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In Vivo Administration of Recombinant IL-2 to Individuals Infected by HIV Down-Modulates the Binding and Expression of the Transcription Factors Ying-Yang-1 and Leader Binding Protein-1/Late Simian Virus 40 Factor

Chiara Bovolenta,* Laura Camorali,* Alessandro L. Lorini,* Giuliana Vallanti,* Silvia Ghezzi,* Giuseppe Tambussi,† Adriano Lazzarin,† and Guido Poli*

Leader binding protein-1 (LBP-1)/late SV40 factor (LSF) and ying-yang-1 (YY1) transcription factors are involved in the regulation of HIV expression. In particular, YY1 and LBP-1 have been shown to cooperate in repressing HIV-1-long terminal repeat reporter gene expression by in vitro cotransfection experiments. However, no information is available on the levels of expression and activation of these transcription factors in PBMC of HIV-infected individuals. Therefore, we have evaluated the expression and DNA binding activity of YY1 and LBP-1 (LSF) in PBMC of HIV-infected individuals before, during, and after administration of IL-2 in association with antiretroviral therapy (ART), a regimen under consideration for broad clinical use in this disease based on its ability to stably raise the absolute number of circulating CD4+ T lymphocytes. Both YY1- and LBP-1 (LSF)-DNA binding were profoundly down-modulated during administration of IL-2/ART, and a proteolytic activity probably responsible for the reduced expression of the two cellular transcription factors was found activated in PBMC of individuals receiving the immunotherapeutic regimen. This study is the first evidence of modulation of cellular transcription factors following IL-2/ART administration and provides a potential correlate of the transient raises in plasma viremia early reported in patients receiving IL-2 in the absence of ART, thus underscoring the importance of always administering this cytokine to HIV-infected individuals together with potent antiretrovirals. The Journal of Immunology, 1999, 163: 6892–6897.


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6893

The arabic number indicates the day within the cycle of IL-2 administration; the cycle numbers are indicated as subscripts.

In contrast to the solid in vitro evidence of the involvement of YY1 and LBP-1 (LSF) in the modulation of HIV-LTR, no information on the state of expression and DNA binding of these transcriptional regulators in cells of HIV-infected individuals has been reported to date. Because LBP-1 (LSF)-DNA binding activity in T lymphocytes can be enhanced by mitogenic stimulation in vitro (11), we investigated whether in vivo IL-2 administration could somehow affect both LBP-1 (LSF) and YY1-DNA expression and binding activities in PBMC. In this regard, IL-2 is a cytokine responsible for the activation, proliferation, and differentiation of T lymphocytes and other immune cells (23) that has been previously shown to increase the absolute number of circulating CD4+ T cells in HIV+ individuals in a stable manner to normal or near normal levels (24–27). However, transient peaks of IL-2 replication after infusion of IL-2 in the absence of antivirals have been clearly documented (24), and since then, administration of the cytokine has been always associated with potent antiretroviral therapy (ART) (28). In the present study we investigated the state of activation of YY1 and LBP-1 (LSF) before, during, and after administration of IL-2/ART to HIV-infected individuals in vivo. We have observed that YY1- and LBP-1 (LSF)-DNA bindings are profoundly down-modulated by IL-2 administration; we also found that a proteolytic activity is induced in PBMC by administration of this cytokine in vivo, and it is probably responsible for the diminished expression of the two cellular transcription factors.

Materials and Methods

Patients

Six HIV-infected individuals (three women and three men; age, 21–60 years; average, 40 years) were chosen among patients enrolled in a randomized phase II study of administration of rIL-2 (Proleukin, Chiron, Emeryville, CA) after obtaining signed informed consent. All HIV-seropositive individuals had CD4+ T cell count between 200–500 cells/mm³ and were antiretroviral-experienced at study entry. After enrollment, they received a mixture of antivirals, consisting of a combination of a protease inhibitor (PI) (Saquinavir) plus two reverse transcriptase inhibitors (RTI) together with IL-2. All tested individuals but one received 3 million international units (MIU) of IL-2 twice daily s.c. for 5 days of a 5-wk treatment cycle for a total of 12 cycles; one individual received ART plus 15 MIU by continuous infusion for 5 days for two cycles with an 8-wk interval, followed by four cycles of 7.5 MIU twice daily for 5 days. The cumulative amount of IL-2 administered over 12 mo was equal for all patients. These individuals belonged to an open-label trial designed as a four-arm study enrolling 15 individuals/arm, in which the control group received antiretrovirals (two RTI and one PI) only. The results of the trial, fully supporting the superiority of IL-2-containing regimens vs ART alone in terms of reconstitution of physiologic levels of circulating CD4+ T lymphocytes (Table I), are being reported separately (our manuscript in preparation). PBMC were isolated from either peripheral venous blood of HIV-infected individuals or buffy coats of healthy normal donors by Ficoll-Hypaque gradient sedimentation (Pharmacia Biotech, Uppsala, Sweden), as previously described (29). Aliquots of 1 × 10⁶ cells were washed twice with RPMI 1640 (Life Technologies-BRL, Grand Island, NY) and spun at 13,000 × g for 2–3 min, and the pellets were stored at −80°C for further analyses.

