Defective Helper Function of Purified T4 Cells and Excessive Suppressor Activity of Purified T8 Cells in Patients With B-Cell Chronic Lymphocytic Leukemia. T4 Suppressor Effector Cells Are Present in Certain Patients

By Jolanta E. Kunicka and Chris D. Platsoucas

We investigated helper and suppressor functions to B-cell responses and T-T cell interactions of purified T4 and T8 cells from 20 untreated patients with B-cell chronic lymphocytic leukemia (CLL). Appropriate mixtures of purified T4 or T8 cells from patients with CLL were cultured with purified B cells or T4 and T8 cells from normal donors for 7 days with pokeweed mitogen (PWM). IgM, IgA, and IgG produced were determined in the supernatants of these cultures by a heavy chain-specific enzyme-linked immunosorbent assay (ELISA) and compared to those obtained by the corresponding mixtures of T4, T8, and B cells from normal donors. Purified T4 cells from 14 of 20 patients with CLL exhibited defective helper function (P < .001) to immunoglobulin (Ig) production by purified B cells from normal donors. Purified T4 cells from 6 of these 14 patients were able to suppress significantly (P < .001) and in a concentration-dependent manner Ig production by mixtures of T4 and B cells from normal donors, in the absence of T8 cells. These suppressor effector T4 cells from certain patients were partially radiosensitive. Purified T8 cells from 8 of 20 patients with CLL exhibited excessive suppressor activity. These cells significantly suppressed (P < .001) Ig production by mixtures of T4 and B cells from normal donors to a degree significantly higher (P < .005) than that observed by equal numbers of T8 cells from normal donors. This inhibition was dependent on the numbers of the T8 CLL cells added to the cultures. Excessive suppressor activity by T8 CLL cells was at least in part radiosensitive in four of eight patients. These results demonstrate a wide range of immunoregulatory T-cell abnormalities in patients with CLL. Naturally occurring T4 suppressor effector cells, directly inhibiting Ig production by mixtures of T4 and B cells, in the absence of T8 cells, are present in certain patients with CLL.

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MATERIALS AND METHODS

Patients. Twenty untreated patients with B-cell CLL provided venous peripheral blood for this study. Informed consent was obtained by the Hematology/Lymphoma Service of Memorial Hospital. Staging of the patients was determined according to the Rai classification. Twenty age-matched healthy volunteers, free of hepatitis antigen and antibody, provided peripheral blood.

Preparation of peripheral blood E rosette-positive and E rosette-negative cells. Peripheral blood mononuclear leukocytes (PBMCs) were isolated by centrifugation on a Ficoll/Hyphaque density cushion from heparinized peripheral blood from patients with CLL or normal donors. Monocytes were removed by ingestion of iron carbonyl particles, followed by centrifugation on a Ficoll/Hyphaque density cushion. E rosette-positive and E rosette-negative cells were prepared by rosetting twice with 2-aminoethylisothiourea bromide (AET, Sigma Chemical, St Louis)-treated sheep RBCs. E rosette-negative cells from patients with CLL prepared by this method were >95% surface Ig-positive cells, contained <1% of E rosette-forming cells and were completely devoid of monocytes, as determined by nonspecific esterase staining and immunofluorescence analysis using the anti-Leu M3 mAb. E rosette-negative cells from normal donors prepared by this method contained 80% to 95% Ig-positive cells, <1% E rosette-forming cells, and were completely devoid of monocytes. These cells will be referred to as B cells. E rosette-positive cells were >95% T lymphocytes as determined by rosetting with SRBCs and by immunofluorescence analysis using the anti-Leu 5 mAb (Becton Dickinson, Sunnyvale, CA). These cells contained <1% Ig-bearing cells and were completely devoid of monocytes.

Isolation of T4 and T8 cells. T4-positive and T8-positive cells from patients with CLL or normal donors were isolated from E rosette-negative cells by negative selection by treatment with, respectively, the OKT8 or the OKT4 (Ortho, Raritan, NJ) mAb plus rabbit complement (Pel Freeze, Little Rock, AR). The cells were centrifuged through a cushion of FCS (3 mL), and washed three times with RPMI 1640 supplemented with 10% fetal calf serum (FCS) before use. The OKT4 mAb plus complement-treated cells contained >90% T8 cells and <1% T4 cells. The OKT8 mAb plus complement-treated population contained >90% of T4 cells and <1% of T8 cells. These cells will be referred to as T8 and T4 cells, respectively.

