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Original Article

Computational evaluation of biological effects of dimthylsulphoxide for radiotherapy

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Studies show that dimthylsulphoxide (DMSO) is a radical scavenger that can protect cells against radiation such as γ-rays and helium particles. This study used computational methods to evaluate the biological effects, i.e. cell survival under different concentrations of DMSO for cells exposed to various types of radiation. The repair-misrepair-fixation (RMF) model has been shown to better connect the DNA double strand break (DSB) formation and cell survival. We used Monte Carlo Damage Simulation code to computationally obtain DSB for cells exposed to γ-rays and helium particles and regression analysis of experimental survival data to determine other parameters in the RMF model. We then calculated the radiosensitivity parameters α and β of the linear-quadratic (LQ) model formulated by the RMF model to obtain survival curves. The model-derived survival curves generally agreed well with the experimental results. The analysis in radiosensitivity parameters α and β of LQ model for ^{60}Co and helium particles suggests that radioprotection by DMSO increases dramatically at DMSO concentration 0-0.2 M but more slowly when the concentration is over a specific point such as 0.5 M. The proposed algorithm can also be used for the estimation of radioprotection by DMSO for other types of radiation such as carbon ions and neon ions for radiotherapy.

Key words: DNA strand break, DMSO, cell survival, radiotherapy

Introduction

The biological effects of radiation result mainly from DNA damage caused by direct and indirect action of radiation. DNA double strand breaks (DSBs) are believed to be the main lethal lesions produced after exposure to ionizing radiation. Studies have shown that the DSB induction increases with dose[1-4] and can be classified by the damage caused. For example, clustered damages are considered intrinsically unrejoinable and lethal because there are more breakages or base damages within a short portion of DNA. These clustered DNA damages are the so-called "complex DSB" and it has been shown that the degree of complexity of DNA damage plays an important factor in the repair process[5,6]. That is, if the cell contains too many complex damages and becomes too complex for repair, reproductive cell death may occur[7].

Dimthylsulphoxide (DMSO) has been used to suppress the production of reactive oxygen species involved in the indirect actions of radiation. Results from experiments show that DSB induction is reduced 32-50% in the presence of DMSO, and that DMSO provides 50-70% protection against cell killing by X-rays or high linear energy

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transfer (LET) radiation[8,9]. Therefore, it has been suggested that DMSO be used in the optimization of radiotherapy treatment plans[10].

Recently, the concept of biologically based treatment planning (BBTP) has been brought into radiotherapy[11-13]. The goal of treatment planning is to deliver a radiation dose precisely to the target (cancer) and spare critical tissues. For BBTP, the use of a biological response has served as guidance for radiobiologically optimized radiation therapy. For example, the treatment planning system can take the information of relevant patient-specific biological parameters such as tumor and normal tissue radiosensitivity to better determine the treatment plan[14]. Here, the repair-misrepair-fixation (RMF) model[15] has been developed for linking DSB induction to reproductive cell death, and can be used to better predict the biologically-based treatment efficiency. This model includes the mechanisms regarding binary misrepair models, such as the repair-misrepair (RMR) model[16] and the lethal-potentially lethal (LPL) model[17]. The RMF model can be reduced to the linear-quadratic (LQ) model[18] that is widely used for cell survival and radiotherapy[19]. The LQ model assumes that there are two components for cell killing induced by radiation—one that is proportional to dose, and the other is proportional to the square of the dose [19]. LQ radiosensitivity parameters α and β can be formulated in terms of DSB induction, rejoining and fixation parameters of the RMF model[15].

The aim of the present study was to evaluate the biological effects, i.e. cell survival under hypoxia and different concentrations of DMSO for radiotherapy by computational methods and the RMF model. In this article, the "estimated" survival ratio was calculated by the LQ model using RMF model-derived radiosensitivity parameters α and β in both hypoxia and aerobic cases, and compared with experimental survival data. The analysis of parameters α and β showed that the protective effects on cell survival and DSB induction are increased as DMSO concentration increases, yet the portion of radioprotection increases only slowly after the concentration approaches 0.5 M. Similar trends of α and β may be observed for other heavy ions, such as carbon ions and neon ions, and further studies and experiments with DMSO may provide more tools for heavy ions radiotherapy protection.

