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Tumors Arising in SCID Mice Share Enhanced Radiation Sensitivity of SCID Normal Tissues

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ABSTRACT

We addressed the question of whether cancers arising in an abnormally radiation sensitive normal tissue are also abnormally sensitive to ionizing irradiation. Germ line mutation-carrying mice with an enhanced radiation sensitivity of the normal tissue, the severe combined immunodeficient (SCID), and normally radiation sensitive mice (C3H) were used to study the sensitivity of normal and tumor tissues *in vivo* and *in vitro*. The lethal dose for 50% of the irradiated animals after single dose whole body irradiation was 2.6-fold higher in C3H compared to SCID mice. The dose for an isoeffective acute skin reaction after single dose irradiation was end point dependent 1.7 to 3.7 times higher in C3H than in SCID mice. Embryonic fibroblast and methylcholanthrene induced soft tissue sarcomas derived from C3H and SCID mice were established *in vitro* and colony-forming assays after single dose irradiation were carried out. Choosing mean inactivation dose as the end point, SCID fibroblast lines were 3.0-fold and SCID tumor cell lines 2.7-fold more radiation sensitive than C3H fibroblast lines and C3H tumor cell lines. Tumor control and growth delay assays for 110-mm³ tumors were used to compare the radiation sensitivity of SCID and C3H tumors *in vivo*. The doses for 50% local tumor control and a growth delay of 40 days were 2.6 times higher in C3H tumors compared to SCID tumors. Tumors arising in an abnormally radiation sensitive normal tissue are also sensitive to irradiation. The difference in radiation sensitivity of normal tissues predicted the difference in tumor tissues in these two murine systems.

INTRODUCTION

SCID[2] mice were first described in 1983 by Bosma *et al.* (1). The *SCID* mutation occurred in the CB-17 mouse, which itself is a substrain of the BALB/c mouse (1). The SCID mouse is severely deficient in B- and T-cell mediated immunity; consequently, it has been demonstrated that SCID mice are excellent recipients for human xenografts (2–4). Recently another unique feature of the SCID mice has been discovered: the enhanced radiation sensitivity of its normal tissue (5), a phenomenon shown to be a result of a deficiency in DNA double strand break repair (6). This double strand break repair deficiency appears to be related to a defect in the same metabolic pathway that impairs *V(D)J* recombination and leads eventually to nonfunctional B- and T-cells (7). Thus, the SCID mouse provides radiation biologists with a mammalian animal model to study the impact of a genetically determined repair deficiency on radiosensitivity, fractionation effects, and mutagenesis in normal and tumor tissues. In the present study we used normal (C3H) and SCID mice to compare quantitatively the radiation sensitivity of their normal and tumor tissues. We addressed the question whether the enhanced radiation sensitivity of SCID normal tissue would be shared by their tumor tissues.

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[2] The abbreviations used are: SCID, severe combined immunodeficient; LD_{50}, lethal dose for 50% of irradiated animals; ER, enhancement ratio; MID, mean inactivation dose(s); SF, surviving fraction; AT, ataxia telangiectasia.

MATERIALS AND METHODS

Animals. SCID and C3H/SED (C3H) mice were maintained in a colony with a defined flora. They were fed with sterile high calorie food and drank acidified sterile water *ad libitum*.

LD_{50} for Whole Body Irradiation. Eight to 10-week-old SCID and C3H mice were irradiated with graded dose levels between 2.6 and 8.5 Gy by using a Gammacell ^{137}Cs unit at a dose rate of 0.9 Gy/min. The survival at day 30 after irradiation was used to calculate the LD_{50} for SCID and C3H mice by fitting a logistic regression (8) to the quantal data, assuming a lognormal distribution.

Acute Skin Reaction. The right hind legs of SCID and C3H mice were irradiated under clamped hypoxic conditions with dose levels between 10 and 86 Gy. The acute skin reaction was scored daily according to the system published by Douglas and Fowler (9): A skin reaction of ≥1.5 and ≥2.5 corresponded to a moist desquamation in an area smaller than 5-mm diameter, and a moist desquamation larger than 5-mm diameter on both sides of the leg, respectively. The dose to induce a peak in skin reaction of ≥1.5 and ≥2.5 was estimated by a logistic regression as described before.

