Statistical Analysis of the Physical Model of Hyper-radiosensitivity/Radioresistance in Irradiated Cells

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Abstract

This study investigates the hyper-radiosensitivity (HRS) and induced radioresistance (IRR) effects in cells exposed to low-dose radiation, focusing on identifying critical dose thresholds and exploring underlying molecular mechanisms. By analyzing cell survival data using a normal distribution-based mathematical model, we determined two key dose thresholds: D0, where repair mechanisms are activated, and D1, where repair and damage rates equilibrate. Our findings reveal that ATM (ataxia-telangiectasia mutated) and p53 proteins play central roles in modulating these thresholds, with wild-type p53 cells demonstrating faster repair initiation and mutant p53 cells exhibiting broader response curves. The results show that cellular outcomes depend on both genetic background and radiation dose, with potential implications for optimizing radiotherapy protocols and developing radioprotective strategies. This work provides a quantitative framework for understanding HRS and IRR phenomena and contributes to advancing personalized approaches in radiation medicine.

Full Text

Preamble

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Abstract

This study investigates hyper-radiosensitivity (HRS) and induced radioresistance (IRR) effects in cells exposed to low-dose radiation, focusing on identifying critical dose thresholds and exploring underlying molecular mechanisms. By analyzing cell survival data using a normal distribution-based mathematical model, we determined two key dose thresholds: D_0, where repair mechanisms are activated, and D_1, where repair and damage rates equilibrate. Our findings reveal that ATM (ataxia-telangiectasia mutated) and p53 proteins play central roles in modulating these thresholds, with wild-type p53 cells demonstrating faster repair initiation and mutant p53 cells exhibiting broader response curves. The results show that cellular outcomes depend on both genetic background and radiation dose, with potential implications for optimizing radiotherapy protocols and developing radioprotective strategies. This work provides a quantitative framework for understanding HRS and IRR phenomena and contributes to advancing personalized approaches in radiation medicine.

Keywords: Hyper-radiosensitivity · Induced radioresistance · Low-dose radiation · ATM protein · P53 protein · Cell repair mechanisms

Introduction

The application of nuclear technology has been instrumental across industry, agriculture, and scientific research, notably in areas such as industrial irradiation and diagnostic imaging. In most cases, people are primarily exposed to low-dose radiation, while high-dose radiation exposure is extremely rare. Early theoretical models generally described radiation-induced damage as following a linear or exponential dose-effect relationship, as illustrated in the high-dose range of Fig. 1 [Figure 1: see original paper]. However, due to limited experimental conditions, including imprecise techniques for cell dilution, counting, and inoculation, significant random errors were introduced. As a result, cell survival at radiation doses below 1 Gy could not be accurately observed, and the cell survival fraction in the sub-1 Gy range was mainly extrapolated from radiation biological effect data using Linear Quadratic (LQ) Models [1]. With advances in experimental techniques such as flow cytometry and microscopic localization, both the measurement accuracy and statistical reliability of cell survival fractions have significantly improved, facilitating more precise studies of cell survival under low-dose radiation conditions, as shown in the low-dose range of Fig. 1.

In 1963, Eriksson G conducted experiments on maize exposed to γ rays, finding that the mutation rate and mortality rate of maize pollen grains under low-dose

(< 0.5 Gy) radiation increased significantly compared with those under high-dose exposure. This discovery led him to propose the concept of low-dose hyper-radiosensitivity (HRS) response [3]. It has been suggested that HRS responses are associated with radiation doses below 0.3 Gy, while doses within the 0.3–0.6 Gy range induce increased radioresistance (IRR) [4, 5]. Jin later observed that high linear energy transfer (LET) radiation from ^{12}C ions also triggers HRS/IRR responses in the dose range between 0 and 2.5 Gy, with HRS appearing at doses below 0.75 Gy (shown in Fig. 2 [Figure 2: see original paper] [6]). Additionally, our study identified the HRS phenomenon in C. elegans, but occurring at a higher dose threshold below 20 Gy [7]. The HRS/IRR phenomenon has proven to be of great significance in the context of low-dose radiation protection for occupational staff and for normal tissue protection during radiotherapy [8].

