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The characteristic of stem-related genes with pancreatic carcinoma cell after irradiation

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ABSTRACT

Purpose: To investigate stem-related differentially expressed genes (DEGs) and their potential mechanism in pancreatic cancer cells (MIAPaCa-2) exposed to x-ray and proton radiation, as well as how these factors affected the prognosis of patients with pancreatic adenocarcinoma (PADC).
Methods: The stem-related DEGs were screened using the online tool Stemchecker after protons and x-rays were used to irradiate MIAPaCa-2 cells. Analysis was done on the probable processes and prognostic significance of the DEGs in PAC patients.
Results: Four datasets containing 401 DEGs were filtered, and the stem-related DEGs for each irradiation type indicated a variety of radiobiological characteristics. In pancreatic cancer cells, a number of stem-related DEGs may serve as biomarkers of radiation effects. Patients with pancreatic cancer demonstrated predictive significance for GRB7, B2M, and PMAIP1.
Conclusions: MIAPaCa-2 cells exposed to x-rays and protons repeatedly displayed heterogeneous expression of stem-related DEGs involved in complex radiosensitivity, radio-resistance, and radio-induced mortality pathways. GRB7 and B2M were considered potential radiation sensitivity indicators for pancreatic cancer.

1. Introduction

Pancreatic carcinoma is one of the most common causes of mortality from human cancers [1]. The prognosis of pancreatic cancer was discovered to be correlated with the clinical and genetic factors [2–4]. One of the most crucial treatments for pancreatic cancer is radiation therapy, and it was argued that the delivery dose might increase the effectiveness of the local control [5]. The dosage limitation of the organs at risk (OAR) around the pancreas tissues was long thought to make increasing the radiation dose challenging [6]. Importantly, a major contributing factor to a bad prognosis is the genetic features linked to radioresistance [7,8]. To date, one of the characteristics of radioresistance has been the stem-like nature of tumor cells [7–9]. What modifications take place in the stem-related genes of pancreatic cancer cells following radiation is still unknown. The expressional alterations of stem-related genes in pancreatic cancer cells (MIAPaCa-2) exposed to x-ray and proton radiation were the focus of this work. Researchers also looked into the underlying mechanisms and prognostic significance of stem-related genes in pancreatic cancer radiotherapy.

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2. Materials and methods

2.1. Data resource and design

From the gene expression omnibus (GEO) database, the expression matrix (GSE107440-GSE107444) was retrieved [10]. Agilent-014850 whole-human-genome microarray 4 × 44K G4112F was used to create the super microarray GSE107444. Three related designs were considered in the study. In the initial design, GSE107440, MIAPaCa-2 cells were exposed to primary x-ray (XRT) and proton radiotherapy (PRT) treatments using protons or x-rays at 2 Gy or 8 Gy, respectively. Cells were collected, RNA was extracted, and their gene-expression profile was analyzed by DNA microarray for a total of eight distinct radiotherapy situations (n = 8) following 3 h or 12 h of irradiation. To boost the performance, a control condition without irradiation was added. In the second experiment, GSE107441, MIAPaCa-2 cells were exposed to either 8 Gy of protons or x-rays before being continuously cultivated for 7–17 days. The colonies were then selected, grown, and collected. The cells, now known as survival cells, were subsequently exposed to x-rays (SXRT) or proton irradiation (SPRT). Then RNA was extracted and used in the gene-expression microarray analysis procedure. Five and four, respectively, of the gathered colonies were exposed to proton and x-ray radiation. The cells with potential radio-resistance were the ones that survived after SXRT or SPRT. The data for the last design, GSE107442 and GSE107443, were combined and given the name GSE107442 for simplicity. The above clone surviving cells that underwent 8 Gy of protons for SXRT or SPRT were amplified and re-irradiated. After a 4-h reirradiation, the cells were harvested, and the RNA was extracted. DNA microarray was used to examine the gene-expression profile, which was given the names proton irradiation (RPRT) and proton re-irradiation after x-ray (RXRT). The cells in this group theoretically lost the capacity to proliferation.

2.2. Data processing and control setting

The control parameter of the differentially expressed genes (DEGs) filter settings was slightly different, according to the aforementioned research content. The irradiation dose, source, and cell harvest timings for the XRT/PRT group were not taken into consideration based on the original author's research objectives and findings. Importantly, biological repetition was not affected by variations in radio source, energy, or time. Unirradiated cells were utilized as controls on the basis of the aforementioned parameters, and the DEGs for this subgroup were obtained. Since there were multiple amplified clones in the SXRT and SPRT group, which can be a sign of repetition, we used non-irradiated cells as the control for screening DEGs. However, for the RXRT/RPRT group, the clone surviving cells receiving re-irradiation had the best contrast for matched suitable culture conditions compared to those without re-irradiation. Log fold change |LgFC| >0.5 and $p < 0.05$ were used to base each DEG. For DEG screening, the online tool GEO2R, which was generated from the GEO website, was utilized.

