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REVIEW

Application of Radiosensitizers in Cancer Radiotherapy

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Liuyun Gong[1]
Yujie Zhang[2,3]
Chengcheng Liu[2]
Mingzhen Zhang[2,3]
Suxia Han[1]

[1]Department of Oncology, The First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China; [2]School of Basic Medical Sciences, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China; [3]Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University, Ministry of Education, Xi'an, Shaanxi, 710061, People's Republic of China

Abstract: Radiotherapy (RT) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. Although great success has been achieved on radiotherapy, there is still an intractable challenge to enhance radiation damage to tumor tissue and reduce side effects to healthy tissue. Radiosensitizers are chemicals or pharmaceutical agents that can enhance the killing effect on tumor cells by accelerating DNA damage and producing free radicals indirectly. In most cases, radiosensitizers have less effect on normal tissues. In recent years, several strategies have been exploited to develop radiosensitizers that are highly effective and have low toxicity. In this review, we first summarized the applications of radiosensitizers including small molecules, macromolecules, and nanomaterials, especially those that have been used in clinical trials. Second, the development states of radiosensitizers and the possible mechanisms to improve radiosensitizers sensibility are reviewed. Third, the challenges and prospects for clinical translation of radiosensitizers in oncotherapy are presented.

Keywords: radiosensitizers, cancer radiotherapy, therapeutics, nanomedicine, mechanism

Introduction

Cancer remains one of the greatest challenges to human health. World Health Organization (WHO) reported that about 8.8 million deaths worldwide were due to cancer in 2015, and the deaths are expected to break through 13 million in 2030 according to the report by the International Agency for Research on Cancer (IARC). To reduce the deaths from cancer, several strategies have been developed in recent years to improve cancer therapy including surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant and precision medicine.[1] Among them, radiotherapy (RT) is considered as one important and effective modality to kill or control tumors since Marie Curie, the Nobel Prize winner, discovered radioactivity.[2] Typically, RT is a treatment modality to cancer cells by using high-energy photon radiation such as X-rays, gamma (γ)-rays, and others. RT can take effect via direct and indirect mechanisms to destroy cancer cells and tumor tissue (Figure 1).

In the direct action, radiation directly induces single-strand breaks (SSB) and double-strand breaks (DSB) in DNA, resulting in the termination of cell division and proliferation, or even cell necrosis and apoptosis. In the case of indirect action, radiation induces the generation of ROS, which can induce cellular stress in, and injure biomolecules, and and ultimately alter cellular signaling pathways. Clinical studies have shown that more than half (about 70%) of patients need to receive RT,

Correspondence: Mingzhen Zhang; Suxia Han
Email mzhang21@xjtu.edu.cn; shan87@xjtu.edu.cn

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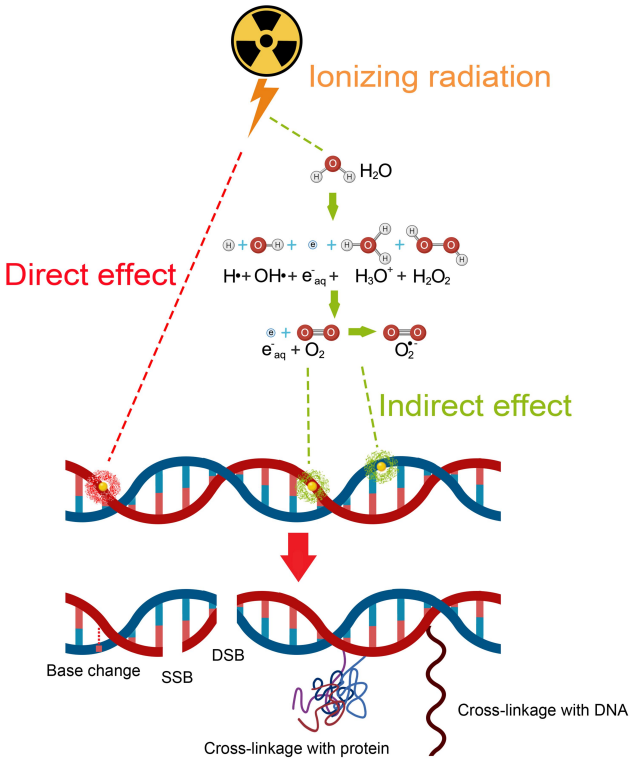

Figure 1 Schematic of the mechanism of ionizing radiation (IR) in RT. In the case of direct effect, IR directly damages the DNA, which, if unrepaired, results in cell death or permanent growth arrest. In the case of indirect effect, ROS are formed by the radiolysis of a large amount of water and oxygen, and then the ROS damage the DNA. There are many types of DNA damage, such as base change, SSB, DSB, cross-linkage with protein or with other DNA molecules.

and in some cases RT is the only kind of cancer treatment.[3] Therefore, there is a great need to develop approaches to improve radiosensitivity.

Innovative technologies can provide alternative strategies to improve RT efficiency. For example, image-guided radiation therapy (IGRT) is the use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery. IGRT can be used to treat tumors in areas of the body that move, such as the lungs. RT machines are equipped with imaging technology to allow your doctor to image the tumor before and during treatment. By comparing these images to the reference images taken during simulation, the patient's position and/or the radiation beams may be adjusted to more precisely target the radiation dose to the tumor. To help align and target the radiation equipment, some IGRT procedures may use fiducial markers, ultrasound, MRI, X-ray images of bone structure, CT scan, 3D body surface mapping, electromagnetic transponders or colored ink tattoos on the skin.[4] Intensity-modulated radiation therapy (IMRT) is an advanced mode of high-precision RT that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor.[5] Although the abovementioned innovative technologies greatly improve the therapeutic effect, there are still obstacles such as cancer stem cells and tumor heterogeneity making it difficult to use RT alone to cure tumors. Radiosensitizers with the ability to increase the radiosensitivity of tumor tissue and pharmacologically decrease normal tissue toxicity are expected to be an efficient way to improve RT.[6]

Radiosensitizers are compounds that, when combined with radiation, achieve greater tumor inactivation than would have been expected from the additive effect of each modality. G E Adams, a pioneer in the field of RT, classified radiosensitizers into five categories: (1) suppression of intracellular thiols or other endogenous radioprotective substances; (2) formation of cytotoxic substances by radiolysis of the radiosensitizer; (3) inhibitors of repair of biomolecules; (4) thymine analogs that can incorporate into DNA; and (5) oxygen mimics that have electrophilic activity.[7,8] This classification was based on the mechanism of DNA damage and repair and indicated the direction for radiosensitizers at the early stage. However, with the continuous technological innovation, more and more materials and drugs with radiotherapy sensitization have been defined as radiosensitizers. In addition, some in-depth mechanisms for radiosensitization have also been discovered.[9,10] According to the latest research, radiosensitizers can be classified into three categories based on their structures: small molecules (Figure 2), macromolecules (Table 1), and nanomaterials (Table 2).[11] In the following part, the applications, the main role, and influencing factors of these three types of radiosensitizers are first summarized, especially those have currently entered clinical trials. Second, the development status and the mechanism of action of the radiosensitizer are also summarized. Third, the future development and application of the radiosensitizer was presented.

