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IL-17 Receptor Knockout Mice Have Enhanced Myelotoxicity and Impaired Hemopoietic Recovery Following Gamma Irradiation

Weihong Tan,*† Weitao Huang,* Qiu Zhong,* and Paul Schwarzenberger†*†

IL-17A is a T cell-derived proinflammatory cytokine required for microbial host defense. In vivo expression profoundly stimulates granulopoiesis. At baseline, the hemopoietic system of IL-17R knockout mice (IL-17Ra−/−) is, with the exception of increased splenic progenitor numbers, indistinguishable from normal control mice. However, when challenged with gamma irradiation, hemopoietic toxicity is significantly more pronounced in IL-17Ra−/− animals, with the gamma irradiation-associated L50 being reduced by 150 rad. In spleen-derived T cells, gamma irradiation induces significant murine IL-17A expression in vivo but not in vitro. After sublethal radiation injury (500 rad), the infusion of purified CD4+ T cells enhances hemopoietic recovery. This recovery is significantly impaired in IL-17Ra−/− animals or after in vivo blockade of IL-17Ra in normal mice, resulting in a reduction of hemopoietic precursors by 50% and of neutrophils by 43%. Following sublethal radiation-induced myelosuppression, in vivo overexpression of murine IL-17A in normal mice substantially enhanced granulopoietic restoration in mice with a 4-fold increase in neutrophils and splenic precursors on day 8 (CFU-granulocyte-macrophage/granulocyte-erythrocyte-megakaryocyte-monocyte, CFU-high proliferative potential), as well as 2- and 3-fold increases of bone marrow precursors, respectively. This establishes IL-17A as a hemopoietic response cytokine to radiation injury in mice and an inducible mechanism that is required for recovery of granulopoiesis after radiation injury. The Journal of Immunology, 2006, 176: 6186–6193.

Interleukin-17A is a cytokine induced primarily in activated T cells with profound stimulatory activity of the hemopoietic system, particularly granulopoiesis. IL-17A was initially cloned by Rouvier et al. (1) from an activated T cell library. It is highly preserved between species and shares homology to the open reading frame 13 of herpes virus samirii (2). In vivo expression of IL-17A leads to expansion of hemopoietic progenitors and neutrophilia (3, 4). Although IL-17A was recently found to be present in neutrophils, activated T cells remain the major source for IL-17A (2, 5–7). IL-17A is a known proinflammatory cytokine, with none or only minimal expression under physiologic conditions. Its expression in T cells can be induced nonspecifically with reagents such as Con A or through exposure to bacterial lipoproteins (8, 9). IL-17A expression is induced in vivo in T cells in response to infections with bacterial and fungal pathogens and is critical for microbial host defense. Because IL-17A is induced during stress or such emergency situations, it is felt to be a response or emergency cytokine for microbial infections (8, 9). The expression of IL-17A was also found to be associated with certain pathologic conditions, especially with various autoimmune diseases such as rheumatoid arthritis (10). To further study the in vivo role of IL-17A, an IL-17Ra receptor knockout mouse was generated. Although this mouse appears to be phenotypically normal, it was found to have significantly reduced resistance to bacterial and fungal infections (8, 9). This suggested that T cell-derived cytokine directly being involved in microbial host defense. T cells, the predominant source for IL-17A, have long been known to exert regulatory properties on hemopoiesis, although the exact mechanisms remain elusive (11, 12). For instance, patients with T cell deficiency syndromes such as AIDS have substantially reduced tolerance for myelosuppressive cancer therapies such as chemotherapy or radiation. Therefore, treatment compromising dose reductions are being recommended for these patients to avoid serious or potentially fatal toxicities (13, 14). T cells were also found to play an important role in engraftment in the field of bone marrow transplantation. T cell depletion of grafts, although beneficial for reducing graft-vs-host incidence or the severity of it, leads to delayed engraftment and also has an increased rate of engraftment failure (15).

