Recent findings have indicated that megakaryocytes may be susceptible to human immunodeficiency virus (HIV) infection, suggesting a potential role for megakaryocytes as viral reservoirs in HIV-infected patients. We report that the megakaryocytic cell line Dami could be productively infected with the HTLV III-B strain of HIV-1, in 26 different experiments (results of 16 experiments are reported); productive infection lasted up to 30 weeks. Despite a lack of detectable surface expression of the CD4 molecule and very low levels of CD4 mRNA, between 40% and 60% of megakaryocytic cells produced viral proteins after contact with HIV-1. Neither cytopathogenic effects nor syncitia formation was observed. Production of high levels of functional viral particles was indicated by analysis of p24 protein levels, reverse transcriptase activity, ultrastructural studies, and the capacity of supernatants from infected Dami cells to infect the Molt-4 T-lymphocytic cell line. HIV-1 RNA and protein levels in infected Dami cells were enhanced by treatment with tumor necrosis factor-α (TNF-α), and decreased by treatment with interferon-α (IFN-α) and IFN-γ. Transient transfection of the megakaryocytic cells with various constructs of the HIV-1 promoter (LTR) linked to the luciferase reporter gene suggested that the effect of TNF-α was related, as in monocytic and T-cell lines, to transactivation of the enhancer region of the HIV-1 LTR. These findings indicate that signals provided by the immune system may modulate HIV-1 expression in cells of the megakaryocytic lineage.

MATERIALS AND METHODS

Dami cell line. Dami cells, originally described by Greenberg et al.,8 were cultured in Iscove’s modified Dulbecco’s medium (IMDM; GIBCO-BRL, Cergy-Pontoise, France) supplemented with 10% horse serum or in some experiments, with 2% Ultroser HY (IBF, Villeneuve-la-Garenne, France). Expression of surface markers was analyzed by flow cytometry (EPICS; Coulter, Margency, France) using IgGl mouse monoclonal antibodies (MoAbs) directed against CD2 (T11, Coulter), CD4 (T4, Coulter; and IOT4a; Immunotech, Marseille, France), CD41b (GPIlb) (IOP41b; Immunotech) and CD61 (GPIIIa) (IOP61; Immunotech). Intracellular cytokines were detected using IgGl mouse monoclonal antibodies (MoAbs) directed against TNF-α (R&D Systems, Minneapolis, Minn) and against interferon-γ (IFN-γ) (PharMingen, San Diego, Calif). Expression of TNF-α and IFN-γ was then determined by reverse transcription-polymerase chain reaction (RT-PCR). The capacity of megakaryocytes to produce IL-1 was assessed by measuring IL-1β and IL-1α levels in culture supernatants.

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HIV-ROMBOCYTOPENIA is a common finding in patients infected with the human immunodeficiency virus (HIV). Its cause is believed to be multifactorial, involving immune-mediated peripheral platelet destruction as well as impaired thromboctypoiytesis. Recent studies have indicated that megakaryocytes may be a target for HIV infection, suggesting both a potential mechanism for defective thrombopoiesis, and a role for megakaryocytes as viral reservoirs in the bone marrow (BM). Investigation of the expression of the CD4 molecule, the high-affinity receptor for HIV, on megakaryocytes has led to divergent results expression at best was detected in about 25% of this cell population. In situ hybridization studies by Zuckerman and Cao have allowed identification of HIV-type 1 (HIV-1) virus RNA in megakaryocytes from HIV-infected patients. Recently, Sakagushi et al. reported that certain clones of the megakaryocytic cell line CMK expressed the CD4 molecule could be productively infected in vitro with HIV-type 2 (HIV-2) strains. Susceptibility of CMK cells to the HTLV III-B strain of HIV-1 was very poor, however, leading to infection of less than 1 in 10⁶ cells and requiring coculture with CD4+ T-cell lines to detect production of viral particles. We investigated the susceptibility to HIV-1 infection of the Dami megakaryocytic cell line, originally described by Greenberg et al., which expresses several morphologic and biochemical features of BM megakaryocytes, no detectable surface CD4 molecule, and only low levels of CD4 mRNA. The Dami cell line could be infected productively by the III-B strain of HIV-1 and produced high levels of functional virions. This cell line, which expresses functional receptors for several cytokines, provided a model to explore the effect of these cytokines on HIV-1 transactivation and protein synthesis in cells of the megakaryocytic lineage.