Human hepatoma cells (SMMC-7721) were irradiated with ^{60}Co γ rays and 50 MeV/u ^{12}C ions, respectively. The HRS/IRR reaction curve observed in these cells was found to fit the model expressed in formula (1) [6]:

where 1( ) = exp (− 훾 denotes the survival fraction of hepatocellular carcinoma (HCC) cells; D is the absorbed dose in Gy; represents the direct cell death effect caused by a single dose of radiation, while corresponds to the cumulative lethal effects of radiation damage. The parameter is defined as follows:

훾 = 훾푟푒 /훾푟푒

where $\alpha\{res\}$ *is the slope derived from the LQ model;* $\alpha\{\text{sen}\}$ is the slope derived from the IR model; $D_1 - / 1$ represents the absorbed dose at the inflection point of the curve, in Gy. Experimental results indicate that the dose threshold for inducing HRS by ^{60}Co γ rays and ^{12}C ions is 0.33 Gy and 0.28 Gy, respectively.

The normal distribution is a key probability distribution widely used in mathematics, physics, engineering, and various statistical applications. HRS and IRR phenomena are generally considered as two distinct states: "repair uninitiated" and "repair initiated," representing different phases within the probability distribution of radiation-induced damage and repair processes. This paper proposes that the low-dose HRS/IRR phenomenon follows a normal distribution and seeks to establish a consistent morphological mathematical model for HRS/IRR curves by fitting extensive HRS/IRR data to this model.

Hypothesis and Analysis

The prevailing theory of the HRS phenomenon suggests a "cellular radar" mechanism that plays a crucial role in the repair of DNA double-strand breaks (DSBs) [9]. When radiation-induced DNA damage is below a certain threshold, this "cellular radar" does not detect the radiation damage, leaving the immune system inactive in the low-dose range. As a result, radiation appears more severe than estimated by the LQ model, a condition termed HRS. As the dose increases, the "cellular radar" begins to detect damage, activating the immune response and increasing the repair rate, leading to IRR characteristics in the survival curve.

To analyze HRS/IRR data in our research, we first proposed three hypotheses as follows: (1) In the absence of irradiation, cells remain in a stable, homeostatic state, characterized by the stability of DNA molecules, as well as the stability of biological signal molecules and associated proteins within each cell. (2) When cells are exposed to ionizing radiation, the damage extends beyond traditional radiation targets (DNA) to affect essential biological signaling molecules, resulting in structural changes and functional decline across multiple molecular types. (3) Following exposure to ionizing radiation, cells undergo two concurrent processes of damage and repair. When the cell damage rate exceeds the self-repair rate, the survival rate declines, and vice versa; when both rates are equal, the survival rate remains stable.

Based on these hypotheses, we speculate that the survival rate of cells in the low-dose range follows a normal distribution, denoted as $F_2(D)$, and referred to as the Damage-Repair Response (DRR). Specifically, the response variable follows a probability distribution characterized by a low-dose parameter D_0 and a scale parameter σ, with the probability distribution function defined as:

where D is the absorbed dose in Gy; D_0 is the initiation point of DNA DSB repair in Gy; characterizes the acute repair dispersion parameter of cells; and A is the normalized coefficient for the normal distribution.

When the dose is below D_0, the "cellular radar" does not detect radiation damage, making the damage rate the dominant factor. Based on the first and second hypotheses, radiation-induced damage to DNA molecules, biological signaling molecules, and associated proteins disrupts the original homeostatic state, resulting in the appearance of HRS. As the dose increases, the "cellular radar" detects the radiation damage and activates the repair mechanism at doses above D_0.

In line with previous research suggesting that radiation damage follows an exponential dose-response relationship, we speculate that cell survival fraction can be fitted by the sum of a normal function and an LQ function. The formula is:

$= 1 + 2 = - - 0$

where represents cell survival fraction.

We obtained experimental results on low-dose HRS in tumor cells and normal cells through literature review. Curve fitting was performed using MATLAB' s least squares method. After fitting, relevant parameters (D_0, σ, α, β, and A) were listed in Table 1 , and the correlation coefficients R^2 for all curve fitting were greater than 0.9. To identify the inflection points between the HRS and IRR regions, as well as from the IRR region to high-dose behavior (the D_1/D_2 values), we took the derivative of formula (4). When $d(F(D))/dD = 0$, the D_1/D_2 values were obtained, as summarized in Table 1.

To elucidate the characteristics of HRS/IRR, we selected T98G cells as a representative example. According to formula (4), the survival fraction is modeled as a combination of a normal distribution and an exponential function. The

components of $F_1(D)$, $F_2(D)$, and $F(D)$, along with experimental results from literature, are presented in Fig. 3 [Figure 3: see original paper].

