Replication pattern of human immunodeficiency virus type 1 in mature Langerhans cells

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Langerhans cells (LC), the dendritic antigen presenting cells of the skin, mature into potent immunostimulatory cells during migration to regional lymph nodes, where they are identified as interdigitating cells (IDC). Since mature Langerhans cells (mLC) resemble IDC in phenotype and immunostimulatory capacity, we examined whether these cells were susceptible to infection with macrophagetropic and lymphotropic strains of human immunodeficiency virus type 1 (HIV-1). Highly purified cell preparations of mLC migrating from human epidermis expressed high amounts of major histocompatibility complex (MHC) class I and II antigens and of the accessory molecules CD40, CD80 and CD86, indicative of the phenotype of potent immunostimulatory cells. CD4 expression was up-regulated on mLC during cultivation, independent of the presence of tumour necrosis factor α (TNF-α) and granulocyte–macrophage colony-stimulating factor (GM-CSF) in the culture medium. The macrophagetropic HIV-1 strain SF162 replicated to higher titres in mLC than the lymphotropic strain IIIB. Both strains induced syncytia, with SF162 showing a more rapid cytopathic effect. Addition of TNF-α enhanced virus production, due to better cell viability under TNF-α treatment, whereas GM-CSF did not significantly influence viability of cells and replication pattern of the virus. These findings suggest that in the infected individual IDC in lymph nodes may function as target cells for HIV-1.

Introduction

Dendritic cells (DC) play a key role in the initiation of adaptive immune responses (Steinman, 1991). Langerhans cells (LC), the dendritic antigen-presenting cells of epidermis, migrate to regional lymph nodes after acquisition of antigen (Kripke et al., 1990), where they are found as interdigitating cells (IDC) and function as efficient activators of primary and secondary T cell responses (Steinman, 1991; Moll et al., 1993). During migration LC undergo a profound functional and phenotypical switch and mature into potent immunostimulatory cells (Larsen et al., 1990). In contrast to cultured LC, freshly isolated epidermal LC cannot induce primary proliferative responses of autologous T cells (Moulon et al., 1993), whereas during culture, LC acquire the phenotype and immunostimulatory capacities of lymphoid DC (Romani et al., 1989).

Cells of the dendritic leukocyte family, LC, IDC, blood dendritic cells (BDC) and spleen DC, but not follicular DC, originate from a CD34+ haematopoietic bone marrow progenitor cell. The migration of DC progenitor cells from bone marrow to non-lymphoid tissues, such as skin, is not yet completely understood. It has been shown in vitro, however, that the cooperation of granulocyte–macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor α (TNF-α) is crucial for LC differentiation (Caux et al., 1992). In vitro, GM-CSF is the principal mediator of LC maturation (Witmer-Pack et al., 1987) whereas TNF-α maintains LC viability (Koch et al., 1990). Both cytokines have been shown to enhance human immunodeficiency virus type 1 (HIV-1) replication in vitro (Koyanagi et al., 1988; Folks et al., 1989).

Although infection of BDC and LC in HIV-positive individuals is controversial (Kalter et al., 1991; Cameron et al., 1992a), there is increasing evidence that BDC and skin LC are infected with HIV-1 in vivo (Tschachler et al., 1987; Dusserre et al., 1992; Gianetti et al., 1993; Patterson et al., 1993). There are conflicting reports concerning the susceptibility of BDC and LC to infection.
with HIV-1 in vitro (Patterson & Knight, 1987; Langhoff et al., 1991; Cameron et al., 1992b; Delorme et al., 1993; Pope et al., 1994; Pinchuk et al., 1994). In the course of HIV-1 infection there is persistent viral replication in lymphoid tissues, even during clinical latency (Embritson et al., 1993; Pantaleo et al., 1993). In this study we used mature Langerhans cells (mLC), resembling IDC of lymphoid tissues, to examine the susceptibility of these cells to infection with representative macrophage-tropic and lymphotrophic HIV-1 strains. Furthermore, we investigated whether GM-CSF and TNF-α have modulatory effects on the replication pattern of HIV-1 in mLC.

