Radiotherapy resistance in glioblastoma: Mechanistic insights and novel therapeutic approaches (Review)

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Abstract. Glioblastoma (GBM) is currently the most lethal type of primary brain tumor, with a median survival time of 15-20 months despite the use of multimodal therapy. Although radiotherapy (RT) remains a cornerstone of GBM treatment, a subset of patients who initially respond to RT eventually acquire resistance, leading to tumor relapse. The emergence of radioresistance severely impairs the long-term efficacy of RT, highlighting the importance of understanding its underlying mechanisms. The present review synthesizes emerging evidence that therapy-induced remodeling of the blood-brain barrier (BBB), upregulation of ATP-binding cassette efflux transporters, hypoxia-driven hypoxia inducible factor-1α signaling and tumor microtube (TM)-mediated intercellular communication converge to create a self-reinforcing resistance network. These interconnected mechanisms collectively drive adaptive radioresistance, rather than acting in isolation. Based on this framework, the present review evaluates therapeutic strategies designed to disrupt distinct nodes of this network, including epigenetic modulators, poly (ADP-ribose) polymerase inhibitors, BBB-penetrant agents and TM-targeting approaches, such as connexin43 peptide inhibitors and high-linear energy transfer particle therapy. The clinical implications of these findings are discussed, with emphasis on biomarker-driven patient stratification and combinatorial regimens that concurrently target multiple resistance mechanisms.

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Abbreviations: GBM, glioblastoma; RT, radiotherapy; BBB, blood-brain barrier; TM, tumor microtube; PARPi, Poly (ADP-ribose) polymerase inhibitors; TMZ, temozolomide; GSC, glioblastoma stem cells; TME, tumor microenvironment; IR, ionizing radiation; DSB, double-strand breaks; DDR, DNA damage response; ATM, ataxia-telangiectasia mutated; DNA-PK, DNA-dependent protein kinase; NHEJ, non-homologous end joining; HR, homologous recombination; CHK, checkpoint kinase; MGMT, O6-methylguanine-DNA methyltransferase; OXPHOS, oxidative phosphorylation; EVs, extracellular vesicles; H3K27me3, histone H3 lysine 27 trimethylation; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; TAMs, tumor-associated macrophages; CDC, cell division cycle; APC, anaphase-promoting complex; BRD, bromodomain-containing protein; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; dsDNA, Double-stranded DNA; OS, overall survival; mOS, median overall survival; PFS, progression-free survival

Key words: glioblastoma, radiotherapy resistance, glioblastoma stem cells, tumor microenvironment, DNA repair

Contents

1. Introduction

Glioblastoma (GBM) is recognized as the most aggressive and common malignant primary brain tumor in adults, accounting for ~49% of all primary malignant brain tumors (1,2). According to the World Health Organization classification of central nervous system tumors, GBM is classified as a grade IV astrocytoma, the most aggressive type within this category (3). Consequently, the average 2- and 5-year survival rates of

GBM are 18.38 and 4%, respectively, which are markedly lower than those of other tumors, such as breast, prostate, and colorectal cancers (4-6). Several key factors contribute to this limited survival rate, including tumor heterogeneity, intrinsic resistance to standard therapies and the protective nature of the blood-brain barrier (BBB) (7), which notably impedes the efficacy of systemic treatments.

Radiotherapy (RT) is frequently paired with chemotherapy, particularly temozolomide (TMZ), to form the standard Stupp protocol, which has been used as the first-line treatment for GBM since 2005. This protocol has increased 2-year survival rates from 10.4 to 26.5% when compared with radiation alone (8,9). RT aims to target residual tumor cells, with the purpose of controlling local disease and extending patient survival; however, the efficacy of RT is often hindered by rapid repopulation of the tumor and the emergence of resistance mechanisms (10). Radioresistance, wherein tumor cells adapt and survive despite radiation, is a notable obstacle to long-term therapeutic success. Tumors often recur within the irradiated field, which highlights the challenge of achieving complete eradication of GBM cells with existing RT protocols (11). The phenomenon of radioresistance in GBM is multifaceted, involving various factors including the enhanced DNA damage repair capabilities of the tumor, the presence of therapy-resistant GBM stem cells (GSCs), and alterations in signaling pathways that promote cellular survival and proliferation under radiation stress (12,13). Additionally, the tumor microenvironment (TME) plays a pivotal role in mediating resistance, with elements such as hypoxia, immune suppression and the secretion of growth factors contributing to a resistant phenotype (14) (Fig. 1).

Given these limitations, understanding the underlying mechanisms of radiation resistance in GBM is imperative for developing novel therapeutic strategies. The present review aims to investigate the intricate biological processes that contribute to radioresistance, explore existing solutions for overcoming these hurdles and evaluate potential future therapeutic options. By assessing the interaction between GBM and its microenvironment, therapeutic options that may markedly improve patient outcomes and lead to the development of more effective treatment modalities could be identified.

2. Mechanisms of RT resistance in GBM

Enhanced DNA damage repair capacity. Radiation damages cancer cells through several mechanisms, including senescence, necrosis, mitotic catastrophe, autophagy and apoptosis (15). Among these, direct breakage of DNA by ionizing radiation (IR), particularly the disruption of phosphodiester linkage in the DNA double helix [also known as double-strand breaks (DSBs)], is a key event (16). Normally, the DNA damage response (DDR), involving proteins such as ataxia-telangiectasia mutated (ATM) and DNA-dependent protein kinase (DNA-PK), prevents the progression of cells with DNA damage into mitosis and promotes DNA repair (17). These DDR kinases facilitate two primary repair mechanisms: Non-homologous end-joining (NHEJ) and homologous recombination (HR) (18,19). Faulty repair of DSBs or defects in the DDR can lead to genomic instability, contributing to drug resistance and tumorigenesis (20). Consequently, targeting DNA damage repair pathways has emerged as a potential strategy to enhance the efficacy of RT (21).