2.3. Gene ontology (GO) annotation and function enrichment

We identified and categorized stem genes and associated transcriptional regulatory components using the online tool Stemchecker (http://stemchecker.sysbiolab.eu/). The progenitor cell biology consortium (PCBC) database on the gene expression of nine different stem cell types and a gene database for multi-drug resistance serve as the foundation for the online tool Stemchecker. Key stem-related DEGs were functionally annotated, hierarchically clustered, and prognostic assayed using the websites and programs Omicsbean (http://www.omicsbean.cn/), GraphPad Prism 7.0, MEV4.9, Cytoscape 3.7.1, and plugin Clue GO. The cutoff for statistical significance was $p < 0.05$.

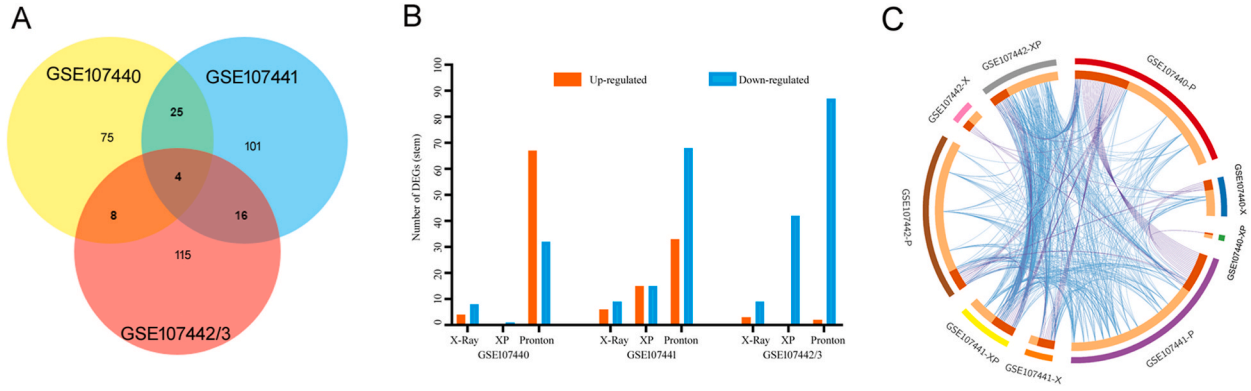

Fig. 1. Distribution of stem-related DEGs: (A) Venn diagram of DEGs in the irradiation groups. (B) Gene ontology analysis of upregulated and downregulated Common DEGs in irradiation groups with different radiation sources. XP, both x rays and protons. (C) The interactions of stem-related DEGs in different irradiation groups and radiation sources. DEGs: differentially expressed genes, X, x-rays; P protons; XP, both x rays and protons.

2.4. The prognosis of DEGs in patients with pancreatic carcinoma

The univariate Cox regression analysis of overall survival (OS) with 25% and 75% expression cutoffs for low and high expression of DEGs was carried out using the Oncolnc database(http://www.oncolnc.org/, pancreatic adenocarcinoma, PAAD) in order to comprehend the prognostic value of the stem-related DEGs, their capacity to predict responses to radiotherapy, and the relationships between changes in their expression and prognosis of patients with pancreatic carcinoma. The cutoff for statistical significance was $p < 0.05$.

This study's data originates from previously published studies and datasets that have been cited. The processed data are available from the corresponding author upon request.

3. Results

3.1. Screening of stem-related DEGs

401 stem-related DEGs were discovered based on the filter threshold used to match the 2459 stem-related genes that were retrieved from Stemchecker. Fig. 1A shows that, in initial irradiated cells (XRT, PRT), clone survival cells after irradiation (SXRT, SPRT), and re-irradiated cells (RXRT, RPRT), respectively, a total of 112, 146, and 143 stem-related DEGs were gated. Fig. 1A shows the distribution of the four stem DEGs that were vulnerable to all radio sources, regardless of whether they had been exposed to radiation before or not. In the XRT and PRT groups (GSE107440), 12 and 99 stem-related DEGs, respectively, were screened, and one stem-related DEG was found in both groups (Fig. 1B). The SXRT and SPRT groups (GSE107441) each contained 15 and 101 stem-related DEGs, respectively. With SXRT and SPRT, 30 cross-related DEGs were connected. 42 stem-related DEGs were altered in both RXRT and RPRT, making a total of 12 and 89 stem-related DEGs specific to RXRT and RPRT (GSE107442/3) (Fig. 1B). According to the findings, more stem-related genes responded to protons, and a few stem-related DEGs were more responsive to x-rays, as shown in Fig. 1B. Further investigation revealed that the majority of stem-related DEGs were downregulated after SPRT and RPRT while the majority of stem-related DEGs were elevated after primary PRT. In particular, it was found that the RPRT cohort had decreased expression of nearly all stem-related DEGs, with the exception of two. (Fig. 1B). When the three stem-related DEG groups were clustered, it was discovered that the DEGs interacted with one another (Fig. 1C).

3.2. Classification of stem-related DEGs after irradiation

The PCBC database was used to sort the stem-related DEGs, and the results showed that the majority of these DEGs were linked to embryonic cancer, embryonic stem cells, or hematopoietic stem cells (Fig. 2A). Embryonic stem cells were mostly linked to the stem-related DEGs that were coupled with proton radiation. Additionally, we observed that the transcription regulatory factors (TRF) of the stem-related DEGs displayed variety, with Nanog and SOX2 acting as the primary regulators. Additionally, as shown in Fig. 2B, SMAD, SUZ12, and OCT4 may help regulate the transcription of stem-related DEGs.