Tumors. The highly potent chemical carcinogen, methylcholanthrene, was used for tumor induction. A dose of 0.1 mg methylcholanthrene dissolved in 0.1 ml peanut oil was injected into the right gastrocnemius muscle of 10 SCID and 5 C3H mice. Three of the SCID mice died of systemic toxicity after 6–8 weeks; in all other animals, tumors arose at the site of injection and reached 1.5-cm diameter after 71 to 143 days. The tumors were excised, minced, and cell lines were established *in vitro*. Histologically, all tumors were poorly differentiated spindle cell sarcomas. Tumor lines derived from SCID mice were designated FSC1 to FSC7, and tumor lines from C3H mice were designated FSM1 to FSM5. The cell lines were maintained in Dulbecco's modified Eagle's medium supplemented with 10% heat inactivated fetal bovine serum, 0.05 mg penicillin/ml, 0.05 mg streptomycin/ml, and 0.1 mg neomycin sulfate/ml at 37°C in an atmosphere of 5% CO_2 in air.

Fibroblasts. Fibroblast cultures of both SCID and C3H mice were derived from mouse embryos by trypsinizing embryonic tissue and plating the dissociated cells on plastic. SCID fibroblast lines were named FS1 and FS2 and C3H fibroblast lines were named FC1 and FC2. The culture medium was supplemented with 15% heat inactivated fetal bovine serum; otherwise, conditions were kept identical with those described above for the tumor cell lines.

Colony-forming Assays. The cell survival *in vitro* after single dose irradiation was measured for all tumor cell and fibroblast lines in an early passage (passages 2–9). For the experiments, cells incubated in 75-cm² flasks were trypsinized in exponential growth phase to get a single cell suspension. An appropriate number of single cells, depending on the plating efficiency and the dose level, were plated in 25-cm² plastic flasks. Six flasks per dose level were used. Heavily irradiated feeder cells, which had originated from the same cell line, were added to achieve a total cell density of 1600 cells/cm² for tumor cell lines, and 400 cells/cm² for fibroblast lines. The flasks were incubated for 18 to 24 h after plating before single dose irradiation with graded dose levels between 1 and 12 Gy at a temperature of 20°C. A 250-kVp X-ray machine with half-value layer of 0.4 mm copper at a dose rate of 1.71 Gy/min was used for all assays. After irradiation the flasks were incubated for 1 to 2 weeks as described before. Experiments were terminated when a sufficient number of visible colonies were observed in the test flasks. The colonies were fixed with methanol and stained with crystal violet. The number of colonies per flask was determined by counting

cell aggregates of more than 50 cells. To take into consideration the proliferation between plating and irradiation the surviving fractions were corrected for multiplicity:

$$SF = \frac{1 - \left(\frac{1 - CFU}{PL}\right)^{\frac{1}{M}}}{PE}$$

with CFU = colony-forming units (sum of cell aggregates >50 cells in a flask); PL = number of plated cells; M = multiplicity [number of cell aggregates (1–4 cells) at the time of irradiation divided by the number of plated cells in the multiplicity flask]; PE = plating efficiency. The logarithm of the mean SFs of 2 to 4 experiments per cell line weighted by the number of flasks was used to estimate α and β according to the linear quadratic model and D_0 and $\tilde{n}$ according to the single-hit multitarget model using ordinary least-squares analysis. MID were calculated by using α and β of the linear quadratic model (10). The 95% confidence limits were calculated for all data points, taking into account the uncertainties of the plating efficiency.

