Paper Title:-The Role of Dendritic cells in B lymphocytes, T-cell tolerance, Regulatory T Cells, and HIV-1 Pathogenesis as potential target for new Preventive and Therapeutic HIV-1 Vaccine Development (Part Five)

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Abstract

Novel vaccination approaches are needed to prevent and control human immunodeficiency virus (HIV) infection.

Dendritic cells (DCs) and their subsets have multifaceted roles in the early stages of HIV-1 transmission and infection.

DC studies have led to remarkable discoveries, including identification of restriction factors, cellular structures promoting viral transmission including the infectious synapse or the interplay of the C-type lectins, Langerin on Langerhans cells (LCs), and dendritic cell-specific intercellular adhesion molecule- 3-grabbing non-integrin on other DC subsets, limiting or facilitating HIV transmission to CD4þ T cells, respectively.

Studies with cells in culture have addressed different outcomes of the HIV-– DC interaction, which include: direct productive infection of DC; carriage of virus by DC to CD4+ T cells; transfer of virus between DC and T cells at an infectious synapse; and immune evasion strategies of infected DC.

Several studies have recently underscored the crucial role that those noninfectious viruses could play in defective immune function in HIVinfected individuals and in particular, in the dysregulation of dendritic cell (DC) function.

Recent experiments have provided direct evidence that antigen-loaded immature DCs silence T cells either by deleting them or by expanding regulatory T cells.

In this article, I discuss Dendritic cells, Biology of DCs and Their Subsets, Dendritic cells and B lymphocytes, Dendritic cells and T-cell tolerance, Dendritic Cells and Their Role in AIDS Pathogenesis, Induction of DC Chemotaxis by gp120, IN VIVO Infection and IN VITRO Infectivity of DC with HIV, Combining DC vaccination with other therapies and Immunological and clinical efficacy

Key Word: Dendritic cells, B lymphocytes, T-cell, Regulatory T Cells, In VIVO, In VITRO and HIV-1, and Vaccine

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1. Introduction

Dendritic cells (DCs) are derived from bone marrow precursors and have a major role in antigen presentation and induction of host immune responses.Dendritic cells (DCs) and their subsets have been shown to have a major role in immune defence against viral infection by generating and regulating innate and adaptive immune responses. Because of their strategic location at mucosal surfaces, effectiveness at antigen capture, potent migratory ability, and their privileged interaction with effector T cells in lymphoid tissues, DCs are likely critical intermediates of HIV infection and transmission (1),(2). DCs are versatile antigen-presenting cells (APCs) that form a pervasive network in the T cell areas of lymphoid tissues (3),(4), where they induce protective adaptive immune responses, as well as tolerogenic responses (5). DCs express a plethora of pathogen recognition receptors, such as toll-like receptors, scavenger receptors, and lectin receptors, which recognize evolutionarily conserved pathogen-associated molecular patterns and contribute to antimicrobial defense. Concurrently, costimulatory molecules are expressed on the cell membrane, preparing DCs for competent T cell priming. In the T cell areas of the lymph node, fully mature DCs (mDCs) present pathogenderived antigens to T lymphocytes. By these means, DCs coordinate innate and adaptive immune responses against invading pathogens and thus have a critical role in limiting viral infections(6),(7),(8). In the course of the HIV-1 infection, however, the contribution of DCs to the antiviral state could be confounded by their ability to facilitate HIV-1 transmission to bystander CD4+ T cells and promote viral spread. Since DCs express the HIV receptor CD4 and viral coreceptors on their surface (9),(10), they are expected to be infected by HIV-1. Moreover, large amounts of HIV-1 are required to successfully infect DCs. (11),(12). SAMHD1 restricts infection by reducing the nucleotide pool available for reverse transcription, thereby limiting replication of the viral genome (13). In contrast to HIV-1, HIV-2 naturally infects DCs(14), and this function depends on counteraction of SAMHD1 by Vpx, a viral protein not present in HIV-1 (15),(16). Vpx is incorporated into HIV-2 particles and is released after viral fusion, inducing degradation of host cell SAMHD1. However, efficient DC infection is not required for disease progression, since HIV-1 is much more pathogenic than HIV-2. HIV-2 genome replication in infected DCs is detected by the innate sensor cGAS, a cyclic guanosine or adenosine monophosphate synthase that recognizes viral DNA and triggers immune responses (14),(17). while SAMHD1-mediated restriction of HIV-1 prevents cytoplasmic cDNA synthesis and consequently precludes induction of antiviral type I interferon responses (14). Despite low rates of infection by HIV-1, DCs can efficiently capture HIV-1 and mediate potent viral transmission, thus promoting a vigorous infection of CD4 + T cells(12), in the absence of productive DC infection (18), or innate immune detection (19),(20). HIV-1 trans-infection involves capture and internalization of intact virions by DCs,

