HIV Nef Inhibits T Cell Migration*

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Nef is a viral regulatory protein of the human immunodeficiency virus (HIV) that has been shown to contribute to disease progression. Among its putative effects on T cell functions are the down-regulation of CD4 and major histocompatibility complex I surface molecules. These effects occur in part via Nef interactions with intracellular signaling molecules. We sought to better characterize the effects of HIV Nef on T cell function by examining chemotaxis in response to stromal cell-derived factor-1α (SDF-1α) as well as CXCR4 signaling molecules. Here, we report the novel observation that HIV Nef inhibited chemotaxis in response to SDF-1α in both Jurkat T cells and primary peripheral CD4+ T lymphocytes. Our data indicate that HIV Nef altered critical downstream molecules in the CXCR4 pathway, including focal adhesion kinases. These findings suggest that HIV Nef may blunt the T cell response to chemokines. Because T lymphocyte migration is an integral component of host defense, HIV Nef may thereby contribute to the pathogenesis of AIDS.

HIV encodes both structural and regulatory proteins important in the pathogenesis of AIDS. Among the regulatory proteins is Nef, whose role in viral infection and disease progression has been controversial (1–11). Among the putative functions attributed to Nef are the maintenance of high viral load (1) and immune evasion due to its down-regulation of CD4 (2) and MHC I molecules (7). Nef has also been found to protect infected primary T cells against cytotoxic T lymphocytes (3). Although some studies (4–6, 9) have concluded that Nef increases T cell activation, other studies (8, 10–11) indicated that Nef caused decreased T cell activation. Despite these conflicting data, one consistent finding has been that Nef interacts with various signaling molecules, including members of the Src kinase family such as Hck and Lck, the latter a protein tyrosine kinase associated with CD4 and T cell receptor function (12–16); and PAK2, a serine/threonine kinase that modulates the cytoskeletal apparatus (Refs. 17 and 18 and for review see Refs. 19 and 20). Moreover, Nef may affect mediators of apoptosis and thereby foster the longevity of infected cells (18). Recently, Nef was shown to activate ERK1/2 in primary CD4+ T cells obtained from peripheral blood (21). The ERK kinases are members of the MAP kinase family and can participate in a variety of cell functions, including growth and migration (22–26).

In macrophages, the nef gene product has been linked to alterations in chemokine production (6), indicating a possible role of Nef in the regulation of lymphocyte chemotaxis. Furthermore, the capacity of Nef to alter intracellular signaling molecules suggested that mediators of chemotaxis could be affected. To our knowledge, however, there are no reports of Nef affecting T cell chemotaxis. Here we report that HIV Nef significantly inhibited the response of CD4+ T cells to the physiologic chemokine stromal cell-derived factor-1α (SDF-1α).

SDF-1 is a member of the CXC chemokine family. It was first identified as a pre-B-cell growth-stimulating factor and cloned from mouse bone marrow stromal cells (27). Its two forms, SDF-1α and -β, arise from a single gene through alternative splicing. Human SDF-1α, a 7.8-kDa molecule, is a powerful chemoattractant for T lymphocytes, and its function has been well characterized (29–31). SDF-1α binds exclusively to the cell-surface receptor, CXCR4. The CXCR4 molecule is expressed on several cell types, including T lymphocytes, and has been shown to function as a co-receptor for certain strains of HIV (28). In this study, we present a novel observation of HIV Nef inhibiting CD4+ T lymphocyte chemotaxis and altering critical downstream molecules in the CXCR4 pathway, including cytoskeletal regulatory proteins. These findings suggest that HIV Nef may blunt the T cell response to SDF-1α via intracellular disruption of CXCR4 receptor signaling. Because regulated migration of T cells in response to cognate chemotactic ligands is a key component of host defense (32, 33), HIV Nef may act to impair T cell function and contribute to the pathogenesis of AIDS.