As shown in Fig. 3, when T98G cells were irradiated with a dose less than D_0, the "cellular radar" does not detect radiation damage, resulting in a damage-dominant response and a decrease in survival fraction as dose increases. When the dose reaches D_0, the "cellular radar" detects radiation damage and initiates a cellular repair mechanism. It can be seen from Table 1 that $D_0 = 0.32$ Gy represents the minimum value of the $F_2(D)$ function in Fig. 3. For doses greater than D_0, based on the third hypothesis, the repair rate increases, though it remains lower than the damage rate, causing $F(D)$ to continue decreasing. When the dose reaches D_1, the repair rate equals the damage rate, representing a homeostatic point and the transition from HRS to IRR, as shown in Table 1 with $D_1 = 0.35$ Gy, the minimum value of the $F(D)$ function in Fig. 3. Thus, when $D < D_1$, T98G cell survival fraction exhibits HRS characteristics.

For doses above D_1, as shown in Fig. 3, the $F(D)$ value increases because the repair rate surpasses the damage rate, even though the damage rate continues to rise slowly as shown in $F_1(D)$. When the dose reaches D_2, the repair and damage rates are again balanced, as shown in $F(D)$. When $D_1 < D < D_2$, the $F(D)$ curve shows the characteristic of IRR. According to Table 1, $D_2 = 0.67$ Gy is the maximum value of $F(D)$ in Fig. 3, marking the inflection point from IRR to high-dose behavior. For doses exceeding D_2, the damage rate significantly exceeds the repair rate, with $F_1(D)$ becoming dominant and the repair rate in $F_2(D)$ being negligible.

To further investigate changes in HRS/IRR and the corresponding cellular regulating mechanisms, we analyzed key biological factors associated with DNA damage repair and morphological characteristics, namely p53 type and ATM levels. The activation level of ATM after irradiation is positively correlated with the inflection point of the normal distribution, while the type of p53 (wild-type or mutant) is related to σ values. The relationships among cell damage repair parameters, morphological characteristics, and normal distribution features are discussed below.

Discussion

In this study, we propose that formula (4) is applicable to analysis of all cell survival fractions and exhibits generalizability across various cell types. The implications of formula (4) are outlined as follows: (1) If a survival curve does not display HRS/IRR phenomena in the low-dose region, A is set to zero, rendering the survival curve exponential in form. This indicates the absence of HRS/IRR characteristics in such cells. (2) When HRS/IRR phenomena are present but relatively weak in the low-dose region, A takes a small value, and D_1/D_2 values cannot be obtained from formula (4). This scenario applies to cells like DU145 prostate cancer cells, HeLa cervical cancer cells, Be11 melanoma cells, and HGL21 glioma cells, which do not exhibit solutions for D_1/D_2 in Table 1,

indicating minimal HRS/IRR features. (3) For cells with pronounced HRS/IRR phenomena in the low-dose region, the A value is large, and D_1/D_2 values are definable. Cells such as HT29 colorectal cancer cells in Table 1 display clear HRS and IRR dose regions.

D_0 and D_1 Correlate with Cell Line Differentiation

Cell differentiation refers to the process by which unspecialized cells develop specialized functions and is categorized into poorly differentiated, moderately differentiated, and well-differentiated types. It is generally accepted that lower differentiation of tumor cells correlates with faster tumor growth and greater sensitivity to radiation damage. To assess the correlation between cell differentiation and D_0 and D_1, the differentiation status of tumor cells in Table 1 was investigated, with results shown in Table 2 . As seen in Table 2, poorly differentiated tumor cells have relatively smaller D_0 values compared to moderately or well-differentiated tumor cells, indicating higher sensitivity to radiation damage. Additionally, some poorly differentiated tumor cells lack D_1 values, implying that they do not meet the condition of $d(F(D))/dD = 0$, where the repair rate remains consistently lower than the damage rate. This suggests that the repair rate is insufficient, although repair mechanisms may initiate, causing cell survival to be primarily governed by the damage rate.

Contrary to this trend, the correlation between cell differentiation and sensitivity to radiation damage may be restricted by other factors. For instance, as observed in Table 2, although T98G glioma cells are poorly differentiated, they display high D_0 and D_1 values. This anomaly may be attributed to the presence of stem-like cells within these tumors, which possess self-renewal capability and exhibit resistance to radiotherapy [23].

