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Unraveling the complexities of radiation damage through Microdosimetric Kinetic Model: The role of clonogenic data in clinical RBE

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DNA damage produced by ionizing radiation can be divided into two categories: lethal and sublethal lesions. Lethal lesions are those that result directly in cell death. Sublethal lesions do not result in immediate cell death but may combine to become a lethal lesion after a period or may be repaired by the cell. The spatial distribution of damage, and hence the distribution of deposited energy, is relevant in the determination of the biological effect of radiation.

The use of protons in radiotherapy has increased significantly over the last decade. Protons deposit relatively little dose along the initial stretch of their track inside matter up to a region called Bragg peak, in which a great amount of dose is released with almost no dose beyond that point. At this point, a high ionization density is found, leading to a higher local concentration of DNA damage, with increased complexity.

To compare the effect of different types of radiation, the Relative Biological Effectiveness (RBE) is defined as the ratio of the doses required to produce a given biological effect with two different types of radiation, typically using photons as the reference radiation. For proton therapy, the assumption of a constant RBE = 1.1 is the clinically accepted convention. However, existing in vitro experimental data suggest otherwise [1-4]. To potentially account for this in clinical practice, phenomenological and mechanistic models have been proposed to determine the RBE in each case, such as the Microdosimetric Kinetic Model (MKM). The MKM postulates the concept of domain as representing the maximum distance for sublethal lesions to pairwise interact to form a lethal lesion and lead to cell death. The size of the cell nucleus is also relevant to characterize how many lethal and sublethal lesions can be induced by radiation and at what point a lethal lesion is warranted from a given radiation.

Clonogenic experiments are important for this purpose because they determine the percentage of cells that keep their mitotic viability after a given irradiation. The linear-quadratic (LQ) model represents the logarithm of clonogenic survival with linear (α) and quadratic (β) dependences on the delivered dose and typically is fitted to the results from clonogenic experiments. Particle Irradiation Database Ensemble (PIDE) from the GSI, is a database that provides irradiation conditions, cell line information, andthe linear component and quadratic component parameters for different clonogenic experiments the ion used. By analyzing these experiments from exposures to protons, alpha particles, and carbon ions, two main quantities of the MKM can be obtained experiment-wise: the statistical distribution of domain radius values and the cell nucleus radius. The MKM uses these parameters to obtain the α parameter corresponding to a given radiation.

In this work, survival curves obtained from clonogenic assays were employed to determine the values of cell-specific parameters in the context of the MKM in a systematic way. This determination represents an approach to include further information on the cell line-specific radiosensitivity, which is important for proton therapy. Our results showed large variability among different cell lines, illustrating the importance of intrinsic response to radiation of different biological systems when determining RBE. The considerable deviations among groups and experiments raise the question of how valuable RBE models based on clonogenic assays are for the clinics. Also, the significant number of nuances to be considered in these models, and the lack of connection with realistic biological processes in the clinical response to radiation contribute to challenging the translatability of clonogenic survival in the clinic.

It is likely that a significant portion of the reported variability in PIDE comes from the fact that multiple institutions and laboratories carried out these experiments in different experimental conditions. Therefore, standardized methods to perform clonogenic assays for different particles and energies, especially clinical ones, may lead to better results in predicting RBE for clinical practice.

[1] Carabe A, Moteabbed M, Depauw N, Schuemann J, Paganetti H. Range uncertainty in proton therapy due to variable biological effectiveness. Phys Med Biol 2012;57:1159–72. https://doi.org/10.1088/0031-9155/57/5/1159.

[2] McNamara AL, Schuemann J, Paganetti H. A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. Phys Med Biol 2015;60:8399–416. https://doi.org/10.1088/0031-9155/60/21/8399.

[3] McNamara A, Willers H, Paganetti H. Modelling variable proton relative biological effectiveness for treatment planning. Br J Radiol 2019;92:1–11.

[4] Wedenberg M, Lind BK, Hårdemark B, Wedenberg M, Lind BK, A BH. A model for the relative biological effectiveness of protons: The tissue specific parameter α/β of photons is a predictor for the sensitivity to LET changes. Acta Oncol (Madr) 2013;52:580–8. https://doi.org/10.3109/0284186X.2012.705892.

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