POLD2, a subunit of the DNA polymerase Polδ exonuclease complex, participates in DNA damage repair, and its expression is elevated in GBM relative to other glioma subtypes (22). Knockdown of POLD2 sensitizes GBM cells to IR by impairing the repair of therapy-induced DNA lesions (23). Additionally, Lee *et al* (24) used 1-aminoethylimino (bis[N-oleoylcysteinylaminoethyl] propionamide)/small interfering (si)RNA nanoparticle delivery systems to deliver siRNAs targeting ATM and DNA-PK, leading to the prolonged presence of γH2AX foci, indicators of DNA damage, and increased radiosensitivity in GBM tumor cell lines. A previous study demonstrated that the Mre11-Rad50-NBS1 complex, a key component of the HR pathway, is upregulated in GBM, facilitating the repair of DSBs and conferring resistance to both RT and chemotherapy (25). Furthermore, other DDR components, such as the mismatch repair pathway, are upregulated in GBM, contributing to the repair of therapy-induced DNA damage and resistance to treatment (26).

The DDR network in GBM is sustained by multiple repair pathways that collectively counteract RT. PARP1/2 recognize single-strand breaks and initiate repair via the base excision repair (BER) machinery. Recent mechanistic work has revealed that replication-associated BER components (such as XRCC1 and POLB) are recruited through PARP1/2-mediated PARylation, promoting PARPi resistance (27). Depletion of these factors sensitizes cancer cells to PARPi and triggers ATR/checkpoint kinase (CHK)1 activation, uncovering crosstalk between BER integrity and replication stress signaling. PARP inhibition also compromises RAD51 recruitment to break sites and redirects repair toward error-prone NHEJ, thereby potentiating RT (28). In patient-derived GBM samples, elevated expression of multiple DDR genes, no factor, has been shown to be associated with poor survival, independent of isocitrate dehydrogenase or O6-methylguanine-DNA methyltransferase (MGMT) status (29). Thus, DDR-mediated radioresistance arises from coordinated multi-pathway activity rather than linear dependence on individual proteins.

Beyond the canonical sensors ATM and DNA-PK, the DDR network integrates CHK1 and CHK2 to enforce cell cycle arrest upon DNA damage, thereby ensuring that repair is completed before cell division resumes (30,31). CHK1 primarily functions during the S phase, preventing damaged DNA from entering replication, whereas CHK2 operates mainly in the G_1 and G_2/M phases by phosphorylating downstream effectors such as p53, inducing cell cycle arrest (32-34). Dysregulation of these processes may lead to RT failure, when cells continue to proliferate post-DNA repair, resulting in tumor recurrence. Moreover, DDR activation extends beyond repair mechanisms, and also influences gene expression and protein translation. For example, DDR can modulate the mTOR signaling pathway, affecting protein synthesis and subsequently altering the response of GBM cells to radiation (35). Thus, multi-targeted interventions against DDR pathways, including CHK1/CHK2 inhibitors, may serve as effective strategies to enhance RT efficacy.

