A kinetic extension for the Giant Loop Binary Lesion model

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In 2012 the Giant LOop Binary LEsion model (GLOBLE) was proposed [1] and a formalism for the description of dose dependent cell survival probabilities after instantaneous photon irradiation was given. The concept of the model suggests an extension which takes into account dose rate effects. This contribution will summarize an extract of the research that has been done towards this aim.

Theory

DNA double strand breaks (DSBs) are supposed to be the main reason for cell death after irradiation. The GLOBLE is based on a classification of DSB according to their spatial distribution in the chromatin, specifically in giant loops (~ 2Megabasepairs) whose terminal ends are attached to the nuclear matrix.

It is assumed that a single (isolated) DSB within a giant loop is relatively easy to rejoin due to the fixation of the two parts of the loop to the nuclear matrix. However, multiple (clustered) DSBs within a loop imply a high risk for misrejoining followed by cell death since larger fragments of the DNA might get lost in this case. Therefore, a significant higher lethality ε is assigned to clustered DSBs as compared to isolated DSBs: $\varepsilon_c >> \varepsilon_i$.

Given dose dependent expected numbers of isolated and clustered DSBs after irradiation (N_i and N_c) one is able to calculate the corresponding cell survival probability as the Poisson probability for no lethal event:

(1)

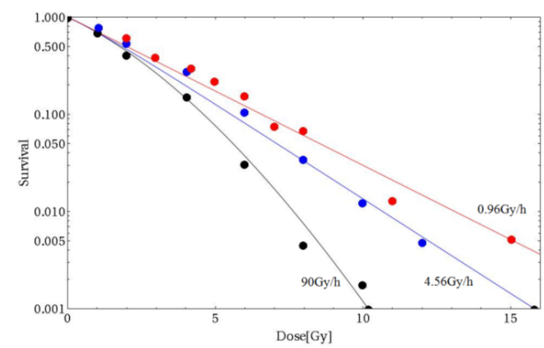
In order to adapt the GLOBLE to the application of arbitrary dose rates during the irradiation the interaction between damage induction and cellular repair has to be accounted for.

The yield of initial DSBs is expected to depend only on the total dose, but not on the dose rate. However, the frequency of clustered DSBs is significantly affected by the dose rate, since a simultaneous existence of at least 2 DSBs in a loop is required to form them. The competition between the rate of DSB induction and rejoining/repair thus determines the relative fraction of isolated and clustered DSBs. In the GLOBLE it is assumed that the rate of DSB induction is proportional to the dose rate and that isolated and clustered DSBs are rejoined with fast and slow kinetics, respectively.

The dynamics involved in damage induction and repair can be expressed in five differential equations – one for each state that a giant loop might take. There are loops without DSB or lethal event, loops with non-processed isolated/clustered DSBs and loops with lethal events after misrejoining of isolated/clustered DSBs. With these differential equations and appropriate initial values one can calculate the expected number of lethal events and the corresponding survival probability.

Applications

With the kinetic extension of the GLOBLE cell survival probabilities after photon irradiation with arbitrary dose rates can be described. For the specific case of constant dose rates and for split dose experiments good agreement between model predictions and experimental data has been found.



The figure above shows that the model (full lines) reflects the increase in cell survival probabilities with decreasing dose rate as observed in the experimental data [2] (dots). The model predictions are based on a single set of parameters (lethalities and rejoining rates) simultaneously describing the whole range of dose rates for the given cell line. The analysis of 15 other published dose rate experiments and of 5 split dose experiments in different cell lines support the conclusion that one is able to find cell line specific parameters with the GLOBLE.

Outlook

The Local Effect Model (LEM) which predicts effects of high LET radiation is based on the same classification of DSBs as the GLOBLE. In analogy to the approach presented here, future work will focus on an extension of the LEM which allows for the description of dose rate effects for ion beam radiation.

References

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