Biophys Rep 2025, 11(X):1–19
https://doi.org/10.52601/bpr.2025.250056 https://cstr.cn/32402.14.bpr.2024.2025056 **Biophysics Reports**

REVIEW

Strategies and mechanisms of radiosensitization in cancer therapy

Gaoyuan Xie[1], Fan Wang[1], Xiaotu Ma[2] ✉

[1] Medical Isotopes Research Center and Department of Radiation Medicine, School of Basic Medical Sciences, International Cancer Institute, Peking University, Beijing 100191, China
[2] Department of Ultrasound, Peking University Third Hospital, Beijing 100191, China

Received: 23 September 2025 / Accepted: 30 October 2025

Abstract More than 50% of patients with malignant tumors require radiotherapy (RT). However, its efficacy is often hindered by inherent or acquired radioresistance and damage to surrounding normal tissues. Radiosensitizers offer the potential to enhance the therapeutic efficacy of radiotherapy while minimizing toxicity to normal tissues. This review provides a comprehensive overview of the current understanding of the multi-dimensional mechanisms underlying radiosensitization. Additionally, we discuss the synergistic role of physicochemical interventions and advanced delivery systems in improving radiosensitization. Advances in clinical translation are summarized, highlighting several radiosensitizers that have entered clinical trials. Despite considerable progress, challenges such as delivery efficiency and tumor heterogeneity remain. Future research should focus on multi-targeted strategies, biomarker-guided patient selection, and integration with immunotherapy to achieve precise and effective radiosensitization.

Keywords Tumor radiotherapy, Radiosensitization, DNA damage repair, Drug delivery, Tumor microenvironment

INTRODUCTION

Radiotherapy (RT) is one of the most effective cytotoxic therapies available for the treatment of localized solid cancers. More than 50% of patients with malignant tumors require RT. RT is widely used throughout all cancer treatment stages in the forms of adjuvant RT, neoadjuvant RT, radical RT, and palliative RT (Zhou *et al.* 2023). Typically, RT utilizes high-energy ionizing radiation (IR), including X-rays and gamma (γ) rays, and particle radiation (alpha (α) or beta (β) particles, carbon ion, electron, proton, or neutron beams). IR damages biomolecules, including proteins, lipids, and particularly DNA, leading to structural damage of biomolecules, such as single-strand breaks (SSBs) or double-strand breaks (DSBs) of DNA and cross-linking of DNA–DNA or DNA–protein, eventually resulting in the termination of cell division and even cell death.

Although it demonstrates strong efficacy against certain tumor subtypes, RT alone is challenged by limited therapeutic efficacy with a high rate of tumor metastasis and recurrence for many patients. Radioresistance represents a major cause of RT failure (Hu *et al.* 2018). The therapeutic efficacy of RT relies on the radiation dose, but increasing the dose will aggravate the radiation damage to normal tissues and organs (Akhunzianov *et al.* 2025). Refining radiotherapy techniques and exploring ideal radiosensitization approaches to improve prognosis have become research hotspots in the field of radiotherapy in recent years. Diverse radiosensitizers have been developed to maximize RT efficacy and minimize side effects. This review provides a comprehensive overview of the multi-dimensional mechanisms underlying radiosensitization, including inhibition of DNA damage repair, promotion of free radical generation, induction of G2/M cell cycle arrest, enhancement of various cell death pathways, modulation of the tumor microenvironment, immune regulation, targeting of cancer stem cells, and

✉ Correspondence: maxiaotu@bjmu.edu.cn (X. Ma)

involvement of the gut microbiota. It summarizes the latest strategies in radiosensitization methods. Furthermore, it introduces radiosensitizers in clinical translation, aiming to provide new insights and directions for future radiotherapy research.

PRINCIPLES OF RADIOSENSITIZATION

Interference with DNA damage repair

The DNA damage repair capacity of tumor cells post-radiotherapy determines their sensitivity to radiotherapy, which is one of the key factors influencing therapeutic outcomes. Radiation directly induces DNA damage, including DNA SSBs and DSBs, with DSBs being the most lethal form (Fig. 1A). SSBs primarily rely on poly(ADP-ribose) polymerase (PARP) for repair and may progress into DSBs. DSBs are mainly repaired through non-homologous end joining (NHEJ) and homologous recombination (HR) (Huang and Zhou 2020). Disruption of DNA damage repair leads to cell cycle arrest, impaired repair, cellular senescence, or death, offering substantial radiosensitization potential. DNA damage repair-associated proteins, such as ATM, DNA-PK, RAD51, and PARP-1, have been identified as potential targets for radiosensitization (Huang and Zhou 2020; Nickoloff *et al.* 2021).

Beyond directly inhibiting the expression of DNA repair proteins, an alternative approach involves epigenetic regulation, such as histone modifications and interference with non-coding RNA expression to modulate DNA repair protein levels. For instance, miR-205 inhibits DNA damage repair by targeting ZEB1 and the ubiquitin-conjugating enzyme Ubc13 (Zhang *et al.* 2014). miR-521 modulates the expression levels of the

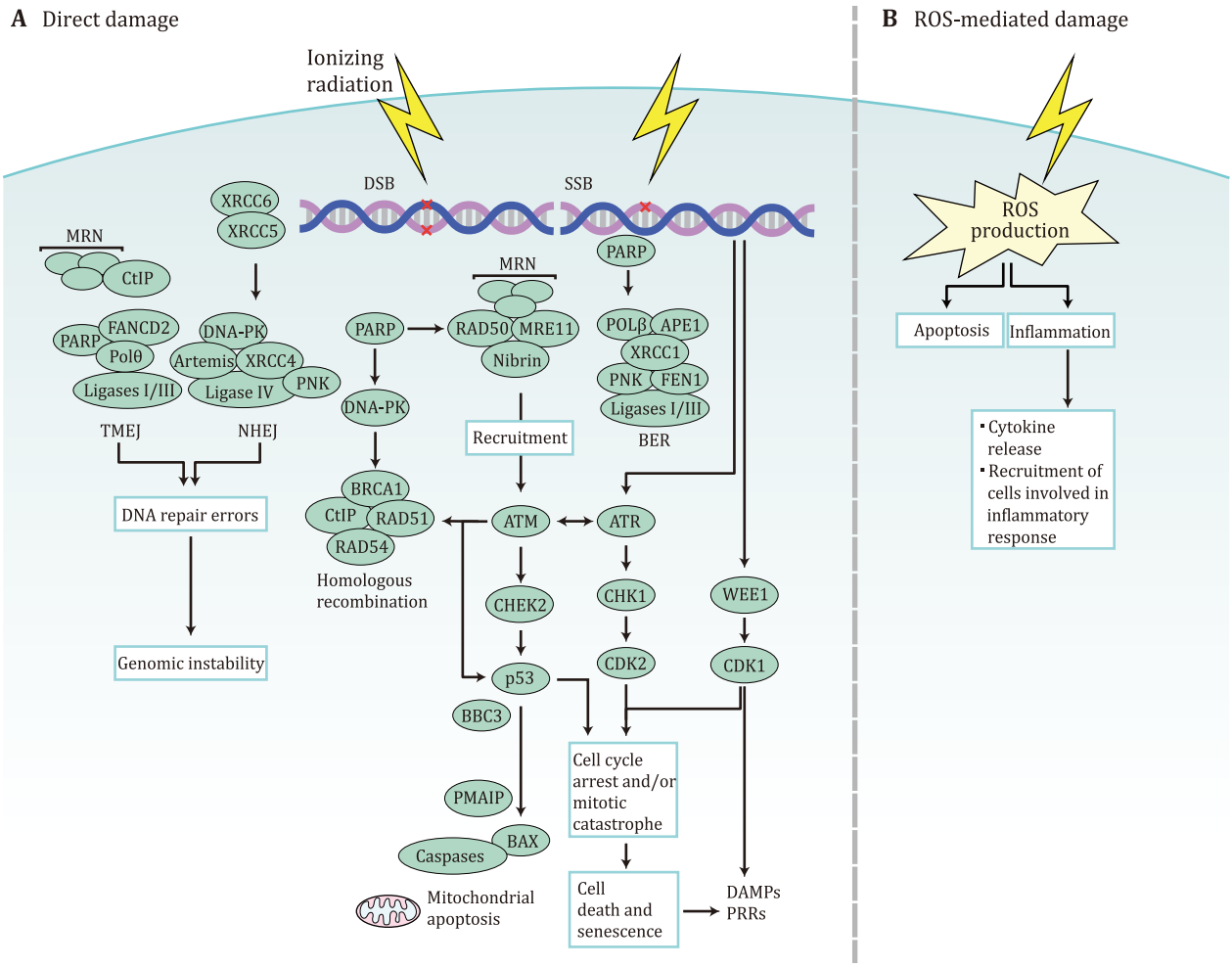

Fig. 1 Mechanism of biological action of ionizing radiation (Price *et al.* 2023). Radiation damages cells via direct damage to DNA (**A**) and indirect damage via the formation of reactive oxygen species (ROS) (**B**)

DNA repair protein CSA and plays an important role in the radiosensitivity of prostate cancer cell lines. Thus, miR-521 can be a potential target for enhancing the effect of radiation treatment on prostate cancer cells (Josson *et al.* 2008). A study reported that radiation-resistant individuals exhibit global histone deacetylation along with changes in histone deacetylase (HDAC) and histone acetyltransferase (HAT) activities. However, HDAC activity also shows heterogeneity among different individuals. Tumoral HDAC activity should be assessed before radiotherapy, and patients with high activity are suitable candidates for radiosensitization using HDAC inhibitors (Sharda *et al.* 2020). Furthermore, regulatory proteins have been found to influence DNA damage repair. The Hsp90 inhibitor PU-H71 suppresses DNA repair via homologous recombination and non-homologous end joining, sensitizing cancer cells to heavy-ion radiation (Lee *et al.* 2016; Li *et al.* 2016).

In summary, DNA damage repair is a primary cause of radiotherapy resistance, and targeting relevant genes or proteins to inhibit or block associated signaling pathways is a classical method to enhance tumor radiosensitivity.

Promotion of free radical generation/ inhibition of endogenous radioprotective systems

Radiotherapy induces cell damage not only through direct DNA injury but also via indirect free radical damage, primarily mediated by water radiolysis generating reactive oxygen species (ROS) (Fig. 1B) (Sanche 2009). ROS, natural byproducts of normal cellular metabolism, are characterized by oxygen-derived free radicals exhibiting high reactivity and concentration-dependent functionalities (Jiang *et al.* 2023). Under physiological conditions, ROS play pivotal roles in cell signaling and maintaining intracellular homeostasis. To counter elevated ROS levels from diverse sources, cells frequently upregulate antioxidant defense systems, including the thioredoxin and glutathione systems, to counteract oxidative stress. Numerous studies emphasize that cancer cells often demonstrate significantly elevated ROS levels relative to normal cells (Du *et al.* 2015; Fath *et al.* 2011; Wondrak 2009; Zhang *et al.* 2017).

Certain radiosensitizers amplify radiation-induced cytotoxicity by enhancing ROS generation. Examples include: nitroimidazole derivatives that capture electrons to impair DNA repair under hypoxia, as in mitochondria-targeted probes (Chen *et al.* 2021); Catalytic systems generating reactive nitrogen species (RNS) through ROS-NO coupling (*e.g.*, peroxynitrite formation) (Liu *et al.* 2022); Metal complexes catalyzing hydroxyl radical (·OH) production via Fenton/Fenton-like reactions (Lin *et al.* 2018). These strategies trigger endogenous radical bursts, exacerbating oxidative stress to promote apoptosis and potentiate RT-induced cell death.

Other radiosensitizers function by inhibiting endogenous radioprotective substances. Glutathione (GSH) functions as a versatile protector in radioprotection. Several distinct mechanisms by which GSH confers radioprotection can be delineated, including radical scavenging, restoration of damaged molecules via hydrogen donation, reduction of peroxides, and maintenance of protein thiols in their reduced state. Among these, hydrogen donation to DNA radicals is likely the most critical (Bump and Brown 1990). Due to the rapid kinetics of competing reactions, this mechanism demands a high concentration of GSH. Xiang *et al.* engineered a proalkylating agent prodrug (designated BamCS) based on H_2O_2-activated boronic acid ester concurrently with the utilization of silica-coated bismuth nanoparticles to generate ROS. This prodrug can be activated by elevated H_2O_2 levels in tumor cells, releasing *p*-quinone methide to irreversibly deplete GSH (Xiang *et al.* 2021).

The thioredoxin (Trx) system is a key antioxidant system responsible for eliminating excessive reactive oxygen species (Arnér and Holmgren 2000). The Trx system is upregulated post-radiotherapy in cancer cells, contributing significantly to radiation resistance, as widely demonstrated (Cao *et al.* 2024). TrxR, the sole enzyme catalyzing oxidized Trx reduction to its reduced form, maintains redox homeostasis via NADPH oxidation to $NADP^+$ (Arnér and Holmgren 2006). Elevated TrxR expression pre- and post-radiotherapy enhances radioprotection in malignancies. Trx function relies on the redox state. Radiation-induced TrxR activation promotes reduced Trx nuclear translocation, modulating AP-1 and NF-κB to bolster resistance (Karimpour *et al.* 2002; Pennington *et al.* 2007; Wang *et al.* 2011; Wei *et al.* 2000). Inhibiting TrxR disrupts antioxidant capacity, triggering ROS accumulation, oxidative stress, and apoptosis, thereby sensitizing cancer cells to radiotherapy, validating its potential as a radiosensitizer target (Bian *et al.* 2019; Liang *et al.* 2014; Rodman *et al.* 2016).

In summary, suppression of cellular antioxidant capacity leads to the accumulation of free radicals, thereby rendering cancer cells highly vulnerable to radiotherapy. Consequently, promoting free radical generation or inhibiting endogenous radioprotective systems represents a promising strategy for developing radiosensitizers, warranting further investigation.

