Inhibition of HIV-1 Replication in Human Lymphoid Tissues Ex Vivo by Measles Virus

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Human immunodeficiency virus (HIV) type 1 replication and disease progression are enhanced by various pathogens in coinfected individuals. However, acute infection with measles virus (MV) has been found to suppress HIV-1 replication in coinfected children. We investigated the mechanisms of this phenomenon using human lymphoid tissues coinfected ex vivo with HIV-1 and MV. MV inhibited both CXCR4-tropic (X4) and CCR5-tropic (R5) HIV-1, but the inhibitory effect was particularly profound for R5 virus, which transmits infection and dominates the early stages of HIV-1 disease. MV inhibits the replication of R5 HIV-1 in coinfected tissues by up-regulation of the CC chemokine RANTES, a well-known inhibitor of R5 HIV-1 infection, and this up-regulation is augmented in tissues coinfected with R5 HIV-1. Deciphering the molecular mechanisms by which MV and other pathogens alter local cytokine/chemokine networks and cause tissue microenvironments to become detrimental to HIV-1 may significantly contribute to the development of effective anti-HIV therapies.

Various pathogens enhance HIV-1 replication and disease progression in coinfected individuals [1–4]. However, 2 viruses and 1 bacterium have recently been reported to inhibit HIV-1 infection in coinfected individuals [5]. In particular, acute infection with measles virus (MV) has been shown to suppress HIV-1 replication in coinfected children [6]. The mechanism of this phenomenon and the contributions of local and systemic factors to MV-triggered HIV-1 inhibition remain largely unknown. To investigate this mechanism, we used a system of human lymphoid tissues infected ex vivo, because critical events of HIV-1 infection occur in lymphoid tissues in vivo. In this ex vivo system, MV inhibited both CXCR4-tropic (X4) and CCR5-tropic (R5) HIV-1, but the inhibitory effect was particularly profound for R5 virus. MV infection up-regulates the CC chemokine RANTES, a well-known inhibitor of R5 infection. Against the background of R5 infection, the MV-induced production of RANTES was augmented, thus providing a major mechanism for the inhibition of R5 HIV-1 replication by MV. Moreover, MV is moderately cytopathic for lymphocytes and decreased the number of R5 and X4 HIV-1 targets in coinfected tissues.

MATERIALS AND METHODS

Viruses. R5SF162 and X4LA04 HIV-1 isolates were obtained from the National Institutes of Health AIDS Research and Reference Reagent Program. Laboratory stocks of MV of the Chicago-1 and Edmonston strains (the latter is a more attenuated strain) were grown on Vero cells and passed through a 0.2-μm filter before titration. MV was obtained from infected Vero cells that had been lysed by freezing and thawing.

Tissue infection. Human tonsils removed during routine tonsillectomies at Children’s Hospital (Washington, DC) were dissected, set up in culture at the air-liquid interface, and maintained as described elsewhere [7]. To infect human lymphoid tissues with MV, each
of 27 tissue blocks from 1 donor was inoculated with 5 μL of a 5 × 10^3-pfu/mL viral stock. For HIV-1 infection, 5 μL of viral stock that contained 100 ng of p24 was applied to each of 27 tissue blocks from 1 donor. For coinfection experiments, tissues were inoculated with both viruses simultaneously. Experiments were repeated n times, each time with tissues from a different donor, and n is indicated in the text and figure legends.

**Evaluation of viral replication.** We evaluated HIV-1 production by measuring the p24 core antigen released into the pooled medium bathing all 27 blocks by using HIV-1 p24 ELISA (Coulter). MV replication in the human lymphoid tissues was assessed by titrating virus in pooled medium and counting the number of plaques produced on Vero cells.

