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# The Interleukin-2 Receptor Subunit Expression and Function on Peripheral Blood Lymphocytes from HIV-Infected and Control Persons

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**The expression of interleukin-2 receptor (IL2R) was studied on circulating lymphocytes from HIV-infected ($HIV^+$) and control subjects, using chain-specific monoclonal antibodies and indirect immunofluorescence flow cytometry. The IL2R α chain expression was decreased on CD4 and CD8 T cells from $HIV^+$ persons compared to controls. Conversely, β chain expression was enhanced on both T cell subsets from the patients. IL2R-subunit levels were similar on natural killer cells from patients and controls. To evaluate the function of IL2R, we investigated to what extent IL2 could induce CD69, an early activation marker of lymphocytes. A dose-dependent increase of CD69 expression was observed on T and NK cells from all subjects. The upregulation of CD69 was similar on CD4 T and NK cells from patients and controls, but was more pronounced on CD8 T cells from $HIV^+$ compared to $HIV^-$ subjects. Based on inhibition studies, both the α and the β chain contributed to the IL-2-induced CD69 expression on CD4 T cells, pointing to involvement of the high-affinity receptor. The early activation of CD8 T cells and NK cells was mainly dependent on the intermediate-affinity receptor. We conclude that significant changes in IL2R α and β chain expression on circulating T cells occur after HIV infection, but that early activation through IL2 is preserved or enhanced, even in advanced stages.** 

## INTRODUCTION

Three polypeptide chains composing the interleukin 2 receptor (IL2R),[1] have been described. The α chain (p55 or Tac antigen) has a low-affinity binding site for IL2 but displays no intracellular signaling capacity. The β chain (p75 antigen) and the γ chain (p64 antigen) separately do not bind IL2 but the β–γ heterodimer binds IL2 with an intermediate affinity. The α–β–γ heterotrimer constitutes the high-affinity receptor (1–4). Early immunofluorescence studies could demonstrate IL2R α (Tac) on activated but not on resting T cells (5). More recent studies have shown that the α chain is also expressed on peripheral blood lymphocytes, mainly CD4 T cells, whereas the β chain is prominent on almost all NK cells and on at least a proportion of resting CD8 T cells. The presence of the α chain on CD8 T and on NK cells and of the β chain on CD4 T cells remains controversial (6–13). At present, the distribution of the γ chain on lymphocyte subsets has not yet been studied because specific monoclonal antibodies (mAb) are not available.

Infection with the human immunodeficiency virus (HIV) is characterized by dysfunction and depletion of CD4 T cells, the major IL2 producers of the immune system. After *in vitro* activation, lymphocytes from symptomatic HIV seropositive ($HIV^+$) patients produce lower amounts of IL2, express less IL2R α and β mRNA, display less high-affinity IL2 binding sites, and show a lower proliferative response compared to control persons (14–16). The reduction of the IL2 production after activation has been ascribed to the action of HIV gene products such as gp120 and Nef (17, 18), whereas the diminished IL2R α upregulation seems to be mediated via an adherent cell-derived inhibitory factor (p29) (19).

Studies on the expression and function of IL2R α and β chains on freshly isolated lymphocytes from $HIV^+$ subjects have only been undertaken recently and the data are still fragmentary, especially with regard to the relative role of both chains in early activation events (20–22). We therefore decided to investigate both expression and function of IL2R α and IL2R β on T cells and NK cells from $HIV^+$ subjects and $HIV^-$ controls. As a functional index of IL2–IL2R interaction we measured the upregulation of the early activation marker CD69 (23–25). The relative contribution of the α and the β chain in this IL2-mediated process was evaluated in blocking experiments.

[1] Abbreviations used: FITC, fluorescein isothiocyanate; HIV, human immunodeficiency virus; $HIV^+$, seropositive for HIV; $HIV^-$, seronegative for HIV; IL2, interleukin 2; IL2R, interleukin 2 receptor; mAb, monoclonal antibody; PE, phycoerythrin.



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## SUBJECTS, MATERIALS, AND METHODS

### *Subjects*

All subjects were screened for HIV-specific antibodies with a recombinant HIV1/HIV2 ELISA (Abbott Diagnostics, Wiesbaden, Germany). Seropositivity was confirmed by Western blot (DuPont de Nemours, Singapore).

The HIV$^+$ group consisted of 59 adult Caucasian persons, recruited from the outpatient clinic at the Institute of Tropical Medicine in Antwerp, Belgium. They were clinically classified according to WHO criteria (26). Eighteen patients were asymptomatic (WHO1), 6 were paucisymptomatic (WHO2), 12 presented ARC symptoms (WHO3), and 18 had established AIDS (WHO4); the 5 others could not be classified. The HIV$^-$ group consisted of 40 healthy adult Caucasian blood donors from the Blood Tranfusion Center (University of Antwerp).

All blood samples were collected in EDTA-tubes (Cat. No. 04.1069 from Sarstedt, Nümbrecht, Germany) and processed within 6 hr. The fluorescence and functional experiments were not always done in parallel on the same blood, but in functional studies, patients from the different clinical stages and with different CD4 T levels were always represented. Their IL2R $\alpha$ and $\beta$ chain expression was also representative for the entire HIV$^+$ population.