trafficking of trapped viruses without membrane fusion, and finally release of infectious virions towards contacting CD4 + T cells (21),(22). Based on their ability to retain virions and travel to lymphoid tissues, it was initially proposed that iDCs act as ‘‘Trojan horses,’’ capturing HIV-1 in the mucosa and then migrating to secondary lymphoid tissues, where stored HIV-1 could be transmitted to CD4 + T cells and contribute to the spread of infection(21),(23). Kinetic analysis suggests that the HIV-1 capture and storage compartment in mDCs gradually connects with the extracellular milieu and is constantly remodeled (24), which may favor both viral accumulation and subsequent transfer. HIV-1 transmission has been suggested to occur primarily at a zone of cell-to-cell contact—the infectious synapse—that resembles the immunological synapse, a spatially segregated supramolecular structure formed by T cells to recognize antigens presented by DCs (25). APC can present antigen to and activate memory T cells, DC almost exclusively initiate primary immune reactions involving naive T cells (26),(27),(28),(29). Much of the modern knowledge about the antigen-presenting function of the DC family comes from the pioneering work of Ralph Steinman and his colleagues (30). Multiple populations of DC have been identified, including lymphoid interdigitating DC; Langerhans cells (LC), the prototypic nonlymphoid, immature DC; and veiled cells of afferent lymph. The main function of DC is to transport antigens, likely both self and nonself, from their site of entrance into the body to the paracortical (T-cell) region of the draining lymphoid organ. DC then initiate an immune response through the activation of antigenspecific T cells which continually recirculate through lymphoid organs. DC potentially important players in the pathogenesis of human immunodeficiency virus (HIV) infection (31),(32),(33).

The outcome of the APC-to-T cell *trans* infection process has been considered to be central to sexual transmission of HIV-1 atmucosal (anal and vaginal) and epidermal (foreskin) sites (34),(35). A further, potentially critical feature is its role in progression of HIV-1 infection. In either case, the initial phase of theHIV-1 *trans* infection process involves unique, *cis* interactions and replication cycles of virus in the major types of professional APC, that is, subsets of dendritic cells (DC), monocytes/macrophages, and B l

2. Biology of DCs and Their Subsets

Dendritic cells (DCs) are essential in order to combat invading viruses and trigger antiviral responses. Paradoxically, in the case of HIV-1, DCs might contribute to viral pathogenesis through trans-infection, a mechanism that promotes viral capture and transmission to target cells, especially after DC maturation. In this review, we highlight recent evidence identifying sialyllactosecontaining gangliosides in the viral membrane and the cellular lectin Siglec-1 as critical determinants for HIV-1 capture and storage by mature DCs and for DC-mediated trans-infection of T cells. DCs capture and internalize, invading pathogens, and subsequently process antigen on major histocompatibility complex class I and class II molecules to CD8þ and CD4þ T cells, respectively (7). However, antigen presentation alone by DCs is not enough to induce effective T-cell responses against pathogens. CD4þT cells need to differentiate into distinct T helper cell subsets depending on the type of infection into T helper1, T helper2, T helper17, or regulatory T cells. Pathogen recognition is critical to this induction of T-cell differentiation (36). DCs express numerous pattern recognition receptors that interact with pathogen-associated molecular patterns inducing cytokine expression and the C-type lectin receptors (CLRs) are a major class of pattern recognition receptors. These CLRs bind pathogens, as well as trigger signaling cascades. The unique position of DCs at the interface with the environment is associated with their pivotal role as sentinels of the immune system. Furthermore, by acting as detectors of foreign danger signals, DCs bridge together the innate and adaptive immune system. Upon pathogen encounter, DCs undergo maturation. During maturation, DCs upregulate molecules on their surface such as the major histocompatibility complex class II, CD80, CD83, CD86, and CD40, which are important for antigen presentation and T-cell stimulation.

DCs also migrate from the periphery to the secondary lymphoid organs where they can induce CD8þ and CD4þ T-cell responses (5). In human skin, at least three DC subsets have been identified: epidermal CD207þ Langerhans cells (LCs), CD14þ dermal DCs, and CD14_CD207_CD1aþ DCs. LCs specifically expressing the CLR CD207 (Langerin) (37),(38), are mainly found in the epidermal layer (39), whereas subsets of dermal DCs, some expressing CD209 dendritic cell–specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), are found throughout the dermis (40),(41),(42). Langerin expressing cells have also been observed in very low numbers in the human dermis and may represent a subset of the CD1aþ dermal DC population (43), or epidermal LCs transitting through the dermis. In peripheral blood, there are at least two major subsets of DCs, which are both antigen presenting cells with some functional differences: CD11cþ myeloid DCs, which express either CD1c (blood dendritic cell antigen-1 (BDCA-1)) or CD141 (BDCA3), and CD11c_CD123þ plasmacytoid DCs (pDCs), which express BDCA-2, BDCA-4, and CD123 (interleukin-3 receptor (IL-3R)) and produce a large amount of type I IFN in response to foreign antigen (44),(45). CLEC9Aþ/BDCA3þ DCs, originally identified in peripheral blood and lymph nodes, have recently been detected in the skin, liver, lung, and intestine. They show a more mature phenotype compared with CLEC9Aþ/BDCA3þ DCs observed in either blood or lymph nodes, indicating that they may represent a mature stage of differentiation (46),(47).

