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Review Article

Targeting the organelle for radiosensitization in cancer radiotherapy

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ABSTRACT

Radiotherapy is a well-established cytotoxic therapy for local solid cancers, utilizing high-energy ionizing radiation to destroy cancer cells. However, this method has several limitations, including low radiation energy deposition, severe damage to surrounding normal cells, and high tumor resistance to radiation. Among various radiotherapy methods, boron neutron capture therapy (BNCT) has emerged as a principal approach to improve the therapeutic ratio of malignancies and reduce lethality to surrounding normal tissue, but it remains deficient in terms of insufficient boron accumulation as well as short retention time, which limits the curative effect. Recently, a series of radiosensitizers that can selectively accumulate in specific organelles of cancer cells have been developed to precisely target radiotherapy, thereby reducing side effects of normal tissue damage, overcoming radioresistance, and improving radiosensitivity. In this review, we mainly focus on the field of nanomedicine-based cancer radiotherapy and discuss the organelle-targeted radiosensitizers, specifically including nucleus, mitochondria, endoplasmic reticulum and lysosomes. Furthermore, the organelle-targeted boron carriers used in BNCT are particularly presented. Through demonstrating recent developments in organelle-targeted radiosensitization, we hope to provide insight into the design of organelle-targeted radiosensitizers for clinical cancer treatment.

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1. Introduction

Radiotherapy (RT) is the most effective cytotoxic therapy for localized solid carcinomas and is widely used in current clinical cancer treatments. Statistics indicate that approximately 60% of cancer patients in the United States receive radical RT during treatment [1,2]. The therapeutic principle of RT is that high-energy ionizing radiation (such as X-rays, γ-rays, and other photons, high-energy particles) interacts directly with cellular DNA to cause DNA damage [3]. Additionally, it founds that particle RT or others can alter the tumor microenvironment (TME) [4], indirectly generating pH value or reactive oxygen species (ROS) [5,6]. So that RT can damage DNA and other cellular components, and then induce apoptosis and necrosis [7]. Compared with other traditional treatment methods, RT has the preferable characteristics of non-invasiveness, deep tissue penetration and highly controllable dose [8,9]. However, toxicity to adjacent normal tissues [10], the hypoxia of TME making cancer cells resistant to radiation and leading to tumor clearance failure [11,12], and anti-oxidation of cancer cells that resist free radicals [13] are all issues associated with RT. For these reasons, simply irradiating tumor tissue or cells is not enough to achieve the desired therapeutic effect. To improve accuracy and efficacy, researchers have developed numerous novel radiotherapies to reach effective RT while also reducing toxic side effects.

Novel RT approaches, such as boron neutron capture therapy (BNCT) [14], have been proven to achieve the above goals. BNCT is characterized as a binary and tumor-selective particle RT, involving the interaction of two agents: boron [15,16] and thermal neutrons [17]. Boron carriers accumulate preferentially in tumor cells [18], followed by irradiation of the region or tumor with a thermal or epithermal neutron beam [19]. The neutrons interact with 10-boron atoms (preferentially accumulated in the cancer cells), producing high-energy α-particles and recoiling 7-Li nuclei, which deposit their energy along a path of one cell diameter, thereby selectively destroying cancer cells from the inside [20–22]. This process minimizes damage to surrounding tissues, thus reducing associated side effects. Up to now, two prominent boron compounds, boronophenylalanine (BPA) and mercaptoundecahydrododecaborate-^{10}B (BSH), have been extensively employed in BNCT clinical trials [23]. Furthermore, clinical studies investigating BNCT were and are being conducted globally, spanning countries such as Japan, the United States, European Consortium nations, Italy, Finland, the Netherlands, Sweden, and China, among others. These trials encompass a range of cancers, including glioblastoma, head and neck cancer, and melanoma, among others [24–28]. The active research and development of new boron compounds and the introduction of accelerators as neutron sources that could be installed in hospitals underscore BNCT's status as a novel and effective RT modality, holding promise for the future of cancer treatment.

Although many other innovative methods like RT combined with immunotherapy [29] made great progress in recent years, challenges like the unclear pathological mechanism for the occurrence of immune-related adverse effects [30] as well as inter-individual variability [31] remain. While different RT technologies like intensity-modulated RT, volumetric modulated arc therapy [32] and helical tomotherapy [33] enhance therapeutic effect, tumor heterogeneity and radioresistance hinder successful cancer treatment. Radiosensitizers, capable of precise radiation targeting and reducing normal tissue toxicity [34], offer potential solutions to improve RT efficacy.

In the past three decades, radiosensitization methods have mainly increased intracellular radiation energy deposition through high-atomic number (high-Z) metal element nanosensitizers [35], as well as more recently developed radioenhancing nanoparticles [36] that catalyze ROS generation [37], adjust TEM (for example, reducing intracellular GSH concentration [38,39], increasing oxygen level in tumor [11]), and modulate cell signaling pathways, etc. Among these and other strategies, radiosensitizers can enhance the radiation sensitivity of cells, improve the effectiveness of RT treatment, and reduce its side effects. Currently, numerous new radiosensitizers have been introduced to clinical research, and some of these nano-preparations have already entered the clinical trial stage [40]. This will be discussed in the review, which is hoped to provide scope for the design of radiosensitizers.

Nonetheless, radiosensitizers continue to face challenges such as low cellular uptake, inadequate accumulation in cells, and radioresistance of tumors [41]. Literature suggests that targeted delivery to subcellular organelles can provide an effective solution to these problems. It is one of the most promising strategies for the complete eradication of tumors, prevention of tumor recurrence, invasion, and metastasis [42,43]. Subcellular organelles such as the nucleus (Fig. 1A), mitochondria (Fig. 1B), endoplasmic reticulum (ER, Fig. 1C), and lysosomes (Fig. 1D) play a critical role in maintaining the balance between cell proliferation and death while regulating cellular metabolic functions [44,45]. Since these organelles are essential for cell energy supply and programmed death (Fig. 1), therapies targeting specific organelles have become a hot topic in research and development, as they offer a highly sensitive and precise approach to attack specific organelles [46]. Selective delivery of sensitizers into organelles can improve their transport and utilization efficiency while maintaining effective concentrations for long-term retention, maximizing therapeutic efficacy and minimizing side effects. At present, there are still few reviews of organelle-targeted RT research. In this article, we mainly focus on the field of nanomedicines-based cancer RT and discuss the organelle-targeted radiosensitizers, specifically including nucleus, mitochondria, ER and lysosomes. Furthermore, the organelle-targeted boron carriers used in BNCT are particularly presented, and some nano-radiosensitizers in clinic are introduced. Through demonstrating recent developments in organelle-targeted radiosensitization, we hope to provide insight into the design of organelle-targeted radiosensitizers for clinical cancer treatment.

