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Spontaneous Production of C-C Chemokines by Individuals Infected with Human T Lymphotropic Virus Type II (HTLV-II) Alone and HTLV-II/HIV-1 Coinfected Individuals

Martha J. Lewis,*† Virginie W. Gautier,* Xue-Ping Wang,* Mark H. Kaplan,‡ and William W. Hall2*  

To investigate the immunological features of human T lymphotropic virus type II (HTLV-II) infection and specific mechanisms whereby HTLV-II might influence the progression of HIV-1 disease in coinfected individuals, we have analyzed the production of the C-C chemokines RANTES and macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β) by PBMCs from HTLV-II-infected and HTLV-II/HIV-1-coinfected individuals. We observed spontaneous production of significant levels of MIP-1α and -1β and, to a lesser extent, RANTES, from individuals infected with HTLV-II alone or with concomitant HIV-1 infection. Spontaneous C-C chemokine production was not observed in PBMCs from uninfected or HIV-1-infected individuals. Although HTLV-II is known to preferentially infect CD8+ lymphocytes in vivo, we observed that whereas RANTES was produced exclusively by the CD8+ -enriched fraction, MIP-1α and -1β were produced by both the CD8+ -enriched and CD8+ -depleted fractions of HTLV-II-infected PBMCs. RT-PCR demonstrated active expression of the HTLV-II regulatory protein Tax in the infected CD8+ T lymphocyte population, and it was further shown that Tax transactivates the promoters of MIP-1β and RANTES. Therefore, it appears that HTLV-II stimulates the production of C-C chemokines both directly at a transcriptional level via the viral transactivator Tax and also indirectly. Although the HTLV-II-infected individuals in this study are all virtually asymptomatic, they certainly display an abnormal immune phenotype. Moreover, our findings suggest that HTLV-II, via chemokine production, would be expected to alter the progression of HIV-1 infection in coinfecting individuals. The Journal of Immunology, 2000, 165: 4127–4132.

The human T lymphotropic viruses type I (HTLV-I) and type II (HTLV-II) are members of a family of mammalian retroviruses that have similar biological properties and a tropism for T lymphocytes (1). HTLV-II is endemic in a number of geographic areas, where infection is associated with an aggressive T cell malignancy, adult T cell leukemia (ATL), and a number of less severe inflammatory processes. These include the neurological disorder, HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a characteristic uveitis, and alveolitis. HTLV-II infection has been shown to be endemic in a number of American Indian populations, and high rates of infection have also been documented in i.v. drug users (IVDUs) in urban areas worldwide. Although the role of HTLV-II in human disease has yet to be completely determined, infection has also been shown to be associated with neurological disorders similar to those observed with HTLV-I (1). HTLV-II and HIV-1 coinfections are common in IVDUs as a result of parenteral transmission. In contrast, for reasons unclear, HTLV-I and HIV-1 coinfections occur relatively infrequently. The influence of HTLV-I and HTLV-II infection on the natural history of HIV-1 disease in the setting of coinfection remains unclear and controversial. Early epidemiological studies have suggested that HTLV-I coinfections are at increased risk for the progression of HIV-1 infection and the development of AIDS (2). This observation was subsequently supported by in vitro studies showing that the HTLV-I regulatory protein Tax can transactivate the HIV-1 long terminal repeat thus enhancing HIV-1 replication (3). However, subsequent studies failed to confirm an acceleration of HIV-1 disease progression in concomitant HTLV-I infection (4), suggesting that the interaction between these two viruses may be much more complex. Recently several studies have shown that HTLV-I-infected cell lines secrete the C-C chemokines RANTES, macrophage inflammatory protein (MIP)-1α, and MIP-1β (5–7). These chemokines are the natural ligands for receptors that are necessary for HIV-1 entry, and a number of independent studies have clearly demonstrated that they can both suppress infection by macrophage-tropic (M-tropic) HIV-1 strains and enhance infection by T cell-tropic strains (6, 8–11). Moreover, it has been suggested that overproduction of the C-C chemokines may actually protect individuals from infection by M-tropic strains of HIV-1. Specifically, it has been shown that certain individuals who have been clearly exposed to HIV-1, yet who have remained uninfected, produce high levels of the C-C chemokines (8, 10, 12).