The Correlation Between p53 Gene and σ

The p53 pathway is a complex cellular stress response network with multiple inputs and downstream effects, playing a critical role as a tumor suppressor. Following exposure to ionizing radiation, an ATM-dependent DNA damage response cascade is mediated by the p53 protein [24], as shown in Fig. 4 [Figure 4: see original paper]. When DNA damage occurs, ATM phosphorylates p53 at Ser-15 and Chk2 at Thr-68, while Chk2 further phosphorylates p53 at Ser-20 to regulate cell cycle arrest and apoptosis. The proper functioning of p53 is therefore essential for DNA damage repair, apoptosis, and radiation-induced cell cycle arrest. However, missense mutations in the TP53 gene produce mutant p53 proteins, which have been confirmed to increase radiation resistance over the wild-type counterpart [25, 26]. Inappropriate cellular survival after stresses such as irradiation and inappropriate replication of damaged DNA caused by mutant p53 may ultimately contribute to malignant transformation.

Under normal conditions, p53 protein is present at low levels, with slight increases upon perturbations. The response to DNA damage, such as from ioniz-

ing radiation, is affected by changes in p53 levels over time. Cells repair DNA damage and re-enter the cell cycle if wild-type or functioning p53 protein levels pulse following irradiation [27]. As a decision-making transcription factor, p53 selectively activates genes as part of specific gene expression programs following DNA damage to determine cellular fate [25]. Loss of p53 function due to TP53 mutations has recently been shown to increase resistance to DNA-damaging agents in human tumor cell lines [26]. Mutations in p53, including the six most commonly mutated residues, are mostly loss-of-function mutations where mutant p53 proteins fail to activate the critical target genes of wild-type p53 necessary for maintaining homeostasis. We hypothesize that the wild-type/mutant status of the p53 gene correlates with the σ parameter, as shown in Table 3 .

As shown in Table 3, the σ values of wild-type cells are generally smaller than those of mutant cells, indicating a narrower normal distribution curve around D_0. We infer that wild-type cells are more sensitive to radiation damage, and the repair response is initiated acutely. In contrast, mutant cells exhibit a more chronic response to radiation damage, characterized by a wider normal distribution. One exception in Table 3 is the Be11 melanoma cell line, possibly due to unique biological characteristics—for example, wild-type melanoma cells do not show radiosensitivity, consistent with clinical radiotherapy resistance, likely related to their poorly differentiated cell type [28].

HRS "Cellular Radar" : ATM Protein

ATM kinases regulate a variety of proteins involved in cell cycle checkpoint, DNA repair, and apoptosis. Following ionizing radiation, the ATM kinase, a key regulator of cellular responses to DNA damage, has been reported to be activated/phosphorylated [29]. As a critical responder to DNA damage, ATM rapidly initiates responses that control cell cycle progression and other processes. Consequently, we propose that the ATM kinase acts as a "cellular radar" for radiation damage, with its kinase activity/phosphorylation levels correlating positively with DNA damage response events [30].

Ionizing radiation increases the occurrence of DSBs or single-strand breaks (SSBs). The Mre11–Rad50–NBS1 (MRN) complex, a "signal modifier," performs initial resection of broken DNA ends to create structures suitable for repair and recruits signal transducers. Meanwhile, the functional MRN complex activates ATM and its downstream pathways promptly. ATM autophosphorylation converts inactive ATM into a potent protein kinase and causes a fraction of the nuclear content of ATM to adhere to DSB sites [31]. The ATM protein levels peak within 2 hours of exposure to ionizing radiation, with induction beginning within 5 minutes, indicating a rapid mechanism. ATM has been demonstrated to act upstream of p53 in an ionizing radiation-induced signal transduction pathway, phosphorylating p53 at serine 15, thereby activating cell cycle checkpoints across G1, S, and G2 phases (see Fig. 5 [Figure 5: see original paper]) [32]. In this way, ATM establishes an unanticipated role in the signaling of DNA damage, contributing to genetic stability and preventing malignant transformation.