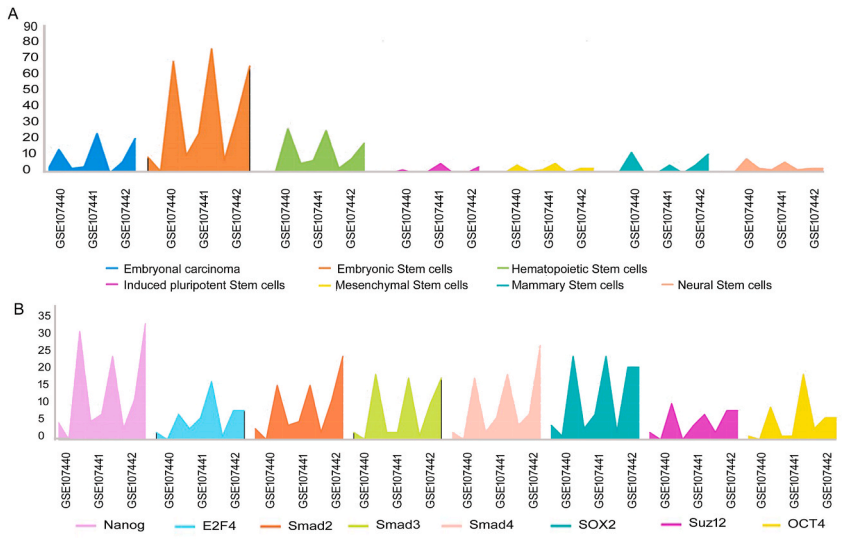

Fig. 2. Distribution of stem-related DEG categories based on PCBC for different irradiation situations and radiation sources. (A) Classification, and distribution of stem-related DEGs; (B) Distribution of transcriptional regulatory factors stem-related DEGs. PCBC: progenitor cell biology consortium.

3.3. Trends in the expression of stem-related DEGs

The quantity of stem-related DEGs differed between x-ray and proton irradiation, as was already mentioned. The expression of stem-related DEGs genes was examined to understand the discrepancies, and Euclidean distance and cluster analysis revealed that the expression appeared to be binary grouping dependent on the radiation source, as shown in Fig. 3. The expression patterns of XRT and PRT were markedly at odds with those of RPRT cells (Fig. 3), for example, the expression of ZFP36, DDIT3, PPP1R15A, AFT3, EGR3, and PMAIP1 was lower in RXRT and RPRT than that in SXRT and SPRT. It was also found that SAT1, LDLR, CYR61, ERRFI1, ATF3, STAT3, CCNL1, and SPAG9 were expressed at higher levels after PRT than XRT.As shown in Fig. 4, the crossing stem-related DEGs were chosen and analyzed based on the fold-change variation in expression to further study the tendencies of change in the stem-related DEGs. However, it was discovered that the three DEGs significantly plummeted suffering from the second strike with RXRT and RPRT, as shown in Fig. 4A and B. It is interesting to note that EGR3, B2M, and PMAIP1 were enhanced in the SXRT and SPRT compared to XRT and PRT. As seen in Fig. 4A and B, GRB7 was consistently expressed at low levels and appeared unaffected by radiation or re-irradiation. It was also discovered that other stem-related DEGs suffered RXRT and RPRT downregulation evidently compared to SXRT and SPRT, and that PIF1 expression remained consistent between SPRT and RPRT, as demonstrated in Fig. 4C and D.

