Targeting glutathione metabolism for tumor radiosensitization (Review)

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Abstract. Radiotherapy represents a cornerstone treatment modality in oncology and primarily mediates tumor cell death through the generation of reactive oxygen species (ROS). Nevertheless, elevated glutathione (GSH) levels within tumor cells can scavenge these ROS, thereby compromising the efficacy of radiotherapy and promoting the emergence of radioresistance. The contemporary understanding of redox regulation in cancer underscores the strategic relevance of targeting GSH metabolism in the context of radiotherapy. This review comprehensively describes the mechanisms through which GSH metabolism contributes to radioresistance and surveys novel therapeutic approaches aimed at inhibiting GSH synthesis or promoting its depletion to achieve radiosensitization. Both pharmacological compounds and nanotechnology-enabled delivery systems have been investigated, with an emphasis on their ability to intensify oxidative stress in tumors characterized by high GSHcontent, thus potentially improving radiotherapeutic outcomes.

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Abbreviations: GSH, glutathione; ROS, reactive oxygen species; RT, radiotherapy; GCL, glutamate-cysteine ligase; GS, GSH synthetase; TME, tumor microenvironment; SS, disulfide bonds; Nrf2, nuclear factor-erythroid related factor 2; Cys, cysteine; IR, ionizing radiation; 2-DG, 2-deoxyglucose; SER, sensitization enhancement ratio; AuNCs, gold nanoclusters; SAS, sulfasalazine; GSTs, GSH S-transferases; PL, piperlongumine; Asc-s, ascorbyl stearate; SNAP, S-nitroso-N-acetylpenicillamine; NO, nitric oxide; ATP, adenosine triphosphate

Key words: tumor radiotherapy, glutathione metabolism, redox modulation, reactive oxygen species, tumor microenvironment

Contents

1. Introduction

Radiotherapy (RT) is a fundamental modality in the clinical management of cancer, with more than half of all patients receiving RT during their treatment course (1). The efficacy of RT primarily stems from the generation of reactive oxygen species (ROS) by ionizing radiation (IR)-induced water radiolysis, a process responsible for the majority of cellular damage (2). Given that water constitutes ~80% of the cellular content, this mechanism leads to significant oxidative stress, making intracellular ROS levels a critical determinant of tumor radiosensitivity (3). High levels of ROS damage critical cellular components, including proteins, nucleic acids, lipids, membranes and organelles. The 'oxidative stress' cancer biology theory highlights the critical role of the antioxidant defense system in counteracting this process (4). This theory elucidates how tumor cells upregulate the activity of antioxidant systems such as glutathione (GSH) to prevent ROS from exceeding a lethal threshold. Bansal and Simon (5) further emphasized that this adaptive redox homeostasis, governed largely by GSH, is a key factor in tumor radioresistance.

A critical determinant of radioresistance is the unregulated redox homeostasis in tumor cells, with GSH metabolism playing a central role. GSH, a tripeptide composed of glutamate, cysteine and glycine, is the most abundant intracellular antioxidant and is synthesized across different cell types (6). Its primary role is to maintain redox balance by scavenging free radicals, thereby protecting cells from damage induced by ROS (7). Notably, compared with normal cells, tumor cells inherently produce more GSH to support their aberrant proliferation (8). This notable increase in GSH is driven by the upregulated uptake of precursors and increased biosynthesis (9). It is a common feature across multiple malignancies, including breast, colon and lung cancer, as well as leukemia, and is closely linked to tumor initiation, progression, metastasis and therapeutic resistance (10).

Despite its success in certain malignancies, direct tumor targeting faces inherent limitations, including intratumoral heterogeneity, the rapid emergence of acquired resistance and a reliance on specific molecular markers that are not universally present across all cancer types (11). By contrast, elevated GSH metabolism represents a shared adaptive hallmark across a wide spectrum of tumors, driven by common stress responses to proliferation-associated oxidative stress (12). This universality makes GSH metabolism an attractive broad-spectrum vulnerability that circumvents the need for individualized molecular targets. Furthermore, elevated GSH levels are intimately linked to radioresistance, as GSH efficiently scavenges radiation-induced ROS (13,14). Therefore, targeting GSH metabolism is not intended to replace radiotherapy but rather to resensitize tumor cells to radiation by disabling their primary antioxidant defense. Thus, targeting GSH metabolism is a broad-spectrum, resistance-resilient adjuvant strategy that resensitizes tumors to radiotherapy by dismantling their primary antioxidant defense. High intracellular GSH levels in the tumor microenvironment (TME) directly undermine RT efficacy (15). The ROS generated by IR are effectively neutralized by GSH, thereby diminishing oxidative damage and allowing tumor cell survival even in the presence of radiation (16). Thus, targeting GSH metabolism represents a promising strategy for overcoming tumor resistance to IR-induced cell death. By promoting GSH depletion or inhibiting its synthesis, tumor cells lose the ability to buffer IR-induced ROS, amplifying oxidative damage (17).

This review explores the multifaceted role of GSH in tumor radioresistance and critically evaluates the evolving strategies for targeting GSH metabolism to achieve tumor radiosensitization. As the field has advanced, a clear developmental trajectory has emerged: From the first generation of crude small-molecule inhibitors that systemically dampen GSH synthesis to the second generation of passively targeted nanomaterials that improve tumor accumulation via the EPR effect and, finally, to the ongoing third generation of integrated platforms. This review will dissect this evolutionary path, highlighting how each generation has built upon the last generation to overcome previous limitations and offering a perspective on the future of innovative GSH-targeting radiosensitizers. Fig. 1 provides an abstract schematic overview of emerging strategies that target GSH metabolism to counteract radioresistance by amplifying cellular oxidative stress and sensitizing tumor cells to radiotherapy.

2. Tumor GSH metabolism and targeting strategies

GSH metabolism in tumor cells. GSH is the most abundant intracellular antioxidant and plays a critical role in maintaining cellular redox homeostasis (18). In normal cells, GSH helps preserve cysteine levels and detoxify xenobiotics. In tumor cells, however, metabolic dysregulation contributes to resistance to therapy, including radioresistance (19). A hallmark of malignant tumor cells is elevated GSH levels. GSH levels in tumor cells are typically 4- to 10-fold higher than those in normal cells (20). GSH is usually synthesized in two ATP-dependent steps. The rate-limiting step, catalyzed by glutamate-cysteine ligase (GCL), produces γ-glutamylcysteine, which is then converted to GSH by GSH synthetase (GS) (21). Its antioxidant function is maintained through a continuous cycle: GSH peroxidase 4 (GPX4) uses it to neutralize lipid peroxides, generating oxidized glutathione (GSSG), which is then reduced back to GSH by GSH reductase (GR) at the expense of NADPH. This process safeguards tumor cells from IR-driven oxidative damage (22).

In GSH metabolism, cystine is tightly coupled to GSH synthesis. Cystine, a disulfide-bonded dimer of cysteine, is a critical GSH precursor (23). Its uptake is mediated by the cystine/glutamate antiporter (xCT). This transporter maintains redox balance and supports GSH synthesis by exchanging extracellular cystine for intracellular glutamate (24). Intracellular GSH reduces the disulfide bond of cystine and generates cysteine in tumor cells (25). Cysteine is a substrate for the GCL- and GS-related reactions involved in GSH synthesis. This interdependence forms a feedback loop. In this loop, GSH modulates the membrane redox environment and enhances cystine uptake. The increased uptake further fuels the synthesis of GSH. Additionally, the reduction in GSSG levels by GR sustains GSH levels while cysteine is recycled, reinforcing cellular defenses against oxidative stress (26,27). Elevated GSH levels in tumor cells contribute to radioresistance by enhancing the scavenging of ROS, thereby compromising treatment efficacy (28). Therefore, targeting GSH metabolism represents a promising strategy to improve RT outcomes (29).

GSH metabolism-related radioresistance mechanisms. RT exerts its cytotoxic effects primarily through IR-induced ROS, which disrupt redox homeostasis and cause lethal oxidative damage to cellular components. However, the TME exhibits dynamic adaptability in response to RT, activating multiple signalling pathways that contribute to radioresistance (30). The elevated GSH metabolism in tumor cells acts as a critical defense against this assault. In addition to its fundamental role in scavenging ROS, GSH actively orchestrates a network of pro-survival signalling pathways. This is achieved primarily through S-glutathionylation, a key posttranslational modification that modulates the redox state of critical cysteine residues in signalling proteins (31).