2. Nano-radiosensitizers in clinic

Recently, nano-radiosensitization has become a research hotspot, usually through high atomic number (high Z)

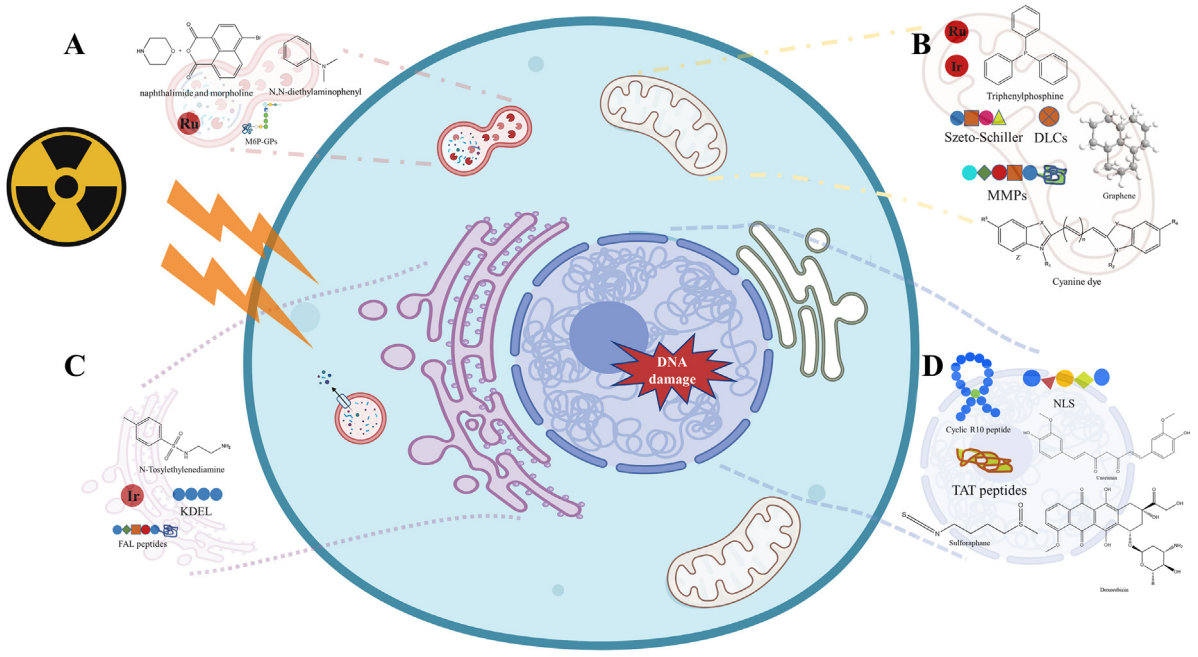

Fig. 1 – Organelle-targeted RT sensitization. Organelle-targeted agents are frequently employed as radiosensitizers to selectively target subcellular organelles. These agents can be categorized based on their specific target organelles: (A) Nucleus-targeted agents include peptides such as TAT and Cyclic R10, as well as molecules like Cur, DOX, and SFN; (B) Mitochondria-targeted agents include cationic ligands and localized peptides, among others; (C) ER-targeted agents include iridium complex, N-tosylethylenediamine, and peptides, among others; (D) Lysosome-targeted agents include naphthalimide and morpholine, as well as mannose-6-phosphate glycopolypeptides (M6P-GPs), among others.

nanomaterial-mediated radiation enhancement to increase radiation deposition in tumor cells [47], and also through catalytic ROS generation, improvement of the hypoxic microenvironment of solid tumors to reduce radioresistance [48] and other synergistic RT treatments. NBTXR3, the product of NANOBIOTIX (trade name: Hensify) has European market approval for the treatment of locally advanced soft-tissue sarcoma patients. NBTXR3 consists of functionalized hafnium dioxide (HfO_2) nanoparticles, administered by a one-time intratumoral injection and activated by RT [49]. In February 2020, the NBTXR3 was granted fast-track designation by the FDA for the treatment of patients with locally advanced head and neck squamous cell carcinoma (with or without cetuximab) who are not candidates for platinum-based chemotherapy [50]. In 2021, the Phase III global registry study of NBTXR3 began in Europe and Asia [49]. Furthermore, there are various trials for soft tissue sarcoma [51], inoperable recurrent non-small cell lung cancer, liver cancer, esophageal cancer [52], and so on, from Phase I to III at various countries and stages. At present, some other nano-radiosensitizers have also entered the clinical research stage (Table 1), which usher in an era of unprecedented radiosensitization research.

Moreover, several researchers have explored various approaches for enhancing the effectiveness of RT using nanomaterials. For instance, some researchers have employed gold nanoparticles as radiosensitizers [58]. Additionally, other investigators have investigated the potential of combining chemotherapy with RT using bismuth oxide or bismuth sulfide nanoparticles [40], and have also developed nano-prodrugs [59]. Several other emerging radiosensitization techniques are currently under investigation. The general strategy behind these approaches involves utilizing nanomaterials to target cells and leveraging indirect stimulus responsiveness to damage DNA or impact the TME. This, in turn, enhances the effects of RT on cancer cells as well as prevents metastasis [60], thereby facilitating low-dose, low-frequency, and highly efficient RT.

Recently, with the continuous development of research on subcellular organelles, a series of organelle-targeted radiosensitizers have emerged, which have become new research hotspots with more accurate and efficient targeting and better accumulation capabilities at target sites.

3. Organelle-targeted RT

Although the aforementioned nano-radiosensitizers have demonstrated some progress, their radiosensitization is generally achieved indirectly through stimulus responsiveness. Moreover, their effectiveness is still limited by the accumulation in tumor tissue and the poor effect of inducing TME, such as ROS. Therefore, there is an urgent need to further enhance their RT effect by precisely controlling the size and shape of nanoparticles or modifying their surface [40,58,61]. However, the preparation methods for these sensitizers are generally complicated, and their versatility is limited. The targeting of organelles is a promising strategy to improve efficacy, not only can the sensitizer be delivered

Table 1 – The nanoparticles in RT clinical trial.

Trial Title	Radiosensitizers	Disease	Trial Phase	Reference
NBTXR3, Radiation Therapy, and Pembrolizumab for the Treatment of Recurrent or Metastatic Head and Neck Squamous Cell Cancer	NBTXR3	Recurrent or Metastatic Head and Neck Squamous Cell Cancer	II/III	[50]
Nano-SMART: Nanoparticles With MR Guided SBRT in Centrally Located Lung Tumors and Pancreatic Cancer	AGuIX Gadolinium-based Nanoparticles	Oncology: Lung, Non-Small Cell; Pancreas	I/II	[53]
Radiotherapy of Multiple Brain Metastases Using AGuIX ® (NANORAD2)	AGuIX	Oncology: Metastatic Cancer; Unspecified Solid Tumor	II	[54]
NVX-108 Combined with Radiation and Temozolomide in Patients with Newly-diagnosed Glioblastoma Multiforme	NVX-108	Oncology: CNS, Glioblastoma	I/II	[55]
Radiotherapy With Iron Oxide Nanoparticles (SPION) on MR-Linac for Primary & Metastatic Hepatic Cancers	Iron Oxide Nanoparticles (SPION)	Hepatocellular; Liver Cirrhosis; Liver Neoplasms	I/II	[56]
New enzyme-targeting radiosensitizer (KORTUC II) treatment for locally advanced or recurrent breast cancer	KORTUC II	Oncology: Breast	II/III	[57]

directly into the organelle, but it can also improve the precise targeting and accumulation ability. Furthermore, it can also increase the effectiveness of RT by damaging the structure or functions of key organelles, such as the nucleus and mitochondria.

3.1. *Nucleus-targeted RT*

The nucleus is the regulatory center of cell inheritance and metabolism, serving as the main site for the storage, replication, and transcription of genetic information. The nucleus is composed of a nuclear double membrane embedded with multiple nuclear pore complexes, nucleoli, and chromosomes, making it a relatively independent structure. A significant amount of genetic material is stored, copied, and transcribed in it. As a result, it plays a vital role in regulating various cellular processes such as cell growth, apoptosis, reproduction, and differentiation [62,63]. Among these components, the nuclear pore complex plays a crucial role in the two-way transport of nucleoplasm, which was first proposed in 1950 [64], and the earliest research on nuclear-targeted photodynamic therapy (PDT) was carried out by Akhlynina in 1997 [65]. Since then, researchers have continued to explore the mechanism of nuclear material transport [66,67], and the signal transduction pathway of DNA damage response [68], which has promoted the research and development of nuclear-targeted therapy. Due to the significant influence of the nucleus on cellular function, nuclear-targeted radiosensitizers that act directly on the nucleus have the potential to induce cell death more effectively than those acting on the cytoplasm [69]. Therefore, these sensitizers represent a promising strategy for improving the effectiveness of RT.

