Modeling Cell Survival in Ion Beam FLASH Irradiation Through DNA Damage Distribution in 3D Genome

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ABSTRACT

Purpose: Ion beam radiotherapy has opened new frontiers for FLASH research by introducing LET as a critical physical parameter for mechanistic investigation. However, current FLASH effect models are restricted to low-LET irradiation, and high-LET adaptations remain empirical, deriving from oxygen enhancement ratio approximations without underlying biological mechanisms. We propose a generalized theoretical framework that bridges this gap, enabling mechanistic extension of low-LET FLASH models to high-LET ion beams.

Methods: We extended a 3D genome-based cell survival model to a generalized framework characterizing radiochemical effects on DNA damage across a range of LET values. The probability-modifying factor (PMF) was introduced as a unified metric for FLASH-induced DNA damage alterations. This framework predicted ion beam FLASH effects by mechanistically integrating oxygen depletion and radical recombination hypotheses, with explicit consideration of LET-dependent radical yields.

Results: Computed PMF and DMF profiles across different LET values demonstrated a PMF elevation as LET increases, a trend attributed to reduced oxygen depletion and diminished peroxyl radical production. Meanwhile, DMF invariance within the intermediate LET range indicated parity in FLASH effects between the plateau and spread-out Bragg peak (excluding the distal end). These predictions are consistent with existing ion beam FLASH experimental results.

Conclusion: We established a unified mechanistic framework rooted in DNA damage-related pathways to investigate the mechanisms of the ion beam FLASH effect. By extending FLASH modeling to ion beam irradiation, this framework enables the validation of mechanistic hypotheses against experimental ion beam data and the quantitative prediction of the ion beam FLASH effect.

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INTRODUCTION

FLASH radiotherapy has advanced rapidly in recent years. Beyond low energy electron and X-ray beams, proton, helium ion, carbon ion and oxygen ion beams have also achieved FLASH dose rates and been included in experimental studies. High-LET beams introduce a new variable (LET) to the FLASH effect, in addition to dose and dose rate.

Most existing FLASH effect models focus on low-LET beams, typically relying on dose-averaged oxygen enhancement ratio (OER). Even for low-LET beams, the exact FLASH mechanism remains controversial, with hypotheses including oxygen depletion and peroxyl radical recombination. Extending these hypotheses to high-LET beams is critical for exploring the FLASH effect mechanism.

Our recent work showed that ionizing radiation-induced cell death is closely linked to DNA damage distribution in the 3D genome, a key high-order chromatin structure. Building on this, we established a mechanistic model that reproduces RBE and OER across LET values without empirical adjustments for LET-related parameters. Based on our previous RBE model, we developed such a framework that separates dose-rate-dependent changes in DNA damage from dose-rate-independent cellular responses. We applied this framework to predict the dose modification factor (DMF, a key indicator for quantitatively measuring the FLASH effect) for cell survival under FLASH high-LET irradiation, based on the oxygen depletion and radical recombination hypotheses. This decoupled framework extends mechanistic FLASH hypotheses to high-LET beams, facilitating both hypothesis validation and quantitative prediction of the FLASH effect in high-LET irradiation.

METHODS AND MATERIALS

Based on the widely discussed hypotheses for the FLASH effect (oxygen depletion and radical recombination), differences in radiochemical processes are considered the primary cause of the FLASH effect. We therefore aimed to decouple the high-LET FLASH mechanism into dose-rate-dependent changes in damage and dose-rate-independent cellular responses under high-LET irradiation (see Figure 1). This unified framework enables the extension of various FLASH mechanisms to high-LET irradiation. A schematic diagram of this framework is presented in Figure 1.

We introduced a probability-modifying factor (PMF), defined as the ratio of p_{DNA} under FLASH to conventional (CONV) irradiation, to quantify dose-rate-dependent radiochemical impacts in FLASH irradiation. The PMF can be computed based on specific FLASH mechanistic hypotheses. Then DMF can be calculated based on PMF.

$$DMF = 1 - \omega \cdot (1 - PMF)$$

The factor ω is determined by the specific cell's survival curve under CONV irradiation, which represents dose-rate-independent cellular responses.

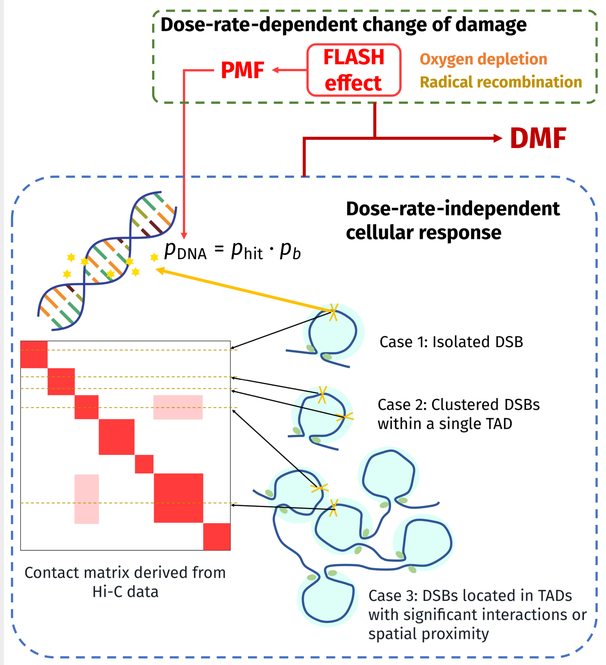

Figure 1. Framework of the decouple of dose-rate-dependent and dose-rate-independent effects in high-LET FLASH irradiation.