**Flow-cytometric analysis.** At day 12 or 13 after infection, single-cell suspensions were prepared from tissue blocks by mechanical dissociation. Tissue blocks were placed into a petri dish with complete medium and gently ground with a pestle. As has been shown elsewhere [7], such a procedure releases lymphocytes from stromal elements. Similarly, cells that had migrated into the collagen sponge were mechanically isolated and collected by centrifugation at 400 g. To determine the level of infection, cells were washed 3 times and stained with a combination of the following monoclonal antibodies: CD8-phycocerythrin (PE), CD4 Cy5.5-PE, CD3 Cy7-PE, or CD45-allophycocyanin (APC; all from Caltag). After surface staining, the cells were permeabilized with Fix&Perm reagent (Caltag) and stained with a fluorescein isothiocyanate (FITC)-labeled monoclonal antibody to MV nucleocapsid (N) protein (Chemicon International). Infection of memory and naive cells was determined as described above, with the following antibody combinations: CD3-Cy7-PE, CD45-PE, CD4-Cy5.5-PE, CD62L-Cy7-APC, and CD45RA-APC (all from Caltag) for cell-surface staining and anti–MV N protein–Alexa 488 for intracellular staining. To estimate cell depletion, cells were stained with the following antigen combinations: CD3-FITC, CD45-PE, CD4-Cy5.5-PE or CD4–peridinin-chlorophyll-protein complex, CD8-APC and CD19-FITC, CCR5-PE (Pharmingen), CCR5 APC (Pharmingen), CD3 Cy7-PE, and CD8 Cy7-APC, in the presence of Caltag Counting Beads. Cell numbers were estimated according to the manufacturers’ instructions, and results were normalized by tissue weight.

**Chemokine/cytokine analysis.** The levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)–γ, interleukin (IL)–1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, interferon-inducible protein (IP)–10, monokine induced by IFN-γ (MIG), macrophage inflammatory protein (MIP)–1α, MIP-1β, RANTES, stroma cell–derived factor (SDF)–1α, and tumor necrosis factor (TNF)–α in culture medium were evaluated by use of multiplex bead-array assays performed on a Luminex-100 platform. Individual Luminex bead sets were coupled to cytokine-specific capture antibodies according to the manufacturer’s instructions. The assays were run by use of 1200 beads/set/well in a total volume of 50 μL. For each bead set, 61 beads were collected.

**Statistical analysis.** Data obtained with tissue from 1 donor constituted the results of 1 experiment. Both the levels of viral replication and the proportion of cells in various leukocyte subsets varied from donor to donor [7, 8]. To compare results obtained in different experiments, we normalized the data for such variation: for each experiment, we compared infected and control tissues obtained from an individual donor in replicates of 27–54 tissue blocks for each data point. To average the results of different experiments and to analyze them statistically, we normalized the data as the percentage of controls. Statistical analysis performed on the normalized results included the calculation of mean and SE and of P values by use of Student’s t test. The significance level was set as P < .05, and the actual P values are indicated for each series of experiments. Statistical analysis of p24 ELISA data was performed with Deltasoft software (version 3.0; BioMetallics), which combines data from 3 dilutions and calculates the interpolated p24 concentration and SE. Data analysis of the median of the fluorescence intensity recorded for 61 beads of each bead set for Luminex assays was performed with Bioplex Manager software (version 3.0; Bio-Rad), by use of a 5P regression algorithm.

**RESULTS**

**MV infection of human lymphoid tissues.** First, we investigated whether MV infects human lymphoid tissues ex vivo. We inoculated tonsillar tissue blocks with 2500 pfu of MV of either the Edmonton or the Chicago-1 strain and monitored infection by estimating the amount of infectious viral particles in culture medium as evaluated by plaque assay with Vero cells. Human lymphoid tissues infected ex vivo supported the productive infection of MV (figure 1). In tissues obtained from 4 donors, MV replication became detectable at day 3 after infection and continued to increase until the end of the experiment on day 12 or 15 after infection. As was reported above for HIV-1 in this system, there was large donor-to-donor variability in MV replication levels. We measured MV replication in tissues from 4 donors. In tissues from 3 donors, MV production was 29,650–38,700 pfu/mL (mean ± SE, 33,600 ± 2700; n = 3), but tissues from the fourth donor had a much higher level of replication (172,500 pfu/mL). The average maximum level of MV production was 68,000 ± 35,000 pfu/mL (n = 4), with a maximum of 172,500 pfu/mL and a minimum of 29,650 pfu/mL.