3.1.1. *Nucleus-targeted photon RT*

3.1.1.1. High-Z materials radiosensitizers The radiobiological effects of ionizing radiation for tumor treatment depend on the excitation and ionization of atoms and molecules of the irradiated tissue, and the occurrence of these effects increases with the atomic number (Z) of the target [70]. High-Z materials usually refer to the range from titanium to bismuth with $Z = 22$ to 83 [71], among them, gold ($Z = 79$), bismuth ($Z = 83$) and iridium ($Z = 77$) and rare earth elements like gadolinium ($Z = 64$) [72] are currently research hotspots.

Wang et al. [73] developed ultra-small iridium nanocrystals (Ir NCs, <5 nm) as nucleus-targeted radiosensitizers. These sensitizers, named Ir-RGD-TAT (Ir-R/T) NCs, were constructed by utilizing polyethylene glycol (PEG) and dual targeting peptides (RGD and TAT) to modify the radiation-depositing iridium nanocrystals. Specifically, cyclic arginine-glycine-aspartic acid (c(RGDyC)), referred to as RGD, was used to target the $\alpha v\beta 3$ integrin overexpressed by cancer cells [74] (Fig. 2A). Meanwhile, the HIV-1 transcriptional activator, known as TAT [75], was utilized as an effective cell penetration and nuclear-targeting agent to enable the targeting of the cancer cell nucleus. Results of the study revealed that Ir-R/T NCs could accumulate in the tumor cell nuclei and effectively induce DNA damage upon X-ray irradiation (Fig. 2B-2E).

Furthermore, the Özçelik group [76] designed 40 nm-sized gold nanoparticles and modified them with cancer cell-targeting peptide RGD and nuclear localization signal peptides to specifically target the nucleus. The evidence indicated that the nuclear-targeted gold nanoparticles synthesized in this experiment served as effective nuclear-localized radiosensitizers.

3.1.1.2. Metal oxides radiosensitizers In addition to high-Z metal materials that can be used as radiosensitizers, certain metal oxides also exhibit the same effects. When combined with radiation, these metal oxides can trigger cascade reactions within cancer cells, resulting in excessive oxidative stress that impairs the damage repair mechanisms of cancer cells [77], ultimately leading to cell death. For example, under the action of high-energy radiation, titanium

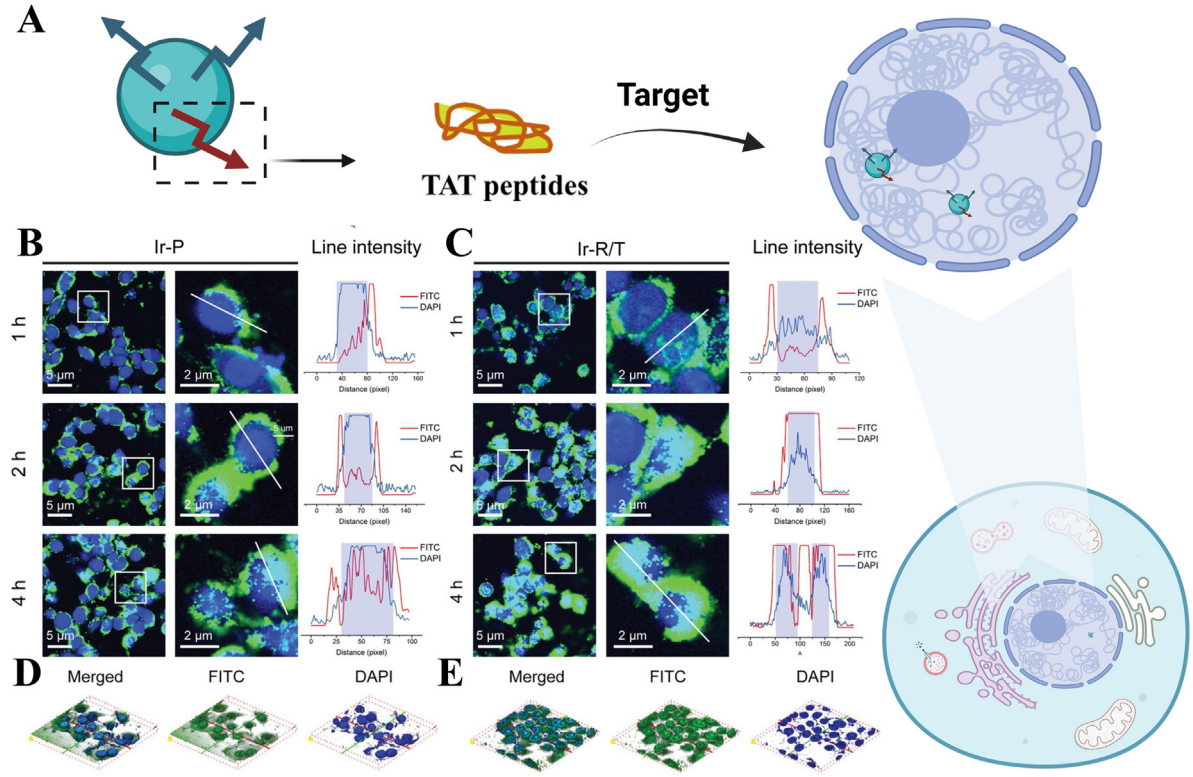

Fig. 2 – The nucleus-targeted High-Z materials radiosensitizers in photon RT. (A) Schematic illustration of nucleus-targeting process. (B and C) Confocal images and corresponding selected linear fluorescence intensity profiles of cancer cells stained with DAPI (nucleus) showed that FITC-labeled Ir-R/T NCs were distributed inside the nucleus. (D and E) 3D confocal laser scanning images of cancer cells after co-incubation with Ir-R/T NCs demonstrated that the dominant localization was inside the nucleus of the cancer cells. Redrawn with permission [73], John Wiley and Sons.

dioxide can absorb radiation energy and transfer the energy to the surrounding oxygen or water molecules, thereby generating active oxygen such as O_2^-, ·OH, etc. These active oxygens can kill tumor cells to treat cancer [78].

Wei et al. [79] developed nucleus-targeted mesoporous TiO_2 nanoparticles ($MTiO_2$NPs, $MTiO_2$(SN-38)-TAT-RGD) as a radiosensitizer to regulate the cell cycle to the G2/M phase. It has been shown that cells are more sensitive to radiation during the G2/M phase [3], which increases the rate of chromosomal aberrations and enhances the radiation effect and the lethality of cancer cells during RT. Among them, the RGD peptide binds to the overexpressed integrin on the cell membrane of cancer cells. The TAT peptide ensures that $MTiO_2$(SN-38)-TAT-RGD NPs enter the cancer cell nucleus, and generate ROS to destroy nuclear DNA under X-ray irradiation. The inclusion of SN-38 helps control the cell cycle of cancer cells in the G2/M phase, contributing to the therapeutic effect. Similarly, polyacrylic acid-modified titanium oxide nanoparticles (PAA-TiOxNPs) [80] have been proven effective radiosensitizers, generating hydroxyl radicals under X-ray irradiation to enhance the radiosensitivity after local injection into tumor tissues. Morita group [81] precisely increased the accumulation and retention time of intracellular O_2^- through PAA-TiOxNPs that adsorbed H_2O_2 [82], and enhanced its radiosensitivity while reducing the toxic side effects of H_2O_2 that diffused into tissues with blood flow.

