A cell survival model with saturable repair after irradiation*

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Summary. A cell survival model with saturable repair has been developed. The model is based on the assumption that after irradiation the cell can be in one of the following three states: In state A the viable cells have no lesions, in state C cells carry lethal lesions and in state B cells exhibit potentially lethal lesions which can be repaired by a saturable enzymatic repair system or which are converted to lethal lesions. The model incorporates five parameters. The applicability of the model has been demonstrated by fitting 11 experimental data sets obtained with different cell lines, different kinds of radiation and variable repair times simulated by liquid holding recovery or inhibition of repair processes by different agents. The model and the results obtained are discussed in relation to published results.

Introduction

Ionizing radiation can act directly or indirectly on biological macromolecules by inducing long-lived lesions. One of the biological effects of this action on living cells after high doses is death followed by lysis of the cells (interphase death), whereas after lower doses the loss of unlimited proliferative ability (reproductive death) is more likely. In a semi-logarithmic plot, survival curves of cells as a function of absorbed radiation dose show a wide range of variation in shape ranging from a pure exponential decrease in survival after high LET irradiation to curves with a shoulder after low LET irradiation. Some mathematical models have been developed to describe quantitatively cell survival after irradiation, several of which are described briefly in the following.

The first attempts to quantify the survival curves assumed a two state model of living and dead cells and defined radiation sensitive structures in the cells called 'targets' [29, 46]. By assuming one or more hits in one

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target or one or more hits in different targets the ‘hit’ theory was able to describe the cell survival curves. The disadvantage of the ‘hit’ theory was that no explanation could be offered as to the nature of the targets and that experimental values could be described often by more than one set of hits and targets.

Further experiments have revealed strong evidence that the critical target is the DNA. Therefore Chadwick and Leenhouts proposed a linear-quadratic (LQ) model [6] which assumed that the lethal events after radiation may be double-strand breaks which primary are induced linear with dose, additionally single-strand breaks are induced linear with dose which can be progressed secondary to lethal double-strand breaks, this process is proportional to the square of dose. On the basis of microdosimetry Kellerer and Rossi [27] developed a theory of ‘dual radiation action’ considering the fact that after uniform irradiation in small critical sites the absorbed energy is of second order kinetics.

Experiments with fractionated doses or variation of the time between irradiation and cell division yielded a marked enhancement in cell survival [14, 30]. This phenomenon called ‘Elkind recovery’ or ‘repair’ shows that the fate of the cell is not irrevocably determined after irradiation but that the cell can eliminate some of the lethal lesions. This behaviour led to a new generation of three stage models, the saturable-repair (SR) model [18], the repair-misrepair (RMR) model [41], the cybernetic model [32, 34] and the lethal-potentially lethal (LPL) model [9, 10, 39]. The models are based on the assumptions that after irradiation, the cell has no damage (stage A) or has lethal damage (stage C) or is in stage B with potentially lethal or repairable lesions. To describe the dose-effect curves correctly it must be assumed that in state B some of the radiation-induced lesions can be healed by an enzymatic repair process in competition with a time-dependent conversion of repairable lesions to irreparable lesions. The advantages and disadvantages of some of the cell survival models for describing experimental data sets are compared by Goodhead [17] and Tobias [41].

The above mentioned models assumed a linear enzymatic repair process, but in 1971 Calkins [4] suggested that the survival of Tetrahymena pyriformis can only be described by assuming a saturated enzymatic process, a suggestion which was verified in the meantime by other authors [18]. The aim of the present investigation was to develop a three state model with saturated enzymatic repair and to test its range of application by fitting the model parameters to experimental results with mammalian cells and considering changes in the repair-time or biochemical modifiers of the repair enzymes.

Mathematical description of the survival model

The basic features of the three state models are visualized in Fig. 1 [32]. Whereas in state A cells are free of lesions or have lesions which do not affect the survival (viable cells), state C cells carry lesions which cannot be repaired and which are lethal (cells with lethal lesions). The rest of the