Antibodies

Affinity-purified rabbit polyclonal Ab raised against a C-terminal epitope of human YY1 (sc-281) was purchased from Santa Cruz Biotechnology (S. Cruz, CA); rabbit polyclonal Ab against human actin (A2066) was purchased from Sigma (St. Louis, MO).

Whole-cell extracts (WCE) and EMSA

WCE were prepared by repeated freeze-thaw cycles, as previously described (30). Briefly, the cell pellets were resuspended in high salt buffer C containing 0.1% Nonidet P-40, a mixture of protease inhibitors that included leupeptin (10 μg/ml), pepstatin A (10 μg/ml), aprotinin (33 μg/ml), E-64 (10 μg/ml), Pefabloc (4-aminoethyl) benzenesulfonyl fluoride (AEBSF; 1 μM), di-isopropylfluorophosphate (3 mM), and the phosphatase inhibitors sodium vanadate (1 mM), and sodium fluoride (50 mM). Following three cycles of freezing and thawing, cellular debris were pelleted by centrifugation at 1200 × g for 15 min at 4°C. The resulting supernatants (WCE) were stored at −80°C. The protein concentration was measured using a kit based on the Bradford method (Bio-Rad, Hercules, CA). EMSA was performed as previously described (30), with minor modifications, in that binding buffers appropriate for each specific oligonucleotide were used. In particular, for the LSF-280 probe, corresponding to the LSF binding site (+260 to +301) within the SV40 major late promoter (5′-ACA CAC ATT CCA CAG CTG GTT TTT CCA GAA GGT ACC TAA C-3′) (10), a binding buffer containing 20% glycerol, 1.2% Nonidet P-40, 127 mM KCl, 8 mM Tris-HCl (pH 7.9), 20 mM HEPES (pH 7.9), 0.18 mM EDTA, and 0.86 mM DTT was used (11). For the UCR probe, corresponding to the YY1 binding site within the Moloney murine leukemia virus promoter (5′-CTG CAG TAA CCC CAT TTT GCA AGG CAT GAA-3′) (18), a binding buffer containing 10% glycerol, 10 mM Tris-HCl (pH 7.9), 100 mM KCl, 5 mM MgCl2, and 1 mM DTT was adopted. For the prolactin-responsive element probe, located within the β-casein promoter (TAG ATT TCT AGG AAT TCG) (31), a binding buffer containing 10 mM Tris (pH 7.5), 100 mM KCl, 5 mM MgCl2, and 1 mM DTT was used. The DNA-protein complexes were resolved on PAGE as previously described (30).

Immunoblot analyses

Immunoblot analyses were performed as previously described (30). Anti-YY1 and anti-actin Abs were diluted 1/2000 and 1/500, respectively, following the manufacturer’s instructions. HRP-conjugated anti-mouse or anti-rabbit secondary Abs were diluted 1/5,000 and 1/15,000, respectively. The signal was revealed by the enhanced chemiluminescence system (ECL, Amersham, Aylesbury, U.K.) following the manufacturer’s instructions.

Table I. Percentage of PBMC subpopulations in HIV-1-infected individuals receiving IL-2

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<th>CD8+</th>
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A *CD3* T lymphocytes.

B *CD8* T lymphocytes.

C *CD14* monocytes.

D *CD16* natural killer cells.

E *CD19* B lymphocytes.