EXPERIMENTAL PROCEDURES
Reagents and Antibodies—Recombinant SDF-1α was purchased from R & D Systems (Minneapolis, MN). Purified antibodies to phospho-ERK1/2, phospho-STAT1, PY99, actin, and p85 were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-RAFTK antibody was a generous gift from Dr. Hava Avraham, Division of Experimental Medicine, Beth Israel Deaconess Medical Center, Boston (34). Myelin basic protein and antibody to 4G10 were obtained from Upstate Biotechnology, Inc. (Lake Placid, NY). Bovine serum albumin was obtained from Sigma. Electrophoresis reagents and nitrocellulose membranes were obtained from Bio-Rad.
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Creation and Maintenance of Permanent nef-expressing T Cell Lines—Permanent nef-expressing Jurkat T cell lines were constructed using the Clontech Tet-Off Gene Expression Systems. These cell lines produce GFP or HIV Nef-GFP proteins under Tet-Off control, meaning that gene expression was turned on when tetracycline was removed from the culture medium. The cell lines were cultured in RPMI 1640 medium (Mediatech-Celgro) containing 10% fetal bovine serum, 1% penicillin/streptomycin, 0.2 mg/ml geneticin (G418), 0.2 mg/ml hygromycin, 2 μg/ml tetracycline (Tet). Gene expression was induced by culturing the cells for 48 h in culture medium without tetracycline.

**Purification and HIV Transduction of Primary CD4+ T Cells**—To confirm that the effect of Nef was not restricted to a Jurkat T cell line, effects of nef expression on migration of primary peripheral blood CD4+ T lymphocytes were examined. Briefly, GFP and nef-GFP fusions were cloned in adenov-associated virus (AAV)-derived vector, and recombinant AAV-packaged GFP and nef-GFP were generated at a multiplicity of infection of 1.4 × 1012 and 1.2 × 1012, respectively, from the Harvard Medical School Core Facility. In this system, 1 multiplicity of infection corresponds to 1 virion particle per cell. For isolation of CD4+ T cells, peripheral blood mononuclear cells (PBMC) were isolated from fresh whole blood by density gradient centrifugation with Ficoll-Paque (Amersham Biosciences), washed with phosphate-buffered saline solution (PBS), and counted on a hemocytometer using the trypan blue dye exclusion method. They were treated with 50 ng/ml SDF-1 (R&D Systems) and then aliquoted into 24-well tissue culture plates at 1 × 106 cells and transduced with the indicated amount of recombinant virions.

**Flow Cytometry**—Jurkat T cells were washed twice with PBS, resuspended in 100 μl of PBS containing 5 μg/ml phycoerythrin-labeled CXCR4 antibody, and incubated for 30 min at 4°C. The cells were then washed twice with ice-cold PBS and resuspended in PBS buffer. They were then analyzed by flow cytometry to determine the levels of surface expression of the receptor.

**Chemokine and Cytokine Detection Assays**—Cell supernatants were assayed for secretion of the chemokines SDF-1α, MIP-1α or -1β, and the cytokine IL-2 using enzyme-linked immunosorbent assay kits (Endogen Inc., Woburn, MA). Samples were assayed according to the manufacturer’s protocol.

**Treatment of cells**—Jurkat T cells were starved for 1 h by placing them in RPMI medium supplemented with 0.5% fetal bovine serum. The cells were counted using the trypan blue dye exclusion method and resuspended to a concentration of 106 cells per ml. Cells were then treated with 50 ng/ml SDF-1α for the indicated times (0–60 min).

**Chemotaxis Assays**—Chemotaxis assays were performed in duplicate using 5-μm pore filters (Transwell, 24-well cell clusters; Costar, Boston, MA). Briefly, Jurkat cells or primary CD4+ T lymphocytes were isolated from 300 μl of migration medium (RPMI + 0.5% bovine serum albumin) and loaded into each Transwell filter. Filters were then transferred to another well containing 600 μl of migration medium with the indicated concentrations of SDF-1α. The plates were incubated at 37°C and 5% CO2 for 3 h. The upper chambers were removed, and the cells in the bottom chambers were washed with 1× PBS, resuspended, and quantitated using the trypan blue dye exclusion method. Results of the chemotaxis assays presented here are representative of multiple repetitions of the same experiment with similar results.

