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Natural Killer Cells from HIV-1\(^+\) Patients Produce C-C Chemokines and Inhibit HIV-1 Infection\(^1\)

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Human NK cells have been shown to produce cytokines (e.g., IFN-\(\gamma\) and TNF-\(\alpha\)) and the chemokine macrophage inflammatory protein (MIP)-1\(\alpha\) following stimulation with the combination of two monokines, IL-15 plus IL-12. The C-C chemokines MIP-1\(\alpha\), MIP-1\(\beta\), and RANTES have been identified as the major soluble macrophage-tropic HIV-1-suppressive factors produced by CD8\(^+\) T cells, which exert their action at the level of viral entry. Here, we demonstrate that monokine-activated NK cells, isolated from both normal and HIV-1\(^+\) donors, produce similar amounts of MIP-1\(\alpha\), MIP-1\(\beta\), and RANTES protein, in vitro. Further, supernatants of monokine-activated NK cells obtained from both normal donors and AIDS patients showed potent (routinely \(\geq 90\%)\) suppressive activity against HIV-1 replication in vitro, compared with unstimulated control supernatants. NK cell supernatants inhibited both macrophage-tropic HIV-1\(_{N^F,N_S}\) and T cell-tropic HIV-1\(_{NL4,3}\) replication in vitro, but not dual-tropic HIV-1\(_{99,6}\). Importantly, the C-C chemokines MIP-1\(\alpha\), MIP-1\(\beta\), and RANTES were responsible only for a fraction of the HIV-1-suppressive activity exhibited by NK cell supernatants against macrophage-tropic HIV-1. Collectively these data indicate that NK cells from normal and HIV-1\(^+\) donors produce C-C chemokines and other unidentified factors that can inhibit both macrophage- and T cell-tropic HIV-1 replication in vitro. Since NK cells can be expanded in patients with HIV-1, AIDS, and AIDS malignancy in vivo, this cell type may have an important role in the in vivo regulation of HIV-1 infection. The Journal of Immunology, 1998, 161: 6433–6438.

The NK cell is a critical component of the innate immune response to a variety of viruses, fungi, parasites, and bacteria (1–4). Resting human NK cells constitutively express a number of cytokine receptors and secrete immunoregulatory cytokines following receptor activation (5, 6). We have previously shown that the monocyte/macrophage-derived cytokines (monokines) IL-15 and IL-12 are potent costimulators of the CD8\(^+\) T cell, which exert their role at the level of viral entry. Here, we demonstrate that monokine-activated NK cells, isolated from both normal and HIV-1\(^+\) donors, produce similar amounts of MIP-1\(\alpha\), MIP-1\(\beta\), and RANTES protein, in vitro. Further, supernatants of monokine-activated NK cells obtained from both normal donors and AIDS patients showed potent (routinely \(\geq 90\%)\) suppressive activity against HIV-1 replication in vitro, compared with unstimulated control supernatants. NK cell supernatants inhibited both macrophage-tropic HIV-1\(_{N^F,N_S}\) and T cell-tropic HIV-1\(_{NL4,3}\) replication in vitro, but not dual-tropic HIV-1\(_{99,6}\). Importantly, the C-C chemokines MIP-1\(\alpha\), MIP-1\(\beta\), and RANTES were responsible only for a fraction of the HIV-1-suppressive activity exhibited by NK cell supernatants against macrophage-tropic HIV-1. Collectively these data indicate that NK cells from normal and HIV-1\(^+\) donors produce C-C chemokines and other unidentified factors that can inhibit both macrophage- and T cell-tropic HIV-1 replication in vitro. Since NK cells can be expanded in patients with HIV-1, AIDS, and AIDS malignancy in vivo, this cell type may have an important role in the in vivo regulation of HIV-1 infection. The Journal of Immunology, 1998, 161: 6433–6438.

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3 Abbreviations used in this paper: MIP; macrophage inflammatory protein; M-tropic, macrophage-tropic; T-tropic, T cell-tropic; HAB, human AB serum; rh, recombinant human; PE, phycoerythrin.