Materials and Methods

Survival Data

Cell survival datasets[8,9,20,21] exposed in vitro to ionizing radiation of various LET were analyzed and estimated by Image J software[22] to obtain the survival fraction as a function of dose from these data. The RMF model parameters are determined from nonlinear regression analysis (see below) using that datasets of cells exposed to X-rays or γ-rays (200-250 kVp and ^{60}Co)[8,9] and helium particles with a peak energy of 3.31 MeV (LET = 120 keV/μm)[20,21].

Linear Quadratic Model

According to the LQ model[18], the survival fraction S, after exposure to dose D, can be formulated by the following equation:

$$S(D) = \exp\left(-\left(\alpha D\left(1+\frac{GD}{\alpha/\beta}\right)\right)\right) \quad (1)$$

where G is the dose protraction factor[18] which accounts for the effects of DSB repair. For a single dose D delivered at a constant rate during a time interval T, G can be expressed as:

$$G(\lambda,T) = \frac{2}{(\lambda T)^2}\left(e^{-\lambda T} + \lambda T - 1\right) \quad (2)$$

where $\lambda = \frac{\ln(2)}{\tau}$ and τ is the cell repair time. τ is set as 2 hour as suggested by Carlson et al. (2008)[15].

Nonlinear Regression Analysis

A standard approach to parameter estimation is to minimize a positively weighted sum of the errors[15,23]. For a dataset (x_1, y_1), …(x_n, y_n), let y_i denote the *i*th estimate of the surviving fraction for a given dose x_i and $f(x,\Omega)$ be the LQ model-derived survival fraction for the same exposure condition, where Ω denotes the set of LQ parameters that can be adjusted to minimize a prescribed loss function listed below:

$$\chi = \sum_{i=1}^{n}[y_i - f(x_i,\Omega)]^2 . \quad (3)$$

Here, n is the total number of data points. For in vitro cell survival data, point estimates of the radiosensitivity parameters such as α and β are obtained by minimizing Eq. (3) manually.

Repair-Misrepair-Fixation (RMF) Model

The details of the RMF model have been described elsewhere[15]. Briefly, the model considers intra- and inter-track binary misrepair and links DSB induction and processing to reproductive cell death. Suppose that complex DSB composed of j or more lesions (strand breaks, damaged bases or abasic sites) are intrinsically unrejoinable; that is, the DSB composed of j-1 or lower number of lesions can be rejoined. Then, the fraction of the initial DSB that are potentially rejoinable can be expressed as

$$f_R = \frac{1}{\Sigma}\sum_{i=2}^{j-1}\Sigma_i \qquad (4)$$

Here, Σ is the total number of DSB Gy^{-1} $cell^{-1}$, and is the expected number of DSB Gy^{-1} $cell^{-1}$ composed of exactly i lesions. The summation in Eq. (4) is from i=2 to j-1 because of all DSB are composed of at least 2 strand breaks. Σ and Σ_i are estimated using Monte Carlo Damage Simulation (MCDS) algorithm[24-26] (introduced below) for DSB induction.

In the limit of low doses and dose rates, the LQ model can be derived from RMF model. The α coefficient accounts for the DSB yields through one-track cell killing mechanisms while two-track lethal damage (β mechanism) is proportional to the square of the initial DSB yields. The α and β coefficients can be formulated as

$$\alpha = [1 - f_R(1-\theta)]\Sigma + \kappa\bar{z}_F(f_R\Sigma)^2 \quad \text{and} \qquad (5)$$

$$\beta = (\kappa/2)(f_R\Sigma)^2, \qquad (6)$$

where Θ represents the fraction of DSB that undergoes lethal first-order misrepair and damage fixation, and χ represents the fraction of initial DSB that undergoes pairwise damage interaction. The parameters Θ and χ are determined by nonlinear regression analysis of α coefficients in the LQ model from survival datasets treated with various concentrations of DMSO.