**Immunoprecipitation and Western Blot Analysis**—For the immunoprecipitation studies, identical amounts of protein from each sample were loaded on different primary antibodies for 4 h at room temperature or overnight at 4°C. Immunoprecipitations of the antibody-antigen complexes were performed by incubation for 2 h at 4°C with 30 μl of protein A-Sepharose beads (10% suspension). Non-specific bound proteins were removed by washing the Sepharose beads 3 times with radiolimmunoprecipitation assay (RIPA) buffer containing 0.15 M NaCl, 0.1% sodium deoxycholate, 0.1% Triton X-2, 1% Triton X-100, and 0.1% sodium deoxycholate. Bound proteins were separated on NuPAGE 4–12% BisTris SDS-PAGE gels and then transferred to nitrocellulose membranes. The membranes were blocked with 5% nonfat milk protein and probed with the appropriate primary antibody for 2 h at room temperature or 4°C overnight. Immunoreactive bands were visualized using horseradish peroxidase-conjugated secondary antibody and the enhanced chemiluminescent detection system (Amersham Biosciences). Data shown are representative of multiple experiments.

**Phosphatidylinositol 3-Kinase (PI3K) Activity**—CD4+ cells treated, described above, were lysed in 300 μl of ice-cold lysis buffer (25 mM HEPES, 150 mM NaCl, 5 mM MgCl2, 0.2 mM EDTA, 0.1% Triton X-100 + 0.5 mM dithiothreitol, 0.1 mM phenylmethylsulfonyl fluoride, 2 μg/ml leupeptin, 4 μg/ml aprotinin). PI3K was immunoprecipitated using anti-p85 antibody. Immunoprecipitates were washed once with wash buffer 1 (25 mM HEPES, 150 mM NaCl, 5 mM MgCl2, 0.2 mM EDTA, 0.1% Triton X-100) and three times with wash buffer 2 (25 mM HEPES, 150 mM NaCl, 5 mM MgCl2, 0.2 mM EDTA). Samples were resuspended in 35 μl of reaction buffer (25 mM HEPES, 5 mM MgCl2, 0.2 mM EDTA, 10 μg of phosphatidylinositol (Avanti Polar Lipids, Alabaster, AL), and the mixture was sonicated for 5 min. The reaction was initiated with the addition of 50 μM γ-[32P]ATP (5 μCi) and carried out at 25°C for 5 min. The reaction was stopped by adding 300 μl of MeOH, 1 h HCl (1:1 v/v). The lipid products were extracted with 250 μl of CHCl3 and the mixture was vortexed and spun briefly. The aqueous phase was washed with CHCl3, and the samples were dried by Speed-Vac. Lipids were separated on silica gel-coated TLC plates. The plates were developed with CHCl3/CH3OH/H2O/NH4OH (28%), 90:90:7:20. The labeled products were visualized by autoradiography.

**Related Adhesion Focal Tyrosine Kinase (RAFTK) Activity**—RAFTK activity was measured as described above. To exclude the effects of Nef on cytotoxicity in our experiments, cell growth was evaluated during induction of expression of the introduced genes, GFP— or nef-GFP-expressing Jurkat T cells were cultured for 2 days in the absence of Tet to induce protein expression. Cell extracts were prepared from the expressing cells and subjected to Western blot analyses with anti-RAFTK antibody. The blot shows bands corresponding to GFP or the Nef-GFP fusion protein (Fig. 1A). When the membrane was stripped and reprobed for actin, equivalent amounts of protein in each lane were detected (Fig. 1A). These results confirmed the fidelity of the cell lines and the inducibility of the genes.

To exclude the effects of Nef on cytotoxicity in our experiments, cell growth was evaluated during induction of expression of the introduced genes by the trypan blue dye exclusion method. Growth kinetics of the GFP— or nef-GFP expressing cells were similar (Fig. 1B), indicating that Nef was not inhibitory for the cells.