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Materials and Methods

Reagents

Purified recombinant human (rh) IL-15 was provided by Immunex Corporation (Seattle, WA). Purified rhIL-12 (sp. act., 4.5 × 10^4 U/mg) was obtained from Genetics Institute (Cambridge, MA). Purified rhIL-2 (spec. act., 18 × 10^6 U/mg) was obtained from Chiron (Emeryville, CA). All cytokines were reconstituted in sterile PBS with 0.1% human albumin (Nemour Pharmaceutical, Kankakee, IL). Neutralizing goat anti-human MIP-1α, MIP-1β, and RANTES polyclonal Abs were purchased from R&D Systems (Minneapolis, MN). Normal goat Ig was used as a control (R&D Systems). PE-conjugated anti-human CD56 mAb was purchased from Coulter Immunology (Hialeah, FL), and PE-isotype control mAb were purchased from Becton Dickinson (San Jose, CA).

Patients

Studies were performed on blood obtained after informed consent from seven HIV+ patients receiving highly active antiretroviral therapy (HAART), with HIV-1 RNA < 200 copies/ml of plasma by PCR. Blood was also obtained after informed consent from two patients with AIDS receiving ultra-low dose IL-2 therapy, as described (23).

Isolation of human NK cells

PBMC were obtained from patients with HIV-1 infection or AIDS, or from normal donors fresh leukocytes (American Red Cross, Columbus, OH) or Ficoll-Hypaque (Sigma, St. Louis, MO) density gradient centrifugation. Red blood cells were lysed, after which PBMC were washed twice in RPMI 1640 supplemented with 10% human AB serum (HAB, C-six Diagnostics, Mequon, WI), antibiotics, and anti-Phagocyte (Life Technologies, Grand Island, NY) (10% HAB), and cultured for 2 h in plastic tissue culture dishes to remove adherent monocytes. T cells, B cells, and remaining monocytes were depleted using goat anti-mouse immunomagnetic beads (PerSeptive Biosystems, Framingham, MA) and a combination of murine mAb reactive against CD3, CD20, and HLA-DR, as described (25). Non-depleted were then stained with CD56-PE mAb, washed in 10% HAB, and isolated by FACs for CD56+ NK cells on a Coulter ELITE flow cytometer (Coulter Immunology). Sorted CD56+ NK cells were routinely ≥97% pure by flow cytometric analysis.

Preparation of human NK cell-conditioned supernatants

Sorted CD56+ NK cells were cultured in 10% HAB at a density of 1 × 10^6 cells/ml in 96-well U-bottom plates. NK cells were then stimulated with IL-15 (10 ng/ml), IL-12 (10 U/ml), IL-15 plus IL-12, or no stimulus (medium alone control). After a 72-h incubation at 37°C in 5% CO2, culture supernatants were harvested, centrifuged to remove cells and debris, and stored at −80°C. In some experiments, sorted CD56+ NK cells were cultured as described above, but at a density of 5 × 10^5/ml.

Measurement of NK cell cytokine production

NK cell production of MIP-1α, MIP-1β, and RANTES was measured from cell-free culture supernatants utilizing commercial ELISA kits, following the manufacturer’s instructions (R&D Systems). RANTES levels were corrected for any background obtained from the culture medium (10% HAB, ≥250 pg/ml). Results represent the mean of duplicate wells ± SD.

Preparation of primary PBL targets

PBMC from normal donors were prepared as described above and cultured in 100-mm tissue culture dishes at a density of 15 × 10^6/ml in 10% HAB. After 2 h, nonadherent cells were removed, centrifuged, and resuspended in RPMI 1640 supplemented with 10% FCS and antibiotics (10% FCS), and incubated with phytohemagglutinin (PHA, 5 μg/ml; Sigma) for 2–3 days. PBL were next washed twice in RPMI 1640, resuspended in 10% FCS supplemented with 10 U/ml IL-2, and seeded (2 × 10^5 cells/well) into 96-well flat-bottom plates for infection assays. PBL were then used as targets for infection assays 0–2 days following IL-2 stimulation (3–5 days postincubation).