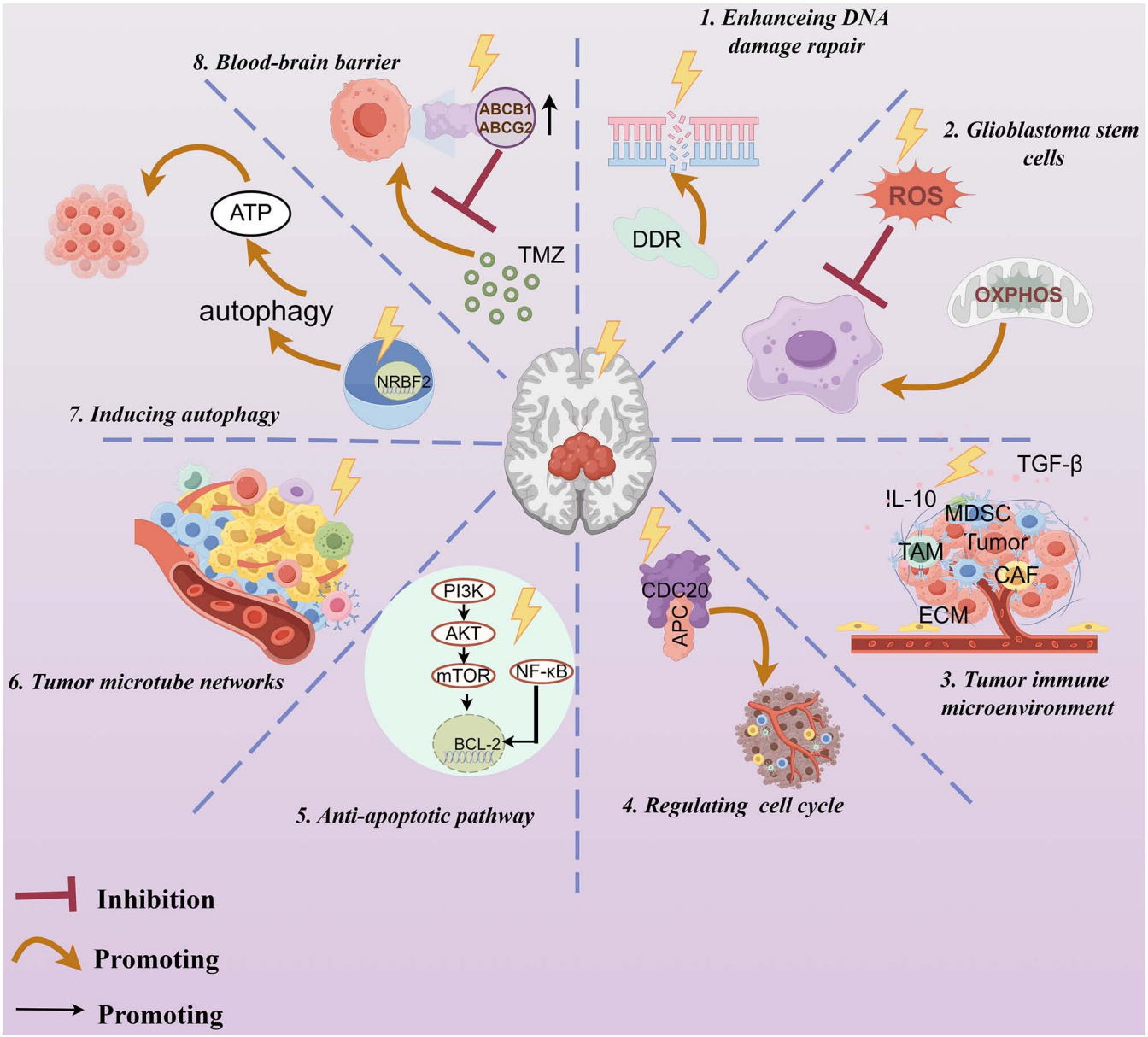

Figure 1. Schematic representation of major mechanisms underlying acquired radioresistance in GBM. Upregulated DDR pathways counteract radiation-evoked DNA lesions. GSCs reprogram their metabolism toward enhanced OXPHOS, thereby evading radiation-induced ROS damage. TAMs, MDSCs and CAFs remodel the immune microenvironment by secreting TGF-β and IL-10, fostering immunosuppression and ECM remodeling. CDC20-APC axis dysregulation drives aberrant cell cycle progression. Pro-survival signaling through PI3K/AKT/mTOR and NF-κB pathways enhances proliferation and suppresses Bcl-2-mediated apoptosis. TM networks enable intercellular dissemination of IR-induced stress. IR upregulates NRBF2, driving cytoprotective autophagy to recycle cellular components and sustain GBM cell survival. IR upregulates ABCB1 and ABCG2, two ATP-dependent efflux transporters that synergistically restrict drug accumulation at the BBB. ABCB1, ATP-binding cassette subfamily B member 1; ABCG2, ATP-binding cassette subfamily G member 2; CDC20, cell division cycle 20; APC, anaphase-promoting complex; BBB, blood-brain barrier; CAFs, cancer-associated fibroblasts; DDR, DNA damage repair; ECM, extracellular matrix; MDSCs, myeloid-derived suppressor cells; NRBF2, nuclear receptor binding factor 2; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TAMs, tumor-associated macrophages; TMZ, temozolomide. Created by Figdraw (https://www.figdraw.com).

Cancer stem cells and their role in resistance. GSCs possess self-renewal and differentiation capacities that drive tumorigenesis (36). Their resistance to radiation stems from enhanced DNA repair and a quiescent state that evades therapies targeting rapidly dividing cells, enabling tumor repopulation and recurrence after initially successful treatment (37). Moreover, the stem-like properties of GSCs are sustained by signaling pathways and molecular mechanisms distinct from those in bulk tumor cells, rendering GSCs a notable obstacle to GBM therapy (38,39).

GSCs maintain their resistance to therapy through various mechanisms, with one of the key contributors being their metabolic flexibility, particularly their reliance on mitochondrial function and oxidative phosphorylation (OXPHOS) to survive in the hypoxic TME (40). This metabolic adaptation allows GSCs to withstand oxidative stress induced by radiation therapy, further contributing to their survival and eventual tumor relapse (41). Additionally, the interaction of GSCs with their microenvironment, including the secretion of extracellular vesicles (EVs) that modulate signaling pathways, serves a notable role in maintaining the GSC state and promoting resistance to both radiation and chemotherapy. For example, radiation-induced EV release of microRNA-603 has been

shown to enhance insulin-like growth factor 1-mediated signaling, supporting GSC survival and therapy resistance (42).

In addition, epigenetic regulation has a key role in radioresistance. Macedo *et al* (43) revealed that RT promotes p53 expression in radioresistant prostate cancer cells by reducing histone H3 lysine 27 trimethylation (H3K27me3) at the p53 promoter, due to increased lysine demethylase 6B activity. Previous studies have shown that DNA methylation and histone modifications can alter gene expression, enabling GSCs to survive and proliferate even after RT in colorectal carcinoma (44,45). Furthermore, the upregulation of enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, has been implicated in treatment resistance in GSCs (46). EZH2 silences tumor suppressor genes through H3K27me3 modification, thereby protecting GSCs from RT-induced cell death (47). Targeting epigenetic modifications with agents such as DNA methyltransferase inhibitors (for example, 5-azacytidine) and histone deacetylase (HDAC) inhibitors (such as LBH589) has been shown to enhance GSC sensitivity to RT by reactivating tumor suppressor genes and inhibiting resistance-related gene expression (48,49). The combination of epigenetic therapy and RT may offer a novel approach to overcoming GBM resistance.

TME. Growing evidence has demonstrated that the immunosuppressive nature of the TME hinders effective immune responses and promotes tumor survival (50). IR has been shown to increase the expression of TGF-β, a cytokine that promotes immunosuppression and aids in the survival and invasion of GBM cells by modulating the TME (51). TGF-β also activates cancer-associated fibroblasts, which contribute to tumor growth and therapeutic resistance by secreting extracellular matrix components (for example, collagen and fibronectin) and pro-inflammatory cytokines (for example, IL-6 and CXCL12), thereby creating a supportive niche for tumor survival (52).

Additionally, radiation-induced changes can lead to the activation of tumor-associated macrophages (TAMs), which further contribute to an immunosuppressive and tumor-promoting environment (53). The TME not only supports tumor growth and resistance but also poses notable obstacles to the efficacy of immunotherapy (54). For example, the administration of dexamethasone, a corticosteroid commonly used to reduce brain edema in patients with GBM, has been shown to severely impair immune responses, especially when administered in combination with immune checkpoint inhibitors (55). This impairment is due to the reduction in T-cell populations and their functional capacity, which diminishes the effectiveness of immunotherapy (56). Furthermore, the unique characteristics of the TME in GBM, such as the presence of the BBB and high levels of immunosuppressive factors (for example, TGF-β and IL-10), limit the access and efficacy of systemic therapies, making it essential to develop strategies that can effectively modulate the TME to improve therapeutic outcomes (57,58). Emerging strategies to target the TME in GBM include the use of engineered EVs to sequester TGF-β and mitigate radiation-induced immunosuppression (51). In preclinical models, these approaches enhance cytotoxic T-cell infiltration and reprogram the TME to support antitumor immunity (59). Nano-immunotherapy targeting TAMs disrupts tumor-promoting interactions within the TME, potentiating the effects of radiation and immunotherapy (60). Collectively, these findings underscore the TME as a key determinant of therapeutic response in GBM, and highlight the need for novel strategies that effectively reprogram the TME to overcome resistance and improve patient outcomes.

