Interleukin-6 Inhibits the Proliferation of B-Chronic Lymphocytic Leukemia Cells That Is Induced by Tumor Necrosis Factor-α or -β

By Dan Aderka, Yasmin Maor, Daniela Novick, Hartmut Engelmann, Yael Kahn, Yoram Levo, David Wallach, and Michel Rovel

Tumor necrosis factor (TNF-α) acts as a growth stimulatory factor on leukemic B lymphocytes from many patients with chronic lymphocytic leukemia (CLL). Because TNF induces production of interleukin-6 (IL-6), which has been shown to be a growth factor for myeloma and other transformed B cells, we examined the possibility that IL-6 mediates the growth-stimulatory effect of TNF on B-CLL cells. In fact, we found that IL-6 is an inhibitor of B-CLL growth. The addition of recombinant human IL-6 markedly decreased the TNF-induced B-CLL growth, and this decrease was even greater when soluble IL-6 receptor, known to act as IL-6 agonist, was added with recombinant IL-6. Conversely, neutralizing monoclonal antibodies to IL-6 and to the IL-6 receptor potentiated the growth stimulation of TNF on B-CLL cells, in line with the possibility that IL-6 functions as a negative feedback regulator of an autocrine TNF action on these B-leukemic cells. Evidence is presented that production of IL-6 by monocytes and B cells of CLL patients is low, suggesting that administration of IL-6 may be beneficial in CLL to reduce the eventual growth stimulation by TNF and, possibly, also the deficiency in platelets and Ig production in this disease.

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MATERIALS AND METHODS

Blood samples and preparation of leukemic B-CLL cells. Peripheral blood mononuclear cells were obtained from a group of 25 patients with B-CLL by centrifugation of 15 mL of heparinized blood on a Ficoll-Hypaque cushion (Pharmacia, Uppsala, Sweden). After removing residual platelets as described,22 the leukemic B cells were enriched by depleting T cells through rosetting but not of monocytes (B+Mo) were depleted of monocytes (B+T+Mo), or total nonadherent cells depleted of monocytes (B+T+Mo) were used. Purified monocytes were obtained by degrading adherent mononuclear cells with 0.25% EDTA in phosphate-buffered saline (PBS) pH 7.4.

B-CLL cultures. Leukocytes were cultured in RPMI 1640 with 10% fetal calf serum (FCS) in 96-well microplates at 5 × 10⁴ cells
per well in 0.2 mL. Cytokines and other additions were made 12 hours after plating. The rate of cell growth was assessed after 7 days by the addition of 1 μCi/well of 3H-thymidine (25 Ci/mmol; Amer- sham, Amersham, UK) for the last 12 hours of culture. Cells were then harvested with a PHD-cell harvester (Cambridge Technology, Watertown, MA), lysed in water, and the filters processed for counting radioactivity incorporated into DNA in a Packard Tricarb liquid scintillation counter (Packard, Downers Grove, IL).

Cytokines, receptors, and antibodies. Recombinant human TNF (rTNF-α; 6 × 10^7 U/mg protein, from Genentech, San Francisco, CA) and human lymphotoxin (rTNF-β; 1.2 × 10^7 U/mg protein) were kindly provided by Dr G. Adolf (Boehringer Institute, Vienna, Austria). Recombinant human IL-6 (1.5 × 10^7 units/mg protein), produced in Chinese hamster ovary (CHO) cells as described, was from InterPharm (Ares-Serono Group, Nes-Ziona, Israel). Homogenous preparations of soluble IL-6 receptor isolated and purified from human urine were obtained as described. Anti-IL-6 receptor was MoAb 34.424 and anti-IL-6 protein, produced in Chinese hamster ovary (CHO) cells as described. Neutralizing MoAbs to human TNF-α was as described. Anti-IL-6 neutralizing monoclonal antibody (MoAb) 34.424 and anti-IL-6 receptor was MoAb 48.8.25 which was shown to neutralize IL-6 binding to cells, with both MoAbs being used as reported therein. Neutralizing MoAb to human TNF-α was as described.