HIV-1 infection assays

PBL, prepared as described above were preincubated in 100% (v/v) NK cell-conditioned supernatants or controls, supplemented with 10 U/ml IL-2, for 1 h before infection. A molecularly cloned virus, HIV-1_DN-SS (26), encoding the envelope of the M-tropic isolate HIV-1_DN-SS (27), was then added to the wells at a final input of 0.5 ng/ml p24 in a total volume of 100 μl and incubated for 4 h at 37°C. Other viruses utilized included dual-tropic HIV-1_96/98 (28) (1 ng/ml p24) and T-tropic HIV-1_18L4-3 (29) (5 ng/ml p24). Target cells were then washed twice with RPMI 1640 to remove excess unbound virus, and the NK cell-conditioned supernatants (100% v/v) or controls in 10% HAB were replaced. PBL were then cultured for 14 days at 37°C. On days 6, 8, and 10 postinfection, half of the culture supernatant (50 μl) was harvested for p24 assessment and replaced with 10% HAB supplemented with 10 U/ml IL-2. Target cells were monitored for viability during the course of the infection assays by vital dye exclusion. To examine the effects of the C-C chemokines, some NK cell supernatants were preincubated of these chemokines with polyclonal neutralizing Abs (R&D Systems). Supernatants were first incubated with human chemokine-neutralizing Abs (anti-MIP-1α, anti-MIP-1β, and anti-RANTES, each at 2–50 μg/ml, concentrations able to neutralize ≥95% of their activity as determined by the manufacturer) or an equivalent amount of normal goat Ig (6–150 μg/ml) for 1 h at 4°C with gentle agitation. Protein G-Sepharose (Bio-Rad, Hercules, CA) was then added, and the supernatants were incubated with gentle agitation for an additional hour. The protein G-Sepharose was then pelleted by centrifugation, and the chemokine-neutralized supernatants were transferred to another microfuge tube without disturbing the Sepharose pellet. This clearing process resulted in monokine-stimulated NK cell supernatants with undetectable MIP-1α, MIP-1β, RANTES, and goat Ig protein by ELISA (data not shown). Target cells infected and cultured in fresh 10% HAB supplemented with 10 U/ml IL-2 and uninfected target cells were additional controls.

Detection of HIV-1 p24 production

Quantitation of HIV-1 p24 protein production in the supernatants of infected targets was performed using a commercial p24 Ag capture ELISA kit (AIDS Vaccine Program, Frederick, MD), following the manufacturer’s instructions.

Statistical analysis

Statistics were determined by using the Student t test, with p < 0.05 considered significant.

Results

Human NK cell supernatants contain abundant C-C chemokines

Human NK cells produce MIP-1α and a variety of cytokines in response to stimulation with the monokine combination IL-15 plus IL-12 (7, 9). We therefore assayed NK cells from normal donors and HIV+ patients for production of the known HIV-1-suppressive C-C chemokines MIP-1α, MIP-1β, and RANTES (13). Fig. 1 shows the levels of these C-C chemokines in NK cell culture supernatants obtained from normal (n = 8) and HIV-1+ (n = 7) donors (5 × 10^4 cells/ml). NK cells from HIV-1+ patients produced equivalent amounts of MIP-1α, MIP-1β, and RANTES in response to IL-15 plus IL-12, when compared with normal donors. Supernatants from NK cells activated with the combination of IL-15 plus IL-12 showed the greatest and most significant increase in MIP-1α (p < 0.0008) and MIP-1β (p < 0.0003), when compared with supernatants from NK cells cultured in medium alone. RANTES was measurable but not significantly different under any culture condition in NK supernatants from normal or HIV-1+ individuals (data not shown).