Here, we investigated ATM protein levels in various cell types and tissues after ionizing radiation, as shown in Fig. 6 [Figure 6: see original paper]. In the C3ABR cell line, a lymphoblastoid cell line immortalized by Epstein-Barr virus from a healthy female, ATM protein levels fluctuated, a phenomenon not observed previously. Using ImageJ, a Java-based public image processing software developed by the National Institutes of Health, we quantified the concentration of protein in SDS-PAGE gel bands and found interesting phenomena. At a dose of 0.1 Gy, ATM content slightly decreased to 0.86 times its resting level, contradicting the theory that irradiation generally increases ATM levels. Based on the second hypothesis of this study, a plausible explanation is that radiation damage would not only increase the damage rate of DNA but also increase the damage rate of ATM and other molecules, resulting in reduced ATM levels. Radman formerly suggested that proteome protection against oxidative damage determines survival fraction after ionizing irradiation and that protein damage determines radiation resistance [33]. Consequently, increased cellular damage rates correspond to the stage of the cell survival curve below D_1.

For doses above 0.1 Gy, the expression of ATM rises, enhancing the cell repair rate and correlating with the stage in the cell survival curve beyond D_1. Subsequently, ATM expression decreases again, likely due to both direct ATM damage from radiation and MRN complex damage. These findings support the theoretical model of HRS/IRR, illustrating consistent trends between the survival fraction curves and ATM levels.

Conclusion

In this paper, we identified the D_1 value derived from formula (4) as the inflection point at which the cell repair rate surpasses the damage rate. Based on our analysis and literature review, we conclude the following:

Below the D_0 threshold, only the damage rate exists, which shows that the survival rate decreases with increasing dose, as the "cellular radar" ATM molecule fails to detect radiation damage. When the dose reaches D_0, ATM detects radiation damage, providing a trigger signal to activate the cell repair mechanism. In Fig. 3, this threshold is estimated at 0.32 Gy. For doses above 0.32 Gy, cell repair in response to radiation is triggered. In the dose range between 0.32 Gy and 0.35 Gy, the DNA repair rate remains lower than the damage rate due to simultaneous damage to both DNA and protein molecules. Consequently, the cell survival curve exhibits HRS characteristics at doses below 0.35 Gy.

At D_1, the cell repair rate equals the damage rate, correlated with increased levels of activated ATM. The D_1 value varies by radiation type. For example, for HeLa cells, the D_1 values are 0.28 Gy for ^{60}Co beams, 0.25 Gy for 6 MV X-rays, and 0.4 Gy for 15 MV X-rays [11]. For doses above D_1, the cell' s repair mechanism is enhanced. At this stage, ATM transmits signals to p53, increasing the repair rate above the damage rate, which leads to IRR, reflecting a radioprotective effect [35, 36]. For p53 wild-type cells, repair rates are rapid,

resulting in a steeply rising survival curve. In contrast, for p53 mutant cells, the normal distribution curve is broader, and σ is larger.

When the dose reaches D_2, the damage rate also increases with dose but remains lower than the repair rate up to D_2. Beyond D_2, as the dose increases, ATM activation levels stabilize, while the damage rate significantly exceeds the repair rate, consistent with the LQ model.

In conclusion, this paper describes the HRS/IRR phenomenon from a biomolecular perspective, exploring related damage and repair mechanisms that merit further investigation. For instance, this phenomenon can also be interpreted from an immunological perspective. Beyond the D_1 inflection point, immunity gradually increases, reducing cell damage. Numerous studies have reported the effects of low-dose radiation on immune function [37]. Low-dose radiation is known to up-regulate the immune factor TCR/CD3, and it has been suggested that the ability of lymphocytes to receive antigen stimulation is increased. Additionally, CD2 expression in T lymphocytes is significantly up-regulated after low-dose radiation exposure [38].

Declarations

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Author Contributions: Zhao Xu, Taosheng Li, and Qi Liu contributed to the conception and design of this review. Zhao Xu and Guangyan Feng wrote the original draft and created all the figures and tables. Wenyi Li, Yu Lu, and Ziyi Ding critically revised and edited the review. All authors read and approved the final version of the manuscript.

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Ethics Declaration: Not applicable.

References

1. Chadwick KH, Leenhouts HP. A molecular theory of cell survival. Phys Med Biol. 1973;18:78-87. doi:10.1088/0031-9155/18/1/007.
2. Joiner MC, Marples B, Lambin P, Short SC, Turesson I. Low-dose hypersensitivity: current status and possible mechanisms - ScienceDirect. Int J Radiat Oncol Biol Phys. 2001;49:379-89.
3. ERIKSSON GS. INDUCTION OF WAXY MUTANTS IN MAIZE BY ACUTE AND CHRONIC GAMMA IRRADIATION. Hereditas. 2010;50:161-78.