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HIV-1 INFECTION OF MEGAKARYOCYTIC CELLS

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HIV-1 infection of Dami cells

Incubation of the Dami megakaryocytic cells with the HTLV III-B strain of HIV-1 was performed 26 times and led, in each case, to a highly productive infection. Results shown in Fig 1 (4 different experiments), Fig 2A (10 experiments), Fig 2B (1 experiment) and Table 2 (1 experiment) involve 16 different infections in all. Four experiments are shown in Fig 1, in which infections were followed for 80 days to 30 weeks. In some but not all infections (Fig 1), peaks of p24 antigen release greater than 1 µg/mL/10⁶ cells were observed. The delay preceding detectable production of p24 antigen in supernatants depended on the reverse transcriptase activity

RESULTS

HIV-1 infection of Dami cells

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Fig 1. Kinetics of p24 antigen production in cell supernatant of Dami cells after exposure to the HTLV III-B strain of HIV-1 (four representative experiments). Cells were infected either with 5,000 cpm/mL (A) or 50,000 cpm/mL (B) of HTLV III-B reverse transcriptase activity. Every 3 or 4 days, cells were counted, p24 levels were assayed in supernatants, and results were expressed in nanograms per milliliter cells.
Fig 2. TNF-α effect on HIV-1 protein and RNA production in infected Dami cells. (A) Ten different infected Dami cells were treated with medium (○) or with 100 U/mL of TNF-α (●) for 7 days and HIV-1 p24 levels were determined in culture supernatants (TNF-induced fold increase is indicated above each experiment). (B) Infected cells (5,000 cpm infection, p24 level of 2 ng/mL/10⁶ cells) were cultivated with medium or TNF-α (100 U/mL) without (○) or with normal rabbit serum (1:500) (□) or rabbit serum directed against human TNF-α (1:500) (■) for 3 days (D3) or 7 days (D7). HIV-1 p24 levels were then determined in cell supernatants. (C) Dot-hybridization detection of HIV-1 RNA in HIV-1–infected Dami cells (50,000 cpm infection, p24 level of 10 ng/mL/10⁸ cells) treated with TNF-α. Total RNA extracted from 5 × 10⁵ HIV-1–infected Dami cells treated for 7 days with medium alone (lane 1) or with TNF-α (100 U/mL) (lane 2), or for 11 days with medium (lane 3) or TNF-α (lane 4) were spotted on Hybond-N membrane. The blots were then hybridized with a radiolabeled HIV-1 cDNA (top) and after stripping with a radiolabeled β-actin cDNA probe (bottom). Each successive line represents a 1:2 dilution of the preceding line.

of the initial HTLV III-B inoculum (Fig 1A [5,000 cpm] v Fig 1B [50,000 cpm]). In the 26 experiments, the earliest p24 antigen detection (p24 ≥ 10 pg/mL/10⁶ cells) was 12 days and 22 days after infection with 50,000 and 5,000 cpm, respectively, but onset of highly increasing viral production was detected only later, at about 50 days (Fig 1A; 5,000 cpm) and 30 days (Fig 1B; 50,000 cpm). Such delays of productive infection have been reported previously for in vitro infection of BM progenitors. There was no detectable loss of cell viability, gross cytopathic effect, or modification in cell proliferation (doubling time of 24 hours) or ploidy in Dami cells up to 30 weeks after HIV infection (data not shown). Viral particles released in cell-free supernatants by Dami cells infected with HIV-1 retained their capacity to infect the Molt-4 T-cell line. Moreover, addition to Molt-4 cells of 5,000 cpm (corresponding to 350 pg p24 protein) of RT activity of virus produced by the Dami cells led, after 8 days, to cytopathogenic effects in the T-cell line (data not shown).

Electron microscopy of infected Dami cells showed morphologically normal HIV-1 viral particles (Fig 3). Immunoperoxidase staining (Fig 4A–C) with an MoAb directed against HIV-1 p24 antigen showed that about 40% of Dami cells expressed this protein (Fig 4B and C) and in Table 1 flow cytometry analysis with the same MoAb showed that up to 60% of infected Dami cells (Dami cells 3) expressed this protein (4 months after infection with 50,000 cpm inoculum, p24 level 320 ng/mL/million cells). In situ hybridization with the 35S-HIV-1–gag RNA probe (Fig 4D through F) showed silver grains localized to some infected Dami cells (Fig 4D and E). A high density of silver grains that resulted from hybridization of the labeled probe with endogenous HIV-1 RNA was detected over certain cells (~30% of cells were highly positive). This high density of silver grains was in contrast to a much lower level of silver grains scattered randomly either throughout all other regions of the slides or when uninfected cells were used (D). As shown in Fig 5A, specific HIV-1 RNA species were detectable by Northern blot analysis; 9.3-, 4.2-, and 2-kilobase (Kb) HIV-1 transcripts were detected using an HIV-1 cDNA probe (8390 to 9130 bp) in HIV-1–infected Dami cells and were not detected in uninfected Dami cells.

