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SURVIVAL RESPONSES AND POTENTIALLY LETHAL DAMAGE REPAIR OF NORMAL 10T1/2 AND ITS TRANSFORMED TCL 15 CELLS AFTER IRRADIATION WITH 43 MEV PROTON PRODUCED NEUTRONS

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Abstract

Normal 10T1/2 fibroblasts and their transformed counterparts (TCL 15) were used in order to evaluate the RBE, TGF and PLD repair for a therapeutic fast neutron beam (43 MeV proton→Be). For plateau-phase culture, the RBE of 10T1/2 cells were 2.0 and 1.7 at 10 and 1% survival levels respectively and 1.3 from D_0. The corresponding RBE values of TCL 15 cells were 2.1, 1.8 and 1.5, and thus the TGF values were 1.05 and 1.1 respectively at 10% and 1% survival levels and 1.8 from D_0. For log-phase culture, the survival responses of 10T1/2 and TCL 15 cells to ^{60}Co gamma-rays or neutrons were not significantly different (the RBE at 10% was 2), and thus the TGF value was unity. For neutrons, as a rule no PLD repair has been reported *in vitro* and *in vivo* in previous studies. However, in the present study PLD repair occurred in plateau 10T1/2 and TCL 15 cells irradiated with neutrons.

Key words: Radiobiology, cell studies; 10T1/2, TCL 15 cells, neutrons, PLD repair, TGF.

One of the advantages of neutrons for therapy is that the neutron has a lower oxygen enhancement ratio (OER) than conventional low LET radiations, because it is supposed that most tumors contain more viable hypoxic cells than do normal tissues. Neutrons are more preferable for therapy, if the therapeutic gain factor (TGF), which is defined as the ratio of RBE for tumor cells to that for normal ones, is more than unity. The effect of neutrons on normal and tumor cells has been thoroughly investigated *in vivo* (1–4), while there is little work done concerning relation between the radiosensitivity of transformed cells in culture and their original normal ones. For the present work we adopted two cell lines, the C3H mouse embryo derived 10T1/2 cell and its 3-methylcholanthrene transformed counterpart TCL 15 cell (14, 15), regarding these as normal and tumor cells respectively, in a model system. The radiosensitivities of log- and plateau-phase 10T1/2 and TCL 15 cells were compared.

Since its discovery by Phillips & Tolmach (12) the repair of potentially lethal damage (PLD) assayed by delayed plating has been repeatedly demonstrated after irradiation with low LET radiations. However, concerning the repair efficiency of this form of damage due to high-LET radiation the reports in the literature are inconsistent. For neutrons, no PLD repair has been reported neither *in vitro* (5, 8) nor *in vivo* (16). In contrast to these findings, Rasey & Nelson showed PLD repair in unfed plateau cultures of EMT-6/UW cells, but not in the same cells *in vivo* (13). Guichard et al. showed PLD repair in human Na 11 melanoma in arthymic nude mice (6). These confusing results might be due to different cell lines, neutron spectra, and/or conditions under which the cells were maintained during and after irradiation, e.g., cell density, medium, etc. Analysis of these results may be important to clarify the mechanism of PLD repair. At present, however, it is important to accumulate data on whether PLD induced with neutrons is repaired or not. Thus, in this study we also examined the PLD repair in neutron-irradiated 10T1/2 and TCL 15 cells.

Material and Methods

C3H mouse embryo derived 10T1/2 cells and their transformed TCL 15 cells (14, 15) were grown in a humid atmosphere of 5% CO_2 in air at 37°C. The growth medium was basal medium Eagle (GIBCO) supplemented with 10% fetal bovine serum (KC Biological Inc.) and the