Induction of G2/M cell cycle arrest

Tumor cells exhibit differential radiosensitivity across cell cycle phases. Specifically, cells in M and G2 phases demonstrate higher radiosensitivity compared to those in S and G1 phases (Pawlik and Keyomarsi 2004). Forcing tumor cells to accumulate in radiation-sensitive phases (*e.g*., G2/M) can amplify the cytotoxic effects of radiotherapy. During the S phase, enhanced DNA repair capacity is observed, whereas this capability is relatively suppressed in G2/M phase. Consequently, G2/M arrest impedes timely DNA damage repair, leading to apoptosis or permanent cellular inactivation. In contrast, normal cells exhibit a lower frequency of rapid division; thus, G2/M phase blockade imposes minimal impact on them. This selectivity mitigates RT-associated side effects, improving therapeutic safety and efficacy (Dillon *et al.* 2014; Pawlik and Keyomarsi 2004). Ding *et al*. demonstrated that X-ray irradiation promotes tumor cell uptake of nanoparticles, while cisplatin induces arrest in radiation-sensitive G2/M phases (Ding *et al.* 2021).

Ionizing radiation-induced DNA damage activates the G1/S checkpoint, subsequently triggering cell cycle arrest at the G1/S phase through signaling pathways such as ATM/p53/p21 and Chk2. This arrest facilitates DNA damage repair, ultimately contributing to radiotherapy resistance (Shiloh 2003). However, tumor cells frequently harbor p53 mutations, leading to G1/S checkpoint dysfunction. Consequently, the G2/M checkpoint represents an especially attractive therapeutic target.

Following exposure to G2/M checkpoint inhibitors, p53-proficient cells, such as normal cells, initiate efficient cell cycle arrest predominantly at the G1 phase to facilitate DNA repair. Consequently, they manifest relative resistance to pharmacological G2/M checkpoint inhibition, although those normal cells that have progressed beyond the G1/S checkpoint remain susceptible to mitotic catastrophe upon G2/M inhibition. In contrast, p53-deficient cancer cells are particularly sensitive to inhibition of residual S and G2/M checkpoints (Levesque and Eastman 2007). These cells enter mitosis with unrepaired radiation-induced DNA damage, leading to mitotic catastrophe and cell death. Therefore, G2/M checkpoint inhibitors can mediate synthetic lethal interactions with ionizing radiation in p53-pathway-deficient tumors. Larsen *et al*. demonstrated that irradiated tumor cells activate caspase-dependent DNases to induce self-inflicted DNA breaks, promoting G2-phase arrest and prolonging DNA damage duration (Larsen *et al.* 2022). Milciclib exhibits anti-tumor activity as a monotherapy in CRC cells and enhances radiotherapy efficacy in combination. It disrupts the G2/M checkpoint and compromises DNA repair mechanisms (Ma *et al.* 2025).

Collectively, potentiating G2/M arrest before radiotherapy and inhibiting post-radiotherapy G2/M arrest constitute an effective strategy to enhance tumor radiosensitivity.

Promotion of cell death

Previous studies indicate that radiation-induced cell death primarily manifests as apoptosis (Ning *et al.* 2024; Wang *et al.* 2023a). Enhancing apoptosis has been extensively investigated for radiosensitization (Muschel *et al.* 1998). Whether radiation induces other unrecognized forms of cell death and their roles in radioresistance remains a critical research focus. Recently, radiobiologists have begun exploring the involvement of radiation-induced ferroptosis, necroptosis, pyroptosis, cuproptosis and autophagy (Fig. 2).

Radiotherapy elevates intracellular ROS levels, promoting the accumulation of lipid peroxidation. It activates ataxia-telangiectasia mutated (ATM) kinase and upregulates intracellular ATM expression to induce tumor cell ferroptosis (Chen *et al.* 2020; Lang *et al.* 2019). Additionally, radiation-mediated p53 activation influences post-radiotherapy ferroptosis (Jiang *et al.* 2015; Liu and Gu 2022). Recently, Shen *et al*. reported that radiotherapy generates double-stranded DNA (dsDNA) to activate the cyclic GMP-AMP synthase (cGAS) signaling pathway, downregulating SLC7A11 and GPX4 expression and thereby promoting tumor ferroptosis (Shen *et al.* 2022). The mechanistic basis for ferroptosis in radiosensitization requires further investigation. Current literature implicates three primary pathways: induction of iron overload, suppression of glutathione synthesis and promotion of cellular lipid peroxidation (Ivanov *et al.* 2015; Lang *et al.* 2019; Lei *et al.* 2020; Pan *et al.* 2019; Shibata *et al.* 2019; Xu *et al.* 2021; Ye *et al.* 2020; Zhao *et al.* 2020).

The mechanism underlying radiotherapy-induced necroptosis remains to be fully elucidated. Necroptosis in tumor cells during radiotherapy exhibits a dual role in cancer therapy: Necroptosis inducers can enhance tumor cell radiosensitivity and therapeutic efficacy (Wang *et al.* 2018). A retrospective study demonstrated improved overall survival (OS) in patients more susceptible to radiotherapy-induced necroptosis. Bioinformatics analyses further revealed better OS in tumor patients with elevated expression of necroptosis-related genes (Li *et al.* 2022a). Conversely, studies indicate that radiation-induced tumor cell necroptosis may promote tumor progression (Wang *et al.* 2019),

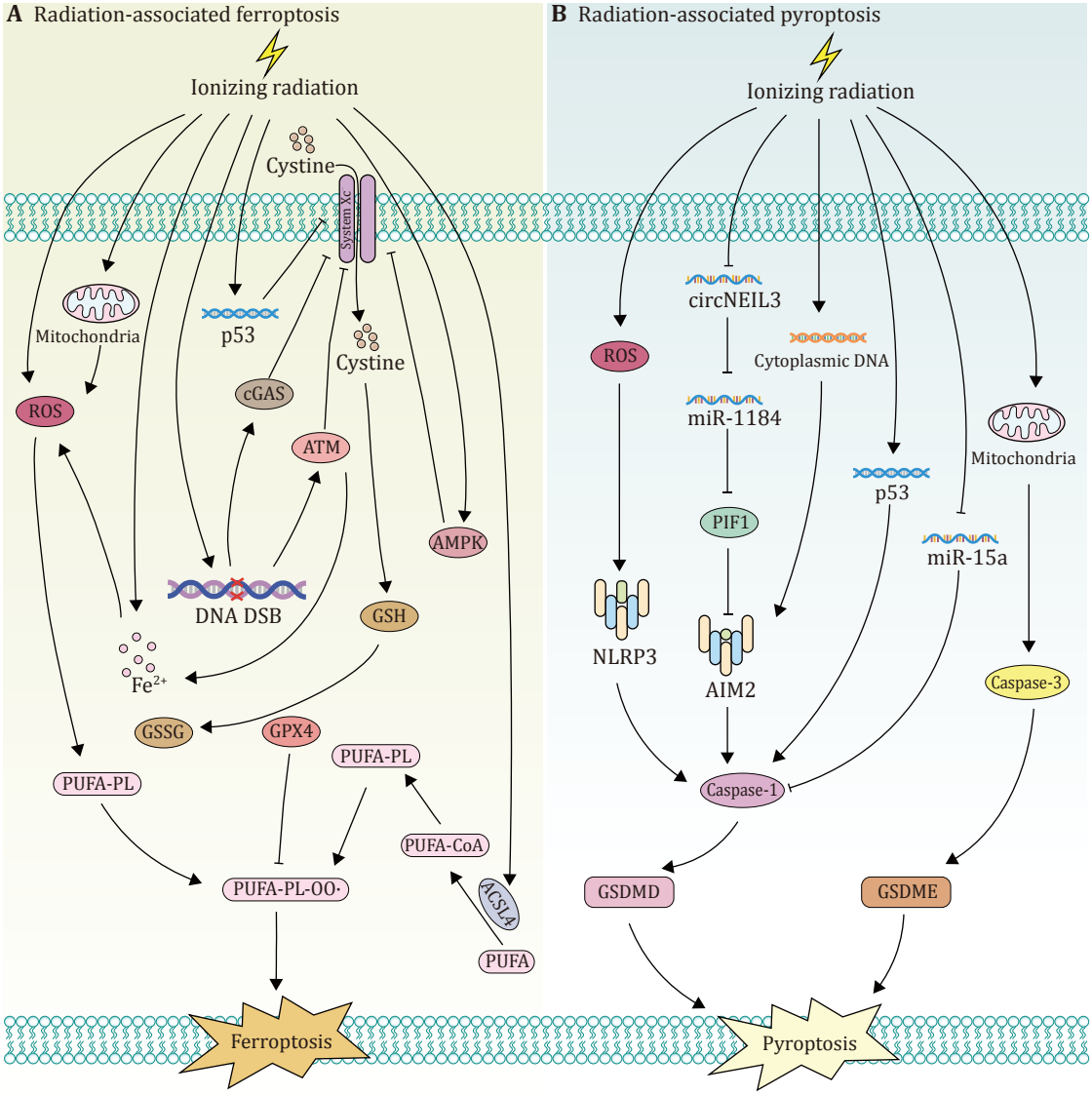

Fig. 2 Known and potential mechanisms of radiation-associated ferroptosis and pyroptosis (Wang *et al.* 2023a). **A** RT promotes PUFA biosynthesis, induces ROS accumulation, elevates iron levels, and suppresses the GPX4-dependent defense system, thereby triggering ferroptosis in tumor cells. **B** RT induces tumor cell pyroptosis through ROS/caspase-1/GSDMD activation, cytoplasmic DNA/inflammasome signaling, p53-mediated caspase-1 activation, miR-15a suppression leading to caspase-1/GSDMD pathway, AIM2 inflammasome activation and caspase-3/GSDME pathway

highlighting the need for further discussion on its context-dependent roles.

DNA damage activates the absent in melanoma 2 (AIM2) inflammasome, inducing GSDMD-mediated pyroptosis in tumor cells (Zhang *et al.* 2022). Rana *et al.* reported that radiation-induced tumor cell pyroptosis is associated with miR-15a expression (Rana *et al.* 2020). High-dose radiation reduces intracellular miR-15a levels, activates the caspase-1 inflammasome, increases Gasdermin D, and induces tumor cell pyroptosis. Ionizing radiation also triggers anti-tumor immunity by inducing Gasdermin E-mediated pyroptosis in tumor cells (Cao *et al.* 2023). It is also found that radiation enhances Caspase-3 activity, recruiting NK cells and activating anti-tumor immunity through the Caspase-3/Gasdermin E pyroptotic pathway, thereby increasing radiosensitivity in colorectal cancer cells (Tan *et al.* 2022). Consequently, upregulating Gasdermin E expression in cancer cells while downregulating it in normal tissues may achieve tumor radiosensitization and mitigate radiation-induced damage to healthy tissues.

Cuproptosis, a newly discovered form of cell death, relies on intracellular copper accumulation to induce cell death by disrupting mitochondrial metabolism and protein homeostasis (Li *et al.* 2025; Zhang *et al.* 2024). Studies demonstrate that residual tumors post-radiotherapy exhibit upregulation of key cuproptosis regulators FDX1 and LIAS, thereby enhancing tumor cell sensitivity to cuproptosis (Liao *et al.* 2024). This suggests leveraging cuproptosis to potentiate radiotherapy efficacy. Researchers developed copper-containing sandwich polyoxometalate (PWCu), which releases copper ions during radiotherapy to trigger cuproptosis, overcome tumor radiation resistance, and activate immunogenic cell death (ICD) to elicit anti-tumor immunity (Liao *et al.* 2024). Notably, cuproptosis is highly sensitive to oxygen presence. To address this, investigators engineered an oxygen-generating copper-delivery carrier ($^{Cu/AP}$H-M) that elevates intratumoral oxygen levels, amplifies cuproptosis, and synergizes with radiotherapy to enhance anti-tumor immune responses (Pei *et al.* 2024). Current research on cuproptosis-mediated radiosensitization remains in its nascent phase, yet its therapeutic potential in oncology has gained significant traction.

In recent years, the combination of autophagy inducers with ionizing radiation has emerged as a promising strategy to enhance the radiosensitivity of cancer cells. Autophagy is recognized as one of the earliest cellular processes activated in response to radiation exposure. However, the role of autophagy in cancer cells varies significantly with the stage and progression of tumors. In the initial stages of tumorigenesis, autophagy primarily functions as a tumor-suppressive mechanism (Russo and Russo 2018). Conversely, in established tumors, autophagy promotes cytoprotection, enabling cancer cells to survive under various stressors and acquire treatment-resistant phenotypes (Singh *et al.* 2018).

Thus, while combining autophagy inducers with therapy may exert anticancer effects during early malignancies, autophagy inhibitors could yield superior radiosensitizing outcomes in advanced disease stages. Consequently, despite their potential, the strategic application of autophagy modulators in cancer therapy remains challenging and has not yet gained widespread adoption as a standard treatment modality (Roy *et al.* 2022).

Among the non-apoptotic pathways, ferroptosis and pyroptosis currently possess the strongest preclinical and translational evidence supporting their roles in radiosensitization. Immunogenic cell death, such as pyroptosis, releases damage-associated molecular patterns (DAMPs), initiating an anti-tumor immune response that amplifies the initial radiation effect. While necroptosis, cuproptosis, and autophagy also contribute to radiation responses, their roles in radiosensitization remain less defined or context-dependent.

Modulating the tumor microenvironment

Previous research on enhancing the efficacy of radiotherapy has predominantly focused on cancer cells, often overlooking the intricate biological interplay between cancer cells and the tumor microenvironment (TME). The TME constitutes a distinct niche formed by cancer cells, infiltrating immune cells, cancer-associated fibroblasts (CAFs), blood and lymphatic vessels, secreted factors, and the extracellular matrix (ECM) (de Palma *et al.* 2017; Koelwyn *et al.* 2017). Understanding and modulating the interactions between RT and the TME are crucial for maximizing radiotherapeutic outcomes (Barker *et al.* 2015).

