Brief Definitive Report

Macrophage-tropic HIV Induces and Exploits Dendritic Cell Chemotaxis

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Abstract

Immature dendritic cells (iDCs) express the CC chemokine receptor (CCR)5, which promotes chemotaxis toward the CC chemokines regulated on activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, and MIP-1ß. By contrast, mature DCs downregulate CCR5 but upregulate CXC chemokine receptor (CXCR)4, and as a result exhibit enhanced chemotaxis toward stromal cell–derived factor (SDF)-1α. CCR5 and CXCR4 also function as coreceptors for macrophage-tropic (M-tropic) and T cell–tropic (T-tropic) human immunodeficiency virus (HIV)-1, respectively. Here, we demonstrate chemotaxis of iDCs toward M-tropic (R5) but not T-tropic (X4) HIV-1. Furthermore, preexposure to M-tropic HIV-1 or its recombinant envelope protein prevents migration toward CCR5 ligands. The migration of iDCs toward M-tropic HIV-1 may enhance formation of DC–T cell syncytia, thus promoting viral production and destruction of both DC and T helper lymphocytes. There-fore, disturbance of DC chemotaxis by HIV-1 is likely to contribute to immunosuppression in primary infection and AIDS. In addition, migration of iDCs toward HIV-1 may aid the capture of R5 HIV-1 virions by the abundant DC cell surface protein DC-specific intercellular adhesion molecule (ICAM)3-grabbing nonintegrin (DC-SIGN). HIV-1 bound to DC cell–specific DC-SIGN retains the ability to infect replication-permissive T cells in trans for several days. Consequently, recruitment of DC by HIV-1 could combine with the ability of DC-SIGN to capture and trans-mit the virus to T cells, and so facilitate dissemination of virus within an infected individual.

Key words: dendritic cell • HIV • chemotaxis • chemokine • CCR5

Introduction

The dissemination of HIV-1 and establishment of infection within an individual involves the transfer of virus from mucosal sites of infection to T cell zones in secondary lymphoid organs. How this happens is not certain. Once at these sites, the virus replicates within CD4+ T helper lymphocytes and macrophages. The immature dendritic cells (iDCs) of the skin and mucosa, Langerhans cells (LCs), have been implicated as the first targets for HIV after sexual contact (1). In the simian immunodeficiency virus/rhesus macaque system, the model that most closely resembles human infection, the first macrophages and monocytes detectable in the peripheral blood of infected subjects were first detected within days after challenge, and the subsequent appearance of antigen-bearing cells within the T cell areas of draining lymph nodes (2) has led to the suggestion that DCs may act as “Trojan Horses” (3), carrying virus to lymph nodes. The efficiency of DCs in interacting with numerous T cells (4) makes them prime candidates for enhancing viral dissemination (5).

iDCs are located in most nonlymphoid tissues, where they capture and process antigens. After exposure to inflammatory signals, they mature and migrate to secondary lymphoid tissues, where they present antigen to T cells (6). iDCs express CC chemokine receptor (CCR)5, which enables chemotaxis to the CC chemokines (7). Mature DCs downregulate CCR5 but upregulate CXC chemokine receptor (CXCR)4, and show enhanced chemotaxis toward stromal cell–derived factor (SDF)-1α. CCR5

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and CXC R4 function as coreceptors for macrophage-
tropic (M-tropic) and T cell–tropic (T-tropic) HIV-1, re-
spectively (8, 9). DCs also express CD4 and are susceptible
to infection by HIV-1 (3). Here, we demonstrate chemot-
axis of iDCs toward M-tropic (R5) but not T-tropic (X4) HIV-1. Furthermore, preexposure to M-tropic HIV-1
or its recombinant envelope protein prevents migration
toward CCR5 ligands. These events might play an impor-
tant role in the recruitment of DCs to mucosal sites of
HIV-1 inoculation, and consequently could explain the
dissemination of infection.

