

Unexpected Effects of the Severe Combined Immunodeficiency Mutation on Murine Lymphomagenesis

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Summary

Strain C.B17 scid/scid (SCID) mice, which lack functional T and B lymphocytes, show heightened susceptibility to the induction of thymic lymphomas by x-irradiation. Susceptibility is highest in thymus-chimeric SCID-BL mice (thymectomized SCID mice bearing a C57BL thymus graft). All SCID-BL lymphomas originate in the cells of the thymic graft (C57BL type) and lack murine leukemia virus expression. Both SCID and SCID-BL lymphomas are phenotypically CD4⁻8⁺ and/or CD4⁺8⁺, but only the SCID-BL tumors express CD3. Injection of C57BL or BALB/c bone marrow into irradiated SCID-BL mice prevents lymphoma development, but SCID marrow is completely ineffective. The results suggest that the scid condition enhances the activity of a putative lymphomagenic agent induced in the bone marrow by x-irradiation and that C57BL thymic cells are highly sensitive targets. Moreover, the failure of SCID bone marrow to protect against lymphomagenesis vs. the efficacy of marrow from immunocompetent donors points to involvement of T or B lineage cells in this process.

Exposure to ionizing radiation in fractionated doses leads to a high frequency of T cell lymphomas in mice of susceptible strains (1, 2). Thymocytes are the target for neoplastic transformation, but an early, critical event appears to occur in the bone marrow. Thus, in C57BL mice, grafting a nonirradiated, histocompatible thymus in previously thymectomized, irradiated hosts produces lymphomas of graft origin, indicating an event in the irradiated host that promotes the neoplastic transformation of grafted thymic lymphocytes. Furthermore, transfer of bone marrow cells from irradiated donors to nonirradiated Thy-1 congenic mice produces thymic lymphomas of host origin (3, 4), demonstrating that irradiated marrow is sufficient to transfer a lymphomagenic agent(s). A murine leukemia virus (RadLV),¹ obtained from cell-free extracts of radiation-induced lymphomas (5), was initially thought to be the agent being transmitted from the irradiated bone marrow to the thymus. However, since RadLV is recovered from only 5–10% of tumors (6), the hypothesis was advanced that radiation activates a non-murine leukemia virus (non-MuLV) unidentified lymphomagenic agent in the

bone marrow, that the agent is transmitted to thymic target cells, and that it causes their eventual neoplastic transformation (4).

Conversely, shielding the bone marrow of irradiated mice or injecting exogenous marrow in whole-body irradiated mice has been shown to prevent lymphoma development (7). To learn more of the interactions between thymus and bone marrow in the radiogenesis of lymphomas, we have made use of mice of the BALB/c substrain C.B-17 scid/scid (hereafter SCID), in which an autosomal recessive mutation on chromosome 16 is associated with aberrant and nonproductive rearrangements in Ig and TCR genes. This leads to the absence of functional B and T lymphocytes and the manifestation of the scid syndrome (8). In addition, multiple organ systems in SCID mice are hypersensitive to the cell-killing effects of radiation, apparently as a result of defective capacity to repair DNA double-strand breaks (9, 10). This characteristic, together with their lack of mature lymphocytes, makes SCID mice interesting subjects for the study of the lymphomagenic effect of ionizing radiation. Here, we present evidence that the scid syndrome enhances the effectiveness of the presumptive lymphomagen, and that it abolishes the ability of normal bone marrow cells to prevent lymphoma development.

¹ Abbreviations used in this paper: MuLV, murine leukemia virus; RadLV, radiation leukemia virus.

Materials and Methods

Mice. The mice used in this study were obtained from specific pathogen-free stock maintained by the Department of Comparative Medicine, Stanford University. SCID mice were put on a regimen of the antibiotics trimethoprim and sulfamethoxazole, as described (11), at the time experimental procedures were initiated. They were thymectomized when 4–5 wk old, grafted under the renal capsule with a whole thymus from a neonatal donor 10 d later, and exposed to 1.75 Gy whole-body x-irradiation 2 wk thereafter. In another group, the mice were irradiated immediately before grafting. Mice used for studies of bone marrow protection were either irradiated with a 3-mm-thick lead shield over one femur or received 10^7 bone marrow cells from unirradiated donors intravenously within 2 h after exposure to whole-body x-radiation.

