Depletion of circulating natural type 1 interferon-producing cells in HIV-infected AIDS patients

Vassili Soumelis, Iain Scott, Ferdous Gheyas, Damien Bouhour, Gregoire Cozon, Laurent Cotte, Laurence Huang, Jay A. Levy, and Yong-Jun Liu

Natural interferon-α producing cells (IPCs) are a newly characterized blood cell type, which is the major source of type I interferons in antiviral innate immune responses. The relationship between the number of circulating IPCs, HIV disease progression, and the occurrence of HIV-related complications was investigated. The study of 25 healthy donors and 54 HIV-infected subjects demonstrated a direct correlation between blood IPC number, interferon-α production, and clinical state of HIV-infected subjects. Asymptomatic long-term survivors had increased IPC number and function relative to uninfected controls and infected individuals with progressive disease. IPC numbers were markedly reduced in AIDS patients developing opportunistic infections and cancer. A negative correlation was found between the IPC number in the blood and the HIV viral load, suggesting that IPCs are important in controlling HIV replication. This study provides the first evidence that IPCs are being affected during the course of HIV infection and suggests that these cells can play a vital role in the protection against opportunistic pathogens and cancer. (Blood. 2001;98:906-912)

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Introduction

A progressive reduction in CD4^+ T-helper lymphocytes is the main feature of HIV infection and leads to a depression in adaptive immunity. Innate immunity is also important in the host response to HIV infection and can be impaired during the course of this infection. Dendritic cells (DCs) can promote HIV transmission, and DC function and number decline with HIV infection. The effector functions of monocytes and macrophages, including phagocytosis and intracellular oxidative responses, can be found decreased in HIV-infected subjects and in cultured cells in the presence of HIV. Superoxide production by neutrophils as well as natural killer cell function as measured by the lymphokine-activated killer activity and responsiveness to interferon-α (IFN-α) have been shown to be defective in HIV-infected subjects.

An important part of the innate defense against virus is the production of the type I IFNs, IFN-α, and IFN-β. IFN-α/β not only directly inhibit HIV replication but also have important adjuvant effects on a variety of immune cell types, such as monocytes, natural killer cells, and T cells. The in vitro type I IFN production by total peripheral blood mononuclear cells (PBMCs) was shown to be impaired during the course of HIV infection, and this impairment was associated with the occurrence of opportunistic infections.

CD4^+CD11c^− lineage marker^− type 2 DC precursors (pre-DC2) were recently shown to be the natural IFN-α/β-producing cells in human blood. IPCs produce up to 1000 times more IFN-α than any other blood cell type in response to viral stimulation. Whether this impairment of IFN-α/β production in HIV-infected individuals is due to a functional defect or to a reduction in number of IPCs is not known.

In this study, we show that blood IPCs are severely decreased in AIDS patients but increased in asymptomatic long-term survivors (LTSSs). The drop in IPC number and a decrease in their induced IFN production are associated with the presence of opportunistic infections and active Kaposi sarcoma. Our findings bring a new insight into the physiopathology of HIV infection and identify the IPC count as a new parameter to monitor the status of the immune system of HIV-infected subjects.

Patients, materials, and methods

HIV-infected subjects

Fifty-four HIV-infected subjects were recruited from 3 centers: the University of California at San Francisco (UCSF), the San Francisco General Hospital, and the Hospices Civils de Lyon, France. This study was approved by the Committee for Human Research, UCSF. Subjects were enrolled consecutively, and the only inclusion criterion was a confirmed HIV-positive serology and a written informed consent. The following conditions, which can nonspecifically affect blood cell counts, were used as exclusion criteria: previous cytotoxic chemotherapy, splenectomy, hypersplenism, and blood transfusion within the past 4 weeks. After inclusion, a full medical history was taken and physical examination was performed. The following biological parameters were obtained: IPC count, complete blood differential, and CD4 count.