Tumor Control and Growth Delay Assays. Two SCID tumor lines, FSC1 and FSC2, and two C3H tumor lines, FSM1 and FSM2, were reestablished *in vivo* by s.c. injection of 10^6 cells of each tumor cell line into SCID mice. The resulting tumors were excised and 2- to 3-mm chunks were transplanted into the s.c. tissue of the right hind legs of 7- to 10-week-old SCID mice. Sixty animals per tumor line were used. The tumor size was measured in two perpendicular diameters and tumor volume was calculated as

$$V = \frac{a \times b^2}{2}$$

where a and b are the long and the short axes, respectively. The animals were randomly assigned to treatment and control groups when the tumors reached a volume of 110 mm^3. Graded doses were applied by using a special designed cesium irradiator (11), featuring parallel opposed 3-cm diameter ports at a dose rate of ~7 Gy/min. The animals were anesthetized with 15 mg/kg body weight pentobarbital i.p. Single dose irradiations were given under acutely hypoxic conditions achieved by clamping the blood supply of the tumor-bearing leg 5 min before irradiation. After irradiation, the tumors were scored one to two times a week until a recurrence was observed, or the experiments were terminated 80 days after the observation of the last recurrence at day 180. The dose yielding 50% local control rate of the irradiated tumors was estimated by fitting a logistic regression. Growth delay was calculated by the difference of treatment and control groups to reach twice the initial tumor volume.

RESULTS

Radiation Sensitivity of Normal Tissues *in Vivo*. The dose response curves for survival at 30 days after single dose whole body irradiation of SCID and C3H mice are shown in Fig. 1. The LD_{50} was 7.8 Gy in C3H mice and 3.0 Gy in SCID mice, yielding a C3H/SCID ER of 2.6. A peak skin reaction corresponding to moist desquamation smaller than 0.5 cm^2 (score ≥1.5) was induced in 50% of the animals by 14 Gy in SCID and 52 Gy in C3H mice. For a peak skin reaction more severe than a moist desquamation of 0.5 cm^2 on both sides of the irradiated leg (score ≥ 2.5) in 50% of the animals, a single dose of 34.4 Gy was necessary in SCID mice, whereas 57.9 Gy were needed in C3H mice (Fig. 2). The ERs of C3H/SCID mice for a peak skin reaction of ≥1.5 and ≥2.5 were 3.7 and 1.7, respectively (Table 1).

Radiation Sensitivity of Fibroblasts *in Vitro*. The survival curves of two C3H and two SCID fibroblast lines are shown in Fig. 3. The MID for SCID fibroblasts were 0.96 and 1.06 Gy compared to 3.5 and 2.6 Gy for C3H fibroblasts (Table 2). The

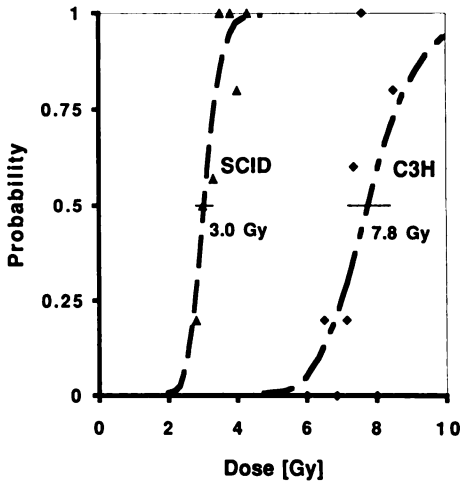

Fig. 1. The probability of survival is plotted against the dose of single dose whole body irradiation. Five to six animals were used for each data point. The *bar* at 0.5 probability indicates the 95% confidence limits of the LD_{50}.

