Effect of Granulocyte-Macrophage Colony-Stimulating Factor on Lymphokine-Activated Killer Cell Induction

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The treatment of cancer with lymphokine-activated killer (LAK) cells in conjunction with high-dose interleukin-2 (IL-2) has been limited by the toxicity of IL-2 and the narrow range of tumors that respond to therapy. Cytokines that are capable of augmenting lower doses of IL-2 are, therefore, a major focus of research. We report here that granulocyte-macrophage colony-stimulating factor (GM-CSF) can augment low-dose IL-2 LAK induction from murine splenocytes. Anti-tumor necrosis factor α (anti-TNFα) or anti-interferon γ (anti-IFNγ) monoclonal antibodies did not inhibit (IL-2 + GM-CSF)-induced LAK generation, indicating that GM-CSF augmentation does not require TNFα or IFNγ activity. Depletion of natural killer cells before culture did not inhibit low-dose IL-2–induced LAK generation or the ability of GM-CSF to augment LAK generation. In contrast, depletion of both CD4+ and CD8+ T cells before culture inhibited the generation of LAK activity. However, depletion of only CD4+ T cells, or only CD8+ T cells, did not inhibit the generation of IL-2 or (IL-2 + GM-CSF) LAK activity. These results suggest that LAK precursors are present in both the CD4+ and CD8+ T-cell populations and suggest that the addition of GM-CSF to low-dose IL-2 may result in the generation of T-derived LAK cells.

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LYMPHOKINE-ACTIVATED killer (LAK) cells are major histocompatibility complex (MHC)-unrestricted cytolytic cells that can be generated when lymphoid cells from various tissues are incubated in vitro with interleukin-2 (IL-2).1,2 LAK activity may develop from several different cell precursors, including natural killer (NK) cells and T cells.3,5 LAK cells have the ability to kill a variety of tumors including NK-sensitive and NK-resistant lines, and have been used in combination with high doses of IL-2 as a therapy for cancer patients.6,7 The doses of IL-2 required to maintain LAK activity in these patients often cause undesirable side effects, thus reducing the effectiveness of treatment.7 In addition, therapeutic responses to this treatment have largely been limited to renal cell carcinoma and melanoma.8

Although IL-2 appears to be sufficient to induce LAK activity, recent reports have suggested that several cytokines, including IL-1,9,10 IL-4,11IL-5,13 IL-7,14IL-12,16,17 tumor necrosis factor (TNF),18 and interferons (IFNs),19,20 may regulate the ability of IL-2 to induce LAK activity. These findings have important clinical implications. Because the toxicity of IL-2 has been shown to be dose dependent,21 adoptive immunotherapy with in vitro-activated LAK cells and lower doses of multiple cytokines may be better tolerated by patients.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was originally described as a growth factor that induces the proliferation and differentiation of myeloid cells.22,23 Clinically, GM-CSF has been used successfully to accelerate recovery of normal neutrophil counts in patients with neutropenia due to aplastic anemia,24 and in patients receiving chemotherapy.22 GM-CSF has also been shown to upregulate MHC class II molecules on macrophages,26 as well as to induce effector functions of mature macrophages, such as the secretion of cytokines27 and the killing of some tumor targets.28 Furthermore, GM-CSF pretreatment of monocytes from peripheral blood upregulated their ability to augment IL-2–induced LAK activity from blood lymphocytes.29

However, it does not appear that GM-CSF's range of influence is confined to the myeloid branch of the hematopoietic system. In vivo administration of GM-CSF has been shown to increase T-cell counts in acquired immunodeficiency syndrome (AIDS) patients30 and to increase NK activity in the peripheral blood lymphocytes (PBL) of nonhuman primates.31 Those observations suggest that other effects of GM-CSF may yet be elucidated. The current studies indicate that GM-CSF has potent costimulatory activity for the induction of LAK activity from murine splenocytes. The ability to generate LAK activity is dependent on the presence of CD4+ or CD8+ cells, suggesting that T cells are the major source of LAK precursors in this system.