Antibodies and Immunological Assays. The antibodies used in this study were: a polyvalent, broadly reactive rat anti-MuLV serum that binds to ecotropic, leukemogenic, as well as nonleukemogenic, murine retroviruses (12); rat mAb to the mouse antigen 1C11, a marker of thymic lymphomas, preleukemic thymocytes, and proliferating progenitor cells (13); mouse mAb 19XE5 (anti-Thy-1.1), obtained from Dr. R. Nowinski, Genetic Systems Inc. (Seattle, WA); rat mAbs 53-2.1 (anti-Thy-1.2), GK1.5 (anti-CD4), and 53-6.72 (anti-CD8), obtained from the American Type Culture Collection (Rockville, MD); and hamster mAb 145-2C11 (anti-mouse CD3), purchased from Boehringer Mannheim Corp. (Indianapolis, IN). The antibodies were used either unmodified or conjugated to biotin or fluorochromes. Fluorochrome-conjugated second-stage reagents, purchased from Caltag Laboratories (South San Francisco, CA) were used to detect antibody binding, and the phenotype of stained thymocytes was analyzed in a FACS[®] equipped with a dual laser (Becton Dickinson & Co., Mountain View, CA). The staining procedure and the analysis of cell populations have been described in detail (13).

Unidirectional MLR. Thymocytes from the thymus in situ or from a thymic graft (5×10^5 cells) were mixed with equal numbers of irradiated (2 Gy) stimulator cells and maintained in culture for 3 d, in quadruplicate wells. The cultures were then pulsed for 18 h with 1 μ Ci [³H]thymidine, and proliferation of the responder cells was determined by measuring counts/min in a scintillation counter.

Results

SCID Mice Are Highly Sensitive to x-Ray Induction of Thymic Lymphomas. The conventional lymphomagenic regimen of fractionated whole-body exposure to x-irradiation, which is optimal for the induction of lymphomas in mice of strain C57BL (1.75 Gy on four consecutive weeks), was not tolerated by SCID mice and treatment was therefore reduced to a single 1.75-Gy exposure. 13 of 25 irradiated mice (52%) developed thymic lymphomas, whereas clinical evidence of spontaneous thymic lymphoma in our SCID mouse colony has been observed in only ~3% of animals in the age range of 5–12 mo (Table 1). The phenotypic profiles of normal SCID thymocytes, and of those of representative thymomas induced by radiation and arising spontaneously, are shown in, respectively, Fig. 1, A, B, and C. A significant difference between normal and neoplastic thymocytes is seen in the patterns of CD4 and CD8 expression. Normal SCID thymocytes are essentially (>96%) CD4⁻8⁻, as reported (14, 15). In the radiation-induced lymphomas, if quadrants are drawn as for the normal thymocytes, there appear to be CD4⁺8⁺ as well as CD4⁻8⁺ cells; nevertheless, the staining pattern clearly depicts a unimodal CD4^{lo}8⁺ population, rather than two distinct subsets. The cells are CD3⁻, indicating that the CD4⁻8⁺ phenotype corresponds to the transitional intermediate between the CD4⁻8⁻ and CD4⁺8⁺ stages in a normal thymus (16). The spontaneous lymphoma consists of two distinct populations, the larger one CD4⁺8⁺, the smaller one CD4⁺8^{lo}, possibly a transitional intermediate in the direction of the CD4⁺8⁻ phenotype, as suggested by the presence of a small number of CD3⁺ cells. Such emergence of differentiated T cells has been described in aging, leaky SCID mice, and is frequently accompanied by neoplastic transformation (8, 14). As in C57BL lymphomas (13), the 1C11 antigen is expressed at high levels by a majority of tumor cells, spontaneous as well as induced. It is noteworthy that the majority (~83%) of normal adult SCID thymocytes are

Table 1. Radiation Lymphomagenesis in SCID Mice

Thymectomy	Treatment		Incidence (%)	Lymphomas		
	Thymus graft	Irradiation		Median latency	Genetic origin*	MuLV [†]
No	None	None	7/200 (3.5)	<i>d</i> –5	ND	None
No	None	1.75 Gy × 1	13/25 (52)	206	ND	None
Yes	BALB/c	1.75 Gy × 1 after grafting	8/24 (33)	166	ND	None
Yes	BL/1.1	1.75 Gy × 1 after grafting	22/24 (92)	92	BL/1.1	None
Yes	BL/1.1	1.75 Gy × 1 before grafting	20/23 (87)	142	BL/1.1	None
Yes	BL/1.1	None	12/39 (31)	153	BL/1.1	None

* Genetic origin determined by Thy-1 allotype expressed on cells.