Although the majority of in vitro studies have attempted to investigate the relationship between HTLV-I and HIV-1 coinfections, concomitant infections with HIV-1 and HTLV-II are of much greater clinical significance as it has been shown that as
many as 30% of all IVDUs in urban areas of North America are coinfected (13–16). The influence of HTLV-II infection on HIV-1 has not been extensively evaluated, and epidemiological studies have failed to agree upon what, if any, influence HTLV-II might have on HIV-1 disease progression (17–20). In this report we describe the results of studies to investigate the immunological features of HTLV-II infection and to analyze mechanisms whereby HTLV-II could potentially influence infection with and the progression of HIV-1 in vivo. Specifically, we have analyzed spontaneous C-C chemokine production by unstimulated PBMCs from HTLV-II-infected individuals and have investigated possible molecular mechanisms involved.

**Materials and Methods**

**Patient population**

The patient population examined in this study included the following: nine individuals with HTLV-II infection, three with HIV-1 infection, four with HTLV-II and HIV-1 coinfection, and seven normal donors. All of the HIV-1 singly infected individuals, all of the HTLV-II-infected individuals, and two of the dually infected individuals were from the New York City Metropolitan area. Two of the dually infected individuals were from Sao Paolo, Brazil. Further details of the patient population are seen in Table I. Venous blood samples were obtained from each individual after proper informed consent was obtained.

**Lymphocyte cultures**

PBMCs were isolated using Ficoll-Hypaque and cultured at a density of 10^6 cells/ml in RPMI 1640 medium supplemented with 10% heat-inactivated FCS in the absence of any additional stimulation. PBMCs from uninfected individuals were also cultured in the presence of PHA (0.005 mg/ml). Cultures were maintained at 37°C, 5% CO2 for 36 h. Viable cells were counted again and then collected by centrifugation.

**Chemokine ELISAs and statistical testing**

Cell-free culture medium was collected at 36 h and assayed for MIP-1α, MIP-1β, and RANTES. Assays were performed using Quantikine Immunoassays (R&D Systems, Minneapolis, MN) following the manufacturer’s instructions. Each sample was assayed in triplicate. Data were analyzed for statistical significance using Student’s t test.

**CD8⁺ cell population separations and culture**

CD8⁺ T lymphocytes were separated from PBMCs using magnetic beads coated with anti-CD8⁺ Abs (Dynal, Oslo, Norway). Cells were bound to the beads at 4°C for 60 min and then washed five times according to the manufacturer’s instructions. Selected CD8⁺ cells were cultured in the presence of the beads. All cells were cultured at a density of 10⁶ cells/ml using the same conditions as for PBMC cultures.

**RT-PCR**

Total RNA was extracted from 2–3 × 10⁶ cells using TRIzol reagent (Life Technologies, Grand Island, NY), a typical guanidine isothiocyanate RNA isolation reagent, according to the manufacturer’s instructions. Total RNA was treated with 1 U of DNase I (amplification grade; Life Technologies) before cDNA synthesis. First strand cDNA was reverse transcribed using an oligo dT primer and the SuperScript Preamplification System (Life Technologies). Two microtiter of the resultant RT product were used as template for Tax and β-actin PCR. Primers for the amplification of Tax were as follows, TR101 5’-TTTCCYAGGRTTTGGACACAG-3’ and TR102 5’-GGGTAAGGACCTTGAGGGTC-3’.

