Immunology 1988 **64** 233–239

Infection of human monocytes/macrophages by HIV-1: effect on secretion of IL-1 activity

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Accepted for publication 11 January 1988

SUMMARY

We have infected peripheral blood-derived monocyte/macrophage cultures with HIV-1 in order to determine the effect of such infection on cellular immunoregulatory function. We have confirmed that monocytes/macrophages are susceptible to infection by HIV-1, as determined by *in situ* hybridization using a HIV-1-specific RNA probe and by the presence of reverse transcriptase activity in culture supernatants. The cells employed efficiently supported viral replication in the absence of significant cytopathic effect, and secreted as little as 20% of the amount of IL-1 activity of uninfected controls in response to stimulation with either latex beads or lipopolysaccharide. This effect was not observed when UV-inactivated HIV-1 was used to infect the cells.

INTRODUCTION

Infection by human immunodeficiency virus type 1 (HIV-1) causes severe suppression of immunological responses, leading to susceptibility to a variety of opportunistic infections and malignancies (Barré-Sinoussi *et al.*, 1983; Gallo *et al.*, 1984). This is due, in part, to the selective tropism and cytopathic effects of HIV-1 on T4-bearing T-helper cells (Dalgleish *et al.*, 1984; Klatzmann *et al.*, 1984). HIV-1-mediated cytopathology seems to occur, at least in part, by causing fusion of cells expressing the T4 antigen, infected or not, leading to the formation of multinucleated giant cells with progression to cell death (Lifson *et al.*, 1986; Sodroski *et al.*, 1986). Although the T-helper population is the major target of infection, increasing evidence suggests that the mononuclear phagocyte system may play an important role in the pathogenesis of AIDS. Brain biopsies from neurosymptomatic AIDS patients have revealed HIV-1 particles within macrophage-like cells, capillary endothelial cells, giant cells and in rare astrocytes and neurons (Gartner *et al.*, 1986a; Koenig *et al.*, 1986; Wiley *et al.*, 1986). Primary alveolar macrophage cultures, obtained by broncho-alveolar lavage of AIDS patients, released low but significant levels of reverse transciptase activity, suggesting that these cells had been infected by HIV-1 (Salahuddin *et al.*, 1986). HIV-1 particles have also been detected in monocytes/macrophages derived from lymph nodes (Gyorkey *et al.*, 1985) and peripheral blood of HIV-1-sero-positive individuals (Gartner *et al.*, 1986b) and in myeloid precursors from bone marrow (Busch *et al.*, 1986). Moreover, peripheral blood monocytes as well as tissue macrophages derived from healthy volunteers were shown to be susceptible to HIV-1 infection *in vitro* (Salahuddin *et al.*, 1986; Ho, Rota & Hirsch, 1986).

It has been shown further that susceptibility of human monocytoid cell lines to infection by HIV-1 can be correlated with the degree of T4 antigen expression on such cells (Asjo *et al.*, 1987). Another paper (Clapham *et al.*, 1987) indicates that uninfected human monocytic cells can form syncytia when exposed to HIV-1-infected T lymphocytes, and that this effect can be blocked by anti-T4 monoclonal antibodies. This again suggests a role for T4 antigen as a portal of entry of HIV-1 into monocytes, and further indicates that monocytes, as well as T lymphocytes, may be involved in HIV-1-induced cell fusion. For the most part, infection by HIV-1 of monocytes themselves, either *in vivo* or *in vitro*, apparently does not lead to significant cytopathologic change. These studies indicate that the mononuclear phagocyte system may be an important viral reservoir and may participate in viral dissemination.

In order to elucidate the role of mononuclear phagocytes in mediating the severe immunosuppression characteristic of AIDS, various studies have focused on the functional analysis of monocytes/macrophages derived from HIV-1-infected individuals (Poli *et al.*, 1985; Nielson, Kharazmi & Faber, 1986). Conflicting results have arisen in some cases, probably due to variations in immunological status between individual patients. In addition, the multiple opportunistic infections and malignancies afflicting these patients may act, in their own right, on the mononuclear phagocyte system. In order to determine possible

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HIV-1-induced alterations in monocyte/macrophage functions, we have isolated these cells from healthy blood donors and infected them *in vitro* with HIV-1. Secretion of interleukin-1 (IL-1) activity in response to stimulants was investigated since this monokine plays an important role in immunological and inflammatory responses.