Cell surface immunofluorescence. Surface Ig-positive cells were determined by immunofluorescence staining, as previously described. FITC-conjugated F(ab')2 fragments of goat antiserum specific for either γ-, α-, or μ-human heavy chain or for either ε- or λ-light chain were obtained from Kallestad (Chaska, MN). Cells expressing the T3, T4, T8, and Leu5 cell surface differentiation antigens were determined by immunofluorescence staining using the corresponding mAb.

Determination of immunoregulatory functions of purified T4 and T8 cells from patients with CLL. Various numbers (0.01 x 10^6 to 8.0 x 10^5 cells/well) of highly purified T4 cells from patients with CLL or normal donors were added to purified allogeneic B cells (0.5 x 10^6 or 1.0 x 10^6/well) from normal donors, in U-bottomed 96-well microtiter plates (Nunc, Copenhagen) in RPMI 1640 supplemented with 10% heat-inactivated FCS, 25 mmol/L Hepes, 2 mmol/L l-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin (complete medium). PWM (10 μg/mL; GIBCO, Grand Island, NY) was added from the beginning of the culture. After 7 days at 37°C in a humidified incubator with 5% CO2, the plates were centrifuged at 200 g for 5 minutes and supernatants were carefully removed for determination of IgM, IgA, and IgG by ELISA. Cultures were set up in four to six replicates.

In experiments designed to investigate the effect of nonirradiated or irradiated (2,000 rad) T4 or T8 cells from patients with CLL or normal donors on Ig production by mixtures of allogeneic T4 (0.1 x 10^6) and B (1.0 x 10^6) cells from normal donors, various numbers (0.1 x 10^5 to 8.0 x 10^5/well) of T4 or T8 cells were added to these mixtures and the cells were cultured as described in the previous paragraph. Supernatants were collected after 7 days for IgM, IgA, and IgG determination.

RESULTS

Patients. Twenty untreated patients with B-cell CLL were used in this study. Their characteristics are shown in Table 1. These patients exhibited significantly decreased (P < .001) proportions of T4 cells and significantly increased (P < .001) proportions of T8 cells in comparison with those of normal donors, resulting in a significantly lower ratio of the T4/T8 phenotype.

Defective helper function of purified T4 cells from patients with CLL. To determine the ability of purified T4 cells from patients with CLL to provide helper function for the differentiation of B cells to Ig-producing cells, various numbers (0.01 x 10^5 to 8.0 x 10^5) of T4 cells from patients with CLL or normal donors were added to 1.0 x 10^6 (or to 5.0 x 10^5 in patients 8 through 11) highly purified E rosette-negative allogeneic cells (B cells) from normal donors and cultured for 7 days at 37°C with PWM. IgM, IgA, and IgG produced were determined in the supernatants by heavy-chain–specific ELISA as described in the Materials and Methods section. Kinetic studies demonstrated that maximum amounts of IgM, IgG, and IgA were produced after incubation for 7 days (data not shown). Representative results, obtained using equal numbers of T4 cells from patients with CLL or normal donors, at ratios of T4 to B cells of 1:10, are shown in Fig 1. Purified T4 cells from nine patients with CLL (patients 1, 3, 9 through 11, 13, 16, 18, and 20) exhibited highly significant (P < .001) defective helper function for the production of IgM, IgA, and IgG by E rosette-negative cells from normal donors when compared with that achieved in the presence of T4 cells from normal donors. Defective helper function of purified T4 cells from patients with CLL was also observed at various other ratios (1:10, 1:2, 2:1, or 4:1) of T4 (CLL) to B (normal) cells (data not shown). Furthermore, purified T4 cells from another four patients (patients 4, 12, 17, and 19) with CLL exhibited defective (P < .001) helper function to the synthesis and secretion of two of the three Igs. Purified T4 cells from an additional patient (patient 2) exhibited significant (P < .001) defective helper function to production of IgM only. Therefore, purified T4 cells from 14 of 20 patients with CLL exhibited defective helper function to Ig production by B cells from normal donors. Purified E rosette-forming cells from certain of these patients were examined for helper function to Ig production by B cells from normal donors and exhibited defective helper function also (data not shown). T4 cells from 6 of 20 patients with CLL (patients 5 through 8, 14, and 15) provided normal helper function to Ig production by B cells from normal donors (Fig 1).
The effect of irradiation (2,000 rad) on helper function of purified T4 cells from patients with CLL was investigated in five patients (patients 16 through 20). Irradiation increased or restored in part, at high (8:1) T4 (CLL)/B (normal) ratios, the helper function of purified T4 cells from two patients (patients 18 and 19; data not shown) but had no effect on T4 cell activity from three others. In this PWM-driven system, mixtures of allogeneic or autologous T4 and B cells from normal donors produced similar amounts of IgG, IgM, and IgA (Table 2).

