Radiosensitivity and relative biological effectiveness based on a generalized target model

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ABSTRACT

By considering both cellular repair effects and indirect effects of radiation, we have generalized the traditional target model, and made it have a linear–quadratic–linear characteristic. To assess the repair capacity–dependent radiosensitivity and relative biological effectiveness (RBE), the generalized target model was used to fit the survival of human normal embryonic lung fibroblast MRC-5 cells in the G0 and G1 phases after various types of radiations. The fitting results indicate that the generalized target model works well in the dose ranges considered. The resulting calculations qualitatively show that the parameter ratio (α/V) in the model could represent the cellular repair capacity. In particular, the significant linear correlations between radiosensitivity/RBE and cellular repair capacity are observed for different slopes of the linear regression curves. These results show that the radiosensitivity and RBE depend on the cellular repair capacity and can be regulated by linear energy transfer. These analyses suggest that the ratio α/V in the generalized target model can also be used for radiation damage assessment in radiotherapy.

KEYWORDS: generalized target model, linear–quadratic–linear characteristic, repair capacity, radiosensitivity, RBE

INTRODUCTION

Ionizing radiation has often been described as a double-edged sword for human health [1]: it can control cancer in radiotherapy, yet it can also induce the potential detrimental health effects associated with secondary cancers as side effects. Hence, controlling tumor cells and minimizing radiation effects on nearby normal tissues are two major goals of radiotherapy. In pursuit of these objectives, cellular radiosensitivity can provide important insights into identifying the different responses of tumor and normal tissues in radiotherapy, as well as screening individuals (like astronauts) to elect suitable candidates for long-term working in a space radiation environment [2].

Charged-particle therapy has many advantages over the common methodology due to the characteristics of their particular physical and radiobiological properties, including giving rise to a sharp maximum in ionization near the end of the range (Bragg peak) and enhanced relative biology effectiveness (RBE) [3]. RBE is defined as the ratio of the dose of a reference radiation (usually assumed to be X-rays or γ-rays) to the radiation under study that will produce an equal level of effect for a given experimental observation [4]. In fact, the complex RBE depends not only on the dose levels, but also on other factors, including the radiation qualities (such as the dose rate, the type and linear energy transfer (LET) of the radiation particles, etc.) and the biological characteristics (such as species, stage of development, and the endpoint under consideration, etc.) [5].

An accurate RBE is critical for a given treatment plan in radiotherapy [6], determining the radiation weighting factor in the radiological protection [7], and estimating the radiation quality factor for space radiation risk assessment in interplanetary missions [8]. In addition, RBE can also be used to reflect the radiosensitivity of lymphoid and germinal tissues, which is very different from inherent cellular radiosensitivity [6]. However, as distinct from the radiosensitivity, RBE is likely to be similar for the various epithelial and mesenchymal tissues in the treatment volume; the differences between the particular RBE values would not clinically significant [6]. Based on these considerations, it is very important to determine both RBE and individual radiosensitivity as accurately as possible in radiotherapy.
In addition, it will be impossible to measure all RBE values for every clinically relevant set of conditions with respect to beam energies and dose levels for a given treatment plan [9]. The biophysical models play a crucial role in understanding the mechanism of the interaction between radiation and organism [10]. Many radiobiological models have been proposed to explain the survival fraction and estimate the RBE in clinical applications [11–13]. The current models used in Heidelberg (Germany), Chiba or Hyogo (Japan) are mainly based on the linear–quadratic (LQ) model [14], with the cell survival (S):

\[ S = \exp(-\alpha D - \beta D^2), \]

where \( D \) is the dose (Gy), and the coefficients \( \alpha \) and \( \beta \) are the radiosensitivity parameters [15]. Generally, the LQ model is rather accurate for doses per fraction employed in the conventional treatment schedules for low-LET radiotherapy [16], but might be less accurate in reproducing the shape of the survival curve at high doses, where it becomes almost a straight line in the semilogarithmic plot [17]. It indicates that survival curves in the high dose ranges can be better described by a linear–quadratic–linear (LQL) model [10].