Monte Carlo Damage Simulation (MCDS)

The MCDS[24-26] provides estimates of the yield of clustered damage after irradiation of a cell by photons, monoenergetic electrons, protons or helium particles. The MCDS also provides the estimates of DSB in the presence of DMSO with the parameters Ø and K. Parameter Ø represents the fraction of strand breaks and base damages that are not scavengeable, and parameter K can be interpreted as the concentration of DMSO that reduces the number of base damages within the DNA segments by 50%[25]. DSB inductions are calculated with the parameters Ø=0.52, K=0.21 M for ^{60}Co and with the parameters Ø=0.75, K=0.14 M for helium particles (3.31 MeV) as suggested[25].

Results

According to Eq. (5) and (6), α and β are quantitatively related to the DSB yields. Figure 1 first shows the measured DSB induction and estimated yields by MCDS for cells exposed to ^{60}Co and helium particles in the presence of various

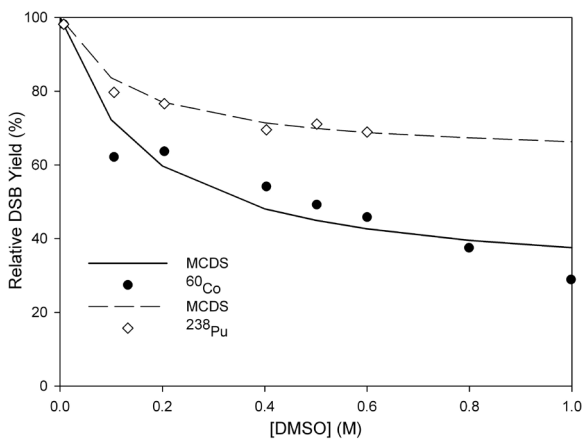

Figure 1. Comparison of MCDS-derived relative DSB yields induced by ^{60}Co and helium particles (^{238}Pu) as a function of DMSO concentration with experimental data. The experimental data were derived from the paper of deLara et al. (1995). The DSB yields for ^{60}Co are simulated according to the methodology mentioned by Hsiao and Stewart (2008) with the parameters Ø=0.52, K=0.21 M. The DSB yields for helium particles (3.31 MeV) are obtained with the parameters Ø=0.75, K=0.14 M.

DMSO concentrations (Fig 1). The DSB yields for helium particles (3.31 MeV) were calculated with the parameters Ø=0.75, K=0.14 M, and those for ^{60}Co were calculated according to the methodology proposed by Hsiao and Stewart (2008)[26] with the parameters Ø=0.52, K=0.21 M. The estimated DSB inductions were in good agreement with the measured data.

Figure 2 represents the survival curves estimated by Eq. (5) with α and β coefficients derived by combining the RMF and LQ models. The model-derived curves were compared with the experimental survival data of Chinese hamster V79 cells exposed to ^{60}Co in the presence of various DMSO concentrations (0-1 M)[8]. The model-derived survival curves showed good agreement with the experimental data at smaller concentrations (0.025-0.5M), but had larger deviations at larger concentrations (0.5-1 M). Both α and β coefficients were decreased as the concentration of DMSO increased. However, larger deviations at larger concentrations suggested that the coefficients may be not correctly estimated or some mechanisms are not included in the RMF model.

To consider the possible effects due to DSB yields, the experimental DSB yields were used to derive the model-derived survival curves. Figure 3 shows the survival curves for Chinese hamster cell line V79-753B exposed to 200 kV X-rays[20] under hypoxia with and without DMSO (2 M). The experimental DSB yield was 16.56 per cell per Gy (no DMSO), and 13.42 per cell per Gy with 2 M DMSO[20]. It showed that the RMF model-derived survival curves could be well approximated with the experimental results. For high-LET helium particles, the MCDS-derived DSB yields were 144.8 per cell per Gy (no DMSO) drops to 101.2 per cell per Gy due to the protection effect of 0.5 M DMSO. The model-derived curve also agreed well with the experimental results[9,21] (Fig 4).