Excessive suppressor activity of purified T8 cells from patients with CLL. Purified T8 cells (0.1 x 10^5 to 5.0 x 10^5) from patients with CLL or normal donors were cultured with mixtures of allogeneic T4 (0.1 x 10^5) and B (1 x 10^5) cells from normal donors in the presence of PWM. T8 cells from all normal donors examined significantly suppressed Ig production by mixtures of normal T4 and B cells (Fig 2). There was no difference in the ability of T8 cells from normal donors to suppress Ig production by mixtures of autologous or allogeneic normal T4 and B cells (data not shown). Purified T8 cells from six of 20 patients with CLL (patients 1, 4, 5, 11, 13, and 20) exhibited excessive suppressor activity to the production of IgM, IgA, and IgG in a concentration-dependent manner (Figs. 2 and 3). Ig levels produced by mixtures of T4 and B cells from normal donors in the presence of T8 cells from these six patients were significantly lower (P at least < .01) to those produced in the presence of T8 cells from normal donors. In addition, IgA synthesis and secretion only was excessively suppressed by T8 cells from two other patients with CLL (patients 6 and 10). These T8 cells may be Ig class-specific suppressor cells. Six (patients 1, 4, 11, 13, 19, and 20) of these eight patients with excessive suppressor activity by T8 cells also exhibited defective helper function by T4 cells. In contrast, purified T8 cells from three other patients with CLL (patients 12, 15, and 18) exhibited defective suppressor activity. Ig levels produced in the presence of purified T8 cells from these three patients were significantly higher than those produced in the presence of equal numbers of T8 cells from normal donors. Purified T8 cells from nine other patients with CLL (patients 2, 3, 7 through 10, 14, 16, and 17) exhibited suppressor activity to Ig production comparable to that of T8 cells from normal donors.

In conclusion, purified T8 cells from patients with CLL exhibited abnormal immunoregulatory functions. In 8 of 20 patients, excessive suppressor activity was observed. T8 cells from three other patients exhibited defective suppressor activity, whereas T8 cells from the remaining nine patients exhibited normal immunoregulatory functions to Ig production.
B cells from normal donors and IgM, IgA, and IgG produced were determined after 7 days. Suppressor activity of T8 cells from 13 patients with CLL (patients 1, 4 through 9, 12, 14 through 16, 18, and 19) was at least in part radiosensitive, although to a variable degree. Nonirradiated T8 cells from three of these 13 patients (patients 1, 4, and 5) exhibited excessive suppressor activity. In some of these patients (patients 4, 6 through 8, 12, 14, 18, and 19) the suppressor activity of T8 cells was completely abolished by irradiation, whereas in others (patients 1, 5, 9, 15, and 16) it was only partially reduced. Suppressor function exhibited by T8 cells from the other seven patients with CLL (patients 2, 3, 10, 11, 13, 17, and 20) was radioresistant. Representative results from two patients with CLL are shown in Fig 3. Purified T8 cells from one of these patients (patient 20) were radioresistant, whereas those from the other patient (patient 4) were radiosensitive. Irradiation (2,000 rad) of T8 cells from normal donors resulted in complete or partial abrogation of their suppressor activity (Fig 3 and data not shown).

The effect of irradiation on purified T8 cells from patients with CLL with excessive suppressor activity was variable. T8 cells from four of eight patients (patients 1, 4, 5, and 6) were radiosensitive, and their excessive suppressor activity was at least in part reduced by irradiation. T8 cells with excessive

### Table 2. PWM-Immunoglobulin Synthesis and Secretion by Mixtures of Autologous or Allogeneic T4 and B Cells From Normal Donors

