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Induction of Interleukin-10 by Human Immunodeficiency Virus Type 1 and Its gp120 Protein in Human Monocytes/Macrophages

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In this study, we evaluated the effects of human immunodeficiency virus type 1 (HIV-1) and its gp120 protein on interleukin-10 (IL-10) expression in cultured human monocytes/macrophages. Infection of either 1-day monocytes or 7-day monocyte-derived macrophages with HIV-1 strain Ba-L resulted in clear-cut accumulation of IL-10 mRNA at 4 and 24 h. Likewise, treatment of these cells with recombinant gp120 induced IL-10 mRNA expression and caused a marked increase in IL-10 secretion. Monoclonal antibodies to gp120 strongly inhibited recombinant gp120-induced IL-10 secretion by monocytes/macrophages. Moreover, the addition of IL-10 to monocytes/macrophages resulted in a significant inhibition of HIV-1 replication 7 and 14 days after infection. On the whole, these results indicate that HIV-1 (possibly through its gp120 protein) up-regulates IL-10 expression in monocytes/macrophages. We suggest that in vivo production of IL-10 by HIV-primed monocytes/macrophages can play an important role in the early response to HIV-1 infection.

Interleukin-10 (IL-10) was originally described as a cytokine, produced by T helper 2 (Th2) cells, capable of suppressing gamma interferon (IFN-γ) production by Th1 cells (12, 26). Further reports showed that IL-10 can also be produced by other cell types, including B cells (27), monocytes (9), and $CD8^+$ T cells (19, 24). It has been suggested that in human immunodeficiency virus (HIV)-infected patients, IL-10 may cause detrimental effects by contributing to Th1/Th2 dysregulation and by inhibiting cell-mediated immune responses (7). In particular, the amount of IL-10 produced by peripheral blood mononuclear cells (PBMC) from AIDS patients was shown to be higher than that of PBMC from healthy donors (8). However, no data are available yet on the direct effects of HIV type 1 (HIV-1) on IL-10 production. Recently, Ameglio and coworkers (1) reported that HIV-1 gp120 was capable of inducing the production of IL-10 in PBMC, but the cells involved in this response were not characterized.

Macrophages are cellular targets of HIV-1 infection and play important roles in the pathogenesis of AIDS (for a review, see reference 25). Human blood monocytes undergo differentiation into macrophages upon migration from the capillary bed to extravascular tissues. In vitro culture of freshly isolated monocytes results in time-dependent differentiation in macrophages (22), which is also associated with increased response to lipopolysaccharide (LPS) (18) and enhanced susceptibility to HIV-1 infection (17, 30). Several reports have shown that monocytes/macrophages can produce different cytokines in response to HIV-1 infection or after exposure to the HIV-1 gp120 protein (5, 14, 20, 32–34). Some of these cytokines (e.g., tumor necrosis factor alpha) can up-regulate HIV expression (10, 13), while others (e.g., IFNs) are powerful inhibitors of HIV-1 replication in macrophages (16, 23). In particular, we recently reported that the infection of monocytes/macrophages with HIV-1 (or treatment with its gp120 protein) results in the induction of low levels of IFN-β, which are very effective in inducing an antiviral state in differentiated macrophages but not in freshly harvested monocytes (17). The different responses to endogenous IFN found in macrophages and monocytes could be somehow related to the increased expression of some membrane markers (e.g., CD14, CD11, and transferrin receptor) (18) and/or to the enhanced production of and response to certain cytokines (17, 18) during in vitro culture and differentiation of monocytes. Moreover, recent studies have described inhibitory effects of IL-10 on cytokine synthesis (4, 9, 28) as well as on HIV replication (31, 35) in monocytes. In light of all these data, it was of interest, therefore, to investigate the direct effects of HIV-1 or its gp120 protein on IL-10 expression in both freshly harvested monocytes and cultured macrophages and to evaluate the possible role of this cytokine in the modulation of HIV-1 replication. The data reported in this article demonstrate that both HIV-1 and its gp120 protein are capable of inducing the expression of IL-10 in both monocytes and monocyte-derived macrophages.