Cell cycle regulation. Cell division cycle 20 (CDC20) is essential for cell cycle progression by associating with the anaphase-promoting complex (APC), an E3 ubiquitin ligase that targets specific proteins for degradation to regulate the metaphase-to-anaphase transition (61). A previous study has shown that CDC20-APC is required for the self-renewal, invasiveness and tumorigenicity of GSCs (62). Under normal conditions, CDC20-APC ubiquitinates Bim, a pro-apoptotic protein, leading to its proteasomal degradation (63,64); thus, upregulation of CDC20 helps GSCs evade apoptosis by regulating the levels of Bim (65). This degradation prevents the initiation of apoptosis, thereby allowing the cells to survive despite DNA damage induced by radiation or chemotherapy.

Another key factor implicated in cell cycle regulation and radioresistance is the pseudokinase Tribble 3 (TRIB3). Specifically, TRIB3 interacts with the protein kinase AKT, disrupting its interaction with the transcription factor forkhead box protein O1 (FOXO1) (66). The increased levels of FOXO1 then enhance the transcription of sex-determining region Y-box 2 (SOX2), a key transcription factor that promotes cancer stemness (67). Moreover, SOX2 itself can further activate the transcription of FOXO1, establishing a positive feedback loop that sustains high levels of both FOXO1 and SOX2. This loop ensures the persistence of the stem-like properties of GSCs, contributing to their ability to resist therapies and drive cancer recurrence. Yu *et al* (68) demonstrated that disrupting the TRIB3-AKT interaction can accelerate the degradation of FOXO1, leading to a reduction in SOX2 expression and a consequent decrease in the stemness of breast cancer stem cells.

Anti-apoptotic signaling pathways. The PI3K/AKT axis promotes cell survival and suppresses apoptosis. Upon activation, PI3K generates PIP3, which recruits and activates AKT, leading to phosphorylation of downstream effectors that inhibit apoptotic programs (69). Dysregulation of this pathway is common in cancer and contributes to cell death resistance. For example, AKT phosphorylates and inactivates the pro-apoptotic proteins BAD and caspase-9. In its unphosphorylated state, BAD binds to and inhibits anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, thereby promoting apoptosis (70). Phosphorylation by AKT prevents BAD from binding to these proteins, allowing Bcl-2 and Bcl-xL to inhibit apoptosis.

Inhibition of the PI3K/AKT/mTOR pathway using specific inhibitors, such as PQR309, has shown promising results in inducing apoptosis and increasing the sensitivity of GBM cells to therapeutic interventions (71). This underscores the potential of targeting the PI3K/AKT/mTOR pathway as part of a multimodal treatment strategy for GBM (72). Additionally, the AKT signaling pathway suppresses the tumor suppressor protein p53 by activating murine double minute 2 (MDM2), a ubiquitin ligase that targets p53 for degradation. When AKT phosphorylates MDM2 on specific serine residues, it enhances the nuclear localization and stability of MDM2, allowing it

to bind to p53 and tag it for proteasomal degradation (73,74). This process markedly reduces p53 levels, thus impairing its ability to induce apoptosis and arrest the cell cycle in response to stress.

Another key anti-apoptotic pathway is mediated by the NF-κB family, which regulates the expression of genes involved in cell survival, inflammation and immune responses (75). In GBM, NF-κB is often constitutively active, leading to the upregulation of several anti-apoptotic genes, including those encoding for Bcl-2 and inhibitors of apoptosis proteins (76). The activation of NF-κB not only helps GBM cells evade apoptosis, but also contributes to resistance to RT and chemotherapy by promoting an inflammatory TME that supports tumor survival and growth (77). Therefore, targeting the NF-κB pathway represents a promising strategy to overcome therapeutic resistance in GBM.

Autophagy. Autophagy occupies a context-dependent role within the radiation response network in GBM. Its activation following irradiation can serve as a cytoprotective mechanism, enabling tumor cells to mitigate lethal stress and thereby promoting radioresistance. This evolutionarily conserved lysosomal pathway facilitates the recycling of damaged cellular components, while concurrently regulating pro-growth signaling and metabolic rewiring (78-80). By degrading and recycling macromolecules, autophagy provides tumor cells with essential nutrients and energy, allowing them to survive under hostile conditions, such as radiation-induced DNA damage or cytotoxic drug exposure. Such a protective function is particularly relevant for fostering treatment resistance in GBM (81). The available evidence suggests that nuclear receptor binding factor 2, a key regulator of autophagy, is upregulated during IR, promoting the recycling of cellular components and ensuring energy production through ATP generation. This metabolic reprogramming enables GBM cells to resist radiation therapy and continue proliferating (82). Furthermore, hypoxia-induced autophagy through hypoxia inducible factor (HIF)-1α and Beclin-1 has been shown to drive radioresistance by promoting the survival of GBM cells in low-oxygen environments typical of tumor cores. This interaction between hypoxia and autophagy creates a feedback loop that enhances the ability of cells to resist radiation-induced apoptosis (83). Additionally, targeting key autophagic regulators such as autophagy-related 4B cysteine peptidase (ATG4B) and MST4 has demonstrated promising results in reducing tumor growth and enhancing radiosensitivity by inhibiting autophagic flux, thereby preventing tumor cells from utilizing autophagy for survival (84).

Substantial advances regarding the interplay between autophagy and other cell survival pathways, such as the PI3K/AKT/mTOR and AMP-activated protein kinase pathways, have further highlighted its complex role in therapeutic resistance (85-87). Autophagy can be modulated by these signaling pathways in response to stress, and inhibiting these pathways may disrupt autophagy and sensitize tumor cells to treatment. However, targeting autophagy in GBM is challenging, as its dual role requires a nuanced approach: Either promoting excessive autophagy to induce cell death or inhibiting it to prevent tumor cell survival. Research has also explored the potential of combining autophagy inhibitors with RT or chemotherapy to enhance anticancer efficacy, offering novel options for therapeutic interventions (88,89).