Tumor hypoxia, a common characteristic of the solid tumor microenvironment, arises from rapid tumor cell proliferation and aberrant vascular architecture (Li *et al.* 2021; Wang *et al.* 2020; Zhuang *et al.* 2023). Hypoxia significantly diminishes RT efficacy because ionizing radiation primarily inflicts DNA damage indirectly through the generation of free radicals, a process critically dependent on oxygen (Guo *et al.* 2024). Furthermore, hypoxia induces the expression of hypoxia-inducible factors (HIFs), which subsequently promote tumor growth, invasion, metastasis, and therapy resistance (Bigos *et al.* 2024; Gonzalez-Avila *et al.* 2023).

Strategies to alleviate tumor hypoxia primarily include: (1) Utilizing oxygen carriers or generators to deliver oxygen to tumor regions (Li *et al.* 2023; Zhu *et al.* 2018). For instance, Ma *et al*. loaded myoglobin (Mb) into Gd-NTs (Mb@Gd-NTs), resulting in efficient relief of tumor hypoxia and significant enhancement of Gd-Tex radiosensitization (Fig. 3) (Ma *et al.* 2023). (2) Promoting vascular normalization. Normalizing the tumor vasculature to improve blood flow and oxygen delivery, consequently enhancing radiosensitivity (Guo *et al.* 2024; Une *et al.* 2021). (3) Applying hyperbaric oxygen therapy (HBOT). Increasing oxygen concentration in tumor regions by elevating inspired oxygen tension. HBOT has been investigated as a means to ameliorate hypoxia and enhance RT efficacy (Braks *et al.* 2015; Fernández *et al.* 2021). (4) Targeting HIF signaling to mitigate hypoxia-driven tumor aggressiveness and treatment resistance (Zhuang *et al.* 2023).

To meet the demands of rapid proliferation, tumor cells undergo metabolic reprogramming, preferentially

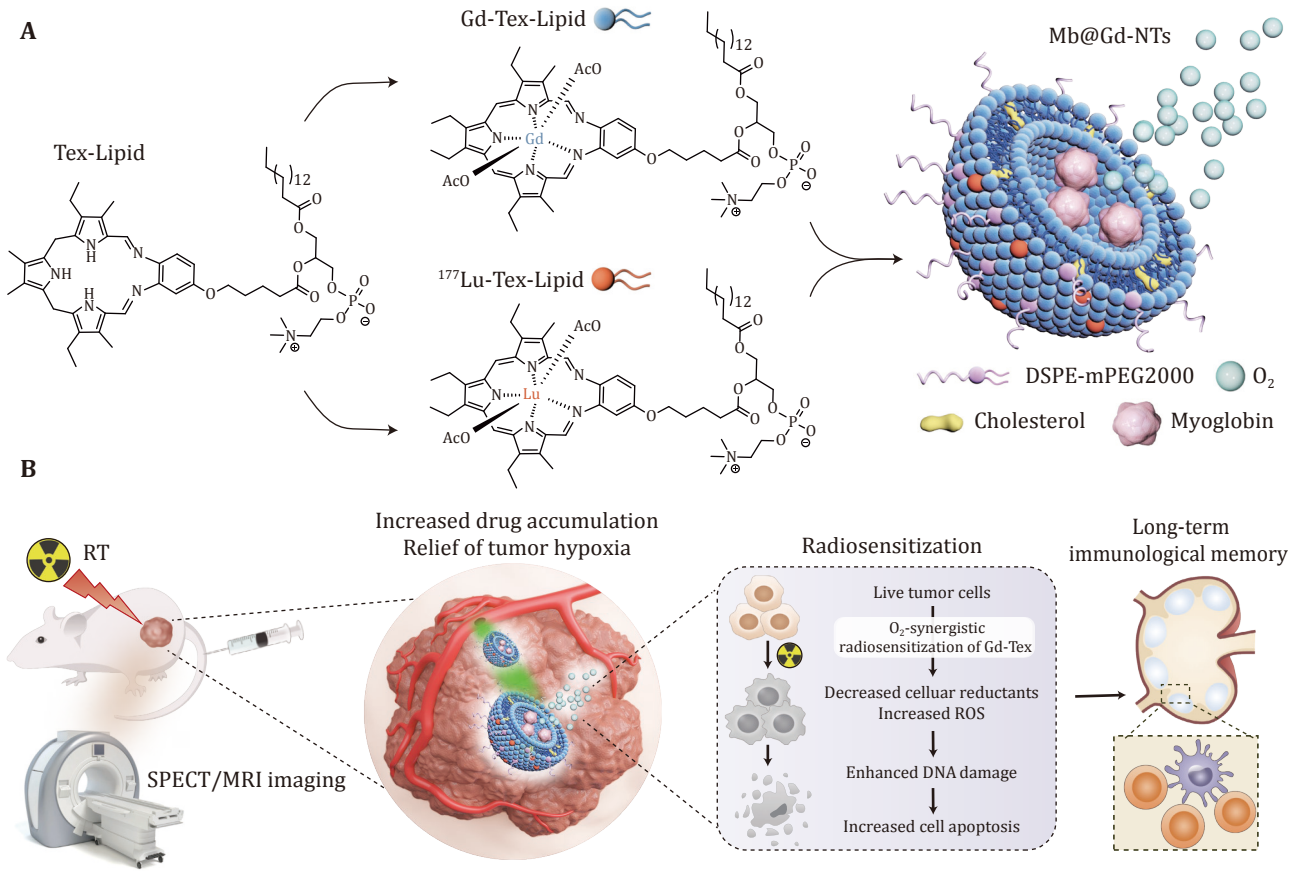

Fig. 3 Utilizing oxygen carriers to relieve tumor hypoxia for radiosensitization (Ma *et al.* 2023). **A** Diagram of the fabrication of myoglobin-loaded gadolinium nanotexaphyrins (Mb@Gd-NTs). **B** Illustration of oxygen synergy and imaging-guided radiosensitization therapy. Mb@Gd-NTs enables SPECT/MRI dual-modality imaging, significantly increases the tumor accumulation of radiosensitizer gadolinium-texaphyrins (Gd-Tex), and obviously relieves tumor hypoxia. O_2 synergically enhances the radiosensitization effect of Gd-Tex, causing enhanced cell apoptosis, eventually inducing long-term immunological anti-tumor memory

utilizing glycolysis even under aerobic conditions (Warburg effect) (Liberti and Locasale 2016). This metabolic alteration not only provides energy and biosynthetic precursors for tumors but also influences TME parameters, including pH and lactate levels, thereby promoting radiation resistance (van Gisbergen *et al.* 2021). Furthermore, extracellular enzymes associated with nutrient consumption, such as indoleamine 2,3-dioxygenase 1 (IDO-1), CD73, and arginase 1, are overexpressed in the TME to accommodate accelerated tumor growth (Zhen *et al.* 2023). This adaptation enables solid tumors to evade immune surveillance by inducing exhaustion and apoptosis of T cells and NK cells, while simultaneously stimulating immunosuppressive cells, including Tregs, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs).

Metabolic regulators have the potential to reprogram the immunosuppressive nature of TME, thereby enhancing the efficacy of radiotherapies. For example, IDO-1 inhibitors enhance radiotherapy efficacy by remodeling the immunosuppressive TME induced by kynurenine (Kyn) accumulation (Lu *et al.* 2018). Targeting glycolytic enzymes or glucose transporters can force glycolytic tumor cells toward oxidative phosphorylation, enhancing their radiosensitivity (Shen *et al.* 2015). Inhibitors targeting different OXPHOS complexes can potentiate radiation response (Ashton *et al.* 2018). Additionally, modulation of nucleotide metabolism, arginine metabolism, fatty acid (FA) metabolism and one-carbon metabolism can increase tumor cell radiosensitivity (de Lima Luna and Forti 2021; Deng *et al.* 2025; Jin *et al.* 2021; Marullo *et al.* 2021; Read *et al.* 2022).

ECM is a critical component of the tumor microenvironment. Its aberrant proliferation and remodeling

not only constitute a physical barrier that impedes the infiltration of therapeutic agents and immune cells but also directly or indirectly promotes tumor immunosuppression (Chen *et al.* 2022; Zhen *et al.* 2023). Dense ECM can restrict the infiltration of effector immune cells (*e.g.*, T lymphocytes) into tumor cores, thereby attenuating anti-tumor immune responses. CAFs, in conjunction with other ECM components, form an impermeable barrier that prevents therapeutic drugs and immune cells from penetrating tumors (Chen and Song 2019; Kalluri 2016). In pancreatic ductal adenocarcinoma (PDAC), the dense fibrotic stroma is a hallmark feature that creates a physical barrier, preventing access of chemotherapeutic drugs and cytotoxic T lymphocytes (CTLs) to the TME while promoting hypoxia, which induces therapy resistance in cancer cells (Ahmad *et al.* 2021).

Enzymatic digestion of ECM, targeting ECM-associated molecules, or modulating CAF functions may enhance radiotherapy efficacy. For instance, in gastric cancer, SERPINE1 deposition correlates with poor prognosis. Downregulating ECM components and reducing interstitial fluid pressure via Losartan can improve radio-immunotherapy outcomes (Zaheer *et al.* 2025). Ni *et al*. designed a bismuth (Bi)-based nanoscale metal-organic framework (nMOF) capable of modulating intratumoral biomechanical properties to amplify RT-RDT (radiodynamic therapy)-mediated immune responses (Ni *et al.* 2022). Fibroblast activation protein (FAP) represents one of the most promising targets for selective CAF intervention. FAP-activated prodrugs demonstrate potential in targeting CAFs and suppressing tumor growth across multiple models (Hou *et al.* 2021; LeBeau *et al.* 2009). FAP-targeted ligands are extensively utilized in radioactive tracers and targeted radionuclide therapy (Lindner *et al.* 2021; Zhao *et al.* 2024).

In summary, ameliorating the tumor microenvironment represents a pivotal strategy for enhancing radiotherapy efficacy, with ameliorating hypoxia, modulating metabolism, and regulating the extracellular matrix serving as critical entry points. Hypoxia alleviation has the clearest evidence for radiosensitization. Future research should delve deeper into understanding the complex interactions among the components of the tumor microenvironment and develop multi-target combination strategies to overcome treatment resistance and improve patient survival rates.

Immune regulation

In 1953, Mole and colleagues first proposed that RT can induce the abscopal effect, referring to tumor responses occurring outside the irradiated field during RT. It is widely acknowledged that RT exerts immunomodulatory effects capable of inducing the abscopal phenomenon (Wang *et al.* 2024b). Anti-tumor immune response acts as an endogenous amplifier of radiosensitivity. However, abscopal effects triggered solely by RT represent rare occurrences in human patients, likely attributable to limited immune activation elicited by RT alone. Numerous therapeutic modalities have been combined with RT to augment the abscopal response, aiming to achieve effective systemic anti-tumor efficacy (Turchan *et al.* 2021). An ideal radiosensitizer should amplify immune activation mechanisms, thereby influencing tumor cells beyond the irradiated region to promote the abscopal effect.

The cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway modulates innate immune responses, with cGAS catalyzing the conversion of pathogen-derived or self-DNA in the cytosol to generate 2',3'-cyclic GMP-AMP (cGAMP). cGAMP activates STING to induce type I interferons (IFN-I) and other inflammatory cytokines through the activation of TANK-binding kinase 1 (TBK1)/interferon regulatory factor 3 (IRF3) and IκB kinase (IKK)/NF-κB signaling cascades (Yum *et al.* 2020). Via cytokine production, STING agonists — including cyclic dinucleotides (CDNs) such as c-diGMP, c-diAMP, and cGAMP — activate dendritic cell maturation and tumor antigen cross-presentation, fostering anti-tumor immunity (Corrales *et al.* 2016; Su *et al.* 2019). Upon exposure to high-dose X-rays, damaged DNA escapes from the nucleus of cancer cells into the cytosol, facilitating cGAMP production and STING activation. The combination of RT and STING pathway activation may yield synergistic anti-tumor effects (Luo *et al.* 2022; Yan *et al.* 2022).

Immune Checkpoint Blockade (ICB) is a therapeutic strategy that aims to restore exhausted T cells by targeting immune checkpoint molecules, such as PD-1 and CTLA-4, thereby rejuvenating anti-tumor immunity and inducing the abscopal effect (Liu *et al.* 2018). Major classes of immune checkpoint inhibitors (ICIs) include agents targeting PD-1 (*e.g.*, nivolumab and pembrolizumab), PD-L1 (*e.g.*, durvalumab and atezolizumab), and CTLA-4 (*e.g.*, ipilimumab or tremelimumab). Inhibition of PD-1 or PD-L1 primarily reverses T cell exhaustion, whereas anti-CTLA-4 agents suppress the immunosuppressive activity of regulatory T (Treg) cells and enhance the $CD8^+$ T cell to Treg cell ratio within the tumor microenvironment (Topalian *et al.* 2016). Multiple studies have demonstrated that ICIs can be combined with radiotherapy (RT) to improve therapeutic outcomes (Fig. 4) (Verma *et al.* 2024; Wang *et al.* 2024a; Yang *et al.* 2022; Zheng *et al.* 2024).

Radiation dose and fractionation profoundly determine the extent of synergy with immune checkpoint inhibitors (ICIs) and STING agonists. High-dose radiation induces robust immunogenic tumor cell death, leading to the release of tumor-associated antigens (TAAs) and DAMPs that initiate dendritic cell activation and antigen presentation. Moderate doses are optimal for activating the cGAS–STING–type I interferon (IFN) pathway without triggering excessive expression of the DNA exonuclease Trex1, which degrades cytosolic DNA and attenuates IFN signaling, thereby potentiating synergy with ICIs (Vanpouille-Box *et al.* 2017). Low-dose radiation primarily promotes inflammatory cytokine release and DAMPs, altering endothelial cell adhesion receptor expression and immune cell trafficking and activation (Jagodinsky *et al.* 2024).