Human NK cell culture supernatants suppress HIV-1 replication in vitro

We next investigated the ability of supernatants from monokine-stimulated NK cells to inhibit HIV-1 replication in vitro. We used the M-tropic HIV-1_18L4-3 (26), which utilizes CCR5 as a coreceptor. The effect of normal donor NK cell supernatants on viral replication was assessed by comparing unstimulated (medium only) to monokine-stimulated NK cell supernatants. Supernatants from unstimulated and IL-15-stimulated NK cells produced high amounts of HIV-1 p24 by day 6 postinfection of target PBL (Fig. 2). Supernatants from IL-12-stimulated NK cells reduced HIV-1 p24 levels by approximately 50% (p < 0.03), compared with medium controls. However, PBL targets infected and cultured in supernatants from NK cells stimulated with IL-15 plus IL-12 demonstrated ≥95% decrease in p24 production, compared with...
medium controls ($p < 0.0005$). We also quantitated the levels of C-C chemokines in the IL-15 plus IL-12-stimulated NK cell supernatants (cultured at $1 \times 10^6$ cells/ml) shown in Fig. 2, and the mean ± SD of MIP-1α and MIP-1β levels by ELISA. Results represent the mean ± SD of eight normal donors and seven HIV+ patients. There was no significant difference between normal and HIV+ donor NK cell production of these C-C chemokines in response to IL-15 plus IL-12. There was a significant increase in the production of MIP-1α and MIP-1β ($*, p < 0.008$) by IL-15 plus IL-12-stimulated NK cells from both HIV-1+ and normal donors, compared with unstimulated (medium) controls.

**NK Cell Culture Condition**

![FIGURE 1. Monokine-stimulated NK cells purified from normal donors and HIV+ patients produce abundant C-C chemokines in vitro. Human NK cells were isolated by FACS (≥98% purity), plated at $5 \times 10^4$/ml, and stimulated with medium (control), IL-15, IL-12, or IL-15 plus IL-12. After 72 h, cell-free culture supernatants were harvested and assayed for (A) MIP-1α and (B) MIP-1β levels by ELISA. Results represent the mean ± SD of eight normal donors and seven HIV+ patients. There was no significant difference between normal and HIV+ donor NK cell production of these C-C chemokines in response to IL-15 plus IL-12. There was a significant increase in the production of MIP-1α and MIP-1β ($*, p < 0.008$) by IL-15 plus IL-12-stimulated NK cells from both HIV-1+ and normal donors, compared with unstimulated (medium) controls.](image)

**FIGURE 2.** Monokine-stimulated NK cell culture supernatants inhibit HIV-1 replication in PBL targets in vitro. Human NK cells were cultured (1 × 10^6/ml) in medium, IL-15 and/or IL-12, for 72 h. PBL targets from healthy donors were preincubated (1 h) with the NK cell supernatants (100% v/v) and then infected with 0.5 ng/ml HIV-1NFN-SX. PBL targets were washed extensively after 4 h and again cultured with the NK cell supernatants. A, Culture supernatants were harvested at days 0, 6, and 8 postinfection and tested for p24 production by ELISA. Results shown are the mean of duplicate measures and are representative of three separate experiments. B, The percentage of p24 production of control supernatants (medium) was calculated at day 6 postinfection, and the mean ± SD of three separate experiments is shown. Supernatants from NK cells stimulated with IL-12 alone (**, $p < 0.027$) and IL-15 plus IL-12 ($*, p < 0.0005$) significantly decreased HIV-1 p24 production compared with medium controls.

**C-C chemokines are only partially responsible for suppression of HIV-1 replication observed with NK cell supernatants**

To directly verify that the inhibition by normal donor NK cell supernatants was also operating in HIV-1+ patients, we tested the supernatants of monokine-stimulated NK cells isolated from HIV-1+ patients for the ability to suppress HIV-1 replication in vitro. Extended leukopheresis of HIV-1+ patients for the purpose of this in vitro assay could not be justified on ethical grounds. Sufficient numbers of human NK cells were therefore isolated from two AIDS patients that had received s.c. ultra-low dose IL-2 ($1.2 \times 10^6$ IU/m^2/day) and, hence, had an expanded NK cell population (23). Supernatants from their NK cells that were activated by IL-15 plus IL-12 significantly decreased HIV-1 replication in vitro by ≥90%, compared with unstimulated control supernatants (Fig. 3, $p < 0.0024$). Likewise, identical supernatants obtained from monokine-activated NK cells of one HIV-1+ patient on highly active antiretroviral therapy (HAART) and not receiving IL-2 inhibited HIV-1 replication in vitro by ≥90% (data not shown).