MATERIALS AND METHODS

Isolation of resident murine peritoneal cells and human adherent cells derived from peripheral blood

Resident murine peritoneal cells were collected from inbred BALB/c mice by lavage, washed once and resuspended in RPMI-1640 medium supplemented with 2 mM L-glutamine, 100 μ/ml penicillin, 100 μg/ml streptomycin and 10% fetal bovine serum (FBS; Flow Labs, McLean, VA). The peritoneal cells were cultured in aliquots of 1 ml containing 3–4 $\times$ 10^6 cells in 24-well plates (Linbro, Flow Laboratories Inc). After 2–4 hr of incubation at 37° under 5% CO_2, non-adherent cells were removed by thorough washing of the plates and adherent cells were further incubated with supplemented RPMI containing 5% FBS (Gery *et al.*, 1981).

Mononuclear cells were separated from whole blood of healthy human donors by density gradient centrifugation on Ficoll–Paque (Pharmacia Inc., Montreal) (Boyum, 1968). Cells were resuspended in RPMI-1640 medium supplemented with 10% FBS and 10% autologous plasma. Five times 10^6 cells were seeded into each well of 24-well plates (Linbro), incubated at 37° under 5% CO_2 for 3 days, following which non-adherent cells were removed by washing the cultures three times with Hanks' balanced salt solution (Flow Labs). Adherent cells were cultured thereafter in supplemented medium containing 10% FBS. In addition, aspects of these studies were conducted using the monocytic human cell line U937 (Sundstrom & Nilsson, 1976) (kindly provided by Dr J. Hiscott, Lady Davis Institute, Montreal), which was grown in the same way as primary cultures of human adherent cells (monocytes/macrophages).

HIV-1 infection of adherent cells

Fresh virus was harvested from cultures of H9 cells that had been infected with the HTLV-III_B strain of HIV-1. These cells (kindly supplied by Dr R. C. Gallo, NIH, Bethesda, MD) were grown in RPMI-1640 medium supplemented with 10% FBS. Culture fluids containing infectious virus were harvested after 3 hr, and were filtered through low binding capacity 0·22 μm filters (Millex GV-22, Millipore Corp., Toronto) to prevent accidental contamination with HIV-1-infected H9 cells. Filtered virus was then added to adherent cells in the presence of 2 μg/ml polybrene. In all experiments, a quantity of virus equivalent to approximately $10^{5.5}$ [50% tissue culture infective dose ($TCID_{50}$)] per 10^6 cells was employed. After 3 hr, unadsorbed virus was removed and serum-supplemented RPMI-1640 medium was added. Mock infection of control cultures was performed in a similar fashion using culture fluids from uninfected H9 cells. In some experiments, HIV-1 was UV-inactivated by placing the virus at a distance of 1 cm from a short-wave ultra-violet lamp for 45 min. The inability of this treated virus to infect the permissive H9 cell line was verified by following such cultures over 14 days and documenting their inability to produce viral-reverse transcriptase activity.

Chemicals and stains

Lidocaine (Astra Pharmaceuticals Canada Ltd, Toronto) was used at a concentration of 12 mM in phosphate-buffered saline (PBS) for 20–30 min at 37° to remove trypsin-resistant adherent cells from the wells of Linbro dishes without altering their viability or morphology (Nathan, Asofsky & Terry, 1977). Cells were then washed once in PBS (pH 7·4) and cell pellets resuspended in a minimal volume of PBS. Single drops of this suspension were dispensed onto wells of multi-test slides (Flow Laboratories Inc.), which were dried overnight , and then fixed in citrate buffer (0·383 M/l, pH 5·4) containing 10% (v/v) methanol and 54% (v/v) acetone (Fisher Chemical Co., Montreal). Cells were stained for non-specific esterases using a alpha-napthyl acetate esterase staining kit (Sigma Diagnostics, St Louis, MO) which specifically recognizes monocytes/macrophages. The secretion of IL-1 activity was studied in adherent cell cultures maintained in RPMI-1640 medium supplemented with 10% FBS in 24-well plates (Linbro) (1 ml per well). The release of IL-1 activity was stimulated by either polystyrene latex beads (1 μm diameter) (Duke Scientific Corp., Palo Alto, CA) or lipolysaccharide (LPS) (from *Escherichia coli* 055:B5, Sigma Chemical Co.) at a concentration of 10 ng/nl.