From the Department of Immunobiology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, CA; Department of Medicine, University of California San Francisco; Department of Biostatistics, Schering-Plough Research Institute, Kenilworth, NJ; Hospices Civils de Lyon, Lyon, France; San Francisco General Hospital, CA.

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V.S. and I.S. contributed equally to this work.

Correspondence: Jay A. Levy, University of California, School of Medicine, San Francisco, CA 94143-1270; e-mail: jalevy@itsa.ucsf.edu; or Yong-Jun Liu, DNAX, 901 California Ave, Palo Alto, CA 94304; e-mail: yong-jun.liu@dnax.org.

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count (CBC) and differential, CD4+ and CD8+ T-cell counts, and HIV RNA level. HIV-infected subjects were classified into 3 clinical stages. The first stage was LTS and included subjects with persistent CD4+ T-cell counts more than 400 cells/µL, no antiretroviral therapy, and no clinical sign of disease for at least 10 years. The second stage was progressors and included patients who were either (1) undergoing antiretroviral therapy and presently had no AIDS-defining condition or (2) had CD4+ T-cell counts less than 400 cells/µL and no AIDS-defining condition. For progressors receiving antiretroviral drugs, therapy was initiated when their CD4+ T-cell count dropped below 400 cells/µL. Three progressor patients were not treated despite CD4+ T-cell counts less than 400 cells/µL because of personal reasons or toxic side effects of the therapy. The third stage was AIDS and consisted of patients with an AIDS-defining condition according to the World Health Organization classification, including CD4+ T cells less than 200 cells/µL, present or previous opportunistic infections, or HIV-related neoplasms. The median age of the study population was 47 years (range: 34-61), and the majority of the subjects (93%) were male homosexuals. Other characteristics are summarized in Table 1.

Healthy controls
Blood donors from the Stanford Medical School Blood Center were used as healthy controls. They were randomly enrolled and then matched for age and gender with the subject population. Twenty-five subjects met the matching criteria. They were all male, with a median age of 45 years (range: 34-60).

Quantification of blood IPCs
Blood was drawn from each study subject in an EDTA- or heparin-coated tube and analyzed within 3 hours. PBMCs were obtained by Ficoll Hypaque separation, washed twice, and resuspended in phosphate-buffered saline containing 2% fetal calf serum and 0.5 mM EDTA. PBMCs (106) were stained for 25 minutes with the following monoclonal antibodies: CD4-PE, CD3, CD14, CD16, CD20, all fluorescein isothiocyanate (FITC) conjugated for 25 minutes with the following monoclonal antibodies: CD4-PE, CD3, CD14, CD16, CD20, all fluorescein isothiocyanate (FITC) conjugated (Becton Dickinson, San Jose, CA), and CD11c-FITC (Caltag, South San Francisco, CA). Cells were fixed in 1% paraformaldehyde and a 2-color flow cytometric analysis (FACS) was performed. After setting the R1 gate on total viable PBMCs, 105 events were acquired through R1 and the flow cytometric analysis (FACS) was performed. After setting the R1 gate on the lymphocyte population. For the healthy donors, CD4+ T cells were quantified as the percentage of CD4 high FITC high cells on the IPC staining profile (Figure 1A). The absolute number of blood IPCs was calculated by using the percentage of cells in relation to the lymphocyte and monocyte count as determined by the automated differential blood count. For each sample, the FACS analysis to determine the percentage of IPCs was performed blinded to the subject’s clinical status. A second analysis was performed independently by another investigator and gave comparable results (data not shown).

Giemsa staining of purified IPCs
The same staining procedure as for IPC quantification was used to sort the CD4+FITC+ cells from undepleted PBMCs. Cytospins of the sorted cells were air dried, fixed in methanol, and stained with Giemsa for cytological analysis.