Methods

Viruses. Culture supernatants of HIV-1 strains IIIB (Popovic et al., 1984) (grown in H9 cells) and SF162 (Cheng-Mayer et al., 1990) (grown in phytohaemagglutinin and interleukin-2-stimulated peripheral blood mononuclear cells; PBMC) were cleared of debris by centrifugation (1500 g), filtered through 0.45 μm pore filters and stored at −70 °C until use. Virus stocks were tested for p24 antigen content using a p24 antigen capture assay (Coulter Immunology); the TCID50 was determined using human T cells of the MT4 cell line for IIIB and cord blood lymphocytes for SF162 (Schneider et al., 1992).

Isolation and culture of mLC. LC were isolated as described (Larsen et al., 1990, Morris et al., 1992), with minor modifications. Human skin was obtained as clinical specimens after corrective plastic surgery. Subcutaneous fat was removed and skin was incubated in Dispase (2 mg/ml in PBS, pH 7.3) (Boehringer Mannheim) overnight at 4 °C. Epidermis was peeled off with fine forceps, the 0.5 × 0.5 cm epidermal sheets were washed twice in PBS and placed on 5 ml LC medium (RPMI 1640, 10% fetal calf serum (FCS), 1 mM-sodium pyruvate, 0.05 mM-fl-mercaptoethanol) containing 400 U/ml GM-CSF (Boehringer Mannheim) and washed four times with RPMI-2% FCS. After the final washing step rosettes were resuspended in 1-3 ml RPMI-2% FCS. Anti-MHC class II coated magnetic beads (Dynal) were added to give an approximate bead to LC ratio of 5:1 and the suspension was gently rotated at 4 °C for 45 rain.Rossetted cells were collected using a magnetic particle concentrator (Dynal) and washed three times with PBS and resuspended in 1 ml LC medium. Medium, supplemented with 100 U/ml TNF-α (Genzyme) or 200 U/ml GM-CSF, was replaced each day and culture supernatant stored in aliquots at −70 °C. Cytospin slides were prepared at different time points after infection and cell-associated p24 antigen was determined by the APAAP technique. Infectious virus titres were determined as described (Schneider et al., 1992).

Electron microscopy. Replicate mLC cultures were infected with strain IIIB at an m.o.i. of 1:0 for 3 h at 37 °C. The inocula corresponded to 75 ng and 45 ng p24 antigen for strains IIIB and SF162, respectively. Cells were washed three times with PBS and resuspended in 1 ml LC medium. Medium, supplemented with 100 U/ml TNF-α (Genzyme) or 200 U/ml GM-CSF, was replaced each day and culture supernatant stored in aliquots at −70 °C. Cytosin slides were prepared at different time points after infection and cell-associated p24 antigen was determined by the APAAP technique. In another set of experiments, cells were lysed using lysis buffer (PBS/1% Triton X-100). In cell supernatants and lysates p24 antigen concentrations were determined using the p24 antigen capture assay as described by the manufacturer (Coulter Immunology). Infectious virus titres were determined as described (Schneider et al., 1992).

Results

Purity and antigenic phenotype of mLC

After cultivating epidermal sheets on GM-CSF-containing medium for 24 h, the first cells migrating from the epidermis were observed in the culture medium. The maximum recovery of viable mLC was achieved after 48 h, in accordance with Larsen et al. (1990). Flow cytometric analysis revealed that 5–10% of these cells expressed the LC marker CD1a. The magnetic separation step further enriched mLC as determined by immunohistochemistry and flow cytometry. Routinely, 97–98% was purchased from Dianova. For flow cytometric analysis all incubation steps were done on ice. PBS containing 5% FCS and 0.1% sodium azide was used for antibody dilution and washing. Non-specific binding was blocked by incubating cells with PBS–10% human serum for 30 min at 4 °C. LC (3–5 × 10⁶) were stained for 30 min using appropriate MAbs dilutions. After three washing steps cells were labelled with goat anti-mouse IgG PE-F(ab)₂ for 30 min. Flow cytometric analysis was performed in a PROFILE II flow cytometer (Coulter Immunology). Forward and right-angle scatter were used to establish appropriate gates on the cells, excluding non-viable cells. Fluorescence of 15000 cells was accumulated for analysis. Background fluorescence was determined by incubation with isotype matched control antibody (MOPC-21) (Sigma) followed by goat anti-mouse PE-F(ab)₂.

Immunostaining (using alkaline phosphatase anti-alkaline phosphatase; APAAP) of formalin-fixed cytopsin centrifuge preparations was performed as described (Kunze et al., 1986) using MAbs against CD1a (B-B5), MHC-II (L243), CD3 (UCHT1) or a pool of anti-p24 MAbs (Niedrig et al., 1988). Photographs of APAAP preparations were taken with an Axioskop microscope (Zeiss) using differential interference contrast.

