Retention of Cellular Radiation Sensitivity in Cell and Xenograft Lines Established from Human Melanoma Surgical Specimens

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ABSTRACT

Six human melanoma xenograft lines have been established in athymic mice from metastatic lesions in six different patients. Permanent cell lines in monolayer culture have been established from four of the xenograft lines. The cellular radiation sensitivity of the donor patients' tumors, the xenograft lines, and the cell lines were measured in vitro. The Courtenay soft agar colony assay was used for the donor patients' tumors, and a conventional plastic surface colony assay was used for the cell lines, whereas both assays were used for the xenograft lines. The cell survival data were analyzed using the multitarget single-hit as well as the linear-quadratic model. The donor patients' tumors differed considerably in cellular radiation sensitivity (the D$_{50}$ ranged from 0.85 ± 0.08 to 1.17 ± 0.09 Gy, the a from 0.25 ± 0.06 to 0.87 ± 0.14 Gy$^{-1}$, and the surviving fraction at 2.0 Gy from 0.15 ± 0.04 to 0.50 ± 0.06). The xenograft lines showed similar survival curves in soft agar and on the plastic surface, and the survival curves of a xenograft line and the corresponding cell line were not significantly different. These survival curves were not significantly different from those of the donor patients' tumors, regardless of which survival curve parameter was considered, i.e., the cellular radiation sensitivity of the donor patients' tumors was retained in the cell and xenograft lines. Moreover, the cell and xenograft lines have growth properties in vitro and in vivo that render a wide variety of experiments possible. Consequently, they show great promise for future studies of human tumor radiation biology.

INTRODUCTION

Human tumor cell lines established in monolayer culture and human tumor xenograft lines transplanted serially in athymic mice are currently used as model systems in studies of the radiation biology of human cancer (1–5). Such studies are often based on the assumption that the cellular radiation sensitivity of the donor patients' tumors is retained in the experimental models (6–8). There is no unambiguous experimental evidence that this assumption is valid (9). In fact, some studies have indicated that the treatment sensitivity of tumor cells is changed after establishment of permanent cell and xenograft lines (4, 5, 10, 11). Stress-induced genetic alterations as well as selection of cell subpopulations during the establishment procedure are possible causes of such changes (12, 13). Moreover, the radiation sensitivity of tumor cells may depend on the pretreatment growth conditions and the assay used for measurement of clonogenic cell survival (14–16).

Six human melanoma xenograft lines have recently been established and characterized in our laboratory (17). Permanent cell lines have been successfully established in monolayer culture from four of the xenograft lines (18). The cell as well as the xenograft lines were found to differ considerably with respect to growth characteristics, physiological parameters, and metastatic potential. Several biological features of the donor patients' tumors were shown to be retained in the cell and xenograft lines, e.g., karyotype, cell ultrastructure, and tumor histology (17, 18). Experiments elucidating the validity of these cell and xenograft lines as clinically relevant models in studies of the radiation biology of malignant melanoma are reported in this paper. The main purpose of the work was to investigate to what extent the cellular radiation sensitivity of the donor patients' tumors was retained during the heterotransplantation and the subsequent establishment of monolayer cell cultures. Thus, survival curves were established in vitro for the cell and xenograft lines and compared with those for cells isolated directly from the donor patients' surgical specimens.

MATERIALS AND METHODS

Mice. Eight to 10-wk-old male BALB/c-nu/nu mice were used. They were bred at the animal department of our institute and were kept under specific-pathogen-free conditions at constant temperature (24–26°C) and humidity (30 to 50%). Sterilized food and tap water were given ad libitum.

Melanoma Lines. Six melanoma xenograft lines (BEX-t, COX-t, HUX-t, ROX-t, SAX-t, WIX-t) have been established in athymic mice from metastases of patients (BEP-t, COP-t, HUP-t, ROP-t, SAP-t, WIP-t, respectively) admitted to the Norwegian Radium Hospital (17). Permanent cell lines (BEX-c, COX-c, SAX-c, WIX-c) have been established in monolayer culture from four of these xenograft lines (BEX-t, COX-t, SAX-t, WIX-t, respectively) (18). The source tumors in the donor patients, the xenograft lines, and the cell lines have been described in detail (17, 18). The donor patients did not receive radiation therapy or preoperative chemotheraphy (17).

The xenograft lines were maintained in athymic mice by serial s.c. transplantation of tumor fragments, approximately 2 x 2 x 2 mm in size (17). Subcutaneous flank tumors in passages 15 to 25, approximately 500 mm$^3$ in volume, were used in the present work. The lines were kinetically stable during the period the experiments were carried out, as ascertained by flow-cytometric measurements of DNA histograms and measurements of volumetric growth rates.