Several intrinsic signalling pathways and their associated proteins critically influence cellular radiosensitivity (Fig. 2). The forkhead box (Fox)O and p53 pathways are critically involved in maintaining redox balance under radiation stress (32). FoxO activation enhances cystine uptake and GSH synthesis via the upregulation of xCT, whereas elevated GSH levels subsequently fine-tune the activity of p53 and its apoptotic targets (33,34). This interplay highlights the role of GSH

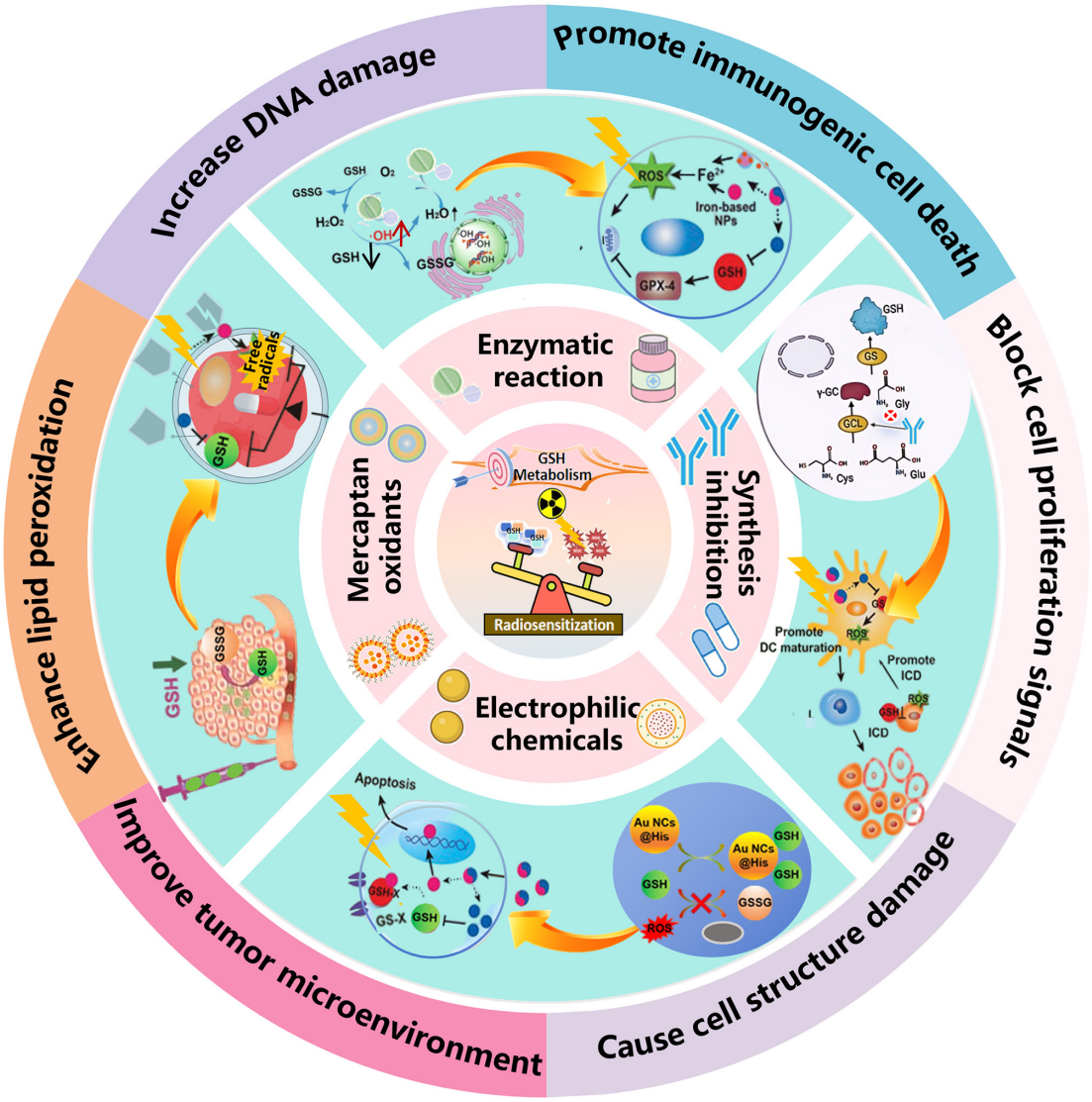

Figure 1. Abstract schematic diagram of targeting GSH metabolism as radiosensitization strategy. The emerging strategies are designed to counteract radioresistance by targeting GSH metabolism. They efficiently amplify cellular oxidative stress and sensitize tumor cells to radiotherapy. GSH, glutathione; ROS, reactive oxygen species; NPs, nanoparticles; DNA, deoxyribonucleic acid; GSSG, oxidized glutathione; GS-X, glutathione polymer; GPX-4, glutathione peroxidase 4; Cys, cysteine; Gly, glycine; Glu, glucose; GCL, glutamate cysteine ligase; GS, glutathione synthetase; DC, dendritic cell; ICD, immunogenic cell death.

in regulating stress response pathways. Notably, p53 activation itself is partially ROS dependent and influences RT outcomes through caspase-mediated apoptosis (35,36).

In addition to intracellular signalling, GSH metabolism provides multilayered protection against radiation-induced damage (37). At the structural level, it directly safeguards membrane and cytoskeletal integrity by maintaining thiol groups in a reduced state, while GPX4 utilizes GSH to suppress lipid peroxidation (38,39). Adaptively, cells can upregulate xCT and GPX4 expression to reinforce this defense under oxidative stress (40,41). Simultaneously, GSH plays a role in a coordinated transcriptional response (42). It activates Nrf2 to increase antioxidant gene expression (43-45) but conversely suppresses NF-κB signalling through S-glutathionylation and stabilization of inhibitor of NF-κB (IκB)α, thereby limiting its nuclear translocation and survival output (46,47). Experimental evidence confirms that GSH depletion disrupts IκB kinase activity and NF-κB activation (48,49). This interconnected regulatory network significantly influences RT efficacy.

Additionally, GSH supports the Hippo-Yes-associated protein (YAP)1 signalling axis by maintaining S-glutathionylation (50). YAP1 can enhance DNA repair by upregulating the expression of factors such as X-ray repair cross complementing 4 and promoting nonhomologous end joining (51). In multiple cancer types, Hippo pathway activation restrains YAP1 nuclear translocation and transcriptional output, thereby reducing the expression of DNA repair and antiapoptotic genes (52). Consequently, the GSH-mediated maintenance of Hippo-YAP1 signalling reduces cellular susceptibility to RT, highlighting another mechanism through which GSH supports tumor cell survival under oxidative stress.

Strategies to modulate tumor GSH metabolism. Recent advances in tumor RT research have enabled more precise targeting of GSH metabolism to improve therapeutic efficacy and reduce off-target effects (53). These strategies can be broadly divided into two complementary methods. One is the inhibition of intracellular GSH biosynthesis, which disrupts