### *Monoclonal Antibodies*

The original anti-Tac $\alpha$-chain-specific mAb was kindly provided by Dr. Thomas Waldman (National Institutes of Health, Bethesda, MD). Two IL2R $\beta$-specific mAb were used: the 2 R-B mAb was kindly donated by Dr. Takashi Uchiyama (Institute for Virus Research, Kyoto University, Japan) (27) and the TU27 mAb was produced by one of the authors (Dr. Kazuo Sugamura) (28, 29). Since all these mAb belong to the IgG1 subclass, we systematically used a control IgG1 containing ascites or purified antibody from clone 56D3, which is directed against an irrelevant parasitic antigen (kindly provided by Dr. J. Brandt from our Institute).

All other mAb used for immunofluorescence studies were purchased from Becton Dickinson (Erembodegem, Belgium) and also belonged to the IgG1 subclass.

### *Expression of the IL2R $\alpha$ and $\beta$ Chain on Resting Lymphocyte Subsets*

Indirect immunofluorescence studies were performed by adding first 0.1 $\mu$g of the unlabeled purified mAb 56D3, anti-Tac, or 2 R-B to 50 $\mu$l of whole blood. After 20 min of incubation at 4°C and a wash step, 1 $\mu$l of fluorescein (FITC)-conjugated F(ab')$_2$ goat anti-mouse IgG (Tago, Burlingame, CA) was added to the blood for another 20 min. After washing, remaining binding sites on the FITC conjugate were blocked with 10 $\mu$g of mouse IgG (purified from mouse serum). Next, 5 $\mu$l of phycoerythrin (PE)-labeled anti-CD4, anti-CD8, or anti-CD56 mAb was added for the last 20 min of incubation. Finally, the red blood cells were lysed (Becton Dickinson lysing solution) and the white cells were fixed (1% paraformaldehyde).

The samples were analyzed on a FACScan (Becton Dickinson) using the LYSIS I software. Lymphocytes were gated on the scattergrams and within this population a second subset-specific gate was defined, based on the PE marker expression. Thus bright CD4$^+$ and bright CD8$^+$ cells were selected separately, representing CD4 respective CD8 T lymphocytes. Anti-CD56-PE was used as a broad NK marker. One restriction of the latter marker is that some NK cells (CD16$^+$, CD56$^-$) are excluded and a small fraction of T cells (CD3$^+$, CD56$^+$) could be included. The binding of anti-IL2R $\alpha$, anti-IL2R $\beta$, and of control mAb was analyzed within the lymphocyte-subset gates and expressed as a percentage of positive cells.

### *IL2-induced Upregulation of CD69*

Whole blood was washed three times in $Ca^{2+}$ and $Mg^{2+}$ free balanced salt solution and once in complete culture medium consisting of 90% RPMI 1640 supplemented with penicillin 100,000 U/liter, streptomycin 100 mg/liter, 2 m*M* L-glutamine (all from GIBCO, Paisley, Scotland), and 10% iron-supplemented bovine calf serum from Hyclone (Logan, UT).

For each subset to be evaluated, cells from 50 $\mu$l blood reconstituted in complete medium were mixed with 50 $\mu$l medium alone or 50 $\mu$l medium containing recombinant human IL2 (sp act 2.5 MU/mg from Janssen Biochimica, Beerse, Belgium). In a first series of experiments the final IL2 concentration was 100 U/ml; in a second series a range of IL2 concentrations between 0.01 and 100 U/ml was used. The cells were incubated in round-bottom sterile tubes for 16 hr at 37°C. After washing, the expression of CD69 was evaluated, using a combination of anti-CD69–FITC or control IgG1–FITC with the PE-conjugated subset-specific mAb. In the dose–response experiments, CD56–PE was replaced by a mixture of CD16–PE, CD56–PE, and CD3 conjugated to Peridinin chorophyll protein. In the later combination NK cells can be precisely defined as the CD3$^-$ CD16 and/or CD56$^+$ cells.

### *Blocking of CD69 Upregulation*

The washed and reconstituted whole blood was first incubated for 30 min at 37°C with complete medium alone (2 tubes), 56D3 ascites final concentration (1/100), TU27 ascites (1/100 or 1/1000), purified anti-Tac (5 or 1 $\mu$g/ml), or anti-Tac 1 $\mu$g/ml and TU27 1/1000 together. In a first series of experiments IL2 was added at 100 U/ml in all cultures except one (medium con-

trol). In a second series, IL2 was added at 0, 1, 10, and 100 U/ml. After overnight incubation at 37°C, the cells were labeled with anti-CD69–FITC combined with PE-conjugated anti-CD4, anti-CD8, or anti-CD56.