MATERIALS AND METHODS

Animals. Eight- to 12-week-old C57BL/6J mice of either sex were used in these experiments. All animals were purchased from Jackson Laboratories (Bar Harbor, ME). All animals were housed in a specific pathogen-free animal facility and provided with Purina rodent chow and tap water ad libitum.

Targets. YAC-1, P815, and EL4 cell lines were maintained in RPMI 1640 (GIBCO, Grand Island, NY) supplemented with 50 to 75 μmol/L 2-mercaptoethanol, 2 to 2.4 mmol/L L-glutamine, 8 to 10 μg/mL penicillin, and 8 to 10 μg/mL streptomycin (GIBCO) (hereafter referred to as complete medium [CM]) and either 5% or 10% fetal bovine serum (FBS; GIBCO).

Cytokines and antibodies. Human recombinant IL-2 (rIL-2; specific activity of 3 × 10^6 U/mg) was obtained from Cetus Oncology Corporation (Emeryville, CA) and was used at the concentrations indicated. Mouse rIFNy (specific activity of 4.5 × 10^6 U/mg) and mouse rTNFα (specific activity of 4 × 10^6 U/mg) were purchased from Genzyme (Boston, MA). Cos 7 supernatant containing mouse rGM-CSF was the generous gift of DNAX Research Institute (Palo Alto, CA) or was produced by us, as described.22 rGM-CSF was titrated against Genzyme recombinant murine GM-CSF (rmGM-CSF; specific activity 5 × 10^5 colony-forming units-committed [CFUc]/mg) on the GM-CSF–dependent cell line DA3.15,25 Goat-antimouse GM-CSF polyclonal antisemur26 was a gift from DNAX Research Institute.

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Fig 1. GM-CSF augmentation of low-dose IL-2 LAK induction. (A) NW-enriched splenocytes were cultured in the presence of the indicated concentrations of IL-2 (C) or (IL-2 + GM-CSF) (E) for 3 days. GM-CSF was used at 10 U/mL. On day 3, the effectors were tested against P815 at an E:T ratio of 50:1. (B, C, and D) NW-enriched splenocytes were cultured in the presence of IL-2 (C) or (IL-2 + GM-CSF) (E) for 3 days. IL-2 was used at 10 U/mL and GM-CSF was used at 10 U/mL. On day 3, the effectors were tested at the indicated E:T ratios against the NK-sensitive target YAC-1 (B) and the NK-resistant targets P815 (C) and EL4 (D). (A) shows a different experiment than (B), (C), and (D).

Rabbit-antisialoGM1 polyclonal antiserum was purchased from Wako Chemicals USA, Inc (Dallas, TX). Hamster antimumine IFN-γ monoclonal antibody (MoAb) was purchased from Genzyme. Rat antimouse TNFα MoAb was purchased from PharMingen (San Diego, CA). Anti-CD4 (clone RL/172),35 anti-IL-2 receptor (clone 7D4),36 and anti-NK1.1 (clone PK136)37 were used as hybridoma culture supernatants. Anti-CD8 MoAb (clone 3.155)39 was used as ascites fluid. The following fluorescent-tagged antibodies were used as indicated: goat antimouse-IgG2a-fluorescein isothiocyanate (FITC) (Southern Biotechnology Associates, Inc, Birmingham, AL), anti-CD4–FITC (PharMingen), anti-CD8–FITC (Becton Dickinson, Mountain View, CA), and Leu4–FITC (Becton Dickinson). Viable cells (×10⁶) (based on forward and 90° angle light scatter, as well as propidium iodide dye exclusion) were analyzed with logarithmic signal amplification on a FACScan (Becton Dickinson).