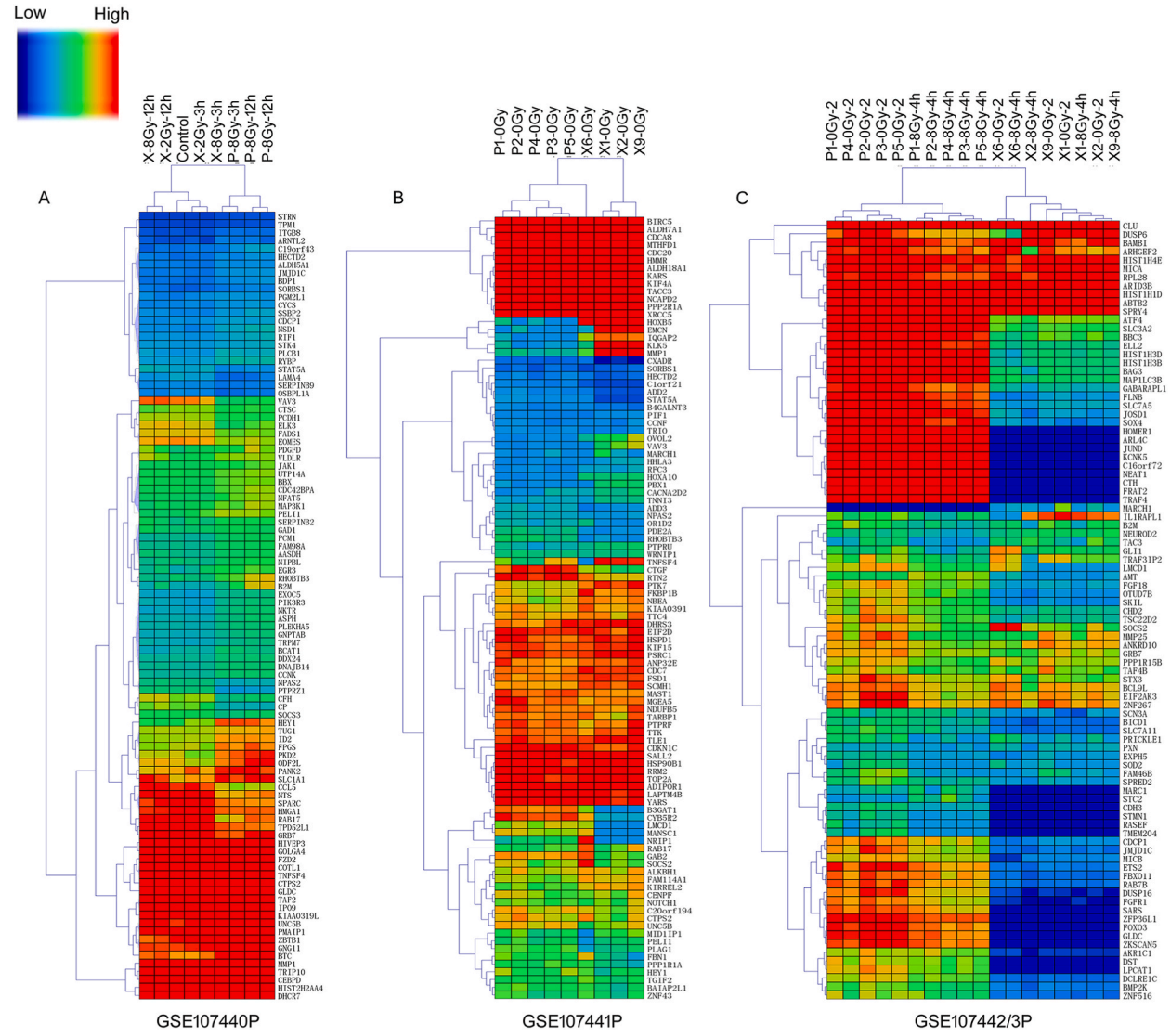

Fig. 3. Expressional heatmap of stem-related DEGs associated with proton irradiation. (A) Gene expression associated with primary irradiation with protons; (B) Gene expression in clone survival cells after proton irradiation; (C) Gene expression in above cells after receiving re-irradiation. X, x-rays; P, protons.

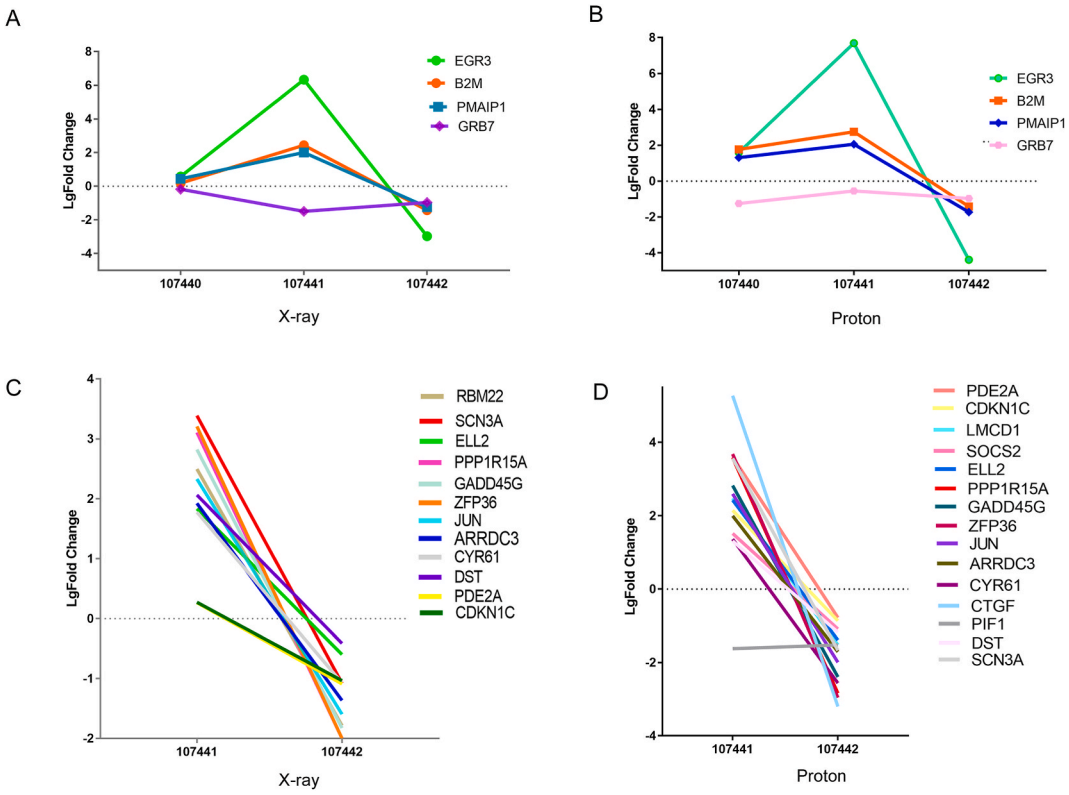

Fig. 4. Fold changes of several stem-related DEGs associated with different irradiation conditions and radiation sources. (A) Four stem-related DEGs common to different irradiation conditions with x-rays; (B) Four stem-related DEGs common to different irradiation conditions with protons. (C) The common stem-related DEGs in survival cells after irradiation with x-rays and re-irradiation with protons; (D) The cross stem-related DEGs in survival cells after irradiation with protons and re-irradiation with protons.

