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Review

Advances in nanoparticle-based radiotherapy for cancer treatment

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SUMMARY

Radiotherapy has long been recognized as an effective conventional approach in both clinical and scientific research, primarily through mechanisms involving DNA destruction or the generation of reactive oxygen species to target tumors. However, significant challenges persist, including the unavoidable damage to normal tissues and the development of radiation resistance. As a result, nanotechnology-based radiotherapy has garnered considerable attention for its potential to enhance precision in irradiation, improve radiosensitization, and achieve therapeutic advancements. Importantly, radiotherapy alone frequently falls short of fully eradicating tumors. Consequently, to augment the efficacy of radiotherapy, it is often integrated with other therapeutic strategies. This review elucidates the mechanisms of radiotherapy sensitization based on diverse nanoparticles. Typically, radiotherapy is sensitized through augmenting reactive oxygen species production, targeted radiotherapy, hypoxia relief, enhancement of antitumor immune microenvironment, and G2/M cell cycle arrest. Moreover, the incorporation of nanoparticle-based anti-tumor strategies with radiotherapy markedly enhances the current state of radiotherapy. Additionally, a compilation of clinical trials utilizing nano-radioenhancers is presented. Finally, future prospects for clinical translation in this field are thoroughly examined.

INTRODUCTION

Cancer constitutes one of the primary causes of mortality on a global scale.[1] According to the 2022 global cancer statistics published by the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases were diagnosed, and nearly 9.7 million cancer-related deaths occurred in that year. Moreover, projections indicate that the global cancer burden will escalate to 35 million cases by 2050.[2] Consequently, cancer poses a significant and persistent threat worldwide. Thus, it is imperative to advance antitumor therapeutic strategies to address this critical health challenge.

At present, traditional cancer treatment modalities primarily encompass surgery, radiotherapy (RT), and chemotherapy. Among these, RT is distinguished by its noninvasive approach to targeting localized tumors. It is estimated that approximately 60% of patients with cancer undergo RT at different stages of their disease.[3] RT kills tumor cells by damaging their DNA, hindering cell growth and division. On one hand, it directly causes double-strand breaks in DNA, which are difficult for cells to repair correctly. Ionizing radiation can also cause DNA single-strand breaks, which are usually repairable but may lead to mutations or cell death if numerous or improperly repaired. It can also chemically alter DNA bases such as adenine and guanine, disrupting replication and transcription. Additionally, radiation can decompose water molecules in cells into reactive oxygen species (ROS) such as hydroxyl radical ($^{\bullet}OH$), superoxide anion ($O_2^{\bullet-}$), and hydrogen peroxide (H_2O_2). ROS are highly reactive, quickly damaging DNA by causing base damage and strand breaks. They also impact cell membranes and proteins, leading to lipid peroxidation and protein denaturation, which can disrupt cell function and trigger apoptosis.[4–7]

Furthermore, intracellular levels of ROS may rise during RT, which can induce apoptosis through either extrinsic or intrinsic pathways.[8–10] However, the efficacy of RT in achieving significant therapeutic outcomes is primarily constrained by three factors: *i*) Unavoidable side effects: High doses of radiation can effectively eliminate tumor cells but may also inflict damage on adjacent healthy tissues, resulting in both acute and chronic toxicity.[11–13] *ii*) Radioresistant tumor microenvironments: The therapeutic effects of RT under hypoxic conditions are approximately one-third of those under normoxic conditions.[14] A hypoxic microenvironment can preserve the stemness of cancer stem cells, thereby enabling them to evade the effects of RT.[15] Furthermore, various DNA repair mechanisms facilitated by hypoxia can further diminish the effectiveness of RT.[16,17] Additionally, elevated levels of glutathione (GSH) in the tumor microenvironment (TME) can inhibit radiation-induced apoptosis by reducing ROS production and protect tumor cells against ROS through extracellular matrix (ECM)

remodeling.[18,19] *iii*) Immunosuppressive tumor microenvironments: Myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and RT-induced increase in suppressive regulatory cells (Tregs) within the TME are crucial in facilitating tumor progression and augmenting cancer cell resistance. This occurs through the recognition of other immune cells and the secretion of immunosuppressive cytokines.[20–26] Consequently, it is essential to enhance the sensitivity of RT and improve its therapeutic efficacy.

In recent years, the swift progression of nanomaterials has highlighted the significant potential of nanoparticles (NPs) for a wide range of applications in drug delivery, diagnostic imaging, and therapeutic strategies within the field of biomedicine. NPs serve as carriers for various therapeutic agents, including chemotherapeutic drugs, immunomodulators, and radiosensitizers, thereby augmenting therapeutic efficacy. Notably, NPs can be directed to specific cells or tissues through surface modification with targeted ligands or antibodies. The targeting capability of NPs confers a substantial advantage in drug delivery applications, facilitating the precise delivery of therapeutic agents or radiosensitizers directly to tumor sites, thereby minimizing collateral damage to healthy tissues. NPs-mediated drug delivery systems, characterized by controlled release mechanisms, can extend the duration of drug efficacy while reducing adverse side effects. Furthermore, advancements in synthesis and surface modification techniques allow for the development of biocompatible NPs with tailored shape, size, and surface properties, thereby enhancing therapeutic efficacy across diverse biological systems.[27–30] Hence, the distinctive physicochemical properties of NPs hold significant potential for improving RT outcomes and the application of nanotechnology in RT is undergoing rapid advancement.

Specifically, numerous NPs, particularly gold NPs (AuNPs) and hafnium oxide (HfO_2) NPs (such as NBTXR3), have been shown to substantially augment the local radiation dose.[31,32] Their high atomic number enables them to absorb a greater quantity of X-rays, resulting in the generation of secondary electrons and free radicals that further damage the DNA of cancer cells, thereby enhancing the efficacy of RT. Additionally, certain NPs can influence the cell cycle of cancer cells, inducing them to remain in a more radiation-sensitive phase (e.g., the G2/M phase), which further amplifies the cytotoxic effects of RT.[33] Furthermore, research has demonstrated that gold and silver NPs can inhibit the expression of DNA repair genes, thereby impeding the ability of cancer cells to repair radiation-induced DNA damage.[34] This mechanism enhances the efficacy of RT in eradicating cancer cells while minimizing damage to normal cells. Additionally, NPs can serve as imaging contrast agents to improve the precision of RT localization. Functionalized NPs have the capability to preferentially accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect, thereby minimizing adverse effects on healthy tissues and enhancing the specificity of therapeutic interventions. Furthermore, NPs can be integrated with RT to activate or modulate the immune system's response to cancer.[35–37] When integrated with NPs, RT facilitates the release of tumor-associated antigens (TAAs) from cancer cells and stimulates antigen-presenting cells (APCs), thereby augmenting the immune response against tumor cells and potentially improving the long-term prognosis of patients with cancer. As more efficient nanoparticle formulations are developed in conjunction with RT, this approach may become a fundamental component of cancer treatment regimens. In this review, we focus on the recent advancements in nanoparticle-based RT for cancer treatment. (Figure 1). The discussion begins by examining the various NPs utilized in RT and exploring the mechanisms that underlie RT sensitization. These mechanisms encompass enhanced ROS generation, inhibition of hypoxia, targeted radiation, improvement of the tumor immune microenvironment, and induction of G2/M cell cycle arrest (Table 1). Subsequently, we introduce synergistic strategies involving RT, including radiodynamic therapy/RT, thermotherapy/RT, immunotherapy/RT, and chemotherapy/RT (Table 2). Following this, we present clinical trials exploring the application of nanotechnology in RT (Table 3). Lastly, we offer our conclusions and discuss future perspectives.

NANOPARTICLES FOR ENHANCED RADIOTHERAPY

Nanomaterials exhibit significant promise in the field of cancer RT, particularly in augmenting treatment efficacy and mitigating adverse side effects. As advancements in nanomaterials persist, an increasing number of innovative radiosensitizers are anticipated to be implemented in clinical settings to further enhance therapeutic outcomes. Different categories of RT-sensitizing nanomaterials possess distinct advantages in terms of their structural attributes, functional performance, and underlying mechanisms. The selection of suitable nanomaterials should be guided by factors including tumor characteristics, therapeutic targets, and the prescribed radiation therapy dosage. This section will discuss the NPs that are predominantly employed in current research.

Metal and metal oxide NPs are widely used in RT, such as AuNPs, silver NPs (AgNPs), zinc oxide NPs (ZnO NPs), cerium oxide NPs (CeO_2 NPs) and so on, mainly to improve the damage efficiency of tumor cells through enhancing the absorption of radiation while reducing the damage to normal tissues. One of the primary advantages of using metal and metal oxide NPs, particularly those with high atomic numbers, is their ability to absorb and scatter ionizing radiation more effectively. This characteristic allows for a higher dose of radiation to be deposited within the tumor, thereby increasing the likelihood of tumor cell destruction while sparing normal cells from excessive radiation exposure.[97,98] Moreover, these NPs can also facilitate the generation of ROS upon irradiation, which further contributes to the induction of apoptosis in cancer cells. The oxidative stress induced by ROS can overwhelm the antioxidant defenses of cancer cells, leading to programmed cell death pathways such as apoptosis and autophagy.[99] For instance, Titanium peroxide NPs (TiOx NPs) can generate intolerable levels of ROS to eliminate pancreatic cancer stem cells.[100] The functioned HfO_2 NPs (NBTXR3) and gadolinium-based NPs (AGuIX) have been used in clinical trials.[80,89]

Polymer-based nanomaterials, such as polylactic acid-hydroxyacetic acid (PLGA) and polyethylene glycol (PEG)-modified NPs,[101,102] with adjustable drug release kinetics, biocompatibility, and biodegradability, possess relatively superior