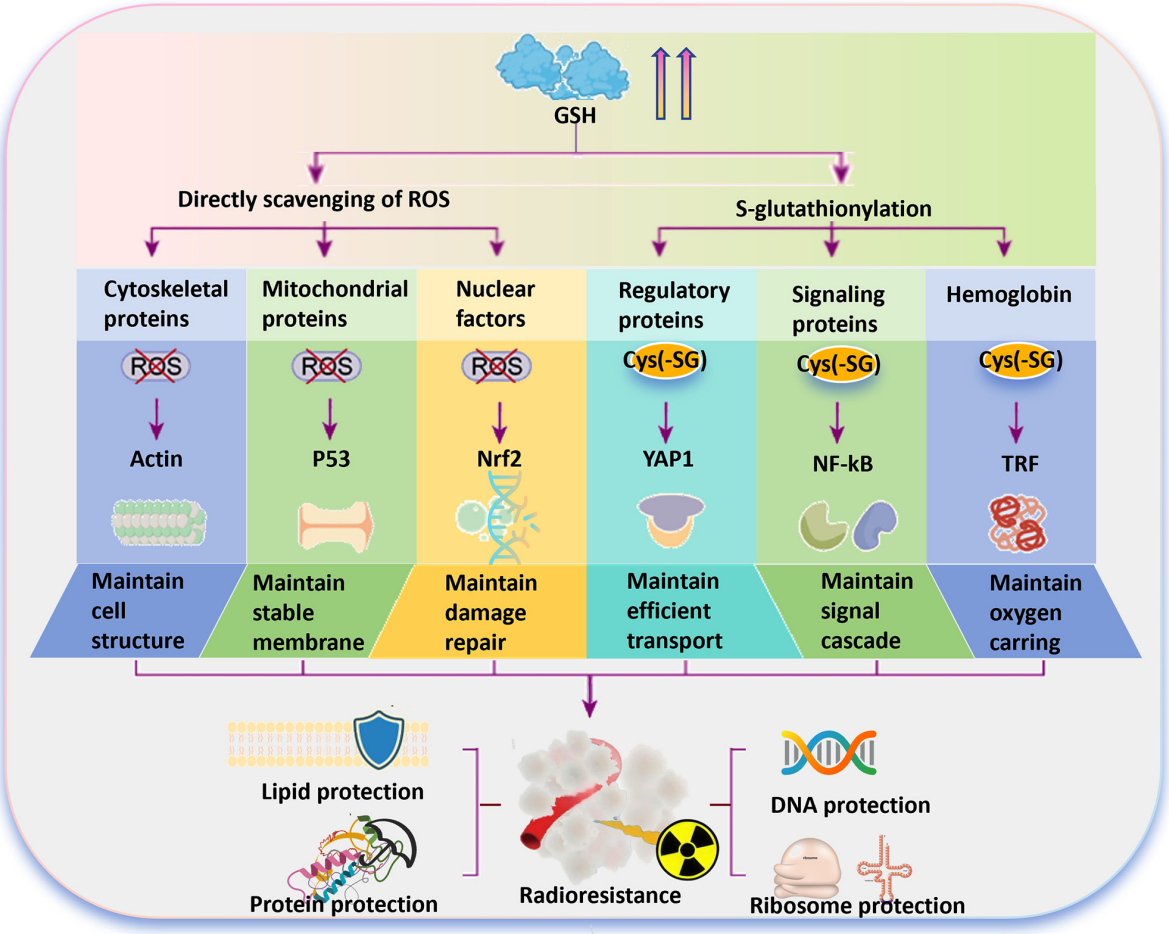

Figure 2. GSH induced radioresistance via regulating signaling pathways. The intracellular GSH metabolism confers radioresistance by enabling cancer cells to counteract RT-induced oxidative stress and damage through its various antioxidant activity. GSH, glutathione; ROS, reactive oxygen species; Cys, cysteine; Nrf2, nuclear factor erythroid 2-related factor 2; YAP1, Yes-associated protein; NF-κB, nuclear factor κB; TRF, transferrin; DNA, deoxyribonucleic acid.

the production of new GSH by targeting key synthesis enzymes or precursor supply pathways. The other is the depletion of existing intracellular GSH, which directly reduces preformed GSH reserves through oxidative or conjugation-mediated mechanisms (Fig. 3). By making rational use of these strategies, researchers aim to overcome radioresistance and significantly increase oxidative stress in tumor cells (54).

Targeting key enzymes or transporters involved in precursor supply is a common way to inhibit intracellular GSH biosynthesis. For example, the natural compound oleanolic acid inhibits GCL activity, thereby blocking the synthesis of γ-glutamylcysteine and ultimately mediating radiosensitization (55). Similarly, inhibiting GS prevents the formation of GSH itself. The key transporter target is xCT, as mentioned above (56). Small molecules such as erastin impair cystine uptake through this transporter, which depletes cysteine pools and limits GSH production (57). Additionally, inhibition of GSH regeneration pathways is an effective synthesis inhibition strategy. For instance, the use of glycolysis inhibitors can reduce NADPH availability. This strategy hinders the GR-mediated reduction of GSSG to GSH, thereby disrupting GSH recycling (58).

While inhibiting GSH synthesis is one viable strategy, a complementary and more rapid approach is to directly deplete intracellular GSH reserves. The depletion of existing intracellular GSH can directly reduce preformed GSH reserves, thereby amplifying tumor-cell oxidative stress. This approach primarily employs two methods (59). One method is oxidative depletion, in which nanoparticles (NPs) containing disulfide bonds (S-S) or metal ions (such as copper or iron) oxidize GSH to GSSG. The resulting GSSG is then either exported from the cell or cannot be efficiently regenerated (60). The other method is conjugation-mediated efflux. This process promotes the conjugation of GSH with xenobiotics via GSH S-transferases. The conjugated products are subsequently extruded by transporters such as multidrug resistance-associated protein 1, reducing intracellular GSH levels (61). However, a single approach involving GSH depletion typically leads to only a transient reduction in GSH levels, as tumor cells compensate by upregulating synthesis pathways. Therefore, a rational combination of biosynthesis inhibition and depletion strategies is essential for achieving sustained GSH suppression, effectively overcoming this adaptive resistance and maximizing tumor radiosensitization (62).

3. Targeting GSH synthesis pathways for tumor radiosensitization

Given that numerous tumors exhibit enhanced GSH biosynthesis to maintain redox homeostasis, targeting its

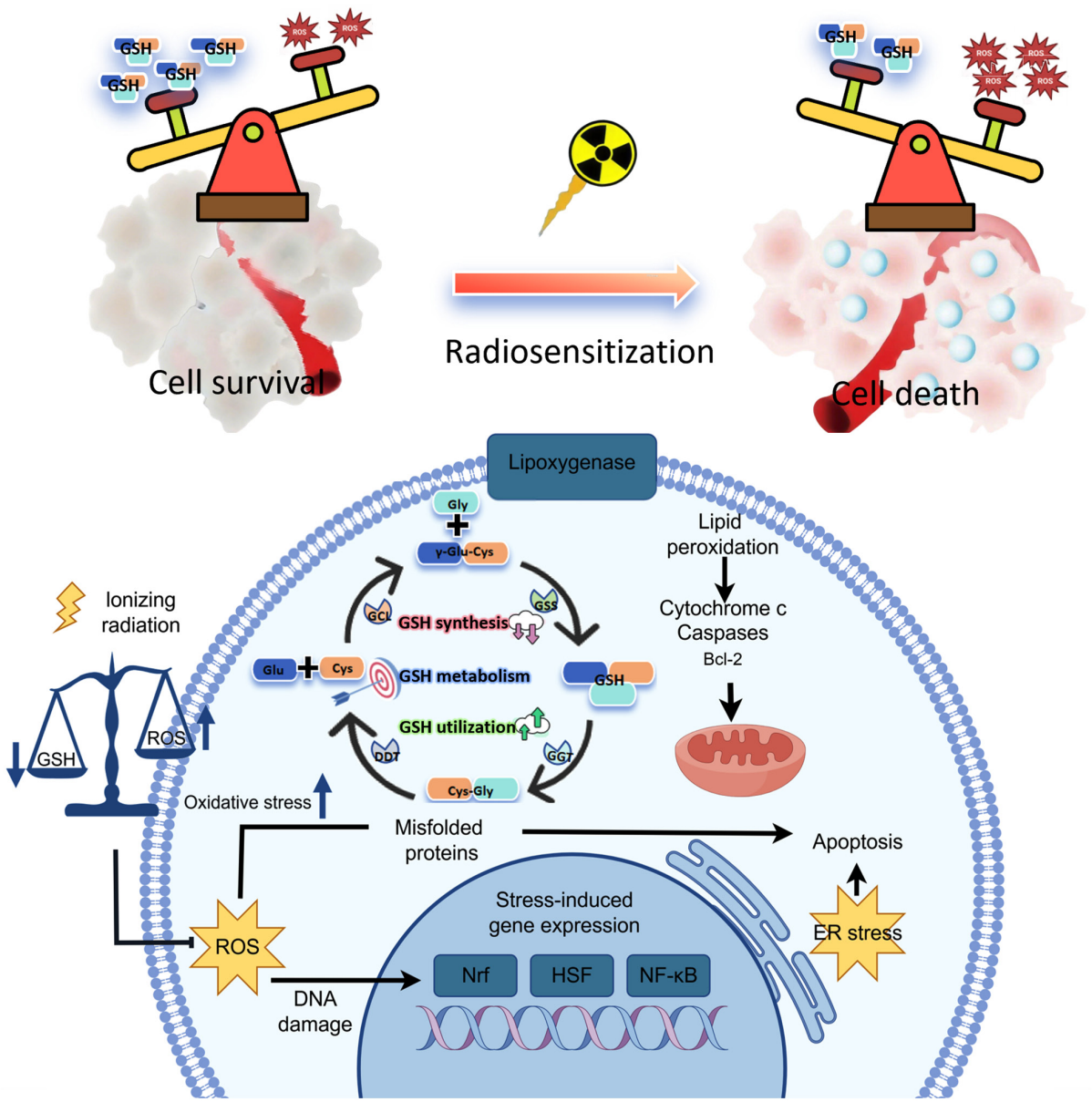

Figure 3. Targeting GSH metabolism for radiosensitization. GSH metabolism supports direct free radical scavenging by maintaining a reducing environment. This antioxidant role underlies radioresistance, and targeting GSH synthesis and utilization in radiotherapy elevates intracellular ROS by impairing this protective function. GSH, glutathione; ROS, reactive oxygen species; GSH, glutathione; ROS, reactive oxygen species; Cys, cysteine; Gly, glycine; Glu, glucose; GCL, glutamate cysteine ligase; GSS, glutathione synthetase; GGT, gamma-glutamyl transferase; DDT, deoxynucleotidyl transferase; ER, endoplasmic reticulum.

synthesis pathways provides a direct strategy to compromise the antioxidant defense at its source (63). This section systematically reviews key molecular targets within the GSH synthesis pathway and the corresponding pharmacological or nanomaterial-based agents designed to disrupt them for effective tumor radiosensitization (Fig. 4).

