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HIV-1 Tat Induces Monocyte Chemoattractant Protein-1-Mediated Monocyte Transmigration Across a Model of the Human Blood-Brain Barrier and Up-Regulates CCR5 Expression on Human Monocytes1

Jonathan M. Weiss,* Avindra Nath, ‡ Eugene O. Major, § and Joan W. Berman2*,†

AIDS dementia is characterized by neuronal loss in association with synaptic damage. A central predictor for clinical onset of these symptoms is the infiltration of monocytes and macrophages into CNS parenchyma. Chronic HIV-1 infection of monocytes also allows these cells to serve as reservoirs for persistent viral infection. Using a coculture of endothelial cells and astrocytes that models several aspects of the human blood-brain barrier, we examined the mechanism whereby the HIV-derived factor Tat may facilitate monocyte transmigration. We demonstrate that treatment of cocultures on the astrocyte side with HIV-1 Tat induced significant monocyte chemoattractant protein (MCP)-1 protein. Astrocytes, but not endothelial cells, were the source of this MCP-1 expression. Supernatants from Tat-treated cocultures induced significant monocyte transmigration, which was detected by 2.5 h after the addition of PBMC. Pretreatment of the supernatants from Tat-stimulated cocultures with an Ab to MCP-1 completely blocked monocyte transmigration. Flow cytometric analysis of Tat-stimulated PBMC demonstrated that Tat up-regulated expression of the chemokine receptor, CCR5, on monocytes in a time-dependent manner. Taken together, our data indicate that HIV-1 Tat may facilitate the recruitment of monocytes into the CNS by inducing MCP-1 expression in astrocytes. These recruited monocytes may contribute to the pathogenesis of HIV-1-associated AIDS encephalitis and dementia. The Journal of Immunology, 1999, 163: 2953–2959.

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1 Abbreviations used in this paper: BBB, blood-brain barrier; CSF, cerebrospinal fluid; MCP-1, monocyte chemoattractant protein-1; EC, endothelial cells; Glut-1, glucose transport protein-1; ggt, γ-glutamyltransferase; MiP, macrophage-inflammatory protein.

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We previously characterized a tissue culture model of the human BBB in which astrocytes and ECs are cocultured on opposite sides of a porous tissue culture insert (17). We demonstrated that direct cell contact between EC and astrocytes through the pores of the insert induces the expression of BBB markers, such as glucose transport protein-1 (Glut-1) and γ-glutamyl-transpeptidase (γGT), on EC. The same coculture system was used by Hayashi et al. (18), who also detected endothelial expression of Glut-1 and γGT, as well as barrier activity against inulin. We demonstrated previously that cytokine-induced MCP-1 plays a central role in directing the transmigration of monocytes and activated lymphocytes across these cocultures (19). In those studies, leukocyte transmigration in response to cytokines and MCP-1 was the same, regardless of whether human umbilical vein or human brain microvascular EC were cocultured in the model. Similarly, we showed that the adhesion molecules that are critical for transmigration were identical, regardless of the source of EC.

A role for chemokines in regulating the progression of HIV infection has also been identified by the ability of chemokine receptors to function as coreceptors that mediate HIV entry. Various HIV-1 isolates are capable of utilizing specific chemokine receptors, including CCR5, CCR3, CXCR4, and possibly CCR2, as coreceptors (20–23). With the exception of CCR2, these receptors have been identified within the normal CNS on microglia and neurons (22, 24, 25). We and others detected CCR5, CXCR4, and CCR2-positive macrophages in the brains of those with pediatric HIV-1 encephalitis (24, 26).

In this study, we demonstrate that Tat induces monocyte transmigration that is mediated through astrocyte-derived MCP-1 expression. Furthermore, Tat up-regulates CCR5 expression on monocytes. Our data support a process whereby HIV-1 Tat protein contributes to HIV-1 infection of the CNS and the progression of AIDS dementia.

Materials and Methods

Source of fetal tissue

The present study is part of an ongoing research protocol that has been approved by the Albert Einstein College of Medicine Committee on Clinical Investigation and the City of New York Health and Hospitals Corporation. Informed consent was obtained from all participants. Fetal tissues were obtained at the time of elective termination of intrauterine pregnancy from healthy females (27).