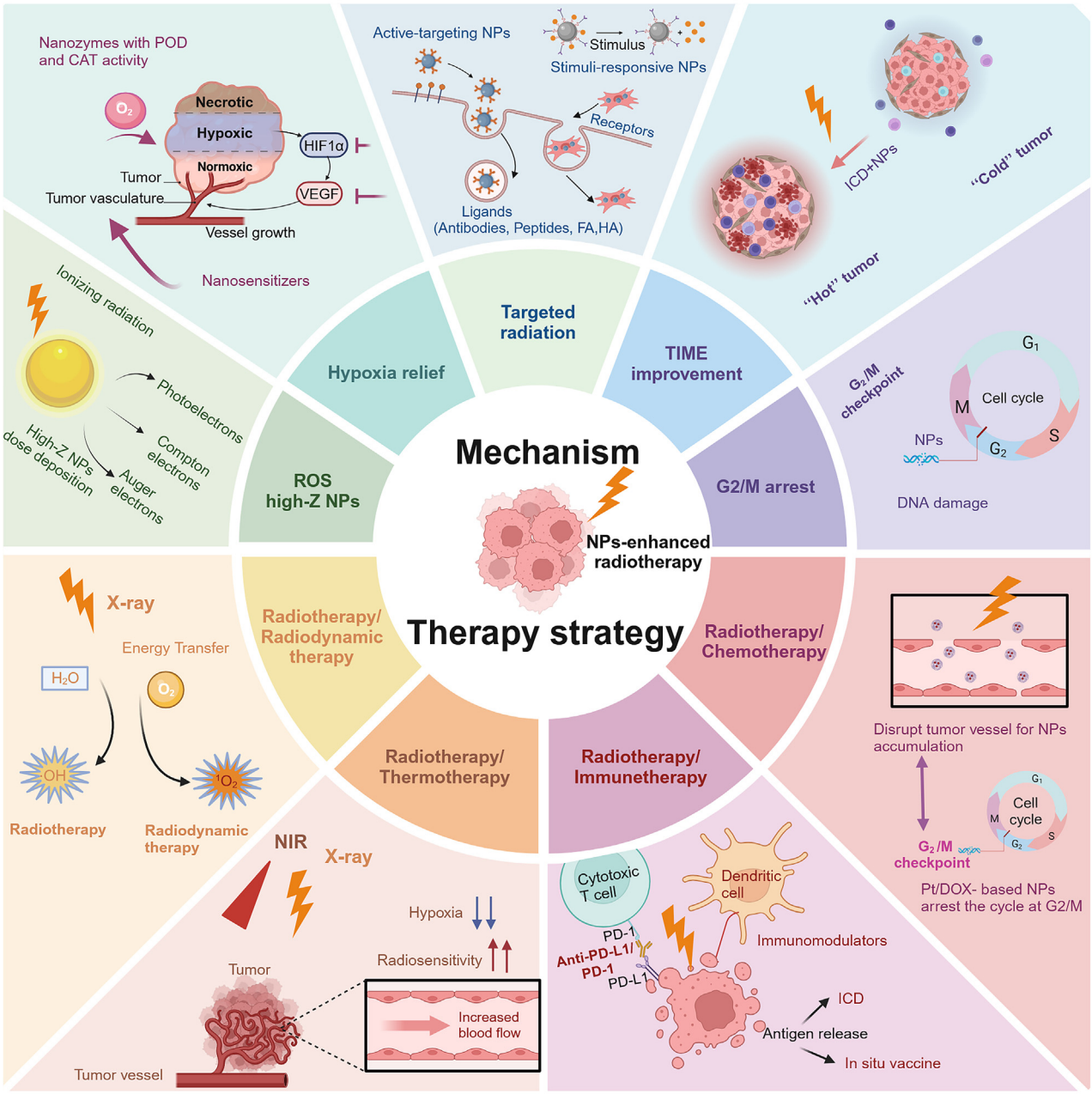

Figure 1. Mechanism of radiosensitization and strategies synergistic with RT
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prospects in RT enhancement by loading radiosensitizers (e.g., small chemical radiosensitizers or high-Z metal NPs).[64,103] In recent years, significant progress has been made in the study of polymer-based delivery nanosystems to specifically target tumor tissue and gradually release radiosensitizers, thereby improving the therapeutic efficacy of RT and reducing damage to healthy tissue. Specifically, nanoscale coordination polymers can sensitize RT via $^{\cdot}OH$ formation and GSH elimination.[104] Nanosensitizer-based dendrimer-entrapped Au NPs can function as a gene delivery system of siRNA to knock down HIF-1α, realizing enhanced tumor RT endogenously and exogenously.[105] Hence, in future studies, polymer-based nanomaterials are expected to play a greater role in cancer therapy, especially in the targeted delivery and reducing side effects.

Carbon-based nanomaterials are effective in generating ROS in RT, leading to damage to the cell membrane and intracellular structures, thus inducing apoptosis of tumor cells. In recent years, researchers have found that carbon nanomaterials such as graphene oxide (GO), can produce photothermal effects under near-infrared light irradiation, and then improve the

Table 1. Summary of the mechanisms of radiotherapy sensitization based on nanoparticles

Mechanism*	Nanoplatforms	Stimulus	Orthotopic/xenograft	Tumor models	References
ROS (High Z NPs)	GNWs	GSH	xenograft	4T1	Bai et al.[38]
	SeNPs	/	xenograft	HeLa/CaSki/SiHa	Xu et al.[39]
	Ta@PVP NPs	NIR	metastatic	4T1-Luc	Ji et al.[40]
–	AGuIX-Bi	/	xenograft	A549	Brown et al.[41]
–	–	–	–	–	
Hypoxia relief	PFTBA@HSA	/	xenograft	CT26/SUM149PT	Zhou et al.[42]
Targeted radiation	GDY-CeO_2	pH	xenograft/PDX	KYSE30	Zhou et al.[43]
TIME improvement	Fe_3O_4@MnO_2 n(GOx-CAT)$_{C7A}$	pH/GSH	xenograft	MCF-7/4T1	Lyu et al.[44]
G2/M arrest	HMOPT@Pt@Au@Dox	pH/GSH	xenograft	4T1	Zhao et al.[45]
	P-RuCu	GSH pH	xenograft	4T1	Peng et al.[46]
	ACF@MnO_2	pH	xenograft	MDA-MB-231	Hu et al.[47]
	AuHQ	H_2O_2	xenograft	CT26/4T1	Meng et al.[48]
	AD-MSCs/Bi_2Se_3	/pH	xenograft	H22	Wang et al.[49]
	RNPs	pH/GSH	orthotopic	A549- Luc	Xiao et al.[50]
	PLGA-$_{SS}$-D@BPQDs	pH	xenograft	EMT6	Wang et al.[51]
	FMC	GSH	xenograft	A375	Chan et al.[52]
	MGTe	/pH	xenograft	4T1-Luc	Xu et al.[53]
	AnCHNPs	pH	xenograft	4T1	Pan et al.[54]
	XCL1@CaMnP	pH	xenograft	B16F10/MB49	Cao et al.[55]
	AIM NPs	GSH pH	xenograft	CT26	Wu et al.[56]
	AmGd-NPs	pH	xenograft	CT26/4T1	Wang et al.[57]
	Pt-STNA		xenograft/metastatic	CT26/4T1	Chen et al.[58]
	UiO@MnS (UM)		xenograft	Hepa1-6	Xiao et al.[59]
	DM1-NO PLGA		xenograft	4T1	Huang et al.[60]
			xenograft	H1299	Gao et al.[61]

therapeutic effects of RT.[106] In addition, graphene-induced hyperthermia combined with RT can release several damage-associated molecular patterns (DAMPs) to elicit specific antitumor immune responses.[107] These carbon-based materials can act not only as photothermal absorbers but also as drug delivery carriers to enhance the efficacy of targeted therapy. For instance,

Table 2. Summary of various treatments performed in combination with radiotherapy

Therapy strategy	Nanoplatforms	Stimulus	Orthotopic/xenograft	Tumor models	References
RT/RDT	$NaCeF_4$:Gd,Tb ScNPs	/	xenograft	A549	Zhong et al.[62]
	SCNPs@DMSN@CeO_x-PEG	GSH	xenograft	CT26/Panc02	Liu et al.[63]
	Hf-AIE-PEG-DBCO	/	xenograft	4T1	Liu et al.[64]
	Hf-DBP-Pt	/	xenograft/orthotopic	CT26/MC38	Guo et al.[65]
	FA-Au-CH	/	xenograft	HCT 116	Li et al.[66]
TRT	MoS_2/HfO_2-Dextran	NIR	metastatic	SMMC-7721-fluc	Fu et al.[67]
	PRC	NIR	xenograft	4T1	Wang et al.[68]
	Ta@PVP NPs	NIR	metastatic	4T1-Luc	Ji et al.[40]
	BNFs	NIR	metastatic	4T1-Luc	Wang et al.[69]
	FePd NDs	NIR	xenograft	4T1	Lyu et al.[70]
RIT	PLGdH	pH	xenograft	CT26	Wang et al.[71]
	TeSe NDs	pH/GSH	xenograft	4T1	Chang et al.[72]
	CCR2-SCM@MSN@αPD-L1	/	orthotopic	GL261/CT2A	Wang et al.[73]
	RGD-EV: siPDL1	/	orthotopic	GL261	Tian et al.[74]
	MAL NPs	/	xenograft	CT26	Sun et al.[75]
	Bc@AZTF	pH/ATP	xenograft/orthotopic	4T1	Deng et al.[76]
CRT	Pt STNA	GSH	xenograft	Hepa1-6	Xiao et al.[59]
	DCM-[PTX]	GSH	xenograft	OSC-3	Jing et al.[77]
	DCNP@P(Se-DOX)@ANG	/	orthotopic	U87-Luc	Su et al.[78]
	D@MLL	MMP-2	orthotopic	GL261-Luc	Kuang et al.[79]

Table 3. Clinical translation of some nanoradiosensitizers

Name	Trial ID	Clinical trial phase	Disease	References
AGuIX	NCT02820454	phase I	brain metastases	Verry et al.[80]
	NCT04789486	phase I/II	lung and pancreatic cancers	Lux et al.[81]
	NCT03308604	phase Ib	cervical cancer	Maury et al.[82]
	NCT04881032	phase I/II	GBM	Thivat et al.[83]
	NCT03818386	phase II	brain metastases	Verry et al.[84]
	NCT04899908	phase II	brain metastases	Bennett et al.[85]
NBTXR3	NCT01946867	phase I	squamous cell carcinoma	Hoffmann et al.[86]
	NCT01433068	phase I	soft tissue sarcomas	Bonvalot et al.[87]
	NCT04484909	Phase I	pancreatic cancer	Bagley et al.[88]
	NCT02379845	phase II/III	soft tissue sarcomas	Bonvalot et al.[89]
	NCT02465593	phase Ib/I	rectal cancer	Huang et al.[90]
Onivyde	NCT04569916	phase II	solid tumors	Shen et al.[91]
Nab-paclitaxel	UMIN000012719	phase I/II	non-small cell lung cancer	Tsuchiya-Kawano et al.[92]
	jRCTs042180077	phase I	non-small cell lung cancer	Omori et al.[93]
	UMINR000015432	phase I	non-small cell lung cancer	Kubota et al.[94]
	NCT01847326	phase I	head and neck squamous cell carcinom	Rosenberg et al.[95]
	ChiCTR1900021079	phase I	esophageal squamous cell carcinoma	Jiang et al.[96]

emerging carbon nanotubes (CNTs) hold significant promise as radiation carriers owing to their exceptional biological activity and ability to permeate cell membranes.[108,109] Moreover, GO nanosheets have the potential to influence cellular apoptosis and downregulate the pro-survival protein B-cell lymphoma-2 (Bcl-2), which is associated with the intrinsic mitochondrial pathway, thereby enhancing the radiosensitivity of nasopharyngeal carcinoma.[110]