Small Molecules

Oxygen

Hypoxia in tumor microenvironment is one of the major limitations to radiotherapy. Tumor cells in the hypoxic microenvironment are much more resistant to radiation than in the normal oxygen microenvironment.[12–14] Oxygen enhancement ratio (OER) or oxygen enhancement effect in radiobiology refers to the enhancement of the

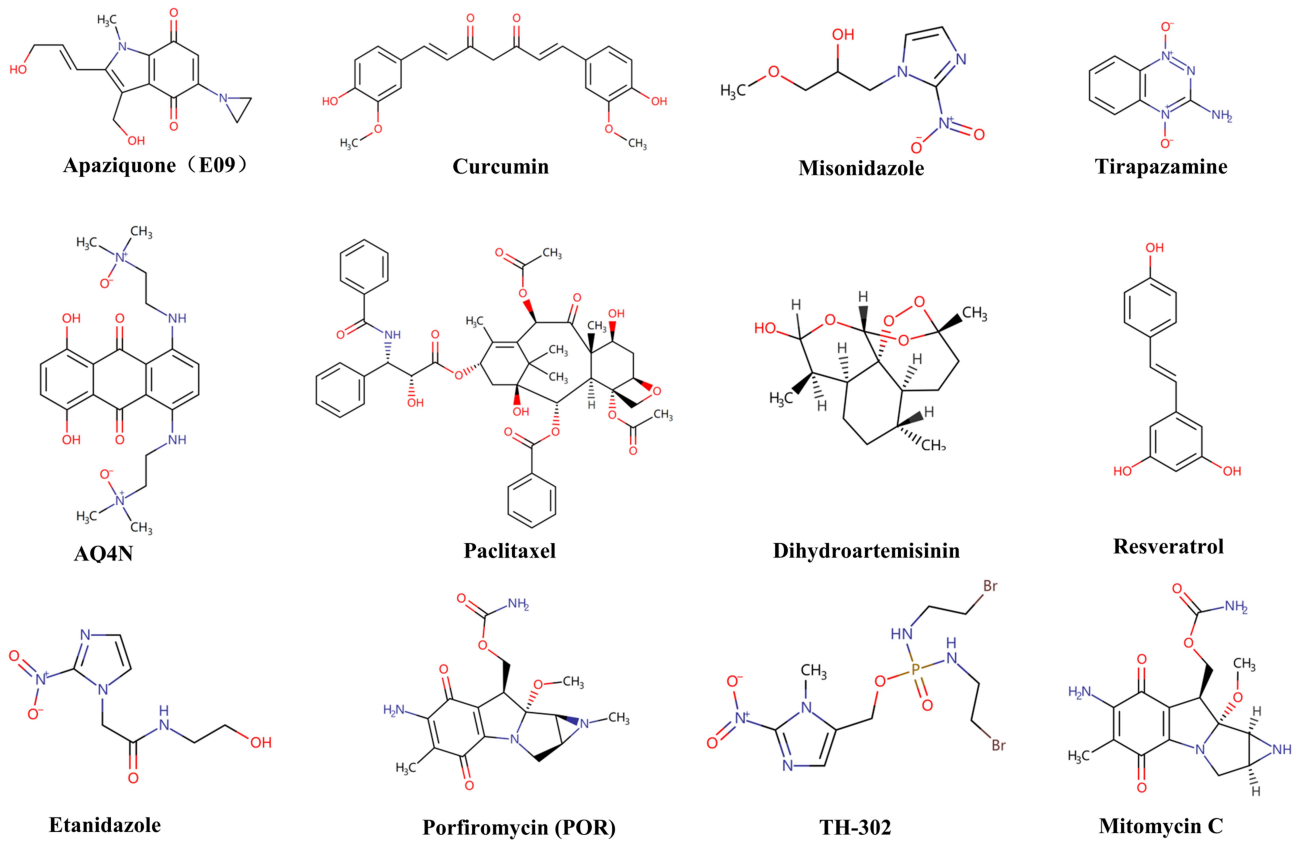

Figure 2 Molecular structures of some representative small-molecule radiosensitizers discussed in this paper.

therapeutic or detrimental effect of ionizing radiation due to the presence of oxygen. This so-called oxygen effect is most notable when cells are exposed to an ionizing radiation dose.[15,16] Oxygen, a potent radiosensitizer, promotes free radical formation through its unique electronic configuration. As the most electrophilic cellular molecule, oxygen is easily reduced by electrons formed from the incident radiation. After oxygenated tumor irradiation, energy transfer results in the radiolysis of water with the initial formation of an ion radical that then forms the highly reactive hydroxyl radical after reaction with another water molecule. Oxygen leads to the formation of peroxide after reaction with the hydroxyl radical. Then, the peroxide results in permanent cellular and DNA damage.[13]

Accompanied with solid tumor growth, the surrounding vasculatures are not in sufficient quantities to supply oxygen to the new cells, the cancer cell mass becomes heterogeneous gradually, and necrosis occurs following ischemia. Normally, cancer cells undergo apoptosis through the p53 pathway, while those heterogeneous cells adapt to the hypoxic environment efficiently by activation of additional signaling pathways, especially the hypoxia-inducible factor (HIF) pathway.[17–19] Studies showed that HIF-1α was associated with vascular endothelial growth factor (VEGF) signaling pathway, glucose transport, and glycolysis pathway, which could help the tumor to build vasculature.[19–21] Under hypoxia, the cancer cells are more aggressive and resisted radiotherapy significantly. Thus, hypoxia often occurs in most solid tumors and leads to radioresistance both through increasing free radical scavenging and changing patterns of gene expression.[22,23]

More and more research has been devoted to overcoming hypoxia problems, from using high-pressure oxygen tanks and blood substitutes that carried oxygen, to using intricate, accurate approaches that proportionated differences in partial pressure of oxygen (PO_2) between tumors and healthy tissue.[24,25] Hyperbaric oxygen is the most direct method to ameliorate hypoxia in tumor cells, while this method is inconvenient and may increase complications sometimes.[26,27] A new radiosensitizer, Kochi oxydol-radiation therapy for unresectable carcinomas (KORTUC), is being evaluated by a Phase I/II clinical trial (NCT02757651) for the treatment of malignant tumors

Table 1 Some Macromolecule Radiosensitizers Discussed in This Paper

Type	Name	Mechanism of Radiosensitivity	Reference
Proteins and Peptides	HER3-ADC	Inhibiting DNA damage repair	130
	SYM004	Inhibiting DNA double strand breaks repair and inducing apoptosis	120
	Cetuximab	Increasing radiation-induced apoptosis and DNA damage	131
	Nimotuzumab	Increasing radiation-induced apoptosis and DNA damage	131
	AMG102	Inhibiting DNA damage repair and increasing radiosensitivity of glioblastoma multiforme	132
	C-reactive peptide	Used as radiotherapy targets	133
	HSP	Used as radiotherapy targets	134
	Paraoxonase-2	Used as radiotherapy targets	135
	ECI301	Assisted by HSP-70 and HMGB1	134
miRNAs	miR-621	Targeting SETDB1	141
	miR-205	Targeting zinc finger E-box binding homeobox 1 (*ZEB1*) and the ubiquitin-conjugating enzyme Ubc13	142
	miR-144-5p	Targeting ATF2	143
	miR-146a-5p	Activating DNA repair pathway	144
	miR-150	Acting on AKT pathway	145
	miR-99a	Targeting mTOR pathway	146
	miR-139-5p	Repressing multiple gene networks of DNA repair and ROS defense	147
	miR-320a	Inducing cancer cell apoptosis	148
siRNAs Oligonucleotides		Silencing genes related to radioresistance Regulating gene expression	151–155 156–159

that contain numerous hypoxic cancer cells and/or large quantities of antioxidative enzymes.[28]

