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Increased Natural Killer Cell Activity in Viremic HIV-1 Infection

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NK cells are a subset of granular lymphocytes that are critical in the innate immune response to infection. These cells are capable of killing infected cells and secreting integral cytokines and chemokines. The role that this subset of cytolytic cells plays in HIV infection is not well understood. In this study, we dissected the function of NK cells in viremic and aviremic HIV-1-infected subjects, as well as HIV-1-negative control individuals. Despite reduced NK cell numbers in subjects with ongoing viral replication, these cells were significantly more active in secreting both IFN-γ and TNF-α than NK cells from aviremic subjects or HIV-1-negative controls. In addition, NK cells in subjects with detectable viral loads expressed significantly higher levels of CD107a, a marker of lysosomal granule exocytosis. The expression of CD107a correlated with NK cell-mediated cytokine secretion and cytolytic activity as well as with the level of viral replication, suggesting that CD107a represents a good marker for the functional activity of NK cells. Finally, killer Ig-related receptor+ NK cells were stable or elevated in viremic subjects, while the numbers of CD3+CD56+CD94+ and CD3+CD56+CD161+ NK cells were reduced. Taken together, these data demonstrate that viremic HIV-1 infection is associated with a reduction in NK cell numbers and a perturbation of NK cell subsets, but increased overall NK cell activity. *The Journal of Immunology, 2004, 173: 5305–5311.

Natural killer cells are a subset of lymphocytes uniquely designed to respond to infection (viral, bacterial, and parasitic) and to tumor cells (1–4) without prior Ag sensitization. NK cells eliminate virally infected cells following the integration of complex signals from an arsenal of inhibitory and activating receptors upon ligation to several classical and nonclassical MHC on the surface of their targets (3, 5, 6). In addition, NK cells are critical in the interplay between the innate and adaptive immune response to infection as these granular lymphocytes are an important early source of cytokines and chemokines (IFN-γ, GM-CSF, TNF-α, RANTES, and MIP-1α) that can help drive the ensuing adaptive immune response (7–9).

Studies assessing NK cell numbers and function in HIV-1 infection have resulted in conflicting results. Early work demonstrated that NK activity was seriously impaired in HIV-1-infected individuals despite the presence of normal NK numbers (10). More recent studies have demonstrated both reduced or enhanced cytolytic activity of NK cells in HIV-1 infection (9, 11–13). As a consequence of these conflicting data, the role of this subset of lymphocytes in eliminating infected cells, as well as in producing antiviral cytokines during HIV-1 infection, remains unclear. The strongest data supporting a role for NK cells in HIV-1 infection comes from a recent study demonstrating a significant association between the coexpression of a particular NK cell receptor, KIR3DS1, and its cognate ligand, Bw4, with a particular amino acid at residue 80, and slower HIV-1 disease progression (14). These data suggest that NK cells recognizing a particular class of MHC class I B molecules may play a critical role in the containment of HIV-1 replication and provides the impetus to characterize and dissect the role of the different NK cell subsets in the context of HIV-1 infection in more detail.

In this study, we characterized different NK cell subsets in HIV-1-infected subjects with treated and untreated infection, as well as in HIV-1-negative controls. We applied an array of sensitive techniques, including the quantification of intracellular cytokines, the measurement of NK cell-mediated cytoxicity, and the expression of CD107a, that is associated with the release of lytic lysosomal vesicles following stimulation (13, 15, 16), to assess NK cell function. Our results suggest that despite a significant reduction in NK cell numbers in the context of ongoing HIV-1 replication, NK cell function is significantly enhanced in viremic-infected individuals, compared with individuals with treated, suppressed infection or HIV-1-negative controls. The reduction in NK cell numbers was mostly evident in the CD3+/CD56+/CD161+ and CD3+/CD56+/CD94+ NK cell compartment, while killer Ig-related receptor (KIR)3+expressing NK cells were stable or slightly elevated. Taken together, these data demonstrate major perturbations in NK cell numbers and function during viremic HIV-1 infection that normalize following successful reduction of viral replication with highly active antiretroviral therapy (HAART).

