Hematopoietic Reconstitution and Prevention of Graft-Versus-Host Disease With UVB-Irradiated Haploidentical Murine Spleen and Marrow Cells

By Marjorie L. Cohn, Richard A. Cahill, and H. Joachim Deeg

We investigated in a murine model whether UVB irradiation of lymphohemopoietic cells would prevent the development of graft-versus-host disease (GVHD). Preliminary experiments showed that spleen colony (CFU-S) formation by hemopoietic cells was preserved at UVB doses that eliminated lymphocyte proliferation. In a parent into F1 model, UVB irradiation (5 to 15 mJ/cm²) of spleen cells added to normal marrow cells prevented the development of GVHD, whereas all recipients given untreated spleen cells developed GVHD. Syngeneic recipients of marrow exposed to 2.5 to 10 mJ/cm² of UVB achieved normal hemopoietic reconstitution. Based on these observations, B6D2 F1 (H-2b X H-2d) recipients were given 1,000 cGy of total body irradiation (TBI) followed by transplantation of 5 x 10⁶ parental B6 (H-2d) bone marrow cells and 10 x 10⁶ B6 spleen cells, either unirradiated or exposed to UVB before infusion. All mice transplanted with cells exposed to 10 or 12.5 mJ/cm² of UVB survived without GVHD. At 2.5 and 5.0 mJ/cm², mice showed signs of GVHD, beginning at day 30, and 100% and 80%, respectively, eventually developed chronic GVHD. At 7.5 mJ/cm², mice had weight loss, from which 60% recovered and survived without GVHD, while 40% died with GVHD. At 15 mJ/cm², some recipients died from graft failure, while some survived without GVHD. All surviving mice were complete donor-type chimeras. Spleen size and cellularity and in vitro lymphocyte responses correlated inversely with the development of GVHD. Mice without GVHD showed specific tolerance to skin grafts from the second parent strain, while animals with GVHD rejected their skin grafts. Thus, in a murine model UVB irradiation of transplanted hemopoietic stem cells allows for hemopoietic reconstitution and prevents GVHD.

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STUDIES IN MURINE models have shown that graft-versus-host disease (GVHD) across both major (H-2) and minor (non-H-2) histocompatibility barriers is mediated by donor T lymphocytes and can be prevented by removal of T lymphocytes from the spleen/marrow cell inoculum.1-3 In man, similarly, the incidence of acute GVHD can be reduced substantially with T-cell depletion from the donor marrow.4 However, this approach has also been associated with an increased incidence of graft failure and recurrence of the underlying disease.5-7 Clearly, alternative approaches are needed.

We have recently shown that treatment of human bone marrow with UVB light selectively inhibits lymphocyte function while preserving hemopoietic colony formation.8 Furthermore, we have shown in a canine model of autologous marrow transplantation that UVB/C treatment of lymphocytes from DLA-incompatible donors transfused posttransplant prevents the development of GVHD,11 In the current study, we investigated in a murine model the effects of UVB irradiation on lymphocyte and hemopoietic precursor functions and determined whether UVB irradiation of donor cells could prevent GVHD while allowing for the development of specific tolerance and complete hemopoietic reconstitution in recipients prepared with lethal doses of total body gamma irradiation (TBI).

MATERIALS AND METHODS

Mice. C57Bl/6J (H-2b), DBA/2J (H-2d), BALB/cJ (H-2d), BALB.k (H-2d), C57H/HeJ (H-2d), and C57Bl/6J x DBA/2J (B6D2) F1 mice were purchased from Jackson Laboratories (Bar Harbor, ME). Mice were 8 to 12 weeks old, and donors and recipients were age- and sex-matched within each experiment.