BBB and multidrug resistance. The BBB and multidrug resistance are frequently cited as independent factors limiting GBM therapy; however, their interplay becomes particularly insidious following RT and chemotherapy (90,91). Radiation disrupts the BBB, potentially improving drug access (92-94). However, accumulating evidence has challenged this oversimplification. Fractionated irradiation can paradoxically enhance the efflux function of ATP-binding cassette subfamily B member 1 (ABCB1) and ATP-binding cassette subfamily G member 2 (ABCG2) on brain endothelial cells, an adaptive response that may attenuate the very drug delivery it was presumed to enhance (95). This duality suggests that the barrier does not simply break down under stress but actively reconfigures its efflux capacity (96).

Chemotherapy exerts a parallel effect on tumor cells. TMZ treatment, for example, selects for GSCs that constitutively express high levels of ABC transporters and MGMT, but beyond selection, it also induces their expression in surviving cells through epigenetic and transcriptional reprogramming (97). Compounding these direct effects, both RT and chemotherapy indirectly foster a microenvironment that amplifies resistance. Hypoxia, exacerbated by radiation-induced vascular damage, stabilizes HIF-1α, which directly transactivates ABC transporter genes and promotes stemness (98), closing a self-reinforcing loop (99). Consequently, the failure of the Stupp regimen cannot be attributed solely to pre-existing resistance mechanisms. Instead, RT and chemotherapy dynamically reshape both the barrier and the intrinsic defense systems of the tumor, creating a permissive environment for acquired resistance. Such a conceptual shift moves the therapeutic focus away from static inhibition of individual targets toward disrupting the adaptive crosstalk between treatment, the BBB and the GSC niche.

TM networks and epigenetic plasticity. TM-mediated intercellular communication and niche-specific epigenetic plasticity are functionally intertwined drivers of acquired radioresistance in GBM (100,101). TMs form a multicellular syncytium that dilutes radiation-induced lethal damage across interconnected cells. Beyond direct intercellular stress sharing, TMs also facilitate the transfer of mitochondria from peripheral macrophages to irradiated glioma cells, a process potentiated by glioma-associated neurons and involving neuronal exosomal fatty acid-binding protein 7 that modifies palmitoylation of TM proteins (102). Conventional low linear energy transfer (LET) X-rays promote TM formation, whereas high LET carbon ion irradiation disrupts TM networks and enhances cell death (103,104). This differential response suggests that standard photon RT may inadvertently reinforce resistance.

Epigenetic heterogeneity across GBM niches generates a multilayered resistance system. Hypoxic cores activate the HIF-sirtuin axis to maintain quiescence. Invasive margins employ EZH2-mediated H3K27me3 to drive proneural-to-mesenchymal transition. Perivascular niches utilize HDAC DNA repair and bromodomain-containing protein (BRD) 4 super enhancer mechanisms to sustain stemness (100). These niche-specific traits are not independent,

they compensate for one another, so that targeting a single node may activate alternative pathways (105). Multiple studies have converged on the concept of a 'resistance loop' wherein niche-specific epigenetic traits collectively subvert RT efficacy (100,106).

BRD2 regulates NF-κB-mediated mesenchymal transition. PTEN loss induces RelA chromatin localization and acetylation-mediated recruitment of BRD2 to mesenchymal gene promoters. By contrast, genetic ablation or loss-of-function mutation of BRD2 bromodomains reverses mesenchymal transition, enhances radiation sensitivity and improves survival in orthotopic xenograft models (107). The FOSL1-PRMT1-CAPS circuit concurrently activates HR and NHEJ repair pathways. FOSL1 physically interacts with and stabilizes PRMT1, enhancing PRMT1-mediated asymmetric dimethylation of histone H4 at arginine 3 (H4R3me2a) and polyadenylate-binding nuclear protein 1 methylation (108). PRMT1 also promotes RT resistance in GSC-like cells by inhibiting ferroptosis, as evidenced by a reduced survival fraction following shRNA-PRMT1 transfection, an effect attenuated by the ferroptosis inhibitor Fer-1 (109,110). An additional adaptive layer is ferroptosis evasion. The senescence-associated gene interferon-γ-inducible protein 16 (IFI16) activates heme oxygenase 1 (HMOX1) transcription, attenuating lipid peroxidation and reactive oxygen species (ROS) production after irradiation (111). Growth differentiation factor 15 drives radioresistance by stabilizing the nuclear factor erythroid 2-related factor 2 protein through reduced ubiquitin-mediated degradation, thereby inhibiting ferroptosis and remodeling the immune microenvironment (112).

3. Strategies to overcome RT resistance

Targeted therapies

Anti-angiogenic therapies. GBM is one of the most highly vascularized tumors, histologically characterized by extensive endothelial cell proliferation (113). Vascular endothelial growth factor (VEGF) is instrumental in promoting vascular proliferation and increasing vessel permeability, which contributes to symptomatic cerebral edema (114). Thus, the combination of anti-angiogenic therapy and RT is a promising method for improving outcomes in GBM. A previous phase II trial (NCT01730950) suggested that the 6-month progression-free survival (PFS) rate improved from 29.1% with bevacizumab monotherapy to 54.3% with concurrent reirradiation and bevacizumab (115). However, the clinical reality has been less encouraging than preclinical models have suggested. Despite initial improvements in PFS, the addition of bevacizumab to standard therapy has consistently failed to demonstrate a statistically beneficial overall survival (OS) benefit in unselected populations of patients with GBM. The AVAglio (116) and RTOG 0825 (117) trials both showed that adding bevacizumab to RT + TMZ improved PFS but did not extend OS compared with the placebo. Notably, this pattern is not unique to bevacizumab; other anti-angiogenic agents have yielded similarly inadequate results (118,119). Collectively, these consistent failures highlight a major gap between preclinical promise and clinical benefit, a gap that has been attributed, at least in part, to the adaptive neovascularization of the tumor (120).

