FGFR2-mediated phosphorylation of PTEN at tyrosine 240 contributes to the radioresistance of glioma

Yuanliang Yan^{1,2} · Zhi Li³ · Shuangshuang Zeng^{1,2} · Xiang Wang^{1,2} · Zhicheng Gong^{1,2} · Zhijie Xu⁴

Received: 5 April 2019 / Accepted: 14 April 2019 / Published online: 25 April 2019
© The International CCN Society 2019

Abstract

Ionizing radiation (IR) is a standard-of-care treatment for glioma patients; however, the clinical efficacy is limited due to therapeutic resistance. A recent study published by Ma et al. (*Cancer Cell* 35:504–518, 2019) reported that the phosphorylation of phosphatase and tensin homolog (PTEN) at tyrosine 240 (pY240-PTEN) promotes the radioresistance of human glioma cells. After treatment with IR, the fibroblast growth factor receptor 2 (FGFR2)-mediated phosphorylation that generated pY240-PTEN could effectively promote the decondensation of chromatin through an interaction with Ki-67, leading to DNA damage repair and radioresistance. However, such promising findings need to be addressed in detail after considering the following points. (1) The authors should take into consideration whether or not the nuclear-cytoplasmic translocation of PTEN occurs. (2) The roles of FGFR2-PTEN downregulation should be validated using both genetic and pharmacological inhibition models. (3) Some of the data shown by the authors are confusing and did not support the conclusion that patients with higher PTEN and FGFR2 expression were relatively IR resistant.

Keywords FGFR2 · pY240-PTEN · Radioresistance · Glioma

Glioma is the most common primary malignant brain tumor, and its treatment remains largely unsatisfactory. Radiotherapy is an important therapeutic strategy for glioma patients. Unfortunately, cancer cells can develop resistance to the cytotoxicity induced by ionizing radiation (IR), greatly limiting its clinical efficacy for glioma (Huang et al. 2017). Thus, clarifying the underlying mechanisms involved in the development of radioresistance in glioma would be beneficial for improving the clinical outcomes. A recent study published in *Cancer Cell* demonstrated that the phosphorylation of phosphatase and

tensin homolog (PTEN) at Tyr-240 (pY240-PTEN) mediates the radiation therapeutic resistance of human gliomas by phosphatase-independent activity (Ma et al. 2019). Using elaborate in vivo and in vitro systems, the authors shown that upon IR treatment, the fibroblast growth factor receptor 2 (FGFR2)-mediated phosphorylation that generated pY240-PTEN could effectively promote the decondensation of chromatin through an interaction with Ki-67, which results in DNA damage repair and radioresistance.

PTEN, a major tumor suppressor, is frequently altered during carcinogenesis. Previous evidence demonstrated that PTEN is present with a distinct subcellular localization in a phosphatase-dependent and -independent manner, leading to the dysregulation of DNA repair and survival signaling pathways (Shen et al. 2018). Recently, Ma et al. further verified the roles of nuclear-localized pY240-PTEN in regulating DNA damage repair, independent of its canonical phosphatase activity (Ma et al. 2019). In particular, After IR treatment, the authors found a greater level of nuclear-localized PTEN than cytoplasmic-localized PTEN in glioma cells. Moreover, the translocation of PTEN from the cytoplasm to the nucleus is regulated by FGFR2. With regard to the underlying mechanism, we hypothesize that the shuttling of FGFR2 between the cytoplasm and nucleus may accelerate the nuclear

✉ Zhijie Xu
xzj1322007@csu.edu.cn

¹ Department of Pharmacy, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

² National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

³ Center for Molecular Medicine, Xiangya Hospital, Key Laboratory of Molecular Radiation Oncology of Hunan Province, Central South University, Changsha 410008, Hunan, China

⁴ Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

translocation of PTEN. The nuclear pore complex-dependent transport mechanism is the major pathway that cells use for transporting molecules into the nucleus (Elosegui-Artola et al. 2017). Moreover, using the cNLS Mapper algorithm (Kosugi et al. 2009), we have identified a potential nuclear localization signal (SRNKRRYQED) in the full-length protein sequence of PTEN. These sequences might cooperatively mediate the nuclear import of PTEN. However, the authors did not take into consideration whether or not the nuclear-cytoplasmic translocation of PTEN occurs.