IFN-α production
The capacity of total PBMCs to produce IFN-α was assessed by culturing 2 × 10⁵ freshly separated PBMCs with 1 plaque-forming unit (PFU)/cell herpes simplex virus type 1 (HSV-1; Kos strain, γ-irradiated; obtained from Robert Chase, Schering-Plough, Kenilworth, NJ) in 96-well round-bottom plates. For purified IPCs, cells were cultured at 4 × 10⁴ cells/well with 10 PFU/cell of HSV-1. Culture supernatants were harvested after 24 hours and stored at −80°C until analyzed. IFN-α protein was measured by sandwich enzyme-linked immunosorbent analysis (Biosource, Camarillo, CA) in duplicate. Type-I IFN activity was measured by a bioassay that quantified the capacity of either the supernatant or an IFN-α standard (Schering-Plough) to protect A549 cells (American Type Culture Collection [ATCC], Manassas, VA) from the lysis induced by mouse encephalomyocarditis virus (ATCC). For this bioassay, each study sample was serially diluted. The viable A549 cells were quantified by using MTS staining (Promega, Madison, WI) and compared with an IFN-α standard curve.

HIV viral load
The HIV RNA level was measured in the serum from each subject sample, using the QUANTIPLEX bDNA method, version 3.0 (Bayer Diagnostics, Emeryville, CA). Results are expressed as the number of viral RNA copies/mL. The lower detection limit of the assay was 50 copies/mL. When statistical analysis was performed, values below 50 were assumed to be equivalent to 50 copies/mL.

Differential blood cell count
The complete differential blood cell count included red cell number, hemoglobin, total leukocytes, granulocytes, lymphocytes, monocytes, and platelets. The CBC for healthy donors was performed on a cell counter that measured the complete differential blood cell count. The differential blood cell count was measured by using the quadrant-stat function (Cellquest, Becton Dickinson, San Jose, CA). The 2 methods gave comparable results.

Lymphocyte subpopulations
The CD4+ and CD8+ T-cell counts were obtained for the subject samples by CD3/CD4+ and CD3/CD8+ double staining of lysed whole blood followed by flow cytometric analysis after gating on the lymphocyte population. For the healthy donors, CD4+ T cells were quantified as the percentage of CD4+FITC+ cells on the IPC staining profile (Figure 1A). The 2 methods gave comparable results.

Statistical analysis
Univariate one-way analyses of variance were performed on the data. The dependent variables were IPC count, CD4+ cell number, HIV RNA level (log₁₀), granulocyte, monocyte, and platelet counts. The group variable was HIV clinical stage. For each of these variables, all pairwise mean comparisons among HIV-infected groups were conducted by using step-down Bonferroni tests. SAS statistical package (SAS Institute, Cary, NC) was used for all computations. The P values are based on comparisons of group means throughout the study.
Results

Validation of a simple method to quantify blood IPCs

Our previous method for isolating IPCs from human tonsils or blood involved 3-color immunofluorescence flow cytometry cell sorting. For clinical applications, we modified this method to simplify quantification of IPCs in a small blood sample (2 mL). Undepleted PBMCs were directly analyzed for IPC number by 2-color immunofluorescence flow cytometry, consisting of anti–CD4-PE and a cocktail of FITC-conjugated antibodies to lineage markers (CD3, CD14, CD16, and CD20) and the DC marker CD11c (Figures 1A, 1B). To confirm that the CD4−/CD11c+ cells identified by this method were indeed IPCs, they were isolated by cell sorting and further characterized. First, the CD4−/CD11c+ cells displayed a typical phenotype (IL-3Rα+ and further characterized. First, the CD4−/CD11c+ cells displayed a typical phenotype (IL-3Rα+ and size profile (between lymphocyte and monocyte) of IPCs by flow cytometry (not shown). Second, the CD4−/CD11c+ cells on cytospin preparations all had a plasmacytoid morphology with herpes simplex virus-1 as compared to cultures in medium alone.