Materials and Methods

Study subjects

In this study, we report data on 40 subjects, 11 of which were HIV-1-uninfected controls. Of the 29 HIV-1-infected subjects, all were in the chronic phase of the disease, having been infected for more than 1 year (Table 1). Nine subjects were treated with HAART for at least 6 mo, and had undetectable viral loads (<50 copies per milliliter). Ten subjects were untreated and had viral loads ranging from 1,800 to 100,000 copies per

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3 Abbreviations used in this paper: KIR, killer Ig-related receptor; HAART, highly active antiretroviral therapy; LAMP, lysosome-associated membrane protein.
milliliter; the remaining 10 individuals were undergoing therapy but had active viral replication ranging from 12,400 to 95,000 copies per milliliter (% NS, compared with untreated individuals). Characteristics of the study subjects are shown in Table I. There were no significant differences between the age and the distribution of sexes among the four different groups studied, but viremic subjects had significantly lower CD4+ T cell counts than treated aviremic individuals (p = 0.01). The Massachusetts General Hospital Institutional Review Board (Boston, MA) approved the study, and each subject gave informed consent for participation in the study.

Intracellular cytokine staining

The frequency of cytokine-secreting NK cells was quantitated by intracellular cytokine staining. PBMCs were resuspended at 10^6 cells/ml in RPMI 1640 (Sigma-Aldrich, St. Louis, MO), 2 mM l-glutamine (Mediatech, Herndon, VA), and 10% FBS (Atlanta Biologicals, Norcross, GA), 2% CO_2, 50 IU/ml penicillin (Mediatech), and 50 IU/ml penicillin (Mediatech). Cells were then stimulated with MHC-devoid targets, K562 cell line (American Type Culture Collection (ATCC), Manassas, VA), at an E:T ratio of 5:1, and medium alone served as the negative control. Cells were incubated for 1 h at 37°C in 5% CO_2, after which brefeldin A (Sigma-Aldrich) was added at a final concentration of 10 μg/ml and incubated for an additional 3 h at 37°C in 5% CO_2. PBMCs were stained for surface NK cell markers (CD16, CD161, CD94, KIR2DL1, KIR2DL2, KIR2DL3, or KIR3DL1)-FITC, CD56-PE, and CD3-PerCP (BD Biosciences, San Jose, CA) for 30 min. Samples were fixed and permeabilized according to manufacturer’s directions (Caltag Laboratories, Burlingame, CA), and stained for intracellular IFN-γ-allophycocyanin or TNF-α-allophycocyanin (BD Biosciences, San Jose, CA) for an additional 30 min. After washing, cells were resuspended in 1% paraformaldehyde (Sigma-Aldrich) until four-color flow cytometric analysis was performed on a FACSCalibur instrument (BD Biosciences). Fifty to 200,000 events were acquired and analyzed using the FlowJo software (Tree Star, San Carlos, CA).

CD107a (lysosome-associated membrane protein (LAMP)-1) expression assay

Degranulation of intracellular vesicles by lymphocytes can be measured using CD107a, as described recently for CD8+ T cells (17). In this study, we used CD107a expression to determine the frequency of degranulating NK cells following stimulation. Similar to the procedure described above for cytokine staining, 10^6 PBMCs were resuspended in RPMI 1640 (Sigma-Aldrich) containing 10% FBS (Atlanta Biologicals, Norcross, GA), 2 mM l-glutamine (Mediatech), and 50 IU/ml penicillin (Mediatech), and stimulated with MHC-devoid targets, K562 cell line (ATCC), at an E:T ratio of 5:1, and medium alone served as the negative control. CD107a-PECy5 Ab (BD Biosciences) was added directly to the stimulation tubes at 20 μg/ml. Following 1 h of incubation at 37°C in 5% CO_2, 6 μl of m-phenensin (Golgi-block; BD Biosciences) was added for a final concentration of 6 μg/ml and incubated for an additional 5 h at 37°C in 5% CO_2. Samples were then surface-stained using NK markers (CD16, CD161, CD94, KIR2DL1, KIR2DL2, KIR2DL3, and KIR3DL1)-FITC, CD56-PE, and CD3-allophycocyanin (BD Biosciences) for 30 min. After washing, cells were resuspended in 1% paraformaldehyde (Sigma-Aldrich) until multi-color flow cytometric analysis was performed on a FACSCalibur instrument (BD Biosciences). Fifty to 200,000 events were acquired and analyzed using FlowJo software (Tree Star). The background activity ranged from 0.05–3.8% of NK cells, with a mean percentage of 2.3% and a SD of 1.26%. Thus, a positive response was defined as the percentage of CD107a expression, following subtraction of the background activity that was three SDs above mean background activity, as defined for all subjects tested.