Immunassays. Sera obtained from 10 mL of blood left to clot for 15 minutes at room temperature (RT) before freezing at −70°C and cell culture supernatants were analyzed for the concentration of IL-6 and IL-6 receptor by enzyme-linked immunosorbent assays (ELISA), according to reported procedures. Briefly, microtiter plates were coated with MoAb to IL-6 or to the IL-6 receptor at 2.4 μg of Igg per well overnight (ON) at 4°C. Plates were washed with PBS containing 0.5% bovine serum albumin and 0.05% Tween-20, and blocked in the same solution for 2 hours at 37°C. Test samples treated with nonidet P-40 (0.5%) and Na azide (0.02%) were added (50 μL/well), the plates left ON at RT, and washed three times with 0.05% Tween-20 in PBS. Rabbit polyclonal antisera to the soluble IL-6 receptor or to IL-6 diluted 1:500 in blocking solution were added, the plates left ON at RT, and washed. Horseradish peroxidase-conjugated goat antirabbit IgG (affinity purified, 1:2,000, 0.1 mL/well; Biomakor, Ness-Ziona, Israel) was added for 2 hours at RT and the plates washed four times. Color was developed by 2,2'-azinobis(3-ethylbenzthiazoline-6-sulfonic acid; Sigma, St Louis, MO) for 30 minutes, the reaction stopped with 0.2 mol/L citric acid, and the plates read by an automatic ELISA reader at 405 nm. The detection limit of both assays, using as standards pure soluble IL-6 receptor and IL-6, was 50 pg/mL.

RESULTS

Subset of B-CLL patients showing leukemic cell growth stimulation by TNF. In line with previous reports, we found that among the 25 B-CLL patients examined, isolated leukemic B cells of 13 patients (52%) proliferated in response to in vitro incubation with TNF (20 ng/mL) as determined by 3H-thymidine incorporation (see for example, Fig 1, lanes 2 v 1). Analysis of a number of clinical parameters indicated that the patients in which TNF stimulated growth of the leukemic lymphocytes (TNF responders) had a more aggressive disease than the “nonresponders” group. Thus, patients in the TNF-responder group were younger (P < .05), more of them required cytotoxic therapy (61.5% v 25%; P < .05), and, when compared at the same Rai clinical stage, seemed to have reached this stage in a shorter time than the nonresponders (30.7 v 63.2 months), although this latter parameter was not statistically significant (Table 1).

Growth stimulation of B-CLL cells by TNF was also seen with total mononuclear cells before depletion of T cells by rosetting and of monocytes by removing adherent cells (Fig 2D). However, the thoroughly depleted leukemic B-cell population used throughout this work (97% to 99% CD19+ cells) showed the strongest growth stimulation by TNF (Fig 2A).

Role of IL-6 in the growth stimulation of B-CLL cells by TNF. To determine if induction of IL-6 by TNF may be responsible for the growth stimulation observed, anti–IL-6 neutralizing MoAbs were added to cultures of purified...
leukemic B cells from several CLL patients of the TNF-responsive group. Contrary to what was expected from the reported role of IL-6 in the growth of EBV-transformed B cells, plasmacytomas, and myelomas, anti–IL-6 antibodies did not reduce the proliferative effect of TNF on the B-CLL cells (Fig 1, lanes 3 v 2). Instead, in a number of patients, this neutralization of IL-6 even enhanced the TNF stimulation of ³H-thymidine incorporation (Fig 1, patients no. 1 and 2), indicating that some endogenous IL-6 acts as growth inhibitor in these cultures of purified B-CLL cells.

A stronger enhancement of the TNF-induced growth stimulation by anti–IL-6 antibodies could be observed if cultures of B-CLL cells were not first depleted of monocytes and T cells (Fig 2D, lanes 3 v 2). Moreover, a neutralizing MoAb to the IL-6 receptor stimulated growth when added with TNF (lanes 7 v 2). The small amount of monocytes and T cells (less than 20% of the B cells) contributes probably little to the TNF-induced thymidine incorporation, but, because monocytes are a main source of IL-6 (see below direct IL-6 measurements), the growth-limiting action of endogenously produced IL-6 is more apparent in these undepleted cultures than in the pure B cells.