Preclinical evidence has suggested that upon VEGF pathway inhibition, GBM can engage multiple alternative vascularization mechanisms that bypass canonical angiogenesis (121). Vasculogenic mimicry (VM) has been associated with the Polo-like kinase 4-EPH receptor A2 axis, which activates PI3K/AKT signaling to promote VM formation independently of VEGF (122). Similarly, GSC-derived endothelial cells have been shown to contribute to tumor neovascularization, a process that is negatively regulated by dual specificity phosphatase 8 (DUSP8) and can be sustained under anti-angiogenic therapy (123,124). These alternative pathways collectively enable the tumor to maintain its blood supply and hypoxic adaptation, thereby undermining the therapeutic efficacy of angiogenesis agents alone or in combination with RT. The vascular normalization window is inherently difficult to capture in patients with GBM. Its duration varies unpredictably across individuals due to differences in tumor genotype, microenvironment and treatment regimen, and no reliable biomarkers exist for real-time monitoring (125). More importantly, the attempt to induce normalization may backfire. Prolonged or excessive VEGF blockade does not maintain a normalized state, instead, it exacerbates intratumoral hypoxia, stabilizing HIF-1α and HIF-2α, which in turn promotes a more aggressive, invasive and stem-like phenotype (126). This hypoxic adaptation not only fuels resistance to RT but also actively remodels the TME, for example by polarizing TAMs to secrete adrenomedullin, which disrupts endothelial junctions and increases vascular permeability (127). The 'window' may not only be narrow but also inherently unstable, closing as the tumor adapts.

Given these complexities, the simple combination of anti-angiogenic agents with RT has not yielded durable survival gains. Newer strategies aim to target the compensatory pathways that drive resistance, including NOTCH, Wnt, C-X-C motif chemokine receptor 4/stromal cell-derived factor-1α and the EGFR/PI3K/mTOR axis (128). Furthermore, retrospective analyses have identified that patients with low estrogen receptor 1 expression and necroinflammatory tumors might derive greater benefit from bevacizumab (129). These observations suggest that molecular or imaging biomarker-based patient stratification could potentially improve clinical outcomes. However, until reliable predictors of the normalization window become available, the clinical potential of combining anti-angiogenic therapy with RT may remain limited. Future trials could benefit from exploring adaptive dosing schedules and multipronged regimens that simultaneously block multiple vascularization pathways, rather than relying solely on VEGF inhibition.

PARPi. PARPi block BER, thereby enhancing the cytotoxic effects of TMZ and RT. Mechanistically, PARP1 is central to single-strand DNA break repair via the BER pathway, and its inhibition leads to the accumulation of DNA lesions that become lethal when HR repair is compromised (130). This synthetic lethal principle has been successfully exploited in breast (131), ovarian (132) and prostate (133) cancer harboring BRCA mutations.

PARPi represent a notable advancement in cancer treatment, particularly for patients with BRCA mutations (134).

Several PARPi, such as olaparib, rucaparib and niraparib, have been approved for clinical use in these BRCA-mutated cancer types, demonstrating promising results in improving patient survival rates. These inhibitors exploit the concept of synthetic lethality, where the concurrent disruption of PARP-mediated DNA repair and radiation-induced DNA damage leads to enhanced tumor cell death (135-137). Notably, the exploration of PARPi as a potential strategy to overcome GBM resistance has gained momentum (138). An open-label phase 0/2 trial evaluated niraparib + RT in 20 evaluable patients with newly diagnosed MGMT-unmethylated GBM [median OS (mOS) 20.3 months; median PFS 14.9 months] (139). Based on these data, a global phase 3 open-label randomized trial (NCT06388733) is underway, comparing niraparib with TMZ in 450 patients with newly diagnosed MGMT-unmethylated GBM, with co-primary endpoints of PFS and OS. However, the clinical application of PARPi is fraught with challenges, including limited penetration of the BBB, the development of resistance to the inhibitors themselves, and overlapping toxicities when used in combination with standard treatments (140). In response to these limitations, newer PARPi with improved brain penetration, such as pamiparib and niraparib, are being evaluated in phase I/II trials for GBM (141). Combinatorial approaches, including PARP inhibition with immune checkpoint blockade, are also under investigation (142,143).

Targeting the TME. The TME is a complex and dynamic network that contributes to the aggressive nature and treatment resistance of cancer (144,145). Targeting the TME has emerged as a promising therapeutic approach to overcoming RT resistance. A key feature of the TME in GBM is the presence of receptor tyrosine kinases (RTKs) and other kinases that promote tumor growth and survival (146,147). Inhibiting these signaling pathways has demonstrated the potential to disrupt the supportive TME and enhance RT efficacy (148).

Research has demonstrated that targeting RTKs and their downstream signaling pathways, such as PI3K/AKT and RAS/RAF/MEK/ERK, can reduce the resistance of GBM cells to RT (147). Heterocyclic compounds, including derivatives of pyrimidine, thiazole and quinazoline, have been identified as potent inhibitors of these pathways. By inhibiting these kinases, these compounds can disrupt the crosstalk between tumor cells and the TME, leading to increased radiosensitivity (149). Additionally, emerging evidence has indicated that targeted therapies can directly address the dual challenges posed by the BBB and multidrug resistance. For example, the brain-penetrant taxane TPI 287, specifically designed to evade ABCB1-mediated efflux, produced three complete and nine partial responses in 23 evaluable patients with recurrent GBM when combined with bevacizumab, highlighting the potential of chemical circumvention of BBB efflux (150). Furthermore, a phase III trial (NCT05902169) is evaluating focused ultrasound to mechanically open the BBB, a strategy shown to improve survival in a patient-derived xenograft model, offering a complementary physical approach to enhance drug delivery. Additionally, these targeted therapies can help in overcoming the BBB and multidrug resistance mechanisms, which are notable challenges in the treatment of GBM (151,152). The development and optimization of such compounds are key for improving the therapeutic outcomes in patients with GBM, particularly in those with recurrent tumors.

Targeting TM networks and ferroptosis. Conventional radiochemotherapy for GBM targets DNA replication, cell division and apoptotic pathways. Two emerging therapeutic modalities address resistance mechanisms that lie outside this framework: Disruption of TM-mediated intercellular communication and the induction of ferroptosis. TMs form a multicellular syncytium that dilutes radiation-induced lethal damage. The integrity of this network depends on connexin43 (Cx43)-microtubule interactions and a Cx43 mimetic peptide (JM2) disrupts this interaction. In GSC-derived and patient-derived xenograft models, JM2 treatment has been shown to reduce GSC survival and suppress tumor growth (101). Notably, the effect of TM disruption is radiation-quality dependent. Conventional low-LET X-rays increase TM connectivity in U87 MG and LN229 cell lines 6-10 h after 1.8 Gy irradiation (103). By contrast, high-LET carbon-ion irradiation reduces TM network connectivity and enhances cell death (104).