Mixed lymphocytic cultures (MLC). The response of spleen cells to allogeneic stimulation in MLC was examined as described:12 Briefly, responder cells (5 x 10⁶/well) were cocultured with allogeneic stimulator cells (1 x 10⁶/well, gamma-irradiated with 3,000 cGy immediately before culture) in 0.2-mL volumes in modified Click's medium in flat-bottom microtiter plates (Costar, Cambridge, MA). After incubation for 5 days at 37°C in a 7% CO₂ humidified air atmosphere, 1 μCi [3H]thymidine per well was added and plates were incubated for another 18 hours. Cells were harvested and uptake counted by standard methods.

Mitogen responses. Spleen cells at 2.5 x 10⁶ cells/mL were cultured as described for MLC. Concanavalin A (Con A, Sigma, St Louis, MO) was added at 1 μg/mL or 0.1 μg/mL; phytohemagglutinin (PHA, Difco, Detroit, MI) was added at 0.2% or 0.02%. After 72 hours' incubation, [3H]thymidine was added to cultures, and after 18 hours, cells were harvested and [3H]thymidine uptake counted as described for MLCs above.

Colony-forming unit-spleen (CFU-S). Recipient mice received 1,000 cGy of TBI and spleen cells (5 x 10⁶ cells/mouse), either unirradiated or irradiated with 0.5 to 10 mJ/cm² of UVB, injected intravenously. On day 8, mice were killed, spleens were fixed in Bouin's solution, and surface colonies were mounted.13

UV irradiation of cells. Cells were exposed to UV light as described.14 Briefly, a UVB lamp (Spectroline XX-15B, Spectron, Harbor, ME) was added at 1 pg/mL or 0.1 kg/mL; phytohemagglutinin (PHA, Difco, Detroit, MI) was added at 0.2% or 0.02%. After 72 hours' incubation, [3H]thymidine was added to cultures, and after 18 hours, cells were harvested and [3H]thymidine uptake counted as described for MLCs above.

From the Programs of Immunogenetics and Bone Marrow Transplantation, Department of Pediatrics, Georgetown University, Washington, DC; the Naval Medical Research Institute, Bethesda, MD; and the Transplantation Biology Program, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA.


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Address reprint requests to H. Joachim Deeg, MD, Fred Hutchinson Cancer Research Center, 1124 Columbia St, Seattle, WA 98104.

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CA) to a maximum depth of 1.5 mm; the open dishes were placed on wet ice and exposed to UV light. Different doses were achieved by exposing cells for different lengths of time at predetermined distances from the UV lamp. Exposure was monitored using a Spectroline DM-300x UV meter measuring in the spectral range from 280 to 320 nm. After irradiation, cells were gently scraped from the dishes, washed, and resuspended in appropriate medium for use.

**Ex vivo assay of GVH reaction.** An ex vivo GVH assay, as described by Sharkis et al., was used as an early assessment of UV effects. C57Bl/6J spleen cells were prepared and UVB-treated as described above and injected into lethally irradiated C57Bl/6J or B6D2F1 recipients (12.5 × 10^6 cells/mouse). On day 5, recipients were killed and spleen cells (3 × 10^7 cells/well) were cultured in 96-well flat-bottom culture plates in the presence of ^3^H-thymidine for 4 hours to determine spontaneous in vitro proliferation of these cells following in vivo exposure to syngeneic or allogeneic hosts.

**Marrow transplantation and care.** Donor mice were killed and marrow cells were flushed from the tibiae and femora with Hank's enriched medium (HEM) containing 1% fetal calf serum (FCS) and processed as described. After appropriate in vitro manipulations, cells were washed three times and the indicated numbers of viable nucleated cells (bone marrow alone or bone marrow plus spleen cells) were injected intravenously into recipients prepared with 1,000 cGy TBI. Mice were given 0.2% tetracycline hydrochloride in their drinking water and housed in sterile cages on a laminar flow rack beginning 1 week before irradiation and maintained on this regimen throughout the experiment. Mice were examined daily for signs of GVHD (weight loss, hunched posture, ruffled fur, alopecia). In all experiments and at each dose level five animals were entered per group.