Addition of rIL-6 inhibits the growth-stimulatory effect of TNF-α and β on B-CLL cells. Exogenous addition of human rIL-6 to the purified leukemic B-CLL cells inhibited the TNF-induced growth (Fig 1, lanes 4 v 2). With B cells from different CLL patients, inhibitions of 35% to 85% were observed with 6 to 25 ng/mL of IL-6 (see also Figs 3 and 4). To take into account endogenously produced IL-6, we compared cultures with anti–IL-6 antibodies to cultures with added rIL-6; the growth inhibition was then consistently 70% to 85% (Fig 1, lanes 4 v 3). IL-6 addition

<table>
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<tr>
<th>Table 1. B-CLL Patients With or Without Growth-Stimulatory Effect of TNF on Their Leukemic Cells</th>
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<tbody>
<tr>
<td>Patients With TNF Growth Stimulation</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Disease duration</td>
</tr>
<tr>
<td>Stage (Rai)</td>
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<tr>
<td>Previous chemotherapy (%)</td>
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Abbreviation: NS, not significant.
had the strongest inhibitory effect on the pure leukemic B-CLL cells (Fig 2A), but the effect was seen also in undepleted cultures (Fig 2B through D), particularly if the cultures with added rIL-6 were compared with cultures with anti–IL-6 antibodies (Fig 2D, lanes 4 v 3). In all experiments shown, we used recombinant IL-6 produced in CHO cells, but similar results were obtained with Escherichia coli-produced unglycosylated rIL-6 (not shown).

Cultures of leukemic B-CLL cells supplemented by TNF-β/lymphotoxin instead of TNF-α also showed increased ³H-thymidine incorporation (Fig 3A, lane 4). The stimulation increased with lymphotoxin concentrations up to 50 ng/mL (not shown). Addition of IL-6 (6 ng/mL) to the B-CLL cell cultures reduced the TNF-α- and TNF-β-induced growth over basal levels by 50% and 80%, respectively (Fig 3A, lanes 3 and 5). Hence, IL-6 prevents the growth stimulation of B-CLL resulting from either macrophage-produced TNF-α or T-lymphocyte-produced TNF-β.

Soluble IL-6 receptor enhances the IL-6 growth-inhibitory effect on B-CLL cells. As previously reported, a soluble form of the IL-6 receptor can be isolated from human urine. This truncated receptor, which binds IL-6 and interacts with the gp130 membrane transducer protein, functions as an agonist of the growth stimulatory effect of IL-6 on plasmacytoma cells, as well as of its growth-inhibitory effect on human breast carcinoma cells and murine M1 myeloleukemic cells. To determine if the soluble IL-6 receptor could also enhance the growth inhibition by IL-6 on human B-CLL cells, we added purified urinary soluble IL-6 receptor (80 ng/mL) to the leukemic B-cell cultures supplemented with TNF and IL-6 (Fig 3B, lanes 4 v 3). In these three experiments, IL-6 alone (6 ng/mL) reduced the TNF growth stimulation by about 35%. Addition of the soluble IL-6 receptor produced a further decrease in cell proliferation to 50% to 60%.

These effects of IL-6 and the potentiation of its growth-inhibitory effect by soluble IL-6 receptor were observed not only by assay of ³H-thymidine incorporation after 3 or 7 days, but also when the number of B-CLL cells was quantitated microscopically. TNF clearly produced an increase in cell number after 7 days. IL-6 inhibited the effect of TNF, and, when IL-6 was added in suboptimal concentrations, the growth inhibition could be potentiated by the addition of the soluble IL-6 receptor (not shown).