† Presence of MuLV determined by expression of MuLV-associated antigens.

‡ Mice in this group were stock. Age range at death from lymphoma was 5–12 mo.

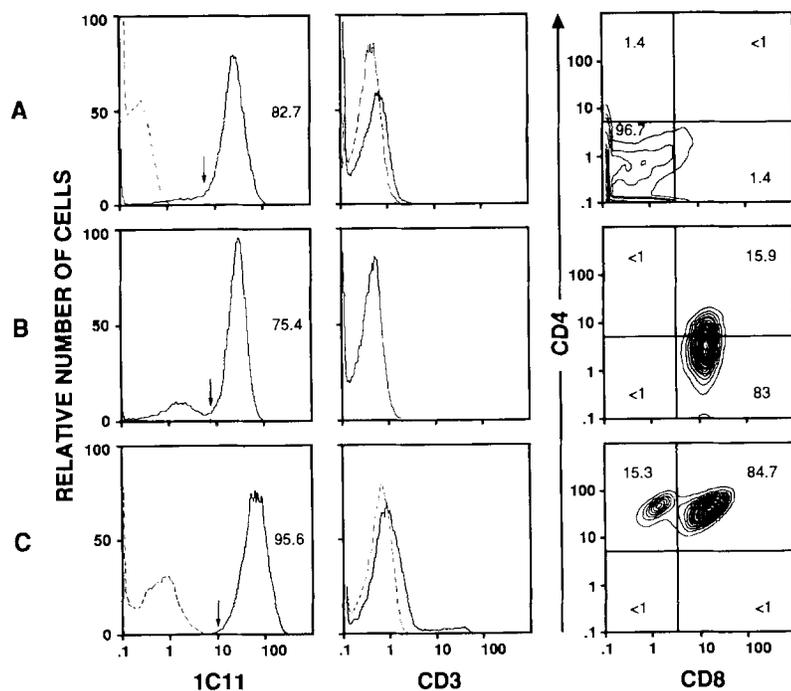


Figure 1. Phenotype of normal and neoplastic SCID thymocytes. (A) Untreated 6-wk-old SCID mouse; (B) thymic lymphoma in irradiated SCID mouse; (C) spontaneous SCID thymic lymphoma. In the single-color fluorescence histograms, fluorescence intensity is presented on the x-axis (log scale), and the relative number of cells is on the y-axis. Cells stained with mAb 1C11 were counterstained with Texas red (TR)-conjugated anti-rat antibody. Fluorescence intensity to the right of the arrows specifies 1C11^{hi} (5–10 times higher than background fluorescence); the percentage of 1C11^{hi} cells is indicated. Broken lines show background fluorescence obtained with an isotype-matched, irrelevant rat mAb. For analysis of CD3 expression, cells were stained with anti-CD3 (FITC); control cells were treated with FITC (broken lines). For two-color analysis, cells were stained with anti-CD4 (PE) and anti-CD8 (TR). The number of contour lines drawn in a particular area depict the frequency of cells exhibiting given levels of fluorescence. The quadrants show the percentages of the total population with the phenotypes CD4⁻CD8⁻ (lower left), CD4⁺CD8⁻ (upper left), CD4⁺CD8⁺ (upper right), and CD4⁻CD8⁺ (lower right).

also 1C11^{hi}, in contrast to only 10–20% (the immature subset) of normal C57BL thymocytes (12; and see Figs. 3C and D), another indication of the immaturity of SCID thymocytes.