Finally, Figure 5 shows the trend of the RMF model-derived α and β coefficients of ^{60}Co and helium particles (LET = 120 keV/μm) as a function of DMSO concentration. It can be seen that DMSO plays a vital role in both low and high-LET radiations, especially in concentrations below 0.5 M. The α coefficient for ^{60}Co irradiation ranged from 0.09 Gy^{-1} to 0.03 Gy^{-1} as the DMSO concentration increased to 2 M, while the β coefficient ranged from 0.05 Gy^{-2} to 0.006 Gy^{-2}.

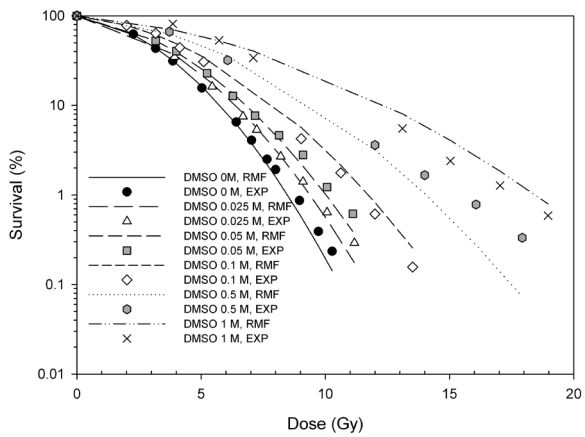

Figure 2. Comparison of RMF model-derived survival curves of X-ray as a function of dose with experimental data. The experimental curves of Chinese hamster V79 cells exposed to 250 kV X-rays are treated with DMSO concentration 0-1 M (Chapman et al. 1979). The parameters for simulating the radiosensitivity parameters α and β by RMF model follow: f = 0.999, θ=0.00077 and κ=0.000043.

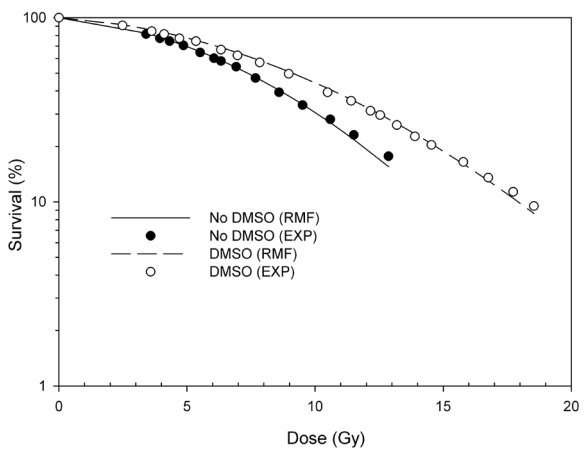

Figure 3. Comparison of RMF model-derived survival curves of X-ray as a function of dose with hypoxia experimental data. The cells exposed to 200 kV X-ray (Sapora et al. 1991) in the condition of hypoxia are treated with and without DMSO (2 M). The parameters for simulating the α and β coefficients by RMF model follow: f = 0.999, θ=0.00050 and κ=0.00007.

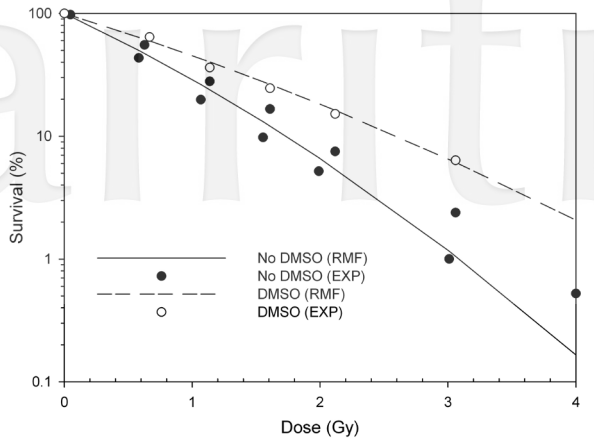

Figure 4. Comparison of RMF model-derived survival curves of cells exposed to helium particles (LET =120 keV/μm) as a function of dose with experimental data. The experimental curves of V79-4 cells are treated with/without 0.5 M DMSO (Jenner et al. 1993, deLara et al.1995). The RMF model-derived survival curves are simulated using the parameters: f= 0.994, θ=0.00011 and κ=0.000012.