**Migration of nef-expressing T Cells in Response to SDF-1α**—The effects of Nef on chemotaxis in nef-expressing Jurkat T cells as compared with its effects in the control GFP-expressing cells were assessed by performing cell migration assays, as described above. The Jurkat cells that expressed HIV Nef (Nef-GFP) showed decreased levels of migration in response to SDF-1α in a dose-dependent manner (Fig. 1C, representative of several experiments). Migration levels never exceeded 8% of the total nef-expressing cells. At 100 ng/ml SDF-1α, control cells expressing GFP showed levels of migration ~3 times higher than the HIV nef-expressing cells. The difference in migration between the two cell populations was statistically significant (p < 0.05) using an ANOVA two-factor test.

**Nef Effects on CXCR4 Expression on the Surface of T Cells**—The observed Nef-mediated inhibition of Jurkat T cell migration could be due to the down-modulation of CXCR4 expression on the surface of the cells. To investigate this possibility, the level of CD4 expression on the surface of the Jurkat clone was...
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To first examine the effects of Nef on T cell migration, we induced HIV-1 Nef-mediated cytotoxicity. Cell viability in AAV-nef-transduced cells was indistinguishable from that in the GFP-transduced CD4+ T cells, the migration of primary CD4+ T lymphocytes expressing HIV Nef show a significant decrease in SDF-1α-mediated chemotaxis in comparison with GFP-expressing control cells. Data are representative of several experiments with similar results, and values represent means; error bars represent means ± S.D. (p < 0.05 by ANOVA).

**Migration of Primary T Cells in Response to SDF-1α**—To confirm that the inhibitory effect of Nef was not restricted to the Jurkat T cell line, and to further confirm that the cell line would provide a model of pathophysiological effects in primary cells, nef was expressed in peripheral blood CD4+ T cells. To this end, PBMC were obtained from fresh whole blood by density gradient centrifugation with Ficoll-Paque (Amersham Biosciences), and CD4+ T lymphocytes were then isolated from the activated PBMC, as described under “Experimental Procedures.” CD4+ T lymphocytes were then transduced with various amounts of recombinant virions. Similar to the Jurkat cells, cell viability in the AAV-nef-transduced cells was indistinguishable from that in the GFP-transduced CD4+ T cells, and the surface expression of CXCR4 was not down-modulated by Nef (data not shown). Two days after transduction, cell migration was assayed in the same manner as in the nef-expressing Jurkat cells, except that the migration was for 1 h instead of 3 h. Consistent with the results from the Jurkat T cells, the migration of primary CD4+ T lymphocytes was significantly inhibited in the presence of HIV-1 Nef (Fig. 1E). This reduction correlated with increasing titers of the AAV construct, indicating that HIV-1 Nef can inhibit the migration of primary peripheral blood CD4+ T cells in response to SDF-1α and that the inhibition was Nef-specific.

**Chemokine and Cytokine Secretion by nef-expressing Cells**—The inhibition of migration by T cells expressing HIV nef could result from a potential increase in chemokine secretion that would compete with the exogenous ligand in the migration assay. To address this possibility, we assayed cell supernatants

![Image](https://example.com/image.png)
For several relevant chemokines, which have been reported to be secreted by macrophages (6), neither the control nor HIV nef-expressing cells secreted the cognate ligand, SDF-1α, or the chemokines, MIP-1α and MIP-1β (data not shown). Moreover, they also did not secrete different amounts of IL-2, a cytokine that can alter CXCR4 receptor expression (data not shown).

**Intracellular Signaling in nef-expressing T Cell Lines**—HIV Nef is known to interact with several intracellular signaling molecules, including those that regulate the cytoskeletal apparatus and are relevant to chemotaxis (12–14, 17–19). We, therefore, examined several signaling molecules known to be involved in the SDF-1α signaling pathway. To determine whether there were any differences between the general phosphorylation patterns of the cell lines, cell lysates were Western immunoblotted with the phosphotyrosine-specific antibodies, anti-PY99 and anti-4G10. Several differences in the cell lines with regard to phosphorylation patterns were observed (Fig. 2A). The cells were then examined for changes in phosphorylation of the extracellular signal-related kinase (ERK), a signaling molecule known to be downstream of the CXCR4 receptor and recently reported to be modulated by HIV Nef in primary T cells (21). To assess the effect of Nef on ERK activation, SDF-1α-treated cell lysates were incubated with anti-phospho-ERK1/ERK2 antibodies. ERK1/ERK2 phosphorylation was detected most strongly in the HIV nef-expressing cells (Fig. 2B, lower panel), with levels several times that of the GFP-expressing cells (Fig. 2B, upper panel). Protein loading in each lane was determined to be equal by reprobing the membrane with anti-ERK1/ERK2 antibody.