Characterization of Thymic Graft Lymphomas in SCID-BL Mice. Definition of the relative roles of cells from the thymus and the bone marrow in the genesis of radiation-induced lymphomas requires that the origin of the cells be identifiable. This can be accomplished by using thymus-chimeric mice, in which the thymus in situ is replaced by a genetically distinct thymic graft at an ectopic site, e.g., a parental strain thymus in an F₁ host (3) or a Thy-1-congenic thymic graft (4). SCID mice, thymectomized to prevent the development of spontaneous or in situ radiogenic thymomas, received thymic implants from immunocompetent neonatal donors under the renal capsule, and were subsequently irradiated. The resulting tumors are characterized in Table 1. Initially, thymus grafts of the BALB/c parental strain were used to determine the susceptibility to radiation lymphomagenesis of an immunocompetent thymus within the scid environment. 8 of 24 grafted and irradiated mice (33%) developed lymphomas involving the graft, an incidence that is statistically similar to that observed in intact, irradiated SCID mice (52%, see above). Next, SCID-BL/1.1 mice were constructed by implanting C57BL/Ka/Thy-1.1 (BL/1.1) thymic grafts in thymectomized SCID recipients, so that cells of graft origin (Thy-1.1) could be distinguished from those of host origin (Thy-1.2). In this group, the incidence of radiogenic lymphomas was a striking 22 of 24 mice (92%), after a relatively short latent period (92 d). All lymphomas were of graft donor (Thy-1.1) origin. The possibility of MuLV involvement in the etiology of the tumors was tested by immunofluorescence

assays for cytoplasmic viral antigens. Lymphoma cells were used directly, and in a more sensitive infectious center test, which allows detection of as few as one infected cell in 10⁶ (17). For this assay, lethally irradiated (5.0 Gy) tumor cells were added to a culture of highly permissive BL/RL12-NP indicator cells (18), and after 10 d (16–20 cell doublings), these were tested for expression of MuLV p30 by immunofluorescence using a rat antiserum as described (12). Infectious MuLV was not detected in either assay (data not shown). Symptoms of a graft-vs.-host reaction (GvHR) in the chimeras, e.g., failure to thrive, splenomegaly, MuLV activation (19–21), which might be expected as a result of H-2 incompatibility, were not observed. To further verify the absence of a GvHR, a unidirectional MLR assay was performed, measuring proliferation of thymic graft cells from SCID-BL/1.1 mice and control BL/1.1 thymocytes on coculture with irradiated autologous cells, SCID spleen cells, and third-party (C3H) spleen cells. The results (Fig. 2) point to two distinct phenomena. One is that SCID spleen cells are not effective stimulators, since they evoked only one-fourth the response induced by C3H spleen cells in normal BL/1.1 thymocytes. This may stem from the reduced presence of stimulating cells or of lymphokines in the mixed culture, as a result of the absence of T and B cells in the SCID spleen. A further conclusion suggested by the results is that thymic graft cells in SCID-BL/1.1 mice have been tolerized to their host, since they did not mount even a weak response to SCID spleen cells, while retaining full reactivity to third-party cells. The phenotype of the graft lymphomas is shown in Fig. 3A. The majority of cells (>87%) expressed elevated levels of the transformation-associated antigen 1C11. The most commonly observed phenotypes consisted of a majority of cells distributed

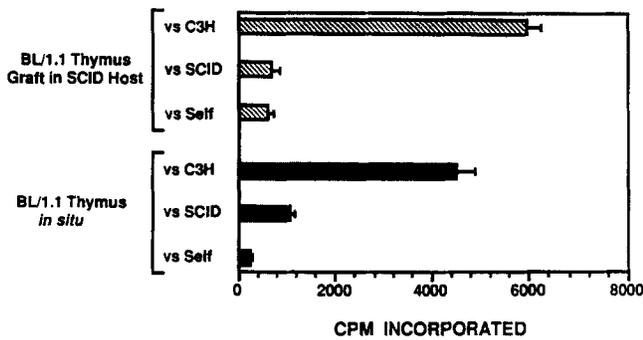


Figure 2. Lack of GvHR of thymic graft lymphocytes in SCID-BL/1.1 chimeras. BL/1.1 thymic graft cells and BL/1.1 thymocyte controls (5×10^5 cells/well) were cultured with equal numbers of radiation-killed autologous cells, SCID, and C3H spleen cells, and pulsed with [^3H]thymidine. Results are expressed as mean isotope incorporation \pm SE.

among the CD4^-8^+ and CD4^+8^+ populations in varying proportions. Similar patterns have been observed in primary radiation-induced C57BL thymic lymphomas (Sen-Majumdar et al., manuscript submitted for publication). In those tumors, the CD4^-8^+ and CD4^+8^+ subsets were obtained separately by FACS[®] sorting and passaged intrathymically in Thy-1 congenic recipients. The resulting tumors again had both CD4^-8^+ and CD4^+8^+ components, regardless of parental

