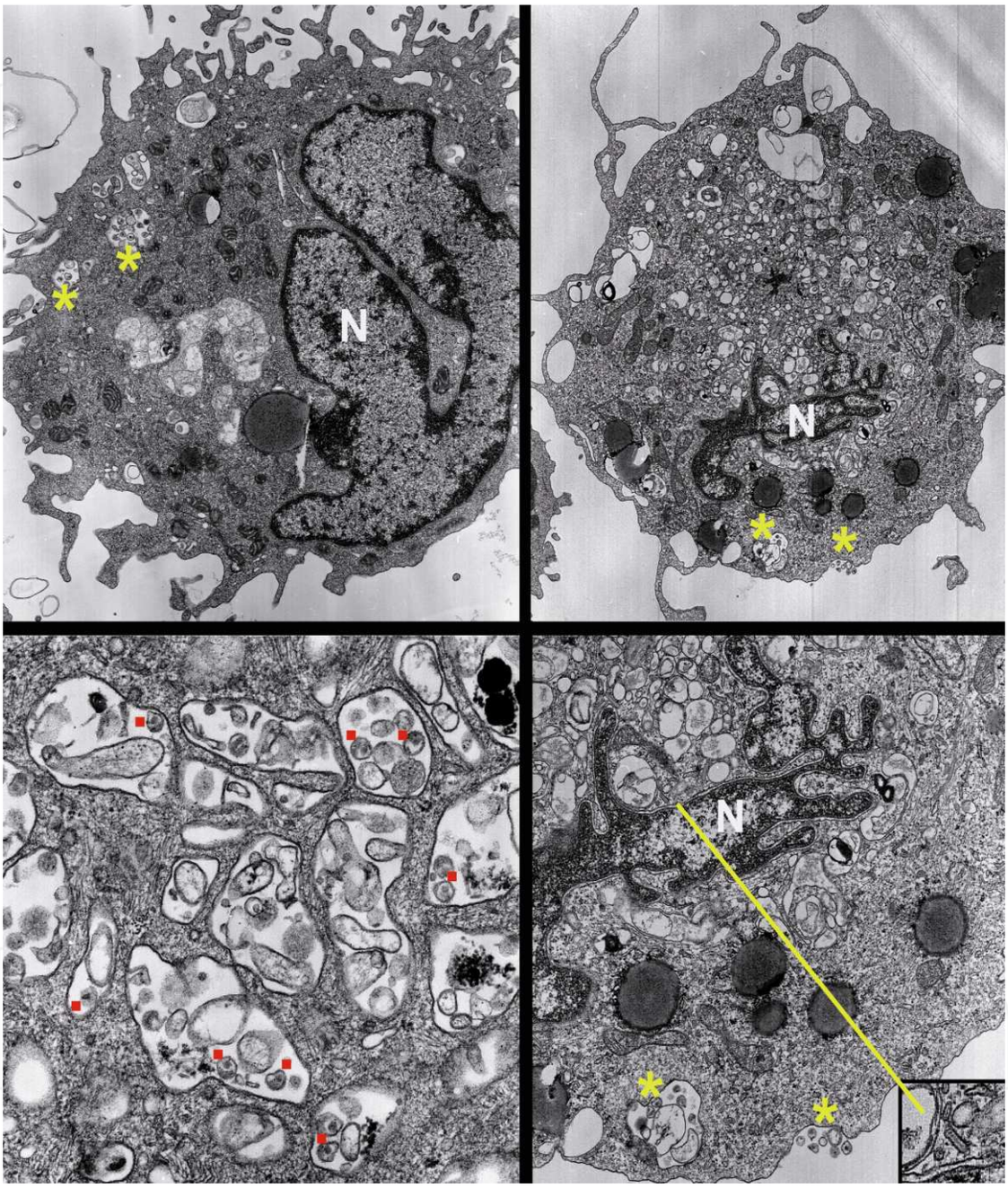

Figure 3. Uptake of HIV into dendritic cells from human skin. Dendritic cells emigrated from whole skin explants were incubated with HIV for 2h and then fixed and embedded for transmission electron microscopy. Variable amounts of viral particles are taken up by dermal dendritic cells (left panels) and epidermal Langerhans cells (right panels). Lower panels show higher magnifications of membrane-enclosed virus particles in a dermal dendritic cell (left panel; some viruses marked with red/black). In a Langerhans cell (lower right panel) viruses can be seen docking onto the surface membrane (right asterisk) and already taken up into vesicular structures (left asterisk). A Birbeck granule is depicted in the inset as the identifying structure for Langerhans cells. N, nucleus.(Photos courtesy of Hella Stössel and Nikolaus Romani).

Beside the different handling of HIV-1 or SIV within iDC and mDC, opsonization of the virus with either complement fragments and/or Abs significantly affects the binding mechanism, internalization and infection of DC as well as their T cell stimulatory capacity [41, 42, 58]. As shown by Pruenster et al. [42], the complement cloud around the virus significantly blocked the accessibility of gp120 and therefore interfered with C-type lectin interaction.

Similar amounts of HIV-1 bound to the surface of DC independent on the opsonization pattern of the virus (Pruenster et al., 2005). The attachment of the differentially opsonized HIV-1-preparations was found to be specific (Figure 4 [*Wilflingseder and Posch, unpublished data*]), since pre-incubation of the DC with blocking Abs against human DC-SIGN, CD11b (CR3-α chain) or CD32 (FcγRII) particularly blocked the interactions with the corresponding virus preparations:

- blocking α-DC-SIGN mAb inhibited interaction with non-opsonized HIV-1 (Figure 4, HIV),
- blocking α-CR3mAb (TMG6.5) significantly interferred with binding of complement-opsonized HIV (HIV-C) to DC (Fig.4, HIV-C) and
- blocking α-CD32mAb (AT10) inhibited binding of Ab-opsonized HIV-1 (Figure 4, HIV-Ig).