**NK cell supernatants from patients with AIDS suppress HIV-1 replication in vitro**

To directly verify that the inhibition by normal donor NK cell supernatants was also operating in HIV-1+ patients, we tested the supernatants of monokine-stimulated NK cells isolated from HIV-1+ patients for the ability to suppress HIV-1 replication in vitro. Extended leukopheresis of HIV-1+ patients for the purpose of this in vitro assay could not be justified on ethical grounds. Sufficient numbers of human NK cells were therefore isolated from two AIDS patients that had received s.c. ultra-low dose IL-2 ($1.2 \times 10^6$ IU/m^2/day) and, hence, had an expanded NK cell population (23). Supernatants from their NK cells that were activated by IL-15 plus IL-12 significantly decreased HIV-1 replication in vitro by ≥90%, compared with unstimulated control supernatants (Fig. 3, $p < 0.0024$). Likewise, identical supernatants obtained from monokine-activated NK cells of one HIV-1+ patient on highly active antiretroviral therapy (HAART) and not receiving IL-2 inhibited HIV-1 replication in vitro by ≥90% (data not shown).

**C-C chemokines are only partially responsible for suppression of HIV-1 replication observed with NK cell supernatants**

To assess whether the measured C-C chemokines were responsible for the observed suppression of HIV-1 replication, we utilized neutralizing Abs to MIP-1α, MIP-1β, and RANTES to block their...
effects on HIV-1 replication. Fig. 4 shows that the inhibition of p24 production by stimulated NK cell supernatants could be only partially abrogated by preclearing with neutralizing Abs against MIP-1α, MIP-1β, and RANTES, compared with supernatants mock cleared with an equal amount of nonreactive goat Ig. To insure that partial abrogation was not a result of insufficient amounts of the neutralizing Abs, the experiment was repeated using a 25-fold excess of the concentrations necessary to neutralize the measured amounts of chemokines present in the supernatants and yielded similar results (data not shown).

**Stimulated NK cell supernatants inhibit the replication of HIV-1NL4-3, but not HIV-189.6**

We also examined the effects of NK cell supernatants on the replication of two additional HIV-1 strains, the T-tropic HIV-1NL4-3 that utilizes CXCR4 as a coreceptor for entry and the dual-tropic HIV-189.6 that can utilize either CCR5 or CXCR4 as a coreceptor, as well as several other potential HIV-1 coreceptors (30). Supernatants from NK cells costimulated with IL-12 alone inhibited HIV-1NL4-3 by approximately 50%, compared with unstimulated control supernatants (Fig. 5, p, 0.0013). However, identical monokine-stimulated NK cell supernatants isolated from HIV-1+ patients, or AIDS patients receiving ultra-low dose IL-2 therapy, were not able to significantly inhibit the replication of HIV-189.6, compared with controls.

**Discussion**

Monokine-stimulated human NK cells have been previously shown to produce several cytokines and the C-C chemokine MIP-1α in vitro (7, 9). In this report, we demonstrate that monokine-stimulated NK cells, isolated from HIV-1+ donors, also produce the C-C chemokines MIP-1α and MIP-1β in amounts equivalent to normal donors. Therefore, human NK cells from normal donors and HIV-1+ patients inhibit HIV-1 infection in vitro.

**FIGURE 3.** Monokine-stimulated NK cell supernatants from two AIDS patients receiving ultra-low dose IL-2 therapy inhibit HIV-1NFN-SX replication in vitro. Infection culture supernatants were harvested at days 6 and 10 postinfection (p.i.) and assayed for p24 production by ELISA. Results are representative of two separate experiments and presented as the mean p24 (ng/ml) from duplicate measures.

**FIGURE 4.** Neutralizing Abs to MIP-1α, MIP-1β, and RANTES only partially block NK cell supernatant inhibition of HIV-1 replication. In vitro infection assays were performed with HIV-1NFN-SX as in Fig. 2, with the exception of preclearing the NK cell supernatants with the indicated neutralizing Abs as described in Materials and Methods. Infection culture supernatants were harvested at days 6 and 10 postinfection (p.i.) and assayed for p24 production by ELISA. Results are representative of two separate experiments and presented as the mean ± SD of duplicate measures.