HIV infection of mLC. Highly enriched mLC, 2 × 10⁶/ml, were inoculated with cell-free HIV-1 strains IIIB and SF162 at an m.o.i. of 0.2 for 3 h at 37 °C. The inocula corresponded to 75 ng and 45 ng p24 antigen for strains IIIB and SF162, respectively. Cells were washed three times with PBS and resuspended in 1 ml LC medium. Medium, supplemented with 100 U/ml TNF-α (Genzyme) or 200 U/ml GM-CSF, was replaced each day and culture supernatant stored in aliquots at −70 °C. Cytosin slides were prepared at different time points after infection and cell-associated p24 antigen was determined by the APAAP technique. In another set of experiments, cells were lysed using lysis buffer (PBS/1% Triton X-100). In cell supernatants and lysates p24 antigen concentrations were determined using the p24 antigen capture assay as described by the manufacturer (Coulter Immunology). Infectious virus titres were determined as described (Schneider et al., 1992).

Electron microscopy. Replicate mLC cultures were infected with strain IIIB at an m.o.i. of 1:0 for 3 h at 37 °C, washed three times with PBS and resuspended at 4 × 10⁶/ml in 24-well plates (Nunc). Medium was replaced every second day and TNF-α was added at 100 U/ml daily to maintain mLC viability. At day 6 p.i. 10⁶ cells were used for preparation of cytopsin slides and the number of p24-antigen-positive mLC was determined using the APAAP technique. The remaining cells were fixed with 2.5% glutaraldehyde for 30 min at room temperature. Cells were collected and, after agar block enclosure and postfixation with OsO₄, processed for thin section electron microscopy as described (Gelderblom et al., 1987).
HIV-1 infection of mature Langerhans cells

T6

CD26, A

MHC-II, MHC-I, IN

Log PE Fluorescence intensity

Fig. 1. Assessment of antigenic phenotype of mLC using flow cytometry. Dotted lines show staining with isotype matched control antibody followed by goat anti-mouse PE-F(ab)_2; solid lines represent relative fluorescence intensity of mLC treated with the indicated antibody. Staining with MAbs against MHC-I and MHC-II is very strong, as shown by the accumulation of fluorescence intensities on the right-hand side of the histograms.

Log PE Fluorescence intensity

Fig. 2. Expression of the CD4 molecule on mLC is up-regulated upon culture but CD1a expression is not changed, as determined by flow cytometry. Solid lines represent CD4 and CD1a expression of mLC after migration from skin; solid thick lines were obtained after culture for 2 days; dotted lines show staining with control antibody followed by goat anti-mouse F(ab)_2.

of the cells stained positive for CD1a (Fig. 1). No CD14+ cells were detectable and CD3+ cells did not exceed 2–3% (not shown).

To demonstrate that cells isolated and cultured by our routine showed the mature LC phenotype, the cells were analysed for relevant surface markers by flow cytometry. mLC stained strongly positive for CD1a, MHC class I and II antigens, and accessory molecules CD40, CD80 (B7-1) and CD86 (B7-2). The adhesion molecule CD11c was expressed weakly, in contrast to the strongly expressed CD54 (ICAM-1). In addition, the cells were found to be positive for the HIV-1 receptor CD4 and the putative second HIV-1 receptor CD26 (Callebaut et al., 1993) (Fig. 1).

In contrast to the down-regulation of CD4 on cultured BDC (O’Doherty et al., 1993), mLC up-regulated CD4 expression after 2 days in culture. The expression of CD1a was not altered and more than 97% of the cells were still CD1a positive on day 2 (Fig. 2). The cytokines TNF-α and GM-CSF had no influence on the up-regulation of CD4 or the expression of CD1a on mLC.