Oxygen Mimics

Oxygen mimetics, using the chemical properties of molecular oxygen as a template, have higher electron affinity and better diffusion properties to anoxic tissue than oxygen. As oxygen mimetics can theoretically substitute for oxygen in "fixing" radiation-induced damage of DNA, making it nonrepairable and hence lethal. Therefore, oxygen mimetics are considered as "true radiosensitizers". The most representative oxygen mimetics are nitro-containing compounds and nitric oxide (NO).[13]

The prototype of electron-affinity radiosensitizers is nitrobenzene, and then researchers focus on nitroimidazole and its derivatives.[29–31] Nitroimidazoles, which undergo enzymatic and radiation-induced redox reactions. These agents are intrinsic inactive, their effect becomes evident only in the presence of ionizing radiation to "fix" or stabilize DNA radical lesions in oxygen-deficient cells.[32] Misonidazole, a 2-nitroimidazole, is one of the earliest developed nitroimidazoles. In preclinical studies, misonidazole showed better radiosensitizing effect than 5-nitro imidazole or metronidazole (Flagyl®) in the majority of solid murine tumors.[33–35] However, the results were unsatisfactory in clinical trials, since severe neurotoxicity was caused by misonidazole.[36–39] Metronidazole, a 5-substituted nitroimidazole, which has less electron-affinic was proven as an inferior radiosensitizer.[40,41] In conclusion, because of the dose-limiting toxicity at clinically tolerable doses, misonidazole and metronidazole are not the ideal candidates in radiotherapy.[42]

In view of the issues discussed above, further efforts have been made to improve the pharmacokinetic

Table 2 The List of Nanomaterials Used for Radiosensitization

Nanomaterial	Modification	Size (TEM)	Cell Line/Model	Reference
Au	GSH	<2 nm	U14 tumor models	166
Au	PEG_{2k}	2, 5, 19 nm	PC3pip and PC3flu cells	167
Ag	PEG	18 nm	C6 cells	171
Ag	PVP	26.87±3.68 nm	U251 and C6 cells	172
Bi,Gd	PEG	11.3±1.6 nm	MCF-7 and 4T1 cells	174
Hf, Nb, Ta		100 nm		178
Gd	DTPA	3.0±1.0 nm	F98 cells	179
AGuIX		2.1±1 nm	F344 rats	181
AGuIX	DOTA	Sub-5 nm	HepG2 cells	182
Hf		7–31 nm		184
Ta	PEG	65.4±5.6 nm	Balb/c mice	188
Zn, Ga, Ge, Cr, Pr, Ta	PEG	62.8±8.6 nm	Nude mice harboring HepG2 tumors	190
Ta	PEG	119±34 nm	4T1 cells	193
Bi	PEG	3.6 nm	LO2 and 4T1 cells	197
Bi		10–70 nm	4T1 cells	200
Si,Gd,Bi	DOTA	4.5±0.9 nm	A549 cells	202
Fe,Pt	PEI,PEG	10nm	A2780 and A2780DDP cells	204
Co,Mn,Fe,Bi	PEG	11.2±1.4 nm and 14.4±2.4 nm	C6 cells	207
Zn,Fe		5–15 nm	LNCaP cells	208
Quantum dots			H460 cells	214
Ti	PAA	50–100 nm	MIAPaCa-2 cells	215
Ti	PAA	135±65 and 124±65 nm		216
R-O2-FA-CHI-SWCNTs			MDA-MB-231 and ZR-75-1 cells	220
Tf,Se		177, 192, and 312 nm	C6,A375 cells	221
GNP	PEG, RGD	20.90±0.14nm.	HeLa, Hs. 895.Sk and Hs 895.T cells	222

properties of nitroimidazoles. Second-generation nitroimidazole radiosensitizers, such as etanidazole or nimorazole, are designed to increase the hydrophilicity of the reagents and thereby reduce neurotoxicity. For example, etanidazole has better hydrophilicity than misonidazole because its side chain is modified by hydroxyl.[43] Although etanidazole presents lower preclinical toxicity and higher efficacy, it shows no obvious benefit for head and neck cancer patients in randomized studies.[44] Nimorazole, a 5-nitroimidazole, is recommended for the treatment of head and neck cancers in Denmark since its beneficial effects in several clinical trials. Moreover, it has been further explored in an EORTC international trial.[45–51] Notably, the DAHANCA 28 trial demonstrated that hyperfractionated, accelerated radiotherapy with concomitant cisplatin and nimorazole (HART-CN) for patients was feasible and yielded favorable tumor control.[52] Other nitro compounds have also been exploited for hypoxia radiosensitization. Dinitroazetidine, RRx-001, has been evidenced as an effective radiosensitizer with low toxicity and is now being evaluated in the NCT02871843 clinic trial.[53]

Nitrogen oxides, in particular, NO, act as radiosensitizers through many direct and indirect mechanisms. Similar to the oxidative stress induced by oxygen, NO can "fix" or stabilize radiation-induced DNA damage through nitrosative stress pathways.[54] Oxidative and nitrosative stress pathways involve the generation of reactive species. For example, nitrous acid, peroxynitrite ($ONOO^-$), and nitric acid produce cytotoxic effects through mechanisms including DNA cross-linking, protein nitrosylation, glutathione depletion, and inhibition of mitochondrial respiration.[55–58]

As an uncharged free radical, NO can diffuse across cell membranes freely and bind to soluble guanylate cyclase (sGC) to induce cyclic GMP production, thereby regulating vascular physiology.[59–61] Researchers have reported that 5-nitroimidazoles and sanazole can release NO.[62,63]

A phase I study of non-small-cell lung cancer (NSCLC) patients suggested that NO donation increased tumor perfusion and, therefore, promoted tumor growth.[64] However, a phase II study of prostate cancer patients claimed that low-dose NO had no direct cytotoxic effect, but could decrease hypoxia through improving blood flow in tumor tissue.[65] Some anticancer drugs approved by US Food and Drug Administration (FDA), such as bevacizumab, sorafenib, and etaracizumab played their roles by blocking the VEGF pathway to some extent.[66] VEGF is overexpressed in anoxia environment, which leads to endothelial cell proliferation and neovascularization. In angiogenesis, there is a positive and negative feedback regulation relationship between VEGF and NO, which maintains vascular homeostasis precisely.[67] In addition, Liebmann et al proved that pretreatment with NO improved the survival of mice after irradiation.[68]