We hypothesized that IL-17A and its receptor system would be part of T cell-mediated regulatory pathways of granulopoiesis, and would be essential in the restoration of myeloid host defense following radiation injury to the hemopoietic system. We have conducted experiments using the IL-17R knockout mouse model as well as in vivo IL-17A neutralization experiments followed by challenge of these animals with increments of myelotoxic gamma irradiation.

Materials and Methods

Animals

The generation of the IL-17Ra−/− mouse has been described previously (8). Animals used for the experiments were backcrossed on C57BL/6 mice (B6.129 IL17Ra−/−). C57BL/6 mice were obtained from The Jackson Laboratory. First-generation hybrid animals originated from an IL-17Ra−/− and C57BL/6 cross and have been described previously (8). All animals were maintained under specific pathogen-free conditions in the animal facility of Louisiana State University Health Sciences (LSUHSC). All experiments were conducted in accordance with LSUHSC Institutional Animal Care and Use Committee protocols. Construction, generation, expansion, and quality control of the adenovirus-expressing murine IL-17A (AdmIL-17A), the soluble mIL-17A receptor Fc (Ad-mIL17RaFc), and the control virus (AdEGFP) as well as quality control measures have been described.

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elsewhere (3, 8, 16). Unless otherwise noted, 3 × 10^5 PFU of adenovirus were i.v. injected. Gamma irradiation was performed by giving a single fraction using a cobalt source (GammaCell 1000; Atomic Energy of Canada).

Cell culture and cell isolation

Murine bone marrow was flushed from both femurs and filtered through nylon mesh for removal of tissue fragments. Spleens were ground between glass slides, and tissue fragments were filtered. RBC lysis was accomplished using hypotonic solution of NH4Cl, and mononuclear cell counts were established. Cell subpopulations were isolated using the Miltenyi bead isolation system following the manufacturer’s instructions (Miltenyi Biotec): mouse CD4 (L3T4) microbeads for CD4^+ T cells. Viability and purity of the separation was confirmed by flow cytometry using 7-aminoactinomycin D viability staining (Molecular Probes) and a noncompeting admixed with 9 pmol of each primer (IL-17A forward primer, 5'-CCA GAA GGC CCT CAG A-3'; IL-17A reverse primer, 5'-CCT TCC; IL-17A forward primer, 5'-6 pmol of FAM-labeled probe (5-ACC TCA CTG CAG TTT GAG), 6 pmol of TAMRA-labeled probe (5-ACC TCA CTG CAG TTT GAC)). Total spleen HPPs were statistically not different between IL-17Ra^−/− animals vs their normal littermates or their heterozygous controls (IL-17Ra^+/−). The experiment was repeated once with similar results. One experiment was performed using age- and sex-matched littermate control animals, which yielded very similar results compared with experiments in which C57BL/6 animals were used as controls (data not shown).

IL-17Ra^−/− mice have normal baseline hemopoiesis with increased radio sensitivity of their granulopoietic system

To determine the effect of radiation on hemopoietic progenitors, the ability of colony formation from hemopoietic organs was determined following increasing doses of gamma irradiation. IL-17Ra^−/− mice and normal control C57BL/6 mice were treated at radiation increments of 100 rad. At baseline, standard peripheral hematological parameters were not statistically different between IL-17Ra^−/− mice and normal control animals (total white blood cell and differential counts, including lymphocytes, monocytes, macrophages, neutrophils, hematocrit, and platelet count) (Fig. 2A and data not shown). However, gamma irradiation reduced the absolute neutrophil count (ANC) significantly and dose dependent more so in IL-17Ra^−/− mice (Fig. 2A). The experiments showed radiation-induced suppression of the ANC at 40–50% in excess of the suppression seen in normal control mice. This effect was more pronounced at lower radiation doses. Two hundred rad resulted in an ANC reduction to 14% of their baseline in IL-17Ra^−/− mice; however, in controls the ANC was reduced only to 46% of baseline (Fig. 2A). To evaluate radiation-mediated toxicity on hemopoietic precursors, colony-forming assays were performed. At baseline, IL-17Ra^−/− mice were found to have a significantly increased number of total splenic progenitors with a 2-fold increase over normal controls. Dose-escalating radiation consistently reduced CFU (GM-GEMM) significantly more in IL-17Ra^−/− than in their normal littermates. At 200 rad, CFU were reduced to 28% of baseline in IL-17Ra^−/− mice, but only to 61% of baseline in control animals (Fig. 2B). Total spleen HPPs were statistically not different at baseline between both mice strains. However, the calculated percentage of reduction after irradiation was ~25% higher in IL-17Ra^−/− over normal controls (Fig. 2C). In contrast to splenic