Additionally, we found variations respecting infection of DC with differentially opsonized HIV-1 preparations [41]. Productive infection of DC and LC with HIV-1 was described to be relatively inefficient compared to HIV-infection of $CD4^+$ T cells and HIV- or SIV-infected DC are rarely detected *in vivo* (rev. in Piguet and Steinman[59]). Our study using non-, complement-, complement-Ig- or Ig-opsonized HIV-1 uncovered that complement-opsonization of HIV-1 significantly enhanced DC-infection compared to non-opsonized HIV [41] and furthermore acted as an endogenous adjuvans for DC-mediated induction of HIV-specific CTLs [58].

In contrast, HIV-1 coated with specific, non-neutralizing Abs significantly impaired infection of and integration in DC and also *´trans´*-infection of $CD4^+$ T cells after delayed addition of T cells [41].

Despite the low-level productive infection of DC, non-opsonized HIV-1 is very efficiently transmitted to T cells either via de novo (*´cis´*-transfer) or without (*´trans´*-)infection [60]. This is also true for Ab-opsonized HIV-1, if $CD4^+$ T cells are added immediately to HIV-exposed DC [41]. Especially C-type lectins, such as DC-SIGN on dermal DC, were connected to transmitting HIV-1 to T cells in the LN [60, 61]. Similar to Langerin, DC-SIGN has high affinity for mannose and fucose structures, but despite sharing this feature these receptors exert completely different effects and functions regarding pathogen processing. Dermal $CD103^-$ DC express DC-SIGN, which captures low titres of HIV-1 by interaction with the envelope glycoprotein gp120 [62]. By complexing DC-SIGN via gp120, HIV-1 is protected from degradation within the DC in contrast to Langerin, which promotes degradation of the virus through Birbeck granules as described above [24, 62]. DC-SIGN-complexed HIV-1 remains stable and infectious over prolonged periods of time within non-lysosomal acidic organelles

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of DC [62, 63]. Thereby, DC-SIGN efficiently transfers HIV-1 to $CD4^+$ T cells, enhances infection in DC-$CD4^+$ T cell co-cultures and facilitates '*trans*'-infection of the T cells [62].