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CD4 (donor 1) or poorly (donor 2) responded to IL-2 treatment in terms of IL-2 administration from two HIV-seropositive patients who either highly obtained from PBMC isolated at different time points during two cycles of IL-2 administration from donor 1, whereas patient 2 (Fig. 1A). To exclude nonspecific degradation due to improper preparation of WCE, selected time points have been tested by quantitative analysis performed with a PhosphorImager (Molecular Dynamics, Sunnyvale, CA; Fig. 3A). The analysis of four other individuals revealed that three of them responded to IL-2 therapy similarly to patient 1, whereas weak binding activity and no substantial modulation by IL-2 were observed in one individual (patient 6), as shown in Fig. 1C. These results demonstrate that IL-2 administration either directly or indirectly causes a reversible disappearance of YY1-DNA binding. We next examined whether the LBP-1 (LSF)-DNA binding activity was also affected by IL-2 administration by using the radiolabeled LSF280 oligonucleotide and WCE of patient 1. As shown in Fig. 2, down-regulation of LBP-1 (LSF)-DNA binding activity mirrored that of YY1-UCR binding both during cycle 1 and after cycle 6.

To analyze whether cell stimulation by IL-2 in vitro could induce similar patterns of YY1- and LBP-1 (LSF)-DNA binding down-modulation, EMSA analyses were performed using WCE obtained from PBMC of either HIV-seronegative healthy donors or HIV-infected individuals. The cells were either left unstimulated or stimulated for 1, 3, and 5 days with IL-2 (20 U/ml). DNA binding of both transcription factors was readily demonstrated after 24 h in culture and was not down-modulated by the cytokine treatment in vitro (data not shown). These findings indicate that a factor(s) induced in vivo by IL-2 administration is probably responsible for the observed down-modulation of YY1 and LBP-1 (LSF) binding to target DNA.

**IL-2 induces a proteolytic activity responsible for YY1-DNA binding down-modulation**

We investigated whether the disappearance of YY1 DNA binding activity in WCE of IL-2-treated individuals was caused by a proteolytic activity. To test this hypothesis, WCE from a normal healthy donor seronegative for HIV was mixed with UCR probe alone or in the presence of increasing amounts of WCE from patient 1 obtained on day 5/cycle 1 either at room temperature or at 37°C for 30 min. Normal WCE showed a band in EMSA corresponding to YY1 binding at both room temperature and 37°C (Fig. 3A, lanes 1 and 6, respectively), whereas WCE from the IL-2-treated individual showed a band that migrated much faster than that observed with the WCE of a normal donor (Fig. 3A, lane 1 vs lane 11, respectively), probably corresponding to a truncated form of YY1 (YY1Δ). At room temperature, mixing different amounts of the WCE of the HIV+ and HIV− individuals resulted in a decrease in the intensity of the YY1 band at all concentrations of IL-2-treated WCE added, and, in parallel, in the appearance of a band migrating at the same level of the IL-2-treated patient’s WCE (Fig. 3A, lanes 2–3). At 37°C, the disappearance of the upper band corresponding to full-length YY1 was almost complete at the highest concentrations of IL-2-treated WCE (Fig. 3A), as demonstrated by quantitative analysis performed with a PhosphorImager (Molecular Dynamics, Sunnyvale, CA; Fig. 3B).

**IL-2-induced proteolytic cleavage of YY1 is specific**

To assure that the proteolytic cleavage of YY1 indeed occurred in individuals receiving IL-2, Western blot analyses of WCE from
patient 1 was performed using an anti-YY1 rabbit polyclonal Ab. The single sharp band corresponding to YY1 and visible on day 0 was no longer detectable on days 3 and 5 of the first cycle of IL-2 administration and on days 1, 3, and 5 of cycle 6, respectively (Fig. 4, upper panel). Several faint bands smaller than the expected 68 kDa were recognized by the anti-YY1 Ab, further supporting proteolytic cleavage of the transcription factor. After stripping the anti-YY1 Ab, the membrane was reprobed with an anti-actin polyclonal rabbit Ab. At all time points, a single band was clearly detectable (Fig. 4, lower panel), demonstrating that the IL-2-induced degradation was relatively specific for YY1. In addition, Western blot analyses were performed using WCE obtained from PBMC of HIV-seronegative healthy donors that were either left unstimulated or were stimulated in vitro for 1, 3, and 5 days with IL-2 (20 U/ml). The expression of YY1 protein during this in vitro culture period remained unaltered (data not shown).