Second, we investigated which cells are productively infected with MV in human lymphoid tissues infected ex vivo. We mechanically isolated cells from infected tissues; stained them for CD3, CD4, CD8, CD45, and CD19, and MV N protein; and analyzed them using flow cytometry. To test that the staining for
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MV reflected viral production rather than adsorption of free virus, we incubated cells with UV-inactivated MV. In the case of UV-inactivated MV, no significant increase was observed in the number of positive cells relative to that of uninfected, matched control cells (data not shown), which indicated that staining for the N protein in MV-infected tissues reflected productive infection. On day 13 after infection, 33% ± 7% (n = 6), on average, of lymphocytes isolated from Edmonston strain–infected tissue blocks were N positive (figure 2), whereas, in tissues infected with the Chicago-1 strain, 5% ± 2%, on average, of lymphocytes were N positive. MV of the Chicago-1 and Edmonston strains infected both B and T cells; among T cells, both CD8 and CD4 subsets were infected. Cells of these subsets were infected in proportion to their presence in human lymphoid tissues. However, there were quantitative differences in infectivity between the MV of the Edmonston and Chicago-1 strains.

To evaluate the cytopathic effect of MV in infected tissues, we counted lymphocytes and compared the amounts of these cells in matched, uninfected control and matched MV-infected tissues. As is shown in figure 3, both strains of MV depleted lymphocytes, albeit with different efficiencies. Although MV of the Chicago-1 strain significantly depleted lymphocytes to the level of 54% ± 9% (n = 8; P = .025) of that in matched, uninfected control tissues, MV of the Edmonston strain depleted, on average, only ∼20% of lymphocytes to the level of 80% ± 11% of that in matched, uninfected control tissues, which did not reach statistical significance (n = 8; P = .36). The cytopathicity was associated with MV rather than with the culture medium from Vero cells used to produce MV stocks: when the medium conditioned by uninfected Vero cells was applied to uninfected tissue blocks and incubated for 13 days, no depletion of lymphocytes of any tested subset was observed (105% ± 16% that of matched, uninfected control tissues) (n = 5; P = .47).

To study whether there is preferential depletion of particular lymphocyte subsets, we stained tissue cells for CD19, CD3, CD4, CD8, CCR5, and CXCR4 and gated them on different lymphocyte subsets. Neither strain preferentially depleted T versus B cells (n = 4; .77 > P > .267) nor CD4 versus CD8 cells (n = 8; .82 > P > .62). There also was no preferential depletion of CCR5+ versus CXCR4+ cells among CD4+ cells (n = 4; .44 > P > .067) (figure 3) or among CD8+ cells (n = 4; .092 > P > .085). In addition, we did not observe a significant decrease in the fluorescence intensity of cells stained for CCR5 or CXCR4. Thus, both MV strains indiscriminately deplete lymphocytes, but MV of the Edmonston strain was much less cytopathic than MV of the Chicago-1 strain. Therefore, to minimize tissue deterioration, we chose MV of the Edmonston strain for the coinfection experiments.

HIV-1 infection of human lymphoid tissues. Human lymphoid tissues were infected with 2 prototypical R5 and X4 HIV-1 isolates—SF162 and LAV.04, respectively. As has been described elsewhere [7, 8] and confirmed here, both viruses replicated in human lymphoid tissues infected ex vivo, as evaluated by measurements of p24 in the medium. In agreement with earlier observations for various HIV-1 isolates, p24 production was first noted on day 6 after infection, and virus replication increased until the end of the experiment, on day 12 or 15 after infection (figure 4A). Although the absolute levels of viral replication in tissues varied from donor to donor, the kinetics of this process were common for tissues obtained from all donors.

Inhibition of HIV-1 infection by MV in coinfectd human lymphoid tissues. We coinfected tissue blocks with MV of the Edmonston strain and 1 of the prototypical R5 or X4 HIV-1 isolates (SF162 or LAV.04). Tissues were infected with MV and then with HIV-1 within 24 h. HIV-1 replication in coinfected tissues was compared with that in matched, singly infected tissues. As is shown in figure 4A, MV dramatically inhibited the replication of R5SF162. This inhibition became evident on day 6 after infection, and the difference between R5SF162 replication in singly infected and MV-coinfected tissues continued to increase over the duration of the experiment. On average, production of R5SF162 in MV-coinfected tissues decreased to the level of 13% ± 4.5% (n = 5; P = .03) of that in matched, singly infected tissues (figure 4B). Replication of X4LAV.04 was also inhibited in MV-coinfected tissues (figure 4A) but to a lesser extent than that of R5SF162. On average, production of X4LAV.04 in MV-coinfected tissues was 54% ± 17% (n = 6; P = .12) of that in matched, singly infected tissues (figure 4B).