Cell culture

Astrocyte cultures were prepared according to a modified protocol of McCarthy and de Vellis (28). Briefly, human fetal CNS tissue was separated from the meninges, minced, and digested in 0.25% trypsin (Life Technologies). The resulting cell suspension was serially filtered through sterile 100- and 99% glial fibrillary acidic protein (GFAP; Sigma, St. Louis, MO), 1% penicillin/streptomycin (Life Technologies). After 12 days, microglial cells were obtained by digesting umbilical cords with type II collagenase (Sigma, St. Louis, MO). The resulting cell suspension was serially filtered through sterile 100- and 99% GFAP, as well as barrier activity against inulin. We demonstrated previously that cytokine-induced MCP-1 plays a central role in directing the transmigration of monocytes and activated lymphocytes across these cocultures (19). In those studies, leukocyte transmigration in response to cytokines and MCP-1 was the same, regardless of whether human umbilical vein or human brain microvascular EC were cocultured in the model. Similarly, we showed that the adhesion molecules that are critical for transmigration were identical, regardless of the source of EC.

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Tat treatment of cocultures or astrocytes, but not EC, induced significant MCP-1 expression. Cocultures were treated with 10 ng/ml HIV-1 Tat in the lower chamber (astrocyte side) for 24 h. ELISA analysis of the lower-chamber supernatant demonstrated significant MCP-1 protein Tat-treated cocultures, as compared with untreated cocultures \((p < 0.04; n = 3)\). Similar levels of MCP-1 protein were detected in Tat-treated astrocytes cultured in the absence of EC \((p < 0.04; n = 3)\) as compared with untreated astrocytes. Tat treatment of EC grown in the absence of astrocytes did not induce MCP-1 expression. The MCP-1 expression in untreated (Unt) cocultures and astrocyte cultures reflects basal astrocyte-derived MCP-1 expression.

Tat for 4, 8, 24, or 48 h. Adherent cells were collected with 0.5 mM EDTA and brought to a final concentration of \(1 \times 10^6\) cells/ml in 1% BSA/PBS containing mAb to CCR5, CXCR4, CCR2, or isotype-matched control Abs (5 pg/ml). Cells were incubated for 30 min at 4°C, washed, and incubated with FITC-conjugated goat anti-mouse IgG (Southern Biotechnology Associates, Birmingham, AL) for 30 min. Cells were fixed in 2% paraformaldehyde and analyzed for chemokine receptor expression by flow cytometry. Gated acquisition of monocytes (10,000 events) was performed based on forward- and side-scatter parameters.

**ELISA**

Culture supernatants were collected from the lower chamber and stored at \(-20°C\) until use. MCP-1 protein was determined using a sandwich-type immunoassay with capture and biotinylated detection Abs (PharMingen, San Diego, CA). TNF-\(\alpha\) and IL-1\(\beta\) were detected using Abs purchased from R&D Systems. The minimum detection limit for these assays is 15 pg/ml for MCP-1 and 5 pg/ml for TNF-\(\alpha\) and IL-1\(\beta\).

**Statistical Analyses**

Results from the duplicate wells of each transmigration experiment were averaged. Student’s paired \(t\) test was used to analyze significance of the numbers of transmigrated monocytes or MCP-1 protein in Tat-treated cultures, as compared with that of untreated cultures. For MCP-1 blocking experiments, significance between anti-MCP-1 and negative control Ab-treated supernatants was similarly compared. Results were considered to be significant for \(p < 0.05\) values.

**Results**

**Tat induces significant MCP-1 protein in cocultures but not in EC cultured alone**

Cocultures of EC and astrocytes were treated with 10 ng/ml HIV-1 Tat protein on the underside (astrocyte side) for 24 h. The lower-chamber supernatant was analyzed by ELISA for MCP-1 expression. Tat treatment of cocultures significantly induced MCP-1 expression, as compared with untreated cocultures \((p < 0.04; n = 3)\). The addition of Tat to astrocytes cultured in the inserts in the absence of EC resulted in similar amounts of MCP-1 protein \((p < 0.04; n = 3)\). Contrast, no significant monocyte transmigration was detected with Tat-treated EC cultured in the absence of astrocytes. As a positive control, exogenous MCP-1 (100 ng/ml in the lower chamber) induced similar transmigration of monocytes across cocultures or EC grown in the absence of astrocytes \((p < 0.04; n = 3)\) each.