The inhibition of IL2 induced CD69 expression in the different subsets was calculated as follows:

$$\% \text{ inhibition} = 1 - \frac{\text{CD69 (IL2)} - \text{CD69 (IL2 + mAb)}}{\text{CD69 (IL2)} - \text{CD69 (med)}} \times 100.$$

CD69 (med) = % $CD69^+$ cells in cultures with medium only

CD69 (IL2) = % $CD69^+$ cells in cultures with IL2 only

CD69 (IL2 + mAb) = % $CD69^+$ cells in cultures with IL2 and control or anti-IL2R mAb.

*Statistics and Graphical Representation*

Data on IL2R-subunit expression and IL2-induced CD69 upregulation were analyzed using nonparametric methods. The results of each group were summarized using the median value and the 25th and 75th percentiles or the confidence interval; the significance of differences between groups was calculated with the Mann–Whitney $U$ test. All statistics were calculated using the Statgraphics Version 2 program (Statistical Graphics Co., U.S.A.).

Representations of fluorescence histograms were created with PC LYSIS for Windows TM (Becton Dickinson) and orderly dispositioned with Paint-Brush for Windows (Microsoft, Seattle, WA). All other graphs were drawn using the Fig.P program (Biosoft, Durham, NC).

## RESULTS

*Lowered Expression of the IL2R α Chain and Enhanced Expression of the IL2R β Chain on T Cells from HIV-Infected Subjects*

Binding profiles of the IL2R α chain-specific anti-Tac and the β-chain-specific 2 R-B mAb on the lymphocyte subsets from one representative $HIV^-$ subject are shown in Fig. 1. Profiles in $HIV^+$ subjects were qualitatively similar. In general, the binding of anti-Tac tended toward a bimodal distribution with a more or less distinct negative and positive population. Compared to the control antibody, the 2R-B rather showed an asymmetric and limited shift in the fluorescence histogram of the CD4 and CD8 T cells. In order to compare our results with previously published data, we have chosen to estimate the IL2R expression as percentage of specific binding, by subtracting the percentage of cells reactive with the control mAb from the total percentage of cells binding to IL2R subunit mAb.

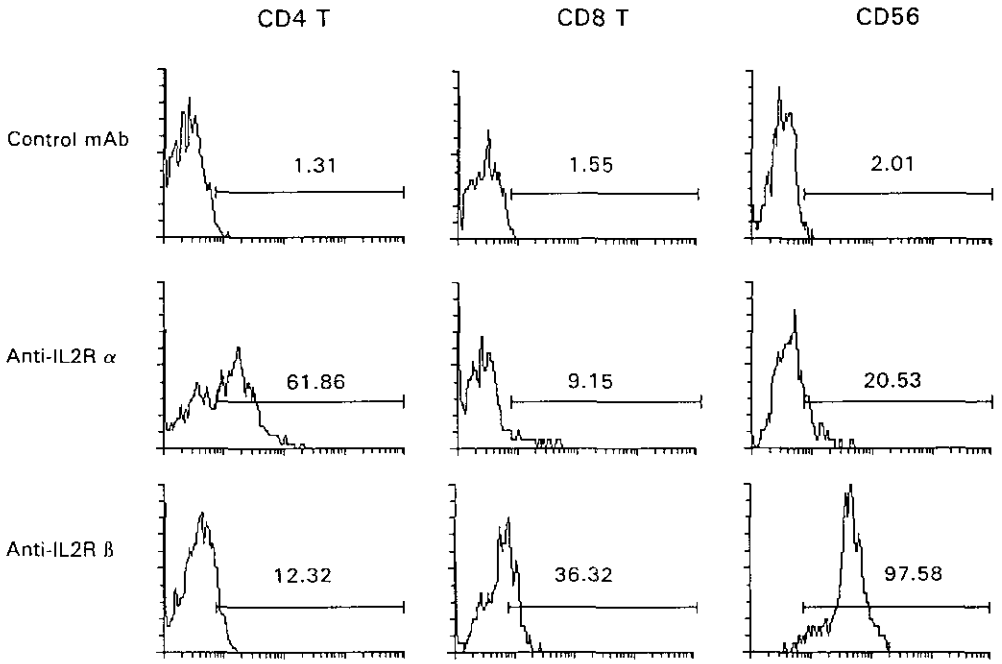


**FIG. 1.** Binding profiles of the control mAb (56D3), the anti-IL2R α (anti-Tac), and the anti-IL-2R β (2R-B) on lymphocyte subsets from a normal individual. The indicated subsets (CD4 T, CD8 T, and CD56) were gated with a specific PE-labeled mAb. Within this selected populations, the binding of the indirectly FITC-labeled control and IL2R-subunit-specific mAb was studied. The data are expressed as percentage of positive cells within each subset. The limit of positivity was channel 56 for all subsets.

In view of the relative weakness of the IL2R α signal on CD8 T cells and NK cells and of the IL2R β signal on CD4 T cells, the limit to discriminate background from specific binding was set narrowly. With this setting, the control mAb bound to less than 5% of the cells in each subset (1.5 ± 1% on T cells and 3 ± 1% on NK cells).