Replication of HIV-1 in mLC

The cells were infected at a relatively low m.o.i. of 0.2 in order to amplify growth differences among the two HIV-1 strains (SF162 and IIIB) and to assess the influence of the cytokines. Both viruses were able to productively infect mLC (Fig. 3b, c and Fig. 4). At day 3 p.i. the first p24-antigen-positive mLC could be detected by APAAP immunohistochemistry. The infected cells showed large lobular nuclei and long cytoplasmic projections, characteristic for LC. Both SF162 and IIIB induced syncytia in mLC cultures. In cultures infected with SF162, syncytia were first detectable at day 3 p.i. and contained two to six nuclei; at day 6 p.i. the number of multinucleate cells had not risen substantially and syncytia remained small in size with few nuclei (Fig. 3d). In contrast, IIIB-induced syncytia appeared later but increased in size, showing 4–15 nuclei at day 6 p.i. (Fig. 3e, f). Syncytia stained strongly positive for the cell surface markers CD1a (Fig. 3e) and MHC class II (not shown), comparable in strength to the surrounding non-fused mLC. Staining with anti-CD3 MAb confirmed the low amount of T cells (2–3%) present in the mLC cultures. T cells were found as single cells (Fig. 3c) or in aggregation with mLC (Fig. 3j). About 30% of the syncytia were found to be weakly CD3+, indicating the ability of the few contaminating T cells to participate in syncytium formation (Fig. 3f).

The number of p24-antigen-positive mLC in cultures infected at an m.o.i. of 0.2 varied between 0.5% and 2% for strain IIIB and 1% and 5% for strain SF162, as determined by APAAP. In order to quantify differences between SF162 and IIIB replication, culture supernatants
were analysed at day 5 p.i. for p24 antigen content and presence of infectious virus. Table 1 summarizes the data of five experiments, which were carried out independently. SF162 allowed a 5- to > 10-fold higher production of p24 antigen and infectious virus in culture supernatants. Quantification of the cell-associated p24 antigen revealed that SF162-infected cell cultures showed a higher amount of cell-associated p24 antigen than cells infected with IIIB (Table 1), reflecting the differences in p24 antigen levels present in supernatants. The mLC from different individuals showed variations in the amount of p24 antigen and infectious HIV-1 produced after infection with the same virus stocks. Peak levels in cultures without cytokine treatment varied from 405–4580 pg/ml p24 antigen and 500–8300 TCID_{50}/ml in culture supernatants for SF162, and 40–234 pg/ml p24 antigen and 66–173 TCID_{50}/ml for IIIB. Statistical analysis of the data using Student’s t-test revealed a two-tailed significance of $P \leq 0.05$ for the effects described here.

Thin section electron microscopy corroborated the high degree of mLC enrichment as determined by APAAP and flow cytometry. The cell profiles showed a high plasma/nucleus ratio with deeply indented lobular nuclei. Birbeck granula, morphological features of skin LC (Romani et al., 1989), were not detected in the cytoplasm of mLC cultured for 6 days, but were present in cells analysed directly after isolation. The surface of mLC was undulated, showing a dense fringe of cell processes and protrusions which formed an interdigitated network. HIV particles were detected in 10–15% of the mLC infected with HIV-1 at an m.o.i. of 1 (Fig. 4). Both mature and immature virus particles were seen associated with the cell periphery. Mature virions showed typical

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**Fig. 3.** Cytospin preparations of uninfected mLC and mLC infected at an m.o.i. of 0.2 with either IIIB or SF162 and investigated by the APAAP technique. (a) Morphology of uninfected mLC; CD1a stain. (b) Single IIIB-infected mLC; p24 stain, day 6 p.i. (c) Single SF162-infected mLC; a separate p24-negative T cell is indicated by an arrow; p24 stain, day 6 p.i. (d) SF162-induced syncytium; p24 stain, day 6 p.i. (e) Syncytia in mLC cultures are CD1a+; CD1a stain, day 6 p.i., IIIB infection. (f) HIV-induced syncytia are CD3+ (small arrows) or weakly CD3+, when T cells fuse into the syncytia (large arrow); CD3 stain, day 6 p.i., IIIB infection. Magnifications: (a, d, e, f) × 900 (bar represents 10 μm); (b, c) × 1400 (bar represents 10 μm).