**CD4 protein and mRNA expression by Dami cells.** Before infection, and at different intervals after infection, cells were analyzed by flow cytometry for surface expression of platelet glycoproteins (GPIIb and GPIIIa) and of the CD4 protein. Two different anti-CD4 MoAbs were used, and gave similar results. Table 1 shows a representative experiment (of four different experiments). Both uninfected and HIV-1–infected Dami cells expressed the GPIIIa highly but not the CD4. In contrast, monocytic and lymphocytic cell lines expressed CD4 but not GPIIIa. As shown in Fig 5B, Northern blot analysis with a CD4 cDNA probe of total RNA extracted from infected and uninfected Dami cells required 10 days of exposure to yield a detectable signal, whereas CD4 mRNA was detected after only 18-hour exposure in human peripheral blood mononuclear cells (PBMC). These experiments indicate that either each Dami cell expresses a very low level of CD4 mRNA or that a very small subpopulation of the cells expresses significant
Fig 3. Electron microscopy of thin sections of Dami cells 73 days after infection with 5,000 cpm of HTLV III-B RT activity (p24 level of 80 ng/mL/10^6 cells). Arrows (A) indicate viral particles in the cell periphery. (B) High magnification of viral particles. (C) Virion budding.

levels of CD4 mRNA. Expression of GPIIIb and GPIIIa mRNA was not modified by HIV-1 infection of the cells (Fig 5C). Hybridization experiments shown in Figs 5A and B were performed on the same blot after stripping and were representative of three independent experiments. HIV-1 infection of Dami cells did not involve serum components such as IgG or complement because productive infection could be obtained in cells cultured in Ultralser HY in the absence of serum, after infection with virus that had been produced in Molt-4 cultured in the same serum-free medium.

Cytokine-mediated modulation of HIV-1 production. HIV-1-infected cells (10^6/mL) were cultured with TNF-α (100 U/mL) or a mixture of IFN-γ and IFN-α (1,000 U/mL each) for 5 to 11 days. As shown in Table 2, HIV-1 p24 production in the supernatants was enhanced by TNF-α, whereas the combination of IFN-γ and IFN-α inhibited p24 production; IFN-α or IFN-γ alone had less effect (data not shown). The enhancing effect of TNF-α was reproducible and is shown in 13 experiments (Fig 2A, 10 experiments; Fig 2B, 1 experiment; Fig 2C, 1 experiment; and Table 2, 1 experiment). As shown in Fig 2B, neutralizing antibodies against human TNF-α prevented the overproduction of p24 induced by TNF but did not affect the basal level of p24 production. No TNF-α secretion by infected or uninfected Dami cells could be detected with a Genzyme enzyme-linked immunosorbent assay (ELISA) kit (Genzyme), strongly suggesting that spontaneous HIV-1 production by infected Dami cells, in medium alone does not involve TNF-α. Dot-hybridization experiments showed that TNF-α-mediated increase in p24 protein expression was associated with increased levels of HIV-1 RNA, whereas the β-actin mRNA level was not modified (Fig 2C). When TNF-α treatment was initiated 4 days before HIV-1 infection, production of virus was detected earlier than in untreated cells. Indeed, in two different experiments, p24 production more than 1 ng/mL/million cells were obtained 10 days after such TNF-α treatment, whereas untreated cells had not begun to produce virus at day 15 (p24 ≤ 10 pg/mL/million cells). In three different experiments, TNF-α treatment was initiated after HIV-1 infection of Dami cells but before productive infection was detected. This induced p24 production in 4 days (p24 level of 50, 140, and 200 pg/mL/10^6 cells), whereas p24 was still undetectable in the untreated cells. In contrast, eight different experiments showed that TNF-α treatment of chronically infected Dami cells, more than 3 months after infection, had no or low (up to 1.5-fold) enhancing effect on p24 production.