3.1.1.3. Advanced drug delivery systems With the potential drawbacks of using high-Z materials like AuNPs, the clinical application of AuNPs as radiosensitizers is limited by the side reactions with biological biomolecules and intracellular structures [83], as well as the challenges of *in vivo* metabolism [84]. In addition to the above-mentioned traditional radiosensitizers, such as several metals or metal oxides, a new type of drug delivery system has recently emerged to achieve specific nuclear-targeted radiosensitization. At the same time, synergistic treatments such as RT, chemotherapy, and phototherapy have also produced impressive results.

Fan et al. [85] developed a strategy to enhance radiosensitivity through a synergistic effect of chemical and RT based on enhanced drug accumulation in the nucleus. They first constructed a 50 nm core/mesoporous nanosystem with a nucleus-targeting structure to transport the radiosensitizing drug mitomycin C directly to the nucleus. This enhanced the synergistic effect of chemo-, radio- and synchronous magnetic upconversion luminescence dual-mode imaging for effective cancer therapy, thereby avoiding multidrug resistance *in vitro* and *in vivo*. Additionally, micro/nanomotors [86] are constructed as positive and effective delivery vehicles to enhance deep penetration. Intranuclear radiosensitization technology and nuclear-targeted nano-diagnostics design can significantly contribute

to the development of cancer therapeutic diagnostics and improve the overall therapeutic effect.

It is noteworthy that graphene quantum dots (GQDs) have demonstrated specific interactions with DNA and inherent nucleus-targeting capabilities due to their small size and layered and aromatic ring structures [87]. In addition, GQDs possess DNA cleavage activity and exhibit good biocompatibility *in vivo* [88]. Notably, the GQD structure comprises abundant oxygen-containing groups, which can produce a synergistic effect with ionizing radiation, resulting in the excessive production of ROS in cells [89], and increasing the apoptosis of cancer cells, leading to a radiosensitizing effect. Hence, it can be seen that GQD has both natural nuclear targeting and radiosensitization, providing novel ideas and possibilities for nucleus-targeted radiosensitizers.

3.1.2. *Radionuclides-based radiosensitizers*

As a type of radiation therapy, radionuclide therapy uses high linear energy transfer radiation emitted by radioisotopes as the radiation source [90]. When injected or orally administered into patients, it is expected to target specific organs, tissues or cells, and then damage intracellular biomacromolecules and induce cell death [91].

A recent study by Qin group [92] developed Ce6-C_{18}-PEG/^{125}I-Cur nano-micelles, amphiphilic poly (maleic anhydride-alt-1-octadecene)-poly (ethylene glycol) (C_{18}-PMH-PEG) was grafted with the photosensitizer chlorin e6 (Ce6) to form nano-micelles (Ce6-C_{18}-PEG). Then Ce6-C_{18}-PEG was combined with the nucleus targeting substance curcumin (Cur), self-assembling to obtain Ce6-C_{18}-PEG/Cur nanoparticles, which showed the ability to block the cellular mass exchange and promoting program cell death [93]. Among them, Cur was labeled with ^{125}I, which, as radioactive iodine, could emit low-energy γ-rays and internal conversion electrons through orbital electron capture decay, inducing DNA double-strand break damage, and killing cells. The results showed that Ce6-C_{18}-PEG/^{125}I-Cur, which accumulated in the nucleus, had a better cancer cell-killing effect and high biological safety.

3.1.3. *Nucleus-targeted particle RT, especially BNCT*

BNCT is a promising cancer treatment method that involves the use of boron carriers to selectively target cancer cells with neutron irradiation. Efficient tumor RT can be achieved by facilitating high accumulation and long-term retention of boron in the tumor cells through nuclear targeting. For example, the boron nuclear-targeting developed by our group [94] was achieved with doxorubicin-carborane (DOX-CB), where the nucleotropic effect of DOX was utilized to accumulate boron in the nucleus of GL261 cells for BNCT. Results demonstrated that the boron concentration in the GL261 nucleus required for BNCT was three times higher than the boron concentration outside of the nucleus. Moreover, a novel nanoliposome delivery system DOX-CB@lipo-pDNA-iRGD had been developed, which combined DOX-CB with CD47 blocking immunotherapy to knock out CD47 through the CRISPR-Cas9 gene editing system [95], thereby enhancing the phagocytic ability of macrophages. This combination of BNCT and immunotherapy had shown promising results in killing glioma and inhibiting recurrence according to the mice glioma model *in situ*. Notably, this system demonstrated improved survival time, reduced recurrence rate, and enhanced curative effects compared to the clinical drug BSH [96]. Moreover, enhancing boron nucleotide incorporation in cancer cell DNA can significantly boost BNCT efficacy [97,98]. The results indicate the potential of combining BNCT with immunotherapy [16] and the significant benefits of nuclear-targeted BNCT in cancer treatments.

3.1.4. *Strategy of organelles-targeted RT*

The majority of the reported radiosensitizers targeted at the nucleus are developed by loading radiosensitizing agents onto a delivery vehicle with nuclear-targeting capability [99]. Similar strategies have been explored for targeting other organelles such as mitochondria, ER and lysosomes. This approach involves combining organelle-targeting ligands with radiosensitizing agents to achieve organelle-targeted RT. Further, cutting-edge drug delivery systems like self-assembled polypeptides [100], nanocarriers [101], and exosomes [102] are hopeful for novel organelle-targeted delivery systems in RT. Various organelle-targeting ligands and radiosensitizing agents that have been widely investigated and reported in the literature are summarized in Table 2.

At present, many organelle-targeted RT strategies are studied. Most of the substances with organelle-targeting functions in the above table are connected with radiosensitizers to form a radiosensitizer with organelle-targeting effects.

3.2. *Mitochondria-targeted RT*

Mitochondria are crucial organelles that generate most of the energy supply of cells, control metabolic pathways, and regulate cell death [131]. Since the "Warburg effect" was first proposed in 1956, research on mitochondria-mediated cell death signaling pathways has received great attention [132]. Being the primary source of endogenous ROS production and the direct receptor of oxidative damage, mitochondria are particularly vulnerable to ROS-induced damage [133]. In cancer cells, mitochondria are characterized by excessive ROS production [134], which contributes to the development of cancer cells by disrupting the genome, modifying gene expression, and participating in signaling pathways. Disrupting ROS homeostasis can lead to mitochondrial dysfunction [134,135], initiate the intrinsic apoptosis pathway, and eventually cause irreversible cell death, thus combating cancer [136,137]. Meanwhile, RT-induced tumor cell apoptosis is regulated by mitochondria, which are considered effective targets [138,139]. Hence, the delivery of radiosensitizers to cancer cell mitochondria holds great promise, and achieving high accumulation and long-term retention of radiosensitizers in mitochondria is an effective way of improving the efficacy of RT.

The design strategy of mitochondria-targeted radiosensitizers parallels that of nucleus-targeted counterparts, emphasizing enhanced delivery and administration of nano-systems loaded with radiosensitizers. In general, most of the substances that target mitochondria

Table 2 – The organelle-targeting ligands used in radiosensitization research.