Even without exogenous IL-6. addition of the soluble IL-6 receptor was found in some CLL samples to produce a small inhibition of the TNF-stimulated ³H-thymidine incorporation in CLL leukemic B cells (Fig 4B, D, and F, lanes 5 v 2). This could be most simply explained as being due to potentiation of the action of minute amounts of IL-6 endogenously produced by the leukemic B cells. The presence of endogenous IL-6 is also indicated by the effect of anti–IL-6...
or anti-IL-6 receptor antibodies on B-cell cultures of some of these patients (Fig 4D and F, lanes 6 and 7 v 2). Therefore, it appears that the growth stimulation by TNF can be limited by IL-6 produced endogenously by leukemic B cells (see also patients no. 1 and 2, Fig 1), and furthermore, that the IL-6 receptor is involved in this autolimitation effect. However, as already noted, the purified B cells produce less IL-6 than cultures undepleted of monocytes, in which antibodies to IL-6 or IL-6 receptor neutralization have a clearer effect (Fig 2C and D, lanes 3 and 7 v 2).

**Effects of IL-6 on B-CLL cell growth without TNF addition.** We addressed the question of whether the basal proliferative activity of leukemic B cells in the absence of exogenous TNF was also inhibited by IL-6 addition. Figure 4 (A, C, and E) shows that IL-6 inhibits B-CLL cell growth measured without TNF, a finding that was consistently seen in 10 other B-CLL patients (Fig 5). The mean decrease in \(^{3}H\)-thymidine incorporation by IL-6 calculated for all these cultures without TNF was 40.6% ± 14.3% (\(P < .001\)). Interestingly, we noted that this growth-inhibitory effect of IL-6 alone was restricted to B-CLL cells from patients who also showed growth stimulation by TNF, suggesting that the effect of IL-6 is somehow linked to that of TNF.

Endogenously produced IL-6 could limit the low basal B-CLL proliferation rate in the absence of exogenous TNF. For example, cells from CLL patient no. 213 showed stimulation of the basal proliferation without TNF upon the addition of antibodies to IL-6 or to the IL-6 receptor (Fig 4E, lanes 4 and 5 v 1). Evidence for growth inhibition by endogenous IL-6 without TNF addition was again more apparent in B-CLL cultures nondepleted of monocytes and T cells to which antibodies to IL-6 or IL-6 receptor were added (Fig 2D, lanes 8 and 10 v 1), which can be attributed to the higher production of endogenous IL-6 by monocytes than by the leukemic B cells (see below). We also examined whether endogenous TNF plays a role in the basal level of B-CLL growth: anti-TNF-\(\alpha\) antibodies had little effect with purified B cells (Fig 1, lane 7 v 1; Fig 2A, lane 9 v 1), but some reduction in the basal level of growth was detectable in the presence of monocytes and T cells (Fig 2C and D, lane 9 v 1).

**Release of IL-6 and IL-6 receptors from B-CLL cells and serum levels.** Having observed that secretion of IL-6 and release of soluble IL-6 receptor may slow down the B-CLL cell growth, we proceeded to measure by immunoassays the release from cell cultures and the serum levels of the two proteins in B-CLL versus healthy donors. We first examined B cells and monocytes for spontaneous IL-6 secretion; in a healthy donor, release of IL-6 was seen from monocytes and less from B or T cells (Fig 6A), whereas in a representative B-CLL case, there was a lowered IL-6 release from monocytes and leukemic B lymphocytes (Fig 6B). Addition of TNF-\(\alpha\) (20 ng/mL) to the pure leukemic B cells did not elevate the very low IL-6 production (0.176 ± 0.011 ng with TNF and 0.159 ± 0.12 ng without TNF for 2.5 \(\times\) 10^6 B cells/mL). The
IL-6 inhibits TNF-induced growth of CLL cells

Fig 5. Growth inhibition by exogenous IL-6 added to B-CLL cells without TNF stimulation. IL-6 was added at 25 ng/mL in the absence of TNF to cultures of leukemic B cells from 10 B-CLL patients. 3H-thymidine incorporation was measured after 7 days. Results are shown in different panels with each patient's number.