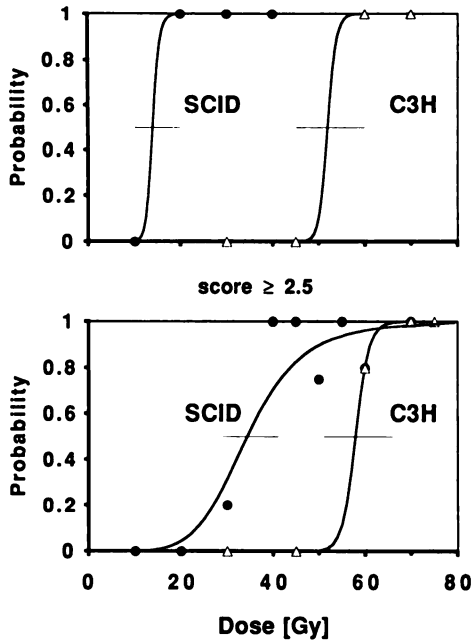

Fig. 2. The probability to develop an acute skin reaction corresponding to a score ≥1.5 (*top*) and ≥2.5 (*bottom*) were plotted against the dose for single dose irradiation under acutely hypoxic conditions. ●, observations in SCID mice; △, observations in C3H mice. Five to six animals were used for each data point. The *bars* at 0.5 probability indicate the 95% confidence limits.

ERs of C3H *versus* SCID fibroblasts for MID, SF at 2 Gy (SF2), and D_0 were 3.0, 3.7, and 2.4, respectively.

Radiation Sensitivity of Tumor Cells *in Vitro*. Fig. 4 demonstrates the survival curves after single dose irradiation *in vitro*. There was a clear separation in the intrinsic radiation sensitivity between the 5 C3H and the 7 SCID tumor lines for all parameters of sensitivity. Table 2 summarizes the survival curve parameters of all investigated tumor lines. The median MID was 1.2 Gy in SCID and 3.1 Gy in C3H tumors. The median values for SF2 and D_0 were 0.19 and 0.95 Gy, respectively, in SCID tumors, and 0.61 and 1.70 Gy, respectively, in C3H tumors. In none of these parameters was an overlap between SCID and C3H tumors observed; the differences were statistically highly significant ($P < 0.005$). The ERs of C3H *versus* SCID tumor cell lines for the mean value of MID, SF2, and D_0 were 2.7, 3.5, and 2.0, respectively.

Table 1 *Radiation response of C3H and SCID normal and tumor tissue in vivo*

Lethal dose 50% after whole body irradiation at day 30

Single dose irradiation		
C3H	SCID	ER: C3H/SCID
7.8 (7.3–8.4)[a] Gy	3.0 (2.8–3.2) Gy	2.6

Dose for acute skin reaction in 50% of animals

Single dose, acute hypoxia		
a. For a peak skin reaction of ≥1.5		
C3H	SCID	ER: C3H/SCID
52 (44.3–61.4) Gy	14 (9.8–19.3) Gy	3.7
b. For a peak skin reaction of ≥2.5		
C3H	SCID	ER: C3H/SCID
57.9 (50.9–66.1) Gy	34.4 (28.8–41.3) Gy	1.7

Tumor control dose 50% (TCD_{50}) and regrowth delay (GD) for SCID and C3H tumors in SCID mice

110 mm^3 tumors, single dose, acute hypoxia				
a. Cell line	SCID TCD_{50}	Cell line	C3H TCD_{50}	ER: C3H/SCID
FSC1	36.3 (30.6–43.2) Gy	FSM1	95.4 (85.6–105) Gy	2.6
FSC2	39.4 (35.0–45.0) Gy	FSM2	103 (91.2–116) Gy	2.6
b. Dose for 40 days GD				
FSC1	30.3 (27.5–33.9) Gy	FSM1	75.8 (69.6–82.1) Gy	2.5
FSC2	27.7 (24.5–31.7) Gy	FSM2	74.2 (70.4–78.6) Gy	2.7

[a] Values in parentheses indicate 95% confidence limits.