Organelle	Types	Targeting ligands	Ref
Nucleus	Molecules	Curcumin (Cur)	[92]
		Doxorubicin (DOX)	[94]
		Sulforaphane (SFN)	[103]
	Peptides	TAT Peptides	[73]
		NLS (nuclear localization signal)	[66,104]
		Cyclic R10 Peptide (cR10)	[105]
Mitochondria	Cationic Ligands	Ru Complex	[106]
		Triphenylphosphine (TPP)	[107]
		Delocalized Lipophilic Cations (DLCs)	[108,109]
	Peptides	Szeto-Schiller (SS)	[110]
		Mitochondria-penetrating Peptides (MMPs)	[111]
		KALK	[112]
		RLA Peptides	[113]
	Molecules	Cyanine Dye; IR-780	[114]
		IR-83	[115]
		Ir (III) Complexes	[116]
	Others	Carbon Quantum Dot (CD)	[117]
		Mitochondria-targeted Graphene (mitoGRAPH)	[118]
Endoplasmic reticulum (ER)	Molecules	Iridium Ir (III) Complex	[119]
		N-Tosylethylenediamine	[120]
	Peptides	ER-targeting pardaxin (FAL) Peptides	[121]
		Lys-Asp-Glu-Leu (KDEL) Peptide	[122]
	Others	ER-Targeting DNA Nanodevice	[123]
Lysosomes	Molecules	Naphthalimide and Morpholine	[124,125]
		N, N-diethylaminophenyl	[126]
		Ruthenium (Ru) Complexes	[127,128]
	Peptides	Mannose-6-Phosphate Glycopolypeptides	[129]
	Others	Lysosome-targeting aptamer (CD63-aptamer)	[130]

possess a positive charge, facilitating their interaction with the negatively charged mitochondrial membrane potential [107] and achieving targeting.

3.2.1. *Mitochondria-targeted photon RT*

3.2.1.1. High-Z materials radiosensitizers High-Z materials like gold nanoparticles are also used in mitochondria-targeted RT, which can enhance X-ray absorption [140] as well as improve ROS generation [2]. Novel mitochondria-targeted and protein sulfenic acid (PSA) reactive gold nanoparticles (dAuNPs-TPP) [141] were reported by Zhao group. The mechanism was that the incorporation of cationic triphenylphosphine (TPP) could help dAuNP-TPP to accumulate preferentially in the mitochondria of cells. CHD (1,3-cyclohexanedione) could immobilize dAuNP-TPP within mitochondria by covalent cross-linking with PSAs [142], which were overexpressed in the mitochondria of cancer cells because of the oxidation of protein sulfur groups by ROS. Thus, the enrichment and retention of AuNPs in tumors were realized, and the results showed that dAuNP-TPP was 5.22 times higher than that of non-fixed AuNP-TPP (Fig. 3A and 3B). In addition, the covalent immobilization of dAuNP-TPP in cellular mitochondria could drastically reduce ATP in its cells, which in turn led to severe mitochondrial destruction, and then combined with high atomic number Au to achieve radiosensitization, leading to effective RT of breast tumors *in vivo*. Similarly, Fang et al. [143] synthesize peptide (CCYKFR) templated Au nanoclusters (AuNCs) as a mitochondria-targeting radiosensitizer, where CCYKFR could target mitochondria and induce autophagic degradation with the mediation of the Parkin protein. It demonstrated that CCYKFR-AuNCs irradiated by 4 Gy X-rays could lead to mitoROS burst and severe DNA damage, causing cancer cell death.

In addition to nanosystems, targeted reactions with radiosensitizers can yield new compounds or complexes for radiosensitization. For example, the lipophilic Gd^{III} complex prepared by the Morrison group [144] was basically non-cytotoxic at the expected therapeutic concentration, and would be more selectively accumulated in cancer cells than normal cells, while achieving efficient mitochondrial localization. Lipophilicity plays a major role in the cytotoxicity, uptake, and selectivity of this class of phosphine-containing complexes [145], which can lead to increased cytotoxicity and decreased tumor cell selectivity, but at the same time, increased lipophilicity has also been observed to enhance mitochondrial localization (Fig. 3D) [146]. The study highlights the intricated balance among these factors in designing phosphine Gd drugs for optimal use in binary therapies like GdNCT and GdPAT.

3.2.1.2. Metal oxide radiosensitizers There are also some metal oxide radiosensitizers used in mitochondria-targeted RT. Li et al. [147] developed novel TiO_2-Au-TPP nanoparticles as radiosensitizers based on titanium dioxide nanoparticles (TiO_2 NPs) and gold nanoparticles (Au NPs) modified on the TiO_2 NPs to build a satellite structure. TPP, a mitochondria-targeted group, was covalently attached to the surface of