Ferroptosis is an iron-dependent, non-apoptotic cell death pathway driven by lipid peroxidation. Several pharmacological agents have been evaluated for their ability to induce ferroptosis in GBM models (153,154). The cholesterol-processing inhibitor lomitapide depletes intracellular ubiquinone and sensitizes TMZ-resistant GBM cells to ferroptosis. In an orthotopic mouse model, lomitapide combined with TMZ was shown to prolong survival and delay tumor recurrence compared with TMZ alone (155). Furthermore, the mevalonate pathway inhibitor atorvastatin has been tested in a phase II trial for newly diagnosed GBM (n=36), reporting an mOS of 19.9 months (156). The NAMPT inhibitor GMX1778 induces ferroptosis via mitochondrial metabolic reprogramming and enhances tumor immunogenicity in GL261 glioma-bearing mice (157). The sulfonylurea compound glyburide disrupts the IFI16-HMOX1 pathway and restores radiosensitivity in GBM cells (111). In addition, a sequential carbon-ion-photon irradiation regimen induces clustered DNA DSBs, leading to cytoplasmic double-stranded DNA (dsDNA) accumulation, activation of the cyclic GMP-AMP synthase-stimulator of interferon genes pathway and nuclear receptor coactivator 4-ferritin heavy chain 1 axis-driven ferritinophagy, ultimately triggering ferroptosis (158). Collectively, these strategies target non-cell-autonomous resistance networks or non-apoptotic cell death pathways. However, their evidence base remains preclinical or early-clinical, with no phase III validation for any TM-targeting or ferroptosis-inducing agent in GBM to date.

Combination therapies in RT resistance of GBM

Integration of chemotherapy with RT. The combination of chemotherapy and RT remains the standard treatment for GBM, with TMZ being the most commonly used chemotherapeutic agent. TMZ works synergistically with RT by inducing DNA damage, thereby enhancing the effects of radiation and improving survival rates. However, resistance to TMZ, often due to MGMT upregulation, remains a notable obstacle (159). Previous studies have suggested that hyperfractionated accelerated RT combined with TMZ yields comparable efficacy to normofractionated RT (mOS 14.9 vs. 16.9 months; P=0.26),

Table I. Summary of clinical trials of medical complications for patients with glioblastoma.

Treatment	Status	Primary outcome measure	NCT number
Focused ultrasound next generation dome helmet	Recruiting, Phase I	Safety	NCT07179328
Oncolytic virus alone	Recruiting, Phase I	MTD	NCT07145047
Laser interstitial thermal therapy (LITT) + lomustine	Not yet recruiting, Phase 1	Safety and tolerability	NCT07145112
MSC11FCD alone (cell therapy)	Not yet recruiting, Phase 1	Treatment-related serious AEs	NCT07143812
Surgery + intraoperative radiotherapy	Recruiting, Phase I	OS	NCT07141732
Sonodynamic therapy (SDT) + SOC	Enrolling by invitation, Phase II	PFS	NCT07130149
TLX-101-Tx + lomustine	Enrolling by invitation, Phase III	Safety and tolerability	NCT07100730
SonoCloud-9 ultrasound + carboplatin	Recruiting, Phase III	OS	NCT05902169
RT + TMZ + ENZ	Completed, Phase III	OS	NCT03776071
RT+ TMZ + Marizomib	Completed, Phase III	OS	NCT03345095
Dose-escalated RT alone	Not yet recruiting, Phase II	OS	NCT06835803
DOC1021 + pIFN + SOC	Recruiting, Phase II	OS	NCT06805305
NK cell therapy alone	Recruiting, Phase II	ORR by interval tumor size	NCT06687681
Oncolytic virus ON-01 alone	Recruiting, Phase II	Safety	NCT06562621
L-TC + SOC	Not yet recruiting, Phase II	OS	NCT06477939
Low-dose RT + sintilimab	Recruiting, Phase II	PFS	NCT06220552
Niraparib alone (PARP inhibitor)	Recruiting, Phase III	PFS, OS	NCT06388733
Retifanlimab + bevacizumab + hypofractionated RT (HFRT)	Recruiting, Phase II	OS	NCT06160206
ATM inhibitor WSD0628 + RT	Recruiting, Phase I	MTD	NCT05917145
STAT3 inhibitor WP1066 + RT	Recruiting, Phase II	PFS, TME	NCT05879250
Liposomal curcumin + SOC	Recruiting, Phase Ib-IIa	DLTs	NCT05768919
Pembrolizumab alone (PD-1 inhibitor)	Recruiting, Phase IV	PFS, OS	NCT05235737
Irinotecan + bevacizumab + RT	Recruiting, Phase I	AEs	NCT05201326
ADI-PEG 20 + SOC	Recruiting, Phase II	OS	NCT04587830
Neoadjuvant camrelizumab alone (PD-1 inhibitor)	Recruiting, Phase II	PFS, OS	NCT04583020
L19TNF + lomustine	Recruiting, Phase II	DLTs, OS	NCT04573192
UCPVax vaccine alone	Recruiting, Phase II	Immunogenicity	NCT04280848
Preoperative single-fraction RT alone	Recruiting, Phase I	MTD, MTIV	NCT03582514

MTD, maximum tolerated dose; AE, adverse event; OS, overall survival; PFS, progression-free survival; SOC, standard of care; RT, radiation therapy; TMZ, temozolomide; ORR, objective response rate; TME, tumor microenvironment; DLT, dose-limiting toxicities; MTIV, maximum tolerated irradiation volume.

while potentially reducing treatment duration (160,161). Despite these advancements, overcoming TMZ resistance remains a key focus, necessitating further exploration of combination therapies to address this challenge.