Chromium release assay

The ability of NK cells to lyse MHC-devoid target cells was examined using a standard chromium release assay (18). K562 cells were labeled with 50 μCi Na_2^{105}CrO_4 (1 Ci = 37 GBq; Perkin Elmer, Boston, MA) for 1 h at 37°C, 5% CO_2. PBMCs were added as effectors at an E:T ratio (E/R) of 50:1. The supernatant was harvested after a 4-h incubation at 37°C and 5% CO_2. The percent lysis was calculated as: ((sample count – spontaneous release)/(maximal release – spontaneous release)) × 100.

Statistical analysis

Unpaired Student’s t tests were used to assess differences in the number and function of NK cells and their subsets between the four groups. Spearman correlation was used to examine the relation between the immune response and a number of clinical and immunological parameters. Values of p < 0.05 were considered significant.

Results

Significant reduction in NK cell numbers in viremic HIV-1 infection

Controversial data have been reported on changes in the number of NK cells in HIV-1 infection (9, 13, 19, 20). To assess the impact of HIV-1 replication on the number of NK cells, we compared the percent of CD3−/CD56+ cells in chronically HIV-1-infected subjects with ongoing viral replication to HAART-treated individuals with suppressed viremia (<50 copies HIV-1 RNA per milliliter of plasma) and HIV-1-uninfected individuals. As shown in Fig. 1, HIV-1-infected individuals with ongoing viral replication had significantly reduced numbers of CD3−/CD56+ NK cells compared with HIV-1-negative controls. Additionally, absolute NK cell numbers were similarly reduced in viremic subjects, to a median of 49 CD3−/CD56+ NK cells per microliter of blood (range 3–324

![FIGURE 1. Proportion of NK cells among the four groups under study measured as the percentage of CD3−/CD56+ cells by flow cytometric analysis. The dot plot represents the number of NK cells for HIV+ treated; HIV− untreated; HIV+ treated viremic; and HIV− controls.](http://www.jimmunol.org/Downloadedfromhttp://www.jimmunol.org/)
NK cells per microliter of whole blood), as compared with aviremic subjects, who had a median of 190 CD3−/CD56+ NK cells per microliter of blood (76–423 NK cells per microliter of blood, \( p = 0.03 \)). Furthermore, in HIV-1-infected individuals with suppressed viremia, NK cell numbers normalized to levels similar to those seen in HIV-1-uninfected subjects. The proportion of NK cell numbers were also reduced in the context of ongoing viral replication in subjects receiving HAART in whom antiretroviral therapy failed to fully suppress viral replication (Fig. 1), suggesting that the normalization of NK cell numbers in treated, suppressed individuals was directly due to the reduction in viremia. Taken together, these data demonstrate a significant reduction in CD3−/CD56+ NK cell numbers in viremic HIV-1 infection.

