Prediction of asynchronous cell survival with the cell cycle extended GLOBLE model

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The Giant LOop Binary LEsion (GLOBLE) model developed at GSI predicts the survival of cells after photon irradiation. This prediction is based on the spatial distribution of Double Strand Breaks (DSBs) in the cell nucleus. An extension of the GLOBLE model was developed in order to predict radiosensitivities of cells, depending on their cell cycle phase. Model predictions are in agreement with measurements from synchronized cell experiments. A next step is to transfer these findings by applying the model to data measured with asynchronous cells. In this context a method to predict the cell cycle specific radiosensitivities from asynchronous cells is investigated. Since the cell cycle plays an important role for photon irradiation, but a less significant one for heavy ion irradiation it is desirable to understand the reasons and implications for therapy.

Methods

One general notion regarding the severity of DNA lesions is that clustered lesions are more harmful to cells than isolated ones. In the GLOBLE model [1] the induction of DSBs on Mbp-chromatin loops after photon irradiation is simulated. One DSB within a loop is defined as an isolated DSB (iDSB), two or more are defined as clustered DSB (cDSB). For photon irradiation the number of iDSBs (n_i) and cDSBs (n_c) is depending on the dose and can be calculated from Poisson statistics. Different lethalities can be assigned to these lesions, ϵ_i for iDSBs and ϵ_c for cDSBs. The cell survival probability S is then given by

$$S = \exp\left[-(n_i \cdot \epsilon_i + n_c \cdot \epsilon_c)\right] .$$

In a recently published work [2] we introduced the option to further distinguish in the GLOBLE model between different repair pathways for the iDSBs. During the G1-phase only the error-prone Non Homologous End Joining (NHEJ) can be used, while in the S-phase the error free Homologous Recombination (HR) gets gradually available. The number of iDSBs which can be repaired with NHEJ (HR) is $n_{i,1}$ ($n_{i,2}$), and their lethality is $\epsilon_{i,1}$ ($\epsilon_{i,2}$). The cDSBs are expected to be equally severe for both pathways. Their lethality ϵ_c does not change. The survival is now given by

$$S = \exp[-(n_{i,1} \cdot \epsilon_{i,1} + n_{i,2} \cdot \epsilon_{i,2} + n_c \cdot \epsilon_c)] .$$

The number of lesions in the different DSB classes can be calculated for all cell cycle phases, and thus their survival probability [2]. To calculate the survival of asynchronous cells the survival rates for all cell cycle phases have to be added and weighted with their proportion. Under the assumption that HR, if available, is error free, this method can also be used in reverse to predict cell cycle phase specific survival from the dose response of asynchronous cell populations. Hence typically measured cell survival curves of asynchronous populations can be exploited to characterize cell cycle dependent dose response.

Results and Conclusion

Predicted survival curves for different cell cycle phases with experimentally inspired lethality parameters are illustrated in fig. 1. They demonstrate a broad variation of radio response within the cell cycle. We checked that the formalism predicts experimental data sufficiently well [2]. The hypothesis above that HR is error free could also be supported.

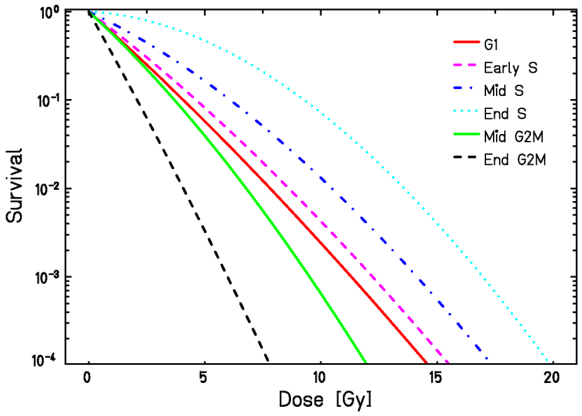

Figure 1: Prediction for cell survival after photon irradiation for cells synchronized in different cell cycle phases.

The prediction of cell cycle specific survival from asynchronous cell populations resulted in similar curves as shown in fig. 1. A first comparison of the model to experimental data is promising.

Our goal for the future is to transfer these findings to ion irradiation, in order to quantify the role of the cell cycle for heavy ion therapy. The presented work is the first step to the cell cycle phase resolved prediction of the relative biological effectiveness for heavy ion irradiation.

References

[1] Friedrich T et al., *Radiat. Res.* 2012 Sept; 178(5): 385-394

[2] Hufnagl A et al., *DNA Repair* 2015 March; 27(1): 28-39

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