Indeed, various LQL models of survival curves have been proposed with the aim of accurately describing the cell-killing effects at high doses [18]. For example, Dale et al. [19] used a modified version of the LQ model with a Lea–Catcheside factor to address the transition of the dose–response curve from the shoulder to an exponential shape at high doses. A similar modified form of the LQ model was proposed by Guerrero and Li [20]. Furthermore, the work of Carlone et al. [21] indicates that these modifications to the LQ model do have a mechanistic justification, i.e. LQL can be derived using the compartmental model, which is similar to lethal–potentially lethal (LPL) [22], repair–misrepair (RMR) [23] and GLOBLE models [24, 25] based on the kinetic viewpoints. In addition, Park et al. [26] proposed a universal survival curve (USC) model by introducing the piecewise-defined function with a transitional discontinuity. Similarly, Astrahon [27] combined the LQ model and the target model to interpret the data in two dose regions, respectively. Considering the fact that the amount of sublethal damage is reduced at high doses (because sublethal damage is converted to lethal damage), Wang et al. [28, 29] proposed a generalized LQ (gLQ) model, a logical extension of the original LQ model. McKenna and Ahmad [18] investigated radiation cell damage at high doses by fitting a variety of formulas to the survival data of 14 cell lines and found that no model is clearly superior for all cell lines.

Recently, we proposed a generalized target model by considering the cellular repair effects together with indirect effects of radiation [30]. Analysis shows that this model can also exhibit LQL features in both the low-dose and high-dose regions, respectively. Preliminary results from reanalysis of survival data in vitro suggested that the parameter ratio \( a/V \) (Gy) in this model could be used as an indicator to effectively predict cellular repair capacity and radiosensitivity, etc [30]. In addition, we had demonstrated that this indicator was superior to the ratio \( \alpha/\beta \) in the LQ model, which tended to overestimate the cellular repair capacity for high LET radiation [30–32].

In this paper, the generalized target model is applied to the experimental data obtained in the G0 and G1 phases of human normal embryonic lung fibroblast MRC-5 cells with different irradiation conditions. It will be demonstrated that the indicator in the generalized target model can be used to estimate the cellular repair capacity. In addition, the dependences of radiosensitivity and RBE on the repair capacity are also explored to clarify the open questions in radiobiology and radiotherapy.

**MATERIALS AND METHODS**

**Summary of the generalized target model**

The generalized target model [30] is a cell survival model, which specially makes the distinction among three categories of events associated with cell radiation. In general, when a cell is subject to irradiation, ‘the irradiated cell will be affected by radiation’ is a deterministic event, while ‘the target in a cell may be hit by radiation particles’ is a stochastic event. However, ‘the cellular response after its target being hit’ should be regarded as a fuzzy event due to the complicated cellular repair effects and indirect effects of radiation.

Thus, the relationship between the hit probability \( p_0 \) and survival fraction \( S \) can be extended by means of the negation operator in the fuzzy mathematics [33],

\[ S = (1 - p_0^a)^{1/a}, \]

where \( a \) is the parameter of negation (\( a > 0 \)). Different values of parameter \( a \) can represent different non-linear molecular lesions and inactivation. Even more specifically, when \( a = 1 \), it means that one hit necessarily lead to one inactivation; \( a > 1 \) means that one hit will lead to less than one inactivation, for the cellular repair mechanisms are likely at work strongly; \( a < 1 \) implies that one hit will lead to more than one inactivation, because the indirect effects, which are caused by the damage of the radiation-induced free-radical attack to the key target in the cell, are likely to become dominant.

We assume that there is only one ‘effective target’ in a cell, and one hit by radiation on the ‘effective target’ could cause varying degrees of cell death by adjusting the parameter \( a \), which depend on the cellular repair abilities and indirect effects, etc. Then, the survival fraction of cells after a dose \( D \) (Gy) is given by

\[ S = [1 - (1 - e^{-1D})^{a/V}]^{1/a}, \]

where the parameter \( V \) (Gy\(^{-1}\)) denotes the proportionality constant to the number of damage per gray, which also reflects the geometrical characteristics of the given cell line and irradiation arrangement. In the previous study, we had proven that Eq. (3) could be naturally reduced to the LQ model and the multitarget model asymptote at low-dose and high-dose ranges, respectively. Moreover, we inferred that the parameters ratio \( a/V \) (Gy) in this model could be an effective indicator to reflect the cellular repair capacity. In addition, we also found that this indicator was better than the ratio \( \alpha/\beta \) (Gy) in the LQ model.