Inhibiting synthetase activity. As the rate-limiting enzyme in GSH biosynthesis, GCL is a prime target for inhibiting GSH production (64). Buthionine sulfoximine (BSO) is a classic GCL inhibitor with excellent radiosensitizing effects (65). At millimolar concentrations, BSO reduces intracellular GSH levels to 40-50% of control values. This GSH synthesis inhibition method has been shown to achieve radiosensitization in various types of tumor cells, including Chinese hamster V79 cells, as well as human lung, renal and head and neck tumor cells, under both oxygenated and hypoxic conditions (66). Notably, BSO also synergizes with other radiosensitizers: Its combination with the hypoxic radiosensitizer misonidazole yields enhanced antitumour effects in multiple preclinical tumor models (67). The safety profile of BSO has been evaluated in an early-phase clinical trial involving cancer patients. A phase I dose-escalation study demonstrated that BSO administered as infusions every 12 h was well tolerated (68).

In addition to classical enzyme inhibitors such as BSO, various functional materials capable of suppressing GS have also shown potential for depleting intracellular GSH. For instance, Mayur *et al* (69) investigated the cytotoxic mechanism of latex-capped silver NPs in human lung carcinoma cells and reported a significant reduction in intracellular GSH levels, attributable to the inhibition of GSH-synthesizing

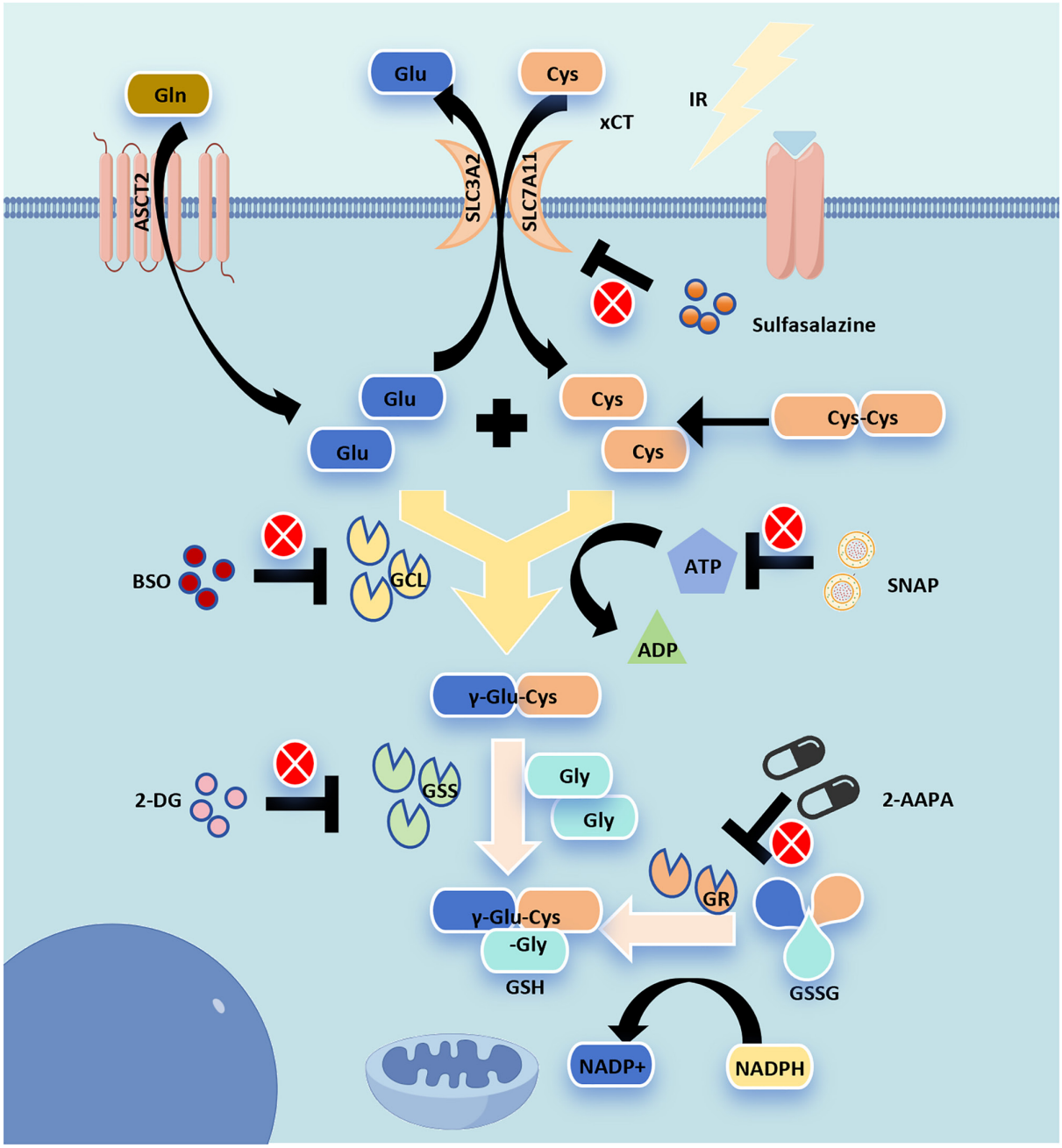

Figure 4. Inhibiting GSH production for tumor radiosensitization. Targeting key enzymes or transporters involved in precursor supply is a common way for intracellular GSH biosynthesis inhibition and has shown promise in radiotherapy. [created with Biorender (biorender.com)]. GSH, glutathione; IR, ionizing radiation; BSO, buthionine sulfoximine; xCT, cystine/glutamate antiporter; Cys, cysteine; Gly, glycine; Glu, glucose; Gln, glutamine; GCL, glutamate cysteine ligase; GSS, glutathione synthetase; GR, glutathione reductase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; 2-DG, 2-deoxy-D-glucose; 2-AAPA, 2-acetylamino-3-[4-(2-acetylamino-3-carboxypropylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid; SNAP, S-nitroso-N-acetylpenicillamine.

enzymes. Continued efforts to develop potent and specific GS inhibitors are therefore highly important for improving RT efficacy. Despite its well-established preclinical efficacy, the clinical application of BSO is limited by its modest potency, requirement for millimolar concentrations and potential systemic toxicity upon prolonged administration. Future efforts should focus on developing more potent and selective GCL inhibitors, as well as tumor-targeted delivery strategies to increase intratumoral accumulation while minimizing off-target effects. Additionally, combination regimens that pair GCL inhibitors with other GSH-depleting modalities may achieve synergistic radiosensitization.

Inhibiting synthesis substrate uptake. An adequate amino acid supply is a fundamental prerequisite for GSH biosynthesis. Impairment in the transport of extracellular amino acids essential for GSH synthesis disrupts the production of GSH, leading to reduced intracellular GSH levels (70). Among these factors, cysteine availability is particularly critical. Cysteine starvation has thus emerged as a common strategy to deplete GSH, primarily through the regulation of xCT ability. This transporter mediates the uptake of extracellular cystine, which is subsequently reduced to cysteine intracellularly to support both protein synthesis and GSH synthesis (71). Consequently, disruption of xCT function blocks cystine uptake and reduces

intracellular GSH production. Growing evidence indicates that regulating xCT represents a promising approach for tumor radiosensitization.

Sulfasalazine (SAS) exerts anticancer effects by specifically inhibiting xCT function. In glioma cells, SAS-mediated GSH depletion increases ROS accumulation, DNA damage and subsequent cell death. When combined with radiation, SAS enhances antitumour efficacy and improves survival in glioblastoma xenograft models (72). However, its clinical translation still requires balancing efficacy and safety. A clinical trial evaluating this combination (NCT00753038) reported a high discontinuation rate of SAS due to hematologic toxicity, with no clear clinical benefit observed (73). Fortunately, as a safer xCT inhibitor, sorafenib has achieved good results in clinical trials (CTR2200066117). This combination of sorafenib and RT was superior to RT alone (74). Further optimization of dosing or delivery strategies may be needed to mitigate drug toxicity and side effects. The new compound DC10 formed by scaffold jumping and structural optimization of SAS performed better in terms of side effects and bioavailability. Sarowar *et al* (75) reported that DC10 is well tolerated and acts as a radiosensitizer by inhibiting cystine uptake. While inhibition of xCT represents a rational strategy for reducing the effects of GSH, its clinical translation is limited by the narrow therapeutic window of existing inhibitors such as SAS, which exhibit dose-limiting hematologic toxicity. Furthermore, compensatory upregulation of alternative cysteine acquisition pathways may limit the durability of xCT-targeting approaches. Future directions include the development of isoform-selective xCT inhibitors with improved safety profiles and the exploration of combination strategies that simultaneously target multiple cysteine uptake routes to overcome adaptive resistance.