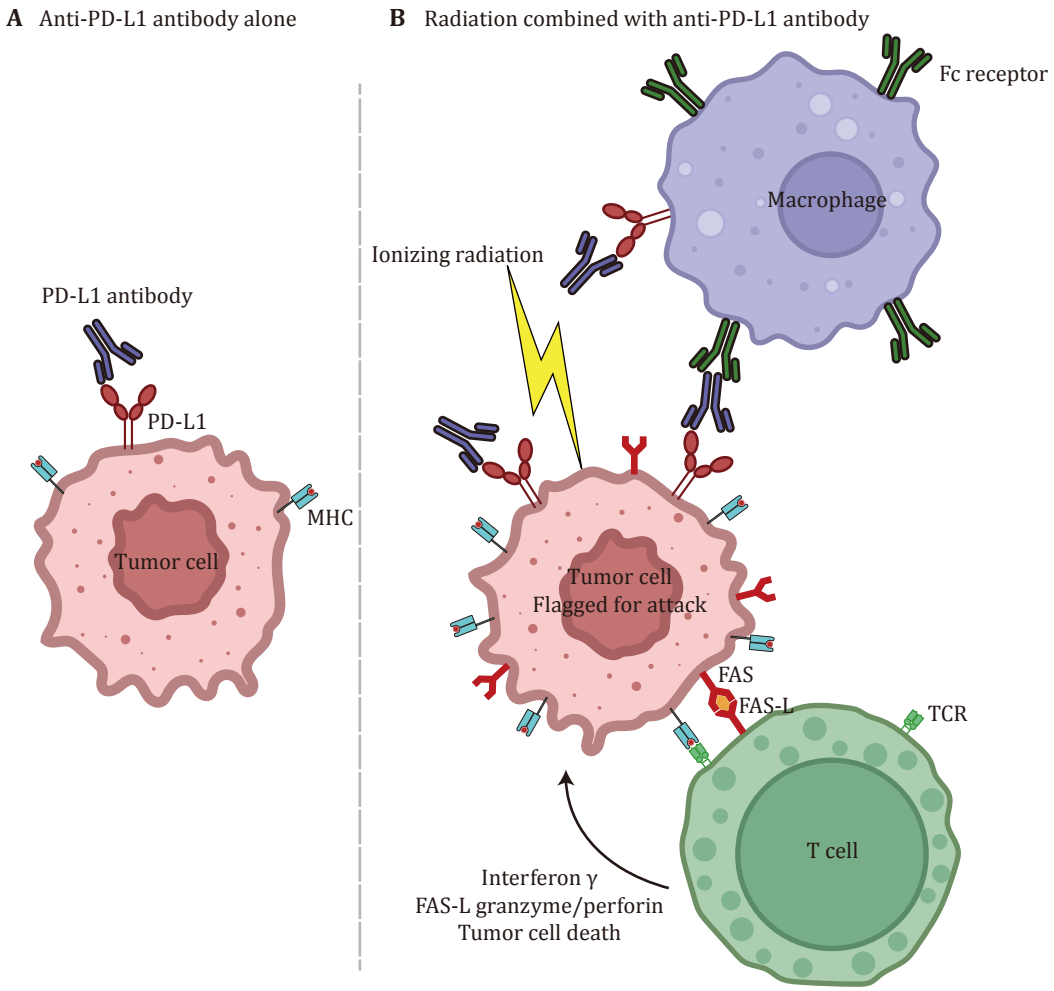

Fig. 4 Radiotherapy combined with immune checkpoint blockade enhances tumor cell susceptibility to T-cell-mediated cytotoxicity (Sharabi *et al.* 2015). **A** Monotherapy with anti-PD-L1 does not exhibit significant direct cytotoxic effects. **B** The combination of radiotherapy and anti-PD-L1 upregulates MHC and FAS, thereby augmenting susceptibility to immune-mediated cell death

Additionally, the tumor microenvironment harbors various immunosuppressive cells, including Tregs, MDSCs, and TAMs. These cells inhibit anti-tumor immune responses by secreting immunosuppressive molecules, inducing apoptosis in immune cells, or altering metabolic states (DeNardo and Ruffell 2019; Gabrilovich and Nagaraj 2009; Li *et al.* 2020; Xue *et al.* 2021). Suppression of the function of these immune cells or depletion of their numbers constitutes a key strategy to enhance radiotherapy efficacy (Feng *et al.* 2022; Ji *et al.* 2020; Ma *et al.* 2022b; Zhang *et al.* 2020). Inhibition of neutrophil extracellular traps (NETs)

formation can also sensitize tumors to radiotherapy (Wang *et al.* 2023a).

However, recent research demonstrates that large radiation doses that are clinically relevant to SBRT induce the expression of the EGFR ligand amphiregulin in tumor cells, which promotes distant metastasis growth (Piffkó *et al.* 2025). This challenges traditional conjectures regarding the mechanism of the abscopal effect. In summary, modulating the immune system constitutes a critical research direction for enhancing radiotherapy sensitivity. Future studies necessitate an in-depth investigation into the molecular mechanisms underpinning these processes, coupled with the development of more efficacious and precise strategies, ultimately to improve the efficacy of cancer therapy.

Targeting cancer stem cells

With the rapid advancement of sequencing technologies, our understanding of tumor heterogeneity — particularly its role in cancer recurrence and therapeutic resistance — has deepened substantially. Accumulating evidence indicates that cancer stem cells (CSCs), a distinct subpopulation within tumors characterized by self-renewal and differentiation capacities, are considered pivotal drivers of tumor initiation, maintenance, metastasis, and therapy resistance. Critically, CSCs demonstrate enhanced survival post-radiotherapy, thereby contributing to relapse (Krause *et al.* 2017; Saw *et al.* 2024).

Given the central role of CSCs in recurrence, targeting these cells to potentiate radiotherapy efficacy represents a major research focus. Multiple strategies have been proposed to eliminate CSCs and enhance radiosensitivity. Platelet membrane-biomimetic manganese carbonate nanoparticles effectively clear breast cancer stem cells, thereby augmenting radiotherapy response (Jiang *et al.* 2024). The small-molecule drug CBL0137 sensitizes glioblastoma stem cells to radiation by inhibiting the FACT complex (Tallman *et al.* 2020). Engineered UniCAR T cells significantly suppress radioresistant cancer stem cell growth in immunodeficient mice (Arndt *et al.* 2020). Combined genetic and pharmacological inhibition of MYC synergizes with BMI1 targeting, enabling sustained CSC eradication and relapse prevention (Qin *et al.* 2025). A self-assembled nanodrug activated by aldehyde dehydrogenase — composed of disulfide-linked all-trans retinoic acid and a photosensitizer — enables targeted diagnosis and treatment of CSC-enriched tumors (Li *et al.* 2024).

Targeting cancer stem cells in combination with radiotherapy represents a critical strategy for enhancing the efficacy of cancer treatment and preventing recurrence. Future research should advance the understanding of the biological properties of CSCs and their interactions with the tumor microenvironment, enabling the development of more specific and efficient CSC-targeted therapies and novel radiosensitizers.

Gut microbiota

The gut microbiota is a complex ecosystem of microorganisms that significantly influences host health and disease states, including the occurrence, progression, and response to treatment of cancers (Nobels *et al.* 2025; Yang *et al.* 2023). In recent years, an increasing number of studies have shown that the gut microbiota can modulate tumor sensitivity to radiotherapy. It exerts radiosensitizing effects or protects normal tissues from radiation damage by influencing the immune system and the TME (Dong *et al.* 2022; Li *et al.* 2022b; Yi *et al.* 2023). These findings provide novel strategies and potential targets for optimizing cancer radiotherapy via modulation of the gut microbiota.

The gut microbiota and its metabolites can regulate the host immune system. For instance, the gut microbiota influences the activation and function of T cells, thereby enhancing or suppressing anti-tumor immune responses (Lu *et al.* 2022). Research indicates that specific compositions of the gut microbiota are associated with patient response rates to radiotherapy. RT-induced cGAS-STING signal transduction in dendritic cells (DCs) may be modulated by metabolites produced by the gut microbiome. Dysbiosis of the gut microbiota impacts radiotherapy efficacy by downregulating host anti-tumor cytotoxic T lymphocyte (CTL) responses and suppressing the activation of IFN-I related pathways (Li *et al.* 2022b).

Metabolites produced by the gut microbiota, such as short-chain fatty acids (SCFAs), particularly butyrate, play a pivotal role in regulating radiotherapy outcomes. SCFAs upregulate the expression of the sodium/iodide symporter (NIS) through epigenetic modifications, promoting iodine (I^-) uptake, which is beneficial for ^{131}I therapy (Samimi and Haghpanah 2020). The bacterium g_Dorea is an independent predictor influencing the efficacy of ^{131}I therapy in thyroid cancer. Increasing the relative abundance of g_Dorea and g_Bifidobacterium in the gut microbiota may improve the response to ^{131}I therapy in thyroid cancer patients (Zheng *et al.* 2023). The commensal bacterium Roseburia intestinalis sensitizes CRC to radiotherapy by producing butyrate. Butyrate promotes autophagy through the OR51E1/RALB axis to induce tumor cell death (Dong *et al.* 2024).

Based on the role of gut microbiota in regulating

radiotherapy efficacy, diverse strategies such as microbiota transplantation (MT), dietary intervention and modulation of gut microbiota metabolites have been proposed for achieving radiotherapy sensitization (Dong *et al.* 2024; Then *et al.* 2024; Wu *et al.* 2019).

Physicochemical synergy

Some methods focus on enhancing energy deposition at the physical level or regulating reactions at the chemical level for radiotherapy sensitization. High atomic number (high-Z) materials, owing to their strong X-ray absorption capability, allow high-Z metal nanocrystals to generate more secondary electrons and Auger electrons under radiation, thereby causing more severe DNA damage in tumor cells and achieving physical sensitization (Zheng *et al.* 2021). Gold nanoparticles (GNPs) are representative examples of high-Z materials, and their sensitization effects have been extensively studied (Wang *et al.* 2023b; Zhang *et al.* 2019). The morphology and size of GNPs significantly influence sensitization efficacy. Acid-triggered aggregation strategies can enhance their accumulation and retention within tumor cells, thereby improving radiotherapy sensitization outcomes (Zhang *et al.* 2019). Furthermore, these nanomaterials serve as carriers for loading multiple drugs and immune inhibitors. Research on hafnium oxide nanoparticles demonstrates that a surface-modified nanoplatform enables efficient siRNA delivery while retaining high atomic number inherent physical sensitization properties, exhibiting enhanced radiotherapy efficacy (Shin *et al.* 2025).

Exploiting the catalytic activity of nanomaterials to modulate the tumor microenvironment represents another crucial physicochemical sensitization strategy. For instance, catalytic reactions can deplete GSH within tumor cells or promote hydrogen peroxide (H_2O_2) decomposition to generate more ROS, thereby exacerbating oxidative stress damage (Wu *et al.* 2022). Manganese dioxide (MnO_2) nanozymes can respond to tumor microenvironment characteristics and enhance radiotherapy efficacy by activating the STING pathway (Tan *et al.* 2024). Cu_2WS_4-PEG nanozymes function in enhancing breast cancer radiotherapy through multiple enzymatic activities, the high atomic number tungsten (W) and their ability to induce ferroptosis (Fu *et al.* 2024).

Other physical stimuli have also been explored for radiotherapy sensitization. Low-intensity ultrasound (LIUS) has been investigated to enhance tumor sensitivity to radiation through multiple mechanisms (Xu *et al.* 2024). Tumor Treating Fields (TTFields), as a physical therapeutic approach, have been shown to inhibit DNA damage pathways and increase replication stress, thereby creating a conditionally vulnerable environment during interphase that renders cells more sensitive to radiotherapy (Bokstein *et al.* 2020; Karanam *et al.* 2023).

The *in vivo* biodistribution and metabolic properties of nanomaterials require further investigation to ensure efficient accumulation in tumor sites and low toxicity in normal tissues. Additionally, the complexity and heterogeneity of the tumor microenvironment impose higher demands on the design and application of nanomaterials. Future research needs to deepen the understanding of interactions between physicochemical factors and tumor biology, developing more targeted and intelligently responsive sensitization strategies.

Novel delivery strategies

Novel delivery strategies for tumor radiosensitization aim to improve radiation sensitivity and minimize damage to normal tissues. By precisely modulating the tumor microenvironment and external factors, stimuli-responsive nanomaterials can enhance radiosensitization through mechanisms such as size and shape transformations, structural degradation, and controlled drug release. These nanomaterials for enhanced radiotherapy are categorized into four types, including endogenous stimuli-responsive strategies, exogenous stimuli-responsive strategies, dual stimuli-responsive strategies, and multi-stimuli-responsive strategies (Xiao *et al.* 2024). Endogenous stimuli include pH, hypoxia, GSH, ROS, and enzymes (Ding *et al.* 2020; Hua *et al.* 2018; Li *et al.* 2019; Lin *et al.* 2021; Zhang *et al.* 2019). Exogenous stimuli encompass X-rays, light, and ultrasound (Du *et al.* 2023; Song *et al.* 2016; Zhong *et al.* 2019). Dual stimuli-responsive systems combine pH/enzyme, pH/ultrasound, or ROS/light (Ma *et al.* 2022a; Yang *et al.* 2019; Zhang *et al.* 2021). Multi-stimuli-responsive approaches integrate pH/ROS/GSH or X-ray/ROS/GSH (Pan *et al.* 2023; Yuan *et al.* 2022).