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antibiotics 50 unit/ml potasium penicillin G, 50 mcg/ml of streptomycin sulfate (M. A. Bioproducts), and 2.5 mcg/ml of fungizone (Flow Lab). 10T1/2 cells were used in passages of up to 16. Confluent cells in plateau phase were obtained by seeding 1×10^4 log-phase cells into 25 cm^2 T-flask (Falcon) 11 days before, and the media were replaced twice with 5 ml fresh medium 8 and 3 days before irradiations. Cells in log-phase were obtained by seeding 2×10^4 log-phase cells into 25 cm^2 T-flask containing 6 ml medium 4 days before, and the medium was replaced by fresh medium one day before irradiation. The survival responses were assayed by postirradiation trypsinization for colony formation. After irradiation, the cells were treated with trypsin (GIBCO) at 37°C for about 5 min, and then an appropriate number of the single cells, adjusted to yield approximately 100 colonies, was plated on 100 mm dishes (Falcon) containing 11 ml medium. Five ml fresh medium were added to the dishes after 6–7 days incubation in a CO_2 incubator, and kept for a further 4–10 days depending on the size of colonies, i.e., delivered doses. The colonies were stained with 1% methylene blue in 20% methanol, and the number of colonies containing at least 50 cells was counted to obtain surviving fractions of cells. The plating efficiencies of cells were 30–40% for both 10T1/2 and TCL 15 cells.

The growth properties of 10T1/2 and TCL 15 cells *in vivo* were examined by subcutaneous injection of 5×10^5 cells into the axillae of C3Hf/Sed mice (kindly supplied by Dr H. D. Suit, MGH) which had been irradiated with 4.5 Gy of ^{137}Cs gamma-rays.

Neutrons were generated from a beryllium target with 43 MeV protons accelerated with the cyclotron at the Lewis Research Center of National Aeronautics and Space Administration in Cleveland. The dose rate measured with a tissue-equivalent chamber was 0.15 Gy/min. ^{60}Co gamma-rays were generated from a therapy unit. The dose rate was 0.4 Gy/min. ^{137}Cs gamma-rays were obtained from an irradiator (J. L. Shepherd and Associates) with a dose rate of 4.35 Gy/min.

Results

1. *Growth characteristics of 10T1/2 and TCL 15 cells in vivo*. The growth properties of both 10T1/2 and TCL 15 cells *in vivo* were established by injecting 5×10^5 cells into the axillae of C3Hf/Sed mice irradiated with 4.5 Gy of ^{137}Cs gamma-rays. A distinct difference was observed between both types of cells. Palpable solid tissues originating from injected cells occurred in TCL 15 cell-injected mice (10/10) within a month, but not in 10T1/2 cell-injected mice (0/10). The result implies that 10T1/2 and TCL 15 cells are characteristic of normal and tumor cells respectively.

2. *Growth characteristics of 10T1/2 and TCL 15 cells in vitro*. The growth properties of both 10T1/2 and TCL 15 cells were established by seeding 10^4 cells in 25 cm^2 T-flask. Fig. 1a shows that the 10T1/2 cells, after approximately a one-day lag, grew into an exponential phase and reached a saturated cell density in about 6 days. Upon repeated refeeding with fresh medium, the cell density could be made to increase only slightly. The corresponding average peaks of the cell-size distribution are shown in Fig. 1b.

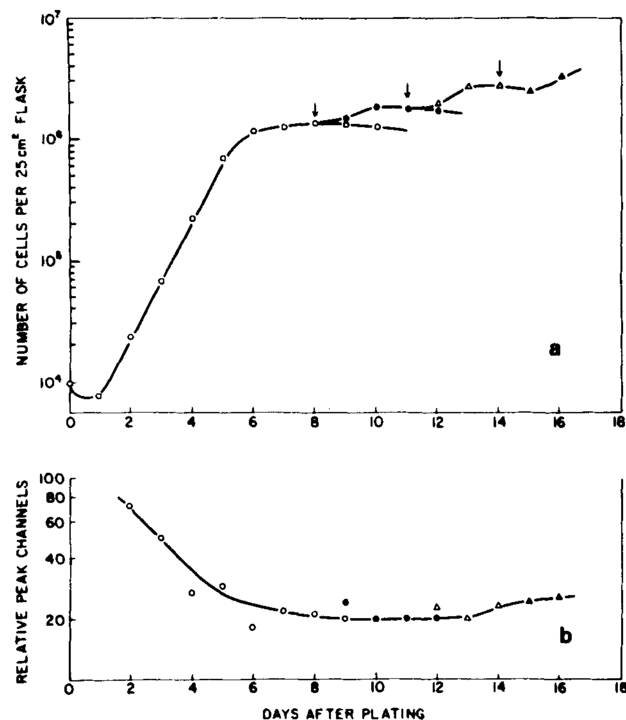

Fig. 1. Growth characteristics of 10T1/2 cells. a) Growth curve of cells 1×10^4 cells were plated into 25 cm^2 flasks on day 0, and the number of cells per flask was counted with Coulter counter after trypsinization every day up to day 16. Arrows denote refeeding. b) Average peaks of the cell-size distribution corresponding to a).

