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IL-17 Mobilizes Peripheral Blood Stem Cells with Short- and Long-Term Repopulating Ability in Mice

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Autologous and allogeneic bone marrow transplantations have evolved as important cancer therapy modalities. For both indications, peripheral blood has been shown to have distinct advantages over bone marrow as the stem cell source. Cytokine combinations for mobilization have enhanced stem cell yield and accelerated engraftment. However, novel mobilizing agents and strategies are needed to further improve clinical outcomes. Within the donor graft, the dynamic equilibrium between T cells and stem cells critically influences engraftment and transplantation results. IL-17 is a cytokine produced almost exclusively from activated T cells. IL-17 was expressed in vivo with adenovirus technology. Here, proof-of-principle studies demonstrate that IL-17 effectively mobilizes hemopoietic precursor cells (CFU-granulocyte-erythrocyte-macrophage-monocyte, CFU-high proliferative potential) and primitive hemopoietic stem cells (Lin−/lowc-kit+/Sca1+). Moreover, mouse IL-17 adenovirus-mobilized peripheral blood stem cells rescued lethally irradiated mice. Bone marrow was found to be 45–75% of donor origin at 1 year. In secondary recipients, donor-derived bone marrow cell ranges from 45 to 95%. These data show that IL-17 mobilizes stem cells in mice with short- and long-term reconstituting capacity. Additional comparative studies are needed as well as studies in tumor models to refine distinct potential clinical applications for IL-17-mobilized peripheral blood stem cells. The Journal of Immunology, 2001, 167: 2081–2086.
certain cytokine that is expressed in activated T cells (27–29). Many of IL-17’s biological effects may be due to its ability to stimulate the release of secondary cytokines, several of which are known HSC mobilizers (IL-8, G-CSF, and SCF; Refs. 22, 23, 26, 28, and 30). In support of this, we found that IL-17-mediated granulopoiesis was attributable in part to a direct effect of mIL-17 on G-CSF release and the induction of the transmembrane form of SCF (31). Although both G-CSF and SCF are known stem cell-mobilizing compounds, it does not predict mobilizing activity for IL-17. IL-17 releases a panel of other cytokines and substances with unknown effects on the hematopoietic compartment. These may interfere or antagonize HSC mobilization. IL-17 could be expressed without toxicity in mice at sustained high levels, suggesting the potential suitability as a therapeutic agent in man (26, 31). Given the importance of T cells as critical accessory cells in stem cell grafts, we decided to investigate whether IL-17 mobilizes PBSC. To test the hypothesis that IL-17 can effectively mobilize PBSC, we conducted proof-of-principle experiments with a previously described murine model in which mIL-17 was overexpressed with recombinant adenovirus (Ad) technology (Ad-mIL-17), which permits sustained in vivo production of IL-17 (26, 31).

Materials and Methods

Animals and transplantation proceedings
C57BL/6 mice ages 6–8 wk were purchased from the National Cancer Institute breeding facility (Frederick, MD). All mice were maintained under specific pathogen-free conditions in the vivarium of Louisiana State University Health Sciences Center (New Orleans, LA). Autoclaved food and water were provided ad libitum. Drinking water was acidified (pH 2.5) and supplemented with polymyxin (104 U/l; Sigma, St. Louis, MO).

Donor mice
Splenectomy was performed under sterile conditions with immediate closure of the incision by removable surgical clamps and application of local antibiotic ointment. Mice were used for additional experiments after a resting period of at least 4 wk. A total of 3 x 10^6 PFU of either Ad-mIL-17 or AdCMVLuc as control were administered via i.v. injection through the internal jugular vein.

Recipient mice
Lethal γ irradiation of recipients was performed with a cobalt source in two fractions of 550 rad every 4 h apart (Gammacell 1000; Atomic Energy of Canada, Ottawa, Canada). For Y chromosome engraftment studies, male donors and female recipients were used. Secondary recipients were female mice that received identical ablative radiation treatment. Blood was collected via cardiac puncture or retroorbital and transferred into heparinized tubes. Organs were harvested under sterile conditions. BM cells from both femurs were flushed into medium (DMEM-15% FBS; Life Technologies). Samples and standard DNA (4 μl) in duplicate aliquots were pipetted into black-sided, clear-bottom 96-well plates (Corning, Cambridge, MA), briefly agitated, and immediately analyzed by flow cytometry.