Engineered bacteria, as drug carriers, demonstrate significant potential in tumor radiosensitization. These bacteria can not only actively target tumors and penetrate complex microenvironments but also be genetically modified to serve as multifunctional platforms for radiosensitizer delivery and hypoxia alleviation (Liang *et al.* 2022). The use of engineered bacteria to deliver gold nanoparticles (AuNPs) can markedly enhance tumor radiosensitivity while minimizing damage to healthy tissues (Lei *et al.* 2025). Engineered bacteria can modulate the tumor

microenvironment through multiple mechanisms to improve radiotherapy efficacy. For instance, certain engineered bacteria can metabolize intratumoral substances, alleviating hypoxia and thereby increasing radiosensitivity (Han *et al.* 2023). Additionally, engineered bacteria can release immunomodulatory factors to activate anti-tumor immune responses (Chen *et al.* 2024).

Biologically derived carriers also serve as excellent tools for radiosensitization. Studies have shown that M1 macrophage-derived exosomes with catalase (CAT) and anti-PD-L1 nanobody expressed on their membrane, along with DNA damage repair inhibitor (DDRi) encapsulated inside, can significantly enhance radiotherapy efficacy (Ma *et al.* 2022b).

Despite the growing body of research on these novel delivery systems, their practical application in clinical settings remains limited. The intricate strategies for achieving enhanced precision radiotherapy pose significant challenges when transitioning from laboratory experiments to real-world applications.

CLINICAL TRANSLATION OF RADIOSENSITIZERS

Over decades of research, substantial efforts have been dedicated to improving tumor cell radiosensitivity through radiosensitizing agents. Although extensive preclinical investigations have demonstrated the therapeutic potential of various radiosensitizers in oncology, their precise mechanisms for enhancing radiation response remain incompletely elucidated, with only a limited number of compounds progressing to clinical validation (Zhao *et al.* 2025).

The clinical development of chemical radiosensitizers originated in the 1970s. Metronidazole emerged as the first clinically tested agent in 1974, though subsequent studies revealed limited therapeutic benefits (Dische 1985). Subsequent research identified efaproxiral (RSR13), initially developed as a hypolipidemic agent, as a promising radiosensitizer (Suh 2004). Multiple clinical trials have evaluated its efficacy in patients receiving radiotherapy for metastatic tumors and locally advanced unresectable malignancies, yielding partially favorable outcomes. Targeted therapies, including cetuximab and alpelisib (BYL719) have been investigated as radiosensitizers in head and neck squamous cell carcinoma management (Dunn *et al.* 2020). Nelfinavir has demonstrated intrinsic radiosensitizing properties, showing tolerable toxicity profiles and improved survival outcomes when combined with chemoradiotherapy in pancreatic cancer treatment (Wilson *et al.* 2016). Notably, pyrotinib administration has been associated with enhanced radiosensitivity in HER2-positive breast cancer with cerebral metastases (Tian *et al.* 2022). (Table 1)

Table 1 Clinically evaluated radiosensitizers and their proposed mechanisms of action

Class	Radiosensitizer	Proposed mechanism of action
Nitroimidazoles	Metronidazole (Dische 1985)	Restores the radiosensitivity of hypoxic cells
Synthetic allosteric hemoglobin modulator	Efaproxiral (RSR13) (Suh 2004)	Enhances the oxygenation of hypoxic tumors by facilitating the release of oxygen from hemoglobin
Anti-EGFR monoclonal antibody, PI3Kα inhibitor	Cetuximab, alpelisib (BYL719) (Dunn *et al.* 2020)	BYL719 is an α-specific PI3K inhibitor that is synergistic and efficacious when combined with cetuximab
PI3K/AKT inhibitor	Nelfinavir (Wilson *et al.* 2016)	Reduces hypoxia and improves vascularity
Pan-ErbB inhibitor	Pyrotinib (Tian *et al.* 2022)	Pyrotinib is an irreversible pan-ErbB inhibitor

SUMMARY AND PERSPECTIVES

Radiotherapy continues to serve as a principal modality for cancer treatment, yet its therapeutic efficacy is frequently compromised by tumor radioresistance and off-target toxicity. The emergence of radiosensitization strategies provides a valuable framework to overcome these barriers. Over the past few decades, a diverse array of radiosensitization mechanisms has been identified, ranging from molecular-level interventions — such as inhibition of DNA repair, ROS modulation, and cell cycle control — to tumor microenvironment remodeling and immune activation.

Importantly, non-apoptotic forms of cell death, including ferroptosis, pyroptosis, necroptosis, and cuproptosis, offer novel avenues for radiosensitization, especially in apoptosis-resistant tumor subtypes. Likewise, targeting cancer stem cells, modulating metabolic

and hypoxic features of the tumor microenvironment, and leveraging the immunological effects of radiotherapy significantly enhance therapeutic response. Recent studies also underscore the role of gut microbiota and its metabolites in regulating tumor radiosensitivity, suggesting opportunities for microbiota-targeted interventions.

Novel delivery strategies such as responsive nanocarriers, engineered bacteria and biologically derived carriers offer precise, stimuli-triggered radiosensitization platforms. In addition to biological strategies, physicochemical approaches employing high-Z nanomaterials and physical stimuli show the potential of interdisciplinary application in radiosensitization. These advances collectively highlight the growing interdisciplinarity of the field, integrating oncology, materials science, immunology, and synthetic biology.

Despite these developments, several key challenges remain. These include variability in patient response, lack of predictive biomarkers, delivery barriers in solid tumors, and limited clinical translation of promising preclinical findings. To address these issues, future research should prioritize: (1) personalized radiosensitization based on tumor molecular profiling; (2) combination regimens with immunotherapies and targeted therapies; (3) development of biomimetic and programmable delivery systems; and (4) large-scale, multicenter clinical trials to validate safety and efficacy.

Ultimately, advancing radiosensitization strategies holds significant promise for improving radiotherapy outcomes, minimizing collateral damage, and contributing to a more effective and personalized paradigm in cancer treatment.

Acknowledgements This work was supported by the National Natural Science Foundation of China (92159201 and 82402291), the National Key R&D Program of China (2022YFA1206100), the Nuclear Energy R&D project (HNKF202223(36)), Young Elite Scientist Sponsorship Program by BAST (BYESS2024010), and grants from Peking University Third Hospital (BYSYRCYJ2023002, and BYSYZD2025036).

Compliance with Ethical Standards

Conflict of interest Gaoyuan Xie, Xiaotu Ma and Fan Wang declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Ahmad RS, Eubank TD, Lukomski S, Boone BA (2021) Immune cell modulation of the extracellular matrix contributes to the pathogenesis of pancreatic cancer. Biomolecules 11(6): 901. https://doi.org/10.3390/biom11060901

Akhunzianov AA, Rozhina EV, Filina YV, Rizvanov AA, Miftakhova RR (2025) Resistance to radiotherapy in cancer. Diseases 13(1): 22. https://doi.org/10.3390/diseases13010022

Arndt C, Loureiro LR, Feldmann A, Jureczek J, Bergmann R, Máthé D, Hegedüs N, Berndt N, Koristka S, Mitwasi N, Fasslrinner F, Lamprecht C, Kegler A, Hoffmann A, Bartsch T, Köseer AS, Egan G, Schmitz M, Hořejší V, Krause M, Dubrovska A, Bachmann M (2020) UniCAR T cell immunotherapy enables efficient elimination of radioresistant cancer cells. Oncoimmunology 9(1): 1743036. https://doi.org/10.1080/2162402X.2020.1743036

Arnér ESJ, Holmgren A (2000) Physiological functions of thioredoxin and thioredoxin reductase. Eur J Biochem 267(20): 6102–6109

Arnér ESJ, Holmgren A (2006) The thioredoxin system in cancer. Semin Cancer Biol 16(6): 420–426

Ashton TM, McKenna WG, Kunz-Schughart LA, Higgins GS (2018) Oxidative phosphorylation as an emerging target in cancer therapy. Clin Cancer Res 24(11): 2482–2490

Barker HE, Paget JTE, Khan AA, Harrington KJ (2015) The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer 15(8): 409–425

Bian M, Fan R, Zhao S, Liu W (2019) Targeting the thioredoxin system as a strategy for cancer therapy. J Med Chem 62(16): 7309–7321

Bigos KJA, Quiles CG, Lunj S, Smith DJ, Krause M, Troost EGC, West CM, Hoskin P, Choudhury A (2024) Tumour response to hypoxia: understanding the hypoxic tumour microenvironment to improve treatment outcome in solid tumours. Front Oncol 14: 1331355. https://doi.org/10.3389/fonc.2024.1331355

Bokstein F, Blumenthal D, Limon D, Ben Harosh C, Ram Z, Grossman R (2020) Concurrent Tumor Treating Fields (TTFields) and radiation therapy for newly diagnosed glioblastoma: a prospective safety and feasibility study. Front Oncol 10: 411. https://doi.org/10.3389/fonc.2020.00411

Braks JAM, Spiegelberg L, Koljenovic S, Ridwan Y, Keereweer S, Kanaar R, Wolvius EB, Essers J (2015) Optical imaging of tumor response to hyperbaric oxygen treatment and irradiation in an orthotopic mouse model of head and neck squamous cell carcinoma. Mol Imaging Biol 17(5): 633–642

Bump EA, Brown JM (1990) Role of glutathione in the radiation response of mammalian cells *invitro* and *in vivo*. Pharmacol Ther 47(1): 117–136

Cao W, Chen G, Wu L, Yu KN, Sun M, Yang M, Jiang Y, Jiang Y, Xu Y, Peng S, Han W (2023) Ionizing radiation triggers the antitumor immunity by inducing gasdermin e-mediated pyroptosis in

tumor cells. Int J Radiat Oncol Biol Phys 115(2): 440–452
Cao Y, Zhou X, Nie Q, Zhang J (2024) Inhibition of the thioredoxin system for radiosensitization therapy of cancer. Eur J Med Chem 268: 116218. https://doi.org/10.1016/J.EJMECH.2024.116218
Chen H, Zhu Y, Zhang C, Hu L, Yang K (2024) Engineered bacteria in tumor immunotherapy. Cancer Lett 589: 216817. https://doi.org/10.1016/j.canlet.2024.216817
Chen P-H, Wu J, Ding C-KC, Lin C-C, Pan S, Bossa N, Xu Y, Yang W-H, Mathey-Prevot B, Chi J-T (2020) Kinome screen of ferroptosis reveals a novel role of ATM in regulating iron metabolism. Cell Death Differ 27(3): 1008–1022
Chen S, Yu S, Du Z, Huang X, He M, Long S, Liu J, Lan Y, Yang D, Wang H, Li S, Chen A, Hao Y, Su Y, Wang C, Luo S (2021) Synthesis of mitochondria-anchored nitroimidazoles with a versatile NIR fluorophore for hypoxic tumor-targeting imaging and chemo-radiotherapy. J Med Chem 64(6): 3381–3391
Chen X, Song E (2019) Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discovery 18(2): 99–115
Chen X, Zhang X, Wu Y, Chen Y, Guo Y, Jana D, Wang D, Yuan W, Zhao Y (2022) Tumor extracellular matrix-targeted nanoscavengers reverse suppressive microenvironment for cocktail therapy. Mater Today 61: 78–90
Corrales L, McWhirter SM, Dubensky TW, Gajewski TF (2016) The host STING pathway at the interface of cancer and immunity. J Clin Invest 126(7): 2404–2411
de Lima Luna AC, Forti FL (2021) Modulation of SCD1 activity in hepatocyte cell lines: evaluation of genomic stability and proliferation. Mol Cell Biochem 476(9): 3393–3405
de Palma M, Biziato D, Petrova TV (2017) Microenvironmental regulation of tumour angiogenesis. Nat Rev Cancer 17(8): 457–474
DeNardo DG, Ruffell B (2019) Macrophages as regulators of tumour immunity and immunotherapy. Nat Rev Immunol 19(6): 369–382
Deng H, Malsiu F, Ge H, Losmanova T, Medová M, Zamboni N, Wang W, Peng R-W, Tang J, Dorn P, Marti TM (2025) LDHB silencing enhances the effects of radiotherapy by impairing nucleotide metabolism and promoting persistent DNA damage. Sci Rep 15(1): 10897. https://doi.org/10.1038/s41598-025-95633-3
Dillon MT, Good JS, Harrington KJ (2014) Selective targeting of the G2/M cell cycle checkpoint to improve the therapeutic index of radiotherapy. Clin Oncol 26(5): 257–265
Ding Y, Sun Z, Tong Z, Zhang S, Min J, Xu Q, Zhou L, Mao Z, Xia H, Wang W (2020) Tumor microenvironment-responsive multifunctional peptide coated ultrasmall gold nanoparticles and their application in cancer radiotherapy. Theranostics 10(12): 5195–5208
Ding Y, Xiao X, Zeng L, Shang Q, Jiang W, Xiong S, Duan X, Shen J, Wang R, Guo J, Pan Y (2021) Platinum-crosslinking polymeric nanoparticle for synergetic chemoradiotherapy of nasopharyngeal carcinoma. Bioact Mater 6(12): 4707–4716
Dische S (1985) Chemical sensitizers for hypoxic cells: a decade of experience in clinical radiotherapy. Radiother Oncol 3(2): 97–115
Dong J, Li Y, Xiao H, Cui M, Fan S (2022) Commensal microbiota in the digestive tract: a review of its roles in carcinogenesis and radiotherapy. Cancer Biol Med 19(1): 43–55
Dong J, Wang B, Xiao Y, Liu J, Wang Q, Xiao H, Jin Y, Liu Z, Chen Z, Li Y, Fan S, Li Y, Cui M (2024) *Roseburia intestinalis* sensitizes colorectal cancer to radiotherapy through the butyrate/OR51E1/RALB axis. Cell Rep 43(3): 113846. https://doi.org/10.1016/j.celrep.2024.113846
Du J, Cieslak JA, Welsh JL, Sibenaller ZA, Allen BG, Wagner BA, Kalen AL, Doskey CM, Strother RK, Button AM, Mott SL, Smith B, Tsai S, Mezhir J, Goswami PC, Spitz DR, Buettner GR, Cullen JJ (2015) Pharmacological ascorbate radiosensitizes pancreatic cancer. Cancer Res 75(16): 3314–3326
Du Z, Wang X, Zhang X, Gu Z, Fu X, Gan S, Fu T, Xie S, Tan W (2023) X-ray-triggered carbon monoxide and manganese dioxide generation based on scintillating nanoparticles for cascade cancer radiosensitization. Angew Chem Int Ed 62(23): e202302525. https://doi.org/10.1002/anie.202302525
Dunn LA, Riaz N, Fury MG, McBride SM, Michel L, Lee NY, Sherman EJ, Baxi SS, Haque SS, Katabi N, Wong RJ, Xiao H, Ho AL, Pfister DG (2020) A phase 1b study of cetuximab and BYL719 (Alpelisib) concurrent with intensity modulated radiation therapy in stage III-IVB head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 106(3): 564–570
Fath MA, Ahmad IM, Smith CJ, Spence J, Spitz DR (2011) Enhancement of carboplatin-mediated lung cancer cell killing by simultaneous disruption of glutathione and thioredoxin metabolism. Clin Cancer Res 17(19): 6206–6217
Feng Q, Ma X, Cheng K, Liu G, Li Y, Yue Y, Liang J, Zhang L, Zhang T, Wang X, Gao X, Nie G, Zhao X (2022) Engineered bacterial outer membrane vesicles as controllable two-way adaptors to activate macrophage phagocytosis for improved tumor immunotherapy. Adv Mater 34(40): 2206200. https://doi.org/10.1002/adma.202206200
Fernández E, Morillo V, Salvador M, Santafé A, Beato I, Rodríguez M, Ferrer C (2021) Hyperbaric oxygen and radiation therapy: a review. Clin Transl Oncol 23(6): 1047–1053
Fu S, Li Y, Shen L, Chen Y, Lu J, Ran Y, Zhao Y, Tang H, Tan L, Lin Q, Hao Y (2024) Cu_2WS_4-PEG nanozyme as multifunctional sensitizers for enhancing immuno-radiotherapy by inducing ferroptosis. Small 20(26): 2309537. https://doi.org/10.1002/smll.202309537
Gabrilovich DI, Nagaraj S (2009) Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 9(3): 162–174
Gonzalez-Avila G, Sommer B, Flores-Soto E, Aquino-Galvez A (2023) Hypoxic effects on matrix metalloproteinases' expression in the tumor microenvironment and therapeutic perspectives. Int J Mol Sci 24(23): 16887. https://doi.org/10.3390/ijms242316887
Guo Z, Lei L, Zhang Z, Du M, Chen Z (2024) The potential of vascular normalization for sensitization to radiotherapy. Heliyon 10(12): e32598. https://doi.org/10.1016/j.heliyon.2024.e32598
Han D, Zhang X, Ma Y, Yang X, Li Z (2023) The development of live microorganism-based oxygen shuttles for enhanced hypoxic tumor therapy. Mater Today Bio 18: 100517. https://doi.org/10.1016/j.mtbio.2022.100517
Hou L, Chen D, Wang R, Wang R, Zhang H, Zhang Z, Nie Z, Lu S (2021) Transformable honeycomb-like nanoassemblies of carbon dots for regulated multisite delivery and enhanced antitumor chemoimmunotherapy. Angew Chem Int Ed 60(12): 6581–6592
Hu M, Jiang L, Cui X, Zhang J, Yu J (2018) Proton beam therapy for cancer in the era of precision medicine. J Hematol Oncol 11(1): 136. https://doi.org/10.1186/s13045-018-0683-4
Hua L, Wang Z, Zhao L, Mao H, Wang G, Zhang K, Liu X, Wu D, Zheng Y, Lu J, Yu R, Liu H (2018) Hypoxia-responsive lipid-poly-(hypoxic radiosensitized polyprodrug) nanoparticles for glioma chemo- and radiotherapy. Theranostics 8(18): 5088–5105
Huang R-X, Zhou P-K (2020) DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduction Targeted Ther 5(1): 60. https://doi.org/10.1038/s41392-020-0150-x