**Data and model fitting**

In this work, the survival fraction and the kinetics of 53BP1 foci for the irradiated G0 and G1 phases of MRC-5 cells [34] were used to investigate the dependences of radiosensitivity and RBE on the repair capacity within the frame of the generalized target model. Table 1 lists the data sources used and the detailed irradiation
parameters, including the particle types and LET (keV/μm), etc. The G1 phase of MRC-5 cells with more vigorous metabolism is more sensitive to various types of radiation than the G0 phase, since the G0 cells stay quiescent, and this can result in less DNA damage than that incurred in G1 cells under the same irradiation conditions [34]. Statistical analysis, regression analysis, and the curve fitting were conducted using ORIGIN 8.0 (OriginLab). The models were fitted by the method of least squares to the experimental data. The statistical values of the adjusted squared correlation coefficient (Adj. $R^2$) were used to evaluate the goodness-of-fit. When evaluating the quality of a fit for a dataset, the weighted sum of squared residuals (also known as $\chi^2$) was calculated. The parameters of the models were expressed in arithmetic mean ± standard error (S.E.) by regression analysis. The virtual results from 5000 simulated experiments were generated using Monte Carlo methods to estimate the intergroup differences based on the hypothesis that the errors were normally distributed (under R version 2.15.3). The change was considered statistically significant if the probability ($P$) was less than 0.05.

### RESULTS AND DISCUSSION

#### Comparison with experiments

The results of fitting the generalized target model and LQ model to the cell survival data for various types of radiation in the G0 and G1 phases of MRC-5 cells are shown in Fig. 1. The Adj. $R^2$ showed that both the models could give significant goodness-of-fits to experimental data (Adj. $R^2 > 0.977, P < 0.05$) (Table 1). Furthermore, the $\chi^2$/df values of two fittings were compared and no significant differences were observed (data not shown), indicating that the fit quality of the generalized target model was as good as that of the LQ model for the whole experimental dataset. This was no surprise, because the present generalized target model can reduce to the LQ for the low-dose region, while the LQ model can perfectly explain the survival curves in the dose range examined in this study.

As demonstrated by numerous studies and clinical applications, the LQ model has achieved great success in helping radiation therapy researchers and clinicians to investigate the cell killing by irradiation in vitro, interpret clinical outcome data in vivo, design new fractionation regimens, and even compare various types of radiation [15, 35, 36]. However, the fundamental debate—about whether the LQ model is appropriate for modeling the effects of a high dose in a single fraction of stereotactic body radiation therapy (SBRT)—has continued [18, 36–38]. Some scholars believe that the LQ model overestimates the cell killing (underestimates the fraction of cells surviving) by more than one order of magnitude in the dose region above 10 Gy [16, 29]. The measurements of cell survival with a dose of up to ~12 Gy are reasonably available, but in SBRT, knowledge of the cell killing response to 20 Gy or higher may be needed; hence, a precise extrapolation model is needed. In general, the LQ models can predict the survival fraction well in the high-dose region, while the present generalized target model has the LQ feature the low-dose and high-dose regions [30].

In order to select a more appropriate model for the high-dose region, the fitting qualities of the generalized target model and other LQ models, including the two- and three-parameters models [18], etc., could be further compared. The possible criteria for selecting the candidate model include: (i) it is able to make reasonable predictions of cell survival at extrapolated doses; (ii) it should be simple, with as few parameters as possible; (iii) it should be a physically plausible

### Table 1. The model parameters and adjusted squared correlation coefficients (Adj. $R^2$) obtained by fitting the experimental data from the published reference with the generalized target model and LQ model