**FIGURE 1.** Tat treatment of cocultures or astrocytes, but not EC, induced significant MCP-1 expression. Cocultures were treated with 10 ng/ml HIV-1 Tat in the lower chamber (astrocyte side) for 24 h. ELISA analysis of the lower-chamber supernatant demonstrated significant MCP-1 protein Tat-treated cocultures, as compared with untreated cocultures \((p < 0.04; n = 3)\). Similar levels of MCP-1 protein were detected in Tat-treated astrocytes cultured in the absence of EC \((p < 0.04; n = 3)\) as compared with untreated astrocytes. Tat treatment of EC grown in the absence of astrocytes did not induce MCP-1 expression. The MCP-1 expression in untreated (Unt) cocultures and astrocyte cultures reflects basal astrocyte-derived MCP-1 expression.

**FIGURE 2.** Tat treatment of cocultures induces monocyte transmigration. Monocyes that had transmigrated across untreated and treated cocultures were collected and quantified by flow cytometry. Treatment of cocultures with 10 ng/ml Tat for 24 h induced significant monocyte transmigration, as compared with untreated cocultures \((p < 0.04; n = 3)\). Because monocytes comprised \(-10\%\) (30,000) of the starting PBMC population, we determined that 5% of the input monocytes had transmigrated across Tat-treated cocultures. In contrast, no significant monocyte transmigration was detected with Tat-treated EC cultured in the absence of astrocytes. As a positive control, exogenous MCP-1 (100 ng/ml in the lower chamber) induced similar transmigration of monocytes across cocultures or EC grown in the absence of astrocytes \((p < 0.04; n = 3)\) each.
alone (Fig. 2). Treatment of cocultures with medium containing Tat diluent buffer had no effect on monocyte transmigration (data not shown).

To determine whether monocyte transmigration was specifically due to Tat-induced MCP-1 expression, the lower-chamber supernatants from 10 ng/ml Tat-treated cocultures were removed and preincubated with a blocking Ab to MCP-1 or an isotype-matched negative control for 1 h before the transmigration assay. As shown in Fig. 3, Tat-induced monocyte transmigration was completely inhibited by anti-MCP-1 pretreatment, as compared with preincubation with an isotype-matched control Ab ($p < 0.03; n = 3$). This was observed for 100 ng/ml Tat as well (data not shown). As a control, the MCP-1-mediated monocyte transmigration was also completely inhibited by anti-MCP-1 treatment (Fig. 3). Thus, Tat-induced monocyte transmigration is dependent on astrocyte-derived MCP-1 expression.

Tat up-regulates CCR5, but not CXCR4 or CCR2, expression on monocytes

In addition to mediating leukocyte recruitment, we hypothesized that Tat may alter the expression of chemokine receptors on PBMC. To test this, freshly isolated PBMC were incubated with increasing doses of Tat protein (1, 3, or 10 ng/ml Tat) for various lengths of time (4, 8, 24, or 48 h). These concentrations of Tat are similar to those detected in the sera of HIV-1-infected individuals and the supernatants of HIV-1-infected cell cultures (15). PBMC were then collected and analyzed for chemokine receptor expression by flow cytometry. Monocytes were gated according to forward- and side-scatter parameters. For all treatment conditions, similar results were obtained from more than one donor.

Fig. 4A illustrates the expression of CCR5, as determined by mean fluorescence intensity, by untreated monocytes as compared with those treated with Tat. After 24 or 48 h of Tat treatment, the expression of CCR5 on monocytes was greater than that of the corresponding cultures that did not receive Tat (untreated). At these later time points, enhanced CCR5 expression was observed for all doses of Tat, which reached significance for 3 or 10 ng/ml Tat at 24 h and for 3 ng/ml Tat at 48 h ($p < 0.02$ each; $n = 2$). No