Table 2. Prevention of Radiogenic Lymphomas in SCID-BL 1.1 Chimeric Mice Is Mediated by Normal but Not by SCID Bone Marrow

Protection protocol	Lymphomas	
	Incidence (%) [*]	Median latency
None [†]	22/24 (92)	92
Femur shielded	19/21 (90)	112
SCID marrow injected [§]	15/15 (100)	115
BALB/c marrow injected [§]	6/27 (22)	111
C57BL marrow injected [§]	1/13 (8)	109

^{*} All lymphomas were of thymic graft donor (BL/1.1) origin, as determined by Thy-1 allotype, and free of MuLV-associated antigens.

[†] From Table 1. All mice were irradiated (1.75 Gy \times 1) after implantation of the thymic graft.

[§] 10^7 bone marrow cells from untreated mice injected intravenously after irradiation.

tumor phenotype. From this, we infer that the observed bimodal populations in the neoplastic grafts probably represent phenotypic variants of a single clone, rather than two

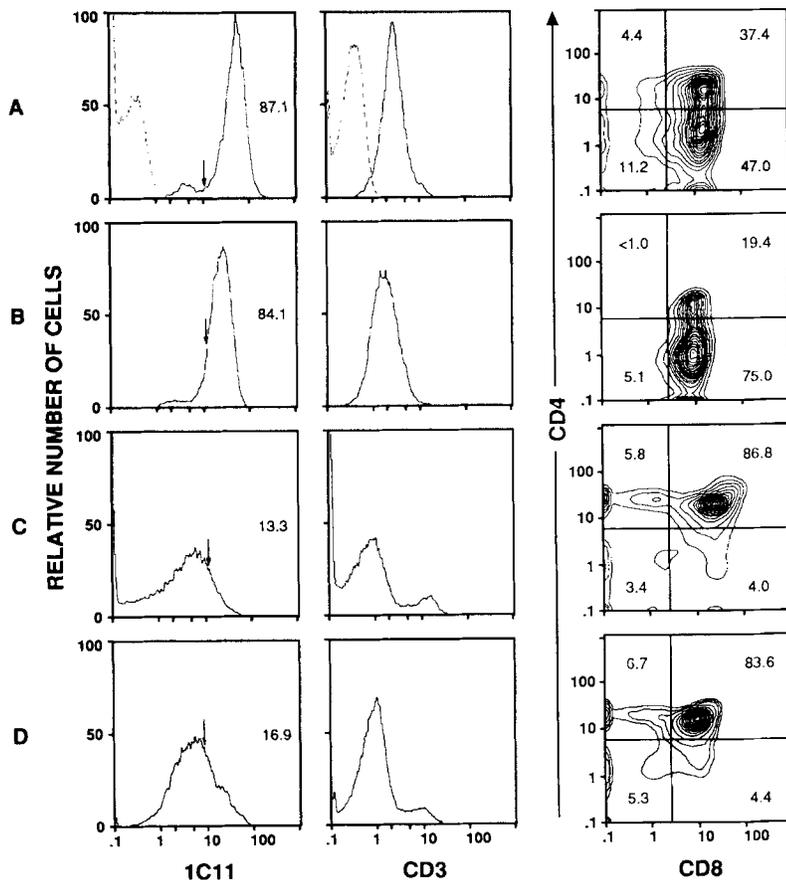


Figure 3. Phenotype of normal and neoplastic thymic grafts in SCID-BL/1.1 mice. (A) Thymic graft lymphoma in an irradiated SCID-BL/1.1 mouse; (B) thymic graft lymphoma in an irradiated SCID-BL/1.1 mouse injected with SCID bone marrow; (C) normal phenotype resulting from injection of C57BL (Thy-1.2) bone marrow; (D) normal phenotype of a C57BL thymus for comparison with C. The staining protocol was as described in Fig. 1.

distinct clones. Fewer cells were CD4⁻8⁻ and very few or none were CD4⁺8⁻. Unlike the radiation-induced SCID tumors, the SCID-BL/1.1 graft lymphomas were CD3⁺. Subsets with, respectively, high and low expression of CD3, which are seen in nonleukemic thymus (Fig. 3, C and D), were not apparent.

