Low dose hypersensitivity after high-LET irradiation

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An unexpected hypersensitivity has been reported for several cell lines at low doses (<1Gy), which is not consistent with the linear-quadratic approach currently used in general for the description of survival curves [1,2,3,4]. The corresponding substructure of the survival curves has been attributed to induced radioresistance. There are indications, that high-LET irradiation with neutron or pion beams does not lead to low dose hypersensitivity [1,3], at least in single dose exposure experiments. But no systematic studies on the LET-dependence have yet been performed.

Measurements of low dose effects require high precision assays for the correspondingly high survival levels, where statistical errors represent a principal limit for the accuracy of the standard dilution assay. This problem can be bypassed by using absolute cell counting by means of either cell sorter assays [5] or automated video microscopy assays like e.g. the DMIPS assay [6].

With respect to application of high LET beams in tumor therapy, it is of particular interest, whether hypersensitivity is also observed in situations, which correspond to the radiation quality and dose levels occuring during therapy in the normal tissue in front of the target volume or in the region beyond the tumor. Both regions are characterized by low dose levels due to the inverted depth dose profile or due to beam fragmentation, which contributes to a small dose deposition beyond the tumor. If hypersensitivity is observed in these situations, this could have impact on the RBE values of the normal tissue surrounding the tumor.

In order to investigate the survival after low doses of high-LET radiation, an automated video microscopy system similar to the DMIPS system has thus been developed recently and used for first experiments. The system is able to automatically find the cells without staining using a phase contrast microscope. Cells can then by relocated by means of a computerized microscope stage at regular intervals to follow the fate and growth characteristics of individual cells. Inspection of a flask with approx. 100 cell positions lasts about 20 min; there will be, however, further improvements to accelerate the automatic cell finding and inspection procedures. The measurements include an automatic determination of the colony area, which is - within certain limits - a measure of the cell number per colony. This information can be used to determine growth curves for the individual cells.

The system has been used for experiments at the UNILAC and SIS. First, the agreement of survival curves obtained with the new technique with those obtained using the standard dilution assay has been investigated. No systematic deviations from the results using conventional techniques have been detected for doses higher than 1 Gy for the different radiation qualities.

The system was thus used to investigate in particular the effects of low doses after irradiation with 100 MeV/u carbon ions; the results are summarized in Fig. 1. Up to now, 8 independent experiments have been performed. A significant hypersensitivity at low doses (0.1 Gy) has been detected, whereas for higher doses (0.5 Gy) a transition to the linear-quadratic shape is observed. The general structure of the survival curves closely resembles those reported for low LET irradiation [3] and can be fitted well using a modified LQ-approach including a term for induced resistance [7]. This result is apparently in contrast to the results reported in the literature, where the effect of induced resistance has been reported to be largely reduced e.g. for peak pion irradiation at similar LET values.

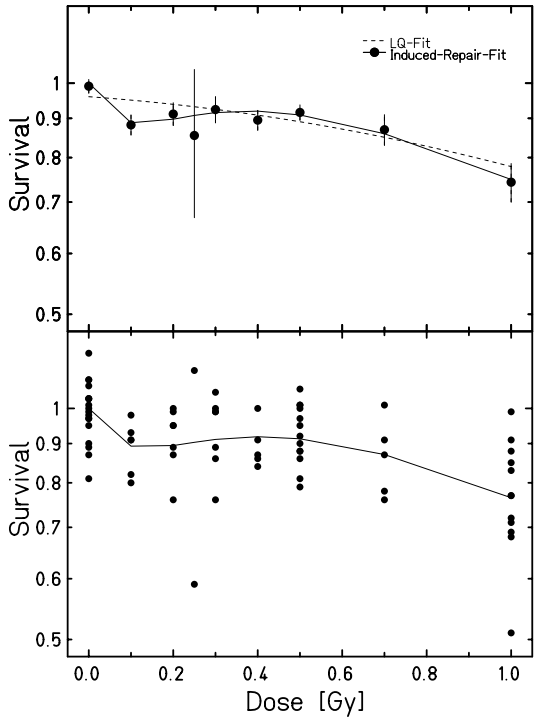

Figure 1: Survival of V79 cells after irradiation with low doses of 100 MeV/u carbon ions. Top: Average values from up to 8 independent experiments. Bottom: Distribution of survival for individual samples. Fits are performed according to an induced repair approach (full line) [7]. For comparison, the backextrapolation from a linear-quadratic fit to the high dose region is shown int the top panel.

References

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