| Cell types (cell cycle) | Particle types | Energy (MeV/u) | LET (keV/μm) | Generalized target model $V$, $a$, Adj. $R^2$ | LQ model $\alpha$, $\beta$, Adj. $R^2$ |
|------------------------|---------------|---------------|--------------|---------------------------------|---------------------------------|
| MRC-5 (G0) X-rays      | Carbon        | 290           | 13.3         | $3.025 \pm 0.196$, $3.528 \pm 0.184$, 0.986 | $0.102 \pm 0.106$, $0.328 \pm 0.072$, 0.994 |
|                        | Neon          | 400           | 30.2         | $3.259 \pm 0.257$, $3.410 \pm 0.179$, 0.988 | $0.091 \pm 0.067$, $0.410 \pm 0.049$, 0.998 |
|                        | Silicon       | 490           | 54.1         | $4.132 \pm 0.549$, $3.352 \pm 0.093$, 0.997 | $0.401 \pm 0.069$, $0.407 \pm 0.061$, 0.998 |
|                        | Argon         | 500           | 88.6         | $4.444 \pm 0.406$, $3.547 \pm 0.050$, 0.999 | $0.476 \pm 0.067$, $0.358 \pm 0.058$, 0.998 |
|                        | Iron          | 500           | 184.9        | $4.792 \pm 0.136$, $4.135 \pm 0.358$, 0.977 | $-0.139 \pm 0.051$, $0.906 \pm 0.058$, 0.999 |
| MRC-5 (G1) X-rays      | Carbon        | 290           | 13.3         | $3.733 \pm 0.284$, $3.139 \pm 0.093$, 0.997 | $0.461 \pm 0.097$, $0.328 \pm 0.072$, 0.998 |
|                        | Neon          | 400           | 30.2         | $3.948 \pm 0.442$, $3.171 \pm 0.160$, 0.991 | $0.163 \pm 0.101$, $0.410 \pm 0.083$, 0.999 |
|                        | Silicon       | 490           | 54.1         | $2.257 \pm 0.525$, $1.595 \pm 0.027$, 0.998 | $0.843 \pm 0.043$, $0.407 \pm 0.039$, 0.999 |
|                        | Argon         | 500           | 88.6         | $1.366 \pm 0.047$, $1.089 \pm 0.028$, 0.995 | $1.170 \pm 0.133$, $0.358 \pm 0.104$, 0.993 |
|                        | Iron          | 500           | 184.9        | $5.951 \pm 0.107$, $3.958 \pm 0.244$, 0.990 | $0.070 \pm 0.113$, $0.906 \pm 0.153$, 0.997 |

The values represent the arithmetic mean ± standard error.
theory associated with the formula, and will allow a check of the formula by comparing one’s intuition with how the parameters of the model change with irradiation conditions; (iv) finally, the formula should also serve to guide physical intuition when new avenues are explored.

As shown in Fig. 1, there is a decrease for the fit quality for some kinds of radiations, especially in the high-dose range. This is primarily due to the existence of some simplifying assumptions made in the generalized target model. For example, only one hit on ‘effective target’ has been considered. However, for the high-dose region of high-LET radiation, there are intertrack interactions between different particles, which were ignored in the present generalized target model. That is, the multi-hit events occurring in the effective target of cells should be considered in the further work. Although these small deviations of fitting have emerged in the high-dose regions, the Adj. $R^2$ values were nearly equal to 1 (Table 1), which suggests that the generalized target model worked well with these experimental data. Hence, we further investigated the application of the present model in these datasets and conducted the subsequent analysis and discussion.

**Validation for cellular repair capacity**

Based on the regression analysis, the parameters $V$ and $a$ in the generalized target model could be obtained for different irradiation conditions (Table 1). Figure 2 showed the ratios $a/V$ calculated by the present generalized target model, indicating that the ratios $a/V$ in the G0 phase of MRC-5 cells were significant higher than those in the G1 phase in various irradiation conditions ($P < 0.05$). However, for the Argon radiation ($LET = 88.6$ keV/$\mu$m), no significant difference was observed in the ratios $a/V$ between the G0 and G1 phases ($P > 0.05$). Because different radiosensitivities of G0 and G1 cells
in response to various radiations were reported in the previous study [34], we inferred that the ratio $a/V$ can represent the endo- 
cogenic radiosensitivity: bigger $a/V$ means more resistive to radiation; 
smaller $a/V$ means more sensitive to radiation. Details of the relation-
ship between the ratio $a/V$ and radiosensitivity will be displayed in 
the subsequent analysis and discussion.