The cell lines were maintained in 80-cm$^2$ tissue culture flasks (Nunclon) to which were added 15 ml of RPMI 1640 medium (25 mm HEPES and l-glutamine) which was supplemented with 13% fetal calf serum, 250 mg/liter of penicillin, and 50 mg/liter of streptomycin (18). They were incubated at 37°C in a humidified atmosphere of 5% CO$_2$ in air and subcultured once a week after trypsinization (treatment with a 0.05% trypsin/0.02% EDTA solution for 2 min). Cells in passages 75 to 100 in vitro were used in the present work. Flow cytometric measurements of DNA histograms and measurements of the rate of cell proliferation showed that the lines were kinetically stable in these passages. The cell lines were verified to be free from Mycoplasma contamination by using both the Hoechst fluorescence and the mycotoxin methods.

Single Cell Suspensions. Tissue specimens from the donor patients' tumors were dropped into culture medium at 4°C immediately after surgery and brought to the laboratory. Normal tissue, necrotic areas, and blood clots were removed using a scalpel and a pair of tweezers. The remaining tumor tissue was rinsed several times in cold culture medium (4°C) and cut into fragments approximately 2 x 2 x 2 mm in size. Some of the fragments were used to establish the xenograft lines.
A standardized mechanical procedure was used to prepare single cell suspensions from the fragments, whether derived from the donor patients' tumors or from xenografted tumors. The fragments were put into a plastic bag with 20 ml of culture medium and disaggregated for 30 s with a stomacher (Lab-Blender 80). The resulting suspension was filtered through 30-μm nylon mesh to remove cell aggregates, centrifuged, and resuspended in complete culture medium [Ham's F-12 medium supplemented with 20% fetal calf serum, 250 mg/liter of penicillin, and 50 mg/liter of streptomycin for growth in soft agar or RPMI 1640 medium (25 mM HEPES and L-glutamine) supplemented with 13% fetal calf serum, 250 mg/liter of penicillin, and 50 mg/liter of streptomycin for growth in monolayer culture]. The quality of the suspensions was examined using a phase-contrast microscope and a hemocytometer. The fraction of doublets was always <5%, and the fraction of larger aggregates was always <0.1%. The number of morphologically intact, metabolically viable cells, i.e., cells having an intact and smooth outline with a bright halo, were counted, and the cell suspensions were diluted to appropriate concentrations for use in radiation experiments.

Irradiation. A Siemens Stabilipan X-ray unit, operated at 220 kV, 20 mA, and with 0.5-mm Cu filtration, was used for irradiation. The irradiation was performed at room temperature at a dose rate of 3.4 Gy/min. The cells were kept in 1 ml of soft agar or liquid culture medium in plastic tubes (Falcon 2057) during the radiation exposure. Cell suspensions from tumors were prepared as described above. Cell suspensions from monolayer cultures were obtained by trypsinization of cultures in exponential growth. Exponential growth was achieved by plating 5 × 10⁴ cells in 80-cm² tissue culture flasks and harvesting the cells after 4 to 6 days (18).

Soft Agar Clonogenic Assay. The soft agar colony assay used in the present work was developed by Courtenay and Mills (19). The soft agar was prepared from powdered agar (Bacto agar; Difco) and culture medium (Ham's F-12 medium supplemented with 20% fetal calf serum, 250 mg/liter of penicillin, and 50 mg/liter of streptomycin). Erythrocytes from August rats were added before melanoma cells were embedded in the soft agar. Aliquots of 1 ml of the soft agar were seeded in plastic tubes (Falcon 2057). The tubes were plunged into crushed ice, and the soft agar was allowed to set.

The cells were incubated at 37°C for 4 to 5 wk in an atmosphere of 5% O₂, 5% CO₂, and 90% N₂. Culture medium (2 ml) was added to the top of the soft agar 5 days after seeding and then changed weekly. Colonies were counted using a stereomicroscope. Cells giving rise to colonies containing more than 50 cells were scored as clonogenic. The PE was calculated from the number of colonies counted and the number of morphologically intact, metabolically viable cells seeded. Previous work has shown that there are potential pitfalls in this soft agar colony assay when used to study survival of cells isolated directly from human tumors (20, 21). Care was taken to avoid these pitfalls. (a) The relationship between number of colonies and number of cells seeded was verified to be linear for all donor patients' tumors and xenograft lines. (b) Reliable criteria to distinguish vital, real colonies from large abortive colonies were established. These criteria were based on examinations of the size, shape, and color of the colonies from unirradiated cells (20). (c) Scoring of artificial colonies due to cell clumps was avoided by examining soft agar cultures of cells given a lethal radiation dose of 30.0 Gy. (d) Finally, measured surviving fractions were corrected mathematically for multiplicity before curve fitting was performed (22).