reduced IL-6 secretion by monocytes and B cells was consistently found in similar comparisons of five other CLL cases to five healthy controls (not shown). Decreased production of IL-6 by lipopolysaccharide (LPS)-stimulated mononuclear cells of B-CLL blood\(^2\) and the absence of IL-6 RNA in CLL B cells\(^3\) were reported. However, constitutive expression of IL-6 mRNA and increased IL-6 bioactivity were also described in B-CLL cell cultures.\(^2,3\) To clarify whether IL-6 levels are increased or decreased in B-CLL, we measured IL-6 in the sera of 76 B-CLL patients versus 23 healthy donors (Fig 7A). The immunoassays showed detectable levels of IL-6 (>50 pg/mL) in 9 of 23 (39%) healthy donors, but in B-CLL patients, this figure varied according to the Rai clinical stage. Stage 0 patients had a higher than normal incidence of detectable IL-6 levels (6 of 11 or 54.5%), but detectable levels of IL-6 were less and less frequent with progression of B-CLL: stage I, 31%; II, 22%; III, 27%; IV, 20% (Fig 7A). Therefore, advanced B-CLL may be associated with lower IL-6 production.

The shedding of IL-6 receptor from B-CLL blood cell cultures was also measured (Fig 6C and D). Mononuclear cells from B-CLL patients, particularly leukemic B cells, shed more IL-6 receptor than cells of healthy donors. The serum levels of soluble IL-6 receptor were elevated in B-CLL patients in correlation with disease stages (Fig 7B). At all CLL stages, the increase in serum soluble IL-6 receptors was statistically significant in comparison to healthy donors (Table 2), and it was significantly higher at stage IV compared with stages 0 through II (stage III being close to IV). These serum levels were consistent with the in vitro production observed and may have prognostic value.

DISCUSSION

TNF promotes the proliferation and viability of the leukemic lymphocytes in about half of B-CLL patients and has been related to progression of the disease.\(^7,10\) Production of TNF by the leukemic B cells is high in early stages of the disease.\(^10,27\) Among the 25 patients that were examined here, those in which TNF stimulates leukemic cell growth seem to experience a more aggressive course of disease. Inhibiting TNF action may, therefore, be of value for some of the B-CLL patients. Our results show that IL-6 can markedly inhibit the stimulatory effects of TNF-\(\alpha\) and TNF-\(\beta\) on the proliferation of purified B-CLL lymphocytes. Growth inhibition by IL-6 was observed in B-CLL cells from all patients studied, of which 10 are shown here. Furthermore, IL-6 is also often able to reduce the basal level of B-CLL cell growth without TNF addition. The growth inhibition by IL-6 is potentiated upon the addition of soluble IL-6 receptors, which act as agonists of IL-6 biologic action.\(^4,5\) Conversely, neutralization of IL-6 or of the IL-6 receptor by specific MoAbs results in an amplification of growth and of the growth-stimulatory effects of TNF on these leukemic B cells. IL-6 appears, therefore, to act in this system as an antagonist of TNF-\(\alpha\) or -\(\beta\). TNF is a common inducer of IL-6 in many cells.\(^15,16,33\) IL-6 can inhibit the production of TNF in macrophages,\(^34\) but inhibition of a TNF function by IL-6 had not been established. Indeed, that the growth stimulation of fibroblasts by TNF may be reduced by TNF-induced IL-6/IFN-\(\beta\)-2\(^15\) was considered unlikely and attributed to a small induction of IFN-\(\beta\).\(^35\) The present study on CLL B-cell growth demonstrates that IL-6 negatively regulates a TNF biologic function.

The growth inhibition by IL-6 of isolated leukemic B lymphocytes of B-CLL patients seems a priori surprising because IL-6 is considered as a growth stimulatory factor for B-cell neoplasms such as human multiple myelomas and lymphomas.\(^18,33\) Yet, the finding is not unexpected in view of the fact that IL-6 acts as a differentiation factor for mature B cells,\(^33\) and in view of IL-6's ability to inhibit growth and...
Induce differentiation of myeloid leukemia cells, as well as to inhibit the growth of breast carcinoma cells. B-CLL lymphocytes probably represent a particular subpopulation of B cells arrested before their terminal differentiation, because B-CLL cells: (1) possess surface markers of both immature and mature B cells, and (2) have the capacity to respond to cytokines such as TNF, a characteristic limited normally to activated B cells and that coincides with their differentiation into Ig-producing cells. TNF induced proliferation, but did not induce IL-6 production in the B-CLL cells. These leukemic B cells possess the IL-6 receptor, as evidenced here by release of soluble (truncated) receptor, and they respond to IL-6 by decreased growth. This could be in line with a role of IL-6 in B-cell maturation/differentiation, although no increase in Ig production by the B-CLL cells was observed when cultured in vitro with IL-6 (not shown).