Inhibiting regeneration reactions. When GSH is oxidized to GSSG during antioxidant reactions, it simultaneously catalyzes its reduction back to GSH. This recycling mechanism not only maintains intracellular GSH pools but also facilitates cysteine regeneration. Targeting this GR-mediated cycle has emerged as a viable therapeutic approach to induce tumor cell death. As evidenced by 2-acetylamino-3-[4-(2-acetylamino-3-carboxypropylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid, a specific GR inhibitor, suppression of GR activity induces oxidative stress that effectively inhibits melanoma metastasis and synergistically enhances the efficacy of chemotherapeutic agents against human glioblastoma cells (76). Furthermore, inhibition of NADPH is essential for maintaining cellular GSH homeostasis, as it serves as a cofactor for the GR-mediated conversion of GSSG back to GSH. Agents that deplete NADPH can thus indirectly inhibit GSH regeneration and increase radiosensitivity (77). For instance, the natural isoflavone genistein has been shown to decrease NADPH reserves in multiple tumor cell types, resulting in significant GSH depletion and increased susceptibility to radiation (78). This effect is partly attributed to the interference of genistein with NADPH-producing pathways, such as the pentose phosphate pathway, although the precise underlying mechanisms remain unclear (79). In addition to natural compounds, pharmacological inhibitors targeting key enzymes involved in NADPH generation (e.g., glucose-6-phosphate dehydrogenase) also exhibit promising radiosensitizing properties by limiting the reducing equivalents required for GR activity (80).

Furthermore, combination strategies that simultaneously target GR activity and the supply of NADPH may yield synergistic effects. For example, compared with single-target approaches, the use of GR inhibitors alongside compounds that induce NADPH consumption could exhaust redox resilience more comprehensively. Notably, it is also worth noting that IR itself can alter cellular metabolism and NADPH availability, suggesting a potential positive feedback loop when combined with metabolic inhibitors (81).

Despite promising preclinical results, the translation of NADPH/GR-targeting strategies into clinical practice requires careful consideration of selectivity and toxicity, given the role of NADPH in normal cellular functions (82). Future efforts should focus on developing tumor-specific delivery systems to minimize off-target effects. Additionally, identifying biomarkers of NADPH pathway activation may help select patients most likely to benefit from such radiosensitization approaches (83). Thus, targeting the GR pathway represents a rational and evolving strategy to overcome radioresistance rooted in antioxidant adaptation.

Inhibiting energy supply. The inhibition of ATP production represents a viable strategy for suppressing the energy supply for GSH synthesis because both steps of GSH biosynthesis are ATP-dependent (84). 2-Deoxyglucose (2-DG), a glucose analogue, functions as a glycolytic inhibitor by targeting hexokinase. Upon phosphorylation by hexokinase, 2-DG is converted into 2-DG-phosphate, which cannot be further metabolized by phosphoglucose isomerase. This results in the intracellular accumulation of 2-DG-phosphate and the subsequent depletion of ATP (85). In preclinical models of cervical cancer and pancreatic tumors, 2-DG has been shown to increase radiosensitivity through mechanisms linked to metabolic oxidative stress and disruption of thiol metabolism (86). Importantly, the combination of hypofractionated RT with orally administered 2-DG (200-300 mg/kg) has demonstrated good tolerability in patients with glioblastoma (87). Notably, 2-DG may also mitigate radiation-induced damage to normal tissues, thereby contributing to an improved quality of patients' life.

In addition to direct ATP inhibition, innovative approaches have been developed to simultaneously disrupt energy metabolism and redox balance. Recently, Qiao *et al* (88) constructed a liposomal nanoplatform loaded with the nitric oxide (NO) prodrug S-nitroso-N-acetylpenicillamine (SNAP). Following systemic administration, the elevated GSH levels in the TME promote NO release from SNAP. The released NO rapidly reacts with superoxide anions generated during RT to form peroxynitrite, a highly reactive nitrogen species that induces severe oxidative damage and cell death. Furthermore, when combined with cold exposure, this strategy triggered systemic thermogenesis, which exacerbated tumor energy starvation and led to a significant reduction in both ATP and GSH levels within the tumor.

Collectively, the strategies used to inhibit GSH synthesis, including targeting GCL, cystine uptake or NADPH-dependent reduction pathways, effectively decrease intracellular GSH levels and enhance radiotherapeutic efficacy (Table I). Although the clinical translation of certain inhibitors, such

Table I. Application of inhibiting GSH production in tumor radiosensitization.

Targeting strategies	Materials	Mechanism of action	Experimental model	(Refs.)
GSH synthetase *inhibition*	Oleanolic acid	Attenuate GCL activity	*In vitro* (C6, A549)	Qi *et al* (64)
	L-buthioninesulphoximine	Irreversibly inhibits GCL	*In vivo* (4T1)	Zeng *et al* (67)
	Latex capped silver nanoparticles	Inhibits GSH synthesizing enzyme	*In vitro* (A549)	Mayur *et al* (69)
Synthesis substrate *inhibition*	Quercetin	Inhibits xCT	*In vivo* (CT26)	Xu *et al* (71)
	Sulfasalazine	Downregulates xCT	*In vivo* (MDA-231-MB, 4T1)	Kerkhove *et al* (72)
	Sulfasalazine	Specifically inhibits xCT	Phase I/II clinical trial (NCT01577966)	Takeuchi *et al* (73)
	Sorafenib	Directly inhibits xCT	Phase II single-arm clinical trial (CTR2200066117)	He *et al* (74)
	DC10	Specifically inhibits xCT	*In vivo* (A375)	Sarowar *et al* (75)
GSH reductase *inhibition*	2-AAPA	Inhibits GSSG recycled back to GSH by GR	*In vitro* (TE-13, KYSE-450, KYSE-510)	Li *et al* (76)
	Temozolomide	Inhibits GSSG recycled back to GSH by GR	*In vivo* (U251)	Zhu *et al* (77)
ATP inhibition	2-Deoxyglucose	Inhibits glycolysis and ATP production	*In vivo* (G361)	Dwarakanath *et al* (85)
	3-bromopyruvate	Disrupts oxidative phosphorylation and glycolysis	*In vivo* (CT26, 4T1)	Hasse *et al* (86)
	SNAP	Inhibits ATP and decreases GSH	*In vivo* (4T1)	Qiao *et al* (88)
	Platelet membrane biomimetic nanomedicine	Inhibits glycolysis and ATP production	*In vitro* (MDA-MB-231, PANC-1)	Chen *et al* (89)

xCT, cysteine/glutamate antiporter; GSH, glutathione; GCL, glutamate cysteine ligase; GR, glutathione reductase; 2-AAPA, 2-acetylamino-3-[4-(2-acetylamino-3-carboxypropylsulfanylthiocarbonyl-amino)phenylthiocarbamoylsulfanyl]propionic acid; SNAP, S-nitroso-N-acetylpenicillamine; ATP, adenosine triphosphate.

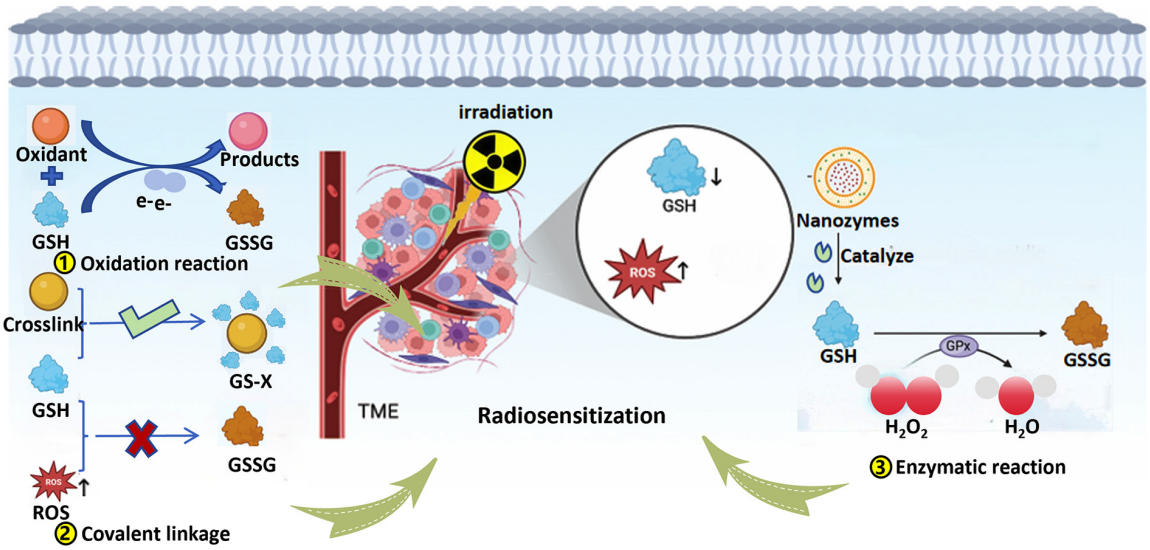

Figure 5. Promoting GSH depletion for tumor radiosensitization. Various targeting strategies of promoting GSH depletion (oxidation reaction, covalent linkage and enzymatic reaction) reduce GSH levels and enhance radiotherapy efficiency [created with Biorender (biorender.com)]. GSH, glutathione; ROS, reactive oxygen species; TME, tumor microenvironment; GSSG, oxidized glutathione; GS-X, glutathione polymer.

as SAS, is limited by systemic toxicity, other agents, such as BSO and 2-DG, demonstrate favorable safety and tolerability profiles, underscoring their potential as radiosensitizers (89).