**FIGURE 5.** Supernatants from monokine-stimulated NK cells inhibit HIV-1NL4-3, but not HIV-189.6, in vitro. Infection assays were performed as described in Fig. 2 and Materials and Methods, with the T-tropic HIV-1NL4-3 and dual-tropic HIV-189.6. A and C, The amount of HIV-1 p24 was quantitated at days 0, 6, and 10 postinfection with HIV-1NL4-3 or HIV-189.6. Results are representative of two separate experiments and presented as the mean p24 (ng/ml) from duplicate measures. B and D, There was a significant decrease in percentage of HIV-1 p24 produced in the IL-15 plus IL-12-stimulated NK cell supernatants when infected with HIV-1NL4-3 at day 6 postinfection (p < 0.002), while there was no significant difference observed with HIV-189.6, when compared with medium controls.
We next investigated whether the measured C-C chemokines present in the NK cell supernatants were responsible for the observed suppression of HIV-1 NFN-SX replication in PBL targets. Interestingly, these known inhibitors of M-tropic HIV-1 replication were only partially responsible for the HIV-1 suppression from the stimulated NK cell supernatants. These data suggest that other factors produced by monokine-stimulated NK cells inhibit M-tropic HIV-1 infection in our assay system. Possible candidates would include unidentified C-C chemokines, which may be able to block HIV-1 NFN-SX infection via binding to CCR5, as well as other factors yet to be fully characterized (31). Since IL-15 plus IL-12-stimulated human NK cells are potent producers of IFN-γ and TNF-α (7), experiments are currently underway to evaluate their role in the HIV-1-suppressive effect of these supernatants. In addition, supernatants from stimulated NK cells significantly inhibited the replication of T-tropic HIV-1NL4-3. This observation suggests that factor(s) produced by NK cells may inhibit the usage of CXCR4 as a coreceptor for viral entry by T-tropic HIV-1, or that NK cell supernatants also exert suppressive action at another point in the viral life cycle. To our knowledge, human NK cells have not yet been shown to produce a C-X-C chemokine that binds to CXCR4, and experiments are ongoing to identify such CXCR4 chemokine ligands within monokine-stimulated NK cell supernatants. One explanation why supernatants from stimulated NK cells were unable to inhibit dual-tropic HIV-1NL4-3 may involve its use of many coreceptors for entry, including CXCR4, CCR5, CCR3, and CCR2b (30). In this scenario, factors within NK cell supernatants may not be able to block all possible coreceptors for HIV-1NL4-3.

Since the identification of chemokine receptors as coreceptors for HIV-1 entry (14, 15, 17), and ability of chemokine ligands to block entry (13, 18, 19), several studies have examined their importance in the pathogenesis of HIV-1 infection. Studies have demonstrated that individuals homozygous for a 32 bp deletion in the CCR5 gene are resistant to HIV-1 infection, while heterozygous individuals have slower progression to AIDS (33–36). Additionally, high-risk individuals who are multiply exposed, yet remain uninfected, have been shown to produce high levels of C-C chemokines (37). These studies highlight the importance of CCR5 interaction with its natural ligands and M-tropic HIV-1 in the natural history of HIV-1 infection.

Ultra-low dose IL-2 therapy has been shown in phase I and phase II trials to selectively expand CD56+ NK cells in vivo in patients with AIDS and AIDS malignancy (21, 23). Here, we show that NK cells obtained from these patients can be stimulated to suppress HIV-1 replication in vitro. Thus, the IL-2-expanded NK cell may be an endogenous source of C-C chemokines and, through the elaboration of these and possibly other factors, may contribute to defense against HIV-1 infection in patients receiving ultra-low dose IL-2 therapy.

Note Added in Proof. A recent report by Oliva et al. (38) described a similar role for NK cell suppression of HIV-1 infection in vitro.

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References