We observed, as did others, that B-CLL monocytes and leukemic B cells show reduced IL-6 production, and that IL-6 was less often detectable in the sera of B-CLL patients at advanced stages of the disease. Increased IL-6 formation, which was also reported in CLL, was found here only in stages 0 and I. We also found increased serum levels of soluble IL-6 receptors in advanced B-CLL, probably reflecting increased shedding from cells. The decrease in the capacity to produce IL-6 may have some importance in vivo because endogenously produced IL-6 is seen to limit the proliferation of the leukemic B-CLL cells. Variations in IL-6 and its receptor may also play a role in the arrested differentiation and

**Fig 6.** Spontaneous production of IL-6 and soluble IL-6 receptor by B lymphocytes of a healthy donor and a B-CLL patient. Peripheral blood mononuclear cells from healthy donors (A and C) and B-CLL (B and D) were separated as described in Materials and Methods. Fractionated cells composed of B cells (B), T cells (T), or adherent monocytes (Mo), or partially depleted cell mixtures, were plated at 5 × 10⁶ cells/well of a 96-well microplate. After 36 hours, medium from each well was assayed for content of IL-6 (A and B) and IL-6 receptor (C and D) by ELISA, as described in Materials and Methods.

**Fig 7.** Serum levels of IL-6 and soluble IL-6 receptors in healthy donors and B-CLL patients. Blood samples were collected (see Materials and Methods) from 23 healthy donors and from 73 cases of B-CLL at different stages of the disease. The serum levels of IL-6 (A) and soluble IL-6 receptor (B) were determined by ELISA, as described in Materials and Methods. The data are shown according to Rai's staging of the disease.
IL-6 INHIBITS TNF-INDUCED GROWTH OF CLL CELLS

Table 2. Serum Levels of Soluble IL-6 Receptor in B-CLL Patients

<table>
<thead>
<tr>
<th>Sera From Patients</th>
<th>No. of Patients</th>
<th>sIL-6 Receptor (ng/mL)</th>
<th>P Values v Healthy Donors</th>
<th>P Values v Stage IV B-CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy donors</td>
<td>14</td>
<td>44.3 ± 6</td>
<td>---</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>B-CLL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>12</td>
<td>55.0 ± 12</td>
<td>P &lt; .05</td>
<td>P &lt; .01</td>
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<tr>
<td>Stage I</td>
<td>9</td>
<td>62.0 ± 6</td>
<td>P &lt; .001</td>
<td>P &lt; .01</td>
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<td>Stage II</td>
<td>16</td>
<td>62.6 ± 17</td>
<td>P &lt; .001</td>
<td>P &lt; .02</td>
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<tr>
<td>Stage III</td>
<td>11</td>
<td>77.4 ± 31</td>
<td>P &lt; .01</td>
<td>NS</td>
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<tr>
<td>Stage IV</td>
<td>16</td>
<td>84.0 ± 28</td>
<td>P &lt; .001</td>
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</table>

Data relate to Fig 7B.
Abbreviation: NS, not significant.

impaired Ig production, which remain to be studied in detail. In addition, because IL-6 activates megakaryocyte differentiation and platelet production, an IL-6 deficiency in stage IV CLL may have some bearing on the characteristic thrombocytopenia observed at this stage.

Antitumor activities of IL-6 have been documented in several murine models, such as acute myeloid leukemia, Friend leukemia, and metastatic sarcomas, melanoma, and lung carcinoma. In view of the ability of IL-6 to antagonize TNF and inhibit the growth of B-CLL cells that we document here, it may be justified to test the therapeutic potential of IL-6 in this leukemia as an antitumoral and thrombopoietic agent as well.

ACKNOWLEDGMENT

We thank Prof B. Ramot and Prof. Y. Ben-Bassat for enabling us to examine their patients and Shoshana Bar-On for examination of cellular markers on B-CLL cells.

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