Materials and Methods
Preparation of DCs from Blood and C Hemotaxis A ssays. H uman
DCs were cultured from commercial buffy coats as described pre-
viously (7). Chemotaxis assays are described elsewhere (7). In
brief, 5 × 10⁴ iDCs in 100 μl culture medium were added to
each 24-well transwell insert (5-μm pores; Costar), with 600 μl
in the lower chamber, with or without chemokine, HIV super-
natant, or recombinant gp120. After 2 h incubation at 37°C, the
transwell inserts were lifted, and the bases were rinsed twice with
200 μl of medium into the lower chamber. Cells in the lower
chamber were collected, transferred into 5-ml U-bottomed clear
tubes, and fixed with 5% formalin. The number of migrating cells
was determined by FACS sort™ (Becton Dickinson) as described
previously (7). Results are expressed as the total number of mi-
grating DCs per transwell. Standard deviations are shown for
three or four replicate transwells. Data is representative of at least
three separate experiments.

HIV Supernatants. Supernatants of HIV-infected and unin-
fected T cells were separated into concentrate (two times) and fil-
trate by centrifugation through a 100-kD cutoff centricon con-
centrator (Amicon). In all figures the >100-kD fraction is used as
"supernatant." Supernatants were quantified for reverse tran-
scriptase (RT) using the Quant-T-RT assay system (Amersham
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Results
IDCs exhibit chemotaxis toward the supernatant of T cells infected
with M-tropic HIV-1. Monocyte-derived iDCs were tested in transwell migration assays as described previously
(7). These cells exhibit significant chemotaxis toward RANTES and the supernatant from T cells infected with
M-tropic HIV-1, but not toward the supernatant from T cells infected with T-tropic HIV-1, or from uninfected
cells (Fig. 1). Cell supernatants were separated into concen-
trate (two times) and filtrate by centrifugation through a
100-kD cutoff centricon concentrator (Amicon). In all fig-
ures, the >100-kD fraction is used as "supernatant." The
>100-kD fraction from HIV-1-infected PM1 cells is

Figure 1. iDCs migrate toward RANTES and M-tropic HIV culture
supernatant but not toward T-tropic HIV or uninfected supernatant. (A)
Chemotaxis of 5 × 10⁴ immatures DCs in a 2-h transwell migration assay
described in Materials and Methods. The number of cells migrating into
the lower transwells (>1,000) as determined by FACSort™ (Becton
Dickinson) is shown with lower transwells containing medium alone
(RPMI 1640), 6 nM RANTES, supernatant from T cells infected with
M-tropic HIV-1, or from uninfected cells (Fig. 1). Cell supernatants were separated into concen-
trate (two times) and filtrate by centrifugation through a
100-kD cutoff centricon concentrator (Amicon). In all fig-
ures, the >100-kD fraction is used as "supernatant." The
>100-kD fraction from HIV-1-infected PM1 cells is

were screened by Western blotting using both anti-FLAG M2
mAb (Sigma-Aldrich) and anti-gp120 mAb (AR P301; Na
tional Institute for Biological Standards and Control). Cell supernatants
were loaded onto an anti-FLAG M2 affinity column (Sigma-
Aldrich) and eluted with pH 3.5 glycine-HCl according to the
manufacturer's instructions. Purified gp120 was checked by SDS-
PAGE (both reducing and nonreducing) and behaved as a monomer
in gel filtration chromatography. Binding to human CD4 was
confirmed by surface plasmon resonance (BIAcore). Stock solu-
tions of gp120 in Tris-HCl pH 8.0 were diluted into RPMI 1
media to the required concentration(s). Tris pH 8.0 in RPMI 1 was
used as "medium" control.
highly chemotactic, even when added in a 10-fold dilution; this large molecular mass chemotactic agent is likely to be HIV-virions/fragments and/or gp120 (see Fig. 3). Migration toward the <100 kD fraction was similar for uninfected and HIV-1-2B7-infected supernatant, and was only 30% of that toward RANTES (not shown); this small molecular chemotactic agent is presumed to be a T-cell-derived chemokine(s).

Soluble CD4 Increases Chemotaxis toward M-tropic HIV Supernatant. The binding of CD4 to M-tropic HIV envelope protein (gp120) increases the efficiency of CCR5 binding (10). Addition of soluble CD4 at 10 μg/ml almost doubled the chemotactic effect of supernatant from cells infected with M-tropic virus, without affecting migration toward supernatant from uninfected cells or RANTES (not shown).