Donor cell preparation
Mice were sacrificed at different time points after vector infusion (Ad-mIL-17 or AdCMVLuc) and blood collected via cardiac puncture in sterile, heparinized tubes. After RBC lysis, cells were washed and resuspended in PBS with 2% FBS. Nucleated cell counts were performed with a hemocytometer and trypan blue staining to account for viability of cells. Smears from peripheral blood were prepared by standard techniques and stained with a modified Wright-Giemsa stain (Diff-Quick; Baxter, Deerfield, IL). Donor cells were normalized for their content in mononuclear cells and reinjected into recipient mice via intrajugular vein injection.

Vector constructs
The Ad vector construction for mIL-17 and luciferase encoding recombinant viruses (Ad-mIL-17 and AdCMVLuc) has been described in detail by our group (26). Briefly, viruses were propagated on 911 cell supernatants by a standard bioassay as described below (28, 34). Virus prep were screened for replication-competent Ad by propagation on A549 cells. This assay has a sensitivity of 1 contaminant/10^6 PFU. All viral preps had a PFU/particle ratio of <100:1. All lots of rAd contained <1 endotoxin U/ml as measured by the Limulus amebocyte lysate assay (BioWhittaker, Walkersville, MD).

Colony-forming assay
Methylcellulose cultures for CFU-granulocyte macrophage (GM), and CFU with high proliferative potential (CFU-HPP) were prepared with MethoCult GF 3434, obtained from Stem Cell Technologies (Vancouver, Canada), as described previously (26). Methylcellulose medium and plated in 35-mm tissue culture dishes (Fisher, Pittsburgh, PA). The dishes were placed in a dedicated incubator and maintained there at 37°C under a 5% CO2 atmosphere and saturated humidified conditions. Analysis for colony formation was conducted at day 10 with an inverted microscope with the definition a colony as an accumulation of at least 50 cells. CFU-HPP is defined as an accumulation of at least 200 cells.

Flow cytometry
To determine relative differences between stem cell fractions in peripheral blood of AdIL-17- and AdCMVLuc-treated animals, flow cytometry was performed to measure Lin<sup>−</sup> c-kit<sup>−</sup> Sca<sup>−</sup><sup>−</sup><sup>−</sup> cells. The method was followed as previously described by Okada et al. and Ikuta and Weissman (26, 36). Briefly, 5 x 10<sup>6</sup> peripheral blood white blood cells were labeled with a mixture of anti-lineage markers (anti-B220, anti-GR-1, anti-Mac-1, anti-CD4, anti-CD8, and TER119 for erythroid lineage; The Jackson Laboratory, Bar Harbor, ME). The dullest 5% of the Lin<sup>−</sup> flow cells were gated and analyzed for the dual expression of c-kit (anti-CD117) and Sca1 (BD Pharmingen, San Diego, CA).

Quantitative real-time PCR (kinetic PCR)
To determine sex-mismatched chimerism in mice, a Y chromosome-sensitive and specific quantitative kinetic PCR procedure was developed by our group, which is specific for the genes zfy1 and the zfy2. The procedure and its validation has been described in detail by our group (4). Briefly, samples consisted of 5 x 10<sup>6</sup> mononuclear cells from peripheral blood or BM. DNA was extracted from cell pellets with a blood DNA extraction kit (Qiagen, Chatsworth, CA). Samples and standard DNA (4 μl) in duplicate aliquots were pipetted into black-sided, clear-bottom 96-well plates (Corning). The mean values of duplicate readings were used for further calculations and generation of standard curves. Data analysis of each sample was determined by the standard curve. To generate male/female DNA standards, limiting dilution of male cells was performed that were subsequently admixed to female cells.