3. Features of mature dendritic cells

No other blood cell exhibits the shape and motility that give rise to the term ‘dendritic’ cell. *In situ*, as in the skin, airways and lymphoid organs, DCs extend large, delicate processes or veils in many directions from the cell body (48). The shape and motility of DCs fit their functions, which are to capture antigens and select antigen-specific T cells. activated by DCs, these T cells can complete the immune response by interacting with other cells, such as B cells for antibody formation, macrophages for cytokine release, and targets for lysis. Immature DCs, on the other hand, are less potent initiators of immunity but specialize in capturing and processing antigens to form MHC peptide complexes. Thus, two key functions of DCs segregate in time: they first handle antigens and then, as mature DCs a day or more later, stimulate T cells. *In vitro* or *in vivo*, only few DCs are necessary to provoke a strong T-cell response. *In vitro*, DCs can induce a so-called mixed leukocyte reaction (MLR), a model for graft rejection. Leukocytes from one individual, the potential transplant donor, are mixed with T cells from the responder or graft recipient.. Normally, the MLR is carried out with equal numbers of stimulators and responders, but only one DC is necessary to turn on 100–3,000 T cells. Now it is clear that DCs prime T cells not only to mismatched MHC, but to a range of foreign proteins, from superantigens, the microbial proteins that bind directly to MHC molecules without prior processing (49), to the larger world of more standard proteins that do require processing, including those from infectious agents (50),(51), and tumours (5),(52),(53),(54). *In vivo*, immunity develops in lymphoid organs, where the DC–T-cell interaction can be seen for all major classes of T-cell ligands (55),(56),(57). DCs form clusters with antigen-specific T cells, creating a microenvironment in which immunity can develop (55),(56),(57). So far, no one has been able to identify a single specific molecule to explain the efficacy of DCs in T-cell binding and activation, and the special effects of DCs seem solely to relate to quantitative aspects and their regulation. For example, MHC products and MHC– peptide complexes (58), are 10–100 times higher on DCs than on other APCs like B cells and monocytes. Mature DCs resist the suppressive effects of IL-10, but synthesize high levels of IL-12 (59),(60),(61), that enhance both innate (natural killer cells) and acquired (B and T cells) immunity. DCs also express many accessory molecules that interact with receptors on T cells (62),(63), to enhance adhesion and signalling (co-stimulation), for example LFA-3/CD58, ICAM-1/ CD54, B7-2/CD86. All these properties (MHC expression, secretion of IL-12 and the expression of co-stimulatory molecules) are upregulated within a day of exposure to many stresses and dangers, including microbial products. Depending on the conditions, DCs can stimulate the outgrowth and activation of a variety of T cells, which affect the immune response differently. They can persuade CTLs, which express the accessory molecule CD8 and hence interact with MHC class I bearing cells, to proliferate vigorously, which is unusual for CD8+ T cells (64),(65),. CD4-expressing T-helper cells, on the other hand, scrutinize cells

that express MHC class II molecules. In the presence of mature DCs and of the IL-12 they produce (59),(60),(61), these T cells turn into interferon-g (IFN-g)-producing Th1 cells. IFN-g activates the antimicrobial activities of macrophages and, together with IL-12, it promotes the differentiation of T cells into killer cells. So the capacity of DCs to produce IL-12 and Th1 cellswill lead to microbial resistance. With IL-4, however, DCs induce T cells to differentiate into Th2 cells which secrete IL-5 and IL-4. These cytokines activate eosinophils and help B cells to make the appropriate antibodies, respectively. The communication between DCs and T cells seems to be a dialogue rather than a monologue in which the DCs respond to T cells as well. CD40 (66), and the newly described TRANCE/ RANK receptor (67),(68), on DCs are ligated by the TNF (tumour-necrosis factor) family of proteins expressed on activated and memory T cells: this leads to increased DC survival (66),(67), and, in the case of CD40, upregulation of CD80 and CD86 (66), secretion of IL-12 (59),(60), and release of chemokines such as IL-8, MIP-1a and b (66).

4. Functions of DC

Briefly, DC, excluding thymic DC, have at least four major functions: they (i) obtain foreign antigens from various tissues of the body, (ii) process the antigens into peptides that associate with MHC antigens on their surfaces, (iii) present these antigens to T cells, and (iv) activate the responding T cells. A number of mechanisms whereby DC obtain antigen have been identified; these include phagocytosis, macropinocytosis, fluidphase pinocytosis, and mannose receptor-mediated internalization (69),(70), (71),(72). It is believed that the functions of DC change as these cells progress through their life cycle. For example, LC and other tissue DC are very efficient processors of antigen but are less able to activate T cells. After DC leave their tissue sites and travel to the paracortical regions of draining lymphoid organs, the T-cell stimulatory action of DC increases, and there may be a decrease in their antigen-obtaining activity (73),(70),(74),(75). This increase in T-cell stimulatory activity has been attributed in part to increases in MHC, adhesion, and coactivation molecules on the surfaces of DC (reviewed in references(76),(73),(70),(74) and is regulated in part by cytokines, such as IL-1, GMCSF, and TNF(75). Fully mature DC are capable of directly activating naive and cord blood CD41 T cells (28),(77), and of inducing the generation of antigenspecific CD81 cytotoxic T lymphocytes (77),(78),(79).

5. Immature antigen-capturing dendritic cells

In most tissues, DCs are present in a so-called ‘immature’ state, unable to stimulate T cells. Although these DCs lack the requisite accessory signals for T-cell activation, such as CD40, CD54 and CD86, they are extremely well equipped to capture antigens and—a key event in the induction of immunity—antigens are able to induce full maturation and mobilization of DCs. The sentinel position of immature DCs stand out when the skin surface, or epidermis, is labelled for DC molecules. Humans have about (80), epidermal LCs, the immature dendritic cells of the skin that are located above the basal layer of proliferating keratinocytes. Freshly isolated LCs are weak T-cell stimulators, have few MHC- and accessory-molecules, but many antigen-capturing Fcg and Fce receptors. This phenotype changes dramatically within a day of culture: the cells undergo extensive transformation, antigen-capturing devices disappear, and T-cell stimulatory functions increase. When a skin patch is explanted and the LCs are challenged with an antigen, the migration of mature DCs into the culture medium can be observed (81). The situation is similar *in vivo*. When they encounter a powerful immunological stimulus, for example a contact allergen or a transplant, most of the LCs from the epidermis mature and move into dermal lymphatics in search of antigen-specific T cells. Small numbers of antigen-capturing DCs can also be isolated from blood, lung, spleen, heart, kidney, and the B- and T-cell areas of tonsils; these cells lack LC-specific markers (Ecadherin, Birbeck granules, Lag-1), but they also acquire accessory molecules within 1–2 days of culture, before any encounter with T cells. Immature DCs have several features that allow them to capture antigen. First, they can take up particles and microbes by phagocytosis (50),(51),(82),(83). Second, they can form large pinocytic vesicles in which extracellular fluid and solutes are sampled, a process called