![Graph](http://www.jimmunol.org/)
CFUs (GM-GEMM), bone marrow CFU (GM-GEMM) were only slightly increased in IL-17Ra−/− mice. IL-17Ra−/− and age- and sex-matched normal control animals (C57BL/6) were treated with increasing doses of gamma irradiation in 100-rad increments, starting at 200 rad (n = 6/group). The peripheral ANC was determined at 7 days (A). CFU were determined from spleen and are calculated for the entire organ (CFU-GM GEMM) (B) and CFU-HPP (C). The effect of radiation on bone marrow precursors is depicted for CFU-GM GEMM in D and CFU HPP in E. Data points constitute the means ± SE obtained from six individual animals per group and are calculated for two femura or the entire spleen from each animal. Statistical significance (p < 0.05) is indicated by *. 

Adenovirus-mediated mIL-17A overexpression accelerates neutrophil recovery and hemopoietic progenitor recovery after radiation insult

C57BL/6 mice were sublethally irradiated with 500 rad. For in vivo mIL-17A expression, mice were i.v. injected with an adenovirus-encoding mIL-17A (Ad-mIL17A) or treated with the control virus Ad-CMVLuc. Animals were sacrificed at 1 and 4 wk, respectively, and analyzed for hemopoietic recovery. A substantially enhanced ANC recovery was seen in Ad-mIL17A-treated animals following irradiation at 8 days (p < 0.0001), although at 4 wk the ANC had nearly normalized in both groups (Fig. 3A). Both mature and primitive progenitor analysis of spleen and bone marrow showed significantly accelerated hemopoietic recovery in Ad-mIL17A-treated animals following radiation (p < 0.05) (Fig. 3, B and C). The experiments were repeated twice with identical results. One additional experiment was performed using littermate control mice instead of C57BL/6 animals, which also revealed identical results.

Gamma irradiation (XRT) induces mIL-17A transcription in splenocytes in vivo within the hemopoietic microenvironment but not in vitro