In Ma's report, the FGFR inhibitor AZD4547 was administered to test whether pY240-PTEN downregulation could sensitize glioma cells to IR treatment (Ma et al. 2019). However, studies have indicated that the agent AZD4547 is not a specific FGFR2 inhibitor, and also significantly impairs the expression of FGFR1 and FGFR3 (Chua et al. 2019). Therefore, more potent and specific FGFR inhibitors should be used to eliminate the side-effects of FGFR1/3 downregulation on the pY240-PTEN-mediated IR response. More importantly, to minimize the off-target effects of the FGFR inhibitor AZD4547, the roles of loss-of-function of FGFR2-PTEN should be further validated using both genetic and pharmacological inhibition models.

Of note, a few of data presented by the authors are confusing. After reviewing the data of the 44 patient-derived glioblastoma stem cells (GSCs) from Table S2 in Ma's paper, we found the median values of PTEN and FGFR2 were 2.5 and 8.65, respectively. This is contradictory with Ma's study, which reported that the median values of FGFR2 were 2.5 for all GSC cells. What is more puzzling is that the expression values of FGFR1, FGFR2 and FGFR3 that are shown are the same in all of the GSC cells. Next, we evaluated the roles of FGFR2-PTEN in the IR response in the GSCs. Unexpectedly, the portion of radioresistant patient samples with high expression of PTEN and FGFR2 was just 50% (8/16) and only 54% (7/13), respectively, but not all of the radiation-sensitive samples in the PTEN-low group showed a low level of FGFR2 expression. These results did not support the conclusion that patients with higher PTEN and FGFR2 expression were relatively IR resistant.

Acknowledgments This work is supported by National Natural Science Foundation of China (No. 81803035, 81703036, 81572946), and China Postdoctoral Science Foundation (No. 2017 M610510).

Author contributions Conception and design: ZC Gong, YL Yan, and ZJ Xu. Writing, review, and/or revision of the manuscript: YL Yan, Z Li, and ZJ Xu. Administrative, technical, or material support: Z Li, SS Zeng and X Wang.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

References

- Chua V, Orloff M, Teh JL, Sugase T, Liao C, Purwin TJ, Lam BQ, Tera M, Ambrosini G, Carvajal RD, Schwartz G, Sato T, Aplin AE (2019) Stromal fibroblast growth factor 2 reduces the efficacy of bromodomain inhibitors in uveal melanoma. *EMBO Mol Med* 11. <https://doi.org/10.15252/emmm.201809081>
- Elosegui-Artola A, Andreu I, Beedle AEM, Lezamiz A, Uroz M, Kosmalska AJ, Oria R, Kechagia JZ, Rico-Lastres P, Le Roux AL, Shanahan CM, Trepas X, Navajas D, Garcia-Manyes S, Roca-Cusachs P (2017) Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell* 171:1397–1410 e1314. <https://doi.org/10.1016/j.cell.2017.10.008>
- Huang T, Kim CK, Alvarez AA, Pangen RP, Wan X, Song X, Shi T, Yang Y, Sastry N, Horbinski CM, Lu S, Stupp R, Kessler JA, Nishikawa R, Nakano I, Sulman EP, Lu X, James CD, Yin XM, Hu B, Cheng SY (2017) MST4 phosphorylation of ATG4B regulates autophagic activity, tumorigenicity, and radioresistance in glioblastoma. *Cancer Cell* 32:840–855 e848. <https://doi.org/10.1016/j.ccell.2017.11.005>
- Kosugi S, Hasebe M, Tomita M, Yanagawa H (2009) Systematic identification of cell cycle-dependent yeast nucleocytoplasmic shuttling proteins by prediction of composite motifs. *Proc Natl Acad Sci U S A* 106:10171–10176. <https://doi.org/10.1073/pnas.0900604106>
- Ma J, Benitez JA, Li J, Miki S, Ponte de Albuquerque C, Galatro T, Orellana L, Zanca C, Reed R, Boyer A, Koga T, Varki NM, Fenton TR, Nagahashi Marie SK, Lindahl E, Gahman TC, Shiau AK, Zhou H, DeGroot J, Sulman EP, Cavenee WK, Kolodner RD, Chen CC, Furnari FB (2019) Inhibition of nuclear PTEN tyrosine phosphorylation enhances glioma radiation sensitivity through attenuated DNA repair. *Cancer Cell* 35:504–518 e507. <https://doi.org/10.1016/j.ccell.2019.01.020>
- Shen SM, Ji Y, Zhang C, Dong SS, Yang S, Xiong Z, Ge MK, Yu Y, Xia L, Guo M, Cheng JK, Liu JL, Yu JX, Chen GQ (2018) Nuclear PTEN safeguards pre-mRNA splicing to link Golgi apparatus for its tumor suppressive role. *Nat Commun* 9:2392. <https://doi.org/10.1038/s41467-018-04760-1>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.