Amplification with the sense primer 5'-TGG AGA GCC ACA AGC TAA CCA-3' and antisense primer 5'-TCC CAG CAT GAG AAA GAT TCT TC-3', which were designed with Primer Express Software (Integrated DNA Technologies, Coralville, IA), generated an 81-nt amplicon. A labeled custom-made probe was designed to recognize a 33-nt sequence on the antisense strand of the amplicon (5'-6-carboxyfluorescein-CAG-TCA-TCA-CAT-TGC-GTC-TTT-TTC-GTC-TTA-AMARA-3'). PerkinElmer Applied Biosystems, Foster City, CA). The final buffer concentration per sample was calculated to be 50 mM potassium chloride, 10 mM Tris, 0.1 mM EDTA, (equivalent of 1× TaqMan buffer A), 0.05 mM passive reference (ROX plus proprietary components), 0.2 μM dATP, 0.2 μM dCTP, 0.2 μM dGTP, 0.4 μM dUTP, 7 mM MgCl2, 300 μM sense primer, 900 μM antisense primer 100 nM TaqMan probe, 0.5 μM AmpErase Uracil N-glycosylase (1 U/μl), and 1.25 μl of AmpliTaq Gold DNA Polymerase (5 U/μl). Samples were amplified by using an ABI 5700 sequence detection system (PerkinElmer). After the initial 2 min 50°C incubation step, two additional heating/cooling cycles (95°C for 1.5 min and 55°C for 2.0 min) were added immediately before AmpliTaq Gold DNA activation with a 6-min incubation at 95°C. This was followed with 45 amplification cycles (94°C for 15 s, 58°C for 20 s, and 60°C for 35 s).

For each reaction series, cycle threshold (Ct) readings from known male/female standard mixtures provided the values used to generate standard curves for each reaction series. The Ct number was computed for each sample using the Sequence Detection Software (PerkinElmer). The Ct baseline was preset at 10 SD above the equipment background. The standard curves for zfy1/zfy2 kinetic PCR were generated by plotting the mean of triplicate Ct values vs the log of the Y copy number and calculating an

a regression line. Only those reactions where the standard curves had a slope value of $-3.3 \pm 0.1$ and an $r$ coefficient $>0.990$ were accepted for further analysis. The copy number for the unknown samples was determined by applying the mean Ct value of triplicates to the standard curve which was concurrently obtained, using the software provided by the manufacturer (PerkinElmer). The $Y$ chromosome copy number was adjusted based on the total amount of DNA present in each reaction.

**Data and statistical analysis**

For all samples, statistical significance of differences was performed with Student’s $t$ test, which was provided within a statistical software program (Sigma Plot; SPSS Science, Chicago, IL). Values of $p < 0.05$ were assumed for statistical significance. Survival analysis was performed by log-rank nonparametric testing and expressed as Kaplan Meier curve.

**Results**

**Ad-mIL-17 mobilizes hemopoietic precursor cells and cells with stem cell phenotype**

To determine the effect of Ad-mIL-17 on peripheral blood in splenectomized mice, morphologic analysis of white blood cells was performed over a 10-day period. Within 24 h, a statistically significant increase in white blood cells was observed that reached a maximum on day 7 (4-fold). This increase was predominantly attributable to an increase in the absolute neutrophil count, which increased by up to 13-fold on day 7. This neutrophil expansion was sustained over the entire 10-day observation period (Fig. 1A). Monocytes increased by 10-fold with a maximum on day 3 ($p < 0.05$). Lymphocytes also increased with the maximum observed on day 3 at 2.6-fold ($p < 0.05$) ($n = 8$ mice/group; Fig. 1B). To determine the optimal time of PBSC mobilization after Ad-mIL-17 administration, peripheral blood was analyzed over a 10-day time course. Hemopoietic precursor frequency in peripheral blood was analyzed with CFU assays. Precursors of granulocytes, erythrocytes, macrophages, and monocytes (CFU-GM/granulocyte-erythrocyte-macrophage-monocyte (GEMM)), as well as precursors with HPP (CFU-HPP), increased significantly in the Ad-mIL-17 group over the control AdCMVLuc group with maxima on days 3 and 7 (Fig. 2, A and B). To determine HSC frequency in peripheral blood, morphologic phenotyping for the previously described murine HSC population Lin$^{-}\text{lowc-kit}^{-}\text{Sca1}^{+}$ was performed (35, 36). This cell population increased significantly in the Ad-mIL-17 group with a maximum on day 3 (1.4% vs 0.03%; Fig. 2C).

