Lymphokine Production by T-Cell Clones After Human Bone Marrow Transplantation

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T cells recovering after bone marrow transplantation (BMT) were analyzed for their phenotypic and functional features by two-color immunofluorescence and a high efficiency cloning technique. A predominance of cells co-expressing natural killer (NK)-related surface antigens, such as Leu 7 (CD57) and CD11b, was detected within both the CD4+ and CD8+ subsets from 5 months postgrafting onward. Such cells are virtually absent among normal circulating CD4+ cells and account for a minority (~30%) of normal CD8+ cells. Postgrafting T cells representative of the wide range of NK-related antigen co-expression were selected from six patients for clonal analyses. In control subjects, 63% and 41% of the CD4+ and CD8+ clones, respectively, produced interleukin-2 (IL-2) whereas ~30% of either CD4+ or CD8+ control clones produced interferon (IFN)-gamma. At variance, and irrespective of their CD4+/CD8+ phenotype, lower proportions of BMT recipient-derived clones produced IL-2 (20% and 12%, respectively), whereas the majority of both CD4+ and CD8+ clones (75% and 71%, respectively) released high amounts of IFN-gamma. Purified populations of CD57+/CD11b+ negative cells from two BMT recipients and two control subjects were cloned and subsequently evaluated for IL-2 and IFN-gamma production. CD57+/CD11b+ cell-derived clones were poor IL-2 producers in both normal subjects and BMT patients. In contrast, IL-2-producing clones were frequent (62% to 79%) among those derived from CD57−/CD11b− cells from normal subjects, whereas they were still represented at lower than normal proportions, i.e., 25% to 41%, among clones generated from BMT recipients. CD57+/CD11b+ cells gave rise to comparably high proportions of IFN-gamma producing clones in both normal subjects and BMT recipients (~80%). In contrast, IFN-gamma producing clones were ~25% to 50% of CD57−/CD11b− cell-derived clones in both normal subjects and BMT patients. Therefore, while the predominance of NK-related antigen-positive T cells may be predictive of poor IL-2 and high IFN-gamma production, the immune derangement in long-term BMT recipients is further enhanced by the finding that all T cells may be poor IL-2 producers. It is also suggested that IL-2 production is a preferential function of T cells that do not express CD57 and CD11b, whereas IFN-gamma production is attributable to T cells that express CD57 and CD11b.

Bone marrow transplant recipients are susceptible to a variety of bacterial, viral, and fungal infections due to a combined cellular and humoral immune deficiency syndrome that spans throughout the first 1 to 2 years postgrafting. Phenotypic and functional abnormalities of T cells have been described consistently in the reconstitution phase after bone marrow transplantation (BMT). These abnormalities comprise inverted CD4+/CD8+ T-cell ratios, defective proliferative responses to mitogens, antigens and alloantigens, defective helper function for B-cell differentiation, and poor interleukin-2 (IL-2) production. Furthermore, a decreased frequency of IL-2-producing T-cell precursors has been demonstrated, although interpretation of these data is hampered by a very low cloning efficiency. T-cell reconstitution in most healthy long-term survivors is successfully completed 6 months to 1 year postgrafting, whereas recipients with chronic graft-vs-host disease (GVHD) exhibit long-lasting immunologic abnormalities.

We have recently identified a predominance of T cells co-expressing NK-related antigens, such as Leu7 (CD57) and CD11b, both within the T-helper and the T-cytotoxic cell subsets, following T-cell depleted allogeneic BMT for hematologic malignancy. These cells were already predominant in the early recovery phase, accounted for up to 85% of the CD4+ and 100% of the CD8+ T-cell subsets around the fifth month post-BMT and remained elevated throughout the first postgrafting year. In normal blood, CD4+ cells co-expressing CD57 and CD11b represent a negligible proportion of T-helper cells. Studies at the population and clonal levels have indicated that CD4+ cells co-expressing NK antigens differ from typical T-helper cells in that they proliferate poorly in response to mitogens and alloantigens, and do not produce IL-2. A phenotypic and functional heterogeneity similar to that described for CD4+ cells is also found within the CD8+ subset of peripheral blood T lymphocytes. Approximately one third of these cells co-express the CD57 and CD11b markers and, in contrast to CD8+ T cells, which do not co-express CD57 and CD11b, proliferate poorly in response to mitogens or antigens, and fail to generate cytolytic effector cells in MLC. It might therefore be anticipated that the predominance of T cells co-expressing NK-related features in the late reconstitution phase after BMT could account, at least in part, for impaired T cell (IL-2)-mediated immune functions.