4. Promoting GSH depletion for tumor radiosensitization

Direct depletion of intracellular GSH serves as a rapid and effective strategy to disrupt redox homeostasis and enhance tumor radiosensitivity. By diminishing the major cellular antioxidant reservoir, this approach significantly amplifies radiation-induced oxidative stress, leading to increased damage to macromolecules and potentiated cancer cell death (90,91). To achieve efficient GSH consumption, a variety of synthetic materials and nanoplatforms have been developed (Table II), which operate primarily through three core mechanistic pathways: i) The oxidation of GSH to GSSG by leveraging its strong reducibility (92); ii) the facilitation of GSH conjugation with electrophilic molecules, often via glutathione S-transferase-mediated pathways, resulting in the formation and export of GS-X conjugates (93); and iii) the acceleration of GSH depletion through enzyme-mimetic or catalytic reactions (94). This section reviews the design principles and mechanisms underlying these distinct GSH-depleting strategies and explores their application in tumor radiosensitization (Fig. 5).

Promoting chemical oxidation. Leveraging the reducing property of GSH, a key strategy to enhance RT efficacy is to use chemical substances that deplete intracellular GSH via oxidation-reduction reactions, thereby amplifying oxidative stress and limiting the ability of tumor cells to scavenge ROS (95). For example, some high-atom-number (high-Z) element nanomaterials are good oxidants. High-Z elements, such as bismuth, gold and gadolinium, exhibit strong X-ray attenuation and photoelectric effect, making them effective radiosensitizers by enhancing local radiation energy deposition. Zhao's group developed gadolinium-containing polyoxometalate-conjugated chitosan (GdW_{10}@CS) NPs via ionotropic gelation, designed to mitigate radioresistance. Upon X-ray IR, the GdW_{10}@CS NPs serve as exogenous radiosensitizers, inducing significant production of ROS (96). Notably, the oxidative tungsten (VI) species released from these NPs reacts with intracellular GSH in tumor cells, reducing ROS scavenging and thereby markedly improving RT effects. Additionally, the reaction between the released species and GSH is rapid and efficient, ensuring that the radiosensitizing effects are maximized during the short window of X-ray exposure (97).

To achieve a more precise RT, the same group recently integrated bismuth heteropolytungstate (BiP_5W_{30}) nanoclusters with reduced graphene oxide (98). This system provides a TME-responsive mechanism. An acidic TME can trigger the cycle conversion of W from W^{5+} to W^{6+}, and the redox reaction between W^{6+} and GSH results in the reversed activity of GSH in tumor cells and increases the production of ROS (99). Cu_2-xSe NPs have recently garnered significant research interest owing to their various advantages: They possess excellent GSH oxidase-like activity and their constituent elements, copper and selenium, are essential trace elements for the human body (100).

In parallel, S-S provides another widely exploited strategy to deplete GSH. These bonds can be cleaved by GSH via a redox reaction, generating sulfhydryl groups and GSSG. This GSH-consuming reaction is typically harnessed in redox-responsive drug delivery systems for controlled drug release within tumor cells with high levels of GSH (101). On the basis of this mechanism, it is reasonable to hypothesize that a sufficient density of S-S within a material could effectively induce intracellular GSH depletion. A prominent strategy to incorporate substantial amounts of S-S into nanocarriers is through framework doping, wherein S-S is preintegrated into molecular building blocks prior to NP assembly (102). For instance, Ling *et al* (103) constructed NPs using disulfide-rich polymers, which demonstrated effective GSH scavenging and enhanced RT efficacy. Despite these advances, a critical question remains unresolved: A large number of S-S need to

Table II. Application of promoting GSH depletion in tumor radiosensitization.

Targeting strategies	Materials	Mechanism of action	Experimental model	(Refs.)
Chemical oxidizing	GdW_{10}@CS nanosphere	Produces ROS and depletes GSH	*In vivo* (Hela, BEL-7402)	Yong *et al* (96)
	Cisplatin	Oxidizes the endogenous GSH	*In vivo* (Hela, 3T3)	Luo *et al* (97)
	BiP_5W_{30} nanoclusters	Oxidizes the endogenous GSH	*In vivo* (HeLa)	Zhou *et al* (98)
	Bi_2WO_6-BP	Oxidizes the endogenous GSH	*In vivo* (MDA-231-MB, 4T1)	Ren *et al* (99)
	Cu_2-xSe	Produces ROS and depletes GSH	*In vivo* (4T1)	Chen *et al* (100)
	Disulfide bonds	Cleaves GSH via redox reaction	*In vivo* (Hela)	Liu *et al* (101)
	Propyl gallate	Produces ROS and depletes GSH	*In vitro* (4T1)	Fu *et al* (102)
	Pt (IV) prodrugs	Oxidizes the endogenous GSH	*In vivo* (A2780)	Ling *et al* (103)
Covalent conjugation	Asc-s	Binds of Asc-s with GSH's thiols structure	*In vitro* (EL4)	Mane *et al* (105)
	AuNCs@His	Conjugated with GSH via Au-S bond	*In vivo* (U14)	Zhang *et al* (106)
	AuNCs-based biohybrid system	Conjugates with GSH via Au-S bond	*In vivo* (A549, 4T1)	Hua *et al* (107)
	PL self-assembled polymeric NPs	Electrophilically attacks and bonds with GSH	*In vivo* (CT26)	Wang *et al* (109)
Enzymatic reaction	Polyaniline inorganic-organic nanohybrids	Catalyzes GSH oxidation through organic hydroperoxides	*In vivo* (4T1)	Wang *et al* (113)
	Iron oxide nanozymes	Catalyzes Fenton-like reactions	*In vitro* (MCF-7)	Liu *et al* (114)
	Cerium oxide nanozymes	Increases GSH conversion	*In vitro* (A549)	Liu *et al* (115)
	MoS_2-based Nanoflowers	Enhances self-cascade catalysis	*In vivo* (Hela)	Wu *et al* (117)
	Mn-based nanosystems	Increases GSH conversion	*In vivo* (4T1)	Pan *et al* (118)
	Au@Mn-MOF	Increases hydroxyl radical levels	*In vivo* (4T1)	Xiong *et al* (119)
	Cuhemin-Au	Reduces GSH via multienzyme-like catalytic reactivity	*In vivo* (4T1)	Qiao *et al* (124)
	Copper-based single-atom nanozyme	Increases GSH conversion	*In vivo* (4T1)	Chen *et al* (127)

GSH, glutathione; ROS reactive oxygen species; Asc-s, ascorbyl stearate; PEG, polyethylene glycol; PL, piperlongumine; MOF, metal-organic framework.

be present to meet the demand for depleting intracellular GSH. The destruction of tetrasulfide bonds depletes GSH, which is more effective than S-S. Thus, tetrasulfide bond frameworks may be a better choice for radiosensitization materials.

Promoting covalent conjugation. The covalent conjugation of GSH, a pivotal antioxidant in tumor cells, has emerged as a sophisticated strategy to disrupt redox homeostasis and potentiate anticancer therapies. This approach exploits the nucleophilic thiol group of GSH to form irreversible adducts with electrophilic agents, achieving dual objectives: Permanent GSH depletion and generation of bioactive conjugates with intrinsic cytotoxicity (104). For instance, Mane and Kamatham (105) examined the radiosensitizing effect of Ascorbyl stearate (Asc-s) in murine T-cell lymphoma cells. They reported that Asc-s significantly decreased the GSH/GSSG ratio and enhanced the RT effect through binding with the thiol structure in GSH.