3.4. GO annotation and function enrichment of stem-related DEGs

The functional enrichment of the stem-related DEGs was examined to examine the various radiobiological impacts and the potential mechanisms of radioresistance or radiosensitivity. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway or Wikipathway, molecular function, cell components, and biological processes are typically all involved in GO annotation. Through KEGG, several pathways specific to cells exposed to radiation from distinct radio sources were found (Fig. 5A). While PPIR increased the chemokine signal pathway genes, the DEGs in XRT were engaged in the Hippo signal pathway. RPRT cells were connected to the MAPK and HIF-1 signaling pathways, which are thought to control radio-induced mortality. Furthermore, public mechanisms for cells exposed to various radiation sources involved pathways such the cell cycle, apoptosis, P53, and JAK/STAT. A critical radiation mechanism called cell chemotaxis was produced by PRT (Fig. 5B). The expression of CCL5, CCR3, CXCR4, GNG11, and PLCB1 was aberrant, which caused cells exposed to proton irradiation to undergo chemotaxis. Following proton irradiation, survivor cells that are subjected to a second proton irradiation challenge would lose their capacity to divide or differentiate via the MAPK signal pathway, with the exception of MAP2K6, which displayed negligible upregulation (Fig. 5C).

3.5. Stem-related DEG expression in pancreatic carcinoma tissue and implications in prognosis

The four public DEGs was selected to prognosis analysis, and B2M and GRB7 were shown to be associated to OS ($p = 0.021$ and 0.046, respectively; Fig. 6A and B), and the patients who had low levels of B2M and GRB7 expression in pancreatic tissue fared better in terms of survival than those who had high expression levels (Fig. 6A and B). While there was no statistically significant difference in the OS curves for heterogenous expression of EGR3 ($p = 0.258$) and PMAIP1 ($p = 0.071$), respectively, as shown if Fig. 6C and D).

4. Discussion

In 1963, Becher, McCulloch, and Till used the term “cancer stem cell” to refer to cells with the capacity for self-renewal and colony formation [11]. At the macromorphological and micromolecular levels, this was known as the cellular stemness signature. Cancer progression, metastasis, recurrence, and therapy resistance were thought to be caused by the CSC or stemness signature [12]. 2459 stem-related genes were screened using the analytical tool Stemchecker, which explores stemness markers in gene datasets, by