Fig. 2 shows the data from similar studies of TCL 15 cells. The growth pattern of TCL 15 cells was similar to that seen with 10T1/2 except that transformed cells could be stimulated to increase in cell density by refeeding more appreciably, i.e., less cell contact inhibition.

3. *Survival responses of plateau-phase 10T1/2 and TCL 15 cells to neutrons or ^{60}Co gamma-rays*. The dose-survival responses of the normal 10T1/2 cells and of the transformed counterparts TCL 15 cells were compared after either neutron or ^{60}Co gamma-ray irradiation of cultures grown to plateau-phase. The survival data are depicted in Fig. 3 and their parameters (D_0, n, and D_q), RBE and TGF derived from these data are given in Table 1. Confluent plateau-culture of 10T1/2 cells were more resistant to neutrons or ^{60}Co gamma-rays than that of TCL 15 cells. The RBEs of 10T1/2 cells were 2.0 and 1.7 at 10 and 1% survival levels respectively and 1.3 from D_0. The corresponding RBEs of TCL 15 cells were 2.1, 1.8, and

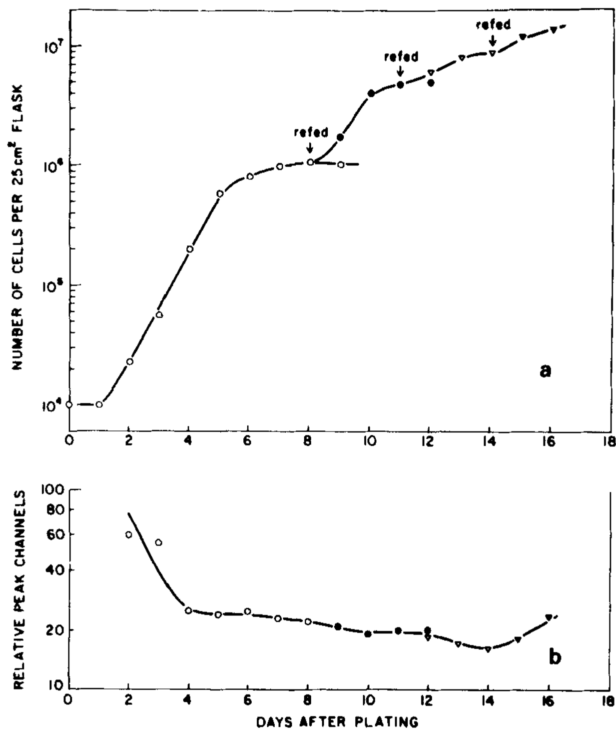

Fig. 2. Growth characteristics of TCL 15 cells. See legend to Fig. 1.

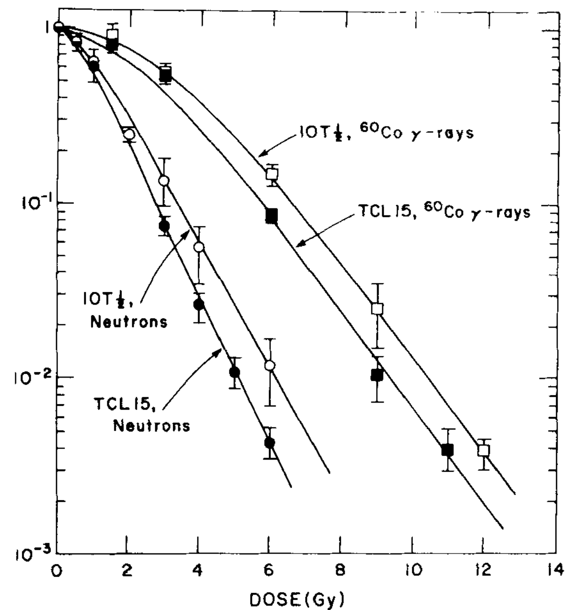

Fig. 3. Survival curves of plateau 10T1/2 and TCL 15 cells irradiated with neutrons and ^{60}Co gamma-rays. 10T1/2 with neutrons (○), TCL 15 with neutrons (●), 10T1/2 with ^{60}Co gamma-rays (□), TCL 15 with ^{60}Co gamma-rays (■). Bars represent standard deviations of 3 separate experiments.