Changes in NK cell function during HIV-1 infection

HIV-1 infection has been demonstrated to result in Nef-mediated down-regulation of HLA class I A and B molecules on infected cells, which serves as an activating signal to NK cells (21–24). Therefore, we decided to use HLA class I-devoid K562 cells to assess the functional capacity of NK cells to secrete antiviral cytokines in treated and untreated HIV-1 infection, as well as in HIV-1-negative subjects. Following stimulation with K562 cells, NK cells from HIV-1-infected viremic subjects secreted substantial amounts of IFN-γ and TNF-α, while NK cells from treated HIV-1-infected individuals with undetectable viremia only exhibited low levels of cytokine secretion, as exemplified by two characteristic subjects in Fig. 2A. Overall, despite reduced NK cell numbers in infected subjects with ongoing viral replication, NK cells from these subjects responded with significantly stronger cytokine production than NK cells from HIV-1-infected individuals with suppressed viremia and uninfected controls (Fig. 2). Secretion of IFN-γ following stimulation was significantly elevated in untreated subjects (\( p < 0.001 \)) and treated but viremic subjects (\( p < 0.001 \)) as compared with HIV-1-infected subjects with undetectable viral replication (Fig. 2B). Similarly, the ability to secrete TNF-α in response to K562 cells was significantly increased in untreated (\( p < 0.001 \)) and treated but viremic HIV-1-positive subjects (\( p < 0.001 \)). Taken together, these data demonstrate increased cytokine secretion by NK cells following stimulation with MHC-devoid cells in the context of ongoing viral replication.

CD107a expression is a marker of NK activity in HIV-1 infection

Degranulation of intracellular vesicles by lymphocytes, reflecting their cytotoxic activity, can be measured using the marker CD107a (LAMP-1), as described recently for CD8+ T cells (17). We investigated the expression of CD107a on the surface of NK cells following incubation with MHC-devoid K562 cells in the context of viremic and aviremic HIV-1 infection. In the 40 study subjects, background CD107a expression in the absence of stimulation with K562 cells ranged from 0.05 to 3.8% of NK cells (mean of 2.3%). In contrast, CD107a expression after stimulation ranged from 6.8 to 29.2%, with a median of 17.4%, which was 7.6-fold above mean background expression (\( p < 0.001 \)). However, among the different study groups, we observed significant differences in the level of

**FIGURE 2.** Levels of IFN-γ and TNF-α secreted by NK cells among the four groups following a 6-h stimulation with K562 cells. A, Representative flow cytometric analysis for an HIV+ treated subject with suppressed viremia (left) and for a HIV+ untreated subject (right). B, Dot plots represent the percent-positive CD3−/CD56+ cells that secreted IFN-γ (left) or TNF-α (right) following a 6-h incubation with K562 cells at an E:T ratio of 10:1 for along the x-axis.
CD107a expression following stimulation with K562 cells. Representative flow cytometry data on the expression of CD107a for the same individuals as in Fig. 2A are present in Fig. 3A. Following a 6-h incubation with K562 cells, CD107a was dramatically upregulated on NK cells in the viremic subject, but to a lesser extent in the aviremic subjects. Comparison of the capacity of NK cells
to up-regulate CD107a following stimulation with K562 cells was performed in all 40 subjects (Fig. 3B). Analogous to increased cytokine secretion in subjects with ongoing replication, CD107a expression was significantly elevated in subjects with persistent viremia. This increased CD107a expression normalized to levels similar to HIV-1-uninfected controls following viral suppression in subjects with undetectable viral loads on HAART. Thus, similar to cytokine secretion, CD107a expression following stimulation was enhanced in the context of ongoing viral replication. Moreover, this marker correlated significantly with both IFN-γ (r = 0.6, p < 0.001) and TNF-α (r = 0.67, p < 0.001) secretion of NK cells (Fig. 3C). More importantly, CD107a expression was significantly associated with the level of NK cell-mediated target cell lysis (r = 0.68, p = 0.004; Fig. 3D).

We next attempted to assess the impact of the level of viral replication or CD4+ T cell count on NK activity determined by cytokine secretion and CD107a expression in the 20 subjects with detectable viral loads. No correlation between any of the functional NK cell readouts and CD4 counts was observed (data not shown). Although neither IFN-γ nor TNF-α appeared to correlate significantly with the level of viral replication, CD107a exhibited a significant relationship with viral load (Fig. 4: r = 0.7, p = 0.007). Overall, these data suggest that the expression of CD107a on NK cells is elevated in viremic HIV-1 infected individuals and represents a close marker of NK activity in HIV-1 infection.