For high-LET helium particles, the range of α coefficient was 1.13 Gy^{-1} to 0.67 Gy^{-1} and that of β coefficient was 0.13 Gy^{-2} to 0.05 Gy^{-2}. Both α and β were affected by DMSO, and the highest drop rate occurred in the range of 0-0.2 M DMSO. It appeared that radioprotection by DMSO increased dramatically at DMSO concentrations from 0-0.2 M, but approached a constant as the concentration was increased up to 0.5 M. The saturation of radioprotection by DMSO was more obvious for low-LET radiation; that is, α and β coefficients reached a constant at a smaller DMSO concentration, such as 0.4 M.

Discussion

Figure 1 shows the comparison of MCDS-derived relative DSB yields caused by ^{60}Co and helium particles (^{238}Pu) as a function of DMSO concentration. The relative MCDS-derived DSB yields agreed well with the experimental results[9]. However, the DSB yields in the presence of DMSO were affected by the MCDS parameters Ø and K chosen by the user. In this study, the parameters Ø and K were obtained by fitting the experimental DSB yields[25]. Moreover, the DSB obtained by MCDS were shown to be substantially larger than the experimental yields[27-32]. For example, the DSB induced by low-LET X-rays were reported to be 8.4 $Gy^{-1}Gbp^{-1}$ by MCDS[26], while the experimental DSB was 6.1 $Gy^{-1}Gbp^{-1}$ [31]. The DSB induced by high-LET 3-7 MeV helium particles were reported experimentally in the range of 10-12 DSB Gbp^{-1} Gy^{-1}, while the DSB simulated by MCDS were in the range of 20-24 DSB $Gy^{-1}Gbp^{-1}$ [15]. Regardless, the RMF model-derived values of α and β were not overly sensitive to the absolute DSB yield because the formula for α and β involved other parameters θ and κ[15]. In our analysis, for a better approximation

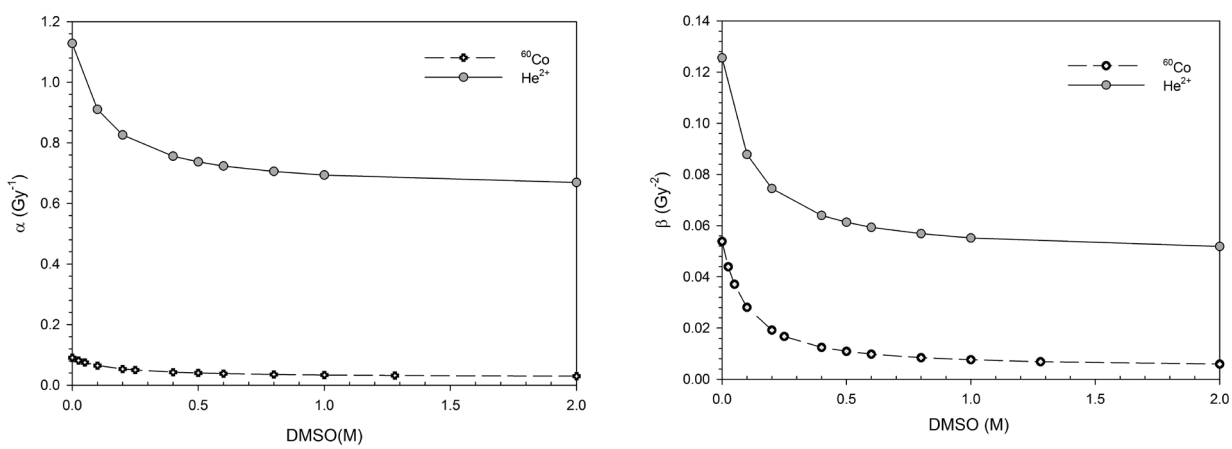

Figure 5. (A) The trend of RMF model-derived α and (B) β values of 60Co and helium particles (LET =120 keV/μm) as a function of DMSO concentration. For ^{60}Co, the set of parameters are used: f = 0.999, θ=0.00077 and κ=0.000043. For helium particles, the parameters, f = 0.994, θ=0.00011 and κ=0.000012 are used to obtain the α and β curves.

of the experiment data, the parameters θ and κ were subjected to change for different types of radiation. Because κ represents the fraction of initial DSB that undergoes pairwise damage interaction, we speculate κ might decrease to zero for higher-LET radiation due to the dominance of the one-track mechanism.