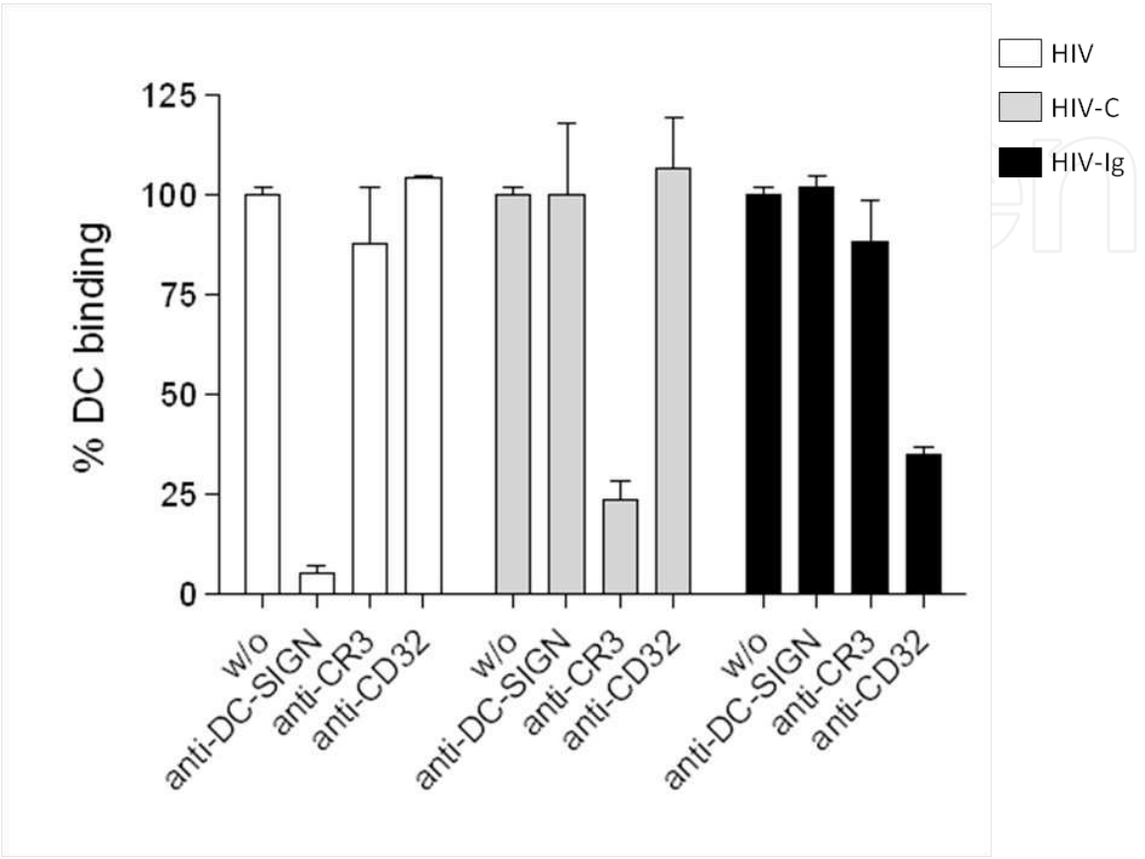

Figure 4. Binding of differentially opsonized HIV (non-opsonized HIV, HIV-C, HIV-Ig) in absence and presence of a blocking anti-human DC-SIGN, CR3 [CD11b] (TMG6.5) or CD32 (AT-10) antibodies. Binding of non-opsonized HIV was signficantly decreased in the presence of a blocking anti-DC-SIGN Ab, but not affected by pre-incubation of the cells with a blocking anti-CR3- or CD32-Ab (white bars). HIV-C-interaction with DC was inhibited using a blocking anti-CD11b (CR3)-Ab TMG6.5, but not by anti-DC-SIGN or CD32 (grey bars). Binding of IgG-opsonized HIV was inhibited by using a blocking anti-human CD32, but not DC-SIGN or CD11b-Ab (black bars).