**Determination of chimerism.** Chimerism was determined as described. Briefly, 10^6 spleen cells, suspended in 0.1 mL HEM, were mixed with 0.1 mL monoclonal antibody supernatant and 0.05 mL rabbit complement (Accurate Scientific and Chemical, Westbury, NY). After incubation at 37°C for 1 hour, cells were washed and resuspended in 0.2% trypan blue for viability determination using light microscopy. Monoclonal antibodies 28-8-6S (anti-H-2K^d^, murine IgG2a) and 34-2-12S (anti-H-2D^d^, murine IgG2a) were generous gifts from Dr David Sachs, National Cancer Institute.

**Skin grafts.** Skin grafts from the parent strain that had not been used as marrow/spleen cell donor and from a third-party strain were performed using standard techniques. Skin grafts were inspected daily for viability.

**Statistical analysis.** Survival and survival free of clinical GVHD in mice transplanted with hemopoietic cells exposed to different doses of UVB light were compared using a log rank trend test as described by Kalbfleisch and Prentice. In mice transplanted with hemopoietic cells exposed to different doses of UVB light as was in vitro proliferation in MLC, B6 spleen cells were UVB-irradiated and injected into gamma-irradiated (1,000 cGy) B6 or B6D2F1 recipients; on day 5, spleens were removed and assayed in vitro for proliferation (Table 1). Untreated B6 spleen cells injected into F, to 25 colonies per mouse were identified on day 8 (Fig 1). This number was not altered by exposure of spleen cells to 0.5 to 7.5 mJ/cm^2^ of UVB before injection; at doses of greater than or equal to 10 mJ/cm^2^, CFU-S decreased to less than 10% of control. Thus, there was a dose range at which lymphocytes capable of lectin and alloantigen responses were eliminated, while colony-forming cells survived.

**Ex vivo assay of GVH reaction.** In an attempt to determine whether in vivo GVH reactivity was as sensitive to UVB light as was in vitro proliferation in MLC, B6 spleen cells were UVB-irradiated and injected into gamma-irradiated (1,000 cGy) B6 or B6D2F1 recipients; on day 5, spleens were removed and assayed in vitro for proliferation (Table 1). Untreated B6 spleen cells injected into F, while MLC responses were reduced to less than 1% of control after 5 mJ/cm^2^, 7.5 to 10 mJ/cm^2^ were required to eliminate Con A- and PHA-induced proliferation. Of note was the observation that the response to Con A at optimal concentration was increased relative to controls at low doses of UVB.

**Effect of UVB irradiation on CFU-S.** Following injection of 5 × 10^6 spleen cells into lethally irradiated recipients, 20

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**RESULTS**

**In vitro lymphocyte proliferation after UVB irradiation.** As in other species, responses of murine spleen cells to gamma-irradiated stimulator cells in MLC were more sensitive to UVB light than were responses to mitogens; while MLC responses were reduced to less than 1% of control after 5 mJ/cm^2^, 7.5 to 10 mJ/cm^2^ were required to eliminate Con A- and PHA-induced proliferation. Of note was the observation that the response to Con A at optimal concentration was increased relative to controls at low doses of UVB.

**Effect of UVB irradiation on CFU-S.** Following injection of 5 × 10^6 spleen cells into lethally irradiated recipients, 20

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![Fig 1. Effect of UVB on CFU-S and PHA responses of spleen cells. C57Bl/6 spleen cells were exposed to UVB as indicated and injected into syngeneic recipients gamma-irradiated with 1,000 cGy or assayed in vitro for PHA-stimulated proliferation. For CFU counts, spleens were removed on day 8 and fixed in Bouin's solution. The data points represent the means of three spleens; results are expressed as percent of control.](image-url)
recipients proliferated more vigorously than the same cells injected into syngeneic B6 recipients, presumably due to stimulation by recipient antigens in vivo. Lymphocytes from recipients given spleen cells exposed to 5 to 10 mJ/cm² of UVB showed a modest decrease of proliferation in F₁ recipients. Exposure to 12.5 mJ/cm² reduced proliferative response to less than 25%, and 15 mJ/cm² to less than 5% of control.