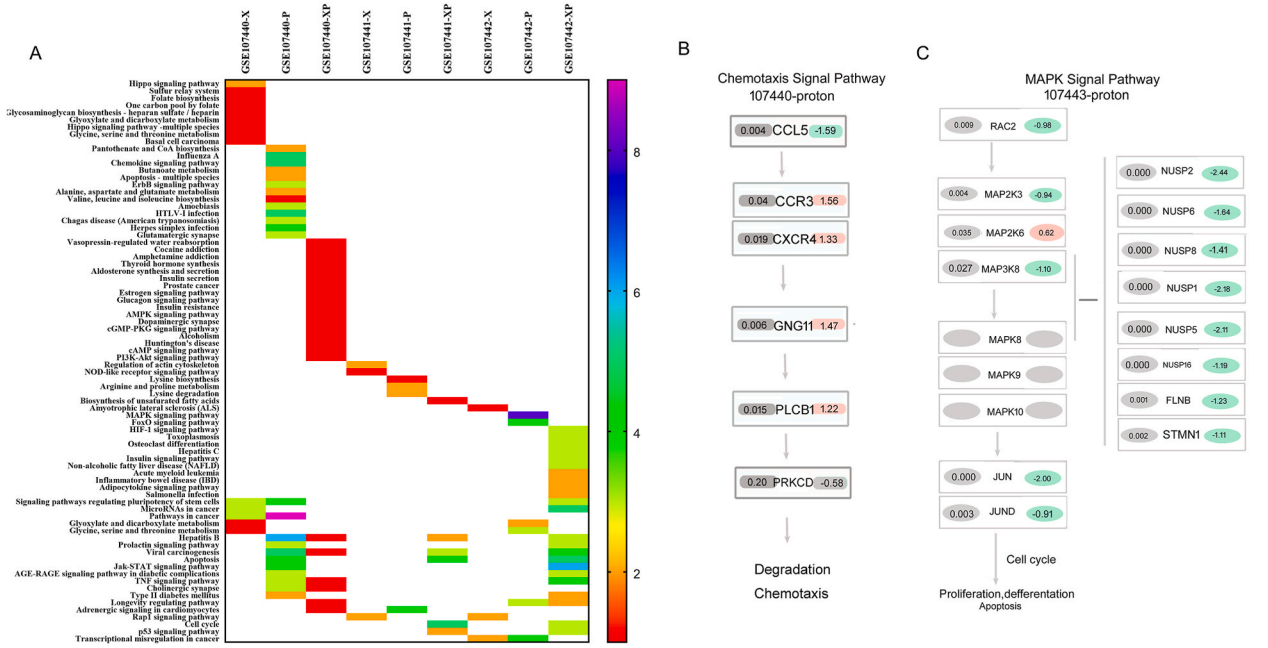

Fig. 5. Mechanistic analysis of different irradiation conditions and various radiation sources. (A) KEGG pathway enrichment analysis of different irradiation conditions and various radiation sources. X, x-rays; P, protons; XP, both x-rays and protons. (B) Alterations in the expression of key genes involved in chemotaxis pathway after primary irradiation with protons; (C) Alterations in key genes involved in MAPK pathway in clone survival cells after proton irradiation and re-irradiation with protons. The colors indicate trend in fold changes: red indicates upregulation and green indicates downregulation. *P*-values were calculated based on the Wilcoxon rank sum test.

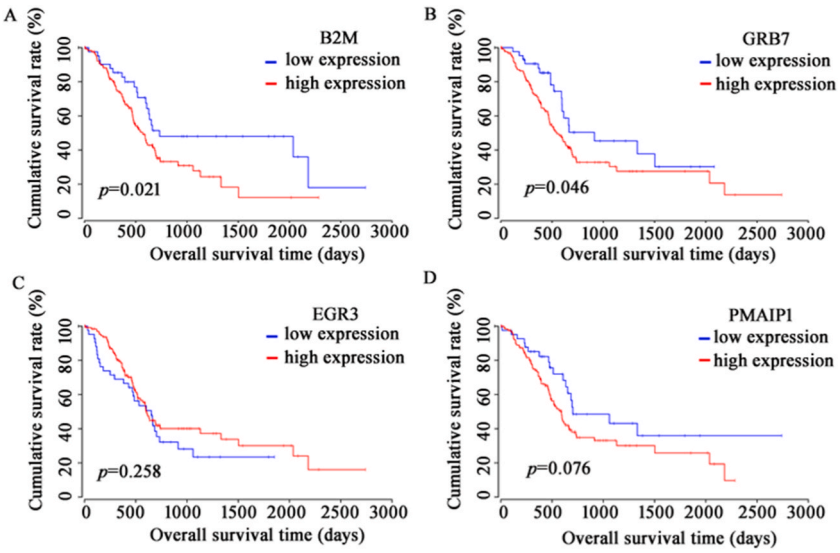

Fig. 6. Kaplan–Meier survival curves for the four commonly expressed stem-related DEGs in low-risk and high-risk pancreatic adenocarcinoma groups. (A) OS for B2M; (B) OS for GRB7; (C)OS for EGR3; (D) OS for PMAIP1. OS, overall survival.

calculating the overlap between our input DEGs and the dataset [13]. The findings demonstrated that proton radiotherapy considerably increased the number of stem-related DEGs induced compared to photon radiotherapy, and that proton radiotherapy and photon radiotherapy induced stem-related DEGs independently, with only a slight overlap. The fact that the protons are highly ionized with high linear energy transfer (LET) values and photons are sparsely ionized with low LET values is well known. The Bragg peak, which concentrates the majority of the proton's energy in the tumor site with little harm to the surrounding healthy tissue, is the most crucial characteristic of proton radiotherapy as compared to photon radiotherapy [14–16]. After high LET proton radiotherapy, stem-like cells overcome resistant to radiation, and they become more sensitive to low LET photons [17,18]. After that, the physical,

chemical, and biological impacts of proton and photon radiation are heterogenous [19]. Corresponding to that, the pancreatic cancer cells exposed to different radiation source also involve in various mechanism. In summary, therapeutic protons and photons cause pancreatic cancer cells to exhibit unique gene expression patterns that are connected to the protons' and photons' unique irradiation properties.

It was found cells at different states of radiation exposure experience diverse biological impacts. The radiobiological process of initial proton irradiation (PRT) was controlled by the chemotaxis signal pathway whereas the Hippo signal pathway was triggered by photon irradiation (XRT). The argument made was that radiotherapy altered the immunological milieu and allowed chemokines to move to tumor cells, which could lead to inflammatory processes in nearby areas or tumor cell proliferation, migration, and metastasis [20,21]. Immune cells were also recruited by chemical agents to target the tumor microenvironment and enhance immune effects [20]. Proton irradiation in the current study demonstrated a chemotaxis effect, indicating that it had a larger impact on tumors. Furthermore, we discovered that proton re-irradiation (RPRT), which downregulated nearly all related molecules, induced cell growth and death via the MAPK signal pathway, and the cells were unable to reproduce after re-irradiation.