**Ad-mIL-17-mobilized peripheral blood cells can rescue lethally irradiated mice**

C57BL/6 mice were lethally irradiated with 1100 rad before the infusion of C57BL/6 mouse donor blood. Splenectomized donors had been treated 3 days earlier with either $3 \times 10^9$ PFU Ad-mIL-17 or AdCMVLuc. Although no survivors were registered in mice infused with AdCMVLuc-treated donor blood (up to $1 \times 10^7$ cells), survival was 85% in the group infused with AdmIL-17-treated donor blood ($1 \times 10^6$ cells). All mice in the AdCMVLuc donor blood group had succumbed by day 17, but no further mortality was observed after that time point in the Ad-mIL-17-mobilized blood recipients. A total of 180 mice in four different experiments were used for these survival studies. The data presented

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**FIGURE 1.** Ad-mIL-17 effects on peripheral white blood cells. Splenectomized C57BL/6 mice were i.v. injected with $3 \times 10^9$ PFU Ad-mIL-17 or AdCMVLuc (control). Peripheral blood smears were analyzed over a 10-day period by light microscopy. Total WBC and absolute neutrophil count (ANC) are plotted in A, and total lymphocyte and monocyte cell count in B. Each data point represents the mean of six individual animals ± SEM, and the results are representative of two independent experiments. *, Statistical significance over control ($p < 0.05$).

**FIGURE 2.** Ad-mIL-17 mobilizes precursor cells and HSC. Splenectomized C57BL/6 mice were i.v. injected with $3 \times 10^9$ PFU of Ad-mIL-17 or AdCMVLuc. Peripheral blood white blood cells ($1 \times 10^7/dish$) were analyzed over a 10-day time course for precursor frequencies of CFU-GM/GEMM and also for CFU-HPP (A and B, respectively). Morphologic phenotyping was performed for HSC (Lin$^{-}\text{lowc-kit}^{-}\text{Sca1}^{+}$) using flow cytometry. Data points represent the mean ± SEM of eight individual animals (C). *, Statistical significance over control ($p < 0.05$).
represent results from the combined four experiments. (Fig. 3). All surviving mice became long-term survivors maintaining normal hemopoiesis, with one cohort followed for 1 year after treatment.

**Ad-mIL-17-mobilized PBSC cells have short-term repopulating potential**

To demonstrate that the Ad-mIL-17-mobilized donor PBSC had engrafted and sustained functional hemopoiesis over a period of 3 mo, individual male/female autotransplanted C57BL/6 mice were sequentially analyzed by CBC and differential cell count at 4 and 12 wk after transplantation (n = 6/group). Hemopoietic reconstitution in Ad-mIL-17 PBSC autotransplanted C57BL/6 mice was observed with cell numbers reaching levels close to nontransplanted control animals at 4 wk and full hemopoietic restoration compared with untransplanted animals at 3 mo (Fig. 4). T and B lymphocyte and also NK cell lineages were present at normal levels (data not shown). Male donor cells were detected in peripheral blood of female recipients by Y chromosome-specific kinetic PCR at 1 and 3 mo in significant levels. Results from 10 individual mice are depicted in Fig. 5.

**IL-17-mobilized PBSC have long-term repopulating potential**

Mice autotransplanted with Ad-IL-17-mobilized donor PBSC were evaluated at 1 year and results were compared with nontransplanted littermates. White blood count (WBC) and differential count were statistically not different (Fig. 4). BM CFU (CFU-GEMM and CFU-HPP) also were not different (data not shown). To demonstrate that the Ad-IL-17-mobilized donor PBSC indeed had engrafted and repopulated mice for prolonged time periods (>6 mo), four mice were analyzed for presence of BM Y chromosome sequences at 1 year after transplantation. Engraftment

**FIGURE 3.** Ad-mIL-17-mobilized PBSC rescue lethally irradiated C57BL/6 mice. Lethally irradiated C57BL/6 mice were infused with 1 × 10^6 of peripheral blood white blood cells obtained from splenectomized mice 72 h after administration of 3 × 10^9 PFU of Ad-mIL-17. Control mice received between 1 × 10^6 and 1 × 10^7 of peripheral blood white blood cells from AdCMVLuc-treated mice (n = 90 mice/group). Survival is plotted over time, and the data are combined from four independent experiments.