Integration of immunotherapy and RT. The combination of immunotherapy and RT presents a promising strategy for GBM treatment, leveraging the ability of RT to enhance tumor immunogenicity. RT can increase tumor antigen expression and modify the TME, making it more vulnerable to immune-mediated destruction (162). This approach has been explored in conjunction with immune checkpoint inhibitors targeting programmed death-1 and cytotoxic T-lymphocyte-associated protein 4 to amplify the immune response against GBM (163). Additionally, gene therapy strategies can further enhance the immunogenic effects of RT. FMS-like tyrosine kinase 3 ligand (Flt3L) stimulates dendritic cell production, improving tumor antigen presentation and promoting antitumor T-cell activation (164). A phase I trial of Flt3L-based immunotherapy plus RT in newly diagnosed high-grade glioma reported an mOS of 21.3 months with no dose-limiting toxicity (165). These approaches may markedly improve the efficacy of immunotherapy combined with RT, potentially leading to improved outcomes for patients with GBM.

Epigenetic modification inhibitors. Abnormal epigenetic changes, including DNA methylation, histone modification and chromatin remodeling, can activate oncogenes or silence

tumor suppressor genes, thereby contributing to cancer progression and therapeutic resistance (166,167). In cancer, hypermethylation of tumor suppressor genes enables cancer cells to evade normal cell death mechanisms and repair the DNA damage caused by RT (168). DNA methylation inhibitors block this process, reactivating tumor suppressor genes and making cancer cells more vulnerable to radiation (169). Additionally, these inhibitors can enhance the ability of the immune system to recognize and destroy cancer cells by promoting the expression of immune-related genes. Research has shown that HDAC inhibitors prevent deacetylation, leading to a more open chromatin structure that facilitates gene expression, including genes involved in cell cycle arrest and apoptosis (170). By inhibiting HDAC, these drugs can increase cancer cell death in response to RT, particularly in cancer with elevated HDAC activity. Moreover, inhibitors targeting histone methyltransferases (such as EZH2) and demethylases [for example, Jumonji domain-containing protein D3 (JMJD3)] reduce repressive methylation marks, thus reactivating genes involved in the DDR and enhancing radiosensitivity (171,172). In TMZ-resistant GBM cells, the EZH2 inhibitor EPZ6438 can increase dsDNA breaks irrespective of irradiation, and combinatorial use with the JMJD3 inhibitor GSK-J4 has been shown to further reduce cell viability following irradiation (173).

Metabolic inhibitors. The metabolic adaptability of GSCs is a key factor in their resistance to therapy. Targeting these metabolic pathways can enhance the efficacy of RT. The glycolysis inhibitor 2-deoxy-D-glucose works by mimicking glucose but prevents its proper breakdown; this effectively starves cancer cells of energy, making them more susceptible to radiation-induced damage (174). These inhibitors also reduce lactate production, a key by-product of glycolysis, which can contribute to the immunosuppressive microenvironment of tumors and enhance resistance to therapy (175,176). In addition, OXPHOS is a mitochondrial process that cancer cells use to produce large amounts of ATP, particularly under nutrient-scarce or hypoxic conditions. Some cancer cells switch between glycolysis and OXPHOS depending on the availability of oxygen and other resources. This metabolic flexibility can contribute to resistance against RT, as cells can use OXPHOS to meet their energy needs when glycolysis is inhibited (177,178). OXPHOS inhibitors disrupt mitochondrial function, leading to reduced energy production and an increase in ROS. Elevated ROS levels exacerbate DNA damage caused by RT, making it harder for cancer cells to repair and survive (179). Previous research has suggested that OXPHOS inhibitors can be particularly effective in cancer with mitochondrial mutations or in tumors located in hypoxic environments, where reliance on OXPHOS is greater (180).

Cancer cells also depend on lipid metabolism for survival, especially in high-stress conditions, such as those induced by RT (181). Fatty acids are essential components of cell membranes and they also serve as energy stores that cancer cells can utilize when glucose is limited (182). Enhanced fatty acid oxidation (FAO) can help cancer cells generate ATP and mitigate the effects of oxidative stress caused by radiation (40). Blocking FAO or fatty acid synthesis disrupts the ability of cancer cells to generate energy and repair radiation-induced damage. This strategy makes cancer cells more vulnerable to RT, particularly in aggressive types of cancer such as GBM, prostate and breast cancer, where fatty acid metabolism serves a notable role (183,184).

4. Conclusion

GBM remains one of the most challenging types of cancer to treat due to its aggressive nature and inherent resistance to conventional therapies. Despite notable advancements in understanding the molecular and cellular mechanisms underlying GBM, the survival rates for patients have seen only modest improvements (185). The integration of advanced RT techniques, such as stereotactic radiosurgery, intensity-modulated RT and proton therapy, offers novel options for enhancing treatment efficacy (12). However, these methods also highlight the ongoing struggle against radiation resistance, which is driven by factors such as tumor heterogeneity, hypoxia and the presence of cancer stem cells. The success of combining RT with other treatment modalities, such as chemotherapy and immunotherapy, illustrates the importance of a multifaceted approach (186,187).

Looking forward, the future of GBM treatment likely lies in the continued refinement of these advanced techniques and the development of novel therapies that can effectively target the underlying mechanisms of radiation resistance. Ongoing research into the TME, genetic and epigenetic modifications, and innovative drug delivery systems will be critical in overcoming the barriers that currently limit the effectiveness of existing treatments (Table I). The integration of these advancements into clinical practice provides the greatest potential to improve outcomes for patients with GBM.

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Authors' contributions

DZ contributed to conceptualization, organizing extracted data into structured tables, performing literature search, screening, and quality assessment, creating figures and diagrams, writing the original draft, writing, reviewing and editing. YZ contributed to organizing extracted data into structured tables, cross-checking extracted data against original sources and verifying methodological consistency, creating figures and diagrams, writing-original draft, writing, reviewing and editing. FL contributed to writing, reviewing and editing. CZ contributed to study conception and acquired funding. SJ contributed to investigation, cross-checking extracted data against original sources and verifying methodological consistency, writing, reviewing and editing. All authors read and approved the final manuscript. Data authentication not applicable.

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Competing interests

The authors declare that they have no competing interests.

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