Preparation of ^{35}S-labelled RNA probes, in situ *hybridization and reverse transcriptase assays*

The pBH10-HIV-1 probe consists of the 9 kb HTLV-III insert of clone BH10 (Hahn *et al.*, 1984) inserted 3′ to 5′ into SacI of the transcription vector pSP64 (Promega Biotec, Madison, WI) (generously supplied by Dr R. C. Gallo, NIH, Bethesda, MD). pBH10 DNA was digested with *EcoRI*, which cuts midway in the viral genome. Two to five μg of BH10 template DNA were transcribed using 5 μM of [^{35}S]UTP (1000 Ci/mmol; Amersham Canada Ltd, Oakville, Ontario), and 20 μM of cold UTP in a final volume of 25 μl of the following reaction mixture: 40 mM Tris-HCl, pH 7·5, 6 mM $MgCl_2$, 10 mM DTT, 2 mM spermidine 0·5 mM of each of ATP, CTP, GTP, 25 U RNasin and 7·5 units of SP6 polymerase (Promega Biotec, Madison, WI). After incubation at 40° for 30 min, 7·5 additional units of SP6 polymerase were added along with unlabelled UTP to a final concentration of 500 μM. The reaction was allowed to continue for an additional 30 min at 40°. The DNA template was then digested with DNase I (RNase free). The ^{35}S-labelled RNA was purified by chromatography through a Sephadex G-50 spun-column. Typically, greater than 90% of [^{35}S]UTP was incorporated into RNA; ^{35}S-labelled RNA generated in this way had a specific activity of 10^9 d.p.m./μg. Purified RNAs were hydrolysed to 50–200 bases in 40 mM $NaHCO_3$/60 mM NA_2CO_3, pH 10·2, at 60° for 40 min and then neutralized with sodium acetate, 0·1 M, pH 6·0, and glacial acetic acid 0·5%. After ethanol precipitation, RNA fragments were stored in aliquots at −70° until use.

Adherent cell suspensions on pre-cleaned multi-test slides were air-dried and fixed by immersion in 4% paraformaldehyde in PBS (pH 7·4) containing 5 mM $MgCl_2$. Slides were rinsed in PBS (pH 7·4) and stored in 70% ethanol/2XSSC (0·3 M NaCl and 0·03 M sodium citrate) at 4° until ready to be hybridized (Harper *et al.*, 1986). Slides were rinsed twice in 2XSSC and acetylated for 10 min in 0·14% (v/v) acetic anhydride/0·1 M triethanolamine (pH 8·0). They were then rinsed twice in 10XSSC, followed by a 30-min treatment with 0·1 M Tris-HCl (pH 7·0/0·1 M glycine). After rinsing twice more in 2XSSC, slides

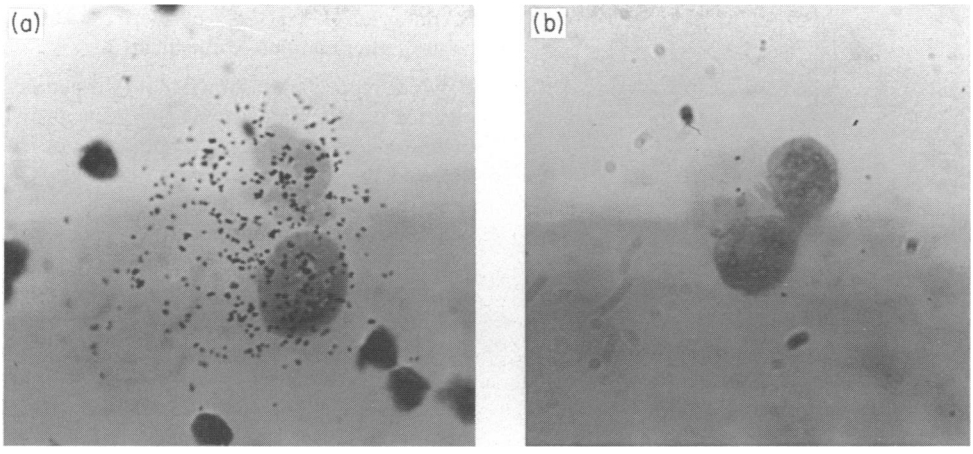

Figure 1. *In situ* hybridization with a ^{35}S-labelled HIV-1-specific RNA probe on human peripheral blood monocytes/macrophages. (a) HIV-1-infected cultures 7 days after infection. (b) Mock-infected control cultures.