**FIGURE 4.** Ad-mIL-17-mobilized PBSC durably restore peripheral white blood cells in lethally irradiated C57BL/6 mice. Total WBC, absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), and monocyte counts (Mono) were determined sequentially in lethally irradiated C57BL/6 mice over a 1-year time period after transplantation (n = 6/data point). The bordered squares indicate the range of cell counts observed in untransplanted littermate controls (n = 6).

**FIGURE 5.** Syngenic Ad-mIL-17-mobilized PBSC provide short-term hemopoiesis in lethally irradiated C57BL/6 mice. Peripheral white blood cells of 10 lethally irradiated female mice transplanted with Ad-mIL-17 male donor cells were analyzed by quantitative real-time PCR for Y chromosome sequences at 4 and 12 wk. The percentage of male DNA is plotted on the y-axis. Mice 11 and 12 are female mice transplanted with female BM.

**FIGURE 6.** Autologous Ad-mIL-17 PBSC provide long-term hemopoiesis in lethally irradiated C57BL/6 mice. BM of four lethally irradiated female mice rescued with male, syngenic Ad-mIL-17-mobilized PBSC was analyzed by quantitative real-time PCR for Y chromosome sequences 1 year after transplantation. The percentage of male to total DNA is plotted on the y-axis (A). Donors for secondary transplantation were female mice who had been rescued 4 mo earlier with male, syngenic Ad-mIL-17-mobilized PBSC. Donor BM from one mouse was used to reconstitute three secondary lethally irradiated female C57BL/6 recipients. The BM of the secondary recipients was analyzed after 4 mo by kinetic PCR for Y chromosome sequences. The percentage is plotted on the y-axis (see Fig. 1B). Control mice are female mice transplanted with female BM (animals 5, 6, 13, and 14 in A and B, respectively).
was significant and ranged between 45 and 75% (Fig. 6A). Second transplantation experiments were conducted with BM from female recipients that had been transplanted 3 mo earlier with Ad-IL-17-mobilized male donor PBSC. One donor mouse provided cells for three recipients. The secondary female recipients were analyzed for presence of Y chromosome sequences at 4 mo after transplantation. A total of 12 animals were analyzed. In all secondary recipients, male-derived cells were detected at significant levels (45–95%; Fig. 6B). The data suggest that Ad-mIL-17 can mobilize PBSC with long-term repopulating ability.

Discussion

The goal of this study was to address the fundamental question of whether the T cell-derived cytokine IL-17 has the ability to mobilize PBSC. The first step to prove potential suitability for clinical transplantation applications was to investigate whether IL-17-mobilized cells can secure immediate posttransplantation survival and whether these cells durably engraft in an animal model. IL-17 induces release of several secondary cytokines from stroma cells with known mobilization capability (IL-8, G-CSF, and SCF; Refs. 22, 24, 26, 28, and 30). Previously, our group reported that mIL-17 releases G-CSF and induces expression of the membrane-bound form of SCF (31). Recent studies with the combination of G-SCF and soluble SCF showed that this cytokine combination improved HSC mobilization over that of single agents (G-CSF), which is presently the most widely used mobilizing strategy (22, 22–24). However, the fact that secondary mobilizing cytokines are released cannot support the automatic assumption that IL-17 would have HSC mobilizing capacity. As numerous other biologic mediators are also released through IL-17, there are potential antagonistic or neutralizing effects. Given the complexity of in vivo cytokine networks cytokine counterregulations and poorly understood stem cell biology, accurate predictions of cytokine effects in vivo are impossible. Therefore, proof-of-principle experiments were conducted with a previously described murine model in which mIL-17 is expressed using Ad technology.