Influence of the Immunodeficient scid Environment on Lymphomagenesis. Irradiation of the graft itself was not necessary for the development of lymphomas. When the allogeneic thymus was implanted subsequent to irradiation of the host, evidence of GvHR was again not observed; tumors developed after a somewhat longer latent period than in the previous experiment (142 d), in 20 of 23 mice (87%), and all were of thymus graft donor origin (Table 1). Their phenotypes were similar to those seen in tumors of mice irradiated after grafting. The persistence of a high frequency of lymphomas in this protocol contrasts with their low incidence (20–25%) in thymectomized C57BL/Ka mice given a histocompatible thymic graft at the end of a lymphomagenic course of x-radiation (3, 4). The results suggest the possibility that SCID-BL/1.1 chimeras have an intrinsic propensity to develop lymphomas. Therefore an additional group of these mice was maintained without irradiation. In this group, 12 of 39 mice (31%) developed lymphomas, all of graft-donor origin (Table 1), suggesting that mere residence in a scid environment may promote the neoplastic transformation of C57BL/Ka thymocytes.

SCID Bone Marrow Uniquely Cannot Prevent Radiation-induced Thymic Lymphomas. In irradiated C57BL/Ka mice, shielding a femur during irradiation or injecting normal histocompatible bone marrow after its completion has been shown to greatly reduce the frequency of lymphomas (7, 22). The mechanism of protection is not clear, but since thymic reconstitution by donor marrow-derived cells is consistently observed in protected mice, repopulation of the thymus may be a crucial step. In SCID mice, the progeny of hemopoietic precursors in the marrow are not capable of normal lymphoid differentiation. Hence, it was of interest to examine the capacity of SCID bone marrow to prevent the development of lymphomas in irradiated mice. SCID-BL/1.1 mice were either irradiated with one femur shielded or received bone marrow cells from unirradiated SCID donors immediately after whole-body irradiation. There was no evidence of protection; the incidence of lymphomas was 91% for the femur-shielded mice and 100% for those injected with SCID bone marrow. The tumor cells were Thy-1.1, i.e., derived from the thymic graft (Table 2). Bone marrow from untreated adult BALB/c and C57BL/Ka donors was used next. Evidence of incompatibility between the irradiated SCID-BL/1.1 mice and the injected marrow was not observed. However, the incidence of lymphomas in these groups was reduced to 22% and 8%, respectively (Table 2). The residual lymphomas were of thymus graft origin, but in all protected mice, analyzed concurrently with mice not receiving bone marrow, thymocytes were Thy-1.2 (data not shown), i.e., the thymus was repopulated by donor marrow-derived cells. In protected mice (Fig. 3 C), the level of 1C11 expression on thymic graft cells was approximately the same as that seen on normal thymocytes (Fig. 3 D), and

that of the differentiation markers CD3, 4, and 8 was typical of normal thymic subsets as well (Fig. 3, C and D). In the unprotected thymus of mice injected with SCID bone marrow, however, the cellular phenotype (Fig. 3 B) was similar to that of thymocytes in the irradiated, uninjected group (Fig. 3 A).