Active Compounds from Chinese Herbs

In recent years, more and more researchers reported that active compounds from Chinese herbs such as curcumin,[69–71] resveratrol,[72–74] dihydroartemisinin[75–77] and paclitaxel,[78–80] could enhance tumor radiotherapy sensitivity (Figure 2). Curcumin is a polyphenolic active compound extracted from turmeric. Curcumin exerts anti-inflammatory effect by inhibiting the transcription factor NF-κB, which is involved in both tumorigenesis and radioresistance.[81] In a preclinical study, Chendil et al reported that when treated with RT and curcumin together, the human prostate cancer cell line, PC3 presented three-fold fewer surviving and the mechanism was supposed to have a relationship with NF-κB.[82] In addition, nanocurcumin as a radiosensitizer is being evaluated by a Phase II clinical trial (NCT02724618). Other relevant research on mutant p53 Ewing's sarcoma cells proved that radiosensitivity of curcumin was associated with other p53-response genes.[83]

Resveratrol is an active compound extracted from grapes, knotweed, peanuts, mulberry and other plants. Tan et al proved that resveratrol enhanced the radiosensitivity in nasopharyngeal carcinoma cells by downregulating E2F1.[73] Liao et al found that resveratrol enhanced radiosensitivity in human NSCLC NCI-H838 cells by inhibiting NF-κB activation.[84] Dihydroartemisinin is a derivative of artemisinin, which can shorten the G_2/M phase, while increases the G0/G1 and S phase, thereby reducing the radiation resistance.[85] Although the relevant clinical research has not yet been carried out, researchers have demonstrated that resveratrol[86–89] and dihydroartemisinin[90–92] possessed radiosensitization on cancer cells in vitro.

Paclitaxel is widely known as a very good natural anticancer drug.[93,94] As a new type of antimicrotubule drug, paclitaxel can inhibit the microtubule networks formation and prevent the tumor cells proliferation to achieve radiosensitization.[95] Results showed that paclitaxel could obviously enhance the radiosensitivity of inoperable patients with locally advanced esophageal cancer and improve the prognosis of patients with acceptable therapeutic effect.[96] A three-arm randomized Phase III trial (NCT02459457)—comparison of paclitaxel-based three regimens concurrent with radiotherapy for patients with local advanced esophageal cancer and a Phase III study (NCT01591135) of comparing paclitaxel plus 5-fluorouracil vs cisplatin plus 5-fluorouracil in chemoradiotherapy for locally advanced esophageal carcinoma are underevaluated.

Hypoxia-specific Cytotoxins

Some bioreductive agents, such as aromatic N-oxides, transition metal complexes, quinones, aliphatic N-oxides and nitro compounds, have radiosensitization effects by virtue of their preferential cytotoxicity toward hypoxic cells.[11] Tirapazamine (TPZ), a hypoxia-selective radiosensitizer, has shown promising results in clinical trials.[97,98] Under hypoxic environments, TPZ can be reduced by reductase in cells to a metabolite that produces free radical and then leads to SSB, DSB, and base damage on DNA.[99] A Phase I clinical trial of TPZ with cisplatin and radiotherapy in small cell lung cancer showed prolonged survival of patients.[100] A Phase II study of TPZ with chemoradiotherapy in locally advanced head and neck cancer reported improvements in failure-free survival and response of patients.[101] However, further phase III trials of TPZ with chemoradiotherapy in locally advanced head and neck cancer concluded that there was no obvious improvement in patient survival.[102] In addition, SN30000 (previously known as CEN-209), an analog of TPZ, with more favorable diffusion property that provides greater toxicity in hypoxic cancer cells than TPZ, is currently

under development by the Drug Development Office of Cancer Research UK.[103]

AQ4N, a representative to aliphatic N-oxide, can be reduced to AQ4 by cytochrome P450 isoenzymes or nitric oxide synthase 2A.[104] In vivo experiments showed that combined utilization of AQ4N with radiotherapy resulted in increased antitumor efficacy, as well as negligible toxicity to normal tissue compared with radiation alone.[105] Positive results were also evidenced in Phase I clinical trials.[106] A Phase I clinical trial in glioblastoma and head and neck tumor patients proved that AQ4N could be specifically activated in hypoxic regions of solid tumors.[107] Unfortunately, a Phase II clinical trial of AQ4N with radiotherapy and temozolomide in glioblastoma began in 2006, was in a pending status (NCT00394628).

TH-302 (evofosafamide), a similar compound that can be reduced to bromo-isophosphoramide mustard in hypoxic conditions, has radiosensitization activity, especially in hypoxic cells.[108,109] In preclinical models of rhabdomyosarcoma (skeletal muscle) and NSCLC, TH-302 combined with radiotherapy treatment resulted in significant tumor growth delay.[110] In addition, in a study in patient-derived xenograft models of pancreatic cancer, combination treatment of TH-302 and radiotherapy was more efficient than either treatment alone.[111] TH-302 can specifically target the hypoxic tumor cells and induce DNA damage simultaneously in adjacent tumor tissue of the hypoxic zone, and thus holds potential radiosensitization effects in solid tumor treatment.[112] However, on the database of US National Institutes of Health clinical trials, only one of the 26 trials listed proposed combination treatment of TH-302 with radiotherapy (NCT02598687), and it was withdrawn because two phase III trials did not meet their primary endpoint.[113]

Mitomycin C, a quinone-based anticancer therapeutic, can be activated via DNA cross-linking. In preclinical study, mitomycin C showed only slight toxicity in hypoxic cells, which promotes the development of other hypoxia-sensitive quinones selection.[114] Among them, porfiromycin (POR) and apaziquone (EO9) are bioreductive prodrugs, represent the leading candidates.[104] Preclinical studies concluded that POR held higher hypoxic selectivity than mitomycin C.[115] Although preclinical trials proved POR had acceptable toxicity, the following Phase 3 trial demonstrated that POR had a poorer therapeutic effect than mitomycin C.[116] Preclinical studies indicated that EO9 had greater antitumor property than mitomycin C, indicating EO9 can be a ideal radiosensitizer.[117]

Other Chemical Radiosensitizers

Other types of chemical radiosensitizers have also seen some progress and some of them are in preclinical evaluations. For example, chemicals that influence cell signaling, suppress radioprotective substances, pseudosubstrates and targeted delivery systems are exploited. With the development of research on radioresistance mechanism, it has been found that multiple signal pathways are related to radioresistance, providing more targets for radiosensitization, such as PI3K–Akt–mTOR,[118] Wnt,[119] MAPK,[120] MDM2[121] and c-MET–PI3K–Akt.[122] For example, BKM120, the oral PI3K inhibitor, can inhibit the activity of PI3K/Akt by targeting the PI3K-Akt pathway, thereby increasing cell apoptosis and inhibiting DNA double-strand break repair in liver cancer cells.[123] BEZ235, a dual PI3K–mTOR inhibitor, can improve the radiosensitivity of colorectal cancer cells.[124] AMG 232, a picomolar affinity piperidinone inhibitor of MDM2, can suppress tumor growth on a mouse model.[121]