In seronegative subjects, about 55% of CD4 T cells, 12% of CD8 T cells, and 9.5% of CD56$^+$ cells expressed the IL2R α chain. Over 90% of CD56$^+$ cells from controls were clearly positive for the IL2R β subunit, whereas the estimated specific binding of IL2R β on CD8 T was about 35% cells and 10% on CD4 T cells. A considerable variation of IL2R-subunit expression on lymphocyte subsets, both from controls and seropositive subjects, was observed (Fig. 2).

Nevertheless, the comparison of IL2R-levels between controls and the entire HIV$^+$ group showed a significantly lower expression of IL2R α on both CD4 and CD8 T cells from the patients ($P < 0.01$ and $P < 0.001$). IL2R β expression, in contrast, was higher on the CD4 T cells ($P < 0.001$) and on the CD8 T cells ($P = 0.06$) from the seropositive group. Comparing IL2R subunit expression in the early (WHO 1 + 2) and late stages (WHO 3 + 4) of the disease indicated that IL2R β levels on CD8 T cells were significantly lower in the advanced stages ($P < 0.05$). The trends of decreasing IL2R α and increasing IL2R β expression on CD4 T cells from late-stage disease compared to earlier stages, seen in Fig. 2, were not significant.

No difference was found between IL2R α and β chain expression on CD56$^+$ cells from 13 patients, compared to 15 controls (data not shown).

### *Subset Sensitivity to IL2-Induced CD69 Upregulation in Lymphocytes from HIV-Infected and Uninfected Persons*

Whole blood from HIV$^-$ and HIV$^+$ subjects was cultured overnight in the absence or presence of IL2 100 U/ml. A representative profile of CD69 expression on resting and IL2-stimulated lymphocytes is shown in Fig. 3. In view of the brightness of the signal, the limit for positivity could be set on channel 70, which essentially excluded background binding of control IgG1–FITC even on stimulated cells.

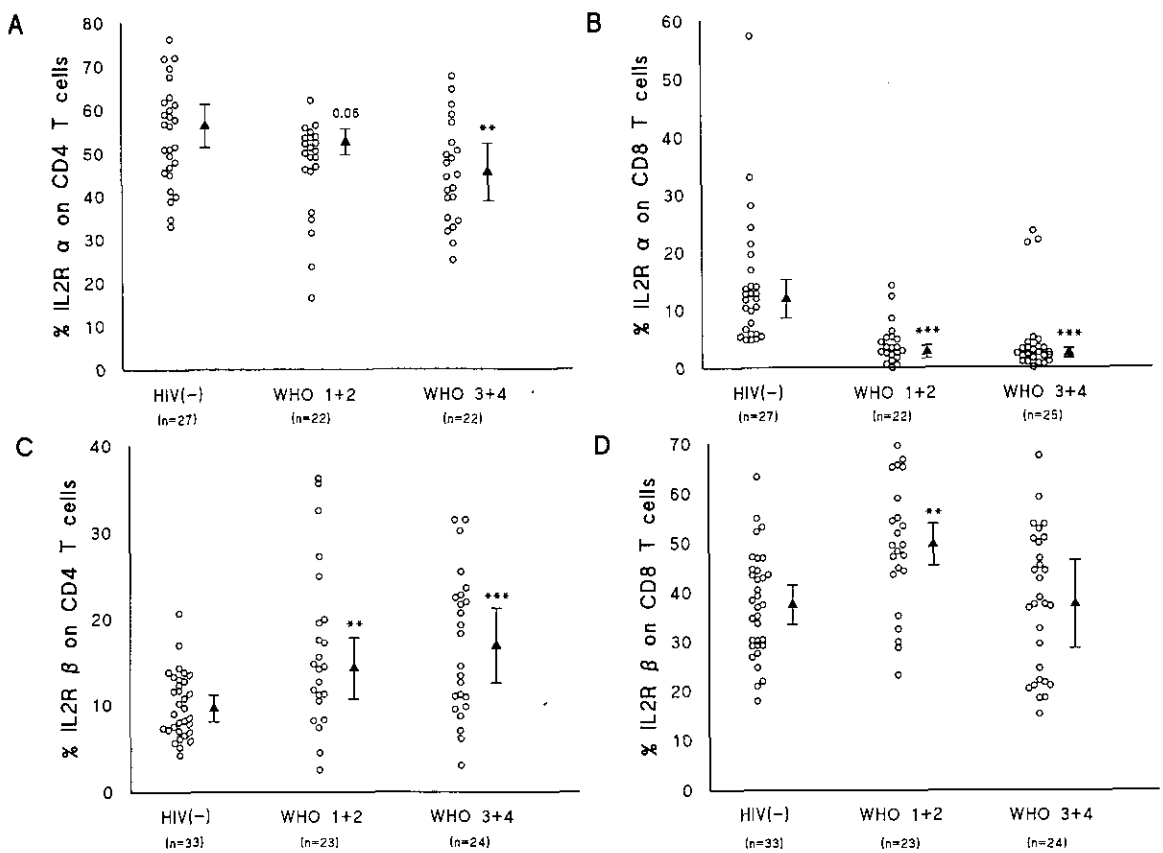


**FIG. 2.** Proportional expression of the IL2R α and β chain on CD4 and CD8 T cells in controls and HIV$^+$ subjects. The individual values of proportional IL2R α (A and B) and IL2R β (C and D) expression on CD4 T (A and C) and CD8 T (B and D) subsets are shown. The HIV$^+$ patients were classified according to WHO criteria. The median value and the confidence interval of IL2R subunit expression as well as the numbers of subjects in each group are indicated. Significance of differences between results in the HIV$^+$ groups and the controls are represented with $^{**}P < 0.01$ and $^{***}P < 0.001$.