Several DEGs (EGR3, B2M, GRB7, and PMAIP1) were found to display similar variation experienced proton or photon irradiation, whether initial beam or clone survival was noted, as well as proton re-radiotherapy. Initial exposure and cloned surviving cells showed far less severe changes in these DEGs' expressions than did repeat proton irradiation, which implies that these DEGs might serve as potential biomarkers of radiotherapy-resistant in pancreatic cancer cells. B2M played a role in the presentation of peptide antigens to the immune system as a part of the class I major histocompatibility complex (MHC I). The increased B2M may have been caused by the active creation of tumor cells, the expulsion of necrotic tumor cells, and the reduction in glomerular filtration brought on by tumor-infiltrating kidney damage [22,23]. B2M overexpression is strongly associated with the development, progression, and prognosis of pancreatic ductal adenocarcinoma (PDAC) [24]. In current study, B2M expression is greatly decreased following second proton irradiation, patients with low B2M expression had much better prognoses than those with high B2M expression in patients with pancreatic cancer. The same is true for pancreatic malignancies, where GRB7 is overexpressed and tumors are more likely to metastasize [25]. Following radiation, cells from survival clones were those that survived or were thought to be radioresistant, while cells received re-irradiation with protons become loss of proliferation or were thought to be radio-lethal. This explains why a number of DEGs showed a considerable down-regulation following re-irradiation. As a result, changes in the expression of DEGs following irradiation can be used to predict the radiosensitivity of the tumor and the patient's prognosis. On the other hand, drugs targeting these DEGs can be developed to increase radiosensitivity.

The following were the limitations of the current study: first, no biological duplication had occurred since the radiation dose and time after the radiation; and second, the survival cells in SXRT had received additional radiation therapy using a proton rather than an x-ray, which could have resulted in an inaccurate analysis of the biological effects of x-ray.

5. Conclusion

Pancreatic carcinoma cells (MIAPaCa-2) receiving identical irradiation doses showed survival after irradiation, and re-irradiation with x-rays and protons resulted in the abnormal expression of stem-related DEGs, which were found to be related to sophisticated mechanisms in radiosensitivity, radioresistance, and radio-induced lethality. Changes in B2M and GRB7 might provide biomarkers for radiotherapy effects and the prognoses of patients with pancreatic adenocarcinoma.

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Data availability statement for this work

The data supporting this research are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

Ethics approval and consent to participate

The study had been ethics approved for original institution.