As shown in Figure 2, the survival ratio estimated by the RMF models for cells exposed to X-rays in the presence of the concentration 0.025-0.5 M DMSO agreed with the experimental curves, indicating that the RMF model may accurately delineate the α and β values under the influence of DMSO. However, for larger concentrations (0.5-1 M), the larger deviation showed the estimation of relative DSB yields may not be accurate. In fact, experimental results showed that the DSB yields with DMSO 0.2-0.6 M were similar, and started to decrease at higher concentrations (> 0.6 M)[9]. The concentration of DMSO which resulted in 50% of relative DSB yield was experimentally estimated to be 0.1±0.05 M, while MCDS predicted that the range lies in 0.3-0.4 M. It seems that MCDS fails to reflect the subtle change in the DSB yields affected by larger concentrations of DMSO.

Figures 3 and 4 show that the survival ratio in hypoxia and higher LET helium particles can be approximated well by the RMF and LQ models, respectively. Recently, a newer version of MCDS[33] has provided the capability of simulating DSB yields for cells irradiated with ions up to and including ^{56}Fe in the environments of various oxygen and DMSO concentrations. This raises the possibility of predicting the survival curves for cells irradiated with heavy ions in radiotherapy for hypoxic and aerobic conditions by RMF models.

The trend of α and β coefficient estimations by the RMF model for cells irradiated with ^{60}Co and helium particles with the DMSO concentration (0-2 M) are shown in Figure 5. The range of α coefficient for ^{60}Co irradiation was 0.09 Gy^{-1} to 0.03 Gy^{-1}, and was somehow different from the reported value 0.14 Gy^{-1} to 0.06 Gy^{-1} [8] for the case of X-rays. The range of β coefficient was from 0.05 Gy^{-2} to 0.006 Gy^{-2}, and also shows some deviation from the reported values of 0.04 Gy^{-2} to 0.01 Gy^{-2} [8]. For high-LET helium particles, α and β coefficients have been reported as 1.52 Gy^{-1} (α) and zero (β)[15] in the case of no DMSO treatment, with the ratios $\alpha_{2M}/\alpha_{control}$ (~0.4) and $\beta_{2M}/\beta_{control}$ (~0.5)[8] when comparing α and β values in the presence of 2 M DMSO to those without DMSO. The RMF model-derived range of α coefficient was 1.13 Gy^{-1} to 0.67 Gy^{-1}, and that of β coefficient was 0.13 Gy^{-2} to 0.05 Gy^{-2}. The RMF model-derived ratios were $\alpha_{2M}/\alpha_{control}$ (~0.6) and $\beta_{2M}/\beta_{control}$ (~0.4), respectively. Although information regarding measured α and β values across DMSO concentrations of 0-2M is scarce, the ratios $\alpha_{2M}/\alpha_{control}$ and $\beta_{2M}/\beta_{control}$ indicate that DMSO provides significant protection for high-LET radiations.

For ^{60}Co irradiation, it seemed that the RMF model captured the trend of the α coefficient value dropping to 1/3 of original during the 0-2 M DMSO treatment. The highest drop rate for both α and β coefficients seemed to occur in the range of 0-0.2 M DMSO, but slowed as the concentration rose over a specific concentration (~0.5 M). Similar trends in α and β coefficients have been reported at 0-0.2 M DMSO[8]. However, the RMF model-derived β coefficient apparently dropped faster than the β coefficient estimated from measured data, indicating the possible mechanisms of DMSO for β coefficient estimations were not included in RMF model. The saturation of radioprotection by DMSO was more obvious for low-LET radiation than higher-LET radiation, suggesting that in low-LET radiation, DMSO can scavenge most DNA damage by an indirect mechanism with smaller concentrations. This observation suggests that the degree of complexity of DSB damage scavenged by DMSO is different between the one at the concentration 0-0.2 M and the one at the concentrations above 0.5 M. Most likely, the DNA damage scavenged by DMSO at lower concentrations can be classified as simple damages, and those scavenged at the concentration above 0.5 M belong to complex damages[5,6]. Also, about 67-85% of DNA damage induced by X-rays and 35-68% of damages by helium particles are repaired by fast-rejoining kinetics[34]; these damages may be considered less difficult to repair and can thus be classed as simple damage. Although the portion of complex damage increased as LET increased,