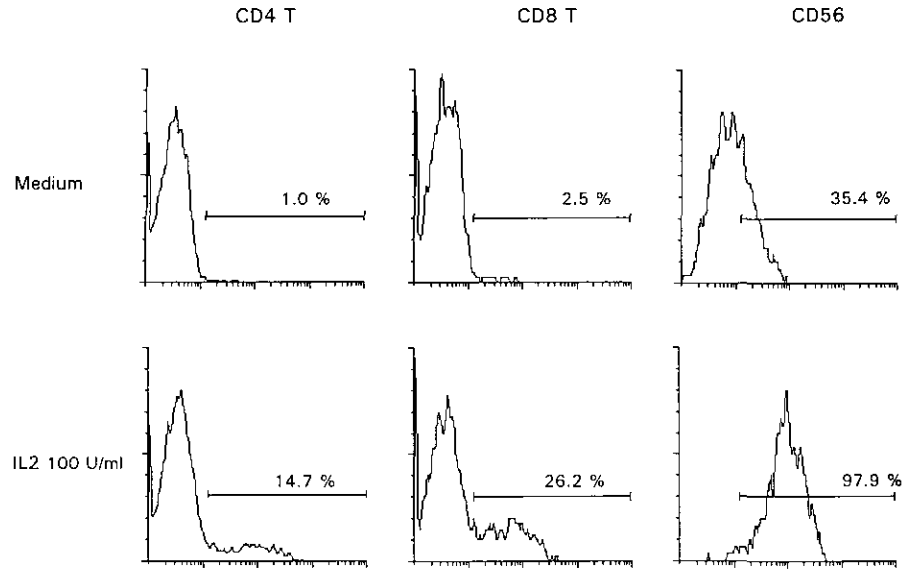


**FIG. 3.** Binding profile of anti-CD69 on unstimulated and IL2-stimulated lymphocyte subsets from a normal individual. Whole blood was cultured overnight in medium or IL2 at 100 U/ml and stained with FITC-labeled control IgG1 or anti-CD69 combined with PE-conjugated anti-CD4, anti-CD8, or anti-CD56. The histogram of the green fluorescence in the lymphocyte subsets, gated as described, was analyzed. The percentages of positive cells within each subset are shown. The limit for positivity was channel 70.

In the unstimulated cultures of $HIV^-$ blood, the CD69 antigen was present on about one-third of $CD56^+$ cells, on about 5% of CD8 T cells and on only 1% of CD4 T cells. Unstimulated CD69 expression on CD4 and CD8 T cells from $HIV^+$ subjects was two times higher (Table 1). Interleukin 2 at 100 units/ml induced a highly significant increase of CD69 expression on all lymphocyte subsets from both $HIV^-$ and $HIV^+$ subjects ($P < 0.0001$). The CD8 T cells from $HIV^+$ subjects showed a twofold higher increase of IL2-stimulated CD69 compared to controls, whereas the CD69 upregulation was quantitatively similar on CD4 T and $CD56^+$ cells from seronegative and seropositive subjects (Table 1). The IL2-induced CD69 expression on CD8 T cells from $HIV^+$ subjects did not differ significantly according to the disease stage (data not shown).

Dose–response curves of the IL2 effect in the different subsets, comparing nine seropositives and nine controls, confirmed that CD69 expression was higher on CD8 T cells from the patients in the absence of IL2 and after stimulation with increasing IL2 concentrations, but the difference was most pronounced at IL2 100 U/ml. The dose–response curves of CD69 induction on CD4 T cells and $CD56^+$ cells from patients and controls were indistinguishable (Fig. 4).

**TABLE 1**
Nonstimulated and IL2-Induced CD69 Expression on Lymphocyte Subsets from $HIV^-$ and $HIV^+$ Subjects

| | % CD69 expression[a] | | | | |
|---|---|---|---|---|---|
| | $HIV^-$ controls | | $HIV^+$ subjects | | |
| | *n* | Median (p25–p75)[b] | *n* | Median (p25–p75) | *P*[c] |
| Nonstimulated | | | | | |
| $CD4^+$ T cells | 16 | 1.0 (0.7–1.5) | 31 | 2.0 (1.4–4.3) | <0.001 |
| $CD8^+$ T cells | 16 | 4.7 (3.1–9.9) | 35 | 11.1 (5.2–14.3) | <0.05 |
| $CD56^+$ cells | 8 | 34.2 (25.7–56.1) | 5 | 42.2 (40.2–45.2) | ns |
| IL2-induced | | | | | |
| $CD4^+$ T cells | 16 | 13.8 (10.4–17.8) | 31 | 15.3 (10.9–20.8) | ns |
| $CD8^+$ T cells | 16 | 21.2 (18.3–30.2) | 35 | 40.4 (34.5–51.9) | <0.001 |
| $CD56^+$ cells | 8 | 91.5 (81.1–95.7) | 5 | 76.6 (75.4–79.3) | ns |

[a] Anti-CD69–FITC staining, expressed as percentage of positive cells within each subset, was evaluated after an overnight incubation of whole blood without or with IL2 100 U/ml.
[b] The median value of CD69 expression as well as the 25th and 75th percentile for each group are represented.
[c] Statistical differences were calculated using the Mann–Whitney *U* test.