Gold nanoclusters (AuNCs) have shown considerable promise as radiosensitizers in preclinical studies, with evaluations at clinically relevant radiation energy levels. Zhang *et al* (106) developed a histidine-capped gold nanoclusters (AuNCs@His) to achieve radiosensitization via intracellular GSH depletion. This is achieved by the formation of Au-S bonds. Treatment with AuNCs@His (at a concentration of 100 μM) reduced the intracellular GSH concentration from 1.86 to 0.42 mM. The sensitization enhancement ratio (SER) was ~1.54. This SER value is significantly higher than that of most metal-based radiosensitizers. As another typical example, Hua *et al* (107) designed an AuNCs-based biohybrid system using covalent conjugation to deplete intracellular GSH. Owing to their small size, AuNCs exhibit prolonged tumor retention and efficient renal clearance and several AuNCs are currently under evaluation in clinical trials for cancer treatment applications (NCT02680535, NCT01270139) (108).

In addition to metal-based radiosensitizers, Wang *et al* (109) reported self-assembled polymeric NPs coloaded with the GSH-depleting agent piperlongumine (PL). *In vivo* antitumour studies confirmed that PL electrophilic attack-mediated GSH depletion potently enhances the RT effect via covalent conjugation of GSH, irreversibly exhausting antioxidant reserves. Compared with their metal-based counterparts, polymer-based nanoradiosensitizers are generally considered to offer superior biocompatibility and greater potential for clinical translation, although their comparative advantages require validation in clinical settings (110).

Promoting catalytic reaction. In addition to directly reducing GSH by oxidizing materials, accelerating GSH oxidation by special materials with corresponding catalytic activity is another effective approach to indirectly promote GSH depletion (111). For example, nanozymes have diverse catalytic properties. They have emerged as promising tools for depleting intracellular GSH in tumors, thereby enhancing the effects of RT by amplifying radiation-induced oxidative stress (112). Nanozymes leverage their catalytic activities to promote GSH depletion and disrupt tumor cell antioxidant defenses, thereby serving as effective radiosensitizers in cancer therapy (113). Various nanozymes have been extensively investigated and shown to exhibit therapeutic potential through GSH depletion and ROS modulation.

Iron oxide NPs (IONPs) have attracted significant attention because they can catalyze Fenton-like reactions. These reactions convert H_2O_2 into highly reactive hydroxyl radicals (•OH). The generated •OH causes direct oxidative damage to tumor cells and oxidizes GSH into GSSG (114). Complemented by their excellent biocompatibility and surface functionalization capacity, IONPs enable targeted delivery to tumor sites. This leads to a marked reduction in intracellular GSH levels. Additionally, cerium oxide NPs (CONPs) are distinguished by their unique redox switching capabilities, arising from the reversible valence transition between Ce^{3+} and Ce^{4+}. This property endows CONPs with dual redox reactivity: Under oxidative stress conditions in the TME, they efficiently catalyze the oxidation of GSH to GSSG and promote ROS accumulation. Conversely, they scavenge excess ROS in healthy tissues. This dual functionality makes CONPs ideal for simultaneously enhancing tumor radiosensitivity and protecting healthy tissues from radiation exposure (115).

Manganese-based nanozymes have recently emerged as potent catalytic agents for depleting intracellular GSH (116). Through rational structural design, these nanozymes can efficiently promote the oxidation of GSH to GSSG. For instance, Wu *et al* (117) demonstrated that MnS_2 functions as an effective catalyst to accelerate GSH oxidation. In another study, Pan *et al* (118) developed a targeted radiosensitizer by hybridizing Mn_3O_4 with the metal-organic framework ZIF-8. The high surface area and porosity of ZIF-8 enhanced reactant adsorption and transport, whereas its integration with Mn_3O_4 strengthened the interaction between manganese species and GSH in the TME, leading to improved GSH depletion efficiency. Furthermore, Xiong *et al* (119) synthesized a heterojunction nanozyme named Au@Mn-MOF, where efficient electron transfer within the heterostructure facilitated energy delivery to catalytic active sites, thereby promoting the Mn^{2+}-catalyzed Fenton reaction.

Emerging strategies for tumor-targeted and ROS-responsive GSH-depleting radiosensitizers. To facilitate clinical translation, next-generation GSH-depleting radiosensitizers must achieve tumor-specific delivery and spatiotemporally controlled activity to minimize systemic toxicity. Recent advances in stimuli-responsive nanoplatforms have opened promising avenues to address these challenges (120,121).

TME-responsive delivery systems exploit unique TME features, such as acidic pH, elevated GSH levels or overexpressed enzymes. Among these, GSH-responsive nanocarriers incorporating S-S or tetrasulfide bonds are particularly attractive, as these linkages are specifically cleaved by high intracellular GSH concentrations in tumor cells, triggering payload release while simultaneously consuming GSH (122). Notably, compared with conventional disulfide bonds, tetrasulfide bonds exhibit higher GSH depletion efficiency, making them superior candidates for radiosensitization.

ROS-responsive prodrugs and nanozymes offer another powerful tool, given that RT itself generates a burst of ROS. ROS-responsive chemical moieties include arylboronic esters, thioketals and proline oligomers (123). When integrated into nanocarriers, these groups undergo structural cleavage upon ROS exposure, enabling radiation-triggered drug release and creating a positive feedback loop: Radiation generates ROS → ROS cleaves the carrier → released GSH-depleting

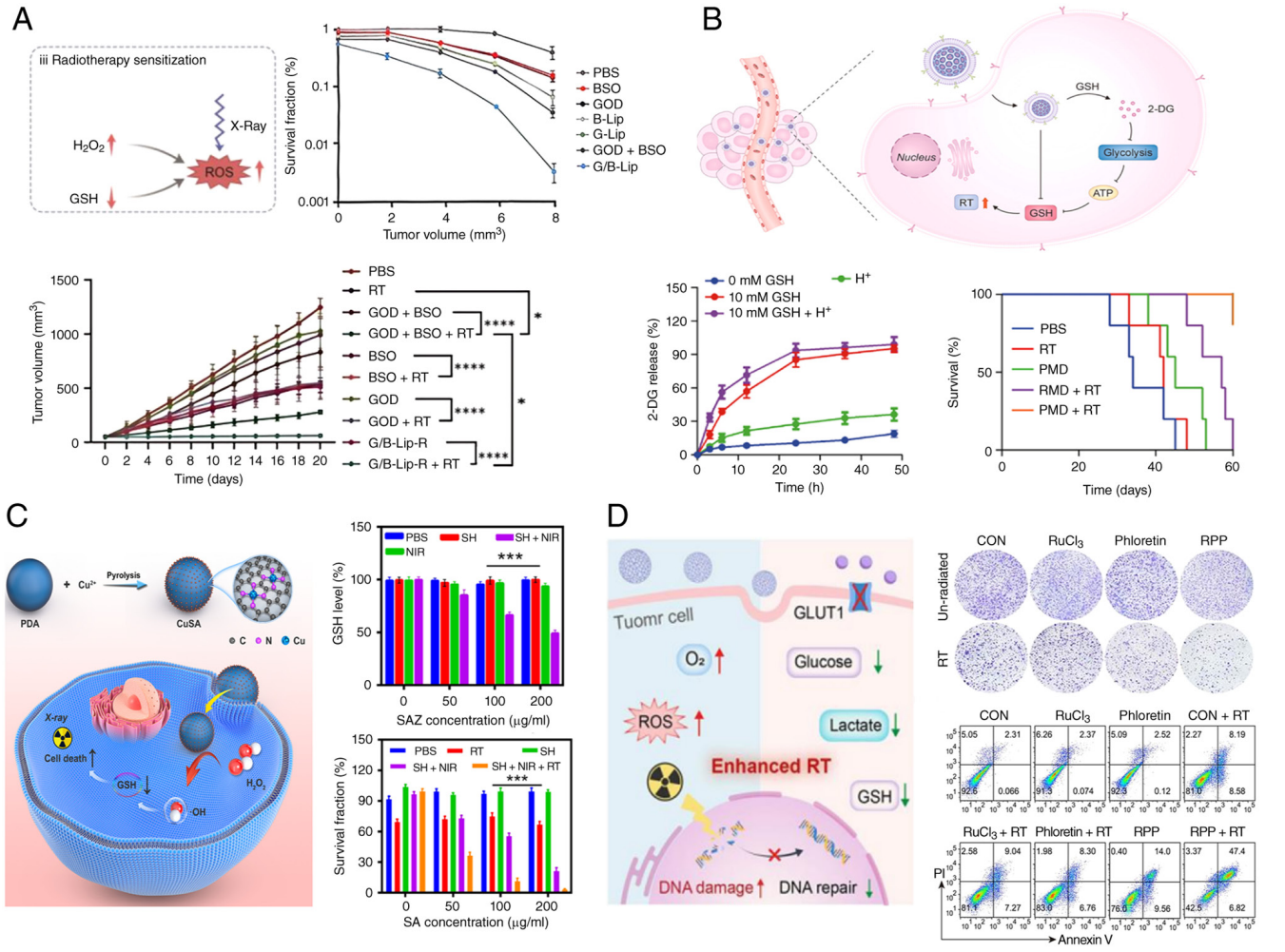

Figure 6. (A) Glucose and GSH synergistic dual-starvation strategy for RT sensitization enhancement. Copyright 2025 Elsevier. (B) Platelet membrane biomimetic nanomedicine induces dual GSH consumption for enhancing cancer radioimmunotherapy. Copyright 2024 Elsevier. (C) Copper single atom nanozyme for GSH-depleted enhanced RT. Copyright 2024 IOP Publishing. (D) RPP nanozyme with multienzyme activities and glucose metabolism inhibition for radiosensitization. Copyright 2025 Elsevier. *P<0.05, ***P<0.001, ****P<0.0001. RT, radiotherapy; GSH, glutathione; 2-DG, 2-deoxy-D-glucose; BSO, buthionine sulfoximine; GOD, glucose oxidase; ROS, reactive oxygen species; NIR, near infrared; PDA, polydopamine; SA, single atom; SAZ, single atom nanozyme; ATP, adenosine triphosphate; PMD, platelet membrane biomimetic nanomedicine; CON, copper single atom nanozyme; GLUT1, glucose transporter 1.

agent amplifies oxidative stress → further ROS production → enhanced radiosensitization.