In this study we have performed functional analyses of a large number of T-cell clones established in the late (≥5 months) reconstitution phase after allogeneic BMT. The...
results indicate that such phenotypic imbalance within the CD4+ and CD8+ T cell subsets is associated with a striking derangement in lymphokine production, with increased proportions of interferon (IFN)-gamma producing clones v greatly reduced frequencies of IL-2 producing clones.

MATERIALS AND METHODS

Patients and controls. BMT was performed in 18 subjects with hematologic malignancies in remission (11 acute leukemias, four chronic myelogenous leukemias, two non-Hodgkin's lymphomas, and one multiple myeloma). Age ranged between 12 and 45 years (mean, 30 ± 9). Patients in remission were prepared for transplantation by cytoreduction using antithymocyte horse immunoglobulin (Merieaux, Paris) and procarbazine, followed by hyperfractionated total body irradiation and cyclophosphamide. The marrow donors were HLA-identical, mixed lymphocyte culture-compatible adult individuals (age >20 years). Control subjects in this study were either marrow donors or normal individuals age-matched to the donors.

Marrow graft preparation. To prevent GVHD, the marrow transplants were depleted of T cells by sequential soybean agglutination and sheep RBC (SRBC) rosetting, according to a procedure described by Reisner et al. Posttransplant follow-up. Marrow graft recipients received no immunosuppressive therapy for GVHD prophylaxis in the posttransplant period. Only one of the 18 patients developed grade I acute GVHD, while none had chronic GVHD. Engraftment was documented by blood group change or by cytogentic analysis of sex marker conversion, or disappearance of Phi chromosome. The minimum follow-up was 11 months in all patients (range, 11 to 33 months). Post-BMT patients selected for this study were all successfully engrafted. No graft failure was observed in the subsequent follow-up of these patients.

Immunofluorescence. Heparinized blood samples were obtained monthly from marrow recipients and normal controls after informed consent. Mononuclear cells were isolated by Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, NJ) density gradient centrifugation, and partially depleted of monocytes by adherence to plastic dishes. The CD4+ and CD8+ cell subsets were enumerated and analyzed for co-expression of CD57 and CD11b antigens by two-color immunofluorescence, using fluorescein-conjugated Leu3 or Leu2 mouse monoclonal antibodies in combination with conjugated Leu7 or Leu15 mouse monoclonal antibodies (Becton Dickinson, Mountainview, CA) developed with rhodamine-conjugated goat anti-mouse IgM or IgG2a antibodies, respectively (Southern Biotechnology Associates, Birmingham, AL). Co-expression of CDw29, an antigen associated with memory I cells, on CD57+ and CD11b- cells by antibody plus complement-mediated cytolysis. In addition, those exceptional cultures exhibiting mixed CD4+/CD8+ cell populations were excluded from the analysis.

Clonal microcultures. Clonal microcultures were washed several times and were resuspended at a cell

used as previously described. Fluorescein-conjugated goat antimouse antibodies (Southern Biotechnology Associates) were used as second step reagents.