Plastic Surface Clonogenic Assay. Melanoma cells, suspended in 1 ml of RPMI 1640 culture medium (25 mM HEPES and L-glutamine) supplemented with 13% fetal calf serum, 250 mg/liter of penicillin, and 50 mg/liter of streptomycin, were plated in 25-cm² tissue culture flasks (Nunclon). The flasks contained 1 × 10⁵ lethally irradiated (30.0 Gy) feeder cells in 4 ml of culture medium, which were plated 24 h earlier. It was verified experimentally that the use of feeder cells increased the PE, particularly for cells isolated directly from xenografted tumors. Moreover, a linear relationship between number of colonies and number of cells seeded was ensured by the use of feeder cells. Finally, the use of feeder cells inhibited migration of viable cells, hence causing dense and easily scorable colonies.

The cells were incubated at 37°C for 1 to 3 wk in a humidified atmosphere of 5% CO₂ in air. One half of the culture medium (2.5 ml) was removed and replaced with fresh medium each week. The cells were fixed in 100% ethanol and stained with methylene blue. Colonies containing more than 50 cells were counted using a stereomicroscope. Surviving fractions were calculated and corrected for multiplicity in the same way as in the soft agar colony assay.

Curve Fitting and Statistical Analysis. Survival curves were fitted to the data by the method of least squares using the multitarget single-hit as well as the linear-quadratic model. The curve fitting was based on surviving fractions from individual experiments as opposed to mean values. A two-tailed t test was used to investigate whether the parameters of two survival curves were significantly different.

RESULTS

Radiation survival curves in vitro for the donor patients' tumors and the corresponding cell and xenograft lines are presented in Figs. 1 to 6. The donor patients' tumors were assayed for cell survival in soft agar, whereas the plastic surface assay was used for the cell lines. The four xenograft lines from which cell lines were successfully established were assayed both...
in soft agar and on plastic surface, whereas only the soft agar assay was used for the other two xenograft lines. The cell survival curve parameters, SF2, and PE are presented in Table 1.

The BEX-t and COX-t lines showed a higher PE on plastic surface than in soft agar, whereas the PE was similar in these two assays for the SAX-t and WIX-t lines. The HUX-t and ROX-t lines were not able to form colonies on plastic surface. The PE of the xenograft lines was somewhat higher or similar to that of the corresponding donor patients' tumors. The cell lines always showed a higher PE than did the xenograft lines. The xenograft lines showed similar survival curves in soft agar and on plastic surface, i.e., the cell surviving fractions did not vary with the in vitro assay. The survival curves of a xenograft line and the corresponding cell line were not significantly different, even though the PE (Table 1) and the fraction of cells in S phase (17, 18) were lower in the xenograft lines than in the cell lines, suggesting that the survival curves were insensitive to variations in these parameters. Moreover, none of these survival curves differed significantly from those of the donor patients' tumors. This conclusion was found to be valid, no matter which of the survival curve parameters in Table 1 were considered in the statistical analysis. Consequently, the cellular radiation sensitivity of the donor patients' tumors was retained in the cell and xenograft lines.

The cellular radiation sensitivity differed considerably among the different donor patients' tumors, xenograft lines, and cell lines. This is illustrated in Fig. 7, where the soft agar survival curves for the xenograft lines are redrawn in the same panel. The ROX-t was the most resistant and the BEX-t the most sensitive line. The α and SF2, for example, varied within a factor of about 3 among the lines. The xenograft lines have also been found to differ significantly in several growth and physiological parameters in vivo (17). There was no relationship between the cellular radiation sensitivity and these parameters. This observation, together with the observation that the donor patients' tumors and the corresponding cell and xenograft lines showed similar survival curves, suggests that the differences in cellular radiation sensitivity in Fig. 7 were not merely a second-
RADIATION SENSITIVITY OF TUMOR MODELS

Fig. 5. Radiation survival curves for SAP-t, SAX-t, and SAX-c human melanoma cells irradiated in vitro. The SAP-t cells were assayed for survival in soft agar, the SAX-c cells on plastic surface in conventional tissue culture flasks, and the SAX-t cells both in soft agar and on plastic surface. Points, surviving fractions calculated from the mean number of colonies in 4 soft agar tubes or 4 tissue culture flasks. Different points at the same dose level refer to independent experiments.