4. Short JKCRMMWMCJS. Low-dose hypersensitivity after fractionated low-dose irradiation in vitro. International Journal of Radiation Biology. 2001;77:655-64. doi:10.1080/09553000110041326.
5. Krueger SA, Collis SJ, Joiner MC, Wilson GD, Marples B. Transition in survival from low-dose hyper-radiosensitivity to increased radioresistance is independent of activation of ATM Ser1981 activity. Int J Radiat Oncol Biol Phys. 2007;69:1262-71. doi:10.1016/j.ijrobp.2007.08.012.
6. Jin X-d, Li Q, Li W-j, Wang J-f, Guo C-l, Hao J-f. The hyper-radiosensitivity effect of human hepatoma SMMC-7721 cells exposed to low dose γ-rays and ^{12}C ions. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms. 2006;245:310-3. doi:https://doi.org/10.1016/j.nimb.2005.11.120.
7. Feng G, Zhang L, Yang Z, Zhang Y, Zhang S, Li T, et al. A DNA Damage-Repair Dynamic Model for HRS/IRR Effects of C.elegans Induced by Neutron Irradiation. Dose Response. 2021;19:15593258211001254. doi:10.1177/15593258211001254.
8. Paunesku T, Stevanović A, Popović J, Woloschak GE. Effects of low dose and low dose rate low linear energy transfer radiation on animals - review of recent studies relevant for carcinogenesis. Int J Radiat Biol. 2021;97:757-68. doi:10.1080/09553002.2020.1859155.
9. Collis SJ, Schwaninger JM, Ntambi AJ, Keller TW, Nelson WG, Dillehay LE, et al. Evasion of Early Cellular Response Mechanisms following Low Level Radiation-induced DNA Damage*. Journal of Biological Chemistry. 2004;279:49624-32. doi:https://doi.org/10.1074/jbc.M409600200.
10. Wouters BG, Sy AM, Skarsgard LD. Low-dose hypersensitivity and increased radioresistance in a panel of human tumor cell lines with different radiosensitivity. Radiat Res. 1996;146:399-413.
11. Das S, Singh R, George D, Vijaykumar TS, John S. Radiobiological Response of Cervical Cancer Cell Line in Low Dose Region: Evidence of Low Dose Hypersensitivity (HRS) and Induced Radioresistance (IRR). J Clin Diagn Res. 2015;9:Xc05-xc8. doi:10.7860/jcdr/2015/14120.6074.
12. Lambin P, Fertil B, Malaise EP, Joiner MC. Multiphasic survival curves for cells of human tumor cell lines: induced repair or hypersensitive subpopulation? Radiat Res. 1994;138:S32-6.
13. Short SC, Mitchell SA, Boulton P, Woodcock M, Joiner MC. The response of human glioma cell lines to low-dose radiation exposure. Int J Radiat Biol. 1999;75:1341-8. doi:10.1080/095530099139214.
14. Lambin P, Marples B, Fertil B, Malaise EP, Joiner MC. Hypersensitivity of a human tumour cell line to very low radiation doses. Int J Radiat Biol. 1993;63:639-50. doi:10.1080/09553009314450831.
15. Short S, Mayes C, Woodcock M, Johns H, Joiner MC. Low dose hypersensitivity in the T98G human glioblastoma cell line. Int J Radiat Biol. 1999;75:847-55. doi:10.1080/095530099139908.
16. Lambin P, Malaise EP, Joiner MC. Might intrinsic radioresistance of human tumour cells be induced by radiation? Int J Radiat Biol. 1996;69:279-90. doi:10.1080/095530096145832.