Infection of monocytes/macrophages with HIV-$1_{Ba\text{-}L}$ results in the accumulation of IL-10 mRNA. We first determined whether the infection of freshly isolated monocytes (1-day monocytes) or monocyte-derived macrophages cultured for 7 days (7-day macrophages) with HIV-1 strain Ba-L (HIV-$1_{Ba\text{-}L}$) resulted in any induction of IL-10 mRNA expression, as evaluated by reverse transcriptase PCR. Barely detectable levels of IL-10 mRNA were occasionally found in unstimulated monocytes/macrophages from some donors upon prolonged exposure of autoradiographs. At 4 and 24 h after HIV-1 infection, there was clear-cut accumulation of IL-10 mRNA in both 1-day monocytes and 7-day macrophages (Fig. 1). In both cell types, clearly detectable levels of IL-10 mRNA were also found 72 h after HIV-1 infection (data not shown). A similar induction of IL-10 mRNA was observed in two additional experiments with HIV-infected monocytes/macrophages from differ-

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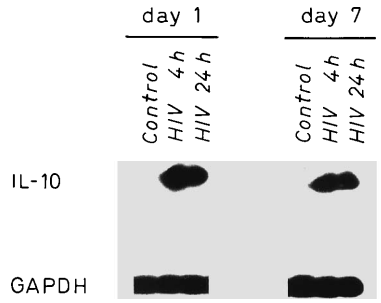

FIG. 1. Induction of IL-10 mRNA in 1-day monocytes and 7-day macrophages infected with HIV-1_{Ba-L}. Human monocytes/macrophages were isolated by Ficoll-Hypaque density gradient centrifugation from the peripheral blood of healthy donors and separated from lymphocytes by adherence to plastic dishes (18). Cells (15×10^6) were seeded in 6-well plates (Falcon) in Iscove's medium supplemented with 15% fetal calf serum, as reported in detail elsewhere (17, 18). Cytochemical (i.e., sodium fluoride-inhibited esterase activity) and fluorescence-activated cell sorter analysis of surface markers (CD14 antigen) revealed that the adherent cell population consisted of >95% monocytes. Cells were infected with HIV-1_{Ba-L} (4,000 pg/ml; obtained from the NIH AIDS Research and Reference Reagent Program, catalog no. 510). HIV was prepared and titered on cultured macrophages as reported elsewhere (29). RNA was extracted by the method of Chirgwin et al. (6). Reverse transcriptase PCR was performed with 0.5 μg of RNA as previously described (21). The sequences for IL-10 primers were as follows: sense primer, 5′AAGGCATGCACAGCTCAGCACT (nucleotides 26 to 47); antisense primer, 5′TCCTAGAGTCTATAGAGTCGCCA (nucleotides 603 to 580). The sequence of the probe was previously reported (3). GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

ent donors. No accumulation of IL-10 mRNA was found in mock-infected monocytes or macrophages (data not shown).

Induction of IL-10 mRNA in monocytes/macrophages treated with rgp120. The finding that a 4-h exposure of monocytes/macrophages to HIV-1 was sufficient to induce clear-cut accumulation of IL-10 mRNA (Fig. 1) suggested that such induction could represent an early event in HIV-1 infection, possibly dependent on the initial virus-cell interaction. We then carried out some experiments aimed at investigating whether the HIV-1 envelope gp120 protein could directly induce IL-10 expression in monocytes/macrophages. As shown in Fig. 2, the addition of 1 μg of recombinant gp120 (rgp120) per ml to either 1-day monocytes or 7-day macrophages resulted in marked accumulation of IL-10 mRNA at 4 and 24 h after stimulation. Similar results were obtained in two other experiments with monocytes/macrophages from different donors (data not shown).

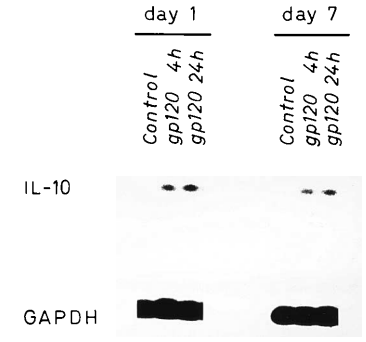

FIG. 2. Induction of IL-10 mRNA in 1-day monocytes and 7-day macrophages after treatment with rgp120. Monocytes/macrophages were prepared as described in the legend to Fig. 1. Total cellular RNA, extracted from cells cultivated for 1 or 7 days and treated for 4 or 24 h with rgp120 (1 μg/ml), was analyzed for the expression of IL-10 mRNA by RNA PCR, as described in the legend to Fig. 1. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

TABLE 1. Effects of gp120 on IL-10 production by monocytes/macrophages[a]