To investigate the effect of gamma irradiation at the transcriptional as well as the protein level in splenocytes on mIL-17A, a real-time PCR protocol was developed. Tissue was concurrently analyzed by ELISA to quantitate IL-17A at the protein level. For controls, C57BL/6-derived mouse splenocytes were analyzed with and without in vitro Con A stimulation for 24 h (Con A and CTL). To determine the in vitro effect of irradiation with 500 rad on splenocytes, splenocytes were irradiated in vitro (XRT) (Fig. 4, A and C).
To determine the effect of radiation on IL-17A expression in vivo, splenocytes were harvested from C57BL/6 mice 7 days following sublethal irradiation (500 rad) (XRT) and another group of mice who had received double-purified CD4+ T cells (1 × 10^7) (XRT/CD4^+). Splenocytes from irradiated animals were processed immediately after harvest for further analysis. Total copy number of mIL-17A transcripts per total RNA (copy number per micrograms) as well as IL-17A protein per total protein (picograms per milligrams) were measured. In vitro Con A-stimulated splenocytes resulted in a 60-fold increase over baseline mIL-17A expression (CTL) (Fig. 4, A and B). IL-17A expression was minimal and not statistically different in splenocytes that were obtained from unmanipulated animals vs unstimulated control splenocytes after 24-h ex vivo culture (data not shown). RNA isolated from spleens that was recovered from animals following sublethal radiation with 500 rads had a 30-fold increase in mIL-17A transcripts 7 days after radiotherapy (XRT) (Fig. 4B). Animals that had 1 × 10^7 CD4^+ T cells transferred following sublethal irradiation showed a 80-fold increase in RNA isolated from their spleens (XRT + CD4^+). The results were statistically significant (p < 0.001) (Fig. 4B). With small deviations, the protein data paralleled the gene expression data. ELISA did not detect any IL-17A in unstimulated splenocytes or in vitro-irradiated splenocytes (CTL, XRT) (Fig. 4C). However, following radiation, 49 ± 12 pg mIL-17A per milligram of protein was detected (XRT) (Fig. 4D). CD4^+ T cell transfusion following irradiation resulted in 110 ± 22 pg/mg protein (XRT/CD4^+) (p < 0.005). Positive control splenocytes stimulated with Con A produced 208 ± 47 pg/mg protein (Con A) (Fig. 4C). Statistically significant results are marked with asterisks (p < 0.05) (Fig. 4). The experiments were repeated twice with identical results.
CD4+ T cell-mediated accelerated hemopoietic recovery following irradiation is significantly impaired in IL-17Ra−/− mice

To evaluate the role of CD4+ T cells on hemopoietic reconstitution following radiation injury, IL-17Ra−/− mice and normal C57BL/6 control animals were infused with 1 × 10^7 double-purified, syngenic C57BL/6-derived CD4+ T cells. Purification eliminated precursors, as CD4+ T cell fractions gave no rise to colony formation in vitro. Spleenic precursor analysis was performed at 7 days following CD4+ T cell transfer by scoring for CFU (GM-GEMM; A) and CFU (HPP; B) and calculated for the entire organ. Statistical significance over baseline is indicated by asterisk (p < 0.05). Statistical significance over IL-17Ra−/− is indicated by ** (p < 0.05).

Specific blockade of IL-17A/IL-17Ra delays CD4+ T cell-mediated enhanced hemopoietic recovery after sublethal irradiation in normal mice

Following sublethal irradiation with 500 rad and infusion of 1 × 10^7 double-selected CD4+ T cells, normal C57BL/6 mice were treated with a previously described construct that neutralizes in vivo activity of IL-17A (8, 16). The soluble mIL-17RaFc-expressing adenovirus Ad-mIL17RaFc or a control virus, AdEGFP, was injected following sublethal irradiation (n = 8/group). At 7 days, mice were sacrificed, and peripheral white blood cells as well as progenitor frequency in bone marrow and spleen were enumerated. Progenitor frequencies were calculated for total organ cellularity (spleen) or the cellularity of one femur. The ANC was increased by 144% in control virus-treated animals (0.78 × 10^6/ml vs 1.4 × 10^6 + 0.12/ml) (p < 0.01) (Fig. 5A). Progenitor analysis showed that both mature (CFU-GM-GEMM) as well as primitive precursors increased in IL-17Ra−/− mice by 5-fold in normal C57BL/6 mice and progenitors increased in IL-17Ra−/− by 7-fold (p < 0.01) (Fig. 6A). Statistically significant results are marked with asterisks. The experiments were repeated twice with identical results and once more using littermate controls instead of C57BL/6 controls, also with identical results (data not shown).

FIGURE 5. Effect of CD4+ T cells on hemopoietic recovery after irradiation in IL-17Ra−/− mice. IL-17Ra−/− and normal control C57BL/6 mice were treated with sublethal gamma irradiation (350 and 500 rad, respectively) (n = 8/group). Two groups of animals received 1 × 10^7 double-purified, syngenic C57BL/6-derived CD4+ T cells. Purification eliminated precursors, as CD4+ T cell fractions gave no rise to colony formation in vitro. Spleenic precursor analysis was performed at 7 days following CD4+ T cell transfer by scoring for CFU (GM-GEMM; A) and CFU (HPP; B) and calculated for the entire organ. Statistical significance over baseline is indicated by asterisk (p < 0.05). Statistical significance over IL-17Ra−/− is indicated by ** (p < 0.05).