Table 1

Parameters of survival curves for plateau-phase 10T1/2 and TCL 15 cells

	10T1/2			TCL 15			TGF
	^{60}Co γ-rays	Neutrons	RBE	^{60}Co γ-rays	Neutrons	RBE	($RBE_{TCL 15}$/ $RBE_{10T1/2}$)
S. F. = 0.1	6.65 Gy	3.30 Gy	2.01	5.60 Gy	2.65 Gy	2.11	1.05
S. F. = 0.01	10.40 Gy	6.20 Gy	1.68	9.40 Gy	5.10 Gy	1.84	1.10
D_0	1.65 Gy	1.27 Gy	1.30	1.63 Gy	1.06 Gy	1.54	1.18
n	5.7	1.3	-	3.2	1.2	-	-
D_q	2.9 Gy	0.4 Gy	-	1.9 Gy	0.2 Gy	-	-

1.5 and thus, the corresponding TGFs were 1.05, 1.10, and 1.18; It appears that TGF is greater at higher doses.

4. *Survival reponses of log-phase 10T1/2 and TCL 15 cells to neutrons or ^{60}Co gamma-rays.* The same normal and transformed cells, grown in log-phase, were irradiated with graded doses of neutrons or ^{60}Co gamma-rays. The survival data are shown in Figs 4 (10T1/2) and 5 (TCL 15) and their parameters (D_0, n, and D_q), RBE and TGF in Table 2. In contrast to plateau-phase cells, there were no significant difference between the dose-survival responses of log-phase 10T1/2 and TCL 15 cells to neutrons or ^{60}Co gamma-rays. The RBEs were almost the same in both types of cells, namely 2.0, 1.6, and 1.2 at 10% and 1% survival levels and from D_0 respectively. Therefore, TGF was 1.0, which indicates no therapeutic gain with neutrons in these systems.

5. *PLD repairs of 10T1/2 and TCL 15 cells with neutrons.* Confluent plateau culture of 10T1/2 cells in 3-day-old medium was irradiated with single doses of neutrons, and the repair of PLD was evaluated by plating the cells at various times postirradiation. As shown in Fig. 6, the cells irradiated with 1 Gy did not show appreciable PLD repair, but they showed slight repair with 3 Gy, and distinct repair with 5 Gy.

Confluent plateau culture of TCL 15 cells in 3-day-old medium was also irradiated with 0.97, 2.9, and 4.8 Gy of neutrons. The result shown in Fig. 7 demonstrates a similar dose dependent PLD repair as in the 10T1/2 cells (Fig.

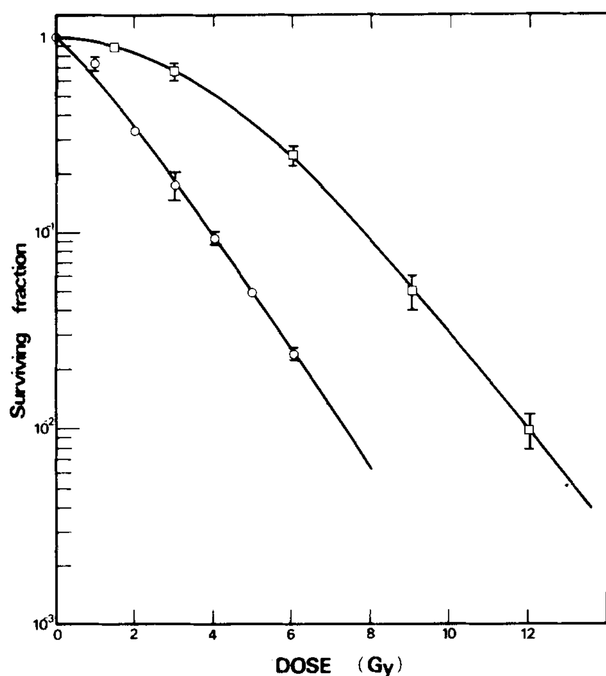

Fig. 4. Survival curves of log-phase 10T1/2 cells irradiated with neutrons (O) and ^{60}Co gamma-rays (□). Bars as in Fig. 3.