Suppression of radioprotective substances, such as glutathione (GSH), is another strategy of radiosensitization. Inhibition of GSH can prevent DNA damage repair and lead to increased damage in tumor cells, which improves the efficacy of radiotherapy in turn.[125] In addition, pseudosubstrates lead cells undergoing DNA synthesis unable to distinguish thymidine and its halogenated analogs efficiently. It is a new area of clinical research to use halogenated pyrimidine analogs, like bromodeoxyuridine (BrdUrd) and iododeoxyuridine (IdUrd), as potential clinical radiosensitizers.[126] One study demonstrated that electron affinities of 5-halogenated deoxyuridine led to enough ability to bind a radiation-produced secondary electron, thereby increasing the sensitivity of radiotherapy.[127]

In addition, research on new indications for existing drugs provides a new paradigm for the development of radiosensitizers. For instance, papaverine, an ergot alkaloid first isolated from *Papaver somniferum* in 1848, has been used for treatment of vasospasm, cerebral thrombosis, pulmonary embolism and erectile dysfunction.[128] Denko et al identified papaverine as an inhibitor of mitochondrial complex I and proved that papaverine could increase oxygenation and enhance radiation response.[128] A phase I trial (NCT03824327) study on papaverine and stereotactic body radiotherapy (SBRT) for NSCLC or lung metastases is under evaluation. In summary, small-

Table 3 Registered Ongoing Clinical Trials (https://Clinicaltrials.gov/) of Small-molecule Chemical Radiosensitizers

Identifier	Drugs	Conditions	Phase	Initiation
NCT02363829	Nelfinavir	Uterine cervix cancer	I	February 2015
NCT02459457	Paclitaxel	Stage III esophageal squamous cell carcinoma	III	July 2015
NCT02598687	TH-302	Esophageal cancer	I	December 2015
NCT02724618	Curcumin	Prostate cancer	II	March 2016
NCT03066154	Docetaxel	Prostatic neoplasms	I	September 2016
NCT02757651	Hydrogen peroxide	Breast cancer	I/II	January 2017
NCT02871843	RRx-001	Glioblastoma	I	February 2017
NCT03101995	Gemcitabine	Cervical cancer	II	July 2017
NCT03824327	Papaverine Hydrochloride	Lung non-small-cell carcinoma	I	February 2019

molecule chemicals as radiosensitizers initiated in the past five years under clinical trials are summarized in Table 3.

Macromolecules

Proteins and Peptides

Proteins and peptides, such as antibodies and short peptides, have high affinity with antigens and receptors overexpressed on the surface of tumor cells, making them usable as radiosensitizers.[129] For instance, HER3-ADC, a maytansine-based antibody-drug conjugate targeting HER3, which induces cell arrest in the G_2/M phase to inhibit DNA damage repair and thereby improves radiosensitivity of HER3-positive pancreatic cancer cells.[130] SYM004, a epidermal growth factor receptor targeting antibody, can inhibit DNA double strand breaks repair and induces apoptosis via downregulating MAPK signaling, and thereby improves radiosensitivity in tumor cells.[120] Cetuximab and nimotuzumab, binding the epidermal growth factor receptor (EGFR), can increase radiation-induced apoptosis and DNA damage, and thereby improve the radiosensitivity of human epidermal-like A431 cells.[131] The hepatocyte growth factor (HGF)/Met signaling pathway which mediates DNA double-strand break repair is upregulated in the majority of cancers. AMG102, a monoclonal antibody against HGF, can inhibit DNA damage repair and increase radiosensitivity of glioblastoma multiforme.[132] In addition, proteins and peptides in serum, such as C-reactive peptide,[133] HSP[134] and paraoxonase-2[135] contribute to radioresistance and can be used as radiotherapy targets. ECI301, a mutant derivative of macrophage inhibitory protein-1a, can be assisted by HSP-70 and HMGB1, thereby enhancing the effect of radiotherapy.[134] Other proteins, like DNAzyme (DZ1)[136] and NKTR-214,[137] can also improve the effect of radiotherapy.

miRNAs

MicroRNAs (miRNAs), which encode by endogenous genes are noncoding single-stranded RNA molecules containing about 22 nucleotides. Studies have shown that some specific miRNAs can be used to improve radiotherapy efficacy[138,139] and some miRNAs can be used as radiotherapy sensitization targets.[140] For example, miR-621 targets SETDB1 in hepatocellular carcinoma can be used as a tumor radiosensitizer directly.[141] miR-205 targets zinc finger E-box binding homeobox 1 (*ZEB1*) and the ubiquitin-conjugating enzyme Ubc13 to enhance the radiosensitivity of breast cancer cells.[142] miR-144-5p targets ATF2 to enhance radiosensitivity of NSCLC.[143] miR-146a-5p enhances radiosensitivity in hepatocellular carcinoma through activation of DNA repair pathway.[144] miR-150 modulates AKT pathway in NK/T cell lymphoma to enhance radiosensitivity.[145] miR-99a targets mTOR pathway to enhance the radiosensitivity of NSCLC.[146] miR-139-5p modulates radiotherapy resistance in breast cancer by repressing multiple gene networks of DNA repair and ROS defense.[147] Transcriptional activation of miR-320a induces cancer cell apoptosis under ionizing radiation conditions.[148] However, inhibition of miR-21-5p promotes the radiation sensitivity of NSCLC.[149] Inhibition of miR-630 enhances radiotherapy resistance in human glioma by directly targeting *CDC14A*.[150] Furthermore, a clinical study included 55 atypical meningioma patients found in seven upregulated miRNAs (miR-4286, miR-4695-5p, miR-6732-5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p) and seven downregulated miRNAs (miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129,

miR-6891-5p) in patients. Those miRNAs may induce radioresistant and radiosensitive, respectively.

siRNAs

siRNA, known as short interfering RNA or silencing RNA, is a class of double-stranded RNA, noncoding RNA molecules, typically 20–27 base pairs in length, similar to miRNA, and operating within the RNA interference (RNAi) pathway.[151] HuR is a protein related to radiotherapy resistance, knockdown of HuR by siRNA resulting DNA damage and enhanced radiosensitivity.[152] *S100A4*, a member of the S100 family of transcription factors, modulates various activities of malignant tumor cells through different mechanisms. A short siRNA against *S100A4* enhances the radiosensitivity of human A549 cells.[153] NBS1 plays an important role in the radiation-induced DNA double-strand breaks reparation, siRNA targets NBS1 can increase radiation sensitivity of cancer cells.[154] Survivin, a member of the inhibitor of apoptosis (IAP) protein family, is overexpressed in most cancers resulting in aggressive behavior of tumor and therapy resistance. Downregulation of survivin by siRNA can enhance radiosensitivity in head and neck squamous cell carcinoma.[155] Therefore, numerous siRNAs can be used as radiosensitizers by silencing genes related to radioresistance.