![FIGURE 3. Monocyte transmigration across cocultures is mediated by MCP-1. Tat (10 ng/ml) was added to the lower chamber (astrocyte side) of cocultures for 24 h. Following Tat treatment, the lower-chamber supernatants were removed and incubated with either anti-MCP-1 or isotype-matched control Ab (10 μg/ml) for 1 h. These supernatants were then placed in new culture wells, and the inserts containing cocultures were placed over their original supernatant. PBMC were then added for the standard transmigration assay. Monocyte transmigration induced by Tat was completely inhibited by anti-MCP-1 treatment, as compared with control Ab ($p < 0.03; n = 3$). Monocyte transmigration in response to exogenous MCP-1 (100 ng/ml) was similarly inhibited by anti-MCP-1 ($p < 0.03; n = 3$).](http://www.jimmunol.org/)

![FIGURE 4. Tat-stimulated monocytes have increased CCR5 expression. PBMC were plated and treated with either Tat diluent buffer (untreated) or various doses of Tat protein. Cells were collected after 4, 8, 24, or 48 h and analyzed for CCR5 expression by flow cytometry and compared with isotype-matched control Ab. A. Mean fluorescence intensities of Tat-stimulated monocytes. Treatment with HIV-1 Tat protein increased CCR5 expression at 24 and 48 h, reaching significance for 3 and 10 ng/ml Tat at 24 h and for 3 ng/ml Tat at 48 h ($p < 0.02; n = 2$ each as compared with the corresponding untreated cultures). B, Untreated monocytes (plated for 24 h) expressed CCR5, as compared with control Ab staining. C, Tat treatment (10 ng/ml for 24 h) increased CCR5 expression on monocytes, as compared with untreated cells. D, Tat treatment (10 ng/ml for 24 h) had no effect on control Ab staining.](http://www.jimmunol.org/)
CCR5 expression (Fig. 4; ing). Treatment of PBMC with 10 ng/ml Tat for 24 h increased CCR5 expression, as compared with the negative control Ab stain- ing. Untreated monocytes (plated for 24 h) had a low level of CCR5 expression detected for 10 ng/ml Tat at 24 h. As shown in Fig. 4B, Tat treatment of monocytes had no effect on CXCR4 staining. C. Untreated monocytes expressed CCR2, as compared with control Ab staining. D. Tat treatment of monocytes did not alter CCR2 staining. The histograms are each representative of at least three experiments.

change in CCR5 expression was detected at either 4 or 8 h of Tat treatment, regardless of the dose of Tat (Fig. 4A). For each treat- ment condition, PBMC cultures were also incubated with an iso- type-matched control Ab. A. Untreated monocytes expressed CXCR4, as compared with control staining. B. Tat treatment of monocytes had no effect on CXCR4 staining. C. Untreated monocytes expressed CCR2, as compared with control Ab staining. D. Tat treatment of monocytes did not alter CCR2 staining. The histograms are each representative of at least three experiments.

Discussion

Our data demonstrate a role for HIV-1-derived Tat in inducing the transmigration of monocytes across a coculture of ECs and astrocytes that models several aspects of the human BBB. This process appears to be dependent on the induction of astrocyte-derived MCP-1 expression. We suggest that the expression of Tat in the CNS during the course of HIV infection mediates the recruitment of infected and/or uninfected monocytes across the BBB. As il- lustrated in Fig. 6, multiple pathways are likely to exist for this process. They include the following: 1) Tat may induce monocyte transmigration across the BBB through astrocyte-derived MCP-1 expression (Fig. 6A); 2) HIV-1 Tat may also directly induce mono- cyte transmigration (Fig. 6B); 3) Tat may activate monocytes and microglia for enhanced cytokine (e.g., TNF-α and IL-1β) and chemokine production, including MIP-1α, MIP-1β, and RANTES (Fig. 6C); and 4) Tat up-regulates CCR5 expression on monocytes, which may facilitate their migratory response to these chemokines as well as their infectivity (Fig. 6D) (21).

We also determined whether Tat treatment altered PBMC expression of CCR2, as this is the receptor for MCP-1 (32). As ex- pected, untreated monocytes expressed CCR2 (Fig. 5C; n = 4); however, Tat treatment (10 ng/ml for 24 h) did not significantly modulate this expression (Fig. 5D).

The effect of Tat on PBMC chemokine receptor expression thus appears to be specific for CCR5 at the time points tested.
such as TNF-α, nitric oxide, platelet-activating factor, or arachidonic acid metabolites that may directly contribute to neuronal injury and/or death (34).