<table>
<thead>
<tr>
<th>T4 Cells/Well</th>
<th>B Cells/Well</th>
<th>IgM (μg/dL)</th>
<th>IgG (μg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>1 x 10⁵</td>
<td>11 ± 2</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>0.1 x 10⁶</td>
<td>1 x 10⁵</td>
<td>118 ± 5</td>
<td>203 ± 6</td>
</tr>
<tr>
<td>0.5 x 10⁶</td>
<td>1 x 10⁵</td>
<td>338 ± 6</td>
<td>283 ± 8</td>
</tr>
<tr>
<td>2.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>179 ± 1</td>
<td>143 ± 6</td>
</tr>
<tr>
<td>4.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>80 ± 7</td>
<td>63 ± 1</td>
</tr>
<tr>
<td>8.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>27 ± 3</td>
<td>32 ± 4</td>
</tr>
<tr>
<td>Allogeneic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>1 x 10⁵</td>
<td>15 ± 4</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>0.1 x 10⁶</td>
<td>1 x 10⁵</td>
<td>127 ± 7</td>
<td>199 ± 7</td>
</tr>
<tr>
<td>0.5 x 10⁶</td>
<td>1 x 10⁵</td>
<td>324 ± 4</td>
<td>275 ± 6</td>
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<td>2.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>163 ± 8</td>
<td>153 ± 8</td>
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<td>4.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>84 ± 3</td>
<td>70 ± 4</td>
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<tr>
<td>8.0 x 10⁶</td>
<td>1 x 10⁵</td>
<td>22 ± 1</td>
<td>36 ± 4</td>
</tr>
</tbody>
</table>

Cultures were set up and immunoglobulin levels were determined as described in the Materials and Methods section.
Fig 2. Suppressor function of purified T8 cells from patients with B-cell CLL. Significant suppression (P < .001) of Ig levels by T8 cells from normal donors are marked by (O). Significant differences (P < .001) between Ig levels produced in the presence of equal numbers of T8 cells from allogeneic normal donors v T8 cells from patients with CLL are marked by ( OO). Significant differences (P < .001) between Ig levels produced by mixtures of T4 and B cells from normal donors in the presence of irradiated v nonirradiated T8 cells from patients with CLL are marked by (p ). IgM, O; IgA, △; IgG, □; Immunoglobulins (Micrograms/dl).

Fig 3. Suppressor function of purified T8 cells from patients with B-cell CLL. Production of IgM, IgA, and IgG is shown by mixtures of T4 and B cells from normal donors in the presence of various numbers of purified T8 cells from patients with CLL (IgM O---O, IgA △---△, IgG □---□) or normal donors (IgM O---O, IgA △---△, IgG □---□).* Statistically significant (P < .001) differences from controls. Production of IgM, IgA, and IgG is shown by mixtures of T4 and B cells from normal donors in the presence of irradiated (2,000 rad) purified T8 cells from patients with CLL (IgM O---O, IgA △---△, IgG □---□) or normal donors (IgM O---O, IgA △---△, IgG □---□).
Suppressor effector T4 cells, directly suppressing Ig production by mixtures of T4 and B cells, in the absence of T8 cells. Purified T4 cells from 6 of 20 patients with CLL (patients 1, 2, 9, 13, 17, and 20) regularly and reproducibly suppressed Ig production by mixtures of T4 and B cells from normal donors, in the absence of T8 cells (Fig 4). Suppression of Ig production was highly significant ($P < .001$) when compared with the Ig produced by either (a) mixtures of T4 and B cells from normal donors, or (b) mixtures of these T4 and B cells and allogeneic normal T4 cells added to the cultures in numbers equal to those of the T4 CLL cells. Suppression by T4 CLL cells was concentration dependent (Fig 5 and data not shown). Furthermore, purified T4 cells from all these six patients (patients 1, 2, 9, 13, 17, and 20) exhibited defective helper function to Ig production (Fig 1). These results can be explained only if suppressor effector cells are present in purified T4 cells from these patients with CLL and cannot be attributed to the kinetics of the antibody production by mixtures of T4 and B cells from normal donors or to other nonspecific means such as cell crowding.

Addition of purified T4 cells from normal donors to mixtures of normal T4 and B cells significantly increased Ig production in 14 of 20 normal donors examined. In three other donors, addition of purified T4 cells to the T4 and B cell mixtures resulted in significant decrease in IgM production but not in that of IgA or IgG. In another donor, addition of T4 cells resulted in significant decrease of IgM and IgG production but not of IgA (Fig 4). These decreases may result from the different characteristics of the T4:B curve of Ig production (Fig 5).