macropinocytosis (84). And third, they express receptors that mediate adsorptive endocytosis, including C-type lectin receptors like the macrophage mannose receptor7 and DEC-205 (85), as well as Fcg and Fce receptors6. Macropinocytosis and receptor-mediated antigen uptake make antigen presentation so efficient that picomolar and nanomolar concentrations of antigen suffice7, much less than the micromolar levels typically employed by other APCs. However, once the DC has captured an antigen, which also can provide a signal to mature, its skills to capture antigens rapidly decline, and the time has come to assemble antigen–MHC class II complexes. The antigen enters the endocytic pathway of the cell. In macrophages most of the protein substrate is directed to the lysosomes, an organelle with only few MHC class II molecules, where the antigen is fully digested into amino acids. Much of this success may be due to specialized, MHC class II-rich compartments (MIICs) that are abundant in immature DCs (86),(48),(71),(87). MIICs are late-endosomal structures that contain the HLA-DM or H–2M products, which enhance and edit peptide binding to MHC class II molecules. During maturation of DCs, MIICs convert to non-lysosomal vesicles that discharge their MHC–peptide complexes to the surface (87),(88). Immature DCs have been compared to idling motors in neutral gear, constantly degradingMHCclass IImolecules in their MIICs (87),(88). To generate cytotoxic killer cells, which have the capacity to eliminate infected cells and attack transplants and tumour cells, DCs have to present antigenic peptides complexed to MHC class I molecules to CD8-expressing T cells. Adedicated peptide transporter then translocates these peptides from the cytosol to the endoplasmic reticulum, where they bind to class I molecules. The peptide-loaded MHC class I complexes travel to the cell surface where they are displayed for scrutiny by T cells (89). It is clear that maturation of DCs is crucial for the initiation of immunity. It can be influenced by a variety of factors, notably microbial and inflammatory products.Whole bacteria (48), the microbial cell-wall component LPS7, and cytokines like IL-1, GM-CSF and TNF-a, all stimulate DC maturation, whereas IL-10 blocks it (90). Ceramide, which is induced by maturation signals, can shut down antigen capture by the DC (91). Mature DCs express high levels of the NF-kB family of transcriptional control proteins (Rel A/p65, Rel B, Rel C, p50, p52) (92), which regulate the expression of many genes encoding immune and inflammatory proteins. Signalling through the TNF-receptor family, for example TNF-R (CD120a/b), CD40 and TRANCE/RANK, results in activation of NF-kB. Therefore, to induce the immune response through activation of DCs, a pathogen or antigen may have to engage the signal transduction pathways of the TNF-R family and TNF-R-associated factors (TRAFs).

6. Dendritic cells and B lymphocytes

DCs, famous for their T-cell-stimulatory properties, are now known to have major effects on B-cell growth and immunoglobulin secretion. B cells and DCs are both APCs and both are essential for antibody responses but for entirely different reasons; DCs activate and expand T-helper cells, which in turn induce B-cell growth and antibody production. But during this *me´nage a` trois*, there is more direct DC–B-cell dialogue as well. Naive B cells respond uniquely to the interstitial, non-LC type of DC (93),(94), and by secretion of soluble factors (94), , including IL-12, DCs stimulate the production of antibodies directly and the proliferation of B cells that have been stimulated by CD40L on activated T cells. DCs also orchestrate immunoglobulin class-switching of T-cellactivated B cells: IL-10 and TGF-b can induce secretion of IgA1, but expression of IgA2 appears to be strictly dependent on a direct interaction between the B cell and the DC (95). This indicates that DCs are in control of mucosal immunity, and, in fact, DCs can be found in mucosal lymphoid tissues beneath antigen-transporting M cells (96),(97),(98), and in T-cell areas. Follicular dendritic cells, or FDCs, directly sustain the viability, growth and differentiation of activated B cells. They also organize the primary B-cell follicles, as shown by the absence of FDCs and follicles in TNF-a-knockout mice. FDCs differ from ordinary DCs: they are not bone-marrow-derived, they lack the leukocyte marker CD45, and they display a unique set of molecules at their surface (99), including all known complement receptors (CD11b, a long isoform of CD21 (100), and CD35).With their receptors for complement and Fc, FDCs capture antibody–antigen complexes and display whole complexes, rather than processed antigens, at their surface for long periods. FDCs are abundantly present within antigen-stimulated B-cell areas, or germinal centres. There, proliferating B cells (centroblasts)

undergosomatic mutation, after which they stop dividing (centrocytes) and wait to be triggered by an immune complex on FDCs. B cells that recognize an immune complex with high affinity process the antigen and present it as peptide–MHC complexes to antigenspecific T cells. The T–B-cell interaction ensures the survival of these high-affinity B cells, while the non-stimulated low-affinity B cells apoptose and are phagocytosed by tingible body macrophages. It is now known that germinal centres contain a second type of dendritic cell, the CD11c+ DC. It also carries immune complexes, and is a much more powerful stimulator of T cells that the germinal centre B cells (101).