Perturbation in the number and function of NK cell subsets during HIV-1 infection

Given the clear reduction but increased functional activity of NK cells in HIV-1-infected viremic subjects, an in-depth analysis was performed to assess potential perturbations within the different subsets of NK cells. Therefore, we characterized the proportion of NK cells expressing CD161; human NKR-P1A, a C-type lectin molecule located on the surface of 75–95% of NK cells (9); CD94, another C-type lectin molecule, located as a heterodimer with NKG2 on the surface of up to 90% of NK cells (3); as well as KIR molecules (KIR2DL1, KIR2DL2, KIR2DL3, and KIR3DL1) in the four groups under study. The proportion of KIR expressing NK cells was elevated in both groups that exhibited ongoing viral replication, yet the increase only reached statistical significance for the KIR2DL3-expressing subset of NK cells. In contrast, both CD94 (p = 0.01) and CD161 (p = 0.03) expressing CD3+/CD56+ cells were significantly reduced in the context of untreated persistent viral replication as compared with HIV-1 subjects with suppressed viral replication on HAART (Fig. 5A). These data illustrate perturbations in the different NK cell subsets in the context of viremic HIV-1 infection.

To investigate potential functional disparities between the different NK cell subsets, we assessed the functional capacity of NK cell subsets for cytokine secretion and CD107a expression as described above. The ability of different NK subsets to produce IFN-γ following stimulation with K562 cells revealed a uniform increase in IFN-γ production across studied NK cell subsets in HIV-1-infected individuals with ongoing viral replication (Fig. 5B). Similarly, although the differences did not reach statistical significance, TNF-α secretion and degranulation (CD107a) expression were elevated across all subsets in the viremic groups as opposed to HIV-1-uninfected controls and subjects with suppressed viremia on HAART (Fig. 5, C and D). These data demonstrate that NK cell activity was increased across all NK cell subsets studied in the presence of HIV-1 replication.

Discussion

HIV-1 infection is characterized by high viral loads in acute infection that subsequently decline but persist over the course of infection at a replication “set point” (25). Although virus-specific CD8+ T cells have been shown to be critical in the control of viremia following acute infection, the innate immune response, and in particular NK cells may also play a crucial role in the control of viral replication before the development of adaptive immune responses, as described for several viral infections (2, 4, 5, 26). In addition, NK cell activity may complement the adaptive immunity throughout the course of infection, as suggested by a recent report demonstrating a significant association between slower HIV-1 disease progression and the coordinate expression of a particular KIR with a specific group of HLA-Bw4 molecules (14). In this study, we report decreased numbers of NK cells in subjects with persistent HIV-1 replication, yet these numbers appear to return to nearly normal levels in treated subjects with undetectable viral replication. Despite reduced NK cell numbers, we observed increased cytokine secretion as well as enhanced expression of CD107a in the setting of detectable viremia. Levels of CD107a correlated well with the level of viral replication in subjects with detectable viremia, indicating that this marker can serve as an indicator of the level of NK cell activity. Finally, further analyses of NK cell subset distributions among HIV-1-infected and -uninfected subjects revealed subset-specific perturbations in viremic subjects.