Lastly, the antigen-presenting capacity of DC was also shown to be modulated by the opsonization pattern of the virus [58]. Earlier studies illustrated the role of complement opsonization respecting induction of effective CTL responses against viral infections, but the exact mechanism was not determined [64-66]. The exclusive role of DC in priming naïve $CD8^+$ T cells in response to exogenous cell-associated as well as endogenously synthesized Ags has been shown [67, 68]. Endogenously synthesized antigens from DC infected with LCMV (choriomeningitis virus) mediated strong CTL responses, while macrophages and B cells infected with LCMV did not induce CTLs [68].

We recently found that opsonization of retroviral particles with complement fragments enhanced the ability of DC to induce CTL responses both *in vitro* and *in vivo* [58]. HIV-C-loaded DC mediated significantly higher $CD8^+$ T cell expansion and signficantly better antiviral activity than DC exposed to non-opsonized HIV *in vitro*. This was further verified

in vivo using the murine Friend virus model. These results indicated that ´complement acts as natural adjuvant for DC-induced expansion and differentiation of specific CTLs against retroviruses´ [58].

Additionally, we demonstrated that in contrast to complement opsonization, antibody-coating of the viral surface attenuated the CTL-stimulatory capacity of HIV-exposed DC [69]. In some HIV-1-positive individuals, high levels of antibodies and low levels of complement fragments coat the HIV-1 surface and therefore we investigated the effects of the non-neutralizing Abs bound to the surface of HIV-1 on the CTL-stimulatory capacity of DC. We observed *ex vivo* and *in vitro* that DC loaded with IgG-opsonized HIV significantly impaired the HIV-1-specific $CD8^+$ T cell response compared to the earlier described efficient $CD8^+$ T cell activation induced by DC exposed to complement-opsonized HIV. These novel modulatory effects of the HIV-1-opsonization pattern on the CTL-activating capacity of DC might influence future vaccination strategies, since strong transient Ab responses subsequent to vaccination might weaken the CTL-induction by DC, which has to be considered [69].

Preferential expression of CCR5 on immature LC and DC restricts the transmission of X4-tropic isolates at the site of infection. Additionally, *ex vivo* analyses revealed that X4-tropic HIV replicate worse in DC and LC compared to R5-tropic viruses [31, 70, 71]. The relatively low susceptibility of DC to HIV-1-infection but efficient transfer of virus to CD4+ T cells was lately ascribed to an HIV-1 escape mechanism from innate recognition by DC [72, 73]. Manel et al. [72] showed that if DC by-pass resistance to HIV-1 infection [74, 75], they mature, exert a type I IFN response as well as adaptive immune responses. More recently, Laguette et al. [73] described the restriction factor SAMHD1 (SAM domain and HD domain-containing protein 1) to be responsible for inhibiting HIV-1 replication in DC and other cells of the myeloid lineage by degrading or preventing accumulation of HIV-1 DNA due to a putative nucleotidase activity. As shown by Lahouassa et al. [76], SAMHD1 depletes the pool of intracellular dNTPs and thus restricts HIV-1 infection in DC by blocking reverse transcription. These recent important findings respecting a formerly unknown cryptic innate sensor in DC, SAMHD1, and the induction of an efficient type I IFN and adaptive immune response due to DC infection might pave the way for novel therapeutical approaches to treat retroviral infections.