Superparamagnetic NPs, particularly those composed of iron oxide such as Fe_3O_4, have garnered significant attention in the field of nanomedicine due to their unique magnetic properties and potential applications in enhancing the efficacy of RT. These NPs can be utilized as radiosensitizers, which are agents that increase the effectiveness of radiation therapy by enhancing the formation of ROS, ferroptosis, and cell-cycle arrest within tumor cells.[111] Moreover, the size and surface characteristics of superparamagnetic iron oxide NPs (SPIONs) play a crucial role in their performance as radiosensitizers. For instance, the synthesis of SPIONs with controlled sizes and surface modifications can significantly influence their cellular uptake and distribution, which in turn affects their ability to enhance RT.[112] In addition to their role in RT, SPIONs are also being explored for their potential as magnetic resonance imaging (MRI) contrast agents. Their superparamagnetic properties allow for significant contrast enhancement in MRI imaging, which can be particularly beneficial for monitoring tumor response to therapy.[113] The development of functionalized SPIONs that can target specific tumor types further enhances their utility in both diagnostic and therapeutic applications, paving the way for more efficient cancer treatment strategies.[114–116]

Quantum dots (QDs) are a class of nanomaterials with semiconductor properties, usually consisting of compounds such as cadmium, sulfide, selenide, or telluride. QDs that emit in the near-infrared IIb (NIR-IIb) range (1500–1700 nm) facilitate high-resolution deep tissue imaging and enhance radiosensitivity by increasing the Compton effect.[117–119] The NIR-IIb-emitting QDs including high-Z elements such as Pb and Ag, can realize radiosensitization.[120,121] In addition, black phosphorus (BP) QDs (BPQDs) can be utilized in RT sensitization as well through the photoelectric effect or Compton scattering. Moreover, BPQDs absorb light across a wide spectrum and have high photothermal conversion efficiency for photothermal therapy (PTT), making it ideal for the treatment of hypoxic tumor cells through the integration of PTT with RT.[122] Thus, leveraging QDs nanotechnology, we can create a multifunctional nanoprobe to improve the precision and effectiveness of RT.

Overall, different RT-sensitizing nanomaterials offer distinct structural and functional benefits. Choosing the right nanomaterial should be based on the tumor's characteristics, therapeutic targets, and how the material enhances treatment. For instance, selecting high-Z element NPs for dose enhancement or oxygen-releasing NPs to address tumor hypoxia depends on the treatment's specific requirements. Advancements in nanotechnology are expected to produce materials with enhanced capabilities for precise targeting and controlled release, leading to RT sensitizers that boost treatment effectiveness and minimize side effects. It is worth noting that NPs must be biocompatible and long-lasting *in vivo* to serve as effective RT sensitizers. Surface modifications can extend their circulation time, enhancing RT outcomes. Poor biocompatibility can lead to inflammation or toxicity, limiting their application. This is especially important for metal ion nanomaterials such as gold, silver, and platinum (Pt), which metabolize slowly and may accumulate in organs such as the liver, spleen, and lungs, posing toxicity risks.[123,124] Therefore, in the design of metal NPs for RT sensitization, it is imperative to develop degradable or stimuli-responsive materials that can systematically disintegrate under specific conditions, such as variations in pH or enzymatic activity, to reduce the risk of prolonged accumulation within the body. The stability of metal nanomaterials under physiological conditions can also be enhanced through the implementation of polymer coatings or surface modifications, which

effectively limit the release of metal ions and attenuate potential toxicological effects. Moreover, continued research will likely bring novel sensitizing nanomaterials to clinical use, promoting personalized and effective RT protocols. In the subsequent section, we will examine the mechanisms by which nanomaterials augment the efficacy of RT, elucidating their interactions with biological, chemical, and physical processes to enhance tumor radiosensitivity.

MECHANISMS UNDERLYING RADIOTHERAPY SENSITIZATION

Generate reactive oxygen species

Radiosensitization enhances the responsiveness of tumors to RT through multiple mechanisms, with a key mechanism being the augmentation of radiation-induced cellular damage via increased ROS. Notably, ROS generated during RT can directly target cellular DNA, leading to the formation of DNA double-strand breaks (DSBs). DNA damage constitutes a pivotal mechanism in the induction of cell death by RT. If these damages are not promptly repaired, the cell is likely to undergo apoptosis or necrosis. The accumulation of ROS plays a crucial role in activating apoptotic pathways within tumor cells.[9] For instance, ROS can initiate programmed cell death by compromising the integrity of the mitochondrial membrane, resulting in the release of cytochrome *c*, which subsequently activates the caspase cascade.[125] ROS can not only cause DNA damage directly, but can also inhibit DNA repair mechanisms to enhance radiosensitization. Additionally, ROS facilitate the infiltration and activation of T cells within the TME.[126,127] Consequently, ROS may contribute to the remodeling of tumor-associated immune cells, ultimately improving therapeutic efficacy.

However, ROS can be consumed by the high concentration of GSH in the TME.[128] To generate more secondary electrons for the production of ROS, high-Z NPs containing numerous elements have been designed, such as gold, Pt, Bismuth (Bi), Europium (Eu), Selenium (Se), Ruthenium (Ru), et al.[129–132] Among them, gold NPs are more commonly used as radiosensitizers due to their strong surface plasmon resonance effect. Most related research has primarily focused on spherical gold NPs. Moreover, gold NPs can undergo shape transformation into nonspherical nanostructures, such as nanowires (GNWs). It was observed that gold nanowires coated with DSPE-PEG (2000) Amine exhibited a 20.8% increase in $^{\cdot}OH$ production under irradiation, in contrast to a 2.7% increase for gold nanospheres. This enhanced production is attributed to the relatively large surface area and the intrinsic anisotropic morphology of the nanowires, which possess a high density of surface atoms.[38] Besides, numerous studies have documented that Se-based drugs also play an important role in tumor RT. To determine the synergic X-ray activities against tumor cells, different forms of Se therapeutic agents were constructed (−2, 0, +4, +6 valence) (Figure 2A). Results indicated that SeNPs (0) and organic Se (−2) exhibited significant enhancement in RT treatment with negligible toxicity, suggesting the great potential of SeNPs as radiosensitizers.[39]

To improve prognosis, high-Z NPs with diagnostic capabilities hold great promise in antitumor applications. For instance, highly biocompatible poly(vinylpyrrolidone)-coated Ta NPs (Ta@PVP NPs) can significantly inhibit primary breast cancer due to their high X-ray mass attenuation coefficient. They can also migrate to nearby sentinel lymph nodes (SLN) for metastatic treatment. Owing to the feasibility of Ta in photoacoustic imaging and CT imaging, Ta@PVP NPs enabled real-time monitoring of the RT and PTT process.[40] Furthermore, ultrasmall gadolinium (Gd)-based AGuIX NPs (Activation and Guiding of Irradiation by X-ray) has been translated into clinical use due to their MRI monitoring capability and efficacy under irradiation at small doses.[133] With the addition of Bi^{3+}, second-generation Bi-gadolinium NPs (AGuIX-Bi) have been designed for MRI guidance and enhanced local radiation dose amplification, providing a theranostic approach to RT in non-small cell lung cancer (NSCLC) model.[41]

The modulation of ROS levels as a therapeutic strategy for cancer treatment is not without potential risks. Elevated ROS levels can result in damage to healthy tissues.[134] Excessive ROS can lead to chronic inflammation, which is associated with an increased risk of cardiovascular disease and renal insufficiency.[135] Furthermore, oxidative stress induced by high ROS levels can compromise immune cell functionality, thereby promoting inflammation and facilitating tumor metastasis.[136] Specifically, ROS can push macrophages toward immunosuppressive states, increase programmed cell death 1 ligand 1 (PD-L1) expression, reduce immune checkpoint blockade (ICB) therapy effectiveness, deactivate T cells, and prevent immunogenic cell death (ICD).[137] In conclusion, the therapeutic application of ROS in cancer treatment necessitates a cautious approach due to the substantial risk of collateral damage to healthy tissues. It is imperative to develop strategies that precisely regulate ROS production to enhance therapeutic efficacy while minimizing adverse side effects.

Overcome hypoxia

With respect to radiation-induced DNA damage, studies show that approximately 70% of the damage is indirect, which is mainly due to free radicals produced by water molecules. Oxygen molecules (O_2) are able to capture and fix free radicals produced by the indirect effects of RT, especially $^{\cdot}OH$, thereby increasing permanent damage to DNA. The production of free radicals is closely correlated with the presence of oxygen, enhancing the effect of oxygen significantly increased cell mortality during RT.[138] Study also found that oxygen plays a larger role in indirect effects than for direct effects.[138] Tumor hypoxia significantly restrains the therapeutic effects of RT because of the inability to form stable DNA peroxides (DNA-OO$^{\cdot}$) between DNA radicals (DNA$^{\cdot}$) and O_2, thereby promoting DNA repair.[139–141] Therefore, oxygen is crucial in augmenting RT efficacy by facilitating the generation of free radicals and inhibiting cellular mechanisms for DNA damage repair. To address the challenges associated with hypoxia within the TME, several strategies have been developed to enhance oxygen availability during treatment, including direct oxygen supply and intra-tumoral O_2 generation. Exogenous oxygen delivery can be achieved through the use of oxygen reservoirs, such as perfluorotributylamine (PFTBA). Utilizing albumin as a carrier (PFTBA@HSA), PFTBA can release oxygen when accumulated in the tumor, increasing red blood cell infiltration into tumor to supply oxygen