**Transfection assays**

Luciferase reporter assays were performed by transiently transfecting COS-7 cells with an HTLV-II subtype B Tax construct and a chemokine promoter-luciferase reporter construct. The RANTES promoter was cloned into pGL2-Basic Vector (Promega, Madison, WI) (provided by A. Krensky, Stanford University, Palo Alto, CA). The MIP-1β promoter (provided by W. J. Leonard, National Institutes of Health, Bethesda, MD) was subcloned into pGL3-Basic Vector (Promega). HTLV-II subtype B Tax was cloned into the eukaryotic expression vector pCAGGS. Six-centimeter dishes of cells were transfected with 3 µg of the Tax2B plasmid or control vector and 2 µg of the luciferase reporter plasmid with 10 µl Lipofectamine (Life Technologies). Cells were lysed after 48 h and assayed for luciferase activity using Promega’s Luciferase Assay System. Each transfection experiment was repeated three times.

**Results**

PBMCs from nine HTLV-II-infected and four HTLV-II/HIV-1-coinfected individuals were cultured for 36 h in the absence of any mitogenic stimulation, and culture supernatants were assayed by ELISA for production of MIP-1α, MIP-1β, and RANTES. Results

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Mode of Infection</th>
<th>Sex</th>
<th>±</th>
<th>CD8⁺/CD8⁻ Count</th>
<th>HIV Viral Load</th>
<th>Clinical Status</th>
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<td>–</td>
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</tr>
<tr>
<td></td>
<td>IVDU*</td>
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<tr>
<td></td>
<td>IVDU</td>
<td>F</td>
<td>ND</td>
<td>–</td>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVDU</td>
<td>F</td>
<td>ND</td>
<td>–</td>
<td>Asymptomatic</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>IVDU</td>
<td>F</td>
<td>125/532</td>
<td>–</td>
<td>Asymptomatic</td>
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<table>
<thead>
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<th>Mode of Infection</th>
<th>Sex</th>
<th>±</th>
<th>CD8⁺/CD8⁻ Count</th>
<th>HIV Viral Load</th>
<th>Clinical Status</th>
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<tbody>
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<td>Hep C</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>IVDU</td>
<td>F</td>
<td>639/960</td>
<td>ND</td>
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</table>

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Mode of Infection</th>
<th>Sex</th>
<th>±</th>
<th>CD8⁺/CD8⁻ Count</th>
<th>HIV Viral Load</th>
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<td>Hep B</td>
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<tr>
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<td>IVDU</td>
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<td>665/826</td>
<td>50³</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>IVDU</td>
<td>M</td>
<td>82/623</td>
<td>120³</td>
<td>Hep C</td>
<td></td>
</tr>
</tbody>
</table>

* Cells per microliter.
* IVDU, i.v. drug user.
* As measured by Nuclisen HIV-1 QT.
* As measured by nucleic acid sequence based amplification.

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**Table I. Characteristics and infection status of the HTLV-II and HIV-1-infected population**

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are summarized in Table II. Culture supernatants from unstimulated HTLV-II-infected and HTLV-II/HIV-1 dually infected PBMCs produced significantly higher amounts of MIP-1α than normal donor PBMCs (p < 0.025 and p < 0.05, respectively) (Fig. 1A). HTLV-II-infected PBMCs, with or without concomitant HIV-1 infection, also produced significantly higher amounts of MIP-1β compared with normal donor PBMCs (p < 0.01 and p < 0.001, respectively) (Fig. 1B). RANTES production by HTLV-II-infected PBMCs was also elevated but less significantly than that of MIP-1α and -1β (Fig. 1C). However, RANTES production was significantly lower both in PBMCs from individuals infected with HIV-1 (p < 0.01) and dually infected individuals (p < 0.025) compared with normal donors, suggesting that HIV-1 infection might down-regulate the expression of this chemokine. The results of these studies also confirm previous observations, which demonstrated that normal PBMCs do not produce significant levels of C-C chemokines (12, 21) but that upon exposure to mitogenic stimuli, in this case PHA, C-C-chemokine expression is induced (Fig. 1). Our results demonstrate that, in the context of coinfection with HTLV-II and HIV-1, spontaneous chemokine production is a consequence of HTLV-II and not HIV-1, as coinfected PBMCs behave in a similar fashion to those from individuals solely infected with HTLV-II. Consistent with this view is the observation that PBMCs from individuals infected with HIV-1 alone behave similarly to normal, uninfected donors.