2.1.3. Blood DC and HIV

2.1.3.1. $BDCA1^+$ DC, $BDCA3^+$ DC, $CD56^+$ DC and HIV

$BDCA1^+$ myeloid DC can be directly isolated from human blood. This population was described to be reduced in the blood of HIV-infected individuals [76-78]. We found that $BDCA1^+$ DC exerted a decreased transmission of HIV-1 to autologous $CD4^+$ T cells, when the virus was opsonized with specific IgGs in contrast to non- or complement-opsonized HIV-1 and when the T cells were added delayed [41]. When $CD4^+$ T cells were immediately added after washing the differentially loaded DC, the same infection efficiency was observed using HIV, HIV-C or HIV-Ig [41]. The two-phase transfer of HIV to DC as described above (*trans*-infection: by-passing of the virus from endolysosomal compartments, first 24 hrs; *cis*-infec-

tion: ´de novo´ HIV-1-infection of DC before transfer to T cells) was also observable in BDCA1$^+$ DC, because non- and complement-opsonized HIV-1, which cause productive infection of DC, efficiently infected autologous CD4$^+$ T cells in short- and long-term co-cultures. BDCA1$^+$ DC exposed to IgG-opsonized HIV-1, which were not productively infected by the virus, were not able to promote long-term transfer of HIV-1 to susceptible T cells [41].

BDCA3$^+$ DC represent the human equivalent to mouse CD8α^+ DC and they are the major producers of IFN-λ in response to dsRNA poly I:C [80].As recently described by Dutertre et al. [81] using an 11-color flow cytometric strategy, circulating BDCA1$^+$ DC and BDCA3$^+$ DC counts were reduced in 15 viremic, untreated patients compared to 8 HIV-1-positive individuals under treatment and 13 healthy donors. By using this method, they illustrated that both blood DC subsets expressed characteristic lineage markers: BDCA1$^+$ DC expressed CD14, while particularly BDCA3$^+$ DC displayed CD56 on their surface. BDCA3$^+$ DC were shown to be more significantly down-modulated in viremic patients compared to controls [82] and it remains to be investigated by longitudinal studies, if combined antiretroviral therapy can restore the pool of circulating myeloid BDCA1$^+$ and BDCA3$^+$ DC.

Blood CD56$^+$ DC were recently described by Gruenbacher et al. [83] and comprise intermediate-sized lymphocytes with an HLA-DR^{high}, CD80$^+$ and CD86$^+$ expression profile. Upon cultivation they acquire DC-like morphology with increased levels of above mentioned surface markers. Upon stimulation, they are able to efficiently stimulate CD56$^+\gamma\delta$ T cells, which results in secretion of IFNγ, TNF-α, and IL-1β [84]. The role of CD56$^+$ DC respecting HIV-1 infection and pathogenesis needs to be further investigated.

2.2. pDC and HIV

Plasmacytoid DC (pDC) (Figure 1) or type 1 IFN-producing dendritic cells are innate immune cells in blood, which are specialized in releasing massive amounts of IFNα and IFNβ upon viral challenge, including HIV-1 [83]. They constitute <0.2-0.5% of peripheral blood mononuclear cells (PBMC) [85] and in humans, pDC express the characteristic surface markers BDCA-2 (CD303, CLEC4C) and CD123 along with BDCA4 (CD304, NRP1), but they do not express CD11c, a marker of myeloid DC, or CD14 [86].

pDCs are key players of the innate immune response *in vivo* and they can prime adaptive immunity due to the afore mentioned production of high type I interferon levels, especially upon exposure to viral products [15, 83]. Upon stimulation with DNA or RNA viruses, they produce up to 1000-fold higher amounts of type I interferons than other cells [84, 87, 88]. The IFNα production in pDC by viruses represents a two-step process – uptake of viruses occurs due to recognition of envelope glycoproteins by C-type lectin receptors, e.g. mannose receptor or BDCA2, but induction of IFNα in fact starts in endosomal compartments by ligation of TLR9 or TLR7 [89-91]. Pathogenic single-stranded RNA or unmethylated DNA are mainly recognized by TLR7 and TLR9 expressed inside pDC [92]. Thus, the viruses have to be ingested by pDC into endosomes and NFkB- and MAPK signals through MyD88 must be stimulated [93]. Not only viruses, but also virus-infected cells can potently activate IFNα production from pDC [94]. Once activated, pDCs mature and produce large quantities of pro-inflammatory and antiviral cytokines [95-97]. pDC respond with high amounts of differ-