Treatment	IL-10 production (pg/ml)[b]			
	Expt 1		Expt 2	
	1-Day monocytes	7-Day macrophages	1-Day monocytes	7-Day macrophages
None	5	15	<5	<5
rgp120	401	434	89	284
p24	ND	ND	<5	<5
Anti-CD4	ND	ND	<5	<5

[a] A total of 3×10^6 cells, isolated from the peripheral blood of healthy donors, were seeded in 48-well cluster plates as previously described (18). After 1 or 7 days, cells were treated with 1 μg of rgp120 per ml, which had been produced in a baculovirus expression system (purchased from Neo-system; >90% pure as estimated by analysis of Coomassie blue-stained sodium dodecyl sulfate-polyacrylamide gels), 1 μg of HIV-1 p24 (obtained from the NIH AIDS Research and Reference Reagent Program, catalog no. 382), or monoclonal antibodies to human CD4 (Q428; obtained from the NIH AIDS Research and Reference Reagent Program, catalog no. 1377) or left untreated. After 24 h at 37°C, cell supernatants were harvested and tested for IL-10 levels by an ELISA specific for IL-10 (Bender Medsystems, Vienna, Austria).

[b] Each value represents the mean of duplicate culture samples. Standard deviations did not exceed 10%. ND, not determined.

Secretion of IL-10 by monocytes/macrophages treated with rgp120 protein. It was of interest to assess whether treatment of monocytes/macrophages with rgp120 could also result in any IL-10 secretion, as evaluated by measuring cytokine levels in culture medium by using a specific enzyme-linked immunosorbent assay (ELISA). As shown in Table 1, gp120 induced a definite increase in IL-10 secretion in both 1-day monocytes and 7-day macrophages at 6 and 24 h after treatment. In contrast, no increase in IL-10 secretion was observed after treatment with a different HIV-1 protein (i.e., p24) or anti-CD4 monoclonal antibodies. No major differences in the amount of gp120-induced IL-10 production were observed between 1-day monocytes and 7-day macrophages, even though occasionally higher levels of IL-10 were found in cultures of 7-day macrophages (Table 1, experiment 2).

Specificity of rgp120-induced secretion of IL-10 by monocytes/macrophages. As LPS is a potent inducer of IL-10 in macrophages (9), we first excluded any detectable presence of this molecule in our rgp120 preparations by using the *Limulus* amoebocyte assay (data not shown). To further support the specificity of rgp120-induced IL-10 secretion, we treated monocytes/macrophages with rgp120 in the presence or ab-

TABLE 2. Effects of anti-gp120 antibodies on gp120-induced IL-10 secretion by monocytes/macrophages

Treatment	IL-10 production (pg/ml)[a]	
	1-Day monocytes	7-Day macrophages
None	11	13
rgp120	67	89
Anti-gp120	14	11
rgp120 + anti-gp120	27	13

[a] Freshly isolated human monocytes were cultured as described in footnote *a* to Table 1. After 1 or 7 days, cells were treated with rgp120 (1 μg/ml), monoclonal antibodies to gp120 (purchased from NEN Research Products, Du Pont; NEA-9301; 1:50 dilution), or rgp120 together with anti-gp120 antibodies or left untreated. Culture supernatants were collected 24 h later and tested for IL-10 secretion as described in the same footnote. Each value represents the mean of duplicate culture samples. Standard deviations did not exceed 10%. Similar results were obtained in a subsequent experiment with monocytes/macrophages from a different donor.