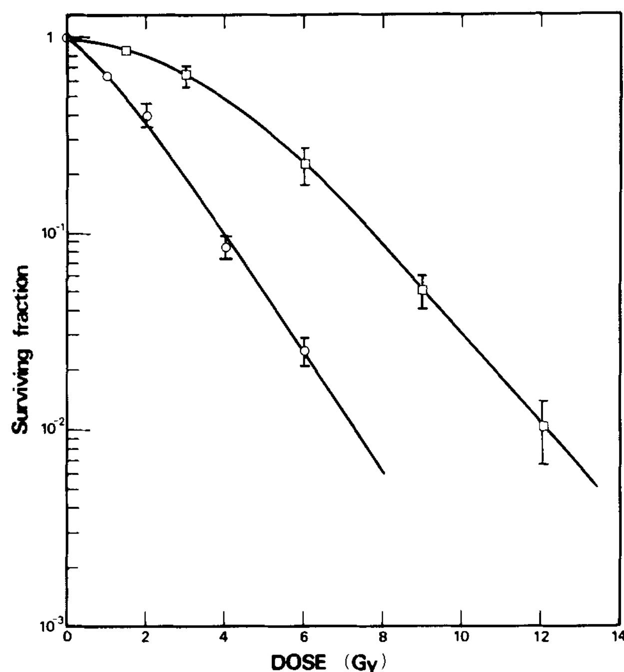

Fig. 5. Survival curves of log-phase TCL 15 cells irradiated with neutrons (O) and ^{60}Co gamma-rays (□). Bars as in Fig. 3.

Table 2

Parameters of survival curves for log-phase 10T1/2 and TCL 15 cells

	10T1/2			TCL 15			TGF
	^{60}Co γ-rays	Neutrons	RBE	^{60}Co γ-rays	Neutrons	RBE	($RBE_{TCL\,15}$/ $RBE_{10T1/2}$)
S. F. = 0.1	7.80 Gy	3.92 Gy	1.99	7.80 Gy	3.87 Gy	2.02	1.01
S. F. = 0.01	12.00 Gy	7.30 Gy	1.64	12.05 Gy	7.30 Gy	1.65	1.00
D_0	1.84 Gy	1.53 Gy	1.20	1.81 Gy	1.46 Gy	1.24	1.03
n	7.4	1.3	–	5.8	1.4	–	–
D_q	3.6 Gy	0.4 Gy	–	3.3 Gy	0.5 Gy	–	–

6). These results indicate that repair of PLD after neutron irradiation occurs in both 10T1/2 and TCL 15 cells under the described conditions.

Although the doses delivered to TCL 15 cells were not the same as those to 10T1/2 cells due to correction of dosimetry after irradiation, the extent of PLD repair of 10T1/2 seemed slightly greater than that of TCL 15 cells.

To examine whether or not the discrepancy of PLD repair with neutrons in the literature is attributable to the medium used for incubation after irradiation, we used two kinds of media in the experiment of PLD repair; one was a 3-day-old medium, and the other a fresh medium. Plateau cultures of 10T1/2 cells in these media were irradiated with 5 Gy of neutrons, and PLD repair was assayed. Fig. 8 shows that the extent of PLD repair was greater in a 3-day-old medium than in a fresh one, but it still took place even in the latter. The result indicates that the lack of PLD repair with neutrons reported in the literature cannot be explained by freshness of medium alone.