Consent for publication

All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, A Cancer Journal for Clinicians, CA, 2020.
[2] A.P. Klein, Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 493–502, https://doi.org/10.1038/s41575-021-00457-x.
[3] M.D. Fesinmeyer, M.A. Austin, C.I. Li, A.J. De Roos, D.J. Bowen, Differences in survival by histologic type of pancreatic cancer, Cancer Epidemiol, Biomarkers Prev 14 (2005) 1766–1773, https://doi.org/10.1158/1055-9965.EPI-05-0120.
[4] A. Vincent, J. Herman, R. Schulick, R.H. Hruban, M. Goggins, Pancreatic cancer, Lancet 378 (2011) 607–620, https://doi.org/10.1016/S0140-6736(10)62307-0.
[5] E.J. Koay, A.N. Hanania, W.A. Hall, C.M. Taniguchi, N. Rebueno, S. Myrehaug, K.L. Aitken, L.A. Dawson, C.H. Crane, J.M. Herman, B. Erickson, Dose-escalated radiation therapy for pancreatic cancer: a simultaneous integrated boost approach, Pract Radiat Oncol 10 (2020) e495–e507, https://doi.org/10.1016/j.prro.2020.01.012.
[6] L.E. Colbert, N. Rebueno, S. Moningi, S. Beddar, G.O. Sawakuchi, J.M. Herman, A.C. Koong, P. Das, E.B. Holliday, E.J. Koay, C.M. Taniguchi, Dose escalation for locally advanced pancreatic cancer: how high can we go? Adv Radiat Oncol 3 (2018) 693–700, https://doi.org/10.1016/j.adro.2018.07.008.
[7] J.G. Scott, A. Berglund, M.J. Schell, I. Mihaylov, W.J. Fulp, B. Yue, E. Welsh, J.J. Caudell, K. Ahmed, T.S. Strom, E. Mellon, P. Venkat, P. Johnstone, J. Foekens, J. Lee, E. Moros, W.S. Dalton, S.A. Eschrich, H. McLeod, L.B. Harrison, J.F. Torres-Roca, A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study, Lancet Oncol. 18 (2017) 202–211, https://doi.org/10.1016/S1470-2045(16)30648-9.
[8] J.G. Scott, G. Sedor, P. Ellsworth, J.A. Scarborough, K.A. Ahmed, D.E. Oliver, S.A. Eschrich, M.W. Kattan, J.F. Torres-Roca, Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis, Lancet Oncol. 22 (2021) 1221–1229, https://doi.org/10.1016/S1470-2045(21)00347-8.
[9] Machine Learning Identifies Stemness Features Associated with Oncogenic Dedifferentiation - PubMed, 2022. https://pubmed.ncbi.nlm.nih.gov/29625051/.
[10] H. Fujinaga, Y. Sakai, T. Yamashita, K. Arai, T. Terashima, T. Komura, A. Seki, K. Kawaguchi, A. Nasti, K. Yoshida, T. Wada, K. Yamamoto, K. Kume, T. Hasegawa, T. Takata, M. Honda, S. Kaneko, Biological characteristics of gene expression features in pancreatic cancer cells induced by proton and X-ray irradiation, Int. J. Radiat. Biol. 95 (2019) 571–579, https://doi.org/10.1080/09553002.2019.1558297.
[11] A.J. Becker, E.A. McCULLOCH, J.E. Till, Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells, Nature 197 (1963) 452–454, https://doi.org/10.1038/197452a0.
[12] J.E. Till, E.A. McCULLOCH, Early repair processes in marrow cells irradiated and proliferating in vivo, Radiat. Res. 18 (1963) 96–105.
[13] J.P. Pinto, R.K. Kalathur, D.V. Oliveira, T. Barata, R.S.R. Machado, S. Machado, I. Pacheco-Leyva, I. Duarte, M.E. Futschik, StemChecker: a web-based tool to discover and explore stemness signatures in gene sets, Nucleic Acids Res. 43 (2015) W72–77, https://doi.org/10.1093/nar/gkv529.
[14] A. Dutz, A. Lühr, E.G.C. Troost, L. Agolli, R. Bütof, C. Valentini, M. Baumann, X. Vermeren, D. Geismar, B. Timmermann, M. Krause, S. Löck, Identification of patient benefit from proton beam therapy in brain tumour patients based on dosimetric and NTCP analyses, Radiother. Oncol. 160 (2021) 69–77, https://doi.org/10.1016/j.radonc.2021.04.008.
[15] B. Kopp, M. Fuglsang Jensen, S. Mein, L. Hoffmann, H. Nyström, M. Falk, T. Haberer, A. Abdollahi, J. Debus, A. Mairani, FRoG: an independent dose and LETd prediction tool for proton therapy at ProBeam® facilities, Med. Phys. 47 (2020) 5274–5286, https://doi.org/10.1002/mp.14417.
[16] M. Dell'Oro, M. Short, P. Wilson, C.-H. Hua, M. Gargone, T.E. Merchant, E. Bezak, Influence of target location, size, and patient age on normal tissue sparing-proton and photon therapy in paediatric brain tumour patient-specific approach, Cancers 12 (2020) E2578, https://doi.org/10.3390/cancers12092578.
[17] X. Zhang, S.H. Lin, B. Fang, M. Gillin, R. Mohan, J.Y. Chang, Therapy-resistant cancer stem cells have differing sensitivity to photon versus proton beam radiation, J. Thorac. Oncol. 8 (2013) 1484–1491, https://doi.org/10.1097/JTO.0b013e3182a5fdcb.
[18] V. Dini, M. Belli, M.A. Tabocchini, Targeting cancer stem cells: protons versus photons, Br. J. Radiol. 93 (2020), 20190225, https://doi.org/10.1259/bjr.20190225.
[19] Y. Hirota, S.-I. Masunaga, N. Kondo, S. Kawabata, H. Hirakawa, H. Yajima, A. Fujimori, K. Ono, T. Kuroiwa, S.-I. Miyatake, High linear-energy-transfer radiation can overcome radioresistance of glioma stem-like cells to low linear-energy-transfer radiation, J. Radiat. Res. 55 (2014) 75–83, https://doi.org/10.1093/jrr/rrt095.
[20] Radiotherapy and Immunotherapy: a Beneficial Liaison? - PubMed, 2022. https://pubmed.ncbi.nlm.nih.gov/28094262/.
[21] M. Zhang, L. Yin, K. Zhang, W. Sun, S. Yang, B. Zhang, P. Salzman, W. Wang, C. Liu, S. Vidyasagar, L. Zhang, S. Ju, P. Okunieff, L. Zhang, Response patterns of cytokines/chemokines in two murine strains after irradiation, Cytokine 58 (2012) 169–177, https://doi.org/10.1016/j.cyto.2011.12.023.
[22] H. Wang, B. Liu, J. Wei, Beta2-microglobulin(B2M) in cancer immunotherapies: biological function, resistance and remedy, Cancer Lett. 517 (2021) 96–104, https://doi.org/10.1016/j.canlet.2021.06.008.
[23] C. Luchini, A. Mafficini, D. Chatterjee, M.L. Piredda, C. Sciammarella, P. Navale, G. Malleo, P. Mattiolo, G. Marchegiani, A. Pea, R. Salvia, L.A. Brosens, G. Paolino, M.G. Mastrosimini, N. Silvestris, M. Milella, L. Cheng, V.N. Adsay, R.T. Lawlor, A. Scarpa, Histo-molecular characterization of pancreatic cancer with microsatellite instability: intra-tumor heterogeneity, B2M inactivation, and the importance of metastatic sites, Virchows Arch. 480 (2022) 1261–1268, https://doi.org/10.1007/s00428-021-03205-3.
[24] C. Liu, Z. Yang, D. Li, Z. Liu, X. Miao, L. Yang, Q. Zou, Y. Yuan, Overexpression of B2M and loss of ALK7 expression are associated with invasion, metastasis, and poor-prognosis of the pancreatic ductal adenocarcinoma, Cancer Biomarkers 15 (2015) 735–743, https://doi.org/10.3233/CBM-150515.
[25] S. Tanaka, S.C. Pero, K. Taguchi, M. Shimada, M. Mori, D.N. Krag, S. Arii, Specific peptide ligand for Grb7 signal transduction protein and pancreatic cancer metastasis, J Natl Cancer Inst 98 (2006) 491–498, https://doi.org/10.1093/jnci/djj105.