7. Dendritic cells and T-cell tolerance

Most studies focus on the power of DCs to activate T cells, but before T cells encounter foreign antigens, the T-cell repertoire should be tolerized to self-antigens. This occurs in the thymus (central tolerance) by deletion of developing T cells, and in lymphoid organs (peripheral tolerance) probably by the induction of anergy or deletion of mature T cells. In both cases, the DC system that initiates immunity to foreign antigens also appears to tolerize T cells to self-antigens. In the thymic medulla, DCs present self-antigens in the context of MHC molecules. Thymocytes that have too high an affinity for selfantigens are deleted (negative selection). In the thymic cortex, macrophages digest large numbers of dying thymocytes that have failed to undergo positive selection. As these macrophages handle large amount of self-antigens, they seem ideally suited to delete autoreactive T cells, yet they do not seem to do so: if MHC class II molecules are solely present on DCs in the medulla, negative selection ensues (102). If, on the other hand, MHC class II molecules are only expressed by cortical epithelium, and not by DCs in medulla, the propensity to autoimmunity increases80, indicating that DCs in the medulla are responsible for the deletion of autoreactive T cells (103). Recent studies point to an important role for DCs in the induction of peripheral tolerance as well. DCs can capture and present self-antigens that are exclusive to specialized tissues. For example, bone-marrow-derived APCs present peptides, which are derived from insulin-producing b-cells of the pancreas, to T cells in the draining lymph nodes (104),(105),(106), tolerance ensues, probably as a result of T-cell anergy or deletion (105),(106).. It has recently been shown that DCs present peptides from apoptotic cells. Accordingly, DCs may be able to present many self-antigens, derived from the normal turnover of somatic cells, to T cells and thus induce tolerance to selfproteins that have no access to the thymus. What determines whether a DC turns the immune system on or off ? Lymphoid DCs are long-lived cells and express very high levels of MHC–self peptide complexes (58), , and maybe T cells become anergic or die in response to abundant and persistent antigens (107).

8. HIV-1 Binding and Capturing

HIV-1 infection mostly occurs through vaginal or rectal routes, as these submucosal areas are rich in DCs and their subsets. HIV-1 infected DCs are difficult to detect compared with the rapid and massive simian immunodeficiency virus (SIV) infection detected in CD4þCCR5þ T cells (108),(109),(110). Nevertheless, it is likely that DCs, because of their localization, act as early targets for the virus and subsequently contribute to the spread of HIV-1 infection to CD4þ T cells via infectious synapses (IS) (111),(112),(1). Viral uptake mainly occurs via endocytosis after binding to CLRs (DC-SIGN, Langerin, CLEC4A (also known as DC immunoreceptor. Apart from HIV-1 binding to DCs expressing the CLR DCSIGN (21),(113), other specific DC subsets also express receptors that are able to bind glycoprotein envelope gp120 (10),(114), In the subepithelia and lamina propria, DCs bind HIV-1 via DC immunoreceptor (115),(116). However, gp120 binding and HIV recognition by pDCs are mainly via CD4-mediated endocytosis, despite pDCs also expressing CD4 and the CLR, BDCA-2 (117),(45). HIV-1 capture involving interactions with glycosphingolipids in the virus lipid bilayer have also been described on immature or matured DCs (118),(119),(120). HIV-1 capture in a glycosphingolipid-dependant manner via the type I IFN-inducible Siglec-1 (CD169) has recently been shown (121). Selective down regulation of

CD169 expression or depletion of glycosphingolipids from virions blocked DC-mediated HIV-1 viral capture and transinfection. DC lectin receptors are also important molecules involved in foreign antigen presentation (Engering et al., 2002). Most HIV-1 virions captured by DCs are known to be at least in part degraded (122),(123),(124), but HIV-1 binding to DC-SIGN does not lead to full degradation. Instead, some is retained in intracellular compartments connected to the cell surface, often termed virus containing compartment (123),(125). which may facilitate delivery to uninfected T cells via the IS. In macrophages, a similar structure was described (126),(127). In mature DCs, HIV-1 uptake and infection leads to its co-localization within cholesterolenriched and tetraspanin-containing compartments, with subsequent delivery of virus via an exosome-like pathway (120). However, in epidermal LCs, virions are directed to acidic compartments for rapid viral degradation (114), and in pDCs endocytosed HIV-1 localizes to early endosomes triggering type I IFN (128). This shows that the interplay between HIV-1 and its binding receptors on DC subsets is quite complex as opposing outcomes are seen between C-type lectins on LCs and DCs. This may have implications on designing microbicides, as disarming DC-SIGN on DCs could decrease HIV-1 transmission, whereas disarming Langerin on LCs could prove counterproductive. This could be one reason why Mannan proved ineffective in a SIV model of mucosal transmission, as it inhibited both DC-SIGN and Langerin (129). In contrast, inhibiting CCR5, viral fusion, or both CD4/CCR5 seemed more promising in this model.