As HTLV-II is known to preferentially infect CD8+ T lymphocytes in vivo (22), we attempted to determine which T lymphocyte population was responsible for C-C chemokine production. PBMCs from normal donors, HIV-1-infected individuals, and HTLV-II-infected individuals were separated into CD8+ -enriched and CD8+ -depleted fractions using an anti-CD8+ Ab bound to magnetic beads. The results are summarized in Table II. On average, RANTES production by PBMCs with HTLV-II infection occurred exclusively in the CD8+ T lymphocyte-enriched population, whereas MIP-1α and -1β were produced at relatively equal levels by both lymphocyte fractions (Fig. 2). In contrast, normal donor lymphocytes stimulated by PHA produce MIP-1α and RANTES primarily in the CD8+ -depleted fraction, whereas MIP-1β is only present in slightly higher levels in the depleted fraction relative to the CD8+ -enriched fraction. The observation that chemokine production in HTLV-II infection differs from that in stimulated normal lymphocytes suggests that the production of C-C chemokines at least in the CD8+ T lymphocyte population is a direct result of HTLV-II infection as opposed to a physiological response to chronic viral infection. In fact, in one of the HTLV-II-infected individuals examined, production of all three chemokines occurred exclusively in the CD8+ -enriched fraction.

To investigate whether there is active HTLV-II expression in the separated T lymphocyte populations we focused our studies on the

### Table II. Summary of chemokine production by PBMCs and lymphocyte subpopulations

<table>
<thead>
<tr>
<th></th>
<th>MIP-1α (pg/ml)</th>
<th>MIP-1β (pg/ml)</th>
<th>RANTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL+PHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTLV-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8+</td>
<td></td>
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<td>NL donor</td>
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<tr>
<td>NL+PHA</td>
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</tr>
<tr>
<td>HTLV-II</td>
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<td></td>
</tr>
<tr>
<td>HIV-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depleted</td>
<td></td>
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<td></td>
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</tbody>
</table>

### FIGURE 1. Spontaneous production of C-C chemokines by PBMC cultures. PBMCs from uninfected (n = 7), HTLV-II-infected (n = 10, nine separate individuals and one tested twice), HTLV-II/HIV-1-coinfected (n = 4), and HIV-1-infected (n = 3) individuals were cultured for 36 h in the absence of mitogenic stimulation. PBMCs from uninfected individuals were also cultured in the presence of PHA (n = 6). Culture supernatants were assayed in triplicate by ELISA for the presence of MIP-1α, MIP-1β, and RANTES. +, Mean values; *, significant difference from normal donor PBMC level; p values are listed in the text.

### Notes:

- All values are expressed as mean ± SD. See figure legends for sample number.
- NL, Normal (uninfected) blood donor.
- UD, Undetectable (below the limit of detection).
- Normal donor cells stimulated with PHA.
- Value is significantly different from normal value, p < 0.05; specific p values are listed in the text.