**Fig. 4.** Thin section electron microscopy of mLC showing productive infection by IIIB. (a) Virus particles are released in the interdigitated network of cell processes. Two budding particles are indicated by an arrow and shown in (b) at higher magnification. (c) Formation of HIV by budding at the plasma membrane. (d) Mature and immature virions surrounding the processes of a mLC at intermediate magnification. Cells were infected with IIIB at an m.o.i. of 1. Magnifications: (a) × 10000 (bar represents 3 μm); (b) × 100000 (bar represents 100 nm); (c) × 30000 (bar represents 1 μm).
Fig. 4. For legend see opposite.
Table 1. Determination of HIV-1 production using p24 antigen capture assay and TCID_{50} assay at day 5 p.i.*

<table>
<thead>
<tr>
<th>HIV-1 strain</th>
<th>Cytokine treatment</th>
<th>p24 Antigen assay (pg/ml)</th>
<th>Cell-associated p24 antigen (pg)†</th>
<th>Infectivity assay (TCID_{50}/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF162</td>
<td>No</td>
<td>1546 (405-4580)</td>
<td>1405 (480-3200)</td>
<td>3810 (500-8300)</td>
</tr>
<tr>
<td>SF162</td>
<td>GM-CSF</td>
<td>1521 (310-4690)</td>
<td>1679 (420-3526)</td>
<td>4030 (500-9500)</td>
</tr>
<tr>
<td>SF162</td>
<td>TNF-α</td>
<td>3435 (961-9980)</td>
<td>4939 (1470-10216)</td>
<td>9580 (1100-25000)</td>
</tr>
<tr>
<td>IIB</td>
<td>No</td>
<td>120 (40-234)</td>
<td>210 (92-426)</td>
<td>117 (66-173)</td>
</tr>
<tr>
<td>IIB</td>
<td>GM-CSF</td>
<td>124 (39-242)</td>
<td>217 (100-419)</td>
<td>113 (76-173)</td>
</tr>
<tr>
<td>IIB</td>
<td>TNF-α</td>
<td>251 (105-415)</td>
<td>795 (201-1412)</td>
<td>250 (114-395)</td>
</tr>
</tbody>
</table>

* Results of five separate experiments are expressed as the mean with ranges given in parentheses.
† Cells were harvested at day 6 p.i. and lysed in 150 μl lysis buffer; 50 μl of lysate was analysed for p24 antigen content.

Table 2. Influence of the m.o.i. on the number of infected mLC.

<table>
<thead>
<tr>
<th>Strain/m.o.i.</th>
<th>Infected mLC (%) at day 6 p.i. in experiment no.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB/0.2</td>
<td>1-6 0-8 1-9</td>
</tr>
<tr>
<td>IIB/1.0†</td>
<td>11-8 10-2 13-5</td>
</tr>
</tbody>
</table>

* Infected p24 antigen-positive mLC in APAAP preparations were determined by two observers counting at least 500 cells.
† Data represent the mean of the percentage of infected mLC determined using APAAP and electron microscopy.

Virus assembly occurred by budding from the plasma membrane of the cell body (Fig. 4b) and also from the processes. In cytopsin preparations of mLC infected at an m.o.i. of 1 and prepared in parallel to the electron microscope samples 10–15% of the mLC were p24-antigen-positive, indicating that these cells are producing virus. In mLC cultures infected at an m.o.i. of 0.2 the number of p24-antigen-positive mLC was lower (Table 2). The differences observed in the number of infected cells reflect the different ratios of infectious virus per cell.

Effects of GM-CSF and TNF-α on HIV-1 replication in mLC

To determine the influence of TNF-α and GM-CSF on HIV-1 replication in mLC daily p24 antigen production was determined. TNF-α led to increased p24 antigen production in culture supernatant (Fig. 5), whereas GM-CSF did not significantly influence replication pattern. These findings were confirmed by the determination of released infectious virus and cell-associated p24 antigen (Table 1). In accordance with Koch et al. (1990) we found that TNF-α maintains LC viability; TNF-α markedly enhanced viability of mLC (11 ± 1 days), in comparison to untreated and GM-CSF-treated mLC which expressed a viability of less than 5% at 7 ± 1 days. No significant differences between the viability of infected and uninfected mLC were observed.

Discussion

Clinical and experimental data indicate a crucial role for DC in the pathogenesis of AIDS (Macatonia et al., 1990, 1992; Cameron et al., 1992b). Since HIV-1 infection...
occurs primarily in lymphoid tissues (Pantaleo et al., 1993), we established a model for infection of lymph node IDC using their in vitro equivalent, the mLC. The migratory capacity of LC and the use of a magnetic separation technique enabled us to isolate highly purified mLC. Cells purified by this method have the antigenic profile of lymphoid DC, as shown by flow cytometric analysis. These results are consistent with data described for maturation of BDC (Harr et al., 1993; O'Doherty et al., 1993), with high level expression of MHC class I and II antigens and strong expression of the co-stimulatory molecules CD40, CD54, CD80 and CD86. BDC, however, down-regulate CD4 expression upon cultivation (O'Doherty et al., 1993), whereas mLC up-regulate expression of this receptor during cultivation independently of the presence of TNF-α or GM-CSF. Controversial reports on the infection of freshly isolated (immature) LC or BDC with HIV-1 (Cameron et al., 1992b; Delorme et al., 1993) might be due to varying levels of CD4 expression, depending on the in vitro differentiation stage of the cells.