Discussion

The therapeutic gain factor (TGF) has been defined as the ratio of the RBE for tumor to that for normal tissue. The TGF values at 10 and 1 % survival levels and from D_0 were calculated using the RBE values obtained from plateau- and log-phase 10T1/2 and TCL 15 cells. The TGF values appear to increase with dose. However, these values of plateau-phase cells are not appreciably greater than 1 at lower doses, and much less for log-phase cells. Hence, so far as the normal 10T1/2 cell and its trans-

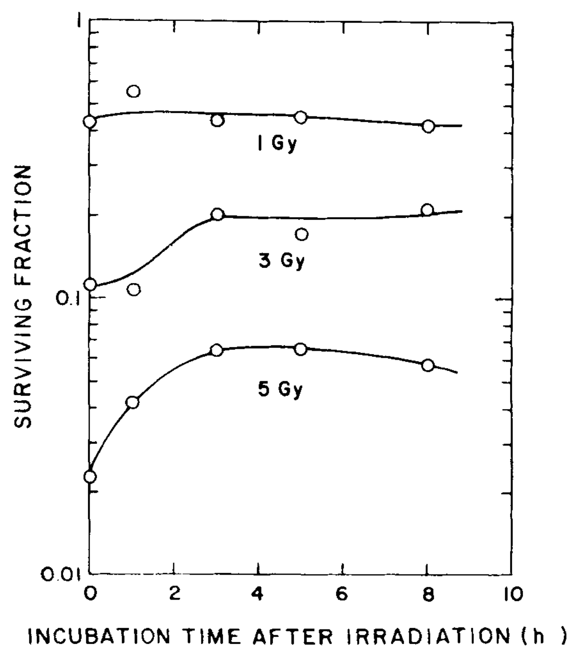

Fig. 6. PLD repair of 10T1/2 cells irradiated with neutrons. Confluent plateau cultures of 10T1/2 cells in 3-day-old medium were irradiated with 1, 3, and 5 Gy of neutrons, and then subcultured after incubation at 37°C for various times. The figure represents one typical result in similar 5 experiments (different incubation-times and doses).

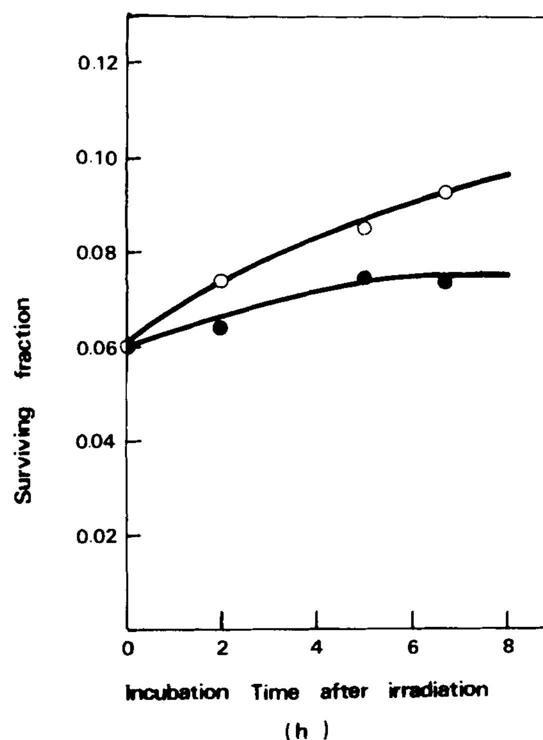

Fig. 8. PLD repair of 10T1/2 cells irradiated with neutrons. Confluent plateau cultures of 10T1/2 cells in 3-day-old (○) and fresh (●) media were irradiated with 5 Gy of neutrons, and then subcultured after incubation at 37°C for various times.

