


Commentary: Kinesin Family Member C1 Increases Resistance of Glioblastoma to Temozolomide Through Promoting DNA Damage Repair

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Keywords

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We have read with great interest the recently published work of Wu and colleagues¹, in which the authors established temozolomide (TMZ)-resistant glioblastoma (GBM) cell lines through applying escalating doses of TMZ and demonstrated that overexpression of kinesin family member C1 (KIFC1) conferred GBM cells resistance to TMZ. The repair of TMZ-induced DNA lesions involves primarily the MGMT enzyme, DNA base excision repair (BER), and DNA mismatch repair (MMR), and persistent unrepaired damage may also lead to replication fork collapse and the formation of lethal DNA double-strand breaks (DSBs)^{2,3}. Interestingly, Wu and colleagues showed that KIFC1 overexpression in TMZ-resistant GBM cells promoted the phosphorylation of DNA-PKcs, accompanied by a decreased accumulation of γ -H2AX compared with KIFC1-knockdown controls. Considering the fact that concomitant radiation plus TMZ is currently the first-line treatment in the adjuvant setting for GBM, the implication of these findings in radiotherapy resistance is in our opinion worthy of a further discussion.

Owing to the cell cycle independent nature, non-homologous end-joining (NHEJ) is the major mechanism of repair of ionizing radiation (IR)-induced DSBs and is therefore directly linked to tumor radiosensitivity⁴. As DNA-PKcs acts as a core component of NHEJ, myriad efforts have been made in recent decades toward developing novel molecular targeted agents that could potentially inhibit DNA-PKcs to eradicate radioresistant tumor cells and thereby limit tumor regrowth. However, a cardinal principle of radiation oncology—maximizing dose to tumor while minimizing normal tissue injuries—is apparently overlooked in this therapeutic strategy. As normal cells also require functional NHEJ to survive IR, systemic administration of DNA-PK inhibitors (DNA-PKi) concomitant with radiotherapy may intensify normal tissue toxicity as much as tumor toxicity. This concept is confirmed by the discontinued clinical translation of DNA-PKi wortmannin and LY294002 due to severe systemic host toxicities in preclinical models⁵. The concern is further

raised by data released from an ongoing phase I trial (NCT02516813) from Merck testing the tolerability of DNA-PKi M3814 in combination with radiotherapy, reporting enhanced normal tissue reactions including dysphagia, prolonged mucosal inflammation/stomatitis, and radiation skin injury⁶. In another completed phase I trial (NCT02316197) from Merck testing the tolerability of M3814 monotherapy, unsurprisingly, none of these normal tissue toxicities were observed⁷.

Radiotherapy remains the most important nonsurgical modality for solid malignancies, yet its efficacy in high-grade brain tumors is severely plagued by high rates of intrinsic and acquired radioresistance. Therefore, a pressing need exists within the clinical community to devise novel radiosensitizing strategies for GBM that selectively and effectively eliminate radioresistant persister cells while maximally sparing normal tissues. In this regard, we would like to highlight the significance of the findings of Wu and colleagues. As KIFC1 is overexpressed in GBM tissues compared with paracancerous normal tissues, targeted inhibition of this differentially expressed protein holds the promise of significantly circumventing the problematic normal tissue toxicities of

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DNA-PK i while preserving a similar level of radiosensitization. In addition, given the role of KIFC1 in TMZ resistance characterized in this article, targeting KIFC1 may also improve TMZ sensitivity¹, which further boosts the synergy between TMZ and radiotherapy and thereby enhances the palliative survival benefits for patients with GBM.

Author Contributions

LY and PL did the literature research and drafted the manuscript. SQ supervised the study and reviewed the manuscript. All authors approved the final version of the manuscript. LY and PL contributed equally as co-first authors.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

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