Blood IPCs are increased in asymptomatic LTSs but severely reduced in AIDS patients

With the use of the above procedure, the blood IPC number was quantified in 54 HIV-infected subjects, including 23 LTSs, 12 progressors, and 19 AIDS patients (Figure 2A). LTSs are HIV-infected subjects with normal CD4+ T-cell counts and no clinical sign of disease for at least 10 years following seroconversion. In this particular population, we found that the IPC count was higher (median: 8.89 cells/μL; range: 3.04-28.3) as compared to healthy controls (median: 5.5 cells/μL; range: 2.15-16.0) (Table 2). The difference was statistically significant ($P < .001$) (Figure 2A). As expected, the AIDS group also had the lowest CD4+ T-cell count and LTSs ($P < .001$ for all pairwise comparisons) (Table 2). The IPC count was comparable in progressors (median: 5.4 cells/μL; range: 2.4-10.09) to that noted in healthy controls (median: 5.5 cells/μL; range: 2.15-16; $P = .77$) (Table 2). The CD4+ T-cell count in progressors (median: 400 cells/μL; range: 231-925) was significantly lower than that of healthy controls (median: 680 cells/μL; range: 460-1350; $P = .58$) (Table 2 and Figure 2B).

In the AIDS patients, the IPC count was found markedly decreased, with a median of 1.38 cells/μL (range: 0-10.8) (Figure 2A). It was significantly lower than in healthy donors, progressors, and LTSs ($P < .001$ for all pairwise comparisons) (Table 2). As expected, the AIDS group also had the lowest CD4+ T-cell count (median: 47 cells/μL; range: 12-619; $P < .001$ for comparison of each group versus AIDS) (Figure 2B).

In the progressor and AIDS groups, 25% and 27% of the subjects, respectively, were not undergoing antiretroviral therapy. Because therapy could have an effect on IPC numbers, we performed a subgroup analysis to compare IPC numbers in subjects receiving or not receiving antiretroviral therapy. The mean IPC number was not statistically different between the treated and untreated subjects studied (6.75 and 5.11 IPC/μL, respectively, in progressors; 2.80 and 1.03 IPC/μL, respectively, in AIDS patients; $P > .05$). Nevertheless, the potential role of antiretroviral therapy on IPC number requires longitudinal studies that are in progress.

Figure 1. Validation of the flow cytometry method to quantify blood IPCs. (A) Total viable PBMCs were gated based on their forward and side scatter (left panel). After a 2-color staining with anti–CD4-PE and (CD3, CD14, CD16, CD20, CD11c)-FITC, IPCs were identified as CD4−/FITC+ cells (right panel). CD4+ T cells were identified as CD4+/FITC+ cells (right panel). For the IPC quantification, 10^5 PBMCs were analyzed and the percentage of cells was determined by using the quadrant-stat function (CellQuest). For purification of IPCs, CD4−/FITC− cells were sorted. (B) Purified IPCs display a typical plasmacytoid morphology on cytospin preparation after Giemsa staining (<100). (C) Purified IPCs produce high amounts of type I IFN following 24 hours' stimulation with herpes simplex virus-1 as compared to cultures in medium alone.
the complete differential blood counts in the clinical groups of subjects. The monocyte and granulocyte counts (Figure 3) as well as platelet and hemoglobin counts (not shown) were not significantly different among the healthy controls and the 3 HIV-infected groups (P > .05).

**Blood IPC count correlates negatively with the HIV viral load**

As shown by the quantification of IPCs in the different groups of HIV-infected subjects, IPCs are increased in the LTS group, which has the lower HIV viral load levels (median: 440 copies/mL; range: < 50-62 961), and are decreased in AIDS, where the higher viral loads are observed (median: 21 366 copies/mL; range: < 50-500 000; P < .01 for comparison of each group versus AIDS) (Figure 2C). We therefore determined the relationship between IPC counts and HIV viral load in the 54 HIV-infected subjects (Figure 4A). A statistically significant negative correlation was found between those 2 parameters (r = −0.347; P < .05), suggesting a role of IPCs in the control of HIV replication.