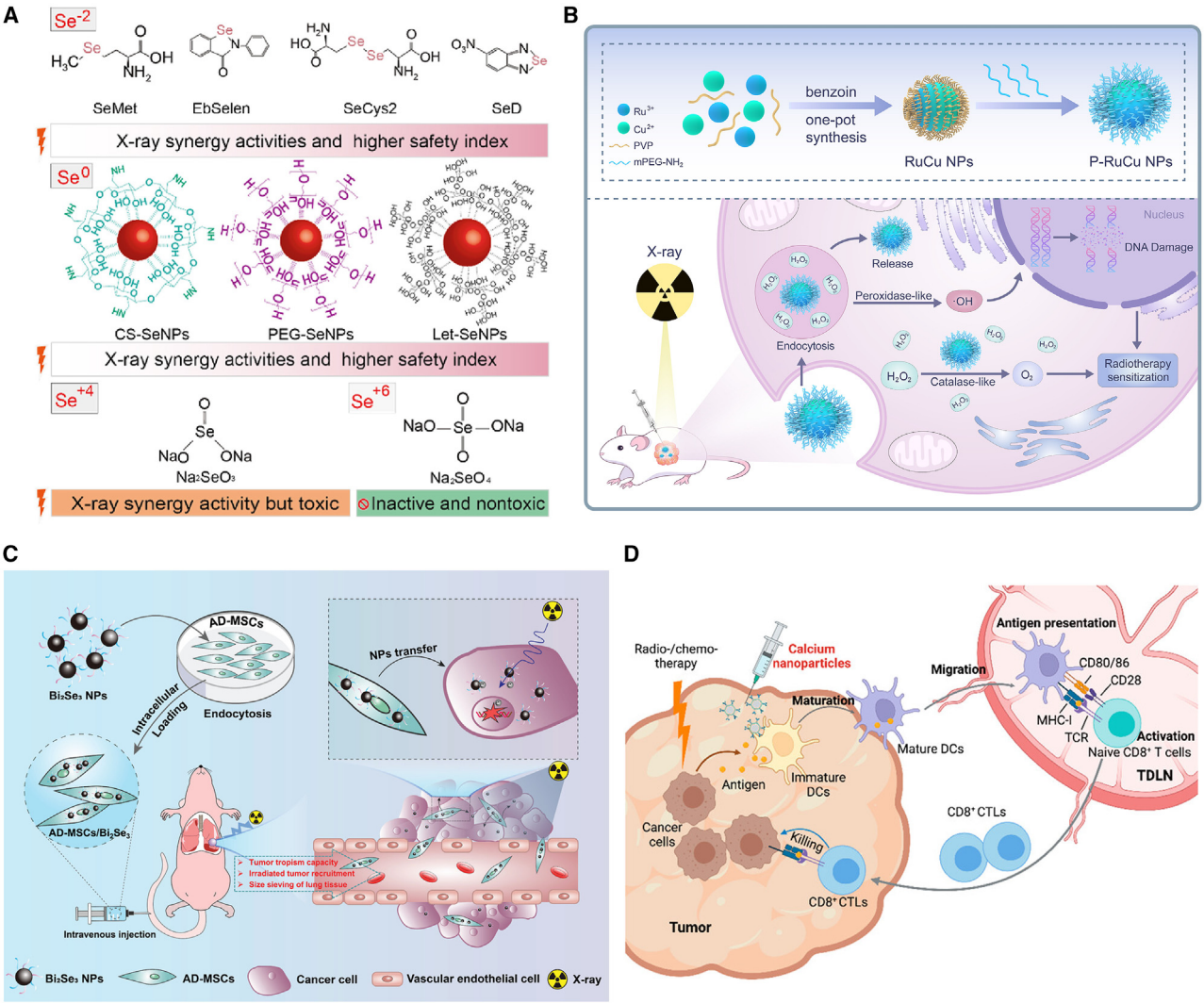

Figure 2. Various methods to enhance the effects of RT

(A) The radiation synergistic effects and the safety index induced by different Se species.[39] Copyright 2023 Elsevier Ltd.

(B) Schematic illustration of the treatment and synthesis of P-RuCu NPs which can function as a theranostic nanozyme to enhance RT.98 Copyright 2022 Elsevier Ltd.

(C) Adipose-derived mesenchymal stromal cells (AD-MSCs) loaded with bismuth selenide (Bi2Se3) NPs for targeted RT treatment of orthotopic lung cancer.119 Copyright 2022 Wiley-VCH GmbH.

(D) Schematic preparation of calcium NPs for dendritic cells (DCs) maturation triggered by released calcium ions to argument the efficacy of RT by upregulated expression of costimulatory and antigen-presenting molecules.128 Copyright 2024 American Chemical Society.

by exploiting its platelet inhibition capability.[42] Catalytic nanomaterials with enzyme-mimicking characteristics, referred to as nanozymes, demonstrate significant potential for intratumoral oxygen generation. Nanozymes exhibiting peroxidase (POD)-like and catalase (CAT) activities can efficiently catalyze the decomposition of H_2O_2 to produce oxygen within the TME. For instance, NPs composed of manganese oxide (MnO_2) and Fe ions have been employed as POD mimics,[142,143] while cerium oxide (CeO_2) nanozymes are linked to CAT activity.[144] To enhance the enzyme-like activities of CeO_2 NPs, a novel 2D graphdiyne (GDY) was designed to anchor numerous ultrasmall CeO_2 NPs nanozymes (GDY-CeO_2).[43] Compared to CeO_2 NPs, the catalytic ability of GDY–CeO_2 is more sensitive, constant, and efficient. Specifically, GDY-CeO_2 can decompose H_2O_2 at a lower concentration, with a rate constant for O_2 production approximately 4.2 times greater than CeO_2 NPs. After 40 reaction cycles, GDY-CeO_2 retained over 60% of its optimal enzyme activity. However, oxygen production by these methods heavily depends on H_2O_2, which has a concentration of less than 0.1 μM in the TME. Recently, Lyu et al. synthesized Fe_3O_4@MnO_2 nanozymes combined with glucose oxidase (GOX).[44] GOX can catalyze glucose into gluconic acid and abundant H_2O_2. Intracellular overproduction of H_2O_2 can generate significant amounts of oxygen, thereby alleviating tumor hypoxia and

forming stable DNA peroxides. Furthermore, in solutions treated with Fe_3O_4@MnO_2 NPs, the GSH level decreased from 95.8% to 12.1%, whereas the Fe_3O_4 group exhibited a reduction of 28%. This decrease is attributed to the oxidation of GSH to glutathione disulfide (GSSG) facilitated by the MnO_2 shell. In a separate study, dual-enzyme nanocascades, comprising GOX and CAT, demonstrated effective elimination of H_2O_2 and reduced off-target effects during blood circulation.[45] The GOx-CAT pair within close spatial proximity (<10 nm), enabled efficient and simultaneous breakdown of H_2O_2 in the acidic TME with the coating of hexamethyleneimine (C7A) moieties (n(GOx-CAT)$_{C7A}$), thereby functioning as an endogenous oxygen generator to release oxygen continuously *in situ*. In a similar manner, dual nanozymes composed of Au and Pt can initiate a cascade catalytic reaction to alleviate hypoxia (HMOPT@Pt@Au@Dox).[46] Au NPs can convert glucose into gluconic acid and H_2O_2 through a GOX-mimicking activity, while Pt NPs facilitate the conversion of H_2O_2 into H_2O and O_2. In another study, the POD-like ability and CAT-like abilities of a bimetallic nanozyme (copper-modified ruthenium NPs coated with PEG, P-RuCu NPs) were investigated to evaluate its potential for RT enhancement based on tumor hypoxia alleviation (Figure 2B).[47] It is noteworthy that the adsorption process of H_2O_2 is facilitated by the interfaces doped with Cu atoms. Furthermore, RuCu NPs with varying Cu/Ru ratios exhibited different levels of POD-like catalytic activity.

Hypoxic conditions can also initiate the activation of the hypoxia-inducible factor (HIF) signaling pathway within tumor cells, with HIF-1α serving as a pivotal regulatory molecule. In response to hypoxia, HIF-1α undergoes stabilization and subsequently induces the transcription of a multitude of genes associated with cellular survival, metabolic adaptation, angiogenesis, and invasion, including vascular endothelial growth factor (VEGF). This transcriptional activation enhances the invasiveness of tumors and facilitates their evasion of immune detection and resistance to radiation-induced damage by promoting angiogenesis. Furthermore, HIF-1α is implicated in DNA repair processes that contribute to cellular resistance against RT.[145–147] Moreover, HIF-1α-mediated activation of the anti-apoptotic pathway renders tumor cells resistant to RT-induced apoptosis.[148] The suppression of HIF-1α by oxygen nanobubbles has been confirmed to be effective in overcoming hypoxia-induced resistance to RT.[149] While strategies aimed at enhancing oxygen generation have yielded promising outcomes, the degradation of HIF-1α by oxygen remains incomplete. This partial degradation may lead to cellular proliferation, immune exhaustion, and metastasis.[140] Meng et al. designed a smart drug delivery system based on MnO_2 NPs, delivering the HIF-1 inhibitor acriflavine (ACF) to tumor (ACF@MnO_2).[48] In comparison to the MnO_2+ACF mixture group, the ACF@MnO_2+RT group demonstrated a reduced expression of several downstream signaling molecules associated with HIF-1α, including VEGF, matrix metalloproteinase 9 (MMP-9), glucose transporter 1 (GLUT-1), and P-glycoprotein (P-gp). Treatment with ACF@MnO_2+RT led to an 84.70% decrease in tumor growth, significantly reduced PD-L1 expression on tumor cells, and inhibited metastasis, likely due to HIF-1α degradation and impaired HIF-1 function.

Tumor growth and progression require oxygen and nutrients through angiogenesis. However, tumor blood vessels are abnormal compared to normal tissue, causing large hypoxic areas. This irregular vasculature affects tumor growth and reduces RT effectiveness. Tumor blood vessels are irregular with abnormal endothelial cells, leading to increased wall permeability and plasma protein leakage. This raises interstitial pressure, disrupts blood flow, and causes local hypoxia.[150] The tumor's rapid growth surpasses the oxygen supply from these vessels, resulting in widespread hypoxia in the central necrotic zone, while the edges remain well-oxygenated. Without sufficient vascular support, the tumor's center struggles to access oxygen and nutrients, leading to chronic hypoxia.[151,152] In recent years, vascular normalization has aroused great attention in alleviating hypoxia and providing a long-term solution to overcome hypoxia-induced resistance in RT. Wang et al. developed a gold nanoparticle-based nanosensitizer modified with 8-hydroxyquinoline (AuHQ) to alter tumor vasculature.[49] AuHQ suppressed endothelial cell proliferation by downregulating angiopoietin-2 (Ang-2), VEGF, and fibroblast growth factor (FGF) signaling. It facilitated the attachment of endothelial cells and pericytes, forming elongated blood vessels. The tumor inhibition rate for the AuHQ+RT group was 86.4%, notably higher than the HQ + RT group (27%) and Au NPs+RT group (48%). However, there is also a potential risk that vascular normalization may stimulate tumor growth or promote metastasis by increasing tumor blood flow and oxygen supply. Research indicates that anti-angiogenic therapies targeting VEGF Receptor 2 (VEGFR2) induce a "window of normalization" in which the tumor vasculature becomes more structured and functional. This period allows for enhanced tumor oxygenation, thereby increasing the efficacy of RT. Administering RT outside this window results in merely additive or potentially diminished therapeutic effects.[153] The effectiveness of antiangiogenic therapy depends on the disease stage. Anti-VEGF treatments work well in primary tumors by inhibiting growth, but during the initial stages of micrometastasis, blocking VEGF can increase tumor aggressiveness and metastasis through adaptive responses such as epithelial-mesenchymal transition (EMT). In established metastases, VEGF inhibition might speed up metastasis by encouraging revascularization or adaptive changes in tumor cells.[154] To address this potential risk, optimizing the timing and dosage of antiangiogenic therapy according to the various stages of tumor progression, along with the strategic integration of complementary therapies, constitutes an effective approach to mitigating adverse effects.