Antibodies Remove the Chemotactic Effects of HIV Supernatant. Immunoprecipitation with anti-HIV antibodies reduced the chemotaxis induced by the supernatant of PM1 cells infected with HIV-1-2B7 to the level induced by the supernatant from PM1 cells infected by HIV-1_FAD, suggesting that HIV-1 is virions and/or gp120 induce chemotaxis (Fig. 2).

iDCs Migrate toward M-tropic gp120. To confirm that iDCs migrate toward HIV and rule out a requirement for M-tropic virus-induced T-cell-derived lymphokines, we examined chemotaxis toward M-tropic recombinant gp120 envelope. iDCs migrate toward M-tropic gp120 from HIV-1-2B7 (Fig. 3 A) and HIV-1_FAD (Fig. 3 B). By contrast, chemotaxis was not observed toward recombinant gp120 from T-tropic HIV-1-2B7 (Fig. 3 C) or recombinant gp120 from the T-tropic strains SF2, M N, W61D, and HXB2 (not shown). Cross-linking of the FLAG-tagged HIV-1-2B7 gp120 with anti-FLAG antibody increased its chemotactic potential by ~30% (not shown). Treatment of iDCs with anti-CCR5 antibodies prevented migration toward R5 gp120 (Fig. 3 D). Because M-tropic but not T-tropic gp120s induce chemotaxis, and gp120/CCL5 binding induces an intracellular signal indistinguishable from that of a natural chemotactic ligand (11, 12), we conclude that binding of M-tropic gp120 to CCR5 can induce DC chemotaxis.

Exposure to M-tropic HIV or Its Recombinant Envelope Inhibits the Response of iDCs to Chemokines. Pretreatment of iDCs for 90 min with 6 nM of the CC chemokines RANTES (binds CCR1, 3, 4, and 5), MIP-1α (binds CCR1 and 5), or MIP-1β (binds CCR5 and 8) substantially diminishes subsequent chemotactic responses to all these chemokines, but not to the CXCR4 ligand SDF-1 (not shown). Pretreatment of iDCs with supernatant of T cells infected with HIV-1-2B7, but not the supernatant from uninfected cells, likewise reduced responses to these CC chemokines (Fig. 4 A). Conversely, pretreatment of iDCs with CC chemokines reduced subsequent chemotaxis toward HIV-1-2B7 supernatant (not shown). Pretreatment of iDCs with supernatant from T cells infected with T-tropic HIV-1-2B7 had no effect on migration toward MIP-1α or RANTES (not shown).

Addition of 3 nM M-tropic HIV-1-2B7 recombinant gp120 to the upper transwell (Fig. 4 B) abolished responses to MIP-1β at concentrations up to 24 nM. In contrast, similar pretreatment with recombinant gp120 from the T-tropic HIV-1-2B7 (1, 6, 24, and 48 nM) was without effect on migration toward CC chemokines (not shown).

Discussion

We demonstrate the migration of iDCs toward M-tropic but not T-tropic HIV-1, and substantiate this finding using recombinant envelope (gp120) proteins. These observations have important implications for the establishment, dissemination, and progression of HIV-1 infection within an infected individual. HIV Tat has been reported to induce chemotaxis of DCs and monocytes (13, 14). Our results, which show that the migratory action of HIV-1 is confined to M-tropic HIV virus, indicate that any chemotactic action of Tat is not apparent in the culture supernatant of T cells infected with HIV-1 (Fig. 1 B). We were unable to observe migration of iDCs toward 10 or 100 nM basic Tat peptide (amino acids 31-71; reference 14) or a pool of Tat peptides (amino acids 1-30, 16-45, and 31-71; data not shown). HIV Nef has been reported to induce expression of MIP-1α and MIP-1β by HIV-1-infected macrophages (15). This induction can mediate the chemotaxis of lymphocytes (15), and presumably iDCs. Although HIV Nef–induced CC chemokine production may be responsible for some CCR5-mediated chemotaxis in our system, we believe this effect to be insignificant compared with the direct effects of gp120 for several reasons: (a) examination of several viral isolates indicates that the dominant chemotactic element exhibits M-tropism (R5) specificity; (b) addition of 10 μg/ml soluble CD4, which enhances the
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binding of CCR5 to gp120 (10), doubled chemotaxis toward M-tropic viral supernatants without affecting chemotaxis toward CC chemokines (data not shown); (c) the difference in chemotaxis induced by supernatant from uninfected cells and cells infected with T-tropic viruses, including HIV-1_{IIIB} that bears Nef, is negligible (data not shown); (d) immunoprecipitation with anti-HIV envelope antibodies removes the majority of chemotactic activity and reduces it to the level induced by HIV-1_{IIIB} (nef^+) supernatant; (e) we show the dominant chemotactic agent to be $>100$ kD; and (f) as recombinant gp120 is active in the nM region (Fig. 3), there is sufficient envelope protein in the viral supernatants to account for all the observed chemotaxis. Supernatants were produced in T cell cultures at $2 \times 10^6$ cells/ml. Each cell need only produce a total $10^3$ virions during the several days of infection to put the gp120 concentration (assuming $>200$ gp120s/virion) in the nM range. Detailed studies of supernatants from HIV-1_{HXB3}-infected T cell cultures are relevant (16, 17). It was shown that viral supernatants contained $10^9$-$10^{10}$ physical particles/ml. In freshly isolated viral stocks, the ratio of infectious to noninfectious viral particles ranged from 1:10^4-1:10^7 (16). HIV-1_{HXB3} virions spontaneously shed gp120 proteins with a half-life of $\sim30$ h (16), and typical viral stocks were found to have $>0.5$ nM soluble gp120 in addition to virus-associated protein (17). An envelope particle, consisting of a single envelope spike, contains three gp120s. The avidity of such a trimeric interaction with CCR5 is likely to be considerably more than the sum of the individual affinities. In addition, observations in other systems indicate that higher multimerization of a soluble ligand can yield a significantly greater intracellular signal (18). Thus, virions/virion fragments in the supernatants may induce more chemotaxis than the sum of migration induced by their individual component gp120 molecules.