To determine whether the changes observed in ERK1/2 activation in the HIV nef-expressing T cells reflected a global activation of multiple signaling pathways or was restricted to specific signaling molecules, we examined the activation status of STAT1 and another member of the MAP kinase family, p38. The SDF-1α-treated cell lysates were probed with anti-phospho-STAT1 antibody. Similar levels of STAT1 phosphorylation were observed for the GFP- and HIV nef-expressing T cells (Fig. 2C). Similarly, p38 was not differentially activated in the presence of Nef (data not shown). In addition, a recent publication that reported that HIV Nef increased ERK activity in primary T cells, also examined p38 and found it not to be activated by Nef in the same primary T cells (21). These results supported our data, which suggest specificity with regard to the effects of HIV Nef on intracellular signaling pathways.

**Effect of Nef on Kinase Activities upon SDF-1α Activation**—P3K is known to play an important role in cell migration. Previous studies (35–37) have shown P3K to be an important intracellular regulator of cell migration. Thus, we studied the effect of HIV Nef on P3K activity in nef-expressing cells as compared with control cells. P3K activity was assayed as described above. The level of P3K activity was unchanged in the HIV nef-expressing cells, despite treatment with SDF-1α (Fig. 3A, lower panel). In contrast, control GFP-expressing cells showed the expected increase in P3K activity in response to SDF-1α treatment (Fig. 3A, upper panel). Densitometric scanning of this autoradiograph indicated distinct differences in P3K activity between GFP- and nef-GFP-expressing Jurkat T cells (Fig. 3B).

We next studied RAFTK, a platform kinase that coordinates upstream signals including those from Src kinases, phosphatases, and adapter proteins and transmits the signals downstream to the cytoskeletal apparatus and to transcriptional regulators such as ERK1 and ERK2 (34, 38). RAFTK is known to be an important component of the SDF-1α signaling pathway. Cells were assayed for the enzymatic activity of RAFTK, as described above. The HIV nef-expressing cells were found to have a higher basal level of RAFTK activity than the GFP-expressing cells (Fig. 3C, lower versus upper panel). Furthermore, the kinetics of the enzymatic activity of the HIV nef-expressing cells in response to SDF-1α treatment differed from those of the GFP-expressing cells. Taken together, these data suggest that changes in these kinases might be associated with the Nef-mediated effects on T cell migration.

**DISCUSSION**

This study is the first to our knowledge indicating that HIV Nef may modulate CD4+ T lymphocyte migration. This effect was observed in both model Jurkat T cells as well as in primary peripheral blood CD4+ lymphocytes in response to the physiological chemokine SDF-1α. Chemotaxis is an essential component of the immune response, wherein immune cells respond to invading pathogens by moving toward the site of infection along chemokine concentration gradients. This inhibition of cell migration in response to SDF-1α could contribute to HIV disease progression and pathogenicity.

Several different hypotheses were entertained with respect to how HIV Nef could abrogate the response to SDF-1α. Because HIV Nef is known to down-modulate important cell surface molecules like CD4 and MHC class I (2, 7), we considered whether CXCR4, the receptor for SDF-1α, might also be reduced in expression by Nef. We did not detect down-regulation of CXCR4, indicating that alterations in cognate receptor expression would not explain the abrogated chemotactic response. Similarly, if nef expression caused T cells to produce SDF-1α, then competition at the CXCR4 receptor between exogenous SDF-1α and the Nef-induced chemokine would alter migration. Whereas HIV nef expression has been reported to induce secretion of several chemokines in macrophages (6), we...
did not observe induction of SDF-1α, MIP-1α, or MIP-1β secretion in T cells.