Lafrenie et al. (35) found that HIV-1 Tat directly induced monocyte transmigration across Matrigel-coated inserts without any cells grown on it. This was particularly evident when the monocytes were pretreated with HIV-1 Tat. Tat may therefore directly facilitate the transmigration of monocytes across the BBB.

HIV encephalitis is often associated with elevated levels of proinflammatory cytokines in the CNS (36). Astrocytes are a potential source of TNF-α (37, 38), and both EC and astrocytes can produce IL-1β (39). We examined whether Tat induced either TNF-α or IL-1β production in our cell cultures, because these cytokines can also induce MCP-1 expression. However, by ELISA we did not detect the expression of either cytokine in Tat-treated EC, astrocytes, and cocultures. This is consistent with previous observations that Tat, at 10 ng/ml (714 pM), was unable to induce TNF-α production in astrocytes (40). Specifically, in that study, at least 1 μM Tat was necessary to induce the production of TNF-α from human fetal astrocytes. Tat has been shown to be a potent stimulus of TNF-α in macrophages; however, at least 10 nM Tat for 4 h was required for this effect (40). Thus, our findings rule out the possibility that TNF-α is involved in Tat-induced MCP-1 expression in our cocultures. This is not surprising, given that we treated cells with Tat at a concentration that does not induce TNF-α expression in astrocytes (40). Furthermore, any potential TNF-α-induced MCP-1 expression is also not a mechanism in our studies, given that Peterson et al. (41) have shown that at least 20 ng/ml TNF-α is required to induce MCP-1 expression in astrocytes and that we did not detect any TNF-α in our Tat-treated cultures. These observations suggest an important and direct role for Tat-induced MCP-1 production by astrocytes in the transmigration of monocytes.

We demonstrate that HIV-1 Tat up-regulates CCR5 receptor expression on human peripheral blood monocytes. This effect was observed using as little as 1–3 ng/ml Tat, doses that are similar to the levels of Tat that have been found in the sera of HIV-infected patients (15, 16). We further show that at least 24 h of Tat treatment was required for the induction of CCR5 expression. Our findings complement those of Huang et al. (42), who recently reported that Tat induces CCR5, as well as CXCR4 and CCR3 expression on monocytes. In that study, PBMC were incubated with 100 ng/ml Tat for at least 2–8 days. Taken together, our data and theirs demonstrate that the effects of Tat on chemokine receptor expression in PBMC occur as early as 24 h and persist for at least 8 days. Furthermore, our own finding, that Tat, at lower concentrations and earlier times, increases CCR5 expression but not that of CXCR4, suggests that the induction of these chemokine receptors by Tat is mediated through distinct pathways. The up-regulation of CCR5 expression by Tat is an interesting observation, because studies suggest that proinflammatory cytokines such as TNF-α may decrease CCR5 expression (43). The ligands for CCR5, specifically MIP-1α and MIP-1β, have also been detected in AIDS encephalitis (44). We demonstrated that human microglia (45), as well as Tat-treated astrocytes (26), are potential sources of these chemokines. Thus, in addition to MCP-1, it is possible that MIP-1α or MIP-1β participates in Tat-mediated leukocyte transmigration across the BBB in vivo. However, MCP-1 was demonstrated in chemotaxis assays across EC to be the most potent of these monocyte chemotactants (46). Our finding that Tat up-regulates CCR5 expression on monocytes may have important implications in vivo for CCR5-mediated chemotrafficking and/or infection of monocytes.

CCR5 is a coreceptor that mediates fusion and entry of M-tropic strains of HIV (21). Its up-regulation may therefore indicate a process whereby HIV facilitates its own replication. However, the chemokines MIP-1α, MIP-1β, and RANTES are capable of binding to this receptor and suppressing HIV infection (47). Thus, the overall balance of chemokine and virus concentrations is likely to determine the susceptibility of CCR5+ cells to infection.

We demonstrate that HIV-1 Tat facilitates the transmigration of monocytes via astrocyte-derived MCP-1 expression. We further show that Tat up-regulates the expression of CCR5 on human monocytes. Our findings indicate important mechanisms whereby HIV-1 Tat may not only facilitate the entry of infected and/or uninfected monocytes into the CNS, but also may render monocytes more susceptible to HIV-1 infection, thereby contributing to the pathogenesis of AIDS dementia.

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