iDCs express CCR5 and migrate toward the CC chemokines RANTES, MIP-1x, and MIP-1y (7). Preformed stores of RANTES (19) are released by CTLs when they encounter antigen. Activated CTLs also transcriptionally upregulate MIP-1x and MIP-1y (20). As CTLs are the only cells capable of recognizing MHC I-restricted antigen, this chemokine secretion might facilitate the recruitment of bone marrow-derived APCs, including DCs, into infected areas (21). M-tropic gp120 is also a ligand for CCR5 and can generate an intracellular signal similar to that generated by natural ligands (11, 12). Thus, HIV-1 may exploit the...
migration of iDCs toward CCR5 ligands, and subsequently to the T cell areas of draining lymph nodes, to aid both the establishment and dissemination of infection.

HIV-1 is almost entirely M-tropic during primary infection (22, 23), and the use of coreceptors other than CCR5 by such viruses is rare (24). The iDCs of the skin and mucosa, LCs, have been implicated as the first targets for HIV after sexual contact (1). In the simian immunodeficiency virus/rhesus macaque system, the model which most closely resembles HIV-1 infection in humans, the first cellular targets of infection after vaginal challenge are mucosal DCs (2). The subsequent appearance of antigen-bearing cells within the T cell areas of draining lymph nodes (2) has led to the suggestion that DCs may act as “Trojan Horses” (3), carrying virus to lymph nodes. Freshly isolated epidermal LCs express CCR5 but not CXCR4 on their surface (3), carrying virus to lymph nodes. Indeed, at low virus titer, infection of CD4/CCR5-expressing cells was not detected without the help of DC-SIGN in vivo. HIV-1 may then exploit the subsequent migration of DCs as they mature to gain access to sites of inoculation to gain access to cells that are permissive for viral infection. The modulation of iDC chemotaxis by R5 strains of HIV-1 may enhance the binding of virus to DC-SIGN in vivo. HIV-1 may then exploit the subsequent migration of DCs as they mature to gain access to the T cell compartment in lymphoid tissues, where it can replicate and spread freely.

In summary, the recruitment of iDCs toward M-tropic HIV-1 is likely to assist the establishment of infection by either increasing the productive infection of iDCs or by promoting the binding of virions to DC-SIGN. The inhibition of chemotaxis induced by preexposure to M-tropic HIV-1 (Fig. 4) may result in local arrest of iDCs in vivo. The proficiency of DCs in recruiting numerous T cells in lymphoid tissues (4) makes them strong candidates for further dissemination of the virus (5). Indeed, the preferential recruitment and infection of HIV-specific Th cells by antigen-bearing DCs may be instrumental in the preferential loss of these cells in most patients during primary infection (37, 38). Thus, the recruitment of iDCs by M-tropic HIV-1 is likely to promote the establishment, dissemination, and maintenance of HIV-1 infection.

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