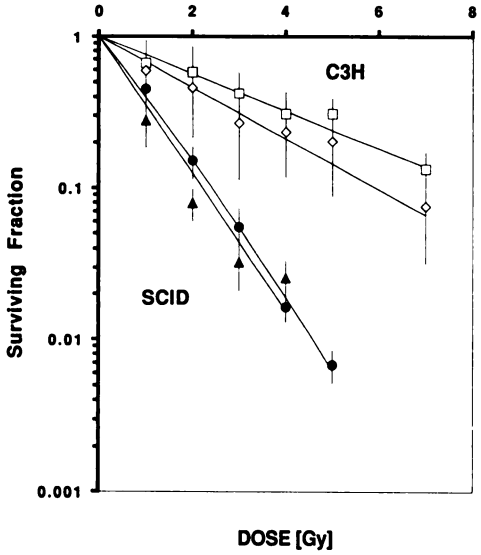

Fig. 3. The dose for single dose irradiations is plotted against cell survival of C3H and SCID fibroblasts *in vitro*. The *data points* and *error bars* indicate the mean and the 95% confidence limits of 2 independent experiments for each cell line.

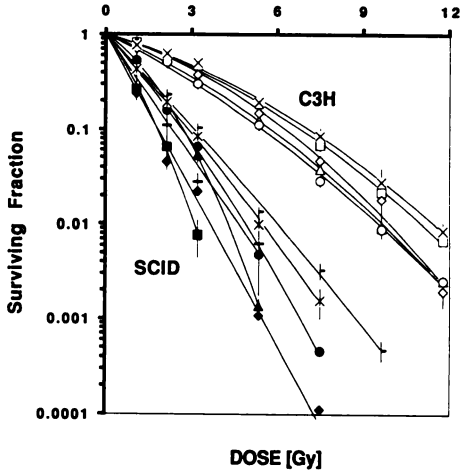

Fig. 4. The dose for single dose irradiations is plotted against cell survival of C3H and SCID tumor cell lines *in vitro*. The *data points* and *error bars* indicate the mean and the 95% confidence limits of 2 to 4 independent experiments for each cell line.

Radiation Sensitivity of Tumor Tissues *in Vivo*. The results of tumor control and growth delay assays of 2 SCID and 2 C3H tumor lines, all grown on the right hind leg of SCID mice, are summarized in Table 1. The tumor doubling times for SCID and C3H tumor lines growing in SCID mice ranged from 2.5 to 3.5 days. The average 50% local control rates in SCID tumor lines was 38 Gy compared to 99 Gy in C3H tumor lines (Fig. 5). The average dose for 40 days GD was 29 Gy in SCID and 75 Gy in C3H tumor lines (Table 1; Fig. 6). The ER of C3H/SCID for both assays was 2.6.

DISCUSSION

The radiation sensitivity of normal and tumor tissues derived from SCID and C3H mice were quantitatively compared. SCID tumors *in vivo* and SCID tumor cell lines *in vitro* were considerably more radiation sensitive than C3H tumors and tumor cell lines (Figs. 4–6; Table 1). This difference in radiation sensitivity cannot be attributed to tumor type or grade, since tumors from SCID and C3H mice were histologically indistinguishable, poorly differentiated spindle cell sarcomas. The mechanism behind the increased sensitivity of SCID tumor cell lines is most likely the inability of the tumor cells to overcome their genetically determined deficiency in DNA double strand break repair, as shown for SCID fibroblasts by Biedermann *et al.* (6). The ERs, calculated as quotient of the doses to elicit a defined radiation response in C3H compared to SCID cell lines, are determined by the end point of comparison. However, for the most commonly used parameters of *in vitro* radiation sensitivity, D_0 and MID, SCID fibroblasts and sarcoma cell lines were 2- to 3-fold more radiation sensitive than the similarly derived C3H cell lines.

Similar results were derived from the *in vivo* testing of normal tissue and tumor tissue response. The ER of C3H/SCID for LD_{50}, tumor control, and tumor growth delay was 2.6, whereas the ERs for the acute skin reaction ranged, end point dependent, from 1.7 and 3.7 (Table 1). The wide range of the latter might reflect the subjectivity of the scoring of skin reactions.

Table 2 *In vitro radiation sensitivity of SCID and C3H cell lines*

The survival curve parameters for single dose irradiations are summarized. FSC = SCID tumors; FSM = C3H tumors; FC = C3H fibroblasts; FS = SCID fibroblasts; PE = plating efficiency; multiplicities are averaged from 2 to 4 experiments; $\bar{n}$ = extrapolation number; $SF2_c$ = calculated surviving fraction at 2 Gy; runs = number of experiments.