were dehydrated in ethanol. The hybridization mixture contained the ^{35}S-labelled probe (10^8 d.p.m./ml; 100 ng/ml), 50% formamide, 2XSSC, 10 mM dithiothreitol (DTT), 1 mg/ml sheared salmon sperm DNA and 2 mg/ml tRNA (from *E. coli* strain W, type XXI, Sigma Chemical Co.) and was heated for 10 min at 90° and subsequently transferred to 55°. Approximately 20 μl of hybridization mixture were then applied to each well for 3 hr at 50°. Slides were rinsed twice in 50% formamide/2XSSC at 52° and four times in 2XSSC at room temperature. Ribonuclease treatment was next carried out by immersing slides in 2XSSC containing ribonuclease A (100 μg/ml) and ribonuclease T_1 (1 μg/ml, 10 U/ml) (Boehringer-Mannheim, Canada Ltd, Montreal) for 30 min at 37°. Slides were rinsed twice with 2XSSC at room temperature and again in 50% formamide in 2XSSC at 52° for 5 min. After rinses in 2XSSC and 1XSSC at room temperature, the slides were dehydrated in ethanol and autoradiographed with NTBZ nuclear track emulsion (Eastman Kodak, Rochester, NY) diluted 1:1 with distilled water. Slides were exposed for 2–5 days at 4°, developed with Dektol, dried and stained with Wright's Giemsa stain (Fisher Scientific, Montreal, Canada).

Reverse transcriptase assays were performed using culture supernatants by a procedure described previously (Prince *et al.*, 1985). Volumes of 0·75 ml of clarified culture supernatants were mixed with 0·25 ml polyethylene glycol 6000 (30% in PBS, pH 7·4), stored overnight at 4° on ice and subsequently centrifuged at 500 *g* at 4° for 30 min. The recovered precipitate was resuspended in 25 μl virus solubilizing buffer (NaCl 0·8 M, Triton 0·5%, phenyl methyl sulphonyl fluoride 0·5 mM, glycerol 20%, DTT 1 mM, Tris-HCl 50 mM) (pH 7·9) and frozen at −70° until ready to be assayed.

IL-1 assay

Culture fluids from murine and human adherent cells were removed at various times after addition of stimulant and centrifuged at low speed for 10 min. Supernatants were cleared of viral particles by ultracentrifugation at 143,000 *g* for 30 min and frozen until ready to be measured for IL-1 activity. This assay is based on the unique property of IL-1 to stoichiometrically induce the proliferation of thymic lymphocytes (Gery *et al.*, 1981). Six to 12-week old BALB/c mice were killed and their thymuses removed. Single cell suspensions of thymic lymphocytes were obtained by gently teasing the thymuses, following which thymic lymphocytes were washed twice and resuspended in RPMI-1640 medium supplemented with 10% FBS, PHA-P_1 0·1% (v/v) (Difco) and 20% (v/v) of the IL-1 containing supernatants. These tests were performed using four replicate samples. After a 48-hr incubation at 37° under 5% CO_2, cultures were pulsed with tritiated thymidine (1 μCi/well) (ICN Radiochemicals, Irvine, CA) for 24 hr and harvested with a multiwell Titertek MASH cell harvester (Flow Labs). IL-1 activity is expressed as the number of counts per minute (c.p.m.) representing incorporated radioactivity by murine thymic lymphocytes.

RESULTS

Susceptibility of human adherent cell cultures to HIV-1 infection *in vitro*

Our initial experiments dealt with the use of cultures of adherent cells derived from healthy blood donors. These cultures remained viable for over 21 days. Over 90% of these cells were positive for non-specific esterase actvity using the monocyte-specific substrate alpha-naphtyl acetate. Successful infection of such monocyte/macrophage cultures by HIV-1 was demonstrated by *in situ* hybridization using a HIV-1-specific RNA probe. The results of Fig. 1 indicate significant labelling of HIV-1-infected cells showing identical morphology to monocytes/macrophages, but not of mock-infected control cells. In fact, depending on the individual culture studied, between 5% and 20% of HIV-1 exposed monocytes/macrophages could be shown to be infected by this technique.