ent IFNα subsets, IFNβ, IFNκ, IFNλ and IFNω on a wide range of enveloped viruses including HIV-1. They additionally produce pro-inflammatory cytokines TNFα, IFNγ and IL-6 as well as chemokines CXCL-10, CCL-5 and CCL-4 among others [98]. Thereby, pDC also act as a linker between innate and adaptive immunity.

Data by Zhou et al. [99] indicate that subsequent to HIV-1 challenge, signaling via TLR7 triggers autophagy and increased IFNα production from human pDC. The IFNα secretion mediated by an autophagy-dependent pathway may play an important role for T cell triggering during HIV-1 pathogenesis.

Beside acting as pro-inflammatory cells, pDC also provide negative regulatory signals and thus induce tolerance. pDC express IDO (indoleamine 2,3-dioxygenase) and PDL-1 (programmed death ligand; 1) which are associated with the negative modulation of T cell responses and regulatory T cell induction [100-102].

During acute HIV-1 infection, NK cells are recruited and activated by pDC to the sites of infection and to LN due to IFNα secretion [103, 104]. IFNα was demonstrated to increase the perforin levels in NK and $CD8^+$ T cells. At the sites of infection ´DC-editing´ occurs by NK cells, since activated NK cells delete immature pDC to select for the more immunogenic mature pDC [105-108].Beside NK cell recruitment and activation, pDC-secreted IFNα promotes maturation and migration of other DC subsets. Due to their localization, it is unlikely that pDC are involved in HIV-1 capture, transport and transmission, but they are supposed to control HIV-1 in the acute phase of infection due to their immediate antiviral and NK priming activity.

Chronic exposure to HIV-1 leads to hyperactivation of pDC resulting in simultaneous type I IFN secretion and IDO expression. Thus, pDC concurrently exert cytotoxic and suppressive effects on T cells during chronic HIV-1 infection [109].

HIV-1 infection not only disrupts DC homeostasis within myeloid DC subsets, but also pDC homeostasis is defective during chronic HIV-1 infection. cDC and pDC are lost from blood, which correlates with high viral loads and low $CD4^+$ T cell counts [76, 110-113]. Deficiencies in pDC function were among the earliest observations of immune dysfunction in HIV-1 infection and some of the earliest studies of the ´natural IFN-α-producing cells´ (i.e. pDC) illustrated that PBMC from AIDS patients were severely compromised in their ability to produce IFN-α *in vitro* after stimulation with the virus.

Cell death and/or a failure of bone marrow progenitors to differentiate into pDC might contribute to the loss of pDC from blood of chronically infected individuals. In non-pathogenic models of SIV infection, no depletion of blood pDC was observed [114, 115] and HIV-1-positive individuals, who are able to control infection (= long-term non-progressors) were also shown to have increased numbers of blood pDC [111].In contrast, it was described that during HIV-2 infection, which is highly attenuated compared to HIV-1 infection in humans, also the numbers of blood pDC is found reduced [116]. Thereby, the exact role of pDC depletion during HIV infection is not clear yet.

The depletion of cDC from the sites of infection was ascribed to a higher expression of CCR7 on the surface of cDC and a signficantly increased CCL19 expression in LN of SIV-infected

animals, thus suggesting that inflamed LN lure cDC away from the sites of infection early during progressive SIV infection [117]. A similar mechanism can be imagined for pDC, which are recruited to inflamed LN via CXCL9 and E-selectin [16, 118], but the pDC loss could also be due to direct infection, enhanced apoptosis or CD95 up-regulation [119-123].