9. Dendritic Cells and their Role in AIDS Pathogenesis

Dendritic cells (DCs) play a pivotal role in linking innate and adaptive immunity by their ability to induce appropriate immune responses upon recognition of invading pathogens (130). Because of their central role in the induction of immune responses, modulation of DC function represents thus a strategic mechanism for a pathogen to evade immune surveillance. Supporting this theory, there is growing experimental evidence of the capacity of some viruses, including HIV-1, to affect DC biology (131),(132). DCs are among the first cellular targets of HIV-1 (133),(134),(135),(136), and their migratory nature makes them strong candidates for viral spreading and transmission, either as directly infected cells or by passively transporting viruses sequestered in endosomal compartments (133),(136). Finally, DCs in lymphoid tissues may serve as reservoirs of HIV-1 that continually contribute to infection of newly recruited T cells (12). It is now becoming clear that HIV-1 exploits multiple stages of the intercellular processes involved in the generation and regulation of the adaptive immune response to gain access to its main target cell population, the CD4_ T cells (137). Thus, the central role of DCs in stimulating T cells not only provides a route for viral transmission, but also represents a vulnerable point at which HIV-1 can interfere with the initiation of T cell-mediated immunity. HIV infection is associated with a gradual loss of immune competence, leading to an increased susceptibility to infection and cancer. While HIV infection is associated with abnormalities in most compartments of the immune system, defects in cell-mediated immunity appear to be of the greatest clinical importance. Impaired APC function is thought to be a critical component of HIV-associated immunodeficiency, and a variety of functional defects have been reported in macrophages and DCs isolated from HIV-infected patients (138),(139). It is interesting that defects in the number (140),(141),(142),(143), and function (141),(144), of DCs have been observed during disease progression, although the extent of this impairment remains controversial (145),(146). In particular, it is not well established whether these defects are directly due to infection of DCs by HIV, or to their exposure to HIV products independently of viral infection. An important aspect of HIV pathogenesis is the concept of affected “bystander” cells. These are cells of the immune system that become functionally impaired via exposure to viral gene products, and not via direct infection. In this respect, interactions of gp120 with immune cells, independently of productive infection, can profoundly influence cellular functions in vivo, contributing to the progressive immune suppression observed in AIDS patients (147),(148). gp120 is present in tissues (149), and in the blood of HIV-infected donors (150),(151), on the surface of virions both infectious and non-infectious and as a free protein. Of note, only a limited fraction (_0.1%) of circulating virions are demonstrably infectious (152),(153),

therefore exposure to inactivated viruses may mimic the most frequent type of CD4-HIV interactions that occurs in vivo.

10. Induction of DC Chemotaxis by gp120

Leukocyte infiltration at the sites of infection or inflammation is a key event in host defense, and it has been recognized that gp120 or AT-2 inactivated viruses could recruit both T cells and monocytes (154),(155),(156). Parallel studies carried out in MDDCs have shown migration toward R5 but not X4 HIV-1 strains. Furthermore, pre-exposure of MDDCs to R5 HIV-1 or its recombinant gp120 protein prevents migration toward CCR5 ligands (157), which is likely due to gp120-mediated internalization of a number of chemoattractant receptors, including HIV-1 fusion co-receptors. These latter results provide an explanation for the reported viral interference following initial infection, as well as for the suppression of APC-dependent inflammatory reactions.

11. Induction of Regulatory T Cells by DC Affected y HIV Infection

One important consequence of dysregulated HIV-mediated DC activation, through direct or indirect mechanisms, could be that immature or partially mature DCs, following their interactions with HIV gp120, can subsequently engage additional antigen-specific CD4_ T cells and drive them to become regulatory T cells (Treg). Indeed, recent studies performed in murine models and with human cells have now clearly established that the role of DCs is not only to sense danger, but also to tolerize the immune system to antigens encountered in the absence of maturation/inflammatory stimuli (158),(159). Our results are in agreement with that hypothesis, because we have shown that naı¨ve allogeneic T cells, following their stimulation by DCs cultured with HIV-exposed T cells, exhibit a profile reminiscent of that of Tr1-type regulatory cells, i.e., low proliferation, reduced production of IFN-_, but increased production of IL-10 (160). Along the same line, after co-culture with HIV-infected immature DCs, T cells suppress proliferation of allogeneic T cells in a mixed lymphocyte reaction (161). DCs exposed to whole HIV, but not DCs pulsed with the gag protein, induced this defect, underscoring a potential role of gp120 in this phenomenon (161), recent studies support a model in which HIV-mediated DC dysregulation not only impairs activation of effector T cells, but also promotes Treg emergence in the lymphoid tissues, where HIV concentrates. This latter effect would be predicted to have long-lasting detrimental consequences on the capacity of the immune system to control HIV replication. Moreover, because Treg-mediated suppression appears to be largely antigen non-specific, the resulting Treg may also suppress effective T cell responses to other pathogens, as might occur in subjects progressing to AIDS.

12. In VIVO Infection and In VITRO Infectability of DC with HIV

The in vitro infectability of DC with HIV and the extent of infection of DC isolated from HIV-infected individuals were initially examined by purifying DC from the peripheral blood of healthy volunteers or HIV-infected individuals by a variety of methods, including in vitro culture and density gradient centrifugation. DC from healthy volunteers were initially found to be highly infectable in vitro, and cells from HIVinfected individuals were found to be infected in vivo with HIV; however, these studies used relatively impure populations of cells (162),(163),(164),(165). Follow-up studies by multiple groups were discordant in their results; some groups found that DC purified from peripheral blood of healthy volunteers by negative selection were easily and productively infected with multiple strains of HIV (166),(167),(168),(169),(170). other groups found that peripheral blood DC isolated by similar methods were not infectable (171),(172). A number of studies have examined LC from the skin of HIV-infected individuals. The general agreement is that these cells can contain HIV DNA, which signifies infection; however, this situation occurs at a very low frequency, at most equal to the level of infection found in peripheral blood CD41 T cells and often 10 to 100 times less (173),(174),(175),(176). Since these studies,