Up-regulation of RANTES by MV in infected human lymphoid tissues. We evaluated the production of cytokines and
chemokines in tissues infected with MV, infected with HIV-1, and coinfected with these viruses, as well as in matched, uninfected control tissues. Using multiplex bead technology, we measured the levels of GM-CSF, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IP-10, MIG, MIP-1α, MIP-1β, RANTES, SDF-1α, and TNF-α secreted by tissues into the culture medium between days 3 and 12 of culture. As shown in figure 5A and 5B, MV up-regulates the production of RANTES. On average, the levels of RANTES in MV-infected tissues were 200% ± 27% of those in matched, uninfected control tissues (n = 10; P = .001). MIP-1α and MIP-1β were slightly but significantly increased in MV-infected tissues, by 55% ± 20% (n = 10; P = .01) and 55% ± 10% (n = 10; P = .002), respectively. Another cytokine up-regulated by MV infection was SDF-1 (60% ± 10% increase; n = 10; P = .0002). As has been shown elsewhere [9, 10] and confirmed in the present study, R5SF162 does not significantly change the levels of the tested chemokines and cytokines, relative to that in matched, uninfected control tissues (P > .2; n = 3). Strikingly, R5SF162 boosts the MV-induced up-regulation of chemokines, most notably of RANTES, which, in coinfected tissues, reached an average level of 0.43 nmol/L—360% ± 110% (n = 3; P = .025) of that in matched, uninfected control tissues (figure 5A). Similarly, the secretion of MIP-1α in tissues coinfected with MV and R5SF162 was 260% ± 40% (n = 3; P = .01) and the secretion of MIP-1β was 190% ± 20% (n = 3; P = .02) of those in matched, uninfected control tissues (figure 5A). Other cytokines and chemokines that were significantly up-regulated in these tissues were SDF-1 (figure 5A) and GM-CSF (data not shown).

In contrast to R5SF162 single infection with X4LAV04 up-regulated the 3 chemokines MIP-1α, RANTES, and SDF-1, as has been described elsewhere [10] and confirmed in the present study. In medium from tissues coinfected with MV and X4LAV04, the concentrations of MIP-1α and RANTES were further increased, relative to those in tissues singly infected with X4LAV04 (P < .042; n = 3).

**DISCUSSION**

Coinfection of HIV-infected individuals with other pathogens often stimulates HIV-1 replication and can enhance HIV-1 disease progression [11]. However, unexpected observations in vivo have recently revealed microbes that can inhibit HIV-1 replication. The list of these microbes is short and consists of the virus GB virus type C (GBV-C) [12–14] and the intracellular bacillus Orientia tsutsugamushi, the causative agent of scrub typhus [15]. Recently, MV was added to this list, because HIV-1 replication was demonstrated to be transiently suppressed during acute MV infection in coinfected children [6]. Also, it has been shown that human herpesvirus 6 (HHV-6) inhibits the replication of HIV-1 in vitro [9], but no data for a similar in vivo phenomenon are available.

Establishing the emerging field of HIV-1 suppression by non-HIV microbes requires an understanding of how general this phenomenon is by testing viruses of different groups as well as microbes for their ability to suppress HIV-1 replication, identifying mechanisms of this suppression that are specific for different microbes, and finding shared pathways (e.g., common cell-surface receptors, such as CD46 for MV and HHV-6). In addressing these issues, we have demonstrated that the inhibition of HIV-1 replication by MV can be reproduced in blocks...
of human lymphoid tissues coinfected ex vivo, and we report on a mechanism of this inhibition.

Infection of human lymphoid tissues with a laboratory-passage wild-type (*wt*) isolate or an attenuated MV strain resulted in productive infection and the release of infectious virions. As has been shown by flow-cytometric analysis of N protein-stained cells, both strains readily infected B and T lymphocytes in human lymphoid tissues, including CD4+ and CD8+ subsets. These cells were infected indiscriminately, in proportion to their relative abundance in human lymphoid tissues. Lymphocytes that stained for MV N protein in tissues infected with MV of the Edmonston strain represent productively infected cells rather than cells with passively adsorbed virus, given that non-infectious MV was not adsorbed to these cells in detectable amounts. Thus, in ex vivo human lymphoid tissues, MV and HIV-1 share cellular targets, the majority of which survive in MV-infected tissues. This may contribute to their interaction in coinfected individuals.