*Effect of IL2 Receptor Subunit Blocking on CD69 Upregulation*

In four pairs of experiments, always including one seropositive person and one control, anti-IL2R subunit antibodies or control ascites were added to whole blood during stimulation with IL2 100 U/ml. Anti-Tac and anti-TU27 separately partly inhibited CD69 upregulation on CD4 T cells but together they nearly completely abolished the IL2 effect (Figs. 5A and 5B). The early activation of CD8 and CD56-positive cells was primarily diminished by the β-chain-specific mAb. α chain blocking produced only a limited inhibitory effect on CD8 T cells at this concentration of IL2 (Figs. 5C–5F). The inhibition patterns were similar in cells from $HIV^-$ and $HIV^+$ subjects.

In two additional pairs of experiments the effect of anti-IL2R α mAb was examined at three IL2 concentrations (100, 10, and 1 U/ml). Inhibition of CD69 upregulation on CD4 T cells by anti-Tac was around 30%

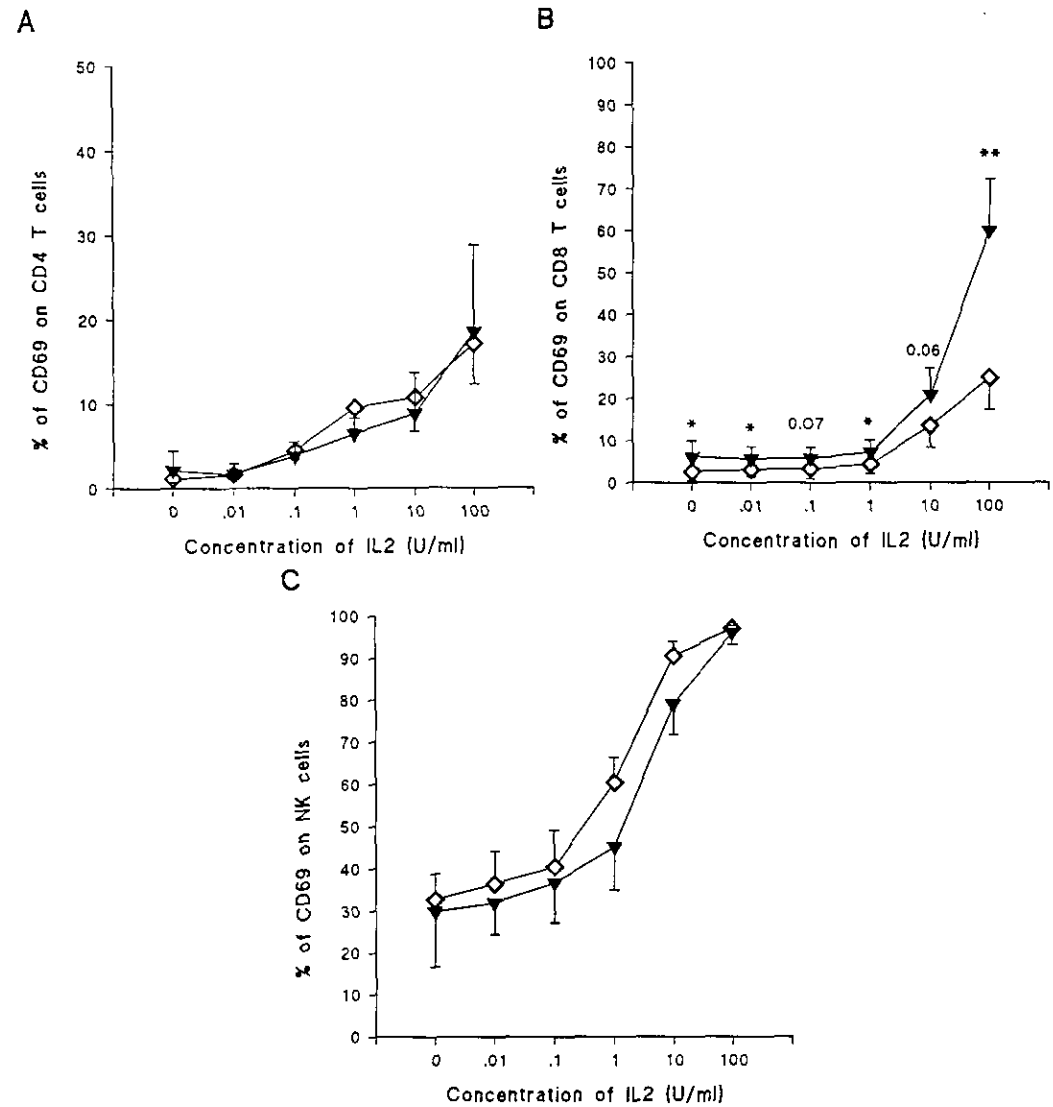


FIG. 4. Dose–response curve of IL2-induced CD69 expression. Whole blood from 9 controls (◇) and 9 HIV+ patients (▼) was incubated overnight with the indicated concentrations of IL2 and stained as explained under Subjects, Materials, and Methods. The CD69-specific expression on CD4 T cells (A), CD8 T cells (B), and CD3− CD16/56+ NK cells (C) is represented for the different IL2 concentrations. Significant differences between the HIV− and HIV+ groups are indicated with $*P < 0.05$ and $**P < 0.01$.

at 100 U IL2/ml and increased to 55% at 10 U/ml and to 100% at 1 U/ml. The inhibition of CD8 T cell activation by anti-IL2R α increased from 0% at IL2 100 U/ml to 30% at 10 U/ml and to 45% at 1 U/ml. α chain blocking had no effect on CD56+ cell activation at any IL2 concentration used. In this limited number of experiments, again no difference of inhibition profile was observed between lymphocytes from HIV+ and HIV− subjects.

## DISCUSSION

In the present paper, we demonstrated that CD4 and CD8 T cells from HIV+ subjects express less IL2R α but more IL2R β compared to controls. On a functional level, IL2 induced a stronger CD69 expression on CD8 T cells from HIV+ subjects than from controls, whereas this parameter of early activation by IL2 on CD4 T cells and on NK cells was unaffected by HIV infection.

Our data on decreased IL2R α expression on CD4 and CD8 T cells from HIV-infected people confirm and extend those of Zola *et al.* and of Hofmann *et al.* (20, 21). Several authors previously reported an increased level of soluble IL2R α in sera from HIV+ persons (30–32). It is unlikely that the observed decrease in membrane bound IL2R α expression results only from shedding, since Hofmann *et al.*, who measured both phenomena in the same group of patients, did not find any correlation between soluble and lymphocyte bound IL2R α (21).

The proportionally increased expression of IL2R β chain on CD4 and CD8 T cells from seropositive persons, we observed, is in contradiction with the data of