**Induction of GVHD.** Lethally irradiated B6D2 F₁ mice were injected with 1.0 to 10.0 × 10⁶ of C57B1/6 spleen cells (to induce GVHD) and 5 × 10⁶ C57B1/6 unmanipulated bone marrow cells; with 5 × 10⁶ spleen cells, all mice died with GVHD (median, 45 days). With 10 × 10⁶ spleen cells, deaths occurred earlier (median, 23 days) and this cell dose was used subsequently to examine UVB effects on GVHD.

**Prevention of GVHD by UVB irradiation of spleen cells.** Lethally irradiated B6D2 F₁ recipients were given unmanipulated C57B1/6 spleen cells and 10 × 10⁶ untreated or UVB exposed C57B1/6 spleen cells. All mice given unmanipulated spleen cells developed GVHD and 80% died before day 40. All mice injected with spleen cells that had been exposed to UVB at doses of 5 to 15 mJ/cm² survived more than 250 days. At 5 and 7.5 mJ/cm² of UVB, beginning at day 30, mice experienced a transient weight loss of 18% to 25%. However, all mice had recovered completely by day 70. Studies on day 120 showed all mice to be complete donor hemopoietic chimeras. Chimera cells were unresponsive to DBA/2 (parental) stimulators, but responded vigorously to third-party (C3H) stimulators (data not shown).

**Effect of UVB on hemopoietic reconstitution.** Results are summarized in Fig. 2. All radiation controls (not given marrow) died within 16 days, while all recipients of sham-treated syngeneic bone marrow survived beyond 250 days. Similarly, all recipients of syngeneic bone marrow treated with 2.5 to 10 mJ/cm² survived with complete hemopoietic reconstitution. At 12.5 mJ/cm² and 15 mJ/cm², 20% and 80%, respectively, died. Spleen cells from long-term survivors responded normally to allogeneic (BALB.k, H-2k) stimulator cells (Table 2) and to mitogens (data not shown), indicating that UVB treatment of bone marrow had not impaired T-cell recovery.

**Hemopoietic reconstitution and prevention of GVHD with UVB-treated marrow and spleen cells.** Results are summarized in Figs 3 and 4. All mice given untreated cells developed GVHD at a median of 30 days and died (median survival, 80 days). Mice transplanted with cells exposed to 2.5 mJ/cm² developed GVHD at a median of 100 days. The appearance of GVHD was chronic in nature, and 60% of animals survived more than 200 days. As the dose of UVB increased to 5 and 7.5 mJ/cm², the incidence of clinically apparent GVHD decreased, although survival was not different from that seen with 2.5 mJ/cm². At 10 and 12.5 mJ/cm², none of the mice developed GVHD and all survived more than 200 days. At 15 mJ/cm², none of the mice developed GVHD, but only one animal survived more than 200 days. Thus, the probability of developing clinically apparent GVHD significantly decreased (P = .001) and the probability of survival increased (P = .003) with increasing doses of UVB.

As illustrated in Table 3, examination of spleen cells on day 200 showed that at all dose levels recipients were complete chimeras, suggesting that even at 15 mJ/cm² of

![Graph](https://www.bloodjournal.org)
UVB, some hemopoietic stem cells capable of reconstituting the recipient had survived. Spleens of recipients of cells exposed to 2.5, 5.0, or 7.5 mJ/cm² of UVB were small and cell numbers reduced to 70% to 15% of normal; spleens were larger and cell numbers higher (50% to 80% of normal) at 10 to 15 mJ/cm².