In addition, reverse transcriptase activity was measured at various times after HIV-1 infection (Fig. 2), and could be shown to peak after 7 days. Subsequently, a diminution in activity was observed, although it continued to be present at levels higher than those associated with control cultures. Indeed, culture fluids from adherent cells, taken 14 days after infection, were capable of productively infecting each of the HIV-1-permissive H9 cell line, the monocytic cell line U937, as well as cultures of adherent cells obtained from the same donors (Table 1).

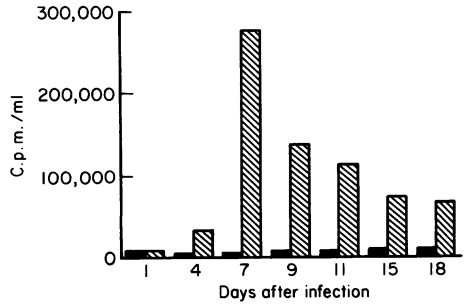

Figure 2. Reverse transcriptase activity in supernatant fluids derived from mock-infected (■) and HIV-1-infected human peripheral blood monocytes/macrophages (▩) at various times after infection.

Table 1. Ability of HIV-1 harvested from cultures of infected monocytes/macrophages to infect other cell types

Culture fluids derived from	Cell type infected	Reverse transcriptase activity (c.p.m.) Days after infection		
		Day 3	Day 7	Day 10
Uninfected monocytes/macrophages	H9 cells	5641	4732	6109
HIV-1-infected monocytes/macrophages	U937 cells	21,392	64,911	1,929,650
HIV-1-infected monocytes/macrophages	H-9 cells	17,752	1,185,811	952,352
HIV-1-infected monocytes/macrophages	Fresh monocytes/ macrophages	20,638	58,224	49,730

Table 2. Time-course of secretion of IL-1 activity

Cell type*	Time (hr)†	[^{3}H]TdR incorporated (c.p.m.)
Unstimulated human monocytes/macrophages	0–24	1206 ± 135‡
	24–48	1173 ± 220
	0–48	846 ± 123
Stimulated human monocytes/macrophages	0–24	3608 ± 263
	24–48	583 ± 37
	0–48	1321 ± 130
Unstimulated mouse adherent cells	0–24	1047 ± 118
	24–48	798 ± 129
	0–48	661 ± 75
Stimulated mouse adherent cells	0–24	2142 ± 175
	24–48	1056 ± 149
	0–48	814 ± 95

* Culture fluids from latex bead-stimulated cells were tested at a concentration of 20% (v/v) in a mouse thymocyte assay.

† Duration of time during which culture fluids were harvested.

‡ ± standard error.

Secretion of IL-1 activity by murine and human adherent cell cultures after addition of stimulant

Previous reports have shown that IL-1 activity is produced and secreted by stimulated monocyte/macrophage cultures. Moreover, the time at which maximum levels of IL-1 activity can be detected depends on the stimulus used (Gery *et al.*, 1981). Culture fluids from latex bead-/ or lipopolysaccharide (LPS)-stimulated cells were assayed for IL-1 activity at each of 24 hr, 48 hr, and between 24 hr and 48 hr after addition of stimulant. Sources of IL-1 activity in our studies included HIV-1-permissive human adherent cell cultures derived from the peripheral blood of healthy volunteers and HIV-1 non-permissive adherent cells derived by peritoneal lavage of mice. IL-1 activity, expressed as the amount of tritiated thymidine ([^{3}H]TdR) incorporated by murine thymic lymphocytes, was found to be maximal at 24 hr after stimulation (Table 2). The results indicate that a drop in amount of such IL-1 activity occurred between 24 hr and 48 hr. We further found that latex beads effectively stimulated the secretion of IL-1 activity by both human and mouse cell cultures (Table 2). Again, a peak of production of IL-1 activity levels was noted at 24 hr, following which a decline ensued. The overall decrease in activity of fluids tested from the 0–48 hr time-point compared to 0–24 hr may be due to instability, digestion, or inhibitory factors of secreted IL-1 activity.