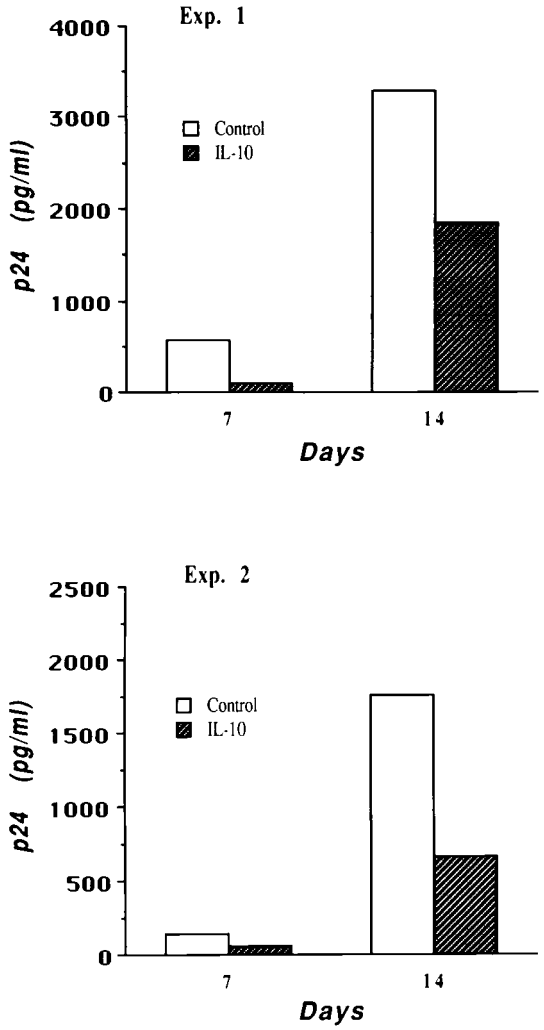

FIG. 3. Effects of exogenous IL-10 on HIV-1 production in virus-infected human monocytes. Freshly isolated human monocytes from two healthy donors were prepared and seeded in 48-well cluster plates, as previously described (18). After 1 or 7 days, cells were infected with HIV-1_{Ba-L} (4,000 pg/ml). After a 4-h adsorption, cells were extensively washed and 1 ml of growth medium was added to each well. Human recombinant IL-10 (20 ng/ml; purchased from Pepro Tech, Inc., Rocky Hill, N.J.) was added at the time of infection and after each wash. Culture supernatants were collected for p24 determination 7 and 14 days after HIV-1 infection. Data are the means of duplicate samples. Standard deviations did not exceed 10%. In each experiment, the final wash was tested for p24 antigen and shown to be free of residual inoculum.

sence of monoclonal antibodies to gp120. As shown in Table 2, anti-gp120 antibodies strongly inhibited gp120-induced secretion of IL-10 by monocytes/macrophages.

Effects of exogenous IL-10 on the replication of HIV-1_{Ba-L} in monocytes/macrophages. We then evaluated whether the addition of IL-10 to human monocytes/macrophages could result in any effect on HIV-1 replication. Figure 3 shows the results of two representative experiments of the four performed with monocytes from different donors. In all four experiments, IL-10 significantly inhibited HIV replication in monocytes, as evaluated by measuring the p24 levels in culture supernatants 7 and 14 days after infection. A similar inhibition of HIV-1 replication was observed when IL-10 was added to 7-day macrophages (data not shown). At the dosage used (20 ng/ml), recombinant IL-10 did not affect cell viability in monocyte/macrophage cultures (data not shown).

Some reports have recently described an increase in IL-10 production by peripheral blood lymphocytes from HIV-infected patients compared with that of healthy individuals (8). The increased production of IL-10 has generally been considered to be a marker for the switch from a Th1 pattern to a Th2 pattern of lymphokine secretion, which appears to be predictive of disease progression (7, 8). However, direct evidence has yet to be provided of the specific role of monocytes/macrophages in enhanced IL-10 secretion during HIV-1 infection. Recently, however, Fior and coworkers (11) reported preliminary evidence which indicated that the vast majority of IL-10 production in peripheral blood lymphocyte cultures from HIV-infected individuals arose from either macrophages or B lymphocytes and that such cytokine production was an early event during HIV infection and was not necessarily associated with the progression to AIDS. Likewise, some of us have recently found (i) that sera from HIV-positive subjects exhibit higher levels of IL-10 than those from HIV-1-negative controls (2) and that (ii) rgp120 induces IL-10 production in PBMC (1) and monocytes appear to be the most important cell type involved in this response (4a). The data reported here represent the first direct evidence for the induction of IL-10 by HIV-1 or its gp120 protein in monocytes/macrophages. Our results also indicate that IL-10 can significantly inhibit HIV-1 replication in monocytes/macrophages. This finding is in agreement with recent studies by others (31, 35). In particular, it has recently been shown that the inhibitory effects of IL-10 on HIV-1 production in monocytes/macrophages are the result of IL-10-induced inhibition of the synthesis of other cytokines, such as tumor necrosis factor alpha and IL-6, capable of up-regulating HIV-1 expression in these cells (35). We also envisage that IL-10 may induce other cytokines, such as IFNs, endowed with anti-HIV activity in monocytes/macrophages. Whatever mechanisms are involved in IL-10-induced inhibition of HIV-1 replication, our data suggest that IL-10 secretion by HIV-1-primed monocytes/macrophages can be considered an early antiviral response to HIV-1 infection and that in vivo production of IL-10 should not be regarded simply as a progression factor to AIDS in HIV-infected patients.

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