Cell depletions. In vivo NK cell depletions were accomplished by intraperitoneal (IP) injection of 200 µL of a 1:40 dilution of antisialoGM1 as described.39 Mice injected with phosphate-buffered saline (PBS) were used as controls. Splenocytes were harvested 18 hours after injection and cultured as described below. NK depletion was verified by a cytotoxicity assay as described below using YAC-1 as the target. T-cell depletions were performed before culture as follows. Splenocytes were incubated at 1 × 10⁷ cells/mL with a 1:2 dilution of anti-CD4 MoAb and/or a 1:1,000 dilution of anti-CD8 MoAb as indicated, plus either a 1:10 or 1:15 dilution of rabbit complement (Accurate, Westbury, NY) or 1:5 dilution of guinea pig complement (GIBCO) for 30 minutes at 37°C. Cells were then spun down and resuspended in complement one-half the initial volume with 0.1 mg/mL DNase type II from bovine pancreas (Sigma, St Louis, MO) and incubated for an additional 30 minutes at 37°C.
The cells were then washed twice, resuspended in medium, recounted, and plated as described below. CD4 and CD8 depletions were verified by immunofluorescence and flow cytometry, using the original depleting MoAbs and a fluorescent-labeled anti-Ig second MoAb.

**LAK cell generation.** Single-cell suspensions of splenocytes were obtained by abrasion of the spleen on a sterile stainless steel screen, and the cells were washed in PBS plus 5% FBS. Removal of nylon wool (NW)-adherent cells was performed essentially as described. 40 The cells were incubated for 3 days in 5 mL CM plus 10% FBS at 2 x 10^6 cells/mL in 6-well plates (Corning Glass Works, Corning, NY) at 37°C in a humidified atmosphere of 5% CO2. Cytokines and antibodies were added as indicated.

**Cytolysis assays.** Effectors were collected from culture, washed three times with PBS plus 5% FBS, counted, and resuspended at an appropriate concentration in CM plus 5% FBS. Target cells were collected, washed, and resuspended in approximately 0.1 mL of medium, 0.05 mL of FBS, and 100 μCi Na^1^CrO_4 (Amersham, Arlington Heights, IL, or NEN, Dupont, Boston, MA) for 60 to 90 minutes at 37°C. Targets were then washed, counted, and resuspended in CM plus 5% FBS at an appropriate concentration. Varying numbers of effectors and 500 targets cells were plated, in triplicate, in 150 μL of CM plus 5% FBS in V-bottomed microtiter plates (Costar, Cambridge, MA), spun at 100g for 5 minutes, and cultured at 37°C in a humidified atmosphere of 5% CO2 in air. After 4 to 6 hours, the plates were spun at 700g for 10 minutes, 100 μL of supernatant was collected, 1.5 mL Cytoscint scintillation fluid (ICN Biomedicals, Irvine, CA) was added, and radioactivity in the supernatant was measured in a beta-counter. The cytotoxic activity was calculated from triplicate cultures using the formula: 

\[
\text{% cytotoxicity} = 100 \times \left( \frac{\text{experimental release} - \text{spontaneous release}}{\text{maximum release} - \text{spontaneous release}} \right)
\]

Supernatant was determined by culturing target cells in the absence of effectors. Maximum release was obtained from target cells that had undergone three cycles of freezing and thawing, or lysis by 10% Triton X (Sigma). The percent cytotoxicity measured from effectors cultured in medium alone was routinely less than 1%. Each figure or panel depicts a representative experiment.

**RESULTS**

The present study examined the ability of GM-CSF to augment low-dose IL-2 LAK induction from murine splenocytes. LAK induction, measured by the ability of the ef-

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**Fig 3.** Effect of anti-TNFα MoAb, anti-IFNγ MoAb, and anti-GM-CSF Ab on LAK induction. NW-enriched splenocytes were cultured in the presence of cytokines and antibodies as indicated. Cytokines and antibodies were used at the following concentrations: IL-2, 10 U/mL; TNFα, 100 U/mL; anti-TNFα MoAb, 5 μg/mL; IFNγ, 20 U/mL; anti-IFNγ MoAb, 2 μg/mL; GM-CSF, 10 U/mL; and anti-GM-CSF Ab, 1/1,000 dilution. On day 3, effectors were tested against P815 at an E:T ratio of 50:1 (A), 100:1 (B and C), or 150:1 (D). Each panel depicts an independent experiment.