Significantly lower levels of Ig were produced in cultures of T4 ($0.1 \times 10^6$) and B ($1 \times 10^6$) cells from normal donors and T4 CLL cells from 12 of 20 patients (patients 1 through 4, 6, 9, 10, 13, 15 through 17, and 20), in comparison to those produced in cultures of normal T4 ($0.1 \times 10^6$) and B ($1 \times 10^6$) cells and equal to (to the T4 CLL) numbers of T4 cells from normal donors. T4 cells from six of these patients (patients 1, 2, 9, 13, 17, and 20) contained suppressor effector cells as previously described. T4 cells from the remaining patients exhibited defective helper function but did not contain suppressor effector cells. Furthermore, T4 cells from another seven patients with CLL (patients 7, 8, 11, 12, 14, 18, and 19) exhibited helper function similar to that observed with T4 cells from normal donors, whereas T4 cells from an additional patient (patient 5) contained significantly higher helper activity (Fig 4).

Studies on the radiosensitivity of T4 suppressor effector cells from patients 1, 2, 9, 13, 17, and 20 are shown in Figs 4 and 5. Suppression of the production of certain Ig isotypes was in part radiosensitive. Irradiation of T4 cells from patients 5 through 7 and 19 resulted in significant increase in Ig production by T4 and B cells from normal donors (Fig 4).

In vitro treatment of T4 suppressor effector cells from patients with CLL with the OKT4 mAb plus complement (Fig 6) or OKT11 mAb plus complement (data not shown), completely abrogated their suppressor activity of Ig production by mixtures of T4 and B cells from normal donors. These results demonstrate that these effector suppressor cells are of the T4+, T11+, T8− phenotype.

![Fig 4. Purified T4 cells from certain patients with B-cell CLL directly suppressed Ig production by mixtures of T4 and B cells from normal donors in the absence of T8 cells. Significant differences ($P < .001$) between Ig levels produced by mixtures of T4 and B cells (ratio 1:10) from normal donors in the presence or absence of additional T4 cells from normal donors are marked by (O). Significant differences ($P < .001$) between Ig levels produced in the presence of equal numbers of T4 cells from normal donors or patients with CLL are marked by (O). Significant suppression ($P < .001$) of Ig levels by purified T4 cells from patients with CLL are marked by (Δ). Significant differences ($P < .001$) between Ig levels produced in the presence of equal numbers of nonirradiated or irradiated T4 cells from patients with CLL are marked by (Δ). IgM, [ ]; IgA, [ ]; IgG, [ ]; Immunoglobulins (Micrograms/dl).]
Fig 5. Purified T4 cells from certain patients with B-cell CLL directly suppress Ig production by mixtures of T4 and B cells from normal donors, in the absence of T8 cells. Production of IgM, IgA, and IgG is shown by mixtures of T4 and B cells from normal donors in the presence of various numbers of purified T4 cells from patients with CLL (IgM O, IgA △, IgG ■■■■) or normal donors (IgM O, IgA △, IgG ■■■■). *Statistically significant (P < .001) differences from controls. Production of IgM, IgA, and IgG is shown by mixtures of T4 and B cells from normal donors and various numbers of irradiated (2000 rads) purified T4 cells from patients with CLL (IgM O, IgA △, IgG ■■■■) or normal donors (IgM O, IgA △, IgG ■■■■). **Statistically significant (P < .001) differences from controls.

DISCUSSION

We investigated helper and suppressor functions to B cell responses and T–T cell interactions of purified T4 and T8 cells from patients with B-cell CLL and found a wide range of immunoregulatory T-cell defects in these patients. The defects included defective helper function of purified T4 cells and excessive suppressor activity of purified T8 cells to Ig production by lymphocytes from normal donors. Furthermore, we identified for the first time naturally occurring suppressor effector cells of the T4 phenotype present in certain patients with CLL. These cells were able to suppress Ig production by mixtures of T4 and B cells from normal donors in the absence of T8 cells. These naturally occurring T4 suppressor cells were of the T11+, T4+, T8− phenotype. It is unlikely that suppression of Ig production observed by these effector suppressor cells was due to cell crowding for the following reasons. First, suppression by T4 cells was observed only in certain patients with CLL (30%). T4 cells from the remaining patients added in equal numbers to mixtures of T4 and B cells from normal donors did not suppress. Second, addition of equal numbers of T4 cells from normal donors to the T4 and B cell mixtures did not result in suppression of Ig production. Third, the recoveries of viable cells from all control and experimental cultures after 7 days were similar.