Because antiretroviral therapy can substantially affect the viral load independently of IPCs, we performed a separate analysis on the LTS group in which the subjects had not received antiretroviral therapy. LTS subjects with IPC counts greater than 10/μL had lower viral loads (median: 50 RNA copies/mL; range: 50-1632) as compared with LTS subjects with IPC counts less than 10/μL (median: 1357.5 RNA copies/mL; range: 50-62 961). The difference was statistically significant (P = .014), suggesting that IPCs could play a role in controlling HIV replication independent of any antiretroviral therapy.

**Blood IPC count correlates positively with the capacity of PBMCs to produce IFN-α**

Within the total 42 subjects studied for IFN-α production by PBMCs, a strong positive correlation was found between the IPC count and the in vitro IFN-α production by PBMCs in response to HSV (r = .77; P < .01) (Figure 4B). Importantly, subjects in the LTS group with very high IPC counts also had the highest IFN-α production in response to virus. This finding adds a functional basis to the high IPC counts observed in LTSs.

**Reduction in blood IPC count is associated with the presence of opportunistic infections**

Because of the key role of IPCs in innate immunity, we questioned whether the loss of this cell type was more specifically associated with the presence of opportunistic infections. Among the 19 patients in the AIDS group, 8 had an evolving opportunistic infection (4 Pneumocystis carinii; 2 disseminated cytomegalovirus [CMV]; 1 CMV retinitis; and 1 progressive multifocal leukoencephalopathy) (Figure 5, subject 4). The IPC count of the AIDS patients with an opportunistic infection (median: 1357.5 RNA copies/mL; range: 50-62 961) was lower than the IPC count of AIDS patients without opportunistic infection (median: 32/μL; range: 0.33-10.8). The difference was found highly significant (P < .01), suggesting that the decrease in circulating IPCs could be a predisposing factor for the development of infection by opportunistic pathogens.

Next, we questioned whether a cut-off value with a clinical relevance could be identified to define a low IPC number. On the basis of the distribution of the blood IPC number in the healthy control population, a value of 2 cells/μL was selected. Healthy donors all had blood IPC numbers greater than 2 cells/μL. Among HIV-infected subjects, 13 had less than 2 cells/μL of IPCs and were all found within the AIDS group (total of 19 patients), confirming the validity of the cut-off value. Of these 13 patients, 8 had an
Table 2. Circulating IPC, CD4⁺, and CD8⁺ T-cell numbers, and HIV RNA levels for each clinical subgroup

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy</th>
<th>LTS</th>
<th>Progressors</th>
<th>AIDS</th>
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<tbody>
<tr>
<td>IPC count (µL)</td>
<td>5.5 (2.15-16)</td>
<td>8.9 (3.04-8.3)</td>
<td>5.4 (2.4-10.1)</td>
<td>1.38 (0-10.8)</td>
</tr>
<tr>
<td>CD4 T cells (µL)</td>
<td>680 (347-1 926)</td>
<td>699 (460-1 350)</td>
<td>400 (231-1 350)</td>
<td>47 (12-619)</td>
</tr>
<tr>
<td>CD8 T cells (µL)</td>
<td>ND</td>
<td>974 (222-3 623)</td>
<td>909 (561-4 377)</td>
<td>683 (147-1 798)</td>
</tr>
<tr>
<td>Viral load (copies/mL)</td>
<td>ND</td>
<td>440 (&lt; 50-62 961)</td>
<td>1 145 (&lt; 50-107 188)</td>
<td>21 366 (&lt; 50-500 000)</td>
</tr>
</tbody>
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Results are indicated as median (range). IPC, type-1 interferon-producing cells; LTS, long-term survivors; ND, not determined.