**Fig 4.** Effect of NK-cell depletion on LAK induction. (A) Fresh NW-enriched splenocytes from antiasialoGM1-injected mice (△) and PBS-injected control mice (○) were tested for NK activity against YAC-1 at the indicated E:T ratios. (B and C) The NW-enriched splenocytes from PBS-injected mice (B) and from antiasialoGM1-injected mice (C) were cultured for 3 days with IL-2 (○) or (IL-2 + GM-CSF) (△). IL-2 was used at 10 U/mL and GM-CSF was used at 10 U/mL. On day 3, the effectors were tested against P815 at the indicated E:T ratios.
Fig 5. Anti-NK1.1 staining of NW-enriched splenocytes from PBS-injected and antiasialoGM1-injected mice. NW-enriched spleenocytes from PBS-injected (A and B) and antiasialoGM1-injected (C and D) mice were stained with goat antimouse-IgG2a-FITC (GAMlgG2a-FITC) (A and C) or with anti-NK1.1 followed by goat antimouse-IgG2a-FITC (B and D).

Several cytokines, including IL-7 and IL-12, have been reported to induce LAK activity via an IL-2-independent pathway. To examine if GM-CSF augmented LAK activity by an IL-2-dependent or -independent mechanism, anti-IL-2 receptor MoAb was added to the splenocyte cultures. The antibody completely inhibited the generation of LAK activity from both the IL-2 and (IL-2 + GM-CSF)-induced cultures (Fig 2B). Thus, GM-CSF does not induce an IL-2-independent LAK activation process. Furthermore, GM-CSF by itself was not able to induce LAK activity from the splenocytes (Fig 2C), suggesting that GM-CSF augmentation is not due to IL-2 induction in this culture system.

TNFα and IFNγ have each been reported to augment low-dose IL-2 LAK activity. We examined whether either plays a role in the GM-CSF-augmented cultures. Both TNFα (Fig 3A) and IFNγ (Fig 3B) were able to augment IL-2-induced LAK activity, to a level comparable with GM-CSF-augmented LAK activity (Fig 3C). As expected, anti-TNFα MoAb, anti-IFNγ MoAb, and anti-GM-CSF Ab blocked augmentation by TNFα, IFNγ, and GM-CSF, respectively (Fig 3A through C). Notably, each of these antibodies blocked only the augmenting effect of its cytokine, and did not block all LAK generation, in contrast to anti-IL-2 receptor MoAb (Fig 2B). We then tested whether anti-TNFα MoAb or anti-IFNγ MoAb inhibited (IL-2 + GM-CSF)-induced LAK generation in NW-enriched splenocyte cultures. No inhibition of (IL-2 + GM-CSF)-induced LAK generation was seen in the presence of either anti-TNFα MoAb or anti-IFNγ MoAb (Fig 3D). These results indicate that the GM-CSF augmentation of IL-2-induced LAK generation does not require the activity of either TNFα or IFNγ in the cultures.

Because both NK cells and T cells can be induced to develop LAK activity, we investigated the precursor cell population(s) necessary for the generation of LAK activity and GM-CSF augmentation of LAK generation in this culture system. This was performed by depleting either NK cells or T cells before in vitro culture. As seen in Fig 4A, in vivo depletions of NK cells resulted in diminished LAK generation (Fig 4A vs. 4B). These results suggest that NK cells play a critical role in the generation of LAK activity in this system.

Fig 6. Anti-NK1.1 staining of effectors generated from control and NK-cell-depleted precursors. On day 3, (IL-2 + GM-CSF)-induced effectors generated from control (A and B) or from NK-cell-depleted precursors (C and D) were stained with goat antimouse-IgG2a-FITC (GAMlgG2a-FITC) (A and C) or with anti-NK1.1 followed by goat antimouse-IgG2a-FITC (B and D). The stainings of the IL-2-induced effectors were virtually identical to those shown.
pretreatment with antiasialoGM1 Ab eliminated the NK activity of NW-enriched splenocytes. The depletion of NK1.1+ cells in the antiasialoGM1 Ab-treated mice was also confirmed by immunofluorescence and flow cytometry (Fig 5, compare B and D). AntiasialoGM1 Ab does not cross-block anti-NK1.1 MoAb binding, and the strong reduction in the number of NK1.1-bright cells in Fig 5D, therefore, represents depletion of NK cells. The dimly staining peak in Fig 5C and D may reflect antiasialoGM1 Ab-coated T cells that did not completely clear their surface Ab in vivo and were, therefore, detected by the FITC–anti-Ig. After a standard 3-day culture, effectors from the NK-depleted mice were compared with effectors from PBS-injected mice. The NK-depleted precursors exhibited IL-2-induced LAK activity comparable to the control precursors (Fig 4B and C), and GM-CSF was able to augment the LAK activity generated from both the NK-depleted cultures and the control cultures. The cultures derived from NK-depleted precursors did not regenerate significant numbers of NK1.1+ cells (Fig 6). These data suggest that NK cells are not the major LAK precursors or effectors in this system.