To achieve optimal mobilization and avoid pooling of mobilized cells in the spleen, donor mice were splenectomized prior to vector administration. mIL-17 pharmacokinetics in this splenectomized model were very similar to our previously reported results where mIL-17 plasma levels rose to 40 U/ml of mIL-17 at 12 h after vector administration, 60 U/ml at 24 h, and to a peak level at 72 h (120 U/ml; Ref. 26). From there on, a slow linear decline was observed, with levels still at 70 U/ml/ml on day 10 (data not shown). Thus, stable mIL-17 levels within a 3-fold range could be achieved with the Ad-mIL-17 expression system throughout a 10-day period.

As previously reported by our group in un spleenectomized mice, Ad-mIL-17 treatment resulted in a substantial increase of the total WBC. This was caused predominantly by expansion of neutrophils (26, 31). However, in splenectomized animals, monocytes also increased significantly by 10-fold and lymphocytes by almost 3-fold. Previously, the increase in peripheral blood lymphocytes and monocytes was noted. However, it did not reach statistical significance. We conclude that in these previous experiments, both BM-derived cell types were siphoned and pooled within the spleen and therefore did not appear in the peripheral blood at significant levels.

Peripheral blood of control virus-treated animals did not contain precursor cells (CFU) or HSC. However, both elements were observed at significant levels after Ad-mIL-17 treatment. A time course determined the optimal Ad-mIL-17 mobilizing effect at 72 h, where the maximum mobilization of primitive HSC (Lin−c-kit altaScal+) occurred. Colony-forming ability of peripheral blood was similar on days 3 and 7, with no statistical difference. Therefore, PBSC obtained at 72 h were used for subsequent rescue studies with lethally irradiated mice. Compared with animals infused with Ad-mIL-17-mobilized cells, control animals received excess cells (up to 3-fold white blood cells and 2-fold mononuclear cells) without the rescue of a single animal. Because Ad-mIL-17-mobilized PBSC protected mice from the immediate posttransplantation mortality, lineage committed precursor cells (CFU-GM) must have rapidly differentiated into mature and functional cells protecting the radiated host.

To determine donor cell contribution over time, the male Y chromosome sequences zfy1/zfy2 in female recipients were amplified by kinetic PCR. In peripheral blood, donor sequences were detected in all mice at 4 and 12 wk. In most animals, engraftment was in excess of 30% at both time points. Only two mice had a low percentage of male DNA (10%; mouse 1 and mouse 9) at 12 wk. One possible explanation is the recovery of endogenous hemopoiesis and loss of donor hemopoiesis. In this case, Ad-mIL-17-mobilized precursor cells would have secured survival during the radiation-induced pancytopenia period. However, the composition of peripheral blood, which consists of mature and functional cells, does not correspond stochiometrically to the HSC within the blood-forming organs. Rather, it is believed that the majority of functional blood cells are derived from few, sequentially activated proliferating stem cell clones (37). Should these activated clones be predominantly of host origin, the proportion of donor HSC in the blood-forming organs is not accurately represented by peripheral blood analysis. To eliminate this potential caveat, analysis directly from BM may provide more accurate results of donor/host HSC composition. However, it also is important to realize that BM support cells are more radio-resistant than hemopoietic precursor cells. Therefore, when donor marrow is procured from transplanted animals, it is quite likely that also host-derived stroma and connective tissue cells will be carried over for analysis. Therefore, even in the event of complete replacement of host hemopoiesis with donor HSC, some detection of host DNA is also expected, precluding the result of an entirely donor-derived BM. The BM of four mice was analyzed 1 year after Ad-mIL-17-mobilized PBSC transplantation with male donor DNA contributing 45–75% to total DNA. In the second transplantation series, the BM of each recipient was found to have male donor DNA ranging from 45 to 95%. Although individual variation was observed between mice, donor cells constituted a major portion of host hemopoiesis after a second transplantation. Taken together, the data support that Ad-mIL-17 can mobilize primitive PBSC that can durably reconstitute hemopoiesis in mice.

Given the critical role of T cells in engraftment, follow-up studies are needed to compare directly the engraftment kinetics of IL-17-mobilized PBSC to conventional mobilized PBSC. T cells have numerous roles in transplantation biology, part of which could be explained by mediating cytokines. The hypothesis that IL-17 may have a potential role in GVHD or GVL of allogeneic transplantation is intriguing and requires further investigation.

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References

IL-17 MOBILIZES PBSC IN MICE