Discussion

Human congenital immunodeficiency syndromes are frequently associated with a high incidence of leukemias and lymphomas of varied histopathology and undefined etiology (23–25). The development of T cell lymphomas has been described in SCID mice as well, among the few leaky individuals in which productive TCR gene rearrangement has occurred (8, 26). In this study, we have examined the sensitivity of SCID mice to the lymphomagenic effect of ionizing radiation. A single, low dose of x-radiation sufficed to induce a moderate incidence of thymic lymphomas, which were CD4⁻8⁺ and CD4⁺8⁺, but CD3⁻. In C57BL/Ka mice, irradiation has been observed to induce the entry of CD3⁺4⁻8⁻ target cells into an aberrant differentiation pathway, resulting in the development of CD3⁺4⁻8⁺ and CD3⁺4⁺8⁺ lymphomas (Sen-Majumdar et al., manuscript submitted for publication). Radiation-induced lymphomas in SCID mice exhibited similar CD4/CD8 phenotypes, although, presumably through failure of TCR gene rearrangement, differentiation did not proceed past the pre-TCR stage. Shores et al. (14) reported that the presence in the SCID thymus of TCR⁺ cells, as a result of either the leaky phenomenon or the introduction of bone marrow from non-scid donors, promotes the differentiation of SCID thymocytes into CD4⁻8⁺TCR⁻ and CD4⁺8⁺TCR⁻ cells. The results presented here suggest that radiation may exert a similar effect in the absence of TCR⁺ cells. In irradiated SCID-BL chimeric mice, the frequency of lymphomas was greatly increased and the latent period shortened, particularly when the graft was itself irradiated. These results likely reflect the known high susceptibility of C57BL/Ka thymic cells to neoplastic transformation, but the possibility must be considered that neoplastic transformation may have been the consequence of a GvHR (19, 20). However, this is an unlikely alternative, since none of the described symptoms of GvHR (19–21) were observed in the mice, exposure to SCID spleen cells did not induce a MLR in SCID-BL/1.1 thymic graft cells, and the administration of adult C57BL bone marrow, which should have provided additional effector cells, instead prevented the development of lymphomas. The data suggest several nonexclusive models of the roles of bone marrow and thymus in radiation lymphomagenesis. (a) If, as we have assumed (4), a lymphomagenic agent is induced in the marrow by radiation and is transmitted to thymic targets, then the scid syndrome may favor its induction and/or activity. (b) Lymphomagenesis could alternatively be interpreted as the ultimate result of the residence of the thymus in a host environment that cannot supply the normal precursors needed for its continued maintenance. This stage is presumably reached

in immunocompetent hosts after a series of exposures to radiation, but occurs after a single exposure in SCID hosts and even, to some extent, in the absence of radiation. It might be speculated that, failing normal maturation of bone marrow precursors, the thymus, depleted of lymphocytes by radiation or grafting, only manifests repopulation from within. Such an aberrant process could be self-perpetuating and predispose to neoplastic transformation. (c) Another possibility is that x-rays induce a transmissible lymphomagen that transforms thymic target cells, but that this process can be interrupted or controlled by the progeny of a subset of bone marrow cells. In normal mice, four doses of 1.75 Gy are required to inactivate that regulatory subset of cells, whereas little or no irradiation is required in the case of SCID mice. In this model, it becomes critical to determine the nature of the regulatory bone marrow-derived cells, and why they are ineffective or absent in SCID mice.

The prevention of radiation-induced lymphomagenesis by nonirradiated endogenous or exogenous bone marrow cells is well documented (7, 22). The mechanism of protection is not known; there may be repopulation of the thymus from precursors in the bone marrow or destruction of incipient tumor cells by marrow-derived cells. The present study shows that the high incidence of lymphoma in irradiated SCID-BL mice was not altered by either shielding the femur or injecting marrow cells from normal SCID donors. However, injection of normal C57BL/Ka or BALB/c bone marrow did protect. Since NK cells are abundant and active in SCID mice (27), the ineffectiveness of SCID bone marrow argues that NK

progenitors are probably not a major factor in lymphoma prevention. Indeed, it was shown earlier that bone marrow of C57BLbg/bg mice with low NK activity is as effective as that of C57BL donors in preventing radiation-induced lymphomagenesis (28, and our unpublished results). If, alternatively, protection results from influx into the thymus of T lineage precursors from the unirradiated marrow, the inadequacy of SCID bone marrow cells may be a consequence of the inability of their progeny to mature beyond the pre-TCR stages, and provides a first indication of the mechanism through which protection may occur. Whether it results from a failure of regulated maturation (model b), failure of development of a unique regulatory cell, presumably a TCR⁺ T cell (model c), or some other unanticipated mechanism remains to be determined. Several approaches to answer these questions offer themselves, e.g., determination whether it is the scid mutation (the inability to rearrange antigen receptor genes) or the scid condition (the absence of mature T and B cell populations) that (a) increases susceptibility to radiogenesis of lymphomas, and (b) causes the lack of protection by injected bone marrow. Perhaps the introduction of TCR transgenes in various combinations onto the scid background can alter susceptibility to radiation and/or the protective potential of bone marrow. The high frequency and short latency of lymphomagenesis in SCID-BL thymus-chimeric mice make these animals useful subjects for a better elucidation of the early events in the development of radiation-induced lymphoma and of the antineoplastic activities of bone marrow cells.

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