**IL-2 induces either proteolysis or a potential inhibitor of LBP-1 (LSF)-DNA binding**

We finally evaluated whether LBP-1 (LSF) was proteolytically cleaved by IL-2 administration by performing WCE-mixing EMSA. A concentration-dependent disappearance of the upper canonical band was indeed observed as a function of increasing the concentration of WCE from the HIV-infected individual. However, in contrast to what was observed for YY1, the disappearance of LBP-1 (LSF)/DNA binding was clearly concentration dependent at both room temperature and 37°C, although the effect was much stronger at 37°C than at room temperature (Fig. 5A). Quantitative analysis indeed demonstrated an almost complete lack of LBP-1 (LSF)-DNA binding at the two highest concentrations of IL-2-treated patients’ WCE at 37°C (Fig. 5B). Unfortunately, we could not assess LBP-1 (LSF) expression, because the amount of WCE obtained from the HIV-infected patients required for the

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**FIGURE 3.** Inhibition of YY1 DNA binding activity of a normal healthy donor by the addition of IL-2-treated WCE of a seropositive patient to the binding reaction. A. EMSA using 2.5 μg of WCE from a normal healthy donor either alone (I) or in combination with increasing amount of WCE from donor 1 on day 5 of cycle 1. In the last lane, 10 μg of WCE from donor 1 on day 5 of cycle 1 was incubated at room temperature with the probe. B. Relative estimates of YY1-DNA binding complex. Quantitation of the relative DNA binding activity of EMSA in A was performed by PhosphorImager analysis. Black bars represent the DNA binding activity of full-length YY1 (slower migrating band), whereas white bars indicate that of the truncated YY1 protein (faster migrating band, YY1Δ).

**FIGURE 4.** YY1 expression in an IL-2 treated HIV+ patient. Immunoblot of WCE (10 μg) of PBMC isolated from donor 1 using anti-YY1 Abs (upper panel) and after stripping of the filter using anti-actin Abs (lower panel).

**FIGURE 5.** Inhibition of LSF/LBP-1 DNA binding activity of a normal healthy donor by the addition of IL-2-treated WCE from a seropositive patient to the binding reaction. A. EMSA using 5 μg of WCE from a normal healthy donor either alone (I) or in combination with increasing amount of WCE from donor 1 on day 5 of cycle 6. In the last lane, 15 μg of WCE from donor 1 on day 5 of cycle 6 was incubated at room temperature with the probe. B. Relative estimates of the LBP-1 (LSF)-DNA binding activity. Quantitation of the relative DNA binding activity of EMSA in A was performed by PhosphorImager (Molecular Dynamics) analysis.
detected the LBP-1 isoforms was not sufficient to produce a detectable signal in Western blot experiments (data not shown).

**Discussion**

In the present study we have demonstrated that in vivo IL-2 administration induces a profound down-modulation of both YY1 and LBP-1 (LSF)-DNA binding activities to their specific cognate DNA elements. Evidence of a specific cleavage of YY1 was obtained by EMSA analysis after mixing different amount of WCE from IL-2-treated individuals and from normal seronegative donors and by Western blot analysis. In addition, a concentration-dependent disappearance of LBP-1 (LSF) binding was demonstrated in EMSA in the same WCE mixing experiments. Because no evidence of either YY1 or LBP-1 (LSF) down-modulation was observed after in vitro stimulation of PBMC from either HIV+ or HIV+ individuals with IL-2, these effects are probably the result of a complex action of this cytokine when administered in vivo. No clear-cut correlation was noted between the levels of expression of the two transcription factors and the relative changes among PBMC subpopulations under IL-2 influence (Table 1). Thus, the down-modulation of YY1 and LBP-1 (LSF) seems more likely caused by a soluble factor(s) induced by IL-2 administration or by a different activation state of the PBMC rather than by a different redistribution of cell subsets.

Evidence that WCE of IL-2-treated individuals contain a proteolytic activity that is responsible for YY1 degradation are here shown based on the results of the EMSA mixing experiments, in which the DNA binding of normal WCE was lost when IL-2-treated WCE was added to the reaction before the addition of the probe. By Western blot and EMSA analyses, we demonstrated that YY1 cleavage was relatively specific, because actin was intact and STAT5 binding activity unaltered, respectively, at all time points of IL-2 administration tested. In support of this hypothesis, a higher reduction of full-length YY1 binding to the DNA was observed when the extracts were incubated at 37°C. Moreover, quantitative analysis of the EMSA bands revealed that in contrast to the full-length YY1-UCR, the appearance of the truncated YY1Δ-UCR band was dependent on the amounts of IL-2 extracts added at both room temperature and 37°C, very likely as a consequence of the contribution of the truncated YY1 present in the IL-2-treated WCE. Conversely, quantitative analysis of the LBP-1 (LSF)-DNA binding activity demonstrated that the disappearance of the LBP-1 (LSF)-DNA binding was concentration dependent at both temperatures, although the effect was more evident at 37°C. One possible explanation is that the proteolytic activity required for YY1 degradation is not identical with that responsible for LBP-1 (LSF) cleavage and is still fully active at room temperature. Alternatively, the concentration-dependent decrease in LBP-1 (LSF)-DNA binding activity at room temperature might also depend upon a specific inhibitor of LBP-1 (LSF)-DNA binding induced in WCE of HIV-infected individuals receiving IL-2. In this regard, LBP-1Δd, lacking the DNA binding domain, was, however, shown to be capable of squelching the binding of the other LBP-1 isoforms by protein-protein interaction (12). Thus, we cannot rule out the possibility that in vivo IL-2 administration may result in a superinduction of either the LBP-1Δd isoform or analogous inhibitors.