Oligonucleotides

Similar to siRNAs, oligonucleotides also play important roles in gene expression regulation. Since they are easy to design and synthesize, antisense oligonucleotides have great potential to develop as radiosensitizers.[11] Telomerase expresses in many kinds of tumors (>85%), while the expression of telomerase is restricted in normal tissues. A study indicated that expression of telomerase could be inhibited by radiolabeled oligonucleotides, which targeted the RNA subunit of telomerase, thereby inducing DNA damage in telomerase-positive tumor cells.[156] In addition, the phosphorothioate-modified antisense oligonucleotides (PS-ASODN) against human telomerase reverse transcriptase were reported to promote radiotherapy effect in liver cancer.[157] Furthermore, Park et al reported that inhibition of cyclic AMP response element-directed transcription using decoy oligonucleotides enhanced tumor-specific radiosensitivity.[158] Yu et al demonstrated that antisense oligonucleotides targeted human telomerase RNA (hTR ASODN) could improve the radiosensitivity of nasopharyngeal carcinoma cells.[159]

The radiosensitization mechanism of macromolecules was summarized in Figure 3.

Nanomaterials

Noble Metal nanomaterials

The X-ray absorption coefficient (μ) represents the relationship between the X-ray absorption phenomenon (E) and atomic number (Z), $\mu=\rho Z4/(AE3)$, where ρ is the density and A is the atomic mass of the element.[160] Therefore, the change of atomic number (Z) causes a significant change of X-ray absorption coefficient (μ). Noble metal nanomaterials, such as gold (Au, Z=79), silver (Ag, Z=47) and platinum (Pt, Z=78) can effectively absorb X-ray energy and interact with radiation in tumor cells, and then emit photoelectrons, auger electrons, compton electrons and other secondary electrons. These secondary electrons not only interact with DNA directly, but also react with water to increase the production of ROS and further increase the sensitivity of tumor cells to radiation. This process is a physical sensitization mechanism.[161] Furthermore, functionalized noble metal nanomaterials promote the generation of ROS, transfer the cell cycle into a radiosensitive state, and inhibit p53 signaling pathway to induce cell autophagy and lysozyme body function disorder, thereby increasing radiotherapy sensitivity. This process is a biochemical sensitization mechanism.[162,163]

Gold nanoparticles with good chemical stability, easy preparation, controllable size and shape, easy surface functionalization, high biocompatibility, and low toxicity have proven satisfactory radiosensitizing effects in various tumors.[164–167] Silver nanoparticles and platinum nanoparticles are also commonly used in biomedicine.[168,169] Research found that silver nanoparticles combined with radiotherapy could enhance the radiosensitivity of human glioma cells in vitro and extended the survival time of glioma mice.[170,171] Liu et al demonstrated that silver nanoparticles could induce apoptosis of cancer cells through G_2 /M phase arrest after radiation, and they suggested that silver nanoparticles could be used as a nanoradiosensitizer for hypoxic glioma radiotherapy.[172] Recently, Fathy reported that thymoquinone-capping silver nanoparticles represented a promising engineered nanoformulation for enhancing cancer radiosensitivity.[173] Li et al demonstrated that platinum nanoparticles could enhance radiosensitivity through increasing DNA damage, ROS stress, and cell cycle arrest.[163] They also proved that platinum nanoparticles could convert endogenic H_2O_2 to O_2 in cancer cells,

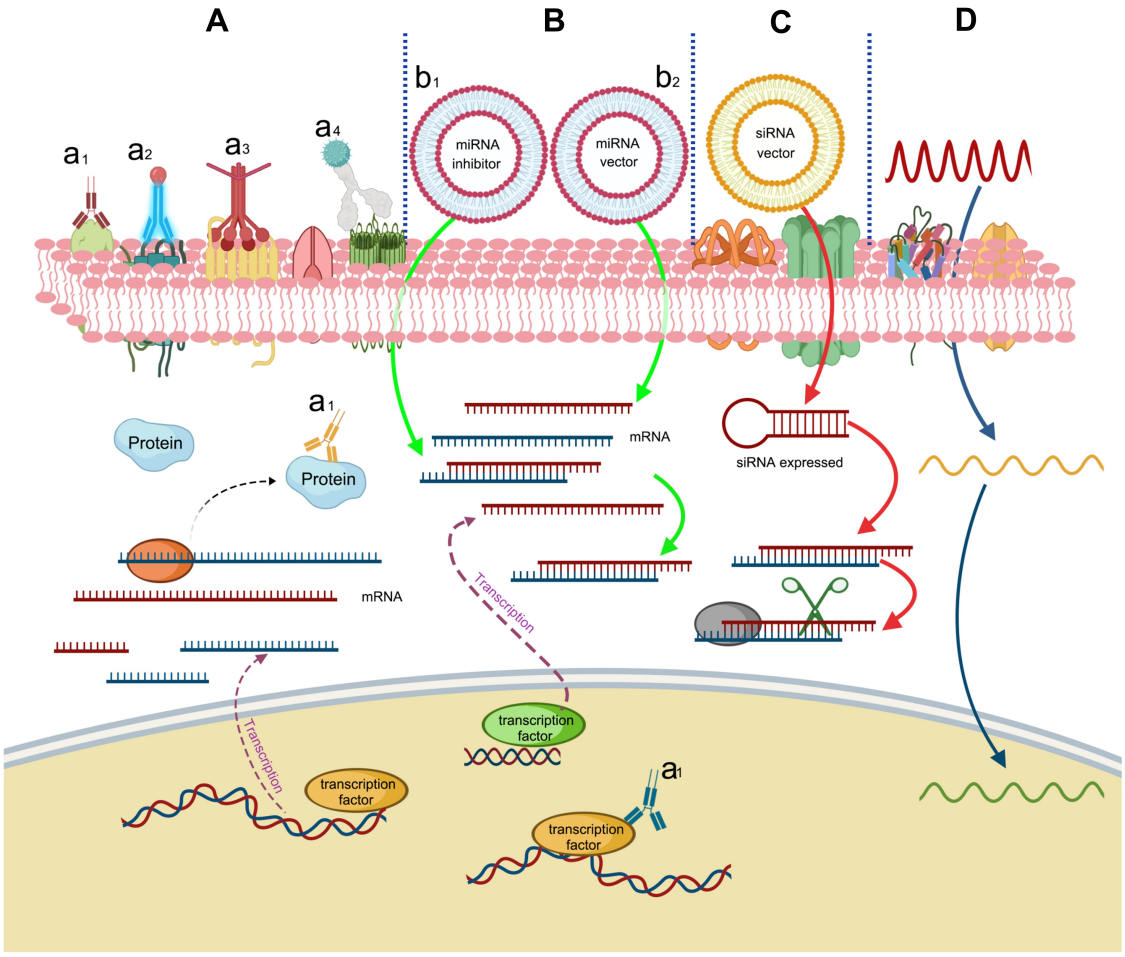

Figure 3 Radiosensitization mechanism of macromolecules. (**A**) Proteins and peptides. (a1) Direct interaction of key proteins. (a2) Loading of radioactive seeds. (a3) Radiosensitizers delivery. (a4) Conjugation with nanomaterials. (**B**) miRNAs can then bind with mRNAs to implement radiosensitization. (b1) Downregulation by inhibitors. (b2) Upregulation. (**C**) siRNAs can improve radiosensitivity by binding and degrading complementary mRNAs. (**D**) Oligonucleotides improve the radiosensitivity by complementary binding with DNAs.