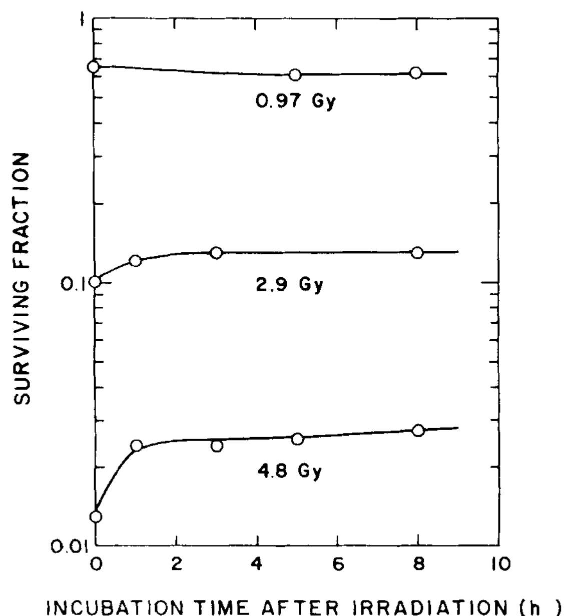

Fig. 7. PLD repair of TCL 15 cells irradiated with neutrons. Confluent plateau cultures of TCL 15 cells in 3-day-old medium were irradiated with 0.97, 2.9, and 4.8 Gy of neutrons, and then subcultured after incubation at 37°C for various times. The figure represents one typical result in similar 5 experiments (different incubation-times and doses).

formed counterpart TCL 15 cell are concerned, ^{60}Co gamma-rays and the fast neutron beam appear to provide similar therapeutic effects as a conventional irradiation regimen (e.g. 2 Gy gamma-equivalent dose per fraction). To confirm this, however, TGF should be estimated at multi-fractionated high doses similar to a clinical dose regimen. Such studies are at present being performed. One of the assumed advantantages of fast neutrons in therapy is that they have lower oxygen enhancement ratio (OER) than low LET radiations, i.e. sterilize viable hypoxic cells more effectively. Taking this into consideration and assuming more hypoxic cells in tumors than in normal tissues, the TGF in tissue would become greater than the values obtained aerobically in this work.

One problem is whether or not the system of 10T1/2 and TCL 15 cells reflects the clinical situation. We started this work with the idea that TGF could be easily obtained by the *in vitro* system. It is, however, likely that in the clinical situation the critical normal tissue is seldom represented by the benign counterpart of the malignant cells. The situation we mimicked is that of the original malignant cells being surrounded by the normal counterpart cells in the tissue. A study taking this type of situation into consideration could be basically important to radiation therapy, even if the *in vitro* system does not completely reflect the clinical situation.

Log-phase cells were more radioresistant than plateau-phase ones. Although the difference may lie within the margin of statistical error, it might be explained in the following way. Most plateau-phase cells are considered to consist of the cell in G_1 or G_0 stage, while asynchronous log-phase cells include cells at various stages. The radiosensitivity of log-phase cells probably expresses an average of the radiosensitivities of cells in G_0, G_1, S, G_2, and M stages. It is known that the cell in S stage is the most radioresistant and the cell in M stage the least. For 10T1/2 cells, however, the proportion of cell at S stage of log-phase cells was much higher than that of plateau-phase cells (17), and the same would be true for TCL 15 cells. These would make log-phase cells more radioresistant than plateau-phase cells.

The next point to be discussed is why the difference in the radiosensitivity of 10T1/2 and TCL 15 cells was observed in plateau-phase culture but not in log-phase one. The conditions for the experiments of log- and plateau-phase cells were different in two respects; one was cell density, and the other the freshness of medium during irradiation. However, gamma-irradiations of confluent 10T1/2 cells in fresh and old media did not result in any significant difference in cell survival (our unpublished data). Cell densities of confluent plateau-phase 10T1/2 and TCL 15 cells were approximately 5×10^4 and 2.5×10^5 cells/cm^2 respectively. Cell density might influence radiosensitivity (with lower radiosensitivity in cells of low density) but a mechanism for such an influence is so far unknown.