Furthermore, according to the previous study, the ratios $a/V$ can 
also be regard as the cellular repair capacity. As shown in Fig. 3, a 
significant linear correlation was observed between the ratio $a/V$ and 
the decrease in S3BP1 foci in MRC-5 cells in the 24 h following 
various types of 0.5 Gy radiation, and the Adj. $R^2$ were 0.794 and 
0.923 for MRC-5 cells in the G0 and G1 phases, respectively 
($P < 0.05$). The S3BP1 foci are a biomarker of DNA damage, and 
are associated with an early participant in the cellular response to 
DNA double-strand breaks [39]. Also, the decrease in S3BP1 foci in 
the 24 h following irradiation is usually used to reflect DNA repair 
capacity [34]. The above linear correlations indicated that the ratio 
$a/V$ could reflect the cellular repair capacity, which is consistent 
with the conclusion from the experimental observations on various 
normal and mutant cell lines being irradiated [30]. Even though 
non-homologous end-joining (NHEJ) pathway functions in both 
G0 and G1 cells, the underlying enhanced repair capacity could be 
observed in G0 cells (Fig. 2), which is in agreement with the find-
ings from Ding et al. [34]. The transcription-coupled repair is active 
during cellular quiescence, which leads to the difference in cellular 
repair capacity between G0 and G1 cells [34].

It is well known that many researchers use the ratio $\alpha/\beta$ in the 
LQ model to represent the cellular repair capacity [31]. However, 
as reviewed in the introduction, the indicator $\alpha/\beta$ in the LQ model 
overestimates the cellular repair capacity for high-dose radiation 
[40], due to the serve limitations in the high-dose ranges in the LQ 
model [20, 26–29]. Wang and his coauthors [28, 29] suggested that 
the problems with the LQ model were caused by ignoring the fact 
that at high doses, the amount of sublethal damage is reduced 
because sublethal damage is converted to lethal damage owing to 
the intensified radiation. Also, the parallel repair process of sublethal 
damage is also considered to reduce the number of sublethal lesions. 
That is, both justifications will reduce the values of the $\beta$ term, 
which lead to the higher $\alpha/\beta$ obtained in the results. Therefore, 
in agreement with the earlier conclusion [30], the ratio $a/V$ obtained 
in the present generalized target model is considered a robust and 
effective indicator for characterizing the cellular repair capacity.

**Cellular repair capacity–dependent radiosensitivity**

The $D_{37}$ (dose required for 37% survival), just like the $D_{10}$, is 
regarded as a classic indicator for radiosensitivity [41]. In the pre-
sent model, $D_{37}$ could be obtained by the following equation:

$$D_{37} = - \ln\left(1 - \left(1 - S^a\right)^{1/\alpha}\right)/V,$$

where $S$ is equal to 0.37. Figure 4A shows the results of the $D_{37}$ in 
the G0 and G1 phases of MRC-5 cells for various types of radiation. 
By comparing with G0 phase of MRC-5 cells, it could be found that 
$D_{37}$ had a significant decrease in the G1 phase ($P < 0.05$), which 
exhibits a similar change trend with the ratio $a/V$.

The above results may indicate that the determinant of cellular 
 radiosensitivity is not the contents of the cellular DNA. Because G0 
and G1 cells have the same DNA [34], the difference in the radio-
sensitivity in the G0 and G1 phases ($P < 0.05$) may not be 
explained by differences in the DNA contents of individual cells, 
although the cells with a greater DNA content tended to be more 
resistant. This point of view is also supported by the results of 
Suzuki et al. [32], where no strong correlation was found between 
the cellular radiosensitivity and the physical parameters of individual 
cell lines, such as the chromosome number or the area of the cell 
nucleus, in the case of either X-rays or carbon-ion beams.

However, it can be seen that, as shown in Fig. 4B, significant lin-
ear correlations were observed between the ratio $a/V$ and $D_{37}$ for 
the G0 and G1 phases of MRC-5 cells ($P < 0.05$), which indicated 
that the ratio $a/V$ can really reflect the radiosensitivity. In addition, 
the cell-cycle–dependent $a/V$ and $D_{37}$ can also be found in Fig. 4B, 
indicating that the radiosensitivity of a particular cell cycle was 
dominated by the cellular repair capacity for radiation damage 
regardless of radiation type.