17. Guirado D, Aranda M, Ortiz M, Mesa JA, Zamora LI, Amaya E, et al. Low-dose radiation hyper-radiosensitivity in multicellular tumour spheroids. Br J Radiol. 2012;85:1398-406. doi:10.1259/bjr/33201506.
18. Słonina D, Gasińska A, Biesaga B, Janecka A, Kabat D. An association between low-dose hyper-radiosensitivity and the early G2-phase checkpoint in normal fibroblasts of cancer patients. DNA Repair. 2016;39:41-5. doi:https://doi.org/10.1016/j.dnarep.2015.12.001.
19. Xue L, Furusawa Y, Yu D. ATR signaling cooperates with ATM in the mechanism of low dose hypersensitivity induced by carbon ion beam. DNA Repair (Amst). 2015;34:1-8. doi:10.1016/j.dnarep.2015.07.001.
20. Marples B, Joiner MC. The Response of Chinese Hamster V79 Cells to Low Radiation Doses: Evidence of Enhanced Sensitivity of the Whole Cell Population. Radiation Research. 1993;133:41-51. doi:10.2307/3578255.
21. Singh B, Arrand JE, Joiner MC. Hypersensitive response of normal human lung epithelial cells at low radiation doses. Int J Radiat Biol. 1994;65:457-64. doi:10.1080/09553009414550531.
22. Horsley RJ, Pujara CM. Study of the Inflexion in X-Radiation Survival Curves for Synchronized Cell Populations of the Green Alga (Oedogonium cardiacum). Radiation Research. 1969;40:440-9. doi:10.2307/3572831.
23. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, et al. Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res. 2004;64:7011-21. doi:10.1158/0008-5472.Can-04-1364.
24. Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature. 2004;432:316-23. doi:10.1038/nature03097.
25. Böhnke A, Westphal F, Schmidt A, El-Awady RA, Dahm-Daphi J. Role of p53 mutations, protein function and DNA damage in radiosensitivity of human tumour cells. Int J Radiat Biol. 2004;80:53-63. doi:10.1080/09553000310001642902.
26. McIlwrath AJ, Vasey PA, Ross GM, Brown R. Cell cycle arrests and radiosensitivity of human tumor cell lines: dependence on wild-type p53 for radiosensitivity. Cancer Res. 1994;54:3718-22.
27. Hafner A, Bulyk ML, Jambhekar A, Lahav G. The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol. 2019;20:199-210. doi:10.1038/s41580-019-0110-x.
28. Lantigua-Dorville Y, Saornil MA, García-Alvarez C, García-Lagarto E. Choroidal melanoma recurrence after episcleral brachytherapy and transpupillary thermotherapy. Arch Soc Esp Oftalmol. 2016;79:48-9. doi:10.5935/0004-2749.20160015.
29. Bernstein JL, Haile RW, Stovall M, Boice JD, Jr., Shore RE, Langholz B, et al. Radiation exposure, the ATM Gene, and contralateral breast cancer in the women' s environmental cancer and radiation epidemiology study. J Natl Cancer Inst. 2010;102:475-83. doi:10.1093/jnci/djq055.
30. Fang ZM, Lee CS, Sarris M, Kearsley JH, Murrell D, Lavin MF, et al. Rapid radiation-induction of ATM protein levels in situ. Pathology. 2001;33:30-6.

31. D' Amours D, Jackson SP. The Mre11 complex: at the crossroads of dna repair and checkpoint signalling. Nat Rev Mol Cell Biol. 2002;3:317-27. doi:10.1038/nrm805.
32. Pandita TK, Lieberman HB, Lim DS, Dhar S, Zheng W, Taya Y, et al. Ionizing radiation activates the ATM kinase throughout the cell cycle. Oncogene. 2000;19:1386-91. doi:10.1038/sj.onc.1203444.
33. Radman M. Protein damage, radiation sensitivity and aging. DNA Repair (Amst). 2016;44:186-92. doi:10.1016/j.dnarep.2016.05.025.
34. Kozlov SV, Graham ME, Jakob B, Tobias F, Kijas AW, Tanuji M, et al. Autophosphorylation and ATM activation: additional sites add to the complexity. J Biol Chem. 2011;286:9107-19. doi:10.1074/jbc.M110.204065.
35. Joiner MC, Marples B, Lambin P, Short SC, Turesson I. Low-dose hypersensitivity: current status and possible mechanisms. Int J Radiat Oncol Biol Phys. 2001;49:379-89. doi:10.1016/s0360-3016(00)01471-1.
36. Martin LM, Marples B, Davies AM, Atzberger A, Edwards C, Lynch TH, et al. DNA mismatch repair protein MSH2 dictates cellular survival in response to low dose radiation in endometrial carcinoma cells. Cancer Lett. 2013;335:19-25. doi:10.1016/j.canlet.2013.01.046.
37. Hattori S. Current status and perspectives of research on radiation hormesis in Japan. Chin Med J (Engl). 1994;107:420-4.
38. Sambani C, Thomou H, Kitsiou P. Stimulatory effect of low dose X-irradiation on the expression of the human T lymphocyte CD2 surface antigen. Int J Radiat Biol. 1996;70:711-7. doi:10.1080/095530096144608.

Note: Figure translations are in progress. See original paper for figures.