Dual-responsive systems (e.g., GSH/ROS or GSH/pH) provide even greater precision. For example, heterojunction nanozymes such as Cuhemin-Au nanosheets have been engineered to simultaneously respond to TME cues and exogenous radiation, resulting in both GSH depletion and catalytic ROS generation (124). These platforms not only consume GSH but also convert H_2O_2 into highly toxic •OH, further exacerbating oxidative damage.

In summary, integrating tumor-targeting ligands, GSH/ROS-responsive linkages and catalytic nanozymes into a single platform represents a frontier in radiosensitizer design. Future efforts should focus on simplifying material synthesis, validating efficacy in large-animal models and establishing scalable manufacturing processes to accelerate clinical adoption.

5. Conclusion

Tumor cells often exhibit elevated levels of GSH, which is closely associated with the maintenance of redox homeostasis, thereby promoting cell proliferation and protecting against free radical-induced damage in numerous instances. On the basis of this understanding, targeting the characteristically elevated GSH levels in tumor cells for depletion represents a viable therapeutic strategy. This approach works by disrupting intracellular redox homeostasis, thereby inhibiting tumor cell proliferation and reversing established radioresistance. The efficacy of GSH-depleting interventions has been empirically validated, with numerous studies demonstrating their ability to suppress tumor cell growth and induce apoptosis. These collective findings provide a solid rationale for the use of GSH elimination as a method to improve therapeutic outcomes in RT (Fig. 6). In this review, the central role of GSH in tumor radioresistance is elucidated and contemporary strategies targeting GSH metabolism to improve RT efficacy are explored. Elevated GSH levels in tumor cells scavenge radiation-induced ROS, thereby mitigating oxidative damage and sustaining survival. To counteract this adaptive mechanism, interventions focusing on both the inhibition of GSH synthesis and the depletion of existing pools have shown considerable promise. Pharmacological agents, such as BSO, SAS and

Table III. Limitations and development prospects of various GSH targeting strategies.

Targeting strategies	Categories	Limitations	Development prospects
Promotion of GSH depletion	Oxidizing agents	Temporary reduction, uncertain biosafety	Design of sustained-release or cascade-reaction nanoplatforms to prolong GSH depletion; incorporation of biodegradable or renal-clearable materials to improve long-term biosafety.
	Metal-based nanomaterials	Quick elimination, unavoidable damage, low cellular uptake	Surface engineering with tumor-targeting ligands or biomimetic membranes to enhance tumor accumulation and cellular internalization while minimizing off-target damage.
	Quinone methide	Unstable structure, short half-life	Develop prodrug strategies or encapsulation within stimuli-responsive nanocarriers to improve stability and extend half-life.
	Nanozyme	Off-target consequences	Engineering tumor microenvironment-activated nanozymes that exert catalytic GSH-depleting activity only within tumor tissues; integration with imaging guidance for precise localization.
	Electrophilic reagents	Short half-life	Conjugation to self-assembling nanoplatforms or use of slow-release depots; combination with radiotherapy-induced reactive oxygen species to create positive-feedback activation loops.
Inhibition of GSH biosynthesis	GCL inhibitors	Short half-life	Encapsulating in long-circulating nanoparticles to protect from rapid metabolism; development of more selective GCL inhibitors via structure-based drug design.
	NADPH inhibition	Unpredictable effect	Integrating with metabolomic profiling to identify predictive biomarkers for patient stratification; combining NADPH-targeting agents with real-time metabolic monitoring.
	Cysteine inhibition	Slow process, uncertain efficiency	Combination with rapid GSH-depleting agents to achieve synergistic and accelerated effect; use of high-efficiency cysteine/glutamate antiporter inhibitors with better pharmacokinetics.
	ATP inhibition	Off-target consequences	Exploit tumor-specific metabolic vulnerabilities to design ATP-uncoupling strategies that spare normal cells; design local delivery via intratumoral injection or radiation-responsive prodrugs to restrict systemic exposure.

GSH, glutathione; GCL, glutamate-cysteine ligase; ATP, adenosine triphosphate.

2-DG, disrupt key synthetic and regenerative pathways, while various nanotechnology-mediated approaches (e.g., catalytic oxidation, covalent conjugation and enzyme-mimetic reactions) enable spatially controlled and efficient GSH consumption within the TME.

Notably, concurrent chemoradiotherapy represents a standard of care for many locally advanced cancers. The rationale is that GSH metabolism plays an equally critical role in chemoresistance, particularly against platinum-based agents (e.g., cisplatin and carboplatin) and alkylating drugs, through direct drug conjugation and enhanced DNA repair (125). Preclinical studies have demonstrated that GSH depletion using inhibitors such as BSO or xCT-targeting agents can resensitize tumors to both chemotherapy and radiotherapy. Therefore, an emerging and highly promising direction is the triple combination of GSH-depleting strategies with concurrent chemoradiotherapy, which could simultaneously overcome chemo- and radioresistance. Although clinical validation is still lacking, the mechanistic framework established in this review provides a solid foundation for future investigations into GSH-targeted chemoradiosensitization, ultimately broadening the therapeutic scope beyond radiotherapy alone.

Despite significant advances in the development of bioactive molecules and inhibitors for GSH depletion, several challenges impede their clinical translation. First, the precise mechanisms underlying the effects of GSH depletion-based therapies remain incompletely elucidated. A deeper understanding of these processes, facilitated by advanced biochemical technologies, is essential to inform the rational design of more effective and specific GSH-targeting strategies. Second, given the indispensable role of GSH in maintaining cellular metabolism, off-target depletion poses a substantial risk of damaging normal tissues and potentially exacerbating conditions such as liver disease or cystic fibrosis. It is therefore imperative to rigorously evaluate the long-term biosafety of molecular and nanoscale GSH-depleting agents before clinical application. Concurrently, developing delivery systems with functional tumor-derived exosome modifications is crucial for minimizing systemic toxicity (126). Third, many current GSH-depleting systems rely on intricately designed molecules or NPs with complex syntheses, which hinders their scalable production and broad clinical adoption. Future efforts should therefore focus on innovative and practical material designs. By simplifying the material design and preparation process, copper-based single-atom nanozymes can also achieve excellent sensitization effects (127).

To accelerate clinical translation, several promising directions merit particular attention. First, the integration of predictive biomarkers, such as baseline intratumoral GSH levels or GCL/xCT expression, could enable patient stratification to identify those most likely to benefit from GSH-targeting radiosensitization. Second, combination regimens that pair GSH modulators with established immunotherapies (e.g., immune checkpoint inhibitors) warrant systematic evaluation, given that GSH-mediated redox regulation profoundly influences antitumour immunity. Third, the development of stimuli-responsive nanoplatforms that enable spatiotemporally controlled GSH depletion within tumors while sparing normal tissues represents a critical frontier. Advances in these areas, coupled with rigorous toxicity assessment and scalable manufacturing processes, will be essential to transition GSH-targeting radiosensitization from bench to bedside as a clinically viable and personalized therapeutic modality. Such improvements will be vital to advancing GSH-targeting radiosensitization into clinically viable and personalized anticancer therapeutics (Table III).

In summary, accumulating evidence suggests that a rational combination of GSH metabolism-related radiosensitizers with IR is an attractive approach to improve the tumor treatment response. Research on GSH-depleting agents is advancing in several areas, including their mechanisms of action, improved specificity and biosafety, and simplified preparation. The discovery of other methods to modulate cellular GSH further supports this progress. Consequently, targeting GSH metabolism is an emerging radiosensitization strategy with great potential for future clinical applications.

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Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed to the study conception and revision. The first draft of the manuscript was written by HX. Literature search and data analysis were performed by MD and XL. ZC and XX provided resources and critically revised the work. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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