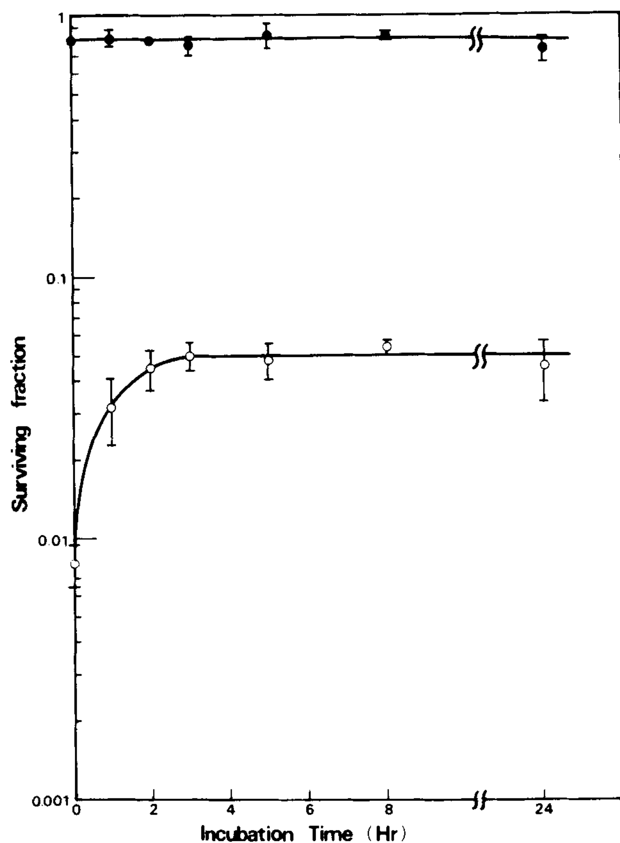

Fig. 9. PLD repair of 10T1/2 cells irradiated with gamma-rays. Confluent plateau cultures of 10T1/2 cells were irradiated with 2 Gy (●) and 10 Gy (○) of ^{137}Cs gamma-rays, and then subcultured after incubation at 37°C for various times. Bars as in Fig. 3.

In the case of irradiation with low LET radiation PLD repair takes place in most cells except special cell lines, e.g. ataxia telangiectasia (20). For neutrons, however, the published data are controversial whether or not PLD repair occurs (5, 6, 8, 13, 16). The data shown in Figs 6 and 7 demonstrate that under the described conditions (see Material and Methods) repair of the PLD after the neutrons was evident at higher doses in both the normal 10T1/2 and its transformed TCL 15 cells. Thus, although repair of PLD is probably different among cell lines (18, 19), it is not correct that repair of PLD does not occur in the cells irradiated with neutrons (7). In addition to cell lines, one of the important factors influencing the repair of PLD is the conditions used for its expression. For low LET radiations, PLD can be repaired after irradiation when cells are confluent, or sparse in conditioned medium or in balanced salt solution. However, as it was uncertain whether repair of PLD with neutrons took place, we adopted combined conditions under which repair of PLD should be most feasible, i.e. confluent plateau-culture of cells in 3-day-old fed medium. When we used more than 3-day-old fed medium, both the number of cells per flask and the plating efficiency of cells decreased slightly.

In general, it is uncertain whether the existence of PLD repair with low-LET radiations or neutrons is more advantageous in radiation theraphy. If normal cells are growing slowly and tumor cells rapidly, then PLD repair is advantageous for therapy since PLD repair is presumed to occur more in normal cells. However, if the reverse applies, it is disadvantageous. For example, it is likely that the cells in the center of tumor cords are not growing but viable and the surrounding normal cells are growing. In that case repair of PLD is presumed to occur more in the tumor cells. Hall et al. reported that neutron irradiation does not result in repair of potentially lethal damage and that this is one of the advantages of neutron therapy assuming PLD caused by x-rays to be repaired in tumors but not in normal tissues (8). However, PLD repair with neutrons takes place, at least, in EMT/6UW cells *in vitro* (13), 10T1/2 and TCL 15 cells. Thus, neutrons may not be so advantageous for therapy as Hall et al. assumed.

When examining the role of PLD repair, one should consider the cells irradiated with 2 Gy of x- or gamma-equivalent dose, which is mostly used for conventional therapy. So far as 10T1/2 and TCL 15 cells are concerned, no significant PLD repair occurred at 1 Gy of neutrons. Although there may be exceptions (10), most cells did not show appreciable PLD repair when they were irradiated

with 2 Gy of x- or gamma-rays. The case of 10T1/2 cells is shown in Fig. 9. Thus, PLD repair, which occurs at higher doses, may not exert seriously impede or affect the curability of tumors in radiation therapy, unless the repairability of cells is changed a great deal by daily irradiation. However, it is often assumed that the repairability of cells after irradiation with a single dose of 2 Gy is the same as or similar to that obtained after fractionated irradiation by daily 2 Gy up to a high total dose, although McNally & Ronde showed that the repairability of V79 cells was decreased after multiple doses of 2 Gy 6 h apart (11). As the assumption should be examined experimentally, the study is currently under way in our laboratory.

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