RESULTS

Dose-rate-independent cellular responses across LET

Within our model framework, the ω parameter represents dose-rate-independent cellular responses across a range of LET values. Using the endpoint of 10% survival, we present the ω factors across LET for proton, He ion, C ion, and Ne ion beams derived from track-structure Monte Carlo simulations, in Figure 2.

Dose-rate-dependent changes in damage

The PMF characterizes dose-rate-dependent changes in DNA damage induced by FLASH irradiation. Figure 3 illustrates the minimum PMF values ($\mathrm{PMF_{min}}$) at a 20-Gy dose for each LET, derived from equations describing oxygen depletion and radical recombination.

Dose modification factor

Based on the ω and PMF, minimum DMF ($\mathrm{DMF_{min}}$) values were calculated for the aforementioned ion beams and presented in Figure 4. Within the intermediate LET range (tens of keV/μm), both hypotheses predict relatively minor variations in $\mathrm{DMF_{min}}$ values. This indicates that the FLASH effect in the SOBP region (excluding the distal end) is similar to that in the plateau region.

Comparisons with related experimental data

Due to the scarcity of direct high-LET FLASH experimental data, multi-perspective validations were performed against plasmid DNA, cancer cell, and OER-LET measurements. Our model's predictions align with experiments, verifying the model's capability to describe radical recombination, oxygen depletion, and high-LET cellular responses. Comparisons are shown in Figure 5.

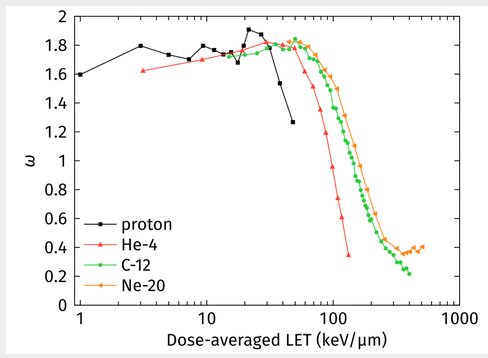

Figure 2. Dose-rate-independent cellular response (ω parameter) across LET for different ion beams derived from track-structure Monte Carlo simulations

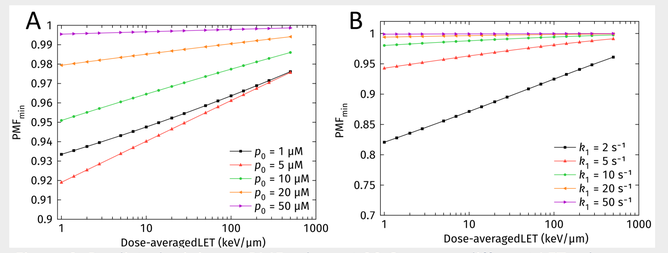

Figure 3. Predicted minimum PMF values at 20 Gy across different LET values derived from chemical reaction equations of two mechanistic hypotheses: (A)oxygen depletion hypothesis (B)radical recombination hypothesis

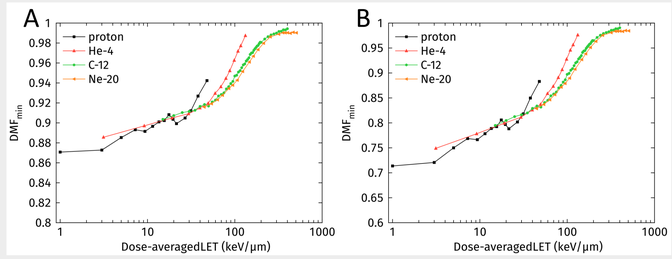

Figure 4. Predicted $\mathrm{DMF_{min}}$ values at a dose of 20 Gy across LET based on (A) the oxygen depletion hypothesis and (B) the radical recombination hypothesis for different ion beams.

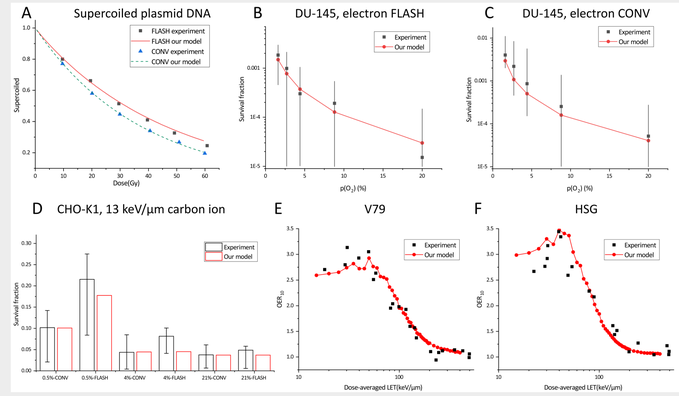

Figure 5. Comparisons of model predictions with experimental data: (A) fraction of supercoiled plasmid DNA under FLASH electron beam irradiation; cell survival of DU-145 under (B)FLASH and (C)CONV electron irradiation across oxygen level; (D) cell survival of CHO-K1 cell under 13 keV/μm carbon ion FLASH and CONV beam; OER-LET curves of (E)V79 and (F)HSG cells.

CONCLUSIONS

In this study, we proposed a decoupled model framework to predict cell survival under high-LET FLASH irradiation. Comparisons with relevant experimental data separately verified the model's ability to account for radical recombination, oxygen depletion, and cellular responses to high-LET beams. Leveraging this framework, we predicted the FLASH effect of ion beams based on the oxygen depletion and radical recombination hypotheses. Our results indicate that the FLASH effect in the SOBP region (excluding its distal end) is similar to that in the plateau region, which aligns with the results of existing ion beam FLASH experiments.

Our decoupled framework provides a viable approach to extend FLASH effect mechanisms to ion beam irradiation, enabling quantitative prediction.

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