It has been reported that peripheral blood T cells need to be activated before they can migrate in response to inflammatory chemokines (39). Moreover, a recent report (40) showed that Zap 70 tyrosine kinase, an important signaling molecule for T cell activation, is involved in the migration of human T cells in response to the chemokine, SDF-1α. All of these data suggest that the activation state of T cells can modulate the chemotactic response. In contrast, another study reported that T cell receptor activation does inhibit chemotaxis to SDF-1 in Jurkat cells (41), although this was accompanied by a decrease in fluorescence intensity of the cell surface expression of CXCR4. This differs from our data. We do not, however, exclude the possibility that the decreased migration to SDF-1α of the nef-expressing cells may be (partially) related to T cell receptor activation by Nef, because CXCR4 receptor recycling (42) may account for the lack of change in CXCR4 expression on the nef-expressing Jurkat cells. Further experiments are required to address the role of activation on migration.

The role of Nef in T cell activation is also controversial. One report indicated that HIV-1 Nef induced transcriptional factors that were 97% identical to those observed after stimulation of Jurkat cells (43). However, other data indicated that Nef alone cannot activate resting T cells, which are manifested by IL-2 secretion from treated cells, but can activate the cells in combination with stimulation through the T cell receptor and the co-stimulus receptor (CD28) (9, 44). Our data show that HIV Nef did not induce significantly different amounts of IL-2 as compared with the control cells, suggesting that activation by this cytokine did not explain the observed phenomenon.

One possible explanation for Nef-mediated inhibition of T cell migration is its effects on intracellular signaling molecules. The different phosphorylation patterns, different basal levels of the enzymatic activities of key intracellular kinases, and their altered kinetics of response to SDF-1α could result in the failure to respond appropriately to the chemotactic stimulus. Such a response requires a highly ordered cascade of intracellular events, specifically, a physiological base line and induced changes in phosphorylation. For example, PI3K, whose lipid phosphorylation products act as second messengers throughout the cell, has been implicated in the activation of complex signaling cascades that mediate chemotaxis, among other cellular functions (34). Recent studies (36, 37) indicate that the disruption or removal of PI3K results in the dysregulation of leukocyte chemotaxis. Our data indicate that Nef can inhibit PI3K-mediated signaling cascades, which implies that PI3K may play an important role in Nef-mediated decreases in T cell migration. It is of note that the literature contains conflicting reports on Nef effects on PI3K, with some investigators finding inhibition (46), as we did, but others observing activation (47).

RAFTK kinase activity was also found to be changed in the presence of HIV Nef. The implications of RAFTK dysregulation could be profound, because this molecule signals downstream to the MAP kinase family, particularly ERK1/2 (48). Prior studies show that alterations in the regulated activation of RAFTK blunt the responses to several chemokines, including SDF-1α (49). Thus, alteration of RAFTK kinase activity in the presence of HIV Nef might also contribute to the abrogated T cell response to this chemokine observed in our experiments.

In addition, the kinases that we examined are known to affect cytoskeletal arrangement and focal adhesions (45, 48, 50), and thus are likely candidates for involvement in the chemotactic changes observed here. The higher basal activation of these kinases in the presence of HIV Nef may indicate a mechanism through which Nef abrogates the response of infected cells to SDF-1α treatment. In causing constitutive activation of kinases in the SDF-1α pathway, HIV Nef may provide further activation of these kinases from having a significant effect upon the chemotactic response of the cells to SDF-1α treatment.

Furthermore, ERK1/ERK2 were differentially phosphorylated in the nef-expressing cell lines versus controls. Changes brought about by the activation of these potent transcriptional regulators could affect the migration of nef-expressing cells by altering the expression of genes whose products are necessary for the chemotactic response. Recently, Schrager et al. (21) reported specific activation of the ERK/MAP kinase signaling cascade in response to the expression of nef in primary T cells, which supports our findings. In that study, however, chemo-
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