Targeted radiation

RT utilizes high-energy radiation to eradicate tumor cells; however, it may also adversely affect normal tissues, leading to side effects that constrain its dosage and therapeutic efficacy. The radiosensitization effect of targeted therapy is pivotal as it augments the tumoricidal efficiency of RT, reduces collateral damage to healthy tissues, and permits the administration of lower radiation doses. Nanomaterials can significantly improve RT by using active and passive targeting. They accumulate in tumors through the EPR effect due to abnormal blood vessels and poor lymph drainage. This passive targeting allows NPs to

remain in the tumor, releasing therapeutic agents that enhance RT while reducing damage to healthy tissues and systemic toxicity.[155,156] Furthermore, nanomaterials can be directed to tumor cells using surface-modified ligands, antibodies, or peptides that attach to specific cell receptors, such as folic acid (FA)/folate receptor,[157] hyaluronic acid (HA)/CD44 receptor,[158,159] Arg-Gly-Asp (RGD) peptides/integrin $\alpha_v\beta_3$,[74] aptamer (AS1411)/nucleolin,[160] and glucose transporter.[161] These mechanisms significantly enhance the cancer-targeting efficacy of RT. Recently, drug delivery systems of bio-vehicle for tumor-targeting therapy have garnered significant attention owing to their enhanced biocompatibility and capability to traverse physiological barriers. Xiao et al. developed adipose-derived mesenchymal stromal cells (AD-MSCs) loaded with bismuth selenide (Bi_2Se_3) NPs for targeted RT of orthotopic NSCLC (Figure 2C).[50] The interaction between chemokine receptors in MSCs and up-regulated chemokine expressed on irradiated tumor cells facilitated MSC migration. Subsequently, the Bi_2Se_3 NPs exocytosed from the AD-MSCs/Bi_2Se_3 were transferred to the tumor cells through an "exocytosis-endocytosis" mechanism, resulting in an approximately 20-fold increase in the accumulation of Bi_2Se_3 NPs.

Stimuli-responsive nanomaterials enable targeted activation or release at tumor sites by responding to external stimuli or the TME, unlike traditional methods that depend on molecular recognition. These nanomaterials take advantage of the distinct differences between tumor environments and normal tissues, such as acidic pH and hypoxia, to trigger specific changes such as drug release, shape shifts, and degradation within tumors, thereby facilitating targeted delivery. Furthermore, stimulus-responsive nanomaterials can react to external triggers such as light, ultrasound, and magnetic fields, allowing targeted activation within tumor areas. This ensures therapeutic agents remain stable during delivery, preventing premature release in the bloodstream and minimizing toxicity to healthy tissues. Wang et al. established a pH-responsive nanopomegranate (RNP) platform for size and charge transformation, self-assembled from ~5 nm Au NPs (Au_5).[51] The RNP, about 110 nm in size with a neutral charge, can avoid kidney clearance, allowing longer circulation in the bloodstream. Studies showed they penetrate and distribute well in 3D multicell spheroids. In acidic tumor environments, they broke down into smaller, positively charged Au_5 entities, enhancing radiation therapy by increasing local irradiation in tumor areas. Chan et al. designed a sophisticated drug delivery system employing BPQDs with surface charge-switching properties, utilizing PLGA modified by RGD (PLGA-$_{SS}$-D@BPQDs).[52] This system markedly improved the targeting of cancer cells and demonstrated a range of bio-responsive properties, making it a highly efficient radiosensitizer. It improved the efficacy of RT while minimizing histological damage to major organs in the treatment of human melanoma cells.

Improve tumor immune microenvironment

The role of RT in oncological treatment extends beyond the direct cytotoxic effects on tumor cells; it also enhances anti-tumor immunity through the induction of antigen release and the activation of immune responses.[162] RT facilitates tumor cell apoptosis, resulting in the liberation of TAAs. These antigens are subsequently internalized, processed, and presented to T cells by APCs, such as DCs and macrophages, thereby initiating specific anti-tumor immune responses. In addition to the release of tumor antigens, RT also triggers the release of various DAMPs, such as high-mobility group protein B1 (HMGB1), calreticulin, and adenosine triphosphate (ATP). DAMPs activate the immune system and trigger anti-tumor responses by binding to receptors on DCs or macrophages. In RT-induced responses, some T cells become memory T cells, persisting long-term and enabling rapid reactivation for future tumor recurrences, providing sustained anti-tumor effects. While RT facilitates antigen release and stimulates anti-tumor immune responses, these responses are frequently insufficient due to the immunosuppressive nature of the TME. Following RT, tumor cells may develop resistance to treatment via diverse immune evasion mechanisms, potentially resulting in the recurrence or metastasis of residual tumor cells. These mechanisms typically entail intricate alterations in the TME, heightened expression of immunosuppressive factors, and a diminished capacity of the immune system to recognize tumor cells.[163–165] Specially, RT can trigger T cell responses but may also increase PD-L1 on tumor cells and associate protein-4 (CTLA-4) on Tregs, aiding immune escape by suppressing effector T cells. Post-RT, MDSCs can accumulate in the TME, hindering DCs and macrophages from effectively presenting tumor antigens and activating T cells. RT shifts macrophages to the M2 type, suppresses effector T cells by releasing interleukin 10 (IL-10) and transforming growth factor β (TGF-β), and encourages angiogenesis, aiding tumor survival and metastasis. Consequently, optimizing the tumor immune microenvironment (TIME) and mitigating immunosuppressive conditions are crucial for augmenting the anti-tumor efficacy of RT.

Strategies to augment anti-tumor immune responses and mitigate radioresistance have been investigated, with a primary focus on enhancing the infiltration of activated effector cells into tumor tissue and directly targeting immunosuppressive cells. Tumor-specific antigens produced by tumor cells, following antigen presentation mediated by APCs, can activate T-cell-specific adaptive antitumor immunity. Among APCs, DCs are the most potent. To maximize the utilization of RT-induced antigen, a nanoadjuvant comprised of CpG-loaded Fe_3O_4 NPs was designed. The activation of Toll-like receptor 9 (TLR9) by adjuvant CpG-ODNs facilitates antigen presentation and cytokine secretion in DCs.[53] Furthermore, the maleimide (MAL) residue on the nanoadjuvant (Fe_3O_4@Mal/CpG, FMC) can capture sulfhydryl-bearing tumor-associated antigens, significantly enhancing the efficiency of RT-induced immunity through the highly efficient click reaction between autoantigens and CpG, thereby boosting the checkpoint blockade immune response to suppress both treated and distant tumor. Considering the limited immunogenicity of RT, recently, hybrid biomimetic nanoplatforms (GSH-decorated tellurium (Te) NPs (GTe)) by the formulation of tumor cell membranes and bacterial outer membrane (MGTe) have been developed to expand the strong immunogenicity of tumor- and bacteria-derived antigens, promoting the efficient immune activation in DCs.[54] In addition, scientific research based on calcium NPs delivered to DCs via anti-CD205 antibodies (AnCHNPs) suggests that the released

calcium ions can efficiently facilitate DC maturation. This enhances the efficacy of RT by upregulating the expression of costimulatory and antigen-presenting molecules, a result of the activation of NFAT and NF-κB pathways (Figure 2D).[55]

RT induces direct cytotoxic effects on tumor cells primarily through the induction of DSBs in DNA. In instances where the DNA repair mechanisms fail to adequately rectify these lesions, residual nuclear DNA fragments may translocate into the cytoplasm. These cytoplasmic DNA fragments are subsequently detected and bound by cyclic GMP-AMP synthase (cGAS). Upon activation, cGAS catalyzes the conversion of GTP and ATP into cyclic GMP-AMP (cGAMP), which subsequently binds to and activates the stimulator of interferon genes (STING) located in the membrane of the endoplasmic reticulum. This activation cascade further stimulates the TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) signaling pathways, culminating in the production of type I interferons. The resultant interferon response facilitates the maturation of DCs and enhances antigen presentation, thereby augmenting the immune system's ability to recognize tumor antigens.[166,167] To ensure efficient STING pathway activation, manganese (Mn)-based nanoplatforms were designed as cGAS-STING agonist, benefiting from the potential role of Mn^{2+} in accelerating the catalytic activity of cGAS and enhancing the binding affinity of cGAMP to STING.[168,169] Since it is essential for X–C motif chemokine receptor 1 (XCR1)-expressing conventional type-1 dendritic cells (cDC1s) to cross-present TAAs during the priming of new responses by tumor-specific $CD8^+$ T cells, a novel strategy based on hydrogel decorated with X-C motif chemokine ligand 1 (XCL1) was proposed to effectively recruit cDC1s into the TME.[56] Manganese phosphate (MnP) microparticles were further incorporated into the calcium phosphate hydrogels (XCL1@CaMnP) to activate cGAS-STING pathway, exhibiting outstanding performance in enhancing the efficacy of RT and the antitumor cytotoxic T lymphocytes (CTL) response in postoperative RT. In addition, the synthesis of Mn-based nanomedicine utilizing MnO_2 NPs with high encapsulation efficiency of anti-programmed death ligand 1 (αPDL1) (αPDL1@MnO_2) has demonstrated the potential to enhance STING activation and facilitate the delivery of ICB inhibitors for synergistic combinatorial cancer immunotherapy.[170] The administration of αPDL1@MnO_2 in conjunction with X-ray irradiation effectively reprogrammed the immunosuppressive TME by reducing the percentage of Tregs and polarizing TAMs from the M2 to the M1 phenotype. This reprogramming resulted in significant abscopal effects, thereby inhibiting tumor metastasis.

Within the tumor immune microenvironment, metabolic immunosuppressive factors impede effector immune cells by modulating metabolic pathways and signaling mechanisms, thereby facilitating tumor evasion of immune surveillance. Targeting these metabolic factors augments the anti-tumor efficacy of RT, rendering the TME more amenable to immune system activation and enhancing the radiosensitivity. For example, Indoleamine 2,3-dioxygenase-1 (IDO-1) is an enzyme that plays a critical role in the metabolism of tryptophan (Trp). It is frequently overexpressed in tumor cells. IDO-1 catalyzes the conversion of Trp to kynurenine (Kyn), resulting in the depletion of Trp and the accumulation of Kyn. This metabolic shift impairs the function of effector T cells and augments the immunosuppressive activity of Tregs.[171] Hence, Wang et al. designed a pH-responsive nanomedicine by coating calcium carbonate ($CaCO_3$) NPs with an IDO-1 inhibitor (4-phenylimidazole (4PI)), creating acidity-IDO1-modulation NPs (AIM NPs). These NPs, in conjunction with zinc ions, synergize with RT, effectively controlling primary tumors and suppressing tumor recurrence and metastasis.[57] $CaCO_3$ reacted with protons to neutralize tumor acidity, while the inhibition of IDO1-mediated Trp metabolism reversed "cold" immunosuppressive TME to a "hot" immunostimulatory one. Adenosine represents another crucial immunosuppressive metabolite within the TME, produced from substantial quantities of ATP secreted by tumor and immunosuppressive cells through CD39/CD73-mediated catabolism. It impedes the proliferation and function of T cells and natural killer (NK) cells while facilitating the activation of Tregs via A2A receptor activation.[172] Study found that, the combination of high-Z metal gadolinium (Gd) and CD73/adenosine axis blockade (AmPCP-Gd NPs, AmGd-NPs) enhanced RT-induced ICD (calreticulin exposure, ATP secretion, HMGB1 release) and boosted immune checkpoint inhibitory therapy by the amplification of $CD8^+$T cell-dependent antitumor immune responses.[58] Consequently, strategies for enhancing the tumor immune microenvironment are diverse (Figure 3). However, given the heterogeneity of tumors and the complexity of the TME, optimizing the sensitization of RT necessitates the consideration of both the specific tumor type and the timing of the intervention.