In any case, when HIV-1 was used to infect cultures of human and mouse adherent cells, as described above, secreted IL-1 activity was reduced by up to 80% in the human but not in the mouse cultures (Table 3). In this protocol, virus was allowed to co-incubate with cells for 3 hr, following which the cells were washed and fresh medium containing latex beads was added. These data indicate that the effect of HIV-1 on secretion of IL-1 activity could only be realized on cells capable of replicating this virus.

In order to determine further whether this effect was dependent on viral infection, these experiments were repeated with human adherent cell cultures which had been exposed to either infectious or UV-inactivated HIV-1. In this case though, LPS rather than latex beads was used as a stimulus of IL-1 secretion and we waited until 9 days after infection before carrying out such stimulation. This was done so as to have an additional time-point in terms of the effect of HIV-1 infection on secretion of IL-1 activity. The results of Fig. 3 indicate that although the supernatant fluids of cultures exposed to infectious HIV-1 contained diminished levels of IL-1 activity, culture fluids of cells exposed to UV-inactivated HIV-1 were not affected. The data further show that LPS was, in general, a far better stimulus of production of IL-1 activity than were latex beads. This experiment was performed on each of three separate occasions.

DISCUSSION

These data provide an added dimension to the role which cells of the mononuclear phagocyte system may play in the development of AIDS. We have confirmed earlier findings that cultures of these cells are highly susceptible to *in vitro* infection by HIV-1, as indicated by high levels of reverse transcriptase activity in culture supernatants and by *in situ* hybridization using a HIV-1-specific RNA probe. It is noteworthy that a relatively small percentage of cultured monocytes/macrophages became

Table 3. Production of IL-1 activity by HIV-1-inoculated cultures

IL-1 activity derived from	[^{3}H]TdR incorporated* (c.p.m.)
Unstimulated human monocytes/macrophages	1984±165†
Unstimulated human monocytes/macrophages exposed to uninfected H9 culture fluids	1640±211
Latex bead-stimulated human monocytes/macrophages	3577±283
Latex bead-stimulated human monocytes/macrophages exposed to uninfected H9 culture fluids	3815±328
Latex bead-stimulated, HIV-1-inoculated human monocytes/macrophages	683±58
Unstimulated mouse adherent cells	861±120
Unstimulated mouse adherent cells exposed to uninfected H9 culture fluids	726±94
Latex bead-stimulated mouse adherent cells	2035±419
Latex bead-stimulated mouse adherent cells exposed to uninfected H9 culture fluids	2409±318
Latex bead-stimulated, HIV-1-inoculated mouse adherent cells	2319±386

* Background c.p.m. incorporated into mouse thymocytes that had been co-incubated with 0·1% PHA only was 388±32.

† ± standard error.

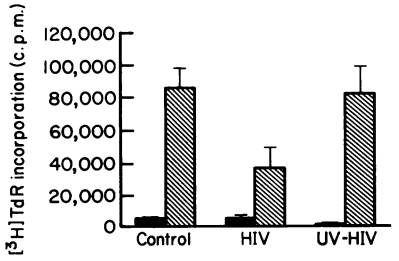

Figure 3. Effect of infectious HIV-1 and UV-inactivated HIV-1 on the secretion of IL-1 activity by human peripheral blood monocytes/macrophages in the absence (■) or presence (▩) of LPS (10 ng/ml).

infected in this study, a result in agreement with the observations of other investigators (Salahuddin *et al.*, 1986; Gartner *et al.*, 1986b). The reasons for restriction of infection are not clear but may be due to the existence of monocyte/macrophage subsets and/or to the heterogeneity of the cells themselves.