FIGURE 6. Effect of IL-17Ra decoy expression on hemopoietic reconstitution following irradiation-mediated myelotoxicity. Normal C57BL/6 mice were sublethally irradiated with 500 rad (n = 8/group). Following radiation, animals were treated with the soluble mIL-17Ra-expressing construct Ad-mIL17RaFc or a control virus, AdEGFP. Peripheral ANC as well as bone marrow and spleen precursor frequency by colony forming assays were evaluated at 7 days (calculated per spleen and 2 femura) (A–C and D and E, respectively). Statistical significance (p < 0.05) is indicated by *.
Discussion

Although phenotypically IL-17Ra\(^{-/-}\) mice appear to be normal and indistinguishable from control animals at baseline, when challenged with pathogens they display serious impairment of their microbial host defense. For instance, when IL-17Ra\(^{-/-}\) mice are challenged intratracheally with Klebsiella pneumoniae or systemically with Candida albicans, their organ-specific myeloid host response is substantially impaired and delayed, resulting in a significantly reduced LD\(_{50}\) compared with normal animals (8, 9). Although unchallenged, IL-17Ra\(^{-/-}\) mice initially display very similar baseline hemopoietic parameters when compared with their normal controls, the data presented demonstrate that their hemopoietic system is much more sensitive to myelotoxic injury caused by treatments with gamma irradiation. The only hemopoietic difference observed at baseline was that IL-17Ra\(^{-/-}\) mice had a 2-fold increased frequency of mature splenic progenitors. Reports from studies in mice genetically deficient of other granulopoietic growth factors or its receptors (stem cell factor (SCF), G-CSF) also observed increased radiation sensitivity. However, in contrast to IL-17Ra\(^{-/-}\) animals, most of these cytokine-deficient strains already displayed substantial baseline hematologic abnormalities such as anemia or granulocytopenia (17–21). This discrepancy would suggest the role of IL-17A and its receptor to be more likely as an acute response cytokine rather than being required for baseline homeostasis of the hemopoietic system. Such characteristics of a cytokine would allow the hemopoietic system to respond to emergency host defense situations by transiently stimulating granulopoiesis, thus boosting myeloid host defense. This concept of a response cytokine is further supported by the absence or only very low mIL-17A gene expression at baseline in normal, unchallenged animals. Induction of IL-17A expression in T cells as a result of pathogen exposure, such as bacterial lipoproteins, has been reported previously. Profound induction of IL-17A occurs in vivo following microbial challenge (5, 8, 9). We show a similar induction of IL-17A message in splenocytes recovered from mice following sublethal irradiation with expression levels similar to positive control splenocytes that had been stimulated with Con A. Such induction was not seen in splenocytes removed from their microenvironment followed by in vitro irradiation. We therefore conclude that the induction of IL-17A in splenocytes following radiation is not a result of direct gamma irradiation but an indirect effect of the gamma irradiation, which requires the in vivo microenvironment.