G2/M cell-cycle arrest

The cell cycle comprises a sequence of distinct phases: G1, S, G2, and M. During the G1 phase, the cell undergoes growth and synthesizes RNA and proteins. The S phase is characterized by DNA replication, resulting in the doubling of the chromosome number in preparation for cell division. In the G2 phase, the cell continues its growth. The M phase, the concluding stage of the cell cycle, involves the process of cell division. Among all the cell division phases, increased G2/M cell arrest can enhance apoptosis and the cytotoxicity of therapeutic agents.[173–175] Cell cycle phases exhibit varying sensitivities to radiation as well, with the G2/M phase generally being the most susceptible. A blockade in the G2/M phase can impede the cellular repair of DNA damage. During the S phase, cells demonstrate enhanced capacity for DNA repair, whereas this capability is comparatively diminished in the G2/M phase. Consequently, when the cell cycle is arrested in the G2/M phase, timely repair of DNA damage is hindered, potentially resulting in apoptosis or the permanent inactivation of cells. In contrast, normal cells are less frequently in the rapid division phase; thus, obstruction of the G2/M phase has a relatively minimal impact on these cells. This selectivity contributes to a reduction in the side effects associated with RT, thereby enhancing the safety and efficacy of the treatment.[176,177] In addition, combining G2/M cell cycle arrest with anticancer drugs can boost RT effects. For example, Pt-based nanomaterials have emerged as promising radiosensitizers for enhanced dose deposition. The released cisplatin (II) from self-targeting nano-assembly NPs (Pt-STNA) can form DNA-binding to enrich tumor cells at the G2/M phase through a phosphorylated Chk1 (*p*-Chk1)-mediated process.[59] Study also

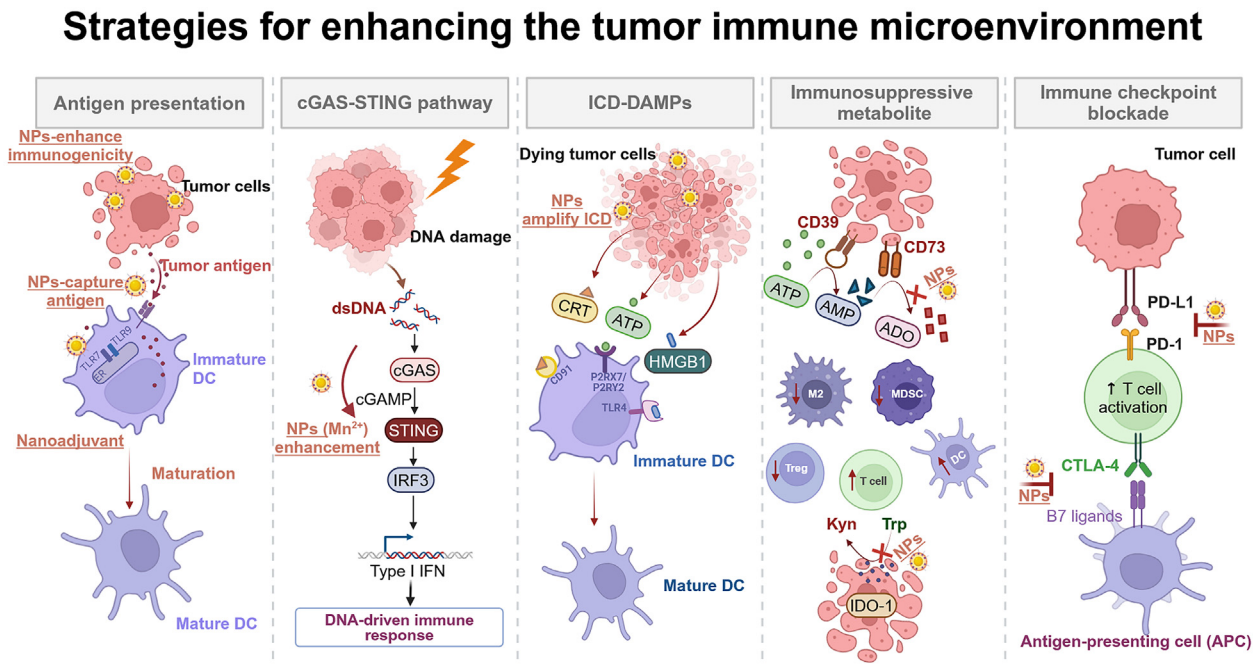

Figure 3. Mechanisms of radiosensitization through the enhancement of the tumor immune microenvironment
Created in BioRender.

found that Mn^{2+}-mediated Fenton-like reaction can induce G2/M cell cycle arrest, enhancing the sensitivity of tumor cells to RT.[60] Furthermore, DM1-NO NPs were designed by loading nitrosylated maytansinoid (DM1) DM1-NO onto poly(lactide-co-glycolic)-block-poly (ethylene glycol) (PLGA-b-PEG) NPs (DM1-NO PLGA).[61] The released DM1 inhibited microtubule formation and increased the G2/M phase cell population to 83.47%. When combined with RT, DM1-NO PLGA enhanced tumor inhibition by 9.64 times compared to RT alone. The aforementioned evidence indicates that arresting cells at the G2/M phase significantly enhances the efficacy of RT.

In summary, mechanisms of radiosensitization are diverse and advancing, yet challenges persist. The dual nature of ROS necessitates balancing dose and effect. While boosting oxygen supply aids sensitization, the complex, dynamic distribution of oxygen-poor tumor regions complicates real-time monitoring and assessment of tumor oxygen levels, making it a key research focus. The application of imaging technologies, such as PET-CT, offers a dynamic approach to monitoring hypoxic regions and enhancing oxygen delivery in a targeted fashion.[178] Furthermore, hypoxia is intricately linked to the tumor immune microenvironment,[179] and exploring strategies to ameliorate the immune microenvironment by alleviating hypoxia warrants comprehensive investigation. Current G2/M cycle blockers such as paclitaxel and cisplatin are highly toxic. Future research should aim to create low-toxicity drugs or inhibitors for precise cell cycle control, minimizing harm to healthy tissues. Additionally, exploring how RT affects the tumor immune environment and identifying the best timing for starting immunotherapy are crucial areas for future clinical studies. Beyond the previously discussed mechanisms of RT sensitization, additional innovative pathways include the suppression of DNA repair processes,[180] the induction of nitrosative stress[181] and so on. These mechanisms offer a diverse array of potential strategies to enhance RT sensitivity and expand the possibilities for developing combination therapy regimens.

NANOPARTICLE-BASED TREATMENTS SYNERGIZE WITH RADIOTHERAPY FOR CANCER THERAPY

Radiodynamic therapy/radiotherapy

By generating cytotoxic ROS from photosensitizer under laser irradiation (ultraviolet, visible, or near-infrared (NIR) light), PDT operates as a noninvasive and specific antitumor therapy.[182,183] However, the limited penetration depth of NIR may restrict its clinical application in cancer treatment.[184] Inspired by the deep penetration capabilities of X-rays, X-ray-mediated radio/radiodynamic therapy (RDT) holds great promise for the treatment of deep tumors. Nonetheless, X-rays cannot directly activate photosensitizers (PSs) due to the significant mismatch in energy levels between X-rays and PSs.[185] Scintillating NPs (ScNPs) can act as energy transducers, converting X-rays into UV/vis luminescence that can activate PSs to generate ROS.[186] For instance, Ce-doped highly fluorescent $NaCeF_4$: Gd,Tb ScNPs can utilize X-rays to activate Tb ions to emit fluorescence and produce X-ray excited fluorescence (XEF) via the sensitization effect of the Ce ions.[62] Moreover, Ce and Tb ions can capture secondary electrons generated by X-rays for ROS production. In experiments where tumor cells were exposed solely to 6 Gy X-ray irradiation, 29.7% of the cells exhibited damage. In contrast, the synergistic treatment combining ScNPs with 6 Gy X-ray irradiation resulted in an increase in the proportion of damaged cells to approximately

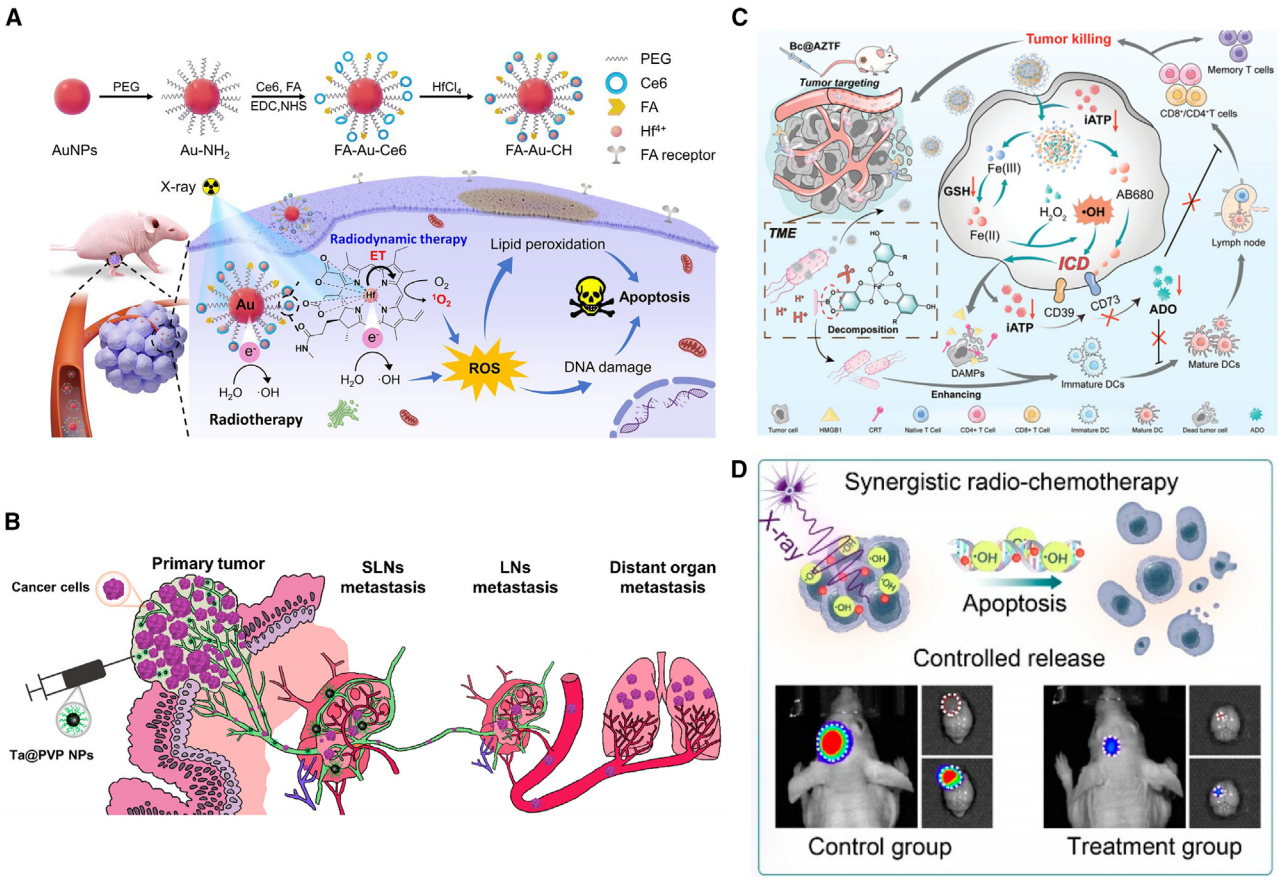

Figure 4. The synergistic application of combined treatment modalities results in improved RT efficacy

(A) Illustration of Hf-bearing gold nanosensitizers FA-Au-CH and the detailed mechanism of RT-RDT for tumor therapy.[66] Copyright 2023 American Chemical Society.