Morphological analysis of HIV-1-infected cell cultures revealed little in the way of cytopathic changes. Nevertheless, these cultures were capable of supporting viral replication and release. These results suggest that monocytes/macrophages may serve an important role as a reservoir for viral persistence and spread. Mononuclear phagocytes play a similar role during the course of other retroviral infections, notably those caused by lentiviruses (Narayan *et al.*, 1982). These agents are a group of non-oncogenic, cytopathic retroviruses with which HIV-1 shares structural and genetic similarities (Chiu *et al.*, 1985). The presence of clusters of macrophage precursor cells, infected by visna/maedi virus within the bone marrow of sheep, suggests that virus-harboring cells might multiply by mitosis in the bone marrow, prior to release into the circulation where they undergo differentiation and maturation (Gendelman *et al.*, 1985). The dissemination of HIV-1 may occur in the same way, since HIV-1 RNA has been detected within myeloid precursors derived from bone marrow samples of AIDS patients (Ho *et al.*, 1986). The infiltration of mononuclear phagocytes into sites of infection could provide large numbers of HIV-1-permissive cells and further promote viral dissemination, in a manner analogous to the potentiation of avian sarcoma virus-induced tumourigenesis by infected macrophages (Wainberg *et al.*, 1983).

We have demonstrated further that HIV-1-infected monocyte/macrophage cultures are partially impaired in their ability to secrete IL-1 activity in response to stimulants such as latex beads and LPS. This inhibitory effect was found to be dependent on viral infectivity, since cultures exposed to UV-inactivated HIV-1 secreted levels of IL-1 activity comparable to those found in mock-infected controls. We have failed to demonstrate any diminution of known IL-1 activity, when supernatants from HIV-1-infected cultures were mixed with either commercially available IL-1 or IL-1-enriched supernatants (results not shown). This suggests that HIV-1 infection is not stimulating the expression of an inhibitor of IL-1 activity or of a product which could mask detection of IL-1. We should point out that these data were obtained studying the HTLV-IIIβ laboratory strain of HIV-1. Studies on a variety of clinical isolates are clearly important and are now in progress.

We have been careful to use the term IL-1 activity rather than IL-1 throughout this paper, in terms of describing our results and their interpretation. Although the assay system used is standard for measurement of IL-1, definitive proof of the involvement of IL-1 in our system would require sensitive northern blot assays for IL-1 mRNA and a sensitive immunodetection assay for IL-1 itself. We have tested several commercially available IL-1 detection kits, but have not found them to be as reliable or reproducible as the biological assay described here.

The mechanism by which HIV-1 infection mediates a decrease in IL-1 secretion after stimulation with latex beads and/or LPS is not clear, especially in view of the fact that the percentage of cells visibly infected is low. Experiments now in progress involve the use of LPS, rather than latex beads, as a stimulant of IL-1 activity, given the seemingly greater efficiency of LPS in this regard (Table 3, Fig. 3). HIV-1 may preferentially infect a functionally distinct subset of mononuclear phagocytes involved in IL-1 secretion. Such a subset has been described previously (Khansari, Chou & Fudenberg, 1985). Alternatively, HIV-1 infection may induce the synthesis and release of factors which inhibit LPS or latex bead-stimulated IL-1 secretion by uninfected neighbouring cells.

The study of functional abnormalities in cultures of HIV-1-

infected monocytes/macrophages, derived from healthy individuals, provides useful insight into a second possible role of mononuclear phagocytes in the pathogenesis of AIDS. Indeed, deficient levels of IL-1 activity following infection could be responsible, in part, for the lymphocytopenia and altered blastogenic responses characteristic of patients with this disease. HIV-1-infected monocytes/macrophages may also undergo other functional changes leading to impairment of chemotactic responses, phagocytosis, and antigen processing and presentation. Moreover, the increased susceptibility of AIDS patients to rare types of malignancies may be, in part, the result of defects in the tumouricidal capacity of mononuclear phagocytes. Although functional alterations have been reported in peripheral blood monocytes of HIV-1-sero-positive individuals (Poli *et al.*, 1985; Nielson *et al.*, 1986), further studies are required to elucidate the effect of HIV-1 infection on the immunological and inflammatory responsiveness of the mononuclear phagocyte system in AIDS.

ACKNOWLEDGMENTS

Most aspects of this work were completed by Sophie Roy in partial fulfillment of the MSc degree from the Faculty of Graduate Studies and Research, McGill University. Ms Roy was supported by a grant from the Cancer Research Society Inc., Montreal. This study was supported by grants to Dr M. A. Wainberg from the Department of Health and Welfare, Canada and from the Medical Research Council of Canada. We thank Michel Tremblay for titering the culture fluids which contained infectious virus, Francine Busschaert for the typing, and Christine Lalonde for her help with preparation of the figures used in this paper.

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