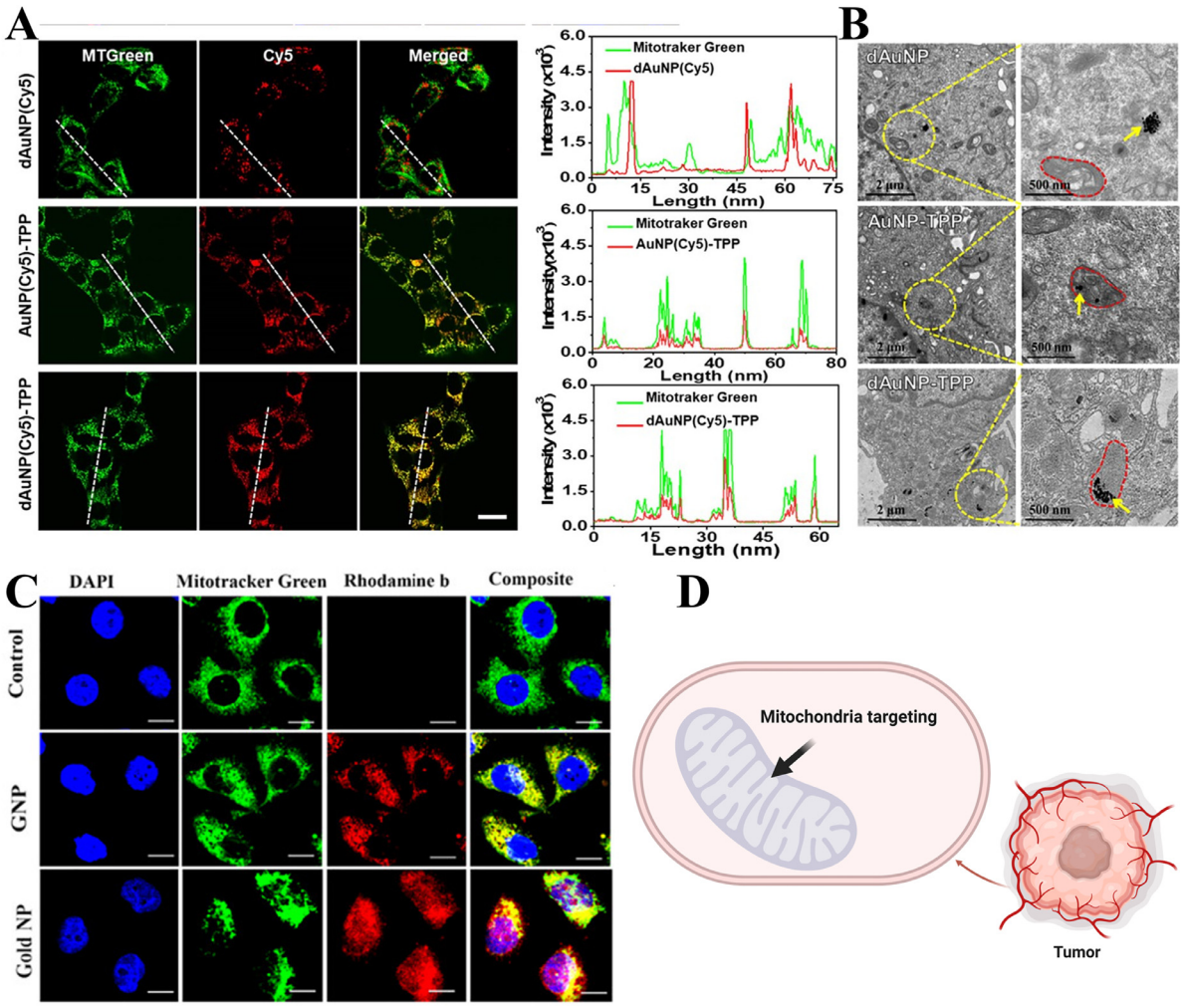

Fig. 3 – Mitochondria-targeted radiosensitizers in photon RT. (A) Confocal microscopy imaging of cancer cells receiving dAuNP(Cy5), AuNP(Cy5)-TPP, or dAuNP(Cy5)-TPP (red), along with MitoTracker Green staining, revealed that dAuNP-TPP nanoparticles accumulated in the mitochondria of living cells. (B) Cells treated with dAuNP-TPP showed a significantly higher concentration of Au nanoparticles in their mitochondria compared to the control cells treated with dAuNP. (C) Cellular uptake studies showing mitochondrial localization of GNP. (D) Capability to target mitochondria in cancer cells. Redrawn with permission [141,148], American Chemical Society, Elsevier.

TiO_2 to realize mitochondria-target. Under X-ray irradiation, TiO_2-Au-TPP could cause mitochondrial ROS burst, and its excessive accumulation in mitochondria led to its destruction, resulting in irreversible apoptosis. Experiments showed that the killing ability of TiO_2-Au-TPP cells was significantly higher than that of the non-targeted group, and it had a stronger radiosensitizing effect.

Additionally, the Sood group [148] reported an alpha-ketoglutarate decorated iron oxide-gold core-shell nanoparticles (GNP), which could improve the radiosensitization effect under Gamma irradiation (Fig. 3C). Alpha-ketoglutarate (AKG), as a mitochondrial TCA cycle intermediate, plays an essential role in mitochondrial metabolism [149]. The core of GNP was iron oxide nanoparticles, with a gold shell (Fe: Au = 1: 7) attached to the surface, and modified with AKG. The results showed that under the 5 Gyγ-rays, GNP existed in the mitochondria of cancer cells, ROS in the cells increased, and DNA fragmentation occurred, causing cell damage and achieving the purpose of radiosensitization.

3.2.1.3. *Advanced drug delivery systems* Advanced delivery systems such as organic polymer-based nanoparticles and oxygen carriers are increasingly utilized in mitochondrial-targeted radiosensitization research. Han et al. [150] developed a polyasparagine nanoparticle loaded with doxorubicin (DOX) and 5-aminolevulinic acid [151] (5-ALA). By grafting MPEG5000-NH_2 and DOX onto polysuccinimide, which was obtained by polymerization of L-aspartic acid [152], and resulting amphiphilic polymer PADO-MPEG self-assembled into nanoparticles. DOX, a commonly used chemotherapy drug [153], damages DNA by intercalation and complexation with topoisomerase II to enhance radiosensitization [154], while 5-ALA can target mitochondria [155] and enhance RT. This strategy constructs a mitochondria-targeted radiosensitizer with good

biocompatibility and high safety, avoiding the use of complex hybrid nanoparticles.

Mitochondria-anchored organic photosensitizers can also act as radiosensitizers. Yu group [156] designed a mitochondria-anchored radiosensitizer (DPA-SCP) that specifically generated singlet oxygen ($^1O_2$) under white light irradiation, enhancing the radiosensitivity of cancer cells to ionizing radiation with a synergistic effect. The design features an α-cyano group as the aggregation-induced emission luminogen skeleton, a diphenylamino group for red emission, and a pyridinium salt for mitochondrial targeting in DPA-SCP. Similarly, Jiang et al. [157] reported that $MoSe_2$-based nanosystems, including two-dimensional nanosheets and three-dimensional nanoflowers, effectively targeted and accumulated in cancer cell mitochondria, contributing to radiation sensitization through ROS generation due to MoSe2's effective photocatalytic properties [158].

3.2.2. *Mitochondria-targeted particle RT, especially BNCT*

For BNCT, the design idea is the same as that of ordinary radiosensitizers. A new substance can be obtained as a mitochondria-targeted radiosensitizer through the chemical reaction of boron drugs with organelle-targeted substances. Mitochondrial targeting is an effective way to improve the therapeutic effect of BNCT. For example, Nakase et al. [113] designed and synthesized boron compounds (dodecaboronic acid carboxyl (DB) derivatives $[B_{12}H_{11}S(CH_2)_2COOH]$ is dehydrated and condensed to the N-terminus of cell-penetrating peptides [159] to complete the conjugation), targeting organelles with cell-penetrating peptides. The RLA (amino acid sequence: $_D[RLARLAR]_2$) played an important role in mitochondrial target, which was a novel peptide with mitochondrial targeting ability and high plasma membrane (PM) permeability. They constructed DB-RLA as a new boron delivery system, achieving increased cellular uptake and control of intracellular location, thereby inducing complex anticancer bioactivity in BNCT. Furthermore, irradiation with neutrons produces ATP-reduced and apoptotic anticancer effects in BNCT assays *in vitro*. Moreover, Kashiwagi et al. demonstrated the efficacy of DPA-BSTPG, a ^{10}B compound targeting TSPO, in BNCT against the F98 rat glioma model [160]. TSPO, a five-transmembrane domain protein situated in the outer mitochondrial membrane, exhibits higher expression in gliomas with a higher WHO grading.

In addition, mitochondria-specific properties can also be used for targeting. For example, the Gianpiero group [161] designed boron-rich carborane compounds functionalized by delocalized lipophilic cations (DLC [108]), selectively targeting the mitochondria of tumor cells. Since the negative inner transmembrane potential of mitochondria (130-150 mV) is much greater than that of any other organelle, functionalization of the DLC moiety represents a means of conferring mitochondrial targeting specificity to carboranes. Treatment of tumor and cancer stem cell (CSC)-induced cell growth arrest with this DLC-functionalized carborane (DLC-carborane) is both highly cancer cell-selective and permanent. Additionally, C6 glial cells were treated with sodium mercaptoborate ($Na_2B_{12}H_{11}SH$, BSH) as the carrier of thermal neutron atomic target (^{10}B) of brain tumor BNCT [162], which showed an effect on mitochondria and preferential accumulation [163].