The nature of the proteolytic activity present in IL-2-treated WCE is unknown at present, but it is very unlikely attributable to the HIV-associated protease for several reasons. First, the IL-2-treated patients were all receiving two RTI and one PI. Although beyond the scope of the present study, this antiviral regimen resulted in a sustained decrease in viremia (from 947 to <400 copies/ml at baseline and after 2 mo of therapy in patient 1, respectively; our manuscript in preparation). Furthermore, no increases in plasma viremia were observed during IL-2 administration. Second, the incubation of WCE from a normal healthy donor with WCE obtained from an HIV+ individual receiving IL-2 but in whom YY1 was not degraded produced no reduction in either YY1- or LBP-1 (LSF)-DNA binding activities, suggesting that the effect was strictly dependent on IL-2 administration. Finally, only a minority of cells (1:100–10,000) are known to be infected in individuals at any particular time point (33, 34), and it is extremely unlikely that the viral protease present in these cells may override the pattern of protein expression of uninfected cells.

Among many genes transcriptionally regulated by YY1, the α-actin genes have been shown to be repressed by this transcription factor in analogy with the effect on the HIV-LTR (35). Of interest, proteolytic degradation of YY1 has been correlated with myogenic differentiation (35). In these cells, cleavage of YY1 during the myoblast–myocyte transition allowed the expression of the sarcomeric α-actin genes, thus facilitating muscle development (35). In the same system the Ca2+-dependent cysteine protease m-calpain has been clearly demonstrated as the enzyme responsible for the post-translational mechanism of YY1 down-regulation (35). Of note, the levels of this endopeptidase were also found increased after activation of T lymphocytes (36). Furthermore, in vitro activation-induced programmed cell death in PBMC from HIV+ individuals has been shown to be specifically inhibited by calpain inhibitor II, suggesting that a calpain-dependent apoptosis might contribute to HIV-associated immunodeficiency (37). Although we did not observe YY1 degradation after IL-2 stimulation of patients’ PBMC in vitro, we speculate that activation of circulating T cells of HIV+-infected individuals by in vivo administration of IL-2 may increase the concentration of m-calpain, resulting in cleavage of YY1 and/or LBP-1 (LSF).

In conclusion, our findings are of potential interest for understanding the biochemical and immunological correlates of IL-2 administration to HIV-infected individuals. In this regard, it has been previously emphasized that one potential drawback of IL-2 administration observed in HIV-infected individuals was the transient increase in plasma HIV RNA levels frequently observed at the end of each cycle of i.v. infusion of IL-2 in the absence of ART (24). Our findings may provide a biochemical correlate of this phenomenon, i.e., the decreased expression or activity of two HIV transcriptional repressors such as YY1 and LBP-1 (LSF). Of note is the fact that increases in plasma viremia were not observed in any of our patients who received IL-2 by either s.c. or continuous infusion routes in the presence of ART (our manuscript in preparation). In addition, the copy numbers of both spliced and unspliced RNA, measured by competitive RT-PCR (38), remained unchanged in patients 2 (with 450 and 500 copies of unspliced RNA and 526 and 500 copies of fully spliced RNA/µg of total RNA after IL-2 vs baseline, respectively; data not shown), but were below the threshold of detection in patient 1 (40 copies of RNA/µg of total RNA) both before and after IL-2 treatment (data not shown), leaving open the question of whether IL-2 and IL-2-induced modulation of YY1 and LBP-1 (LSF) can significantly regulate HIV transcription in vivo in the presence of potent antivirals. Despite the fact the IL-2 is being considered as one of the most promising therapeutic agents to be associated with antiviral mixtures, little is known of its biological effects on HIV-infected individuals. Here, by showing a potential correlation between in vivo effects of IL-2 and down-modulation of YY1 and LBP-1 (LSF), we provide evidence that molecular markers can be found and should be further investigated to define novel sensitive correlates of the response to immunotherapy.
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References


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