for the most part, examined normal-appearing skin from HIV-infected individuals at different stages of disease, the data suggest that infection of DC, at least in the skin, occurs at very low levels. The study of DC infection in lymphoid organs has been more limited. In a study of spleen white pulp from HIV-infected individuals, the level of infection in the DC population as determined by DNA PCR was approximately 100 times less than that observed in the CD41 T cells (177). In an analysis of lymph node biopsy samples, tissue sections from HIV-infected individuals at various stages of disease were stained for DC by using the p55 (178), antibody that recognizes DC but no other lymphoid cells; the presence of HIV RNA was also determined by in situ hybridization. No cells that stained for both p55 and HIV were noted, suggesting that none of the DC were productively infected with HIV at any stage of disease. Thus, these data suggest that in the tissues in which DC reside for the purposes of obtaining antigen or in the lymphoid organs where they activate T cells, DC are not highly or productively infected. This is not to say that DC do not play a role in initiating or propagating HIV infection (179),(180),(181),(182),(183). In a series of experiments which attempted to address the differences between the epidemiology of HIV infection in the United States and Europe and that in sub-Saharan Africa, Asia, and India, infection of LC using different subtypes (clades) of HIV-1 was studied (184). Thus, it is possible that an HIV subtype that can replicate well in LC, likely the major cell involved in the initiation of viral infection through mucosal contact (133), may have a greater ability to be transmitted heterosexually.

13. Dendritic cells in clinical immunology

Given their central role in controlling immunity, DCs are logical targets for many clinical situations that involve T cells: transplantation, allergy, autoimmune disease, resistance to infection and to tumours, immunodeficiency, and vaccines. In autoimmune diseases such as psoriasis and rheumatoid arthritis, increased numbers and activation of DCs have been noted. DCs are important APCs in the lung, possibly contributing to allergy and asthma. In transplantation and contact allergy, DCs have been implicated in the induction of both immunity and tolerance. Recent results paint a paradoxical picture in which DCs, instead of inducing host resistance, provide a safe haven for several viruses (185). For HIV-1 and measles, the consequences of DC infection are more overt: especially upon interacting with memory T cells and activated T cells, they sustain the production of many HIV-1, SIV and measles (12),(186),(171), particles. Measles turn DCs into multinucleated cells, or syncytia, and suppresses dendritic-cell and T-cell function (187),(188). HIV-1 and SIV also vigorously replicate in DCderived syncytia *in vitro*(183),(189), but immunosuppression is not apparent at this time. (183),(187),(190), (188),(189). *In vivo*, infected syncytia have been noted on the surfaces of mucosa-associated lymphoid tissue.. These so-called lymphoepithelia contain numerous memory B and T cells, as well as DCs that are chronically exposed to maturation stimuli from the environment. But, rather than battling with the infection, mature DCs assist in its spreading by transmitting HIV-1 and SIV to T cells (12),(186), (183),(189). FDCs in B-cell areas appear not to be infected with immunodeficiency virus, but they may play a dual role. By displa.ying virions complexed with antibody, they nevertheless can elicit resistance, especially B-cell memory, but at the same time they act as long-lived extracellular reservoirs of potentially infectious virus. DCs that infiltrate colon and basal-cell skin cancers can lack CD80 and CD86 (191), and therefore have reduced T-cell stimulatory activity. Likewise, tumours may secrete factors, such as IL-10, TGF-b and vascular endothelial growth factor, that reduce DC development and function. The immune repertoire carries tumour-reactive T cells, especially CTLs, but there is little evidence that these T cells are being activated *in vivo*. However, when tumour antigens are applied to DCs *ex vivo* and these DCs are then reinfused, specific immunity ensues. In animals this strategy can lead to protection against tumours and even a reduction in the size of established tumours (192),(193),(194), and at present similar studies are carried out in patients. It is interesting that DCs appear to have a direct lytic potential on certain tumour targets as well (195). Vaccine design has yet to target the DC system. DCs can readily elicit helper and killer T cells, antibodies and IL-12, and can operate at mucosal surfaces where protection is needed early during many infections. As some DCs appear to tone down the immune response, vaccines that target these DCs could also be used to induce tolerance, for example to allergens. The classical approach to vaccination

exploits attenuated forms of pathogens to elicit an immune response, and such attenuation is now more feasible using genetic manipulation and new vectors like avipox viruses. *In vitro*, DCs are the only cells that efficiently present inactivated virus (65), and therefore the efficacy of the new generation of attenuated vaccines could be improved by specific targeting to DCs. The immune response can also be boosted by immunization with DNA vaccines; even though the DNA is primarily expressed in weak APCs, like dermal and muscle cells, DNAvaccines can activate both CD4- and CD8-bearing cells. DCs isolated from vaccinated animals both express the vaccine DNA (196),(197), and present the corresponding peptides to specific T cells (197).. The frequency of transfected DCs is low and greater efficiency should prove valuable.