We investigated whether MV alters the replication of HIV-1 of different coreceptor specificity in human lymphoid tissues ex vivo coinfected. We used 2 strains of MV, 1 of which is representative of *wt* isolates (Chicago-1) and the other of attenuated strains (Edmonston) from which vaccine viruses are derived. Both strains efficiently replicated in singly infected and coinfected tissues. To study the interference of MV with HIV-1 replication, we selected the less-cytopathic Edmonston strain (to avoid the trivial consequence of lymphopenia on HIV replication). Unlike the Chicago-1 strain, which killed more than one-half of T cells during the 13 days of infection, such that only 5% of these cells remained infected at the end of the experiment, in tissues infected by MV of the Edmonston strain, 80% of lymphocytes remained, and a higher number of infected cells was retained throughout the duration of the experiment, which potentially facilitated the effect of MV on HIV-1 replication.

In coinfected tissues, MV inhibited R5 and X4 HIV-1 replication differentially. The replication of R5SF162 was inhibited almost completely, whereas the replication of X4LA104 was inhibited only partially. Because only ~20% of CD4+ cells were depleted by MV of the Edmonston strain, it did not seem to account for the observed decrease in p24 production, particularly for the R5 variant. Nevertheless, we checked whether this depletion disproportionately affected R5 targets—namely, CCR5-expressing CD4+ cells. This was not the case: MV decreased the number of CCR5+ and CXCR4+ cells in equal proportions. Thus, the pool of R5 HIV-1 targets is not depleted by MV substantially enough to account for the almost complete inhibition of R5 HIV-1 replication. Whether the depletion of CXCR4+ cells was sufficient to inhibit X4LAV04 replication is unclear, given that 80% of the X4 cell targets remained in tissues, whereas, at any time point, only ~10% of CD4+ cells produce virus [7, 8, 16]. Thus, it seems that the depletion of target cells is not the only cause of the X4 HIV-1 suppression in MV-coinfected tissues.

To further investigate possible mechanisms of MV-induced HIV-1 inhibition, we analyzed levels of key chemokines and cytokines in infected tissues that might be induced by MV and inhibit HIV-1 infection [17]. Analysis of 19 cytokines and chemokines revealed that the ones significantly up-regulated in MV-infected tissues were RANTES, MIP-1α, and MIP-1β—the well-known CCR5 ligands and inhibitors of R5 entry. Up-reg-
Figure 4. Replication of HIV-1 in human lymphoid tissues coinfected ex vivo with measles virus (MV). Tissue blocks were coinfected with MV of the Edmonston strain and either R5$_{SF162}$ or X4$_{LAV.04}$ or infected singly with one of these isolates. HIV-1 replication was evaluated by measurement of the p24 core antigen. A, Typical kinetics of HIV-1 replication in tissue blocks infected singly with HIV-1 or coinfected with MV. Each data point represents a measurement of the pooled medium bathing 27 blocks. B, Average HIV-1 replication in tissues coinfected with MV and HIV-1, relative to that in matched tissues infected singly with HIV-1. Data are mean ± SE of experiments with tissues from 5 donors infected ex vivo with R5$_{SF162}$ and from 6 donors infected ex vivo with X4$_{LAV.04}$.

ulation of these chemokines was observed in tissues singly infected with MV but not in those infected with singly R5$_{SF162}$. Surprisingly, MV and R5 HIV-1 coinfection significantly increased the up-regulation of RANTES, to a level ~4-fold higher than that in uninfected tissues. MIP-1α and MIP-1β were also up-regulated in coinfected tissues. As was demonstrated in our previous experiments [10], these levels of CC chemokines are sufficient to inhibit R5 HIV-1 replication in ex vivo human lymphoid tissues. Why does MV infection inhibit X4 HIV-1 infection as well? MV slightly up-regulates SDF-1, although SDF-1 is up-regulated by X4 HIV-1 infection alone and, at these levels, is not an obstacle for efficient X4 HIV-1 replication (see also [10]). Nevertheless, this slight up-regulation of SDF-1, in combination with the MV-triggered 20% decrease in the number of CXCR4+ cells, may be sufficient to decrease X4 HIV-1 replication by 50%, as was observed in our experiments. Also, MV could selectively deplete CXCR4+ cells, which are specifically infected by X4 HIV-1 (e.g., because of their activation status), or trigger the release of as-yet-unknown chemokine(s) that are inhibitory for X4 HIV-1. However, we have no experimental data to support these hypotheses. Moreover, other mechanisms could contribute to the observed suppression of HIV-1 replication. For example, the infection of cells with MV may prevent superinfection with HIV-1, thus decreasing the
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Figure 5. Production of chemokines in human lymphoid tissues infected ex vivo with measles virus (MV) or coinfected with MV and HIV-1. Tissue blocks were infected with MV or coinfected with MV and either R5SF162 (A) or X4LAV.04 (B). The concentration of chemokines was evaluated by use of multiplex bead array in a sample of medium bathing 27 blocks collected on day 12 after infection. Data are mean ± SE of experiments with tissues from 11 donors infected ex vivo with MV and from 3 donors coinfected with MV and HIV-1. MIP, macrophage inflammatory protein; SDF, stroma cell–derived factor.