The ability of T4 suppressor effector cells to suppress in the absence of T8 cells demonstrates that they are not suppressor inducer cells—at least not of the type previously described.49 Suppressor inducer cells are also of the T4 phenotype and inhibit Ig production by mixtures of T4 and B cells from normal donors only in the presence of T8 cells.
presumably by inducing the differentiation of presuppressor T8 cells to effector suppressor T8 cells (49).

Thomas et al. reported the induction of suppressor cells of the T4 phenotype by treating purified T4 cells form normal donors with PWM for 60 to 70 hours. Suppressor activity was determined by adding these cells to secondary cultures of T4 and B cells from normal donors and determining plaque-forming cell activity after 5 days. These PWM-activated T4 suppressor cells were radiosensitive and did not require the presence of T8 cells to suppress. However, radiosensitive untreated T4 cells were required for suppression by PWM-activated T4 cells. We report that naturally occurring T4 suppressor cells are present in certain patients with CLL (Figs 4 and 5). These suppressor cells may have been activated in vivo as a result of the disease. They are only in part radiosensitive. Whether they require radiosensitive T4 cells to exercise suppression remains to be determined. These T4 suppressor cells may act on another subset of T4 cells that directly or indirectly exercise helper function or they may induce the differentiation of presuppressor cells to suppressor cells of the T4 phenotype. These results underline the significance of T-T cell interactions within the T4 subset for the regulation of the immune response and suggest that significant functional heterogeneity exists within the T4 population.

Significant imbalances of T-lymphocyte subpopulations have been reported in patients with CLL. These include increased proportions of T4 cells, decreased proportions of T4 cells and increased proportions of T8 cells, resulting in a significantly decreased ratio of the T4/T8 phenotypes. Certain of these changes may reflect immunologic aberrations because of the disease or alterations in the distribution of T4 and T8 cells between central lymphoid organs (spleen, lymph nodes) and peripheral blood. Imbalances of T4 and T8 phenotypes in CLL apparently appear during an early phase of the disease and were present in 21 of 24 patients with CLL of stage 0 or I examined in this study and in a previous study. A significant number of T cell functions have been reported to be abnormal in patients with CLL, including a helper T cell defect for the differentiation of B cells from normal donors to Ig-producing cells. Several investigators showed that suppressor T cell activity was excessive in certain patients and others showed it to be normal. Our results suggest that T lymphocyte subpopulations in patients with CLL can exhibit defective helper function and/or excessive suppressor activity to Ig production by B cells.

Patients with CLL often develop irreversible hypogammaglobulinemia of variable severity and profound antibody deficiency syndrome. The basis of this secondary immunodeficiency is poorly understood. Defective helper function and excessive suppressor activity of T lymphocyte subpopulations in patients with CLL may be responsible at least in part for generation of the hypogammaglobulinemia and the immunodeficiency observed in these patients. Severe imbalances of immunoregulatory T-lymphocyte subpopulations may also contribute to the hypogammaglobulinemia. Other factors responsible or contributing to the hypogammaglobulinemia may include first an intrinsic defect of B cells to differentiate into Ig-producing plasma cells and second, the effect of the extensive tumor cell load on the functions and cellular and molecular interactions between nonmalignant lymphocytes.

Leukemic B cells present in high absolute numbers in these patients may interfere with direct T-T and T-B cell–cell communication and may significantly deplete T-cell–derived B-cell growth and differentiation factors. Leukemic B cells from patients with CLL have been reported to respond by proliferation and/or differentiation to conditioned media derived by polyclonal stimulation of T cells, and to recombinant IL-2 and recombinant γ-interferon, and B-cell growth factor. Third, leukemic B cells from patients with CLL may affect antibody production. In addition, abnormal function of cells of the monocyte/macrophage lineage may contribute to the immunodeficiency in CLL. Studies to evaluate these possibilities have not been carried out.

In conclusion, these studies demonstrate that purified T4 or T8 cells from patients with CLL exhibit, respectively, defective helper function or excessive suppressor activity to Ig production by lymphocytes from normal donors. Effector suppressor cells of the T4 phenotype, directly suppressing Ig production by mixtures of T4 and B cells from normal donors in the absence of T8 cells, were found in certain patients with CLL.

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