Ivanov SD, Semenov AL, Kovan'ko EG, Yamshanov VA (2015) Effects of iron ions and iron chelation on the efficiency of experimental radiotherapy of animals with gliomas. Bull Exp Biol Med 158(6): 800–803

Jagodinsky JC, Vera JM, Jin WJ, Shea AG, Clark PA, Sriramaneni RN, Havighurst TC, Chakravarthy I, Allawi RH, Kim K, Harari PM, Sondel PM, Newton MA, Crittenden MR, Gough MJ, Miller JR, Ong IM, Morris ZS (2024) Intratumoral radiation dose heterogeneity augments antitumor immunity in mice and primes responses to checkpoint blockade. Sci Transl Med 16(765): eadk0642. https://doi.org/10.1126/scitranslmed.adk0642

Ji D, Song C, Li Y, Xia J, Wu Y, Jia J, Cui X, Yu S, Gu J (2020) Combination of radiotherapy and suppression of Tregs enhances abscopal antitumor effect and inhibits metastasis in rectal cancer. J Immunother Cancer 8(2): e000826. https://doi.org/10.1136/jitc-2020-000826

Jiang H, Zuo J, Li B, Chen R, Luo K, Xiang X, Lu S, Huang C, Liu L, Tang J, Gao F (2023) Drug-induced oxidative stress in cancer treatments: angel or devil? Redox Biol 63: 102754. https://doi.org/10.1016/j.redox.2023.102754

Jiang L, Kon N, Li T, Wang S-J, Su T, Hibshoosh H, Baer R, Gu W (2015) Ferroptosis as a p53-mediated activity during tumour suppression. Nature 520(7545): 57–62

Jiang Y, Liao X, Tang W, Huang C, Pan Y, Ning S (2024) Platelet membrane biomimetic manganese carbonate nanoparticles promote breast cancer stem cell clearance for sensitized radiotherapy. Int J Nanomed 19: 1699–1707

Jin Y, Chen Z, Dong J, Wang B, Fan S, Yang X, Cui M (2021) SREBP1/FASN/cholesterol axis facilitates radioresistance in colorectal cancer. Febs Open Bio 11(5): 1343–1352

Josson S, Sung S-Y, Lao K, Chung LWK, Johnstone PAS (2008) Radiation modulation of MicroRNA in prostate cancer cell lines. Prostate 68(15): 1599–1606

Kalluri R (2016) The biology and function of fibroblasts in cancer. Nat Rev Cancer 16(9): 582–598

Karanam NK, Shang Z, Timmerman R, Story MD, Saha D (2023) Abstract 3272: Tumor treating fields combined with the PULSAR paradigm for radiotherapy and an immune checkpoint inhibitor enhances antitumor efficacy *in vivo*. Cancer Res 83(S7): 3272. https://doi.org/10.1158/1538-7445.AM2023-3272

Karimpour S, Lou J, Lin LL, Rene LM, Lagunas L, Ma X, Karra S, Bradbury CM, Markovina S, Goswami PC, Spitz DR, Hirota K, Kalvakolanu DV, Yodoi J, Gius D (2002) Thioredoxin reductase regulates AP-1 activity as well as thioredoxin nuclear localization via active cysteines in response to ionizing radiation. Oncogene 21(41): 6317–6327

Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW (2017) Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer 17(10): 620–632

Krause M, Dubrovska A, Linge A, Baumann M (2017) Cancer stem cells: radioresistance, prediction of radiotherapy outcome and specific targets for combined treatments. Adv Drug Delivery Rev 109: 63–73

Lang X, Green MD, Wang W, Yu J, Choi JE, Jiang L, Liao P, Zhou J, Zhang Q, Dow A, Saripalli AL, Kryczek I, Wei S, Szeliga W, Vatan L, Stone EM, Georgiou G, Cieslik M, Wahl DR, Morgan MA, Chinnaiyan AM, Lawrence TS, Zou W (2019) Radiotherapy and immunotherapy promote tumoral lipid oxidation and ferroptosis via synergistic repression of SLC7A11. Cancer Discovery 9(12): 1673–1685

Larsen BD, Benada J, Yung PYK, Bell RAV, Pappas G, Urban V, Ahlskog JK, Kuo TT, Janscak P, Megeney LA, Elsässer SJ, Bartek J, Sørensen CS (2022) Cancer cells use self-inflicted DNA breaks to evade growth limits imposed by genotoxic stress. Science 376(6592): 476–483

LeBeau AM, Brennen WN, Aggarwal S, Denmeade SR (2009) Targeting the cancer stroma with a fibroblast activation protein-activated promelittin protoxin. Mol Cancer Ther 8(5): 1378–1386

Lee Y, Li HK, Masaoka A, Sunada S, Hirakawa H, Fujimori A, Nickoloff JA, Okayasu R (2016) The purine scaffold Hsp90 inhibitor PU-H71 sensitizes cancer cells to heavy ion radiation by inhibiting DNA repair by homologous recombination and non-homologous end joining. Radiother Oncol 121(1): 162–168

Lei G, Zhang Y, Koppula P, Liu X, Zhang J, Lin SH, Ajani JA, Xiao Q, Liao Z, Wang H, Gan B (2020) The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression. Cell Res 30(2): 146–162

Lei L, Xu H, Li M, Du M, Chen Z (2025) Dual-pathway tumor radiosensitization strategy based on engineered bacteria capable of targeted delivery of AuNPs and specific hypoxia alleviation. J Nanobiotechnol 23(1): 254. https://doi.org/10.1186/s12951-025-03329-7

Levesque AA, Eastman A (2007) p53-based cancer therapies: is defective p53 the achilles heel of the tumor? Carcinogenesis 28(1): 13–20

Li B, Tian J, Zhang F, Wu C, Li Z, Wang D, Zhuang J, Chen S, Song W, Tang Y, Ping Y, Liu B (2024) Self-assembled aldehyde dehydrogenase-activatable nano-prodrug for cancer stem cell-enriched tumor detection and treatment. Nat Commun 15(1): 9417. https://doi.org/10.1038/s41467-024-53771-8

Li C, Jiang P, Wei S, Xu X, Wang J (2020) Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. Mol Cancer 19(1): 116. https://doi.org/10.1186/s12943-020-01234-1

Li HK, Matsumoto Y, Furusawa Y, Kamada T (2016) PU-H71, a novel Hsp90 inhibitor, as a potential cancer-specific sensitizer to carbon-ion beam therapy. J Radiat Res 57(5): 572–575

Li X, Wang H, Li Z, Tao F, Wu J, Guan W, Liu S (2023) Oxygen switches: refueling for cancer radiotherapy. Front Oncol 12: 1085432. https://doi.org/10.3389/fonc.2022.1085432

Li X-Y, You J-X, Zhang L-Y, Su L-X, Yang X-T (2022a) A novel model based on necroptosis-related genes for predicting prognosis of patients with prostate adenocarcinoma. Front Bioeng Biotechnol 9: 814813. https://doi.org/10.3389/fbioe.2021.814813

Li Y, Yun K-H, Lee H, Goh S-H, Suh Y-G, Choi Y (2019) Porous platinum nanoparticles as a high-Z and oxygen generating nanozyme for enhanced radiotherapy *in vivo*. Biomaterials 197: 12–19

Li Y, Zhao L, Li X-F (2021) Hypoxia and the tumor microenvironment. Technol Cancer Res Treat 20: 15330338211036304. https://doi.org/10.1177/15330338211036304

Li Y, Han L, Hu H (2025) Research progress on cuproptosis and copper related anti-tumor therapy. Discover Oncol 16(1): 584. https://doi.org/10.1007/s12672-025-02335-3

Li Z, Zhang Y, Hong W, Wang B, Chen Y, Yang P, Zhou J, Fan J, Zeng Z, Du S (2022b) Gut microbiota modulate radiotherapy-associated antitumor immune responses against hepatocellular carcinoma Via STING signaling. Gut Microbes 14(1): 2119055. https://doi.org/10.1080/19490976.2022.2119055

Liang S, Wang C, Shao Y, Wang Y, Xing D, Geng Z (2022) Recent advances in bacteria-mediated cancer therapy. Front Bioeng Biotechnol 10: 1026248. https://doi.org/10.3389/fbioe.2022.1026248

Liang Y-W, Zheng J, Li X, Zheng W, Chen T (2014) Selenadiazole derivatives as potent thioredoxin reductase inhibitors that

enhance the radiosensitivity of cancer cells. Eur J Med Chem 84: 335–342

Liao Y, Wang D, Gu C, Wang X, Zhu S, Zheng Z, Zhang F, Yan J, Gu Z (2024) A cuproptosis nanocapsule for cancer radiotherapy. Nat Nanotechnol 19(12): 1892–1902

Liberti MV, Locasale JW (2016) The warburg effect: how does it benefit cancer cells? Trends Biochem Sci 41(3): 211–218

Lin L-S, Song J, Song L, Ke K, Liu Y, Zhou Z, Shen Z, Li J, Yang Z, Tang W, Niu G, Yang H-H, Chen X (2018) Simultaneous fenton-like ion delivery and glutathione depletion by MnO_2-based nanoagent to enhance chemodynamic therapy. Angewandte Chemie International Edition 57(18): 4902–4906

Lin X, Zhu R, Hong Z, Zhang X, Chen S, Song J, Yang H (2021) GSH-responsive radiosensitizers with deep penetration ability for multimodal imaging-guided synergistic radio-chemodynamic cancer therapy. Adv Funct Mater 31(24): 2101278. https://doi.org/10.1002/adfm.202101278

Lindner T, Giesel FL, Kratochwil C, Serfling SE (2021) Radioligands targeting fibroblast activation protein (FAP). Cancers 13(22): 5744. https://doi.org/10.3390/cancers13225744

Liu S, Li W, Chen H, Zhou J, Dong S, Zang P, Tian B, Ding H, Gai S, Yang P, Zhao Y (2022) On-demand generation of peroxynitrite from an integrated two-dimensional system for enhanced tumor therapy. ACS Nano 16(6): 8939–8953

Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J (2018) Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. J Hematol Oncol 11(1): 104. https://doi.org/10.1186/s13045-018-0647-8