To remove T cells, NW-enriched splenocytes were treated in vitro with anti-CD4 and anti-CD8 MoAbs plus complement. The CD4+CD8− cells and the control cells were cultured for 3 days in IL-2 or (IL-2 + GM-CSF). By immunofluorescence analysis, the (anti-CD4 + anti-CD8)-treated cells remained CD4−CD8− on day 3 (Fig 7). On day 3, the cytotoxic capability of the cells was tested. The depletion of both CD4+ and CD8+ cells from the precursor population inhibited the ability of (IL-2 + GM-CSF) to augment LAK activity (Fig 8), indicating that GM-CSF augmentation requires T cells and suggesting that the LAK precursors in this system are T cells.

Figure 7 also illustrates that both CD4+ and CD8+ cells are present in the control effector population derived from undepleted precursor cells. It was therefore possible that CD4+ T cells, CD8+ T cells, or both contribute to the LAK activity generated in this culture system. To further investigate which T cells are required, NW-enriched splenocytes were depleted of either CD4+ or CD8+ T cells before culture. The LAK activity of the depleted populations was tested after a 3-day culture period. GM-CSF augmented LAK generation from both the CD4-depleted (Fig 9B) and the CD8-depleted (Fig 9C) precursors. When such cultures were analyzed by immunofluorescence, the effector populations generated from CD4-depleted precursors contained CD8+ T cells but not CD4+ T cells, and the effector populations generated from CD8-depleted precursors contained CD4+ T cells but not CD8+ T cells (Fig 10). Together, these results suggest that both the CD4+ and CD8+ T-cell populations have LAK-generating potential that can be augmented by GM-CSF.

**DISCUSSION**

The results presented here show that GM-CSF is able to augment low-dose IL-2-induced LAK activity. Augmentation
Fig 9. Characterization of T cells required for LAK induction. NW-enriched splenocytes were treated with complement alone (A), anti-CD4 MoAb plus complement (B), or anti-CD8 MoAb plus complement (C), and then cultured for 3 days in the presence of IL-2 (°) or (IL-2 + GM-CSF) (○). IL-2 was used at 10 U/mL and GM-CSF was used at 10 U/mL. On day 3, the effectors were tested against P815 at the indicated E:T ratios.

by GM-CSF can be seen most readily at limiting concentrations of IL-2, but GM-CSF does not merely stimulate additional IL-2 production, because GM-CSF does not induce LAK generation in the absence of exogenous IL-2. Augmentation by GM-CSF does not depend on the activity of TNFα or IFNγ, because neither anti-TNFα MoAb nor anti-IFNγ MoAb inhibited (IL-2 + GM-CSF)-induced LAK generation. T cells, and not NK cells, represent the major LAK precursor population activated in this low-dose (IL-2 + GM-CSF) culture system.

LAK effectors can be a heterogeneous population consisting of NK-LAK and T-LAK effectors. In high-dose IL-2-induced LAK populations, the cytotoxic activity appears to be mediated primarily by cells expressing NK1.1. This balance is shifted in IL-4-induced LAKs, with CD8+, NK1.1− cells being the predominant lytic population. One reason that T-LAKs predominated in our culture system may be that IL-2 was used at a concentration insufficient to saturate the IL-2 receptors found on NK cells. NK cells constitutively express only the medium affinity p70 chain of the IL-2 receptor, and normally require high IL-2 concentrations for activation. The T-LAK precursors we were able to stimulate may reflect a subset of T cells that have been reported to express the high-affinity IL-2 receptor before culture.