14. Combining DC vaccination with other therapies

Studies in the late 1970s and early 1980s showed that, in animal models, cytostatic drugs (for example, cyclophosphamide) facilitate adoptive immunotherapy for tumours (198). Recent data that show improved outcomes of vaccination with DCs in myeloablated animals (199),(200), reinforce this concept and indicate that controlled 'immune ablation' might improve the clinical efficacy of DC vaccines administered to patients with cancer. As well as the elimination of TReg cells, the mechanism might also involve the elimination of preexisting memory T cells, which might not be of the most effective phenotype (for example, TH2 cells). So, cyclophosphamide treatment of patients with metastatic cancer before vaccination with DCs is an example of combination therapy and might markedly improve the efficacy of DC vaccines. Indeed, in the late 1980s, clinical trials in patients with melanoma, using whole tumour cells as vaccine, resulted in improved immunity through the elimination of TReg cells when vaccination was combined with cyclophosphamide (201),(202). Other combination therapies can be envisaged that would improve the vaccine itself, provide help for the elicited T cells and/or modulate the tumour environment (203). As discussed earlier, studies in mice show that pre-injection of TNF at the site of vaccination with DCs greatly improves the migration of DCs to the draining lymphoid tissue and the magnitude of the resultant immune response. This approach could be extrapolated to clinical studies, in which the rate of DC migration could be measured using, for example, labelling with indium. Concomitant administration of other cytokines (for example, IFN-α) could improve the efficacy of the DC vaccine40–43, as well as possibly protecting it from tumour-derived inhibitory factors (such as vascular endothelial growth factor or IL-10) (204), and supporting induced T cells. Indeed, studies in mice have indicated that type I IFNs support T cells *in vivo*; this can occur either directly, by sustaining T-cell survival (205). or indirectly, by targeting antigen-presenting cells (possibly DCs) to release IL-15, which in turn enhances T-cell growth (206). The delivery of recombinant IFN-α or IL-2 after vaccination with DCs could protect the elicited T cells from the immunosuppressive tumour environment, thereby improving vaccination efficacy.

15. Immunological and clinical efficacy

Markers indicative of T-cell-migration capacity include differential expression of CCR7 and CD45 isoforms: CCR7+CD45RO+ T cells (known as central memory T cells) most probably migrate to lymph nodes, whereas the shift towards a CCR7– T-cell phenotype (known as effector memory T cells) (207), is usually associated with migration to the tissue. (208). So, monitoring of chemokine receptor expression might provide valuable, and possibly predictive, information regarding the status of tumour-specific T cells. Other immune effectors, including CD4+ T cells, NKT cells, NK cells and B cells, also need to be taken into account. In particular,CD4+ T cells seem to be crucial for priming long-lived CD8+ T-cell memory (209),(210),(211). Furthermore, IFN-γ- producing CD4+ T cells can inhibit tumour-induced angiogenesis. The induction of NKT cells (which kill a wide spectrum of tumour cells (212), or NK cells (which recognize MHC-class-I-deficient tumour cells (213), could be desirable, yet caution must be taken with regard to the cytokines that they produce. For example, IL-13-producing NKT cells might inhibit CTLmediated tumour elimination and favour tumour progression (214). Finally, B cells might inhibit the

induction of T-cell-mediated antitumour immunity by competing with DCs for uptake of tumour-derived antigens (215), or through cytokine secretion (216).Yet, in the active-immunization setting, there could also be desirable humoral responses, and we need to learn more about the types of humoral immunity that are induced by different DC subsets (217) These immune effectors are likely to be differentially regulated by distinct DC subsets. Therefore, it is important to study how human DC subsets generated either from distinct lineages (pDCs versus myeloid DCs) or by environmental regulation (for example, monocytes cultured with IFN-α42,43 versus monocytes cultured with IL-4 and GM-CSF (215),(216), modulate immune effectors.

16. Conclusion Remarks

Antibodies elicited by the vaccine against the HIV-1 envelope correlated with a reduced risk of infection (218),(219). Recent studies involving the role of DC in HIV infection concentrate on the physiologic functions of DC and how HIV might take advantage of these functions to promote its own replication. The main function of DC is to obtain foreign antigens and present them to T cells in order to initiate an immune response. DC are the first immune competent cells to migrate to regions of inflammation in mucous membranes (220), the major site of viral entrance in the sexual spread of HIV. The primary site of HIV replication is in the paracortical regions of lymphoid tissue (133). The amount of HIV produced each day has been reported to be approximately 1010 virions (221),(222),(223), and this viral replication occurs in acutely infected CD41 T cells that are rapidly expanding, likely in response to DC-driven, antigen- specific stimulation (see above) (186). DC loaded with small amounts of antigenic peptide, protein, or inactivated virus in vitro and then used to expand antigen-specific cytotoxic T lymphocytes or as a vaccine can induce potent immune responses (224),(54),(225),(52),(79),(226). Antigen-loaded DC have been used to enhance responses against tumors (225),(52),(79),(226), and infectious organisms (224),(225). DCs are likely to be important targets for any vaccine candidate, because of their critical role in the initiation and shaping of adaptive immune responses. In a double-blind, randomized controlled trial on the effectiveness of a 1% vaginal gel formulation, Tenofovir (reverse transcriptase inhibitor) showed up to 39% reduction in HIV-1 incidence in women (227),(228). Stimulation of autophagy in DCs leads to more rapid and robust adaptive immune responses against HIV-1 (124), therefore targeting stimulation of autophagy in the early events of HIV-1 infection in mucosal tissues could represent a method to circumvent viral propagation (229). Transfer of virus between DCs and T cells at an infectious synapse is also an important outcome that facilitates HIV transmission.,HIV-infected DCs might promote immune evasion by blocking DC maturation and by hampering immune responses. A novel approach to the treatment of HIVinfected individuals may involve the priming of DC with HIV peptides or antigens in order to enhance CTL and other forms of protective immunity (230).

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