- NL donor
- UD
- NL donor UD
- NL+PHA
- HTLV-II
- HIV-1
- CD8+ NL donor
- NL+PHA
- HTLV-II
- HIV-1
- CD8- Depleted
- NL donor
- NL+PHA
- HTLV-II
- HIV-1
regulatory protein Tax. RT-PCR was used to detect expression of Tax mRNA in isolated lymphocyte populations. The expected 256-bp amplified product of HTLV-II Tax cDNA was only detected in the HTLV-II-infected, CD8⁺-enriched fraction (Fig. 3, upper panel, lane 7). Signals were not detected in samples from normal donor PBMCs, in HIV-1-infected PBMCs, or in HTLV-II-infected PBMCs (Fig. 3, upper panel, lanes 1, 3, and 5). The integrity of the cDNA template was confirmed by the amplification of a 259-bp fragment of β-actin cDNA from each sample (Fig. 3, lower panel). The finding that Tax mRNA was only detectable in the CD8⁺-enriched population and not in total PBMCs is presumably due to the concentration of HTLV-II-infected cells in this fraction. These results also show that although expression of Tax mRNA can be demonstrated, it is only present at very low levels, consistent with reports on HTLV-1-infected lymphocytes (23, 24).

To investigate whether Tax might be involved in chemokine production, we investigated the ability of Tax to transactivate the promoters of the MIP-1β and RANTES. Cells were transiently transfected with HTLV-II Tax and the corresponding chemokine promoter with luciferase as a reporter. HTLV-II Tax could be shown to increase transcription from the MIP-1β promoter 5.1 times compared with the expression vector alone (Fig. 4). Similarly, the RANTES promoter was activated 4.5-fold over vector alone (Fig. 4). We were unable to determine whether Tax can transactivate the MIP-1α promoter as this promoter has not been cloned. However, it seems likely that the MIP-1α promoter may also be directly responsive to Tax based on the observations of Baba et al. (5), who reported that MIP-1α mRNA is detectable in uninfected T lymphocytes. Total RNA was isolated from uninfected (n = 2), HIV-1-infected (n = 2), and HTLV-II-infected (n = 3) individuals were separated into CD8⁺-enriched and CD8⁺-depleted fractions using Ab-coated magnetic beads. Fractions were cultured for 36 h in the absence of mitogenic stimulation. Fractions from the uninfected individual were also cultured with the addition of PHA. Culture supernatants were assayed in triplicate by ELISA.

Discussion

This study is the first demonstration that unstimulated PBMCs from HTLV-II-infected individuals spontaneously produce the C-C chemokines MIP-1α, MIP-1β, and RANTES. Previous studies on C-C chemokine production as a consequence of HTLV infection have been conducted on transformed T lymphocyte cell lines or in IL-2-stimulated cultures (5–7, 25), and it had not been established whether this abnormal chemokine production also occurs in unstimulated lymphocytes from infected individuals. It seems likely that spontaneous production of chemokines also occurs in vivo as MIP-1α, MIP-1β, and RANTES are present at higher levels in the serum of HTLV-II-infected individuals compared with uninfected controls (M. J. Lewis, unpublished observations). Additionally, we have also observed that unstimulated PBMCs from HTLV-1-infected individuals can also spontaneously produce C-C chemokines (M. H. Kaplan, unpublished data).

The results of our study also suggest that, in part, the C-C chemokine production, particularly that observed in CD8⁺ lymphocytes, could be a direct result of HTLV-II infection mediated through the activity of the transactivating protein Tax on the chemokine promoters. RT-PCR demonstrated that there was active transcription of Tax mRNA in the CD8⁺ T lymphocyte population, and it was further shown that Tax could transactivate the promoters of MIP-1β and RANTES. The RANTES promoter has been reported to be responsive to NF-κB (21), and it seems likely that the stimulatory effect of Tax on the NF-κB signaling pathway could be responsible for transactivation of the RANTES promoter. The Tax-responsive elements in the MIP-1α and -1β promoters have yet to be determined (26), but they are likely to be different from those of the RANTES promoter. Baba et al. (10) reported that the MIP-1α and -1β mRNAs could be detected within 2–6 h after induction of HTLV-1 Tax expression, whereas RANTES mRNA was not detectable even after 24 h. Thus, although it would appear that Tax can induce the expression of several C-C chemokines at the level of transcription, it is probable that this induction is mediated via different pathways. This could explain why we do not observe significant differences in the amount of RANTES produced by PBMCs from HTLV-II-infected individuals.