To determine whether the TNF-α-mediated increase in HIV-1 p24 production by Dami cells resulted from a transcriptional or a posttranscriptional effect, transient transfection experiments of uninfected Dami cells were performed using HIV-1 LAV Bru LTR-constructs. The LTR of LAV Bru or LAI is similar to that of IIIB; only three bases of substitution in 188 exist in the enhancer-promoter region that are outside the enhancer NF-κB consensus sites. The LTR of LAV Bru and of IIIB have been shown to have similar responses to TNF-α in T-cell lines (seven- to eightfold increase). The response of a given HIV-1 LTR to stimulation has been shown to vary, however, depending on the cell line transfected; eg, two- to 20-fold increases have been reported in response to PMA. In seven transient transfection experiments of the Bru LTR-Luc construct in Dami cells, TNF induced a fivefold ±
Fig 4. Detection of p24 protein expression by immunoperoxidase and of HIV-1 RNA expression by in situ hybridization in Dami cells 85 days after infection with 5,000 cpm HTLV III-B RT activity (p24 level of 350 ng/mL/10⁶ cells). Cells were cytospun and subjected to staining or hybridization. (A) An indirect immunoperoxidase staining procedure. (A) Cells stained with control mouse IgG1 (5 μg/mL). (B and C) Cells stained with an anti-HIV-1 p24 antigen mouse monoclonal IgG1 (5 μg/mL). (A) Cells were counterstained with hematoxylin. No staining was detected after incubation of uninfected Dami cells with the anti-p24 antibody (not shown). Specificity of the staining was also indicated by the presence of unstained cells in B and C (a). In situ hybridization with the HTLV III-B gag probe; slides used were the same as in a and were further fixed with paraformaldehyde (4% in PBS) before hybridization.
Fig 4. (Cont’d). (D) Uninfected cells. (E and F) HIV-1–infected Dami cells. Exposure time was 72 hours.
Fig 5. Northern-blot analysis of total RNA from Dami cells for the detection of (A) HIV-1 RNA in uninfected Dami cells (lanes 1 and 4) and in HIV-1 infected Dami cells (5,000 cpm inoculum) 108 and 115 days after infection with 5,000 cpm of HTLV III-B RT activity (p24 level of 130 and 200 ng/mL/10^6 cells) (lanes 2 and 5), respectively, or 73 and 80 days after infection with 50,000 cpm of HTLV III-B RT activity (p24 level of 80 and 210 ng/mL/10^6 cells) (lanes 3 and 6). Bottom panel: Ethidium bromide staining of the nylon membrane before hybridization. (B) CD4 mRNA on the same blot after stripping and rehybridization with a radiolabeled CD4 cDNA probe. Lanes 1 through 6 represent autoradiography obtained after 10 days of exposure; lane 7 represents an 18-hour exposure of RNA extracted from human PBL. (C) GpIlla and GpIIb mRNA in uninfected (lane 1) and HIV-1-infected Dami cells, 80 days after infection with 5,000 cpm HTLV III-B RT activity (p24 level of 200 ng/mL/10^6 cells) (lane 2), or 55 days after infection with 50,000 cpm of HTLV III-B RT activity (p24 level of 400 ng/mL/10^6 cells) (lane 3).
HIV-1 infection of megakaryocytic cells

The viability of cells were monitored at different intervals. Only treatment with IFNs expressed as nanograms per milliliter per 10^6 viable cells (one representative experiment of four).

Morphologic normal viral particles that were detected in the supernatant were infectious for a CD4 T-lymphocytic (Molt-4) cell line (data not shown). Recent studies of CD4+ T-lymphocytic and monocytic cell lines have led to identification of the regulatory effect of cytokines, including TNF-α. We therefore investigated whether such mediators could influence the level of HIV-1 expression in these cell lines. Furthermore, platelets, which do not express the CD4 molecule, can, like megakaryocytes, internalize HIV-1 viral particles in vitro. 1 HIV-1 infection of other CD4+ cell populations has been reported previously, but in contrast to Dami cells, viral particle production could not be detected directly in these cases and required coculture with CD4+ T-cell lines to be measured.

Human hematopoietic cell lines developed from patients with acute leukemia have become useful tools to explore differentiation and function of cells of the BM lineages. Recent studies of CD4 T-lymphocytic and monocytic cell lines have led to identification of the regulatory effect of various activation signals, including cytokines, on regulation of HIV-1 proviral expression and viral particles production in these cell populations. Cytokines play an important role in megakaryocyte lineage maturation, and Dami cells express functional receptors for several cytokines, including TNF-α. We therefore investigated whether such mediators could influence the level of HIV-1 expression in this megakaryocytic cell line.

As in CD4+ T-lymphocytic and monocytic cell lines, TNF-α significantly increased HIV-1 production in infected Dami cells. As in T lymphocytes and monocyes, IFN-α inhibited HIV-1 production, an effect that was maximal in the presence of interferon-γ. The enhancing effect of TNF-α was repeatedly observed in several experiments.