Cell line	PE (%)	Multiplicity	α (Gy^{-1})	β (Gy^{-2})	MID (Gy)	$\bar{n}$	D_0 (Gy)	$SF2_c$	Runs
SCID tumors									
FSC1	35.5	1.16	0.716	0.008	1.36	1.37	1.21	0.23	3
FSC2	32.9	1.16	0.461	0.144	1.32	12.8	0.59	0.22	3
FSC3	3.16	1.19	1.26	0	0.79	0.44	0.95	0.08	3
FSC4	7.3	1.17	0.761	0.037	1.19	1.69	0.91	0.19	2
FSC5	20.6	1.16	0.991	0	1.01	0.9	1.04	0.14	3
FSC6	2.36	1.13	0.965	0.168	0.83	4.55	0.50	0.07	2
FSC7	19.7	1.17	0.751	0.016	1.27	1.6	1.07	0.21	2
Mean	17.4		0.844	0.053	1.11	3.34	0.90	0.16	
Median	19.7		0.761	0.016	1.19	1.6	0.95	0.19	
C3H tumors									
FSM1	32.3	1.12	0.207	0.019	3.27	3.16	1.93	0.61	4
FSM2	20.5	1.22	0.283	0.02	2.69	3.5	1.63	0.52	3
FSM3	30.3	1.13	0.196	0.027	3.08	5.97	1.53	0.61	2
FSM4	12.2	1.12	0.335	0.015	2.49	2.54	1.70	0.48	3
FSM5	14.4	1.16	0.194	0.018	3.43	2.94	2.04	0.63	2
Mean	21.9		0.243	0.02	2.99	3.62	1.77	0.57	
Median	20.5		0.207	0.019	3.08	3.16	1.70	0.61	
SCID fibroblasts									
FS1	5.2	1.09	0.898	0.023	1.06	1	1.28	0.15	2
FS2	1.7	1.18	1.042	0	0.96	1	1.24	0.12	2
Mean	3.5		0.970	0.012	1.01	1	1.26	0.14	
C3H fibroblasts									
FC1	0.5	1.15	0.282	0.0003	3.51	1.09	3.4	0.58	2
FC2	0.5	1.11	0.388	0	2.56	1.07	2.73	0.46	2
Mean	0.5		0.335	0.0002	3.04	1.08	3.07	0.52	
			α^{-1}		MID		D_0	$SF2_c$	
Enhancement ratios SCID *vs.* C3H tumors									
Mean			3.47		2.7		1.97	3.49	
Enhancement ratios SCID *vs.* C3H fibroblasts									
Mean			2.90		3.01		2.44	3.71	

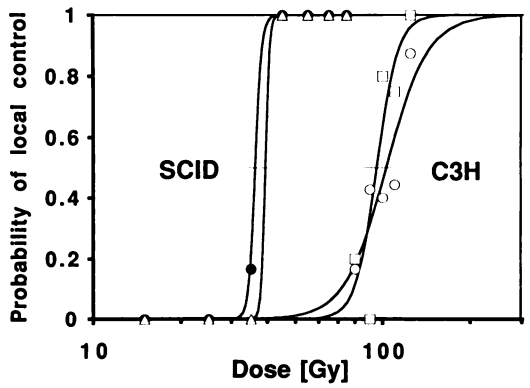

Fig. 5. The probability of local tumor control is plotted against the dose for single dose irradiation under acutely hypoxic conditions. Six to 10 animals were used for each *data point*. The *bars* at 0.5 probability indicate the 95% confidence limits.