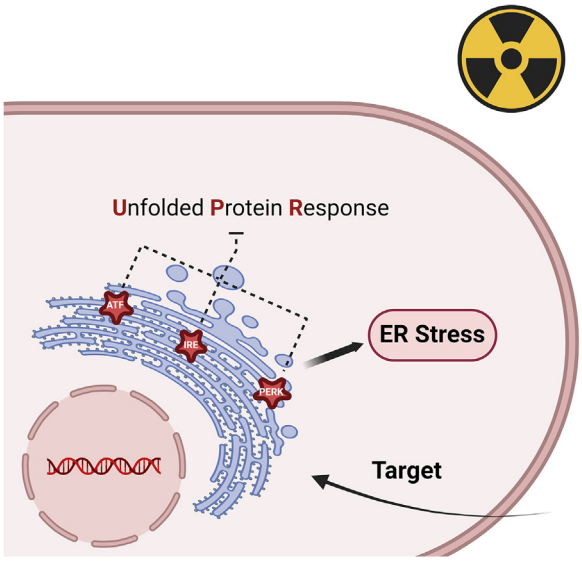

Fig. 4 – ER-targeted therapy: Extracellular stress and intracellular DNA damage have been shown to disturb proteostasis, leading to ER stress that is implicated in the regulation of gene expression and the pathogenesis of several tumor types. Targeting the ER has been promising to improve mechanisms of ER-induced cell apoptosis. Created using Biorender.com.

3.3. *ER-targeted RT*

The ER is an important site for intracellular protein synthesis, post-translational modification, processing and folding, and is also responsible for the biosynthesis of certain steroids and lipids, participates in various signaling pathways and alleviates cellular stress responses [164,165]. What's more, ER is sensitive to changes in cellular homeostasis [121,166]. Recent studies have shown that the ER stress-responsive apoptotic pathway, the unfolded protein response (UPR) under ER stress, is critical in apoptosis [167]. There is a protein quality monitorization system in the ER, which monitors whether the synthesized protein is folded correctly or forms the right complex formation [168]. Almost 30% of newly synthesized proteins are folded within the ER lumen with the assistance of a series of molecular chaperones [169]. The research has shown that UPR induction can cause significant radiosensitization of the radioresistant cells [170]. On the one hand, only correctly folded polypeptides can be released from the ER and transported to their destinations. On the other hand, unfolded or misfolded proteins trigger the UPR signaling pathway, and these erroneous substances are transported out of the ER and subsequently degraded by the proteasome [171]. Disruption of ER homeostasis can lead to severe ER stress if unfolded or misfolded proteins are not cleared in a timely manner [172]. ER stress can be triggered by a variety of factors, such as intracellular energy changes, viral infection, Ca^{2+} disturbances, radiation exposure, cellular protein synthesis

or synthesis of misfolded proteins outpace chaperones, and redox stress [167,173,174]. Among them, IRE1, PERK and ATF6 are recognized as ER stress sensors and UPR activation pathways [175], which can protect ER function or lead to ER-mediated apoptosis signaling pathway [176] (Fig. 4).

In addition, ER stress and UPR have also been confirmed to be closely related to ROS, which has certain toxicity but mediates physiological processes as messenger molecules [177]. Cytoplasm and different organelles, including ER and mitochondria, can produce ROS normally. However, the change of redox state in ER will lead to ER stress, and then ER stress can induce the production of ROS in the ER and mitochondria. Hereafter, the sustained oxidative stress and ER stress will initiate the apoptosis program [178]. Once the cells are in the state of ER stress and experience irreversible ER stress, the cells will up-regulate the expression of pro-apoptotic molecules, and finally trigger a cascade reaction of different pathways in the cell, leading to cell apoptosis [173,179]. With the in-depth study on the mechanism of ER stress, many proteasome inhibitors have been developed to induce apoptosis of tumor cells. For example, bortezomib was approved by the FDA for cancer treatments in 2003 [180]. With the continuous development of ER-targeted drugs, in recent years, radiosensitizers targeting the ER have also attracted attention, which can help kill tumor cells more accurately and efficiently.

However, there is still a lack of studies on agents that sensitize the ER to RT, mostly focusing on the sensitization by affecting subsequent signaling pathways such as ER stress and ROS [181], with few studies directly targeting the ER. In the following, we will discuss the possible mechanisms of ER-targeted radiosensitization, including UPR and specific signaling pathways. It is expected to provide a possibility for radiosensitization studies directly targeting the ER.

3.3.1. *ER-relevant radiosensitization*

With the increasing understanding of the structure and function of the ER, the study of ER-induced radiosensitization has received more and more attention. For instance, the activation of UPR, an important mechanism of ER, enhances the sensitivity of radioresistant cell lines [170] and improves the RT effect. Besides, some proteins within ER have also been proven to increase the radiosensitization of tumors. Among them, JMJD8 [182] is a member of the JmjC domain-only subgroup, which is involved in angiogenesis and cellular metabolism by interacting with pyruvate kinase M2. JMJD8 is mainly localized in the ER [183], and the downregulation of JMJD8 promotes tumor cell growth and enhances their resistance to ionizing radiation [184], which can be a potential target for tumor radiosensitization.

In addition to the structures and proteins within the ER mentioned above, substances with ER-targeting effects have also been shown to enhance radiosensitivity. Protein disulfide isomerase (PDI) has ER-targeting ability and redox activity [185], and high expression of PDI has been detected in many cancers. Wang et al. [186] revealed a novel mechanism wherein PDI contributes to radioresistance by reducing autophagy levels. Consequently, targeting PDI expression (inducing expression reduction) can enhance autophagy, thereby mitigating RT resistance. This introduces a novel concept for radiosensitization. Further, Bian discovered that Cisd2 (KKEV) was targeted to ER by the N-terminal sequence [187], and could alter the morphology of ER. Besides, complexes like triterpenoid-safirinium [188] were found accumulating in ER. Some ER targets are listed in Table 2, providing the probability for radiosensitizers to target ER. The strong hydrophobicity may be the key to ER localization ability [189]. Consequently, ER targeting is expected to become a new means of radiosensitization.

3.3.2. *ER-relevant radiosensitizers*

For ER-targeted radiosensitizers, the modulation of apoptosis is usually carried out through its mechanism of ER stress, which is achieved by inducing ER stress. For example, tunicamycin induced ER stress in the human esophageal cancer cell line EC109 [190], and the results showed that tunicamycin treatment enhanced ionizing radiation-induced cell death and decreased colony survival fraction. It is probably due to the degradation of the proteasome in question, further reducing DNA double-strand break repair, causing DNA damage and making tumor cells more sensitive to radiation. Similarly, β-apopicropodophyllin has also been shown to induce ER stress [191], triggering a cascade response that shows a significant radiosensitizing effect.

In addition, some researchers have found that certain specific organelles also spontaneously generate corresponding mechanisms to achieve radiosensitization after receiving a certain amount of radiation energy. For example, Drake et al. [170] found that rectal tumor cells caused a temporary attenuation of their ER protein synthesis after 2 Gy X-ray radiation, resulting in a reduction of folded proteins in the lumen of ER. This response may contribute to the reduction of G2/M-related radiation therapy resistance and DNA damage-responsive proteins after radiation, leading to the radiosensitizing effect, so that the activation of the UPR is seen to increase radiosensitivity to radiation-resistant cells *in vitro*.

Studies on ER-targeted radiosensitizers are still relatively few, but recently, there has been extensive interest in antitumor agents targeting the ER. For example, among the potential ER stress inducers, metal complexes with redox activity and modular structure have emerged as promising candidates [192]. In the last two decades, dozens of metal complexes have been reported to kill tumor cells via ER stress induction [193], many of which exhibit activity *in vitro* and have potent tumor suppressive effects *in vivo*. Meanwhile, ER-targeted photosensitizers in PDT have been continuously developed, such as iridium (III) complex [116,119,121], which have been proven to be efficient PDT agents. Therefore, it is foreseen that in the field of radiosensitization, targeting the ER will also show great potential.