The observation of a decrease in CD3+/CD56+ NK cells in viremic subjects is in line with other studies describing a reduction of CD3+/CD56+/CD16+ NK cells in HIV-1 infection (20, 27, 28). In contrast, the maintenance of stable CD3+/CD161+ (9), as well as an increase in CD3+/CD56+/CD16+ cell numbers, have been reported in other studies (29). Although the exact proportion of NK cells within these subsets of CD3+/CD56+ leukocytes needs to be further determined, these discrepancies suggest that HIV-1 infection can have a differential impact on particular subsets of NK cells. When we performed subset-specific analyses of NK cell frequencies in this study, we observed a depletion of CD3+/CD56+ and CD3+/CD56+/CD16+ NK cells in viremic patients, while the frequency of KIR-expressing CD3+/CD56+ NK cells was either stable or increased. These data confirm that HIV-1 infection differentially alters the frequencies of particular subsets of CD3+/CD56+ NK cells. It remains unclear as to the mechanism by which NK cell depletion occurs. Although a single study suggested that direct infection of activated NK cells (30) may play a part in the loss of NK cells, a separate report demonstrated increased CCR5 expression on the surface of NK cells potentially contributing to the sequestration of NK cells in infected tissues.
In addition, general immune activation associated with HIV-1 infection may lead to increased apoptosis of NK cells, and thus, a depletion of this cell subset. Ultimately, given the large number of markers that are emerging to define the different NK cell subsets and to monitor changes in these subsets, these data emphasize the need to use multiparameter analysis to begin to elucidate the mechanisms that contribute to NK cell depletion in HIV-1 infection.

HIV-1 has developed several mechanisms by which to evade the host immune response, including HIV-1 Nef-mediated down-regulation of MHC class I A and B expression on the surface of infected cells (21–24). In this study, we chose to use MHC-devoid K562 cells to assess the impact of HLA down-regulation on the functional capacity of NK cells. Using K562 cells to stimulate NK cells, we observed increased cytokine secretion by NK cells in viremic HIV-1-infected subjects, while cytokine secretion returned to nearly normal levels under suppressive HAART. This increase in NK cell cytokine secretion following stimulation with MHC-devoid K562 cells contrasts with reported reduced IFN-γ and TNF-α secretion by NK cells in viremic subjects following a 6-h stimulation with PMA and ionomycin (9). These discrepancies in NK cell activity following stimulation with MHC-devoid cells or PMA/ionomycin may reflect distinct functions of NK cells. Although stimulation with MHC-devoid cells closely mimics the reduction of MHC class I A and B expression observed in HIV-1 infection, stimulation with PMA/ionomycin represents an unspecific stimulation aiming to measure the maximal capacity of NK cells to secrete cytokines. As overall CD3−/CD56− NK cell numbers are reduced in viremic HIV-1 infection, the maximal capacity of this subset of lymphocytes to respond to PMA/ionomycin may

![FIGURE 5. Changes in NK subset numbers and function in viremic and aviremic HIV-1 infection. Bar graphs represent the percent of CD3−/CD56− cells expressing various NK subset markers along the x-axis (A), that are able to secrete IFN-γ (B), are able to secrete TNF-α (C), or are capable of expressing CD107a (D) following a 6-h stimulation with K562 cells for HIV− treated (■), HIV− untreated (■), HIV− treated but viremic (■), or HIV− controls (■). * p < 0.05 for between group differences comparing viremic and aviremic groups for each NK subset.](http://www.jimmunol.org/)
be compromised, while the ability to specifically respond to MHC class I-devoid target cells appears to be enhanced.

Recently, a novel assay to assess the cytolytic potential of CD8$^+$ T cells has been described, measuring the expression of CD107a (LAMP-1) on the surface of cells (17). CD107a is a molecule that is located within membrane-bound lytic lysosomal vesicles containing proteins such as granzyme and perforin (15, 16), and the up-regulation of CD107a has been shown to occur in synchrony with the secretion of perforin. This data suggests that CD107a is a strong marker of cytolytic granule exocytosis. In this study, we assessed the expression of CD107a on NK cells in HIV-1-infected individuals and HIV-1-negative controls, and for the first time, demonstrate that CD107a is expressed on a large subset of NK cells following activation, and correlates significantly with both cytokine secretion, cytotoxic activity, as well as with viral replication, providing a novel marker to monitor NK activity.

Taken together, these studies of NK cell function in HIV-1-infected and HIV-1-negative individuals demonstrate that HIV-1 replication is associated with overall loss of CD3$^+$CD56$^+$ NK cells and perturbations in the individual NK cell subsets. Despite reduced numbers of NK cells, the activity of these cells was increased in viremic HIV-1 infection, but normalized with the successful reduction of viral replication with HAART.

Acknowledgments

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