Radiation is a cornerstone of modern cancer treatment, and it creates nonspecific tissue injury and inflammation, which triggers the release of various proinflammatory cytokines. Such a proinflammatory cytokine milieu caused by radiation is required for adequate tissue restoration and tissue healing. Limanni et al. (24) showed that sublethal gamma irradiation induces expression of various hemopoiesis-stimulating cytokines in vivo within the hemopoietic microenvironment, specifically of IL-6, IL-1\(\alpha\), GM-CSF, and c-kit ligand or SCF. He showed that this milieu of proinflammatory cytokines is required for adequate hemopoietic recovery following radiation injury (22–24). Interestingly, IL-17A also exerts its stimulating effects on hemopoiesis, at least in part, via induction of SCF in bone marrow stroma cells (4). IL-6 is also a T cell-derived proinflammatory, hemopoiesis-stimulating cytokine. Its expression is also induced by radiation injury and is required for restoration of normal hemopoiesis. Following radiation injury, blockade of either cytokine was found to substantially delay hemopoietic restoration and reduce survival, whereas exogenous administration accelerated recovery and enhanced survival (25, 26). Besides the induction of SCF, IL-17A exerts its hemopoiesis-stimulating effects through the induction of other hemopoietically stimulating downstream cytokines, specifically via IL-6 and G-CSF, all of which act synergistically (3, 4, 11, 27).

The data presented in this study demonstrate that in response to myelotoxic radiation, IL-17A expression is induced in T cells that are homing to, or have migrated to, the hemopoietic microenvironment. Stimulation of IL-17Ra via IL-17A is directly facilitating and enhancing restoration of normal hemopoiesis. Alternatively, it would be possible that radiation, which disrupts the mucosal gastrointestinal barrier, could lead to the entry of intestinal microorganisms into the bloodstream, thus leading to mIL-17A expression induced by exposure of T cells to bacterial peptides in the spleen through bacteremia. However, this scenario would be less likely because radiation at 500 rad is not a lethal or fully myeloablative dose. Therefore, this sublethal radiation dose is not expected to result in systemic sepsis, which by itself would carry a high mortality. Mortality, however, was not observed with the sublethal irradiation. We hypothesize that other proinflammatory physiologic mediators induced in vivo by radiation within the hemopoietic microenvironment and capable of triggering IL-17A expression must exist. Nevertheless, because nonlethal bacterial translocation can potentially occur without overt clinical sepsis, additional studies are needed to fully validate this hypothesis. Although the data from our experiments did not suggest involvement of IL-17A in resting hemopoiesis, our experiments have also not entirely ruled it out. However, although expression of IL-17A is reported to be absent or low under normal physiologic conditions, because of the inevitable exposure of T cells to microbes and thus Ag stimulation (e.g., within intestinal tract) each organism must experience at times IL-17A expression to some degree. Therefore, IL-17A might have a possible role in resting hemopoiesis. Additional studies will be needed to better examine the role of CD4\(^+\) T cells and the IL-17A/IL-17Ra system during normal hemopoiesis, specifically in T cell-depleted and Rag\(^{-/-}\) animals.

Pantel et al. (28, 29) previously reported that depletion of CD4\(^+\) T cells in mice substantially enhanced sublethal radiation-induced myelosuppression and delayed hemopoietic restoration. To demonstrate that one mechanism for T cells, specifically for CD4\(^+\) T cells, that exerts hemopoiesis-stimulating activity is via the IL-17Ra, IL-17Ra\(^{-/-}\) animals were sublethally irradiated at doses biologically equivalent to doses in the more radiation resistant normal control C57BL/6 mice. Although the infusion of double-purified (to exclude contaminating repopulating progenitor cells) CD4\(^+\) T cells substantially increased CFU formation in both strains after radiation, this effect was significantly reduced in IL-17Ra\(^{-/-}\) animals. This finding indicates that at least a significant portion of the stimulatory effect conferred by T cells on the hemopoietic system is the direct result of IL-17Ra, which is deleted in IL-17Ra\(^{-/-}\) mice. The intended genetic alteration induced in knockout animals is not always entirely isolated, and occasionally such animals are found to have developmental abnormalities that might affect other organ systems, as, for instance, previously reported with TNF-\(\alpha\) knockout mice (30). To independently validate the findings obtained with the IL-17Ra\(^{-/-}\) animal experiments, we conducted additional experiments in normal C57BL/6 animals by using a transient blockade of IL-17Ra by neutralizing IL-17A. A previously reported molecular decay for mIL-17A was used. This consisted of an adenovirus encoding the soluble mIL-17Ra with a genetically engineered linkage to Fc for prolongation of its half-life (8, 16). The results obtained were very similar to the data obtained with IL-17Ra\(^{-/-}\) mice. Although the hemopoietic stimulatory effect of CD4\(^+\) T cells following irradiation was partially abrogated in IL-17Ra\(^{-/-}\) mice and also partially blocked at comparable levels with the soluble IL-17A receptor, IL-17A did not
account for the entire stimulatory effect that was conferred by T cells, and there was a clear IL-17A/IL-17Ra-independent effect. Therefore, we conclude that T cells stimulate hematopoietic recovery after myelotoxic radiation to a significant portion via IL-17A/IL-17Ra, although yet to be identified additional mechanisms must exist mediating such an effect. It is likely that these additional mechanisms could involve other downstream cytokines of IL-17A, although this hypothesis requires further investigation. Additional irradiation studies with T cell-depleted or deficient strains such as Rag−/− mice will be required to further define the exact role of T cells in this setting. A recent publication by Bonomo and colleagues (31) has further defined the role of CD4+ T cells in resting hematopoiesis. The investigators showed that activated CD4+ T cells are required for normal hematopoiesis.