(B) Scheme of lymphatic metastasis in primary breast carcinoma and SLNs targeting by Ta@PVP NPs.[40] Copyright 2022 American Chemical Society.

(C) Schematic illustration of Bc@AZTF for the disruption of ATP-adenosine axis to remodel immune-suppressive TME.175 Copyright 2024 Wiley-VCH GmbH.

(D) The mechanism and application of synergistic radio-chemotherapy against glioma.181 Copyright 2024 American Chemical Society.

80%. Given that the majority of PSs for PDT depend significantly on oxygen to generate ROS, the development of a dendritic mesoporous silica nanoparticle (DMSN) system incorporating cerium oxide (CeOx) NPs, which exhibited photocatalytic and enzyme-like activities, was further explored to create an oxygen-supplementing ScNPs platform (ScNPs@DMSN@CeO_x-PEG).[63] When CeO_x NPs switch from Ce^{3+} to Ce^{4+}, they can effectively and persistently convert H_2O_2 to H_2O and O_2.

Meanwhile, metal-organic frameworks (MOF)-based nanoplatforms, such as those containing Hf^{4+}, are being utilized for tumor treatment via RT/RDT. These nanoplatforms address the limitations associated with scintillators, including their comparatively low energy conversion efficiency and intricate energy conversion processes. Hf^{4+} serves as a mediator to transfer energy from X-rays to PSs for RDT. Due to the aggregation-caused quenching (ACQ) effect, certain PSs demonstrate suboptimal therapeutic efficacy when in an aggregated state. To address this limitation, a polymer nanoparticle coordinated with Hf^{4+} and incorporating aggregation-induced emission (AIE) PSs (Hf-AIE-PEG-DBCO) was developed. This innovative design mitigates the ACQ effect by regulating molecular spacing and constraining the intramolecular motions of AIE PSs within the aggregated state.[64] Metalating the photosensitizing porphyrin in Hf-based MOF (Hf-DBP) with heavy metal Pt (II) (Hf-DBP-Pt) enhances X-ray absorption and intersystem crossing, boosting the RT/RDT effect.[65] Additionally, the diverse ROS produced during fractionated low-dose X-ray irradiation can trigger antitumor immune responses by differentiating peripheral neutrophils into non-canonical antigen-presenting cells, leading to effective tumor-specific T cell responses and tumor regression. Recently, Hf-bearing gold nanosensitizers (FA-Au-CH), consisting of PS chlorin e6 (Ce6) and FA have achieved great success against malignant tumors by targeted effects of DNA breaks, lipid peroxidation and cell apoptosis in tumor cells, demonstrating that the integration of RT and RDT has a great potential for tumor therapy (Figure 4A).[66]

Thermotherapy/radiotherapy

PTT combined with RT, known as thermoradiotherapy (TRT), has recently emerged as an effective cancer treatment. PTT typically

utilizes NIR-absorbing materials with high light-to-heat conversion efficiency to convert light energy into heat, thereby inducing the death of tumor cells. Research has demonstrated that PTT can increase the sensitivity of radioresistant tumor cells and impede their ability to self-repair following RT. This phenomenon is likely due to the enhanced blood flow promoting oxygen generation within the TME and the induction of cell-cycle arrest at the G1 phase.[187,188] While cells in the G1 phase exhibited greater radioresistance, a variation in radiosensitivity was observed between early and late G1-phase cells.[176] Specifically, late G1-phase cells were more radiosensitive than early G1-phase cells but less so than G2 and M phase cells. Early G1-phase cells efficiently repair RT-induced DSBs using non-homologous end-joining (NHEJ), boosting their RT tolerance. In late G1, while NHEJ remains active, its ability to fix complex DNA damage is reduced, and the lack of homologous recombination (HR) repair leads to damage accumulation. This accumulation makes cells more susceptible to RT. When nano-radiosensitizer HfO_2 NPs are conjugated to the molybdenum disulfide nanosheets (MoS_2 NSs) (MoS_2/HfO_2-Dextran), the high photothermal conversion efficiency of MoS_2 NSs not only ameliorates tumor hypoxia effectively but also enhances peroxidase-like catalytic efficiency for the production of highly oxidized $^{\cdot}OH$, effectively sensitizing RT and inhibiting tumor metastasis.[67] Wang et al. developed a light-controlled agarose hydrogel system encapsulating Prussian blue (PB) NPs (PRC).[68] Under irradiation with an 808 nm NIR laser (NIR-I, 700–950 nm), PB NPs converted light energy into heat, resulting in the hydrolysis and subsequent softening of the agarose hydrogel. Subsequently, PB NPs were released and decomposed endogenous H_2O_2 to generate O_2. Meanwhile, increased blood flow in the tumor environment alleviated hypoxia. The results of synergetic therapy *in vitro* and *in vivo* indicated that this agarose hydrogel system could effectively enhance DNA damage and suppress tumor growth. Similarly, PTT-assisted RT using poly(vinylpyrrolidone)-coated Ta NPs (Ta@PVP NPs) demonstrated significant efficacy in inhibiting the growth of both primary breast carcinoma and its metastatic sentinel lymph nodes (SLNs) due to the high X-ray mass attenuation coefficient and photothermal conversion property of Ta.[40] Moreover, ICD triggered by RT/PTT can induce robust anti-tumor immunity, enhancing the therapeutic effect on metastatic SLNs (Figure 4B). Furthermore, Bi-based nanoflowers (BNFs) engineered into a nano-in-micro dry powder format, exhibiting PTT and radiosensitization capabilities, have demonstrated efficacy in targeted pulmonary treatment for lung metastatic breast cancer.[69] The majority of PTT synergistic with RT is initiated by NIR-I radiation. Research has indicated that second near-infrared (NIR-II, 1000–1700 nm) irradiation, which exhibits reduced absorption by human tissues and enables deeper tissue penetration, has facilitated the investigation of concurrent NIR-II PTT and RT. For example, the photothermal conversion efficiency of cysteamine-decorated FePd bimetallic nanodots (FePd NDs) was 35.4%. The group treated with NDs + NIR + RT exhibited higher expression of caspase 3 *in vitro* and a 97.5% tumor growth inhibition *in vivo*.[70]

Immunotherapy/radiotherapy

In recent years, immunotherapy has emerged as a pivotal strategy in cancer treatment by leveraging the immune system's capabilities. Nevertheless, immunotherapy in isolation frequently falls short of achieving complete tumor cell eradication. RT exerts a profound influence on the TME and systemic immunity. As a result, the integration of RT with immunotherapy, termed radioimmunotherapy (RIT), holds promise for augmenting the immune response, thus offering an innovative approach to tumor management. The interaction between immunotherapy and RT primarily involves tumor vaccination, the utilization of immunomodulatory agents, and the implementation of immune checkpoint inhibitors (ICIs).

Firstly, it has been suggested that tumor-directed RT can act as a *in situ* vaccine, triggering the activation of tumor-antigen-specific T cells. To enhance RT-mediated *in situ* vaccination, strategies have been proposed to potentiate RT-induced ICD, which can generate DAMPs, including calreticulin exposed on the tumor cell surface, HMGB1, and ATP.[189] For instance, integrating an anion inhibitor of 6-phosphogluconate dehydrogenase (physcion, phy) into PEG-modified layered gadolinium hydroxide (PLGdH) nanosheets amplifies oxidative stress and DNA damage by inhibiting pentose phosphate pathway, resulting in ICD and enhanced tumor immunogenicity, thus amplifying the *in situ* vaccination effect.[71] Additionally, Se NPs can induce robust antitumor immunity due to their high atomic number and energy deposition. Study has demonstrated that the radiosensitizer of chalcogen-based TeSe nano-heterojunctions (NHJs) with dumbbell-like morphology (TeSe NDs) can recruit immune cells into the TME, such as helper T cells and CTL cells, by releasing TAAs from damaging tumor cells and ICD-induced activation of APCs.[72] The overexpression of PD-L1 on cancer cells leads to the resistance and insensitivity of malignant tumor to RT.[190,191] Radiation-induced PD-L1 expression on tumor-associated myeloid cells also impairs antitumor immunity.[192] PD-1/PD-L1 inhibitors combined with RT have emerged as promising strategies. However, their synergistic effects are often less than satisfactory due to limited targeted immunomodulation and the immunosuppressive TME. To address the challenges of immunomodulator delivery to the TME, a chemokine-directing nanoplatform based on mesoporous silica NPs (MSNs) was designed using mesenchymal stem cells (MSCs) membrane with overexpressed chemokine receptor CCR2 to facilitate the accurate release of PD-L1 antibodies (CCR2-SCM@MSN@αPD-L1) toward the abundant chemokine ligand CCL2 in the radiation-induced TME.[73] In addition, extracellular vesicles (EVs) with an intrinsic ability to cross biological barriers have emerged as efficient delivery systems. Exosomes conjugated with RGD peptides can enhance the delivery efficiency of siPDL1 (RGD-EV: siPDL1) across the BBB/BBTB, reversing RT-induced PD- L1 expression and significantly activating antitumor immunity against GBM.[74] To further improve the therapeutic effect of ICIs and RT, MAL-modified resiquimod (R848, a small molecule agonist of toll-like receptor 7/8) prodrug (R848-N3) NPs were reported.[75] Notably, R848-N3 can prevent the inflammatory cytokine storm by using azide to block the active amino group of R848.[193] In this system, R848 is produced by radio-reduction and activates DCs to present the RT-induced antigen captured by the MAL-NPs, enhancing tumor-specific immune responses to inhibit tumor growth and prevent recurrence. Since the substantial accumulation of adenosine in the TME followed by

RT-induced ICD plays a critical role in promoting the immunosuppressive TME, inhibition of the ATP-adenosine axis can effectively amplify ICD effect. Deng et al. designed an ATP-responsive nanoplatform to disrupt ATP-adenosine axis by consuming intracellular ATP and inhibit CD73 expression via the CD73 inhibitor AB680 (Bc@AZTF).[76] This nanoplatform not only improves the ICD effect but also overcomes the influence of adenosine on PD-L1 expression and counteracts rechallenged tumors (Figure 4C).