The question whether DC function as target cells and a reservoir for HIV-1 in vivo and as target cells for HIV-1 infection in vitro has remained a controversial issue. Recent studies demonstrated the susceptibility of freshly isolated BDC to various HIV-1 strains. Our results in mLC corroborate data by Chehimi et al. (1993) where the macrophagotrophic strain SF162 has been shown to replicate better than the lymphotrophic strain IIIB in BDC. However, in contrast to our results no cytopathic effect due to HIV-1 replication (e.g. syncytia formation) in BDC has been observed (Langhoff et al., 1991). A productive infection with cell-free HIV-1 in vitro has not yet been shown in freshly isolated immature LC, although in vitro infection of LC using co-cultivation with chronic HIV-1-infected U937 cells was possible (Delorme et al., 1993). Pope et al. (1994), using cells migrating from human skin, observed productive infection and syncytia formation with HIV-1 only in conjugates of DC with T cells, but neither a productive infection of single DC nor T cell-independent syncytia formation were detected. GM-CSF, known to be crucial for LC development (Witmer-Pack et al., 1987) and used in our approach to facilitate LC maturation during migration from epidermis, might be a critical factor for susceptibility of mLC to infection with HIV-1 (GM-CSF was not used by Pope et al., 1994).

The efficiency of mLC infection was dependent on the virus strain and the amount of inoculated virus. It could be shown that an increase in the m.o.i. led to a more efficient infection of mLC. Significantly more cells were found to be infected (10-15%) when the cell culture was inoculated at a high m.o.i. (1), whereas the number of p24-antigen-positive cells was only 0.5-2% when a lower dose (m.o.i. 0.2) was used. Furthermore, we observed a significant enhancement of mLC viability and enhanced HIV-1 replication upon TNF-α treatment. Our data suggest that the effect of TNF-α on HIV-1 replication in mLC is mainly due to enhanced cell viability, although an additional direct effect on HIV-1 replication may be possible. In contrast to HIV-1 replication in monocytes/macrophages (Koyanagi et al., 1988), we did not observe an enhancing effect of GM-CSF on HIV-1 replication in mLC.

The macrophagotrophic strain SF162 replicated well in mLC, as shown by the formation of syncytia and production of high virus titres and p24 antigen. In contrast, the lymphotrophic strain IIIB led only to the production of lower virus titres, less p24 antigen and to slower syncytium formation in mLC.

During clinical latency HIV-1-infected individuals show quantitative and functional changes in the T cell compartment (Clerici et al., 1989; Van Noesel et al., 1990; Lucey et al., 1991). Helbert et al. (1993) and Meyaard et al. (1993) suggested that the gradual deterioration of the immune system, with the steady diminution in T helper cell number and function, result from defective antigen presentation. During all stages of HIV-1 infection macrophagotrophic viruses can be recovered, predominantly in the asymptomatic period (Schuitemaker et al., 1992). The observation that HIV-1, and particularly a macrophagotrophic HIV-1 strain, replicates to high titres in vitro in mLC and is cytopathic to these cells suggests that this might happen in IDC in lymph nodes of HIV-1-infected individuals during clinical latency. The activation of T cells, the transition from naive to activated state, is primarily driven by dendritic antigen-presenting cells in lymphoid tissues. Infection of IDC in vivo might lead to an impairment of antigen presentation which would explain the loss of activated T cells (Klimas et al., 1991) during the asymptomatic infection period, followed by the development of severe immunopathological changes as seen later in disease progression.

The cell system presented here may facilitate further studies on the interaction of HIV-1 with lymph node DC in an in vitro model to evaluate the consequences of HIV-1 infection for DC function. The examination of the transmission mode of HIV-1 from infected antigen-presenting cells to CD4+ T cells may elucidate further the mechanisms underlying T cell deficiency and decay, the central events in the immunopathogenesis of AIDS.

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