**Table 1. CD4, CD61(GPⅡa) and HIV-1 p24 Expression**

<table>
<thead>
<tr>
<th>Positive Cells (%)</th>
<th>CD4</th>
<th>CD61</th>
<th>p24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected Dami cells</td>
<td>UND</td>
<td>UND</td>
<td>95</td>
</tr>
<tr>
<td>Noninfected Dami cells</td>
<td>UND</td>
<td>UND</td>
<td>95</td>
</tr>
<tr>
<td>MOLT4</td>
<td>85</td>
<td>UND</td>
<td>UND</td>
</tr>
<tr>
<td>CEM</td>
<td>92</td>
<td>UND</td>
<td>UND</td>
</tr>
<tr>
<td>U937</td>
<td>95</td>
<td>UND</td>
<td>UND</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Interferons and TNF-α on HIV-1 p24 Secretion**

<table>
<thead>
<tr>
<th>Days</th>
<th>Medium</th>
<th>Interferons</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7.2</td>
<td>2.0</td>
<td>16.8</td>
</tr>
<tr>
<td>7</td>
<td>5.2</td>
<td>1.3</td>
<td>40.0</td>
</tr>
<tr>
<td>11</td>
<td>7.2</td>
<td>0.5</td>
<td>104.0</td>
</tr>
</tbody>
</table>

HIV-1-infected Dami cells (50,000 cpm infection, day 21, p24 level of 3 ng/ml/10^6 cells) were treated with IFN-α and IFN-γ (1,000 U/ml each) or with TNF-α (100 U/ml). p24 levels as well as cell numbers and viability were monitored at different intervals. Only treatment with IFNs had an effect on cell proliferation (inhibition). The p24 level was expressed as nanograms per milliliter per 10^6 viable cells (one representative experiment of four).

**Table 3. TNF-Mediated HIV-1 Transactivation**

<table>
<thead>
<tr>
<th>Construct</th>
<th>Medium</th>
<th>TNF</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTR-Luc</td>
<td>1</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>LTR-Luc + LTR-Tat</td>
<td>1</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Enhancer-Luc</td>
<td>1</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

Dami cells were transiently transfected with different constructs of the HIV-1 promoter (LTR) (described in the Materials and Methods section) and incubated with TNF-α (100 U/ml) or with PMA (2.5 ng/ml) for 18 hours. Cells were counted, viability was assessed, and cells were then lysed to permit luciferase activity determination. Results are expressed as fold increase in the luciferase activity over that of the non-treated cells after normalization to the same number of cells and is representative of seven experiments.
Moreover, when TNF-α treatment was initiated 4 days before HIV infection of Dami cells, the delay preceding production of virus was shortened to 10 days, but TNF-α had no or low enhancing effect on chronically infected Dami cells (>3 months). This was not the result of secretion of TNF-α by the infected cells. Mechanisms involved in this loss of TNF-enhancing effect in time are under investigation.

The enhancing effect of TNF-α on HIV-1 expression in T-lymphocytic and monocytic cell lines has been shown to involve transactivation of the HIV-1 long terminal repeat (LTR) promoter, in part through the binding of NF-κB to the two responsive elements located in the enhancer region of the HIV-1 promoter.39 Dot-hybridization analysis of RNA from HIV-1 infected Dami cells showed that addition of TNF-α increased the quantity of HIV-1 RNA. Transient transfection of uninfected Dami cells with a construct containing the luciferase reporter gene under control of the HIV-1-LTR showed that TNF-α, as well as phorbol esters, induced transactivation of the HIV-1 promoter. This effect was enhanced when an LTR-Tat construct was cotransfected. TNF-α-mediated transactivation was still observed in Dami cells transfected with a construct containing only the two 12-bp NF-κB binding sequences of the enhancer region of the LTR linked to the luciferase gene, suggesting that the effect of TNF-α in the megakaryocytic cells may involve, as in T cells and monocytes, nuclear translocation of an active form of the NF-κB protein.

Because HIV-1-infected patients have elevated serum levels of TNF-α,44,45 our results raise the question of a possible enhancing effect of this cytokine on HIV-1 production by BM megakaryocytes. Because obtaining both significant quantities and pure populations of BM megakaryocytes is difficult, the Dami cell line may represent a useful model to study the possible regulation by cytokines of HIV-1 expression in BM cells of the megakaryocytic lineage.

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Productive human immunodeficiency virus-1 infection of megakaryocytic cells is enhanced by tumor necrosis factor-alpha

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