Discussion

CD4⁺ T-helper lymphocytes are the major cells directly affected by HIV and are routinely used to monitor HIV-infected subjects. IPCs share 2 important characteristics with CD4⁺ T cells: (1) they express high levels of surface CD4 and (2) they can be found in blood, thymus, and secondary lymphoid organs where HIV is able to replicate actively. Moreover, they constitutively express the chemokine receptors CCR5 and CXCR4 (H Kanzler, unpublished data, 1999) that are the main coreceptors for HIV infection of a cell. These characteristics make IPC a potential target for HIV. In this study, using a rapid flow cytometric method (Figure 1), we show that the number of circulating IPCs can be used to monitor the immune system of HIV-infected subjects. The IPCs in the blood are markedly reduced in AIDS patients but increased in asymptomatic LTSs (Figure 2). The number of circulating IPCs correlates negatively with the HIV viral load and a decrease in IPC numbers is associated with the presence of opportunistic infections (Figure 2, Table 3).

From our series, an IPC count less than 2 cells/µL is highly specific for patients with AIDS. Longitudinal studies are now needed to define the predictive value of such a cut-off for the development of HIV-related complications.
LTSs (or long-term nonprogressors) form a particular group of HIV-infected subjects who remain asymptomatic for many years without any biological sign of disease. Several factors, both host and virus related, have been implicated in the resistance to disease progression. These include CCR5 and CCR5 promoter genotypes, heterozygosity (HLA class I loci), the presence of the HLA B*5701 allele, and CD8+ cytotoxic cells and noncytotoxic cellular immune responses. Besides the known antiviral and adjuvant effects of type I IFN, the type I IFN response represents a key factor in the resistance to HIV infection. In this study, we show that the circulating IPC number and their function are increased in LTSs and that LTSs with a low IPC number (Figures 2, 4). These findings strongly suggest that IPCs and the type I IFN response represent a key factor for the control of HIV replication in this particular population.

In AIDS patients, a low CD4+ T-cell count, reflecting impaired adaptive immunity, is thought to be the main factor favoring infection with opportunistic pathogens. In the present study, all the AIDS patients with opportunistic infections have a severe reduction of both blood IPCs and CD4+ T cells (Table 3). This observation is in accordance with early reports suggesting that concomitant impairment of the innate and adaptive immune system is responsible for the development of opportunistic infections, however, the IPC count and CD4+ T-cell count were found to be different in 3 situations. First, asymptomatic LTSs had higher IPC numbers than normal donors (P < .05) but similar CD4+ T-cell counts (Figure 2 and Table 2). Second, 3 HIV-infected subjects who had active Kaposi sarcoma were found to have normal CD4+ T-cell counts but a depletion of IPCs (<2/μL) (Figure 5). Third, 2 HIV-infected subjects who were classified as having AIDS because of a marked depletion of CD4+ T cells were found to have normal IPC counts (>2/μL) and were in a healthy clinical condition (Table 2 and Figures 2, 5). These 2 last cases represent rare individuals, and the results indicate important exceptions that merit further studies. Thus, the monitoring of both CD4+ cells and IPCs enable a more accurate evaluation of the immune system in HIV infection.

The fact that IPC loss is associated with the occurrence of various types of opportunistic infections suggests that the function of IPCs is not restricted to antiviral immunity. In our series of patients with IPC counts less than 2 cells/μL, 3 had active CMV infection, one had progressive multifocal leukoencephalopathy, and 4 had Pneumocystis carinii infection. These clinical observations fit with recent results (N Kadowaki, unpublished data, 2001) showing that nonviral stimuli, such as gram-positive bacteria and mycobacteria, can strongly induce IPCs to produce IFN-α in vitro.

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The identification of IPCs as being severely affected during HIV infection brings a new insight into the pathophysiology of HIV infection and could have important diagnostic and therapeutic implications. The combination of the IPCs with the CD4+ T-cell count should provide an optimal means to evaluate the immune function and to predict the occurrence of AIDS-related complications. Cell therapy or drugs increasing the number and/or function of IPCs could become an option in the future to control both HIV replication and HIV-related clinical conditions.

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