the repair rate for DNA damage was smaller as the degree of complexity of DNA damage increased[7]. We speculate the increase in the portion of complex damage was the reason that the efficiency of cell killing increased. Alternatively, the degree of complexity of simple damages increased as LET increased, and this may result in misrepair or/and reproductive cell death.

The radioprotection by DMSO mainly comes from indirect actions, since DMSO is a radical scavenger and protects the cell from DNA damage caused by the OH radical[8-10,15,20,35]. The contribution by indirect action to cell killing is decreased as LET is increased, and eventually indirect actions accounts for around 30% of cell killing for very high LET radiation (above 1000 keV/μm)[35]. Hirayama et al. (2009)[35] showed the OH radical caused by higher-LET radiation is scavenged more difficultly by DMSO. The survival fractions estimated by the RMF model showed that 0.1 M DMSO can provide 31% of degree of protection (DP) for γ-ray irradiation, and 0.5 M DMSO can provide 32% DP for LET=120 keV/μm helium particle irradiation. Compared with the experimental data, Hirayama et al. (2009) reported that the 0.1 M DMSO provided 37% DP for X-ray irradiation. For helium particle irradiation, the data of deLara et al. (1995)[9] showed 26% DP with 0.5 M DMSO. This deviation may be caused by underestimation of DSB yields by MCDS or some other mechanisms involved in cell killing. Nevertheless, the RMF model provides more information and systematic calculations regarding radioprotective effects of DMSO in DNA damage yields and cell survival.

Conclusion

In this analysis of DMSO for survival datasets of cells irradiated with X-rays, ^{60}Co and high-LET helium particles in aerobic and hypoxic conditions showed that RMF model-derived survival curves generally agreed with the experimental data in the presence of DMSO. The radioprotection by DMSO for ^{60}Co and high-LET helium particles increased dramatically at DMSO concentrations of 0-0.2 M, but more slowly as the concentration increased to 0.5 M before reaching a plateau. Concentration-dependent protection by DMSO may also apply to exposure to other heavy ions such as carbon and neon ions. Further studies combining biological models and radiation treatments can provide more information for patient-specific biological parameters, and can better determine and quantify the treatment plans involving heavy ions or hypoxic conditions.

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Original Article

以電腦演算法估計二甲基亞碸（DMSO）用於放射治療之影響

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研究報告指出在細胞受到輻射線傷害時，二甲基亞碸（DMSO）可有效保護細胞，因此也被應用於各式的放射治療。本篇主要是以電腦演算法估計二甲基亞碸對受到輻射線損傷的細胞的保護作用，以俾用於放射治療時之參考。RMF模型已建立出DNA雙股斷裂和細胞存活率的關係。根據RMF模型，利用非線性迴歸法從實驗數據得出RMF model中所須之參數，並以此參數和隨著DMSO濃度改變而改變的DNA雙股斷裂量，可計算出線性平方模型（LQ model）的參數α和β，從而得出細胞存活率之理論值。首先我們驗證在^{60}Co和氦離子照射下，電腦模擬得出之DNA雙股斷裂量和實驗結果近似。進一步，我們藉由RMF model和LQ model得出細胞存活率的理論值並和實驗的細胞存活率相比較，顯示在X光及^{60}Co和氦離子的照射下，理論值和實驗結果近似。參數α和β的分析結果也顯示，在DMSO濃度0-0.2 M之間的輻射線保護會急遽上升，但到0.5M附近則趨緩。在^{60}Co和氦離子輻射的分析中，都顯示這種和DMSO濃度有關的保護效應。這個方法也可用於計算DMSO對其他離子如碳離子和氖離子輻射的保護作用。

關鍵詞：二甲基亞碸、DNA雙股斷裂、細胞存活率、放射治療

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