thus significantly improving radiosensitivity without apparent toxicity to animals in vivo.[163]

Heavy Metal Nanomaterials

Similar to noble metal nanomaterials, gadolinium (Gd, Z=64), hafnium (Hf, Z=72), tantalum (Ta, Z=73), tungsten (W, Z=74), and bismuth (Bi, Z=83) are also metal elements with large atomic coefficients and have a great X-ray attenuation capability.[174–176] Based on this, numerous studies have focused on these heavy metal nanomaterials to investigate their radiotherapy sensitization. However, they usually cause damage to healthy tissues with direct contact.[177] Therefore, their stable forms such as oxides, sulfides, and selenides are explored as the radiosensitizers.[178–180]

Gadolinium-based nanoparticles are usually known as magnetic resonance imaging (MRI) contrast agents. It should be noted that researchers discovered a family of gadolinium-based nanoparticles called AGuIX for combined MRI and radiosensitization.[181] Results showed that AGuIX could interact with X-rays and γ-rays at a certain concentration. After internalization through the enhanced permeability and retention (EPR) effect, AGuIX could be resident in the tumor for a long time before being cleared by the kidneys.[182] Preclinical animal experiments proved that AGuIX held obvious radiosensitization effects in several tumor models without obvious toxicity.[183] A Phase I clinical trial (NCT03308604) to evaluate the optimal dose of AGuIX combined with chemoradiation in patients with locally advanced cervical cancer; a Phase II clinical trial (NCT03818386) using AGuIX gadolinium-chelated polysiloxane based nanoparticles and whole brain radiotherapy in patients with multiple brain metastases; and a single-arm phase II trial (NCT04094077)

aiming to evaluate the efficacy of AGuIX during fractionated stereotactic radiotherapy of brain metastasis are being evaluated.

Hafnium, in the same family as titanium and zirconium, is chemical inertness. The oxidation state of hafnium, hafnium dioxide (HfO_2), was usually used in radioactive protective coatings, biosensors, and X-ray contrast agents.[184,185] Jayaraman et al demonstrated that HfO_2 nanoparticles had excellent biocompatibility.[185] Researchers from France discovered that HfO_2 can be used as a radiosensitizer with low cytotoxicity.[186] A Phase I trial (NCT03589339) combining hafnium oxide nanoparticles (NBTXR3) with anti-PD-1 therapy in microsatellite instability-high solid malignant tumour and a Phase I–II clinical trial (NCT02805894) of NBTXR3 in prostate adenocarcinoma are under evaluation.

Tantalum is a nontoxic, biologically inert element with good biocompatibility.[187] Studies found that TaOx and Ta_2O_5 could be used as CT imaging contrast agents.[188–190] Brown et al found Ta_2O_5 nanoparticles showed a radiasentizition effect on radioresistant glioma cells.[191] Song et al showed hollow shell tantalum oxide (HTaOx) had a large X-ray attenuation capability and could enhance radiation therapy effects by Compton scattering and Auger effect.[192] In addition, TaOx can be used as functional group carrier to load drugs, thereby improving tumor hypoxic environment. For example, HTaOx loaded with catalase, which reacted with H_2O_2 in the tumor microenvironment, then improved the oxygen content and overcame the radiotherapy tolerance of hypoxic tumor cells, thereby improving the radiotherapy effect.[193]

Tungsten and bismuth also have significative applications in medicine.[194,195] Hossain et al concluded that bismuth nanoparticles had stronger radiosensitizing effect than gold and platinum nanoparticles at the same physical and chemical conditions.[196] Yu et al found that the ultrasmall semi-metallic Bi nanoparticles with LyP-1 peptide modified at 3.6 nm showed obvious radiosensitization effect.[197] Recently, a large number of studies shown that some nanomaterials of tungsten and bismuth had excellent photothermal absorption conversion performance and strong X-ray absorption capacity, therefore they can be used for tumor radiosensitization as well as synergistic therapy of hyperthermia and radiotherapy.[198–201]

In addition, research about several high Z metal elements combined together to further improve the radiosensitization effect were also explored. For example, SiBiGdNP chelated Bi and Gd in organosilane to improve the sensitivity of radiotherapy.[202] $GdW_{10}O_{36}$ contained both W and Gd to expect they had better radiotherapy sensitization effect.[203]

Ferrite Nanomaterials

Ferrite-based nanomaterials can catalyze the generation of free radicals through Fenton's reaction (1) and Haber–Weiss reaction (2) to enhance the effect of radiosensitization.[204]

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH + OH^-$$
$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH + H^+ \quad (1)$$
$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH \quad (2)$$

Studies proved that Fe_3O_4 had a dose-enhancing effect for radiotherapy, especially superparamagnetic Fe_3O_4 nanoparticles (SPIONS) possessing MRI imaging property had good application prospects in image-guided tumor radiotherapy.[205]

The composition of the spinel structure ferrite is usually stated as MFe_2O_4, where M=Fe, Zn, Co, Mn, Ni.[206] Among them, $ZnFe_2O_4$, $MnFe_2O_4$, $CoFe_2O_4$ nanoparticles were widely investigated.[207] For example, Meidanchi et al confirmed that $ZnFe_2O_4$ nanoparticles interacted with γ-rays to produce photoelectric effect resulting in a higher release level of electron in radioresistant cells.[208] Studies also indicated that $ZnFe_2O_4$ nanoparticles could be used as radiosensitizers.[208,209] Salunkhe et al demonstrated that $MnFe_2O_4$ and $CoFe_2O_4$ nanoparticles could improve the therapeutic efficacy of cancer through multimodal image-guided combination therapy.[210]

Semiconductor Nanomaterials

Semiconductor quantum dots have unique properties, such as quantum dimension effect, surface effect, and quantum confinement effect, making them great candidates in biomedicine applications.[211] Until now, numerous studies focused on using semiconductor quantum dots as photosensitizers and radiosensitizers for tumor treatment have been reported.[212–214] When the electronic energy levels are in the range of 1–5 eV, the semiconductor nanomaterials can absorb the photon energy and perform as photosensitizers, showing photocatalytic properties. When the electronic energy levels are at keV and MeV (X-rays and γ-rays), semiconductor nanomaterials can enhance absorption of high-energy photons acting as radiosensitizers and causing damage to cancer cells.[212] Nakayama et al synthesized a semiconductor nanomaterial PAA-TiOx to generate

hydroxyl radicals under the irradiation of X-rays, which increased DNA damage and inhibited tumor growth significantly.[215] Morita et al clarified the radiosensitization mechanism of PAA-TiOx nanoparticles by releasing H_2O_2 to relieve hypoxia in tumor cells.[216] TiO_2 nanotubes have been reported to enhance the radiosensitization effect through regulating G_2/M cycle arrest and reducing DNA repair of tumor cells.[177] The mechanism of radiosensitization of metal-based nanomaterials is shown in Figure 4.