Fig. 6. Radiation survival curves for WIP-t, WIX-t, and WIX-c human melanoma cells irradiated in vitro. The WIP-t cells were assayed for survival in soft agar, the WIX-c cells on plastic surface in conventional tissue culture flasks, and the WIX-t cells both in soft agar and on plastic surface. Points, surviving fractions calculated from the mean number of colonies in 4 soft agar tubes or 4 tissue culture flasks. Different points at the same dose level refer to independent experiments.

DISCUSSION

Experiments performed with human tumor xenograft lines suffer from the uncertainty of whether the xenografted tumors may have other biological properties and treatment responses than the source tumors in the donor patients (4, 5, 23, 24). The same uncertainty also applies to continuous cell lines established in monolayer culture (10, 11, 25). Changes in radiation sensitivity may occur through at least three fundamentally different mechanisms when tumor cells are removed from the host and cultured in an artificial environment in vivo or in vitro. (a) Many tumors consist of cell subpopulations that can differ in several biological properties, including radiation sensitivity (26, 27). Tumor cells are usually subjected to a strong selection pressure in a new environment, which may lead to complete dominance of one of the subpopulations (12). (b) Tumor cells are often genetically unstable, and extensive genotypic and phenotypic changes may occur during growth in a new environment (13, 28). (c) Finally, the radiation sensitivity of tumor cells depends on the cell cycle distribution and the physiological conditions in the microenvironment (14, 29), which often are different for tumors in humans, xenografted tumors, and cells in culture (4, 30).

The six human melanoma xenograft lines studied here were all found to have retained the cellular radiation sensitivity of the donor patients' tumors. Moreover, the four cell lines that were successfully established in monolayer culture showed similar radiation sensitivity to the source xenograft lines. Consequently, processes leading to changes in cellular radiation sensitivity, such as the processes described above, do probably not occur very frequently when cell and xenograft lines are established from human melanoma metastases. However, there is clear evidence from studies of other melanomas that changes in radiation sensitivity indeed can take place during establishment of cell lines in vitro. Studies in our laboratory showed that the cell line FME established from the human melanoma xenograft line E.F. was more sensitive to radiation treatment than the source xenograft line. FME cells in exponential growth showed a D0 of 0.68 ± 0.03 Gy, whereas the D0 of the E.F. cells irradiated in vitro was 1.32 ± 0.08 Gy (10).

The individual donor patients' tumors, xenograft lines, and cell lines studied here differed considerably in cellular radiation sensitivity. This observation is in agreement with results presented in a recent review of the radiation biology of malignant melanoma (31). The review concluded that the differences in
radiation sensitivity among melanoma cell lines irradiated in vitro can be almost as large as those among cell lines from tumors of different histology and with very different clinical radio curability (31). Moreover, recent clinical investigations also suggest that malignant melanoma no longer should be considered to be a typically radiation-resistant tumor type (32, 33). The data rather indicate that melanomas are heterogeneous in clinical radioresponsiveness; some tumors may be resistant but others are sensitive.

Clinically relevant radiobiological studies require adequate experimental tumor model systems. A panel of cell and xenograft lines established from different patients suffering from the same histopathological type of neoplastic disease is described here. These lines constitute an experimental tumor panel that is sufficiently high for most purposes both in soft agar and on plastic surface. The cell survival curves are insensitive to variations in PE and cell cycle distribution. The cellular radiation sensitivity is similar in the soft agar and the plastic surface assay. Consequently, the six xenograft lines and the four cell lines constitute an experimental tumor panel that shows great promise for future studies of human tumor radiation biology in general and the radiation biology of malignant melanoma in particular.

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REFERENCES

5. Petersen, and Heidi Kongshaug is gratefully acknowledged.

Table 1 Radiation survival curve parameters

<table>
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<th>Cells</th>
<th>Assay</th>
<th>$D_0$ (Gy)</th>
<th>n</th>
<th>$\alpha$ (Gy$^{-1}$)</th>
<th>$\beta$ (Gy$^{-2}$)</th>
<th>SF$_0$</th>
<th>SF$_2$</th>
<th>PE (%)</th>
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<td>BEP-t</td>
<td>Soft agar</td>
<td>0.85 ± 0.08</td>
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<td>COP-t</td>
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<td>0.84 ± 0.12</td>
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* Values calculated from the linear-quadratic curve fit.
* Values measured in vitro.
* Mean ± SE.

Fig. 7. Radiation survival curves for BEX-t, COX-t, HUX-t, ROX-t, SAX-t, and WIX-t human melanoma cells irradiated in vitro and assayed for survival in soft agar. The curves are redrawn from Figs. 1 to 6 for comparison.
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