Chemotherapy/radiotherapy

Chemotherapy is a conventional and efficacious clinical intervention, while chemoradiotherapy (CRT) denotes the concurrent administration of chemotherapy and RT. Chemotherapy often encounters challenges such as suboptimal drug accumulation within tumors and detrimental side effects on healthy tissues. In contrast, CRT exhibits enhanced local tumor control compared to chemotherapy or RT alone, attributable to its synergistic therapeutic effects.[194,195] At present, Pt-based drugs function not only as chemotherapeutic agents but also as radiosensitizers, thereby offering an effective strategy for cancer RT.[196,197] To ensure the precise and safe release of Pt-based drugs, a self-targeting nano-assembly (STNA) based on platinum (IV)-amphiphilic prodrug with lactose decoration was designed (Pt STNA). This design specifically targeted the asialoglycoprotein receptor (ASGPR) on the surface of hepatocellular carcinoma (HCC) cells.[59] The released cisplatin (II) from Pt STNA can form DNA binding, inducing DNA damage and cell apoptosis. Furthermore, the Pt-DNA binding can cause cell-cycle arrest in the radiation-sensitive G2/M phase, amplifying the cell-killing effect of RT combined with the radiation dose enhancement of Pt STNA. Additionally, RT can increase the accumulation of chemotherapeutics at tumor sites, thereby facilitating optimal tumor responses to chemotherapy while minimizing systemic toxicity, even at low doses.

Research demonstrated that stereotactic body RT can enhance vascular permeability and disrupt tight junctions by decreasing the expression of tight junction protein ZO-1 and increasing the expression of stromal tissue markers. This promoted the penetration of disulfide cross-linked micelle (DCM)-encapsulated paclitaxel (PTX) across the vascular endothelium barrier, allowing it to accumulate at tumor sites (DCM-[PTX]).[77] Meanwhile, PTX can induce cell-cycle arrest at the G2/M phase, enhancing radiosensitivity. To further overcome poor therapeutic effect and significant side effects of CRT, second-generation near-infrared (NIR-II) window fluorescence (FL) imaging-guided synergistic RT and chemotherapy against brain tumors have also been investigated (Figure 4D). The nano-prodrug utilized down-converted nanoparticle (DCNP) to coat X-ray-sensitive poly (Se-Se/DOX-co-acrylic acid) and Angiopep-2 peptide (DCNP@P(Se-DOX)@ANG), targeting the lipoprotein receptor-related protein expressed on the BBB and glioma cells.[78] Under the precise guidance of NIR-II FL imaging, the therapeutic effect of DOX and RT can be monitored in real time by visualizing the cortical microvascular structure and function in the brain. In addition, the study has found that a low dose of radiation (5 Gy) can induce the chemotaxis of monocytes to central GBM sites by upregulating the expression of monocyte chemokine-1 (MCP-1)/C-C basal chemokine ligand 2 (CCL-2) at the tumor site.[198] Specifically, DOX·HCl loaded MMP-2 peptide-liposome (D@MLL) with lipoteichoic acid modification can target circulating monocytes and then hitchhike on monocytes to the GBM tumor environment. DOX·HCl will be released under the high concentration of MMP-2 in the tumor region for effective GBM treatment.

Taken together, when integrated with other therapeutic modalities, RT offers substantial anti-tumor benefits, primarily due to the synergistic interactions of multiple mechanisms that enhance tumor cell eradication and improve efficacy against drug-resistant and metastatic tumors. Nonetheless, the concomitant side effects, individual variability, and the intricate nature of the TME continue to pose significant challenges to the implementation of combination therapy. RT alone can result in local or systemic adverse effects, and its toxicity may be exacerbated when used in conjunction with chemotherapy, immunotherapy, or thermotherapy. For instance, the combination of RT and chemotherapy can lead to heightened myelosuppression and radiculitis, thereby increasing the treatment burden for patients.[199] Additionally, the integration of immunotherapy with RT may induce immune-related adverse effects, such as adverse immune reactions.[200] Hence, future trends in combination therapy are anticipated to involve multimodal and multi-targeted individualized regimens. These regimens will be capable of dynamically adjusting treatment strategies through real-time monitoring of changes within the TME, thereby maximizing therapeutic efficacy while minimizing side effects.

NANOPARTICLE-BASED RADIOENHANCER IN CLINICAL PRACTICE

Over the past decade, continuous advancements in nanotechnology have demonstrated significant potential for nanoparticle-based strategies to augment the therapeutic efficacy of RT. Among high-Z NPs, AGuIX (Gd-based) and NBTXR3 (Hf-based) NPs have been applied in clinical trials. AGuIX NPs (less than 5 nm) consist of a polysiloxane matrix and gadolinium chelates, enabling MRI guidance and local radiation dose amplification. The first-in-human phase I NANO-RAD (NCT02820454) investigated the combination of AGuIX NPs with whole brain RT in patients with multiple brain metastases from melanoma, lung, breast, or colon cancer.[80] The study assessed the safety and maximum tolerated dose of the systemic administration of AGuIX NPs, finding no dose-limiting toxic effects up to 100 mg/kg. Currently, five clinical trials currently involving AGuIX NPs are underway: Phase I/II trial (NCT04789486) investigating stereotactic magnetic resonance-guided adaptive radiation therapy for centrally located lung tumors and locally advanced pancreatic cancers; Phase Ib trial (NCT03308604) examining chemoradiation and brachytherapy for locally advanced cervical cancer; Phase I/II trail (NCT04881032) exploring TMZ and RT for GBM; Phase II trials (NCT03818386, NCT04899908) assessing whole-brain RT or stereotactic radiosurgery/RT for brain metastases.[81–85] Recently, the second-generation bismuth (Bi)-gadolinium NPs (AGuIX-Bi) have been designed and applied in the ongoing Nano-SMART clinical trial for centrally located non-small cell lung cancer (NSCLC).[41]

Unlike AGuIX, NBTXR3 are 50 nm NPs consisting of HfO_2 NPs, administered intratumorally. In a phase I trial (NCT01946867), 19 elderly patients with locally advanced squamous cell carcinoma of the oral cavity or oropharynx received an intra-tumoral injection of NBTXR3 followed by intensity-modulated radiation therapy (IMRT), demonstrating the feasibility and safety of NBTXR3 activated by IMRT.[86] In another phase I study (NCT01433068) involving NBTXR3 activated by preoperative external-beam RT in adult patients with locally advanced soft tissue sarcomas also illustrated manageable safety.[87] Furthermore, a Phase I study (NCT04484909) described the first patient with pancreatic cancer treated with NBTXR3 and IMRT, demonstrating the initial feasibility of NBTXR3 as a radioenhancer.[88] A phase II–III clinical trial (NCT02379845) further demonstrated the long-term safety of NBTXR3, without affecting postsurgical wound complications.[89] In addition, a phase Ib/II trial (NCT02465593) investigated the efficacy and safety of NBTXR3 with RT and chemotherapy in patients with rectal cancer.[90]

Since chemotherapeutics can function as radiosensitizers, therapeutic effects of clinically approved nanomedicine combined with RT have also been evaluated in clinical trials, including nanoparticle albumin-bound paclitaxel (Nab-paclitaxel, Abraxane) and liposomal irinotecan (Onivyde). A phase II trial (NCT04569916) studied the antitumor efficacy of RT plus Onivyde followed by camrelizumab and antiangiogenic treatment in solid tumors.[91] Updated survival data from a phase I/II study (UMIN000012719) revealed the encouraging feasibility and activity of carboplatin plus nab-paclitaxel and concurrent RT in patients with locally advanced NSCLC.[92] In recent years, phase I trials have demonstrated that carboplatin/nab-paclitaxel and RT exhibited excellent tolerability in patients with locally advanced NSCLC (jRCTs042180077,[93] UMINR000015432[94]) and previously treated head and neck squamous cell carcinoma (NCT01847326).[95] Another phase I study (ChiCTR1900021079) involving patients with locally advanced esophageal squamous cell carcinoma treated with a weekly schedule of cisplatin and nab-paclitaxel in combination with concurrent RT revealed the safety and promising antitumor activity of the regimen.[96]

CONCLUSIONS AND OUTLOOKS

In conclusion, this review has examined recent advancements in the application of nanoparticle-based RT for cancer treatment. Considerable efforts have been directed toward augmenting radiation sensitization through various mechanisms, including the enhancement of ROS generation, the mitigation of hypoxia, the implementation of active targeting strategies, and the utilization of stimuli-responsive nanosystems. Furthermore, the modulation of the immune microenvironment and the promotion of G2/M phase cell-cycle arrest have substantially improved the therapeutic efficacy of RT. Moreover, the synergistic interactions among radiodynamic therapy, thermotherapy, immunotherapy, and chemotherapy in conjunction with RT not only reprogram the tumor-resistant microenvironment to inhibit tumor growth but also enhance the abscopal effect of RT and suppress the metastasis of malignant tumors. Clinical trials involving AGuIX, NBTXR3, Onivyde and Nab-paclitaxel have demonstrated the substantial potential of NPs-enhanced therapy in the clinical transformation against malignant tumors. The unique properties of NPs position them as powerful tools in the fight against cancer.

Future research should explore not only the short-term effects of enhanced RT but also the long-term health impacts of nanomaterials. The potential chronic toxicity and prolonged retention of these materials in the body are significant concerns. Efficient RT sensitization must be balanced with ensuring safe metabolism and clearance, necessitating the design of nanomaterials with excellent biodegradability and controlled metabolic pathways. Nanomaterial development must optimize molecular structure and surface modification to minimize bioaccumulation. The synthesis process should follow green and sustainable principles, using biocompatible materials and eco-friendly methods to lessen environmental impact.[201,202] In tumor therapy, particularly when using RT sensitization, it is crucial to weigh potential risks and side effects, such as ROS's dual impact and the risk of tumor vascular normalization. Thus, each sensitization method should be applied with a personalized approach, balancing short-term effectiveness and long-term safety. For patients with varying tumor stages or molecular traits, selecting the right RT sensitization regimen can reduce side effects and improve treatment outcomes.

Despite the inherent challenges and uncertainties, the future trajectory of nanomaterial-sensitized RT appears promising. Recent technological advancements are enabling the development of NPs with targeted delivery, low toxicity, and controlled release properties, thereby providing safer and more efficacious options for clinical RT applications. The integration of cutting-edge technologies from the fields of biomaterials, imaging, and oncology is expected to significantly enhance the safety and precision of tumor RT and combination therapies.

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AUTHOR CONTRIBUTIONS

M.J.H. and S.X.C. were the main contributors to writing and editing the article to collect and collate studies. H.W. and X.R.Y. provided direction and guidance of this article. H.W.Y., X.H.F., H.W., and Y.H.W. reviewed and made revisions to the article. All authors approved the final article.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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