In vitro proliferative capacity of chimera spleen cells on day 210 posttransplantation is summarized in Table 4. Responses to PHA and Con A were comparable or superior to those observed with donor strain or normal recipient strain cells. Also, spleen cells from chimeras showed responses to third-party (CBA/J) cells similar or superior to those of control cells. Chimera cells showed some proliferation in response to DBA/2 (the nontransplant donor parent strain) cells at UVB doses of 2.5 to 7.5 mJ/cm², suggesting that tolerance had not been achieved. At UVB doses of 10 and 15 mJ/cm², spleen cells showed specific nonresponsiveness to DBA/2 cells; some proliferation was observed at 12.5 mJ/cm².

To further determine the establishment of tolerance and its specificity, skin grafts from DBA/2 and CBA/J mice were placed on chimeras on day 215 or day 240. Two mice transplanted with cells exposed to 2.5 mJ/cm² of UVB rejected both DBA/2 and CBA/J skin grafts on day 7. In contrast, three recipients of cells exposed to 10.0 or 12.5 mJ/cm² of UVB rejected CBA/J skin grafts on day 7, but maintained healthy DBA/2 grafts for more than 115 and 140 days, respectively.

**DISCUSSION**

The present study shows that UVB irradiation of lympho-hemopoietic cells prevents GVHD in a murine parent into F₁ model. The UVB doses used allowed for sustained hemopoietic reconstitution, as well as for the development of specific tolerance as determined by lymphoproliferative responses in vitro and skin graft survival in vivo.

We reported previously that UVB irradiation of human bone marrow cells preferentially eliminates T lymphocytes or inhibits T-lymphocyte function at UVB doses which preserve in vitro hemopoietic colony formation. In addition, we observed in a canine model that UVB irradiation of histoincompatible leukocytes prevents transfusion-induced GVHD in immunosuppressed recipients. Results obtained in the present model follow those findings and show that UVB irradiation not only spares committed hemopoietic precursors in vitro, but also hemopoietic stem cells in a marrow transplant model in vivo. However, in vitro/in vivo correlations must be interpreted cautiously. UVB doses of 5 or 7.5 mJ/cm², while suppressing alloresponsiveness in vitro, did not completely prevent the development of GVHD in vivo. At least 10 mJ/cm², a dose that significantly reduced CFU-S in a syngeneic model, was required to completely suppress GVHD, and 12.5 mJ/cm² were necessary to prevent in vivo alloactivation as determined by an ex vivo assay of GVH reactivity. These data indicate that in vivo allointeractions of cells result in stronger activation signals than those provided in vitro or in syngeneic models, and suggest that additional mechanisms, not tested in the available in vitro assays, are operational in the in vivo abrogation of proliferation of alloactivated donor cells. Similarly, inactivation of spleen cells as determined by CFU-S or in vitro proliferation does not necessarily affect the capacity of hemopoietic stem cells to repopulate a transplant recipient.

Of note was an increase in Con A responses at low dose (2.5 mJ/cm²) of UVB. We had noted previously that the plating efficiency of CFU–granulocyte-macrophage (CFU-GM) from human marrow also increased at low-dose UVB. Similarly, there was an increase in MLC stimulating signals than those provided in vitro or in syngeneic models, and suggest that additional mechanisms, not tested in the available in vitro assays, are operational in the in vivo abrogation of proliferation of alloactivated donor cells. Similarly, inactivation of spleen cells as determined by CFU-S or in vitro proliferation does not necessarily affect the capacity of hemopoietic stem cells to repopulate a transplant recipient.

**Figure 4.** Survival after P → F₁, transplants. B6D2 F₁ recipient mice were gamma-irradiated with 1,000 cGy of TBI and injected with 5 × 10⁸ B6 bone marrow plus 10 × 10⁶ from C57B1/6 parental donors. Donor cells were either unmanipulated (0) or exposed to UVB (2.5 to 15 mJ/cm²). Differences between groups were statistically significant by log rank trend test ($P = .003$).
similar UVB-induced change in cellular activation is responsible for increased lectin responsiveness.