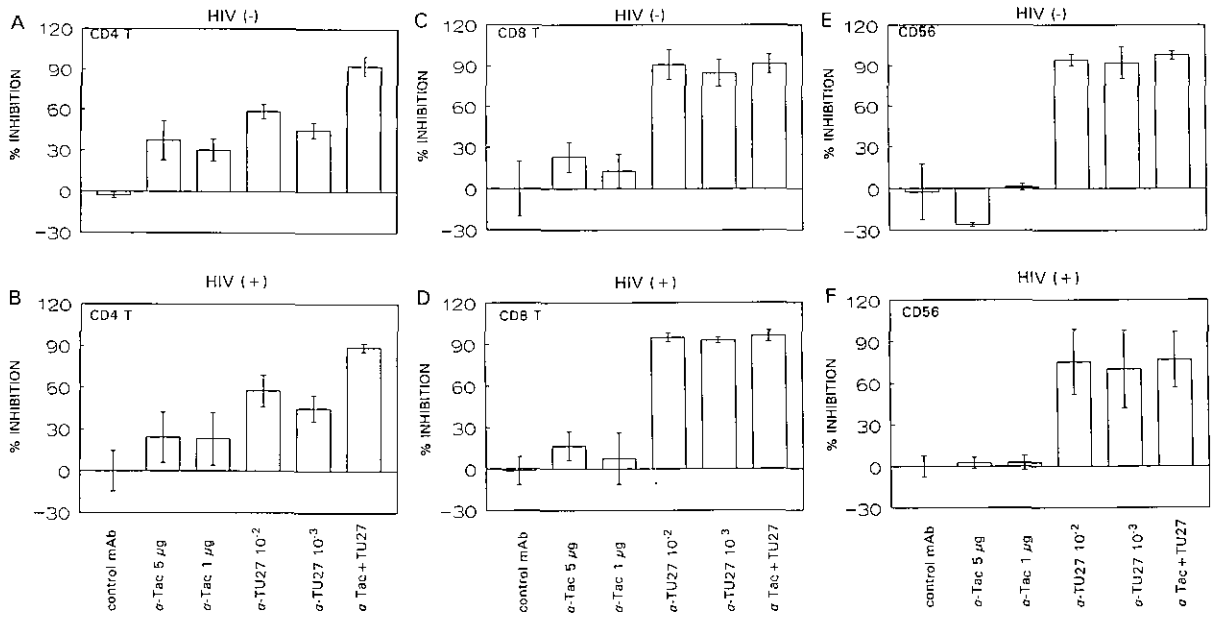


**FIG. 5.** Effect of IL2R-subunit-specific blocking of IL2-induced CD69 upregulation. Whole blood from four HIV$^-$ and four HIV$^+$ individuals was incubated overnight with medium or IL2 100 U/ml alone or IL2 100 U/ml in the presence of different mAb. These included control mAb (56D3 ascites 1/100), anti-IL2R α (anti-Tac 5 or 1 μg/ml, anti-IL2R β (TU27 ascites 1/100 or 1/1000), and finally a combination of anti-Tac 1 μg/ml and TU27 1/1000. The inhibition of IL2-induced CD69 upregulation was studied with anti-CD69–FITC on PE-labeled CD4 T cells (A, B), CD8 T cells (C, D), and CD56$^+$ cells (E, F) separately. Results are expressed as means ± SD in HIV$^-$ (A, C, E) and HIV$^+$ (B, D, F) subjects. The calculation of inhibition was performed as explained under Subjects, Materials, and Methods.

Sahraoui *et al.*, who claimed reduced β chain levels on T cells from HIV$^+$ subjects (22). One difference is that these authors used TU27 for immunofluorescence, whereas we used 2R-B. However, in our hands, both mAb stained an identical percentage of the T cells and NK cells. In the same line as our observations, Zambello *et al.* demonstrated extremely high levels of IL2R β on CD8 T cells in the bronchoalveolar fluid from HIV$^+$ subjects (33).

In order to obtain functional information on the IL2R subunits, we studied IL2-induced upregulation of CD69 expression. This early activation event was chosen to minimize the possibility that secondary cytokine networks triggered by IL2 could be responsible for the observed effects. Using immunofluorescence, the stimulatory effect of IL2 on CD69 expression and the possible inhibitory influence of subunit-specific mAbs on this phenomenon could be directly measured in the different lymphocyte subsets, without the need for subset purification.

The nonstimulated expression of CD69 on CD4 and CD8 T cells from HIV$^+$ subjects was higher than that in controls. Other markers such as HLA-DR and CD38 were previously reported to be even more increased on T cells after HIV infection (34–36). All these observations point to the presence of abnormally "activated" T cells in the circulation of HIV-infected individuals.

The IL2-induced upregulation of CD69 was preserved on CD4 T cells and NK cells from HIV$^+$ patients and even enhanced on their CD8 T cells, indicating a quantitatively efficient interaction between IL2 and its receptor. Sahraoui *et al.*, in contrast, observed decreased IL2-induced Tac expression, proliferation, and LAK generation in mononuclear cells from infected persons (22). The latter relatively late and rather global activation phenomena, however, probably require a lot of intercellular interactions and complex cytokine networks. It seems possible that the abnormal mononuclear cell composition (the reduced CD4/CD8 ratio) with ensuing abnormal immunoregulation could result in decreased global lymphocyte activation, even when the early activation of each subset separately remains intact.