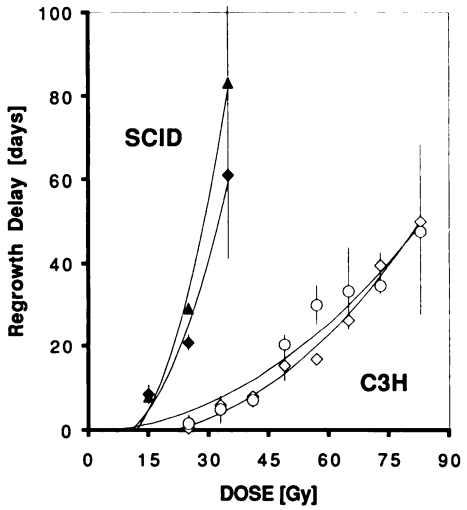

Fig. 6. Tumor regrowth delay assays. The dose is plotted against the tumor regrowth delay for two C3H and two SCID tumor lines *in vivo*. Six to 10 animals were used for each *data point*. The *bars* indicate the 95% confidence limits.

However, the values compare well to the ER of 3.0 for fractionated skin irradiation in the data of Biedermann *et al.* (6). In summary, the ERs for normal and tumor tissues *in vivo* and *in vitro* were entirely consistent. (Table 3). The radiation response of the normal tissue predicted quantitatively the response of tumor tissues, at least in this group of histologically poorly differentiated sarcomas in a murine system. The question arises whether the radiation sensitivity of normal tissue in humans can predict the response of tumors.

Directly comparable results have not been published. The normal tissue of AT patients, an autosomal recessive genetic disorder, is approximately 3 times more radiation sensitive than tissue from normal patients (12). There is some evidence from clinical data that tumors arising in these patients are also radiation sensitive (13). The sensitivity of AT cells is not attributed to a double strand break repair deficiency, but to a misrepair of double strand breaks as measured with the premature chromosome condensation technique (14). Some other genetic disorders like Fanconis's anemia, 5-oxoprolinuria, Cockayne's syndrome, and Gardner's syndrome are associated with a higher radiation sensitivity of fibroblasts *in vitro* (15, 16), whereas fibroblasts from retinoblastoma patients and from individuals with chromosome 13 anomalies are marginally more radiation

Table 3 *Summary of enhancement ratios*
SCID *vs.* normal mouse strains

	ER	Mouse strains	Ref.
Acute skin reaction			
Single dose, hypoxic	1.7–3.7	C3H/SCID	Presented data
Fractionated, oxic	3.0	BALB/c/SCID	Biedermann *et al.* (6)
LD_{50}	2.6	C3H/SCID	Presented data
(whole body irradiation)	>1.4	BALB/c/SCID	Biedermann *et al.* (6)
Bone marrow	2.1	BALB/c/SCID	Biedermann *et al.* (6)
(MID, *in vitro*)	2.7	C3H/SCID	Fulop *et al.* (5)
Fibroblasts	2.8	BALB/c/SCID	Biedermann *et al.* (6)
(MID, *in vitro*)	3.0	C3H/SCID	Presented data
Tumors (MID, *in vitro*)	2.7	C3H/SCID	Presented data
Tumors (TCD_{50}, *in vivo*)[a]	2.6	C3H/SCID	Presented data
Tumors	2.6	C3H/SCID	Presented data
(regrowth delay, *in vivo*)			

[a] TCD_{50}, 50% local control rate.

resistant (16). Most of these syndromes are associated with a cancer proneness (17–22), which is also evident in heterozygotes, at least in AT gene carriers (22). Fibroblasts of AT and 5-oxoprolinuria heterozygotes have been shown to be more sensitive to irradiation than normal fibroblasts (16, 23), even though some overlap with the sensitivity of normal fibroblasts has been reported. Since AT heterozygotes alone may account for 8.8% of premenopausal breast cancer patients (22) and 4.7% of all cancer patients (24), taking into consideration all syndromes, an even higher percentage of patients with unusual response to radiation therapy appears to be likely. Although different mechanisms underlie the enhanced radiation sensitivity of SCID and AT cells, it may be a general phenomenon that tumor cells cannot overcome their genetically determined deficiency in some pathways of the repair of irradiation induced damage. The presented data give indirect evidence that the concept that normal tissue radiation sensitivity predicts tumor sensitivity is not without merit and should be the subject of further studies.

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