Liu Y, Gu W (2022) p53 in ferroptosis regulation: the new weapon for the old guardian. Cell Death Differ 29(5): 895–910

Lu K, He C, Guo N, Chan C, Ni K, Lan G, Tang H, Pelizzari C, Fu Y-X, Spiotto MT, Weichselbaum RR, Lin W (2018) Low-dose X-ray radiotherapy-radiodynamic therapy via nanoscale metal-organic frameworks enhances checkpoint blockade immunotherapy. Nat Biomed Eng 2(8): 600–610

Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, Li Q (2022) Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. J Hematol Oncol 15(1): 47. https://doi.org/10.1186/s13045-022-01273-9

Luo T, Nash GT, Jiang X, Feng X, Mao J, Liu J, Juloori A, Pearson AT, Lin W (2022) A 2D nanoradiosensitizer enhances radiotherapy and delivers STING agonists to potentiate cancer immunotherapy. Adv Mater 34(39): 2110588. https://doi.org/10.1002/adma.202110588

Ma J, Wu S, Yang X, Shen S, Zhu Y, Wang R, Xu W, Li Y, Zhu H, Yan Y, Lin N, Zhang B (2025) Milciclib-mediated CDK2 inhibition to boost radiotherapy sensitivity in colorectal cancer. Front Pharmacol 16: 1557925. https://doi.org/10.3389/fphar.2025.1557925

Ma R, Zheng J, Tian Y, Li C, Lyu B, Lu L, Su Z, Chen L, Gao X, Tang J-X, Choy WCH (2022a) Self-polymerization of monomer and induced interactions with perovskite for highly performed and stable perovskite solar cells. Adv Funct Mater 32(1): 2105290. https://doi.org/10.1002/adfm.202105290

Ma X, Yao M, Gao Y, Yue Y, Li Y, Zhang T, Nie G, Zhao X, Liang X (2022b) Functional immune cell-derived exosomes engineered for the trilogy of radiotherapy sensitization. Adv Sci 9(23): 2106031. https://doi.org/10.1002/advs.202106031

Ma X, Liang X, Yao M, Gao Y, Luo Q, Li X, Yu Y, Sun Y, Cheng MHY, Chen J, Zheng G, Shi J, Wang F (2023) Myoglobin-loaded gadolinium nanotexaphyrins for oxygen synergy and imaging-guided radiosensitization therapy. Nat Commun 14(1): 6187. https://doi.org/10.1038/s41467-023-41782-w

Marullo R, Castro M, Yomtoubian S, Calvo-Vidal MN, Revuelta MV, Krumsiek J, Cho A, Morgado PC, Yang SN, Medina V, Roth BM, Bonomi M, Keshari KR, Mittal V, Navigante A, Cerchietti L (2021) The metabolic adaptation evoked by arginine enhances the effect of radiation in brain metastases. Sci Adv 7(45): eabg1964. https://doi.org/10.1126/sciadv.abg1964

Muschel RJ, Soto DE, McKenna WG, Bernhard EJ (1998) Radiosensitization and apoptosis. Oncogene 17(25): 3359–3363

Ni K, Xu Z, Culbert A, Luo T, Guo N, Yang K, Pearson E, Preusser B, Wu T, La Riviere P, Weichselbaum RR, Spiotto MT, Lin W (2022) Synergistic checkpoint-blockade and radiotherapy-radiodynamic therapy via an immunomodulatory nanoscale metal-organic framework. Nat Biomed Eng 6(2): 144–156

Nickoloff JA, Taylor L, Sharma N, Kato TA (2021) Exploiting DNA repair pathways for tumor sensitization, mitigation of resistance, and normal tissue protection in radiotherapy. Cancer Drug Resist 4(2): 244–263

Ning J, Chen L, Zeng Y, Xiao G, Tian W, Wu Q, Tang J, He S, Tanzhu G, Zhou R (2024) The scheme, and regulative mechanism of pyroptosis, ferroptosis, and necroptosis in radiation injury. Int J Biol Sci 20(5): 1871–1883

Nobels A, van Marcke C, Jordan BF, Van Hul M, Cani PD (2025) The gut microbiome and cancer: from tumorigenesis to therapy. Nat Metab 7(5): 895–917

Pan S, Huang G, Sun Z, Chen X, Xiang X, Jiang W, Xu Y, Chen T, Zhu X (2023) X-ray-responsive zeolitic imidazolate framework-capped nanotherapeutics for cervical cancer-targeting radiosensitization. Adv Funct Mater 33(13): 2213364. https://doi.org/10.1002/adfm.202213364

Pan X, Lin Z, Jiang D, Yu Y, Yang D, Zhou H, Zhan D, Liu S, Peng G, Chen Z, Yu Z (2019) Erastin decreases radioresistance of NSCLC cells partially by inducing GPX4-mediated ferroptosis. Oncol Lett 17(3): 3001–3008

Pawlik TM, Keyomarsi K (2004) Role of cell cycle in mediating sensitivity to radiotherapy. Int J Radiat Oncol Biol Phys 59(4): 928–942

Pei P, Wang Y, Shen W, He Q, Han X, Zhang C, Xie Y, Zhou G, Zhao Y, Hu L, Yang K (2024) Oxygen-driven cuproptosis synergizes with radiotherapy to potentiate tumor immunotherapy. Aggregate 5(3): e484. https://doi.org/10.1002/agt2.484

Pennington JD, Jacobs KM, Sun L, Bar-Sela G, Mishra M, Gius D (2007) Thioredoxin and thioredoxin reductase as redox-sensitive molecular targets for cancer therapy. Curr Pharm Des 13(33): 3368–3377

Piffkó A, Yang K, Panda A, Heide J, Tesak K, Wen C, Zawieracz K, Wang L, Naccasha EZ, Bugno J, Fu Y, Chen D, Donle L, Lengyel E, Tilley DG, Mack M, Rock RS, Chmura SJ, Vokes EE, He C, Pitroda SP, Liang HL, Weichselbaum RR (2025) Radiation-induced amphiregulin drives tumour metastasis. Nature 643(8072): 810–819

Price JM, Prabhakaran A, West CML (2023) Predicting tumour radiosensitivity to deliver precision radiotherapy. Nat Rev Clin Oncol 20(2): 83–98

Qin Z, Liu S, Zheng Y, Wang Y, Chen Y, Peng X, Jia L (2025) Co-targeting BMI1 and MYC to eliminate cancer stem cells in squamous cell carcinoma. Cell Rep Med 6(5): 102077. https://doi.org/10.1016/j.xcrm.2025.102077

Rana S, Espinosa-Diez C, Ruhl R, Chatterjee N, Hudson C, Fraile-Bethencourt E, Agarwal A, Khou S, Thomas CR Jr, Anand S (2020) Differential regulation of microRNA-15a by radiation affects angiogenesis and tumor growth via modulation of acid sphingomyelinase. Sci Rep 10(1): 5581. https://doi.org/10.1038/s41598-020-62621-8

Read GH, Bailleul J, Vlashi E, Kesarwala AH (2022) Metabolic response to radiation therapy in cancer. Mol Carcinog 61(2): 200–224

Rodman SN, Spence JM, Ronnfeldt TJ, Zhu Y, Solst SR, O'Neill RA,

Allen BG, Guan X, Spitz DR, Fath MA (2016) Enhancement of radiation response in breast cancer stem cells by inhibition of thioredoxin- and glutathione-dependent metabolism. Radiat Res 186(4): 385–395

Roy A, Bera S, Saso L, Dwarakanath BS (2022) Role of autophagy in tumor response to radiation: Implications for improving radiotherapy. Front Oncol 12: 957373. https://doi.org/10.3389/fonc.2022.957373

Russo M, Russo GL (2018) Autophagy inducers in cancer. Biochem Pharmacol 153: 51–61

Samimi H, Haghpanah V (2020) Gut microbiome and radioiodine-refractory papillary thyroid carcinoma pathophysiology. Trends Endocrinol Metab 31(9): 627–630

Sanche L (2009) Biological chemistry: beyond radical thinking. Nature 461(7262): 358–359

Saw PE, Liu Q, Wong P-P, Song E (2024) Cancer stem cell mimicry for immune evasion and therapeutic resistance. Cell Stem Cell 31(8): 1101–1112

Sharabi AB, Lim M, DeWeese TL, Drake CG (2015) Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol 16(13): E498–E509

Sharda A, Rashid M, Shah SG, Sharma AK, Singh SR, Gera P, Chilkapati MK, Gupta S (2020) Elevated HDAC activity and altered histone phospho-acetylation confer acquired radioresistant phenotype to breast cancer cells. Clin Epigenet 12(1): 4. https://doi.org/10.1186/s13148-019-0800-4

Shen D, Luo J, Chen L, Ma W, Mao X, Zhang Y, Zheng J, Wang Y, Wan J, Wang S, Ouyang J, Yi H, Liu D, Huang W, Zhang W, Liu Z, McLeod HL, He Y (2022) PARPi treatment enhances radiotherapy-induced ferroptosis and antitumor immune responses via the cGAS signaling pathway in colorectal cancer. Cancer Lett 550: 215919. https://doi.org/10.1016/j.canlet.2022.215919

Shen H, Hau E, Joshi S, Dilda PJ, McDonald KL (2015) Sensitization of glioblastoma cells to irradiation by modulating the glucose metabolism. Mol Cancer Ther 14(8): 1794–1804

Shibata Y, Yasui H, Higashikawa K, Miyamoto N, Kuge Y (2019) Erastin, a ferroptosis-inducing agent, sensitized cancer cells to X-ray irradiation via glutathione starvation *in vitro* and *in vivo*. PLoS One 14(12): e0225931. https://doi.org/10.1371/journal.pone.0225931

Shiloh Y (2003) ATM and related protein kinases: safeguarding genome integrity. Nat Rev Cancer 3(3): 155–168

Shin S, Bae G-H, Han J-H, Shin HE, Park JD, Ko S, Koh E-Y, Han J, Han SC, Lee JJB, Kim D-H, Nam H, Park W (2025) Dual-functional hafnium oxide nanoplatform combining high-Z radiosensitization with Bcl-2 gene silencing for enhanced cancer radiotherapy. Adv Healthcare Mater 14(15): 2404819. https://doi.org/10.1002/adhm.202404819

Singh SS, Vats S, Chia AY-Q, Tan TZ, Deng S, Ong MS, Arfuso F, Yap CT, Goh BC, Sethi G, Huang RY-J, Shen HM, Manjithaya R, Kumar AP (2018) Dual role of autophagy in hallmarks of cancer. Oncogene 37(9): 1142–1158

Song X, Feng L, Liang C, Yang K, Liu Z (2016) Ultrasound triggered tumor oxygenation with oxygen-shuttle nanoperfluorocarbon to overcome hypoxia-associated resistance in cancer therapies. Nano Lett 16(10): 6145–6153

Su T, Zhang Y, Valerie K, Wang X-Y, Lin SB, Zhu GZ (2019) STING activation in cancer immunotherapy. Theranostics 9(25): 7759–7771

Suh JH (2004) Efaproxiral: a novel radiation sensitiser. Expert Opin Invest Drugs 13(5): 543–550

Tallman M, Zalenski A, Deighen A, Schrock M, Mortach S, Grubb T, Kastury P, Huntoon K, Summers M, Venere M (2020) Stem-26. Small molecule drug cbl0137 inhibits the fact complex and sensitizes glioblastoma cancer stem cells to radiotherapy. Neuro Oncol 22(Suppl 2): ii201–ii202

Tan G, Lin C, Huang C, Chen B, Chen J, Shi Y, Zhi F (2022) Radiosensitivity of colorectal cancer and radiation-induced gut damages are regulated by gasdermin E. Cancer Lett 529: 1–10

Tan M, Gao Z, Wang X, Lin C, Wan Y, Xie W, Chen W, Zhang Y, Quan Z, Hou Z (2024) MnO_2 nanozyme with lanthanide-based radiosensitization for advanced radiotherapy by tumor microenvironment triggering STING pathway activation. Chem Eng J 486: 150364. https://doi.org/10.1016/j.cej.2024.150364

Then CK, Paillas S, Moomin A, Misheva MD, Moir RA, Hay SM, Bremner D, Roberts KS, Smith EE, Heidari Z, Sescu D, Wang X, Suárez-Bonnet A, Hay N, Murdoch SL, Saito R, Collie-Duguid ESR, Richardson S, Priestnall SL, Wilson JM, Gurumurthy M, Royle JS, Samuel LM, Ramsay G, Vallis KA, Foster KR, McCullagh JSO, Kiltie AE (2024) Dietary fibre supplementation enhances radiotherapy tumour control and alleviates intestinal radiation toxicity. Microbiome 12(1): 89. https://doi.org/10.1186/s40168-024-01804-1

Tian W, Hao S, Wang L, Chen Y, Li Z, Luo D (2022) Pyrotinib treatment enhances the radiosensitivity in HER2-positive brain metastatic breast cancer patients. Anti-Cancer Drugs 33(1): E622–E627

Topalian SL, Taube JM, Anders RA, Pardoll DM (2016) Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer 16(5): 275–287

Turchan WT, Pitroda SP, Weichselbaum RR (2021) Radiotherapy and immunotherapy combinations in the treatment of patients with metastatic disease: current status and future focus. Clin Cancer Res 27(19): 5188–5194

Une N, Takano-Kasuya M, Kitamura N, Ohta M, Inose T, Kato C, Nishimura R, Tada H, Miyagi S, Ishida T, Unno M, Kamei T, Gonda K (2021) The anti-angiogenic agent lenvatinib induces tumor vessel normalization and enhances radiosensitivity in hepatocellular tumors. Med Oncol 38(6): 60. https://doi.org/10.1007/s12032-021-01503-z

van Gisbergen MW, Zwilling E, Dubois LJ (2021) Metabolic rewiring in radiation oncology toward improving the therapeutic ratio. Front Oncol 11: 653621. https://doi.org/10.3389/fonc.2021.653621

Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S (2017) DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 8(1): 15618. https://doi.org/10.1038/ncomms15618

Verma S, Young S, Boldt G, Blanchette P, Lock M, Helou J, Raphael J (2024) Immunotherapy and radiation therapy sequencing in breast cancer: a systematic review. Int J Radiat Oncol Biol Phys 118(5): 1422–1434

Wang H-H, Wu Z-Q, Qian D, Zaorsky NG, Qiu M-H, Cheng J-J, Jiang C, Wang J, Zeng X-L, Liu C-L, Tian L-J, Ying G-G, Meng M-B, Hao X-S, Yuan Z-Y (2018) Ablative hypofractionated radiation therapy enhances non-small cell lung cancer cell killing via preferential stimulation of necroptosis *in vitro* and *in vivo*. Int J Radiat Oncol Biol Phys 101(1): 49–62

Wang J, Zhang B, Sun J, Wang Y, Wang H (2020) Nanomedicine-enabled modulation of tumor hypoxic microenvironment for enhanced cancer therapy. Adv Ther 3(1): 1900083. https://doi.org/10.1002/adtp.201900083

Wang J, Wang S, Wang Y, Zhang L, Wan J, Zhang H, Shen L, Xia F, Chen FX, Zhang Z (2024a) Multi-omics sequencing unveils tumor microenvironment remodeling induced by combined radiotherapy and immunotherapy in microsatellite-stable locally advanced rectal cancer. Int J Radiat Oncol Biol Phys

120(2): E492–E492
Wang L, Fu J-N, Wang JY, Jin C-J, Ren X-Y, Tan Q, Li J, Yin H-W, Xiong K, Wang T-Y, Liu X-M, Zeng H-H (2011) Selenium-containing thioredoxin reductase inhibitor ethaselen sensitizes non-small cell lung cancer to radiotherapy. Anti-Cancer Drugs 22(8): 732–740
Wang X, Zhang H, Zhang X, Liu Y (2024b) Abscopal effect: from a rare phenomenon to a new frontier in cancer therapy. Biomarker Res 12(1): 98. https://doi.org/10.1186/s40364-024-00628-3
Wang Y, Zhao M, He S, Luo Y, Zhao Y, Cheng J, Gong Y, Xie J, Wang Y, Hu B, Tian L, Liu X, Li C, Huang Q (2019) Necroptosis regulates tumor repopulation after radiotherapy via RIP1/RIP3/MLKL/JNK/IL8 pathway. J Exp Clin Cancer Res 38(1): 461. https://doi.org/10.1186/s13046-019-1423-5
Wang Y, Wang Y, Pan J, Gan L, Xue J (2023a) Ferroptosis, necroptosis, and pyroptosis in cancer: Crucial cell death types in radiotherapy and post-radiotherapy immune activation. Radiother Oncol 184: 109689. https://doi.org/10.1016/j.radonc.2023.109689
Wang Z, Ren X, Wang D, Guan L, Li X, Zhao Y, Liu A, He L, Wang T, Zvyagin AV, Yang B, Lin Q (2023b) Novel strategies for tumor radiosensitization mediated by multifunctional gold-based nanomaterials. Biomater Sci 11(4): 1116–1136
Wei SJ, Botero A, Hirota K, Bradbury CM, Markovina S, Laszlo A, Spitz DR, Goswami PC, Yodoi J, Gius D (2000) Thioredoxin nuclear translocation and interaction with redox factor-1 activates the activator protein-1 transcription factor in response to ionizing radiation. Cancer Res 60(23): 6688–6695
Wilson JM, Fokas E, Dutton SJ, Patel N, Hawkins MA, Eccles C, Chu K-Y, Durrant L, Abraham AG, Partridge M, Woodward M, O'Neill E, Maughan T, McKenna WG, Mukherjee S, Brunner TB (2016) ARCII: a phase II trial of the HIV protease inhibitor Nelfinavir in combination with chemoradiation for locally advanced inoperable pancreatic cancer. Radiother Oncol 119(2): 306–311
Wondrak GT (2009) Redox-directed cancer therapeutics: molecular mechanisms and opportunities. Antioxid Redox Signal 11(12): 3013–3069
Wu Q, Hou M, Zhang P, Jiang Y, Liu M, Xiong L, Hai W, Zhang M, Li X, Li B, Zhang C (2022) Self-cascade nanohybrids boost cell ferroptosis stress for tumor radiosensitization therapy. Appl Mater Today 29: 101558. https://doi.org/10.1016/j.apmt.2022.101558
Wu X, Zhang T, Chen X, Ji G, Zhang F (2019) Microbiota transplantation: targeting cancer treatment. Cancer Lett 452: 144–151
Xiang H, Wu Y, Zhu X, She M, An Q, Zhou R, Xu P, Zhao F, Yan L, Zhao Y (2021) Highly stable silica-coated bismuth nanoparticles deliver tumor microenvironment-responsive prodrugs to enhance tumor-specific photoradiotherapy. J Am Chem Soc 143(30): 11449–11461
Xiao W, Zhao L, Sun Y, Yang X, Fu Q (2024) Stimuli-responsive nanoradiosensitizers for enhanced cancer radiotherapy. Small Methods 8(1): 2301131. https://doi.org/10.1002/smtd.202301131
Xu H, Liu Z, Du M, Chen Z (2024) Progression in low-intensity ultrasound-induced tumor radiosensitization. Cancer Med 13(13): e7332. https://doi.org/10.1002/cam4.7332
Xu Y, Wang Q, Li X, Chen Y, Xu G (2021) Itraconazole attenuates the stemness of nasopharyngeal carcinoma cells via triggering ferroptosis. Environ Toxicol 36(2): 257–266
Xue G, Wang Z, Zheng N, Fang J, Mao C, Li X, Jin G, Ming X, Lu Y (2021) Elimination of acquired resistance to PD-1 blockade via the concurrent depletion of tumour cells and immunosuppressive cells. Nat Biomed Eng 5(11): 1306–1319
Yan J, Wang G, Xie L, Tian H, Li J, Li B, Sang W, Li W, Zhang Z, Dai Y (2022) Engineering radiosensitizer-based metal-phenolic networks potentiate STING pathway activation for advanced radiotherapy. Adv Mater 34(10): 2105783. https://doi.org/10.1002/adma.202105783
Yang Q, Wang B, Zheng Q, Li H, Meng X, Zhou F, Zhang L (2023) A review of gut microbiota-derived metabolites in tumor progression and cancer therapy. Adv Sci 10(15): 2207366. https://doi.org/10.1002/advs.202207366
Yang Y, Chen M, Wang B, Wang P, Liu Y, Zhao Y, Li K, Song GS, Zhang X-B, Tan W (2019) NIR-II driven plasmon-enhanced catalysis for a timely supply of oxygen to overcome hypoxia-induced radiotherapy tolerance. Angew Chem Int Ed 58(42): 15069–15075
Yang Y, Deng L, Yang Y, Zhang T, Wu Y, Wang L, Bi N (2022) Efficacy and safety of combined brain radiotherapy and immunotherapy in non-small-cell lung cancer with brain metastases: a systematic review and meta-analysis. Clin Lung Cancer 23(2): 95–107
Ye LF, Chaudhary KR, Zandkarimi F, Harken AD, Kinslow CJ, Upadhyayula PS, Dovas A, Higgins DM, Tan H, Zhang Y, Buonanno M, Wang TJC, Hei TK, Bruce JN, Canoll PD, Cheng SK, Stockwell BR (2020) Radiation-induced lipid peroxidation triggers ferroptosis and synergizes with ferroptosis inducers. ACS Chem Biol 15(2): 469–484
Yi Y, Lu W, Shen L, Wu Y, Zhang Z (2023) The gut microbiota as a booster for radiotherapy: novel insights into radio-protection and radiation injury. Exp Hematol Oncol 12(1): 48. https://doi.org/10.1186/s40164-023-00410-5
Yuan Z, Liu X, Ling J, Huang G, Huang J, Zhu X, He L, Chen T (2022) *In situ*-transition nanozyme triggered by tumor microenvironment boosts synergistic cancer radio-/chemotherapy through disrupting redox homeostasis. Biomaterials 287: 121620. https://doi.org/10.1016/j.biomaterials.2022.121620
Yum S, Li M, Chen ZJ (2020) Old dogs, new trick: classic cancer therapies activate cGAS. Cell Res 30(8): 639–648
Zaheer J, Shanmugiah J, Kim S, Kim H, Kim JS (2025) Tumor microenvironment modulation by SERPINE1 increases radioimmunotherapy in murine model of gastric cancer. Sci Rep 15(1): 16449. https://doi.org/10.1038/s41598-025-97983-4
Zhang C, Xia D, Liu J, Huo D, Jiang X, Hu Y (2020) Bypassing the immunosuppression of myeloid-derived suppressor cells by reversing tumor hypoxia using a platelet-inspired platform. Adv Funct Mater 30(22): 2000189. https://doi.org/10.1002/adfm.202000189
Zhang C, Huang T, Li L (2024) Targeting cuproptosis for cancer therapy: mechanistic insights and clinical perspectives. J Hematol Oncol 17(1): 68. https://doi.org/10.1186/s13045-024-01589-8
Zhang J, Li X, Han X, Liu R, Fang J (2017) Targeting the thioredoxin system for cancer therapy. Trends Pharmacol Sci 38(9): 794–808
Zhang P, Wang L, Rodriguez-Aguayo C, Yuan Y, Debeb BG, Chen D, Sun Y, You MJ, Liu Y, Dean DC, Woodward WA, Liang H, Yang X, Lopez-Berestein G, Sood AK, Hu Y, Ang KK, Chen J, Ma L (2014) miR-205 acts as a tumour radiosensitizer by targeting ZEB1 and Ubc13. Nat Commun 5: 5671. https://doi.org/10.1038/ncomms6671
Zhang T, Wu D-M, Luo P-W, Liu T, Han R, Deng S-H, He M, Zhao Y-Y, Xu Y (2022) CircNEIL3 mediates pyroptosis to influence lung adenocarcinoma radiotherapy by upregulating PIF1 through miR-1184 inhibition. Cell Death Dis 13(2): 167. https://doi.org/10.1038/s41419-022-04561-x
Zhang Y, Huang F, Ren C, Liu J, Yang L, Chen S, Chang J, Yang C, Wang

W, Zhang C, Liu Q, Liang X-J, Liu J (2019) Enhanced radiosensitization by gold nanoparticles with acid-triggered aggregation in cancer radiotherapy. Adv Sci 6(8): 1801806. https://doi.org/10.1002/advs.201801806

Zhang Z, Niu X, Feng X, Wang X, Yu L, Wang W, Yuan Z (2021) Construction of a pH/TGase "dual key"-responsive gold nano-radiosensitizer with liver tumor-targeting ability. ACS Biomater Sci Eng 7(7): 3434–3445

Zhao L, Pang Y, Zhou Y, Chen J, Fu H, Guo W, Xu W, Xue X, Su G, Sun L, Wu H, Zhang J, Wang Z, Lin Q, Chen X, Chen H (2024) Antitumor efficacy and potential mechanism of FAP-targeted radioligand therapy combined with immune checkpoint blockade. Signal Transduct Target Ther 9(1): 142. https://doi.org/10.1038/s41392-024-01853-w

Zhao Y, Li Y, Zhang R, Wang F, Wang T, Jiao Y (2020) The role of erastin in ferroptosis and its prospects in cancer therapy. OncoTargets Ther 13: 5429–5441

Zhao Y, Tan F, Zhao J, Zhou S, Luo Y, Gong C (2025) Targeting the enhanced sensitivity of radiotherapy in cancer: mechanisms, applications, and challenges. Medcomm 6(6): e70202. https://doi.org/10.1002/mco2.70202

Zhen WY, Weichselbaum RR, Lin WB (2023) Nanoparticle-mediated radiotherapy remodels the tumor microenvironment to enhance antitumor efficacy. Adv Mater 35(21): 2206370. https://doi.org/10.1002/adma.202206370

Zheng L, Zhu R, Chen L, Fu Q, Li J, Chen C, Song J, Yang H (2021) X-ray sensitive high-Z metal nanocrystals for cancer imaging and therapy. Nano Res 14(11): 3744–3755

Zheng L, Zhang L, Tang L, Huang D, Pan D, Guo W, He S, Huang Y, Chen Y, Xiao X, Tang B, Chen J (2023) Gut microbiota is associated with response to ^{131}I therapy in patients with papillary thyroid carcinoma. Eur J Nucl Med Mol Imaging 50(5): 1453–1465

Zheng Z, Yang T, Li Y, Qu P, Shao Z, Wang Y, Chang W, Umar SM, Wang J, Ding N, Wang W (2024) A future directions of renal cell carcinoma treatment: combination of immune checkpoint inhibition and carbon ion radiotherapy. Front Immunol 15: 1428584. https://doi.org/10.3389/fimmu.2024.1428584

Zhong D, Zhao J, Li Y, Qiao Y, Wei Q, He J, Xie T, Li W, Zhou M (2019) Laser-triggered aggregated cubic α-Fe_2O_3@Au nanocomposites for magnetic resonance imaging and photothermal/enhanced radiation synergistic therapy. Biomaterials 219: 119369. https://doi.org/10.1016/j.biomaterials.2019.119369

Zhou Z, Guan B, Xia H, Zheng R, Xu B (2023) Particle radiotherapy in the era of radioimmunotherapy. Cancer Lett 567: 216268. https://doi.org/10.1016/j.canlet.2023.216268

Zhu S, Gu Z, Zhao Y (2018) Harnessing tumor microenvironment for nanoparticle-mediated radiotherapy. Adv Ther 1(5): 1800050. https://doi.org/10.1002/adtp.201800050

Zhuang Y, Liu K, He Q, Gu X, Jiang C, Wu J (2023) Hypoxia signaling in cancer: Implications for therapeutic interventions. MedComm 4(1): e203. https://doi.org/10.1002/mco2.203