So far, from the experimental point of view, a correlation 
between cellular radiosensitivity and repair capacity is still debated 
[32]. Some authors report that there is a good correlation between 
cell killing effects and non-repaired DNA double-strand breaks 
(DSBs) for nine kinds of cell lines with different repair capacities 
for DSBs [42–44]; however, other reports have suggested that there 
is no correlation between the cell killing effect and the repair cap-
acity for DNA DSBs [45–47]. It is not clear whether there is an 
association between cell killing and the repair of DNA DSBs at 
present [32]. In addition, from the theoretical point of view, the 
classical indicator of the repair capacity, like $\alpha/\beta$ in LQ model, 
cannot maintain the robustness under different radiation conditions 
[28, 29, 32]. However, based on the generalized target model, it can 
be concluded that the cellular radiosensitivity is determined by the 
cellular repair capacity. Thus, bigger cellular repair capacity will lead

![Fig. 3. Linear correlation between the ratio $a/V$ (unit: Gy) 
and the decrease of S3BP1 foci in 24 h after irradiation. 
The corresponding experimental data (taken from the work of 
Ding and his collaborators [34]) is obtained in MRC-5 cells 
in the G0 and G1 phases after different types of radiations.](image-url)
to the stronger radioresistance, and smaller cellular repair capacity will result in stronger radiosensitivity.

The calculation results show that the radiosensitivity (the ratio $a/V$) for the G0 phase of MRC-5 cells had good correlation with that of the G1 cells (Fig. 5). This suggests that the factors that regulate cellular radiosensitivity are common for radiation damage caused by various types of radiation with different LET values, which is in agreement with previous research results [30]. In general, it is the combination of radiation quality (e.g., LET, etc.) and intrinsic characteristics (cellular repair capacity) that determines the cellular radiosensitivity.

**Cellular repair capacity–dependent RBE**

According to the calculation results for the $D_{37}$, the RBE at 37% survival for G0 and G1 cells exposed to various types of radiation could be depicted and the results are shown in Fig. 6A. Also, a significant linear correlation was observed between the two RBE values calculated by the generalized target model and by the LQ model (Fig. 6B). Furthermore, it was found that all the RBE values of particle radiation were significantly higher than 1 ($P < 0.05$) (Fig. 6A), demonstrating that the heavy ion particles have greater lethal effects than X-rays. Nevertheless, the RBE LET-dependence of G0 cells was similar to that of G1 cells, with the maximum at ~100 keV/$\mu$m (Fig. 6A). In addition, these data also showed that the RBE in the radioresistance (G0 phase) cells was higher than that in the radiosensitivity (G1 phase) cells.

Significant linear correlations were also found between RBE and the ratio $a/V$ for various types of radiation in G0 and G1 MRC-5 cells ($P < 0.05$) (Fig. 6C), indicating that RBE is also dependent upon the cellular repair capacity. Previous studies indicate that RBE is dependent on ion species, LET, and cell or tissue type, etc. [14, 48]. All these physical and biological factors can ultimately affect the cell repair, through a variety of molecule mechanisms, including NHEJ, homologous recombination, microhomology-mediated end-joining, and alternative non-homologous end-joining [49].

Moreover, the slopes of the linear regression curves are similar for G0 and G1 cells, and are significantly lower than those for V79, HSG, T1 and CHO-K1 cells [30]. Generally, the choice of the appropriate pathway is regulated by the following major factors: (i) the damage complexity and (ii) cell cycle phase [50]. By combining the slopes for the same cells at various stages of the cell cycle, we inferred that the slopes of the linear regression curves were dependent on the LET ranges used in the various radiation conditions. Similarly to radiosensitivity, the above results also indicated that RBE is probably determined by cellular repair capacity and regulated by the LET ranges.
CONCLUSION
In this study, by using the generalized target model, the significant goodness-of-fits were observed by fitting the survival fraction of G0 and G1 phases of MRC-5 cells under different irradiation conditions. Comparing the ratio $a/V$ in the model with the decrease of 53 BP1 foci in the experiments showed that the ratio $a/V$ could be used to estimate the cellular repair capacity, and hence could be regarded as an effective indicator in radiotherapy and even radiation risk assessment. In addition, significant linear correlations with different slopes of the linear regression curves were observed between radiosensitivity/mm RBE and cellular repair capacity. It can be inferred that common mechanisms may exist for radiosensitivity and RBE, which are determined by the cellular repair capacity and regulated by the LET ranges.

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CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

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Fig. 6. The RBE$_{37}$ in the G0 and G1 phases of MRC-5 cells after various types of radiations (A); comparison between the RBE$_{37}$ based on the generalized target model and that based on the LQ model (B); linear correlation between the ratio $a/V$ (unit: Gy) and the RBE$_{37}$ calculated by the generalized target model (C).
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