Nonmetallic Nanomaterials

Many nonmetallic nanomaterials also possess the function of radiosensitization.[217] For example, C_{60}, fullerene, has potent anticancer activities, however, the potential toxicity to normal tissues limits its further use. Therefore, nanocrystals of C_{60} (Nano-C_{60}) with negligible toxicity to normal cells have been developed as a radiosensitizer.[218] In addition, nanodiamonds and carbon nanotubes can reduce radioresistance of tumor cells by promoting ROS generation, destroying DNA double-strands, and regulating the cell cycle.[219,220] Selenium (Se) nanoparticles not only work as chemotherapeutic drugs, but also improve the antitumor effect of X-rays by activating ROS to induce DNA damage in cancer cells.[221]

Nanostructured Chemicals and Drug Delivery Systems

Nano-based delivery systems are efficient approaches for drug targeted transportation, which can deliver radiosensitizers, such as chemicals, oxygen carriers, siRNAs and catalases to the tumor sites and have attracted wide interest of researchers recently.[222] More importantly, nanobased delivery systems can precisely deliver radioactive particles like[223] Ac (releasing a-particles), ^{131}I, and ^{125}I to tumor sites.[223] With the development of nanotechnology, nanobased delivery systems have great potential for radiosensitizer delivery.

However, there is still a challenge to achieve clinical translation of nanobased delivery systems, factors like physicochemical properties of the nanoformulations, radiation sources, and indications block their clinical translation.[223] In addition, long circulation lifetime of nanodelivery systems may increase the risk of long-term toxicity.[224] Another critical factor is stability in body fluid of nanodelivery systems. Because the aggregation of nanoparticles in body fluid will influence the pharmacokinetics and the cellular response and generate serious side effects such as blocking the blood vessels.[222] Therefore, attention should be paid to these factors when designing the nanodelivery systems. Size is also an

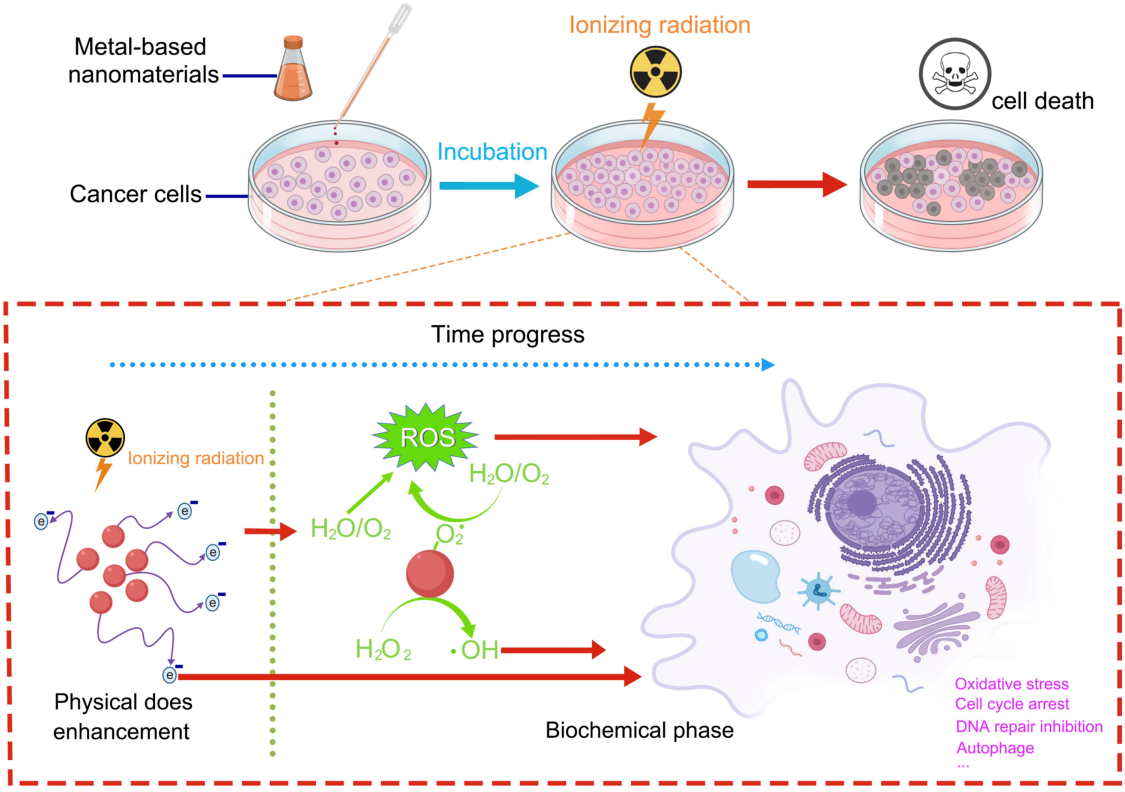

Figure 4 Radiosensitization mechanism of metal-based nanomaterials. The process contains physical and biochemical sensitization mechanism.

important factor, small size and high Z nanoparticles often hold better radiosensitizing effect than larger-size ones.[223] In particular, the small size nanoparticles with positive charge can bind to negative charged DNA and can be eliminated by renal clearance conveniently. In addition, functional modification of nanostructures using biocompatible materials can improve their stability and targeting.[225]

Conclusions and Prospects

Radiosensitizers have been developed for decades from the earliest "free radical damage and fixation" strategies to gene regulation, from chemicals to biological macromolecules and nanomaterials. Although each radiosensitizer has dialectical advantages and limitations, the mechanisms of sensitization are similar. The main mechanisms include: (I) inhibiting radiation-induced repair of DNA damage, increasing the degree of DNA damage; (II) disturbing the cell cycle and organelle function to improve cytotoxicity; and (III) inhibiting the expression of radiation resistance genes or promoting the expression of radiation sensitive genes.

Although small molecules, macromolecules, and nanomaterial radiosensitizers are being developed, and some nanoradiosensitizers have been used for clinical research (Table 4), the result still cannot meet clinical translation needs. Therefore, there is an urgent need to find new targets of radiotherapy and new mechanisms of sensitization, and after that to develop more effective radiosensitizing drugs. First of all, multitarget radiosensitizers often have more obvious efficacy than single target, researchers can focus on screening multitarget radiosensitizers or drug combinations. New approaches, in particular, nanotechnology based as radiosensitizers have shown promise. Nanomaterials with low cytotoxicity, good biocompatibility, and ease of functionalization need to be explored. In addition, other technologies, such as molecular structure analysis, molecular cloning technology, and bioinformatics analysis can accelerate the development of new radiosensitizers. Moreover, development of new drug delivery systems can also improve radiosensitization efficacy. Finally, the application of artificial intelligence and machine learning in new drug discovery and clinical trials, may guide development of new radiosensitizers and optimization of existing radiosensitizers.

Table 4 Clinical Translation of Some Nanoradiosensitizers

Name	Conditions	Phase	Identifier
AGuIX	Cervical cancer	I	NCT03308604
	Brain metastases	II	NCT03818386
	Brain metastases	II	NCT04094077
NBTXR3	Microsatellite instability-high solid malignant tumor	I	NCT03589339
	Prostate adenocarcinoma	I/II	NCT02805894

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Disclosure

The authors report no conflicts of interest in this work.

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