Even less well defined as the mechanisms for the distal effectors of IL-17A are the proximal mechanisms for radiation-induced IL-17A expression. A key proximal regulator of IL-17A expression is IL-23. In response to microbial exposure, dendritic cells secrete IL-23 and contribute largely to IL-17A expression in T cells (32, 33). However, sublethal radiation without microbial translocation would also not be expected to cause release of the proximal mediator IL-23. Tissue distribution of viable and apoptotic neutrophils can affect IL-23 expression in phagocytes as well as the proportion of neutrophils regulatory T cells (Tn) (34). Radiation can massively disturb this delicate and intricate physiologic balance, and additional studies will be required to investigate the exact role of IL-23 as well as Tn in this setting.

Patients suffering from T cell deficiency syndromes such as AIDS experience increased hematopoietic toxicity when undergoing myelotoxic cancer therapy. The enhanced toxicity in this patient population requires significant dose adjustments and therefore is associated with inferior therapeutic options and outcomes (13, 14). Moreover, AIDS patients have a substantially increased incidence for bacterial infections, especially the pulmonary tract, often despite adequate peripheral neutrophil counts (35, 36).

The data presented in this study raise some intriguing questions. For instance, whether IL-17A might be related, at least in part, to some of the increased myelotoxicity that is observed in T cell-depleted individuals. Given the previously demonstrated protective role as an inducible host defense cytokine for microbial infections, IL-17A could potentially be developed as a support cytokine for cancer therapy or for AIDS patients in addition to already approved cytokines (9). The animal data demonstrate that IL-17A expression in vivo accelerates hematopoietic recovery following irradiation. The mechanism for IL-17A in microbial host defense is distinct and unique, and, therefore, this molecule cannot simply be substituted with other, already available support cytokines such as G-CSF or GM-CSF (9). It is therefore likely that its role in hematopoiesis, specifically in granulopoiesis, is also unique. Although IL-17A has been found to be associated with human disease, specifically with autoimmune disorders such as rheumatoid arthritis, we found that rodents tolerate even large doses of IL-17A for prolonged time periods without obvious or noticeable toxicity (3, 4, 9, 10). Nevertheless, clinical development of this cytokine would require careful toxicity evaluations in humans.

In summary, IL-17A is a proinflammatory T cell-derived emergency cytokine, which is induced within the radiated hematopoietic microenvironment. Signaling via its receptor IL-17Ra is required for hematopoietic recovery after radiation injury. Exogenous IL-17A administration accelerates hematopoietic recovery following radiation-related myelosuppression, and its distinct biologic properties make it an interesting candidate for further development as a potential support cytokine for immunosuppressive cancer therapies.

Disclosures
The authors have no financial conflict of interest.

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