Although our results suggest a direct role for Tax, it is likely that other indirect effects of HTLV-2 infection are contributing to increased levels of chemokines. It is especially important when
we consider that both the CD8\(^{-}\)-enriched and CD8\(^{-}\)-depleted lymphocyte fractions produce both MIP-1\(\alpha\) and -\(\beta\), whereas RANTES is produced only by the CD8\(^{-}\)-enriched fraction. The pattern of chemokine production by lymphocyte subpopulations, together with the level of Tax expression and transactivation on the chemokine promoters, indicates that indirect mechanisms are also contributing to the overall increases of MIP-1\(\alpha\) and -\(\beta\) in the PBMC cultures, particularly in the CD8\(^{-}\)-depleted cell population.

It is uncertain to what extent the quantities of C-C chemokines produced by HTLV-II-infected individuals are able to influence the progression of HIV-1 infection in vivo. At present there is no consensus among available epidemiological studies as to whether HTLV-II infection has a positive or negative effect on HIV-1 disease progression (17–20). Unfortunately, interpretation of these studies is limited due to the inability to definitively determine the temporal relationship of infection by the two viruses. However, the observed spontaneous production of C-C chemokines in HTLV-II and HIV-1 coinfected individuals certainly suggests the possibility of unique virus-mediated immunomodulatory interactions. Several independent studies have now clearly established that C-C chemokines inhibit infection by M-tropic strains of HIV-1 and enhance the pathogenicity of T cell-tropic strains (6, 9–11). Therefore, it could be anticipated that, depending on the time course and dynamics of coinfection, HTLV-II infection could have the potential to either inhibit or enhance the progression of HIV-1 infection. Specifically, it might be expected that if HTLV-II infection preceded that of HIV-1, inhibition of M-tropic HIV-1 by C-C chemokines early in infection could delay or prevent the progression of HIV-1 infection. Overproduction of C-C chemokines has also been suggested as a mechanism whereby several hemophiliacs have remained HIV-1 uninfected despite multiple, documented exposures (12). More recently, Garzino-Demo et al. (27) evaluated a cohort of homosexual males at risk for HIV-1 infection but who remained uninfected and demonstrated that these individuals also spontaneously produce high levels of MIP-1\(\alpha\) (27). This study did not evaluate or consider the possibility that some of these individuals may have had HTLV-I or -II infection, but it is possible that this may have been the case in some instances. In this regard we have also observed that a number HTLV-II-infected IVDUs remain uninfected by HIV-1 despite certain repeated exposures (M. H. Kaplan and W. W. Hall, unpublished data), and it is possible that chemokine production could have played a role in the prevention of infection. It would be useful to investigate whether HTLV-I, HTLV-II, or possibly other chronic viral infections could have also observed that a number HTLV-II-infected IVDUs remained uninfected and demonstrated that these individuals also spontaneously produce high levels of MIP-1\(\alpha\) and -\(\beta\) in the PBMC cultures, particularly in the CD8\(^{-}\)-depleted cell population.

It is unclear whether the spontaneous chemokine production we have observed in our cultures is associated with spontaneous proliferation, but it is very likely this is the case and may share the same underlying mechanism(s). It is also likely that the range of chemokines and cytokines produced by HTLV-II-infected lymphocytes may be greater than those observed by this and other studies. Moreover, it is possible that they could play a role in the pathogenesis of the wide variety of HTLV-related diseases, in particular, the neurological and inflammatory disorders associated with infection. On a more basic level, these results suggest that constitutive chemokine or cytokine production by unstimulated lymphocytes from asymptomatic individuals can be used as a marker for abnormal, although clinically silent, immune activation, whether it be caused by HTLV infection, another chronic or latent viral infection, or an autoimmune disease.

References