3.3.3. *ER-targeted particle RT, especially BNCT*

Sato et al. [194] demonstrated that the ER-targeted proteins, lymphoid-restricted protein, undergo fragmentation after BNCT treatment. However, there is limited research on ER-targeted carriers in the field of BNCT. One study indicated that the boron carrier BODIPYs are primarily localized within the cell ER, but the functional significance of ER-targeting has yet to be proposed [195]. Additionally, porphyrin–polyamine

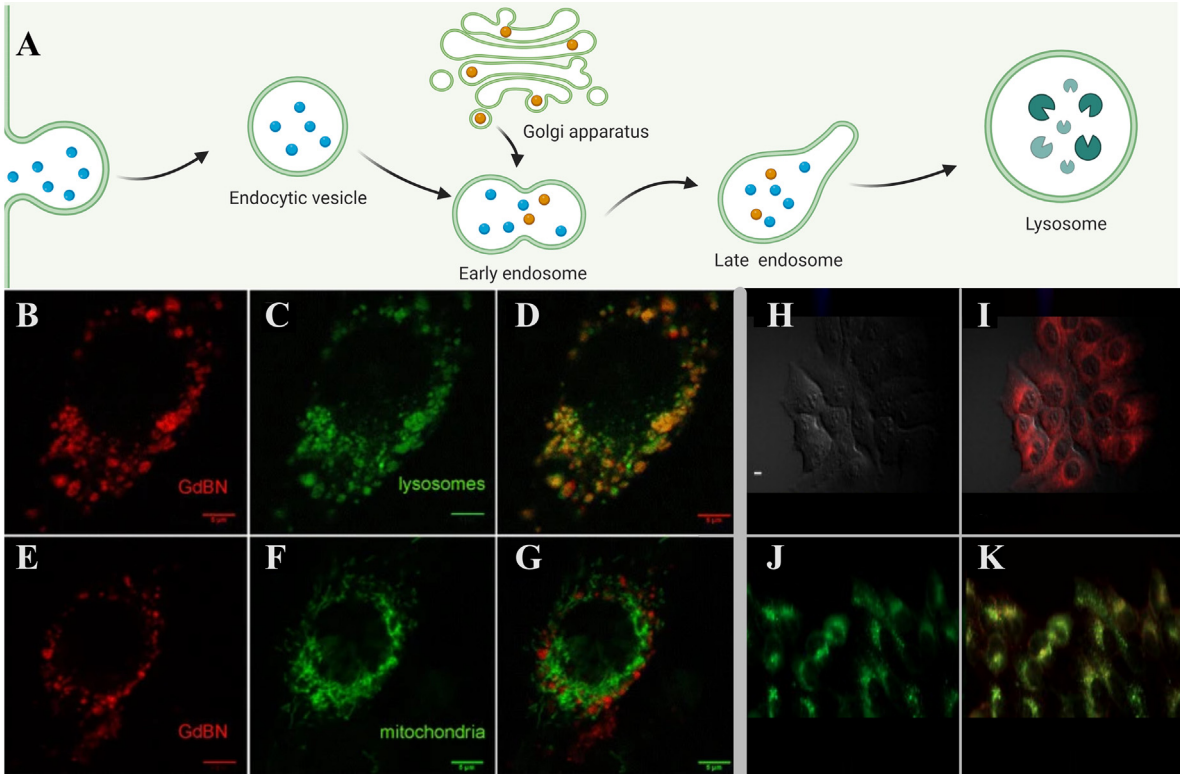

Fig. 5 – Lysosomes-targeted radiosensitizer. (A) The process of lysosome formation. (B and E) The fluorescence images of cancer cells loaded with GdBN–Cy5.5. (C) Cells incubated with Lysotracker-green respectively. (F) Cells incubated with Mitotracker-green. (D and G) The merged images of GdBN–Cy5.5 with Lysotracker-green and Mitotracker-green demonstrate the co-localization of GdBN–Cy5.5 with lysosomes. (H) Phase contrast of conjugate in HEp2 cells at 10 μM for 6 h. (I) Overlay of the conjugate and phase contrast. (J) LysoSensor Green fluorescence. (K) Overlays of organelle tracers with LysoSensor Green fluorescence. Scale bar: 10 μm. Redrawn with permission [196,219], Springer, Elsevier.

conjugates with para-carborane clusters exhibit a distinct preference for localizing in the ER, Golgi, and lysosomes of human glioma T98G cells [196].

3.4. *Lysosomes-targeted RT*

Lysosomes are membrane-bound vesicles surrounded by a single membrane and contain a variety of hydrolytic enzymes [197] that can break biological polymers like lipids, proteins, nucleic acids [198] and so on. It was first discovered by Christian de Duve in the 1950s [199], and now it is perceived as the crucial organelle in recycling and degrading cellular waste (Fig. 5A) [200]. Mature lysosomes have an acidic internal pH, which can activate the hydrolytic enzymes [201]. Meanwhile, there is a glycocalyx that can protect the internal lysosomal perimeter from the acidic environment in the lumen.

As a vital command and control organelle for cellular signaling and metabolism, lysosomes are associated with cell survival and death, including apoptosis, autophagy [202], and regulated necrosis [203]. It has been reported that lysosomes have various functions, such as immune response, signal transduction, cancer metastasis, PM repair and so on [204]. It is worth noticing that lysosomes increase the tumorigenic potential of cancer through autophagy, which is the current hotspot of cancer therapy. As the lysosomes are more sensitive [205], they can be used to inhibit autophagy and enhance cell death induction in diverse cancer cell lines [206]. Compared to normal cells, lysosomes in cancer cells exhibit a violent difference in number, volume and distribution [207], which have close contact with carcinogenesis. Lysosome-mediated cell death programs are termed lysosomal-dependent cell death [208], which is induced by the process of lysosomal membrane permeabilization [209] and exocytosis. In a word, the ruptured lysosomes can release hydrolases to digest the entire cell [210], leading to cell death, which could be an avenue for lysosomes as radiation targets for tumors.

3.4.1. *Lysosomes-relevant radiosensitization*

Lysosome-related factors are proven to promote radioresistance, for example, the mammalian target of rapamycin, which has a well-described role in cancer [211], can be activated by lysosomes. Furthermore, the transcription factor EB is regarded as a master gene for autophagy and the biogenesis of lysosomes [212]. Thus, lysosomes can play an important role in mediating radioresistance [213], and there are great research prospects on it.

Besides, syndecan 1 (SDC1) and transglutaminase 2 (TGM2), associated with glioblastoma multiforme radioresistance, can facilitate autophagosomal-lysosomal fusion [214]. It shows

the possibility for lysosome-positioned SDC1 and TGM2 to become new targets to improve radiosensitivity. The other report also showed that the autophagy of cancer stem cells (CSC) increased significantly after receiving irradiation, and the radioresistance of CSC may be associated with lysosome-mediated autophagy [215], and studies on lysosomes are expected to reduce the radioresistance of CSC with a radiosensitizing effect of RT. All in all, the lysosomes-related inhibitors of autophagy can enhance the radiosensitivity of cells.

3.4.2. *Lysosomes-targeted radiosensitizers*

Recent studies have shown the existence of small molecule compounds, nanoparticles, and other substances capable of sensitizing solid tumors to radiation therapy by targeting lysosomes. One example is trifluoperazine (TFP), a well-known antipsychotic that has been proven to block glioblastoma invasion and extend survival [216]. Zhang group [217] demonstrated that TFP blocked autophagy by inhibiting the acidification of lysosomes and then enhanced the radiosensitivity of GBM cells.

The nanoparticles could also enhance the radiosensitization through lysosomes in both indirect and direct ways. The indirect access, for example, Wu et al. [218] designed RGD/P