Not only pDC numbers are decreased during on-going HIV-1 infection, but also the quality of the cells is suffering. They exert a reduced ability to migrate towards the CXCR4 ligand CXCL12 [124], they stimulate Treg cells to dampen HIV-1 immunity and they furthermore shift the Treg-Th17 balance [125, 126]. So far, interactions of differentially opsonized HIV-1 preparations with pDC has not been investigated.

3. Outlook: Impact of the HIV-1 opsonization pattern on DC function

As follows of investigations on HIV-1 in the last 30 years, antibody responses against the virus are not effective and cellular immune responses not powerful enough to suppress or even control HIV-1. DC, the prime inducers and regulators of immunity and tolerance, are crucial in designing modern vaccines [127-130]. Therefore, nowadays vaccine science shall combine established classical vaccine approaches with new attempts based on the expanded immunological knowledge.

Innate and adaptive immune responses are needed to generate efficient, long-lasting protection. Immediate innate responses involve activation of the complement system, ligation of pattern recognition receptors e.g. TLRs, C-type lectins, activation of NK cells, cDC and pDC, and type I, II, as well as III interferons. For viral clearance, the optimal balance between $CD4^+$ and $CD8^+$ T cells is required during the adaptive immune responses. Current HIV-1 vaccination strategies include the use of peptides or monocyte-derived DC exposed to chemically inactivated HIV-1 and aim in designing a vaccine efficiently inducing both, cellular and humoral immune responses [131-133]. So far, disappointing results have been achieved in clinical trials targeting either cellular [134, 135] or humoral immunity [136, 137]. The most prominent AIDS vaccine trial so far was the RV144 in Thailand [138], which evoked strong, but transient Env-specific $CD4^+$ T cell and Ab responses, but only weak HIV-specific $CD8^+$ T cell responses [131, 138].

HIV-1 induces immediate responses of the immune system upon entering mucosal surfaces. There, the complement system constitutes a first line of defense against the virus. Recently, we illustrated an important role for complement opsonization of retroviruses as an endogenous adjuvant for DC-mediated CTL-induction [58].

Efficient early $CD8^+$ T cell responses are crucial in controlling HIV-1 replication and their key role in HIV-1 control is additionally substantiated by association of certain HLA class I alleles and an improved disease progression [139-141]. In view of our very recent observations ([58], [69]), we propose that $CD8^+$ T cells are efficiently primed by DC during acute viral infection, particularly by enhanced infection of DC with HIV-C [41]. Thus, more efficient presentation of endogenously synthesized viral Ags via HLA-ABC [41], and ore efficient

cross-presentation from incoming complement-opsonized HIV-1 are mediated. In contrast, Ab-opsonization of HIV-1 weakens the CTL-induction by modulation of DC function and might influence future vaccination strategies [69].

As shown by Lu et al. [142-144] *in vitro* and *in vivo*, DC exposed to chemically (aldrithiol-2, AT-2)-inactivated HIV or SIV induced a virus-specific CTL response. This response was strong enough to kill HIV-1-infected $CD4^+$ T cells [142], to control the viral load in SIV-infected monkeys [143] and HIV-infected individuals [144].. The decrease of the viral load in the HIV-1-infected patients was associated with a higher amount of HIV-1-gag-specific $CD8^+$ T cells and HIV-1-specific $CD4^+$ T cells.

LC were described to allow more cross-priming of $CD8^+$ T cells, while dermal DC are more specialized in primingnaive $CD4^+$ T cells [145]. The finding that complement-opsonization of HIV prior loading of DC significantly enhanced the $CD8^+$ T cell-stimulatory capacity of the cells in combination with using specific DC subtypes might efficiently improve future vaccination strategies and there is good reason to address DC of the skin, especially Langerhans cells, for purposes of vaccination.

A greater understanding of the innate and adaptive processes and the different functions of DC subsets to HIV-1 infection will lead to development of an effective vaccine.

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