According to our present understanding, a biological effect of IL2 implies preceding interaction with the intermediate affinity IL2R β–γ heterodimer or the high-affinity α–β–γ heterotrimer (1, 4). Therefore, inhibition of an IL2 effect by anti-IL2R α implies the involvement of the high-affinity receptor, whereas exclusive inhibition by anti-IL2R β points to intermediate-affinity receptor activity. Clearly, our inhibition experiments thus show that the early activation of CD4 T cells even at high IL2 concentrations proceeds at least partly via the high-affinity receptor. In CD8 T cells, the intermediate-affinity receptor predominated at 100 U/ml IL2, but at lower IL2 concentrations, some high-affinity interactions were present. Finally, the CD69 upregulation of NK cells seems to proceed only via the intermediate-affinity receptor, although we clearly demonstrated expression of the α chain and two groups

previously showed high-affinity binding of IL2 to CD56$^+$ NK cells (12, 37).

The more pronounced IL2-induced activation of CD8 T cells from HIV$^+$ subjects is consistent with their increased IL2R β expression. However, a direct correlation between IL2R β expression and sensitivity to IL2 could not be shown. In addition, the decreased expression of the α chain on CD8 T cells from the patients was not reflected in abnormally decreased activation at low IL2 concentrations. Moreover, CD4 T cells from HIV$^+$ subjects, showing IL2R α downregulation and IL2R β upregulation similar to their CD8 T cells, nevertheless displayed a pattern of early activation and receptor usage, which was indistinguishable from control CD4 T cells at any IL2 concentration used. Besides potential alterations in postreceptor phenomena after HIV infection, the expression and function of the IL2R γ chain is another factor which could clarify some of these discrepancies.

In conclusion, IL2R α and β chain expression is clearly altered after HIV infection. One of the early consequences of the interaction between IL2 and IL2R on resting lymphocytes, the CD69 upregulation, proceeds quantitatively normal in CD4 T and NK cells from HIV$^+$ subjects, but is significantly enhanced in their CD8 T cells pointing to a facilitated activation in the latter subset. Since CD8 T cells are considered to have a negative immunoregulatory role, their enhanced activation by IL2 could contribute to functional immunodeficiency from early HIV infection on.

## ACKNOWLEDGMENTS

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