It has been reported that murine T-LAK effectors induced from unseparated precursors by IL-7 appear to represent a homogeneous T-LAK population with the phenotype of Thy1+, asialoGM1−, NK1.1−, CD8+. However, in that study, precursor depletion of CD8+ cells before culture did not eliminate the ability to generate LAK activity. LAK generation was completely inhibited only when the precursors were depleted of both CD8+ and CD4+ cells, suggesting that CD4+ cells could generate LAK activity, but only in the absence of competing CD8+ cells. Previous studies by McCarthy

Fig 10. Anti-CD4 and anti-CD8 staining of effectors generated from control, CD4−, and CD8− precursors. On day 3, (IL-2 + GM-CSF)-induced effectors from control precursors (A and B), CD4-depleted precursors (C and D), and CD8-depleted precursors (E and F) were stained with anti-CD4-FITC (A, C, and E) or anti-CD8-FITC (B, D, and F). Leu4-FITC staining overlapped with the negative cell peak in each panel. The stainings of the IL-2–induced effectors were virtually identical to those shown.
and Singer showed a similar relationship between CD4+ MHC class II-specific cytotoxic T lymphocytes (CTL) and CD8+ MHC class I-specific CTL. The results presented in this study provide evidence that CD4+ T cells can also develop LAK activity. GM-CSF augmentation of LAK activity was completely inhibited only when both CD4+ and CD8+ precursors were depleted, suggesting that the effectors in (IL-2 + GM-CSF)-augmented cultures were predominantly T-LAKs that arose from both CD4+ precursors and CD8+ precursors. An analysis of the relative in vivo efficiency of CD4+ LAK and CD8+ LAK should indicate which population would be better suited for clinical use.

A number of cytokines, including IL-7 and IL-12, have been shown to induce IL-2-independent LAK activity. In contrast, in the present study, GM-CSF-augmented LAK induction was IL-2 dependent, because the addition of anti–IL-2 receptor MoAb completely inhibited the generation of LAK activity. This finding also indicates that GM-CSF augmentation is not mediated through IL-7 or IL-12 production, because these cytokines are capable of inducing IL-2-independent LAK activity, whereas GM-CSF was not. Nevertheless, it would now be interesting to test whether GM-CSF can also augment IL-2-independent LAK generation induced by cytokines such as IL-7 and IL-12.

The cell type on which GM-CSF acts during LAK induction is not clear from our studies. It has been reported that GM-CSF pretreatment of human monocytes upregulated their ability to augment IL-2-induced LAK activity from PH.3,29 This hypothesis is compatible with GM-CSF receptor binding studies that have failed to show measurable GM-CSF receptors on normal mature T cells.45 If the LAK augmentation by GM-CSF in the present study is via an effect on macrophages, it is apparently not through the action of TNFα or IFNγ in the (IL-2 + GM-CSF)-stimulated cultures, because neither anti-TNFα nor anti-IFNγ MoAb inhibited (IL-2 + GM-CSF)-augmented (Fig 3D) or basal IL-2-induced LAK generation (data not shown). Furthermore, GM-CSF did not directly induce macrophage tumoricidal activity, because depletion of CD4+ and CD8+ T cells effectively inhibited lytic-generating capacity.

The use of LAK cells together with IL-2 as an important therapeutic strategy in cancer treatment has been diminished by the adverse side effects that accompany the administration of high-dose IL-23 and the resistance of many tumor cell types to this therapy.4 IL-2 toxicity has been shown to be dose dependent.44 Furthermore, recent studies have shown that much of the IL-2 toxicity is mediated by activated NK-LAK and not by T-LAK effectors.45 We have shown that low-dose IL-2 in conjunction with GM-CSF in vitro generates predominantly T-LAK effectors. Adoptive immunotherapy with T-LAK cells generated with low-dose IL-2 in combination with GM-CSF may result in less toxicity than observed with high-dose IL-2, and may show a different antitumor range than observed with NK-LAK effector cells.

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