number of potential HIV-1 targets. However, this does not explain the differential effect of MV on the R5 and X4 HIV-1 variants. Whichever molecular mechanisms mediate the differential inhibition of R5 and X4 HIV-1 in MV-coinfected tissues, this phenomenon can now be studied in the absence of uncontrolled systemic factors under laboratory conditions in ex vivo tissues.

The differential inhibition of R5 and X4 HIV-1 by MV in human lymphoid tissues coinfect ed ex vivo may be relevant to what happens in vivo when acute MV infection diminishes the HIV-1 load in coinfected children [6]. Median plasma levels of RANTES were elevated in HIV-1–infected children with acute measles, but these remained elevated after HIV-1 loads increased during convalescence [6], which suggests that other mechanisms of HIV-1 suppression may operate in MV-infected children. However, critical events of HIV-1 disease occur in human lymphoid tissues, where 98% of T lymphocytes reside. Because of the compartmentalization of infection, the local production of CC chemokines in human lymphoid tissues may be critical for the suppression of HIV-1 replication by MV, and the up-regulation of chemokines in tissues may not be reflected in plasma chemokine levels. However, it is difficult to investigate lymphoid tissues of coinfected patients. Further support for our hypothesis could come from phenotypic analyses of HIV-1 isolates from coinfected children with measles, because R5 strains would be most sensitive to inhibition by CC chemokines. Preliminary analysis of several HIV-1 isolates from Zambian children with measles has suggested that they were infected with R5 strains (unpublished data).

In general, most experimental data on the HIV-1 infection of human cells comes from experiments in “clean” systems: cultures of cell lines or primary cells infected in vitro with HIV-1 and otherwise sterile. In vivo, however, the situation is dramatically different. Humans are continuously exposed to microbes, some of which establish infection before HIV-1, whereas other opportunistic infections take advantage of the weakened immune system induced by HIV-1 infection. These microbes interact with each other and with HIV-1 in the context of human tissues; however, the molecular, immunologic, and virologic mechanisms that mediate these interactions are not known. Human lymphoid tissues infected ex vivo is rich in a diverse cell repertoire, which allows microbes to find their appropriate cell targets and makes possible the experimental study of viral pathogenesis and intermicrobial interactions, in particular interactions between microbes and HIV-1. Ex vivo lymphoid tissues also may be a useful model system for the study of MV pathogenesis and the immune responses to MV in humans.

We present evidence that MV decreases the replication of R5 HIV-1 in coinfected tissues by the up-regulation of CC chemokines, although other as-yet-unknown mechanisms may contribute to this phenomenon. The up-regulation of RANTES has been hypothesized to mediate interactions between HHV-6 and R5 HIV-1 [9] and between GBV-C and HIV-1 [14]. Mechanisms that mediate HIV-1 suppression by coinfecting microbes are important for the understanding of HIV-1 pathogenesis, and they require investigation. The findings of HIV-1 suppression by viruses support our hypothesis [5] that the cytokine/chemokine network is a universal language by which microbes “talk” to each other in the human host. Learning this language, by deciphering the molecular mechanisms by which MV and other pathogens alter local cytokine/chemokine networks and cause tissue microenvironments to become detrimental to HIV-1, may significantly contribute to the development of efficient anti-HIV therapies.
Acknowledgments

We thank Diane E. Griffin, Bloomberg School of Public Health, Johns Hopkins University, for insightful suggestions and discussions; Children’s Hospital (Washington DC), for the generous donation of tonsillar tissues (in accordance with an institutional review board–approved protocol); and M. R. Santi, for her generous assistance in obtaining tissue samples.

References