Pamphilon et al observed that UVB irradiation of murine marrow cells delays hemopoietic reconstitution. Although we did not formally investigate the kinetics of hemopoietic recovery, marrow cellularity was normal in mice autopsied 120 to 210 days posttransplant. The small spleen size seen in some groups of mice was presumably related to GVHD, since the same animals also had experienced clinically overt GVHD or transient weight loss. Although acute GVHD typically results in an increase in spleen size, splenic and generalized lymphoid atrophy usually occur later. Functional asplenia has also been described in association with chronic GVHD in humans.

All recipients studied were complete allogeneic (donor-type) chimeras. Even after 15 mJ/cm² of UVB, those animals that did not die from early marrow aplasia eventually showed donor-derived hemopoiesis. This is in contrast to the observation by Pamphilon et al, who found a high incidence of mixed donor/host chimerism or reconstitution in host cells in both parent into F₁, and in completely allogeneic chimeras. This could be related to the mouse strain used (BALB/c v C57 BL/6 donor), the UVB wavelength (mean of 310 nm v 302 nm in the present study), or the dose of UVB actually delivered to hemopoietic cells. We have shown previously that the conditions under which cells are UVB exposed, the contamination with erythrocytes, and additional factors strongly influence the dose fraction that reaches the cells.

Regardless of the doses delivered, these data are in agreement with those in the murine model described by Pamphilon et al and in a rat model reported by Chabot et al and Pepino et al. In addition, Ulrich has shown that photosensitization of mice with psoralen and UVA irradiation of their marrow also prevents GVHD in histoincompatible murine recipients. Taken together, these studies provide convincing evidence for the ability of UV light to prevent GVHD and establish tolerance.

The mechanism remains to be defined. Several experimental approaches suggest that UVB induces tolerance by changing allogeneic signals to tolerogenic signals, presumably by eliminating a costimulatory factor. In addition, we and others have shown that UVB modifies class II antigen expression on the cell surface and alters calcium homeostasis. It is also likely that UVB exposure results in the death of certain, especially activated cell populations, via apoptosis. Data by Gruner et al suggest that at longer wavelengths (UVA), exposure in conjunction with photosensitizers results in isomerization of trans- into cis-urocanic acid, which may have immunosuppressive effects.

Long-term effects of UVB light in this setting remain to be determined. It will be of interest to perform sequential transplants into secondary recipients, not only to determine whether the state of tolerance can be transferred, but also to investigate whether UVB irradiation results in mutations manifest in clonal evolution that can lead to the development of lymphohemopoietic malignancies.

In conclusion, we have shown that UVB manipulation of murine spleen and marrow cells at low doses results in chronic GVHD. At higher doses, tolerated by hemopoietic cells, specific tolerance is induced, while full immunocompetence is established.

ACKNOWLEDGMENT

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Table 4. In Vitro Proliferative Responses of C57BL/6J → B6D2 F₁, Chimera Spleen Cells to Lectins and Allogeneic Cells

<table>
<thead>
<tr>
<th>Responder Cells</th>
<th>Dose of UVB (mJ/cm²)</th>
<th>PHA (0.02%)</th>
<th>Allogeneic Cells</th>
<th>CBA/J</th>
<th>DBA/2J</th>
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<tr>
<td>Chimera</td>
<td>2.5</td>
<td>ND</td>
<td>5,500 ± 800</td>
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<td>5.0</td>
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<td>7.5</td>
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<td>41,000 ± 550</td>
<td>1,700 ± 490</td>
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<td>39,500 ± 700</td>
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<td>12.5</td>
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<td>14,000 ± 210</td>
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<tr>
<td></td>
<td>15.0</td>
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<td>39,500 ± 210</td>
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<tr>
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<td>B6D2 F₁</td>
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<td>12,200 ± 300</td>
<td>1,800 ± 120</td>
<td>3,000 ± 900</td>
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</table>

Values are the mean (±SEM) cpm of three experiments, corrected for background, which ranged from 1,400 to 2,100 cpm. Abbreviation: ND, not done.
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