T-cell cloning. Following analysis of 18 BMT recipients for co-expression of CD57 and CD11b antigens on circulating CD4+ and CD8+ cells, six samples (from six individual patients) representative of the observed range of NK-antigen expression were selected for cloning experiments and subsequent functional analyses of the clonal progeny. Co-expression of NK-related antigens on freshly isolated T cells from these six samples was 40% to 87% (range) on CD4+ cells and 70% to 100% on CD8+ cells. Mononuclear cell preparations were plated under limiting dilution conditions and activated with phytohemagglutinin (PHA) for 24 hours before addition of IL-2. Before cloning, the percentage of CD3+ (total T) cells in each sample was determined by immunofluorescence. Cell preparations containing known numbers of CD3+ cells were plated from 2 to 0.5 CD3+ cells/well for control cultures and from 16 to 1 cells/well for BMT recipients' cultures, in groups of 48 microcultures in U-bottom microwells containing 105 irradiated (5,000 rad) spleen feeder cells in RPMI 1640 medium with 10% heat-inactivated fetal calf serum and 0.5% PHA. Recombinant IL-2 (generously provided by the GLAXO Institute for Molecular Biology S.A., Geneva, Switzerland) was added at a final concentration of 25 U/mL after 24 hours. Plates were incubated at 37°C in a humidified atmosphere with 5% CO2. Microcultures were supplemented on day 7 with 103 irradiated feeder cells and IL-2. IL-2 was further added on day 14. Control wells contained irradiated feeder cells, PHA, and IL-2 without addition of responder cells. After 14 to 18 days of culture each microwell was assessed microscopically for cell growth. Immunofluorescence analysis of 50 randomly selected clones revealed that they were all CD3+. Frequencies of proliferating cells were then calculated by the x2 method from the Poisson distribution relationship between the number of CD3+ cells plated per culture and the logarithm of the percentage of nonproliferating cells. According to the Poisson formulae, if the cloning efficiency is 100%, positive cultures growing from 0.25 (or less) T cell plated per well are highly likely to be clonal. In the present experiments, cloning efficiency was ~50% for control cultures and ~10% for patients' cultures (Fig 1). Accordingly, growing microcultures were considered clonal when they were derived from 0.5 T cells plated per well in the case of control cultures and two (or less) T cells plated per well in the case of patients' cultures. Only these cultures were used for functional and phenotypic analyses and are referred to as "clones" throughout the report. In addition, those exceptional cultures exhibiting mixed CD4+/CD8+ cell populations were excluded from the analysis.

To determine the role of CD57+CD11b+ or CD57+CD11b+ T cells. To determine the role of CD57+CD11b+ expression on T cells from BMT patients and control subjects, cells forming E-rosettes were isolated from two normal donors and two BMT recipients. E-rosette-positive fractions were further enriched (±95% as determined by immunofluorescence) for CD57+CD11b+ or CD57+CD11b+ cells by antibody plus complement-mediated cytolysis. In order to enrich for CD57+CD11b+ T cells, E-rosette forming cells were stained with Leu7 (IgM) and Leu15 (IgG1) antibodies and subsequently incubated with rabbit complement (Low-Tox-H rabbit complement; Cedarlane, Hornby, Ontario, Canada), at 37°C for one hour. CD57+CD11b+ cells were purified by lysing the reciprocal, nonoverlapping CD28 + T cell population using the 9.3 (IgM) monoclonal antibody (kindly donated by Dr John A. Hansen, Seattle) and complement-mediated lysis as described below.

These purified populations were cloned using the limiting dilution method at the concentration of 2 to 0.5 cells/well.

Assays for IL-2 or IFN-gamma production. Clonal microcultures were washed several times and were resuspended at a cell
CLONABLE T CELLS AFTER BMT

Fig 1. Following analysis of 18 BMT recipients for co-expression of NK-related antigens, CD57 (Leu7) and CD11b, on circulating CD4+ and CD8+ cells, six samples (from six individual patients) representative of the observed range of NK-antigen expression were selected for cloning experiments and subsequent functional analyses of the clonal progenies. Mononuclear cell preparations from these six patients and two control subjects were plated under limiting dilution conditions (see Materials and Methods section). After 18 days of culture each culture well was scored microscopically for cell proliferation and the CD3+ and CD4+/CD8+ phenotypes of the clones were determined by immunofluorescence. Shown are the limiting dilution analyses of the frequencies of proliferating CD3+ clonal microcultures derived from BMT recipients (A) and control subjects (B). The regression line was fitted to the data by the minimum x^2. Cloning efficiency was ~50% in control subjects and ~10% in BMT recipients.

Concentration of 1 x 10^6/mL in 200 μL culture medium containing 0.5% (vol/vol) PHA. Supernatants were removed after 24 hours for determination of lymphokine activity. As an indicator system for determination of IL-2 activity we used the IL-2-dependent mouse CTLL cell line. Clonal supernatants were added to 5 x 10^4 indicator cells at a final concentration of 25%. IL-2 activity was assessed by ([3H]thymidine uptake of CTLL cells after a six-hour pulse at the end of a 24-hour culture period. IFN-gamma was measured by a cytopathic effect reduction assay, using vesicular stomatitis virus and FLAM cells, as indicator system.

Results

Phenotypic analyses of T cells in BMT recipients. Table I summarizes our survey of a total of 18 graft recipients as for the co-expression of CD57 and CD11b on peripheral blood CD4+ and CD8+ T cells, as determined by two-color immunofluorescence. The data refer to peak values generally observed around 5 to 7 months postgrafting and indicate that, following allogeneic BMT, the recovering CD4+ and CD8+ cell subsets are largely composed of cells co-expressing CD57 and CD11b.

In order to gain information on the significance of the phenotypic imbalance described above, we have analyzed the expression of CDw29, a marker that has been associated with memory T cells, on both CD57+ and negative T cells. To this end, cells forming E-rosettes were costained with anti-CD57 and anti-CDw29 antibodies and the coexpression of the latter marker on CD57+ and negative cells was evaluated by two-color immunofluorescence. Data in Table 2 demonstrate that, in three patients selected for such analysis, on the basis of the high frequencies of CD57+ T cells (~50%), the

Table 2. Co-expression of the Memory T-Cell Antigen CDw29 on CD57+ and Negative T Cells in BMT Recipients and Control Subjects*

<table>
<thead>
<tr>
<th>T Cells</th>
<th>Patients</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>CD57+ T cells</td>
<td>60%−72%</td>
<td>64%−78%</td>
</tr>
<tr>
<td>CD57− T cells</td>
<td>1%−2%†</td>
<td>33%−36%†</td>
</tr>
</tbody>
</table>

*E-rosette-positive mononuclear cell fractions were costained with anti-CD57 and anti-CD29 antibodies and the proportions of CD29+ cells among CD57+ and negative cells was evaluated by two-color immunofluorescence. Co-expression of CD57 on T cells from the three control subjects and the three BMT recipients selected for this analysis was 16% to 18% and 49% to 53%, respectively.

†P < .05 by Chi-square test.
expanded CD57+ cell population, as opposed to CD57− cells, was largely composed of cells co-expressing CDw29. This is in contrast to that found in control subjects in which CDw29 was also expressed on the predominant population of CD57− T cells. It does appear that generation of T-cell memory in BMT recipients is almost exclusively contributed for by CD57+ cells.

**Clonal expansion of T cells in the late reconstitution phase after BMT.** Six of the 18 long-term BMT recipients were randomly selected for cloning experiments. In these patients the expression of CD57 and CD11b on CD4+ or CD8+ cells ranged from intermediate to very high, i.e., from 40% to 87% of the CD4+ cells and from 70% to 100% of the CD8+ cells. Therefore these patients were representative for the overall population of BMT recipients. Cell preparations from these patients were plated under limiting dilution and activated with PHA for 24 hours before addition of IL-2.

As shown in Fig 1, T cells in the reconstitution phase after BMT were capable of clonal expansion, although the frequencies of proliferating cells (=1 in 10) were lower than those of control T cells (=1 in 2). A total of 177 clones from six BMT recipients and 62 clones from two control subjects were examined (see the Materials and Methods section for definition of clonality). Immunofluorescence analyses performed on separate aliquots of each growing microculture (between day 18 and 21) demonstrated that 62 of 177 clones from BMT recipients were CD4+ (35%) and 115 of 177 were CD8+ (65%). On the other hand, of the 62 control clones examined, 35 (56.5%) were CD4+ and 27 (43.5%) were CD8+. This distribution closely reflected the CD4/CD8 ratios detected in the original PBL preparations used in the cloning experiments, i.e., CD4/CD8 = 1.3 in normal control subjects and CD4/CD8 = 0.6 in BMT recipients. This indicates that the relatively low cloning efficiency of BMT recipients' T cells, as opposed to that of control cells, was not a consequence of a selective inability of a given T-cell subset (e.g., CD8+ or CD4+) to give rise to clonal progenies in our system. Likewise, such relatively low cloning ability should not be the consequence of a selective disadvantage of CD57+/CD11b+ T cells to clone in our system. This is indicated by the comparable cloning efficiencies of purified CD57+/CD11b+ or CD57−/CD11b− negative T-cell populations (see below), and of CD8+ cells from the one sample in which the totality of CD8+ cells co-expressed CD57 and CD11b, compared with that of other BMT recipient-derived CD4+ or CD8+ cell populations not co-expressing NK-related antigens at the same rate (see the Discussion section). Analyses of the expression of CD57 and CD11b antigens were not performed in clonal cultures because our previous studies at the clonal level have shown that both antigens may be lost over a relatively short culture period.19

**Lymphokine production after BMT.** In order to evaluate the ability of the clones to produce lymphokines, clonal microcultures (containing 4 × 10^5 cells) were stimulated with PHA for 24 hours. The culture supernatants were then harvested and tested for IL-2 activity and for IFN-gamma production. Sixty-three percent and 41% of control CD4+ and CD8+ clones, respectively, produced detectable amounts of IL-2, whereas ~30% of either CD4+ or CD8+ control clones produced IFN-gamma. In contrast, 20% of CD4+ clones and 12% of CD8+ clones derived from BMT recipients produced IL-2, whereas the majority of both

![Fig 2](image-url)
CD4+ and CD8+ clones (75% and 71%, respectively) produced high amounts of IFN-gamma (Figs 2 and 3). These results indicate that clonable T cells in the late reconstitution phase after BMT contain fewer than normal cells capable of giving rise to IL-2-producing clones and are largely represented by precursors of IFN-gamma producing clonal progenies.

**Functional analysis of clones derived from purified CD57+/CD11b+ and CD57−/CD11b− T cells from BMT recipients and control subjects.** To determine the predictive role of CD57/CD11b expression on T cells from BMT patients and control subjects, cells forming E-rosettes were isolated from two normal donors and two BMT recipients. E-rosette-positive fractions were enriched (≥95%) for CD57+/CD11b+ or CD57−/CD11b− cells by antibody plus complement-mediated cytolysis using anti-CD28 or anti-CD57 + anti-CD11b antibodies, respectively.

These purified populations were cloned using the limiting dilution method at the concentration of 2 to 0.5 cells/well. Cloning efficiencies in these experiments were comparable with those obtained for the total T-cell populations from either control subjects or BMT recipients (Fig 1) (see the Materials and Methods section for definition of clonality).

A total of 43 CD57−/CD11b− cell-derived clones and 31 CD57+/CD11b+ cell-derived clones from two normal subjects, and 38 CD57−/CD11b− cell-derived clones plus 62 CD57+/CD11b+ cell-derived clones from two BMT recipients were evaluated. Cell-derived clones were poor IL-2 producers in both normal subjects and BMT patients (8% to 17% v 5% to 11%, respectively). In contrast, IL-2-producing clones were frequent (62% to 79%) among those derived from CD57−/CD11b− cells from normal subjects, whereas they were still represented at lower than normal proportions, ie, 25% to 41%, among clones generated from BMT recipients. CD57+/CD11b+ cells gave rise to comparably high pro-

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**Table 3. Lymphokine Production by Clones Derived From Purified CD57+/CD11b+ or CD57−/CD11b− Precursor Cells From Normal Donors and BMT Recipients**

<table>
<thead>
<tr>
<th>Cell Precursors</th>
<th>IL-2</th>
<th>IFN-gamma</th>
<th>IL-2</th>
<th>IFN-gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD57+ / CD11b+</td>
<td>8%−17%</td>
<td>70%−94%</td>
<td>5%−11%</td>
<td>73%−85%</td>
</tr>
<tr>
<td>CD57− / CD11b−</td>
<td>62%−79%</td>
<td>32%−51%</td>
<td>25%−41%</td>
<td>25%−40%</td>
</tr>
</tbody>
</table>

Chi-square test: *P < .05 by Chi-square test.*

*Fig 3. Comparison of IL-2 and IFN-gamma production by CD8+ clonal cultures derived from control subjects (A) and BMT recipients (B). IL-2 and IFN-gamma production was determined as described in Materials and Methods. In contrast to control clones, CD8+ clones derived from BMT recipients are characterized by a defective production of IL-2 and an enhanced IFN-gamma production.*
portions of IFN-gamma producing clones in both normal subjects and BMT recipients (>80%). In contrast, IFN-gamma producing clones were ~25% to 50% of CD57−/CD11b− cell-derived clones in both normal subjects and BMT patients. The present data may, therefore, account for some defects of cellular and humoral immunity that occur after BMT.

DISCUSSION

This study identifies previously unrecognized derangements in the lymphokine production pattern of clonable T cells during the late immune reconstitution phase after allogeneic BMT.

Our recent finding of a predominance of cells co-expressing NK-related surface antigens, such as Leu7 (CD57) and CD11b, within both the CD4+ and CD8+ subsets of circulating T lymphocytes from 5 months after BMT onward, suggested that qualitative as well as quantitative changes within the two major T-cell subsets might contribute to the well-recognized post-BMT T-cell functional abnormalities. This phenomenon does not appear to be related to grafting of T-depleted inocula, but is probably a general feature of T cells (reviewed in reference 14).

In the present study, we have extended the above observations to a larger series of patients and have attempted to clarify whether the expanded CD57+/CD11b+ T-cell populations could be somehow associated with T-cell functional abnormalities during the late reconstitution phase after BMT. To this end, we randomly selected six long-term (5 to 7 months) BMT recipients whose freshly isolated CD4+ and CD8+ T cells co-expressed CD57 and CD11b at rates representative of the whole co-expression range observed in the entire series of 18 patients. T cells from these patients were capable of clonal expansion, although at a somewhat lower efficiency than normal donor T cells. The relatively poor cloning efficiency is consistent with the reported defective IL-2 receptor expression of polyclonally activated postgrafting T cells. The analysis of the lymphokine production patterns by these clones indicates that, in contrast to normal CD4+ or CD8+ cells, T cells in the late reconstitution phase after BMT contain fewer cells capable of giving rise to IL-2-producing clones, and are largely composed of precursors of IFN-gamma producing cells. To directly determine the predictive role of CD57/CD11b expression on T cells from BMT patients, purified populations of CD57+/CD11b+ v negative cells from two BMT recipients and two control subjects were cloned and subsequently evaluated for their IL-2 and IFN-gamma production. CD57+/CD11b+ cell-derived clones were poor IL-2 producers in both normal subjects and BMT patients. In contrast, IL-2-producing clones were frequent among those derived from CD57−/CD11b− cells from normal subjects. However, they were still represented at lower than normal proportions among clones generated from BMT recipients. As for the production of IFN-gamma, CD57+/CD11b+ cells gave rise to comparably high proportions of IFN-gamma producing clones in both normal subjects and BMT recipients. In contrast, IFN-gamma producing clones did not exceed ~25% to 50% of CD57−/CD11b− cell-derived clones in both normal subjects and BMT patients. Therefore, while the predominance of NK-related antigen-positive T cells may be predictive of poor IL-2 and high IFN-gamma production, the immune derangement in long-term BMT recipients is further enhanced by the finding that all T cells may be poor IL-2 producers.

IL-2 exerts a central role in the induction of a variety of functions within the normal immune system, such as T-cell proliferation, B-cell proliferation and differentiation, generation of LAK effector cells from their NK precursors. On the other hand, IFN-gamma is a B-cell growth factor, may synergize with IL-2 or other interleukins in the induction of B-cell proliferation and differentiation, but does not support significant B-cell differentiation by itself. Moreover, IFN-gamma has recently been reported to antagonize the effects of IL-4 on human B-cell proliferation and differentiation. In consequence, the observations reported here may depict some of the mechanisms whereby the abnormalities of the humoral and cellular immune systems and the subsequent susceptibility to infections are generated in BMT recipients.

Finally, to gain information on the significance of the expanded CD57+/CD11b+ T-cell populations in long-term BMT recipients, we have analyzed the expression of CDw29, a marker that has been associated with memory T cells, on both CD57+ and negative T cells. Interestingly, the expanded postgrafting CD57+ cell population was largely composed of cells co-expressing CDw29, whereas the reciprocal CD57− T-cell population was not. It does, therefore, appear that generation of T-cell memory in BMT recipients is largely contributed for by CD57+(CD11b+) cells. This observation does not explain why CD57+/CD11b+ T cells are preferentially recruited for the immune response, as opposed to the reciprocal CD57−/CD11b− subset, in the setting of the post-BMT recovery process. Nevertheless, it indicates that CD57+/CD11b+ cells expand by virtue of an ongoing antigen-driven priming process. In view of the selective localization of CD57+/CD4+ T cells into germinal centers, elevated proportion of circulating CD57+, memory, T-helper cells could result from lack of homing to the peripheral lymphoid environment. This is suggested by the observation that involution of lymphoid tissues occurs in the pretransplant induction phase and persists, with lack of germinal centers, in the posttransplant period.

In conclusion, this study indicates that: (1) T-cell clones derived in the late recovery phase after allogeneic BMT, exhibit a very limited ability to produce IL-2 and an enhanced production of IFN-gamma; (2) such functional derangement is associated with phenotypic imbalances, such as co-expression of CD57 and CD11b, within the two major T-cell subsets. However, in long-term BMT recipients, low IL-2 production may be a general feature of all T cells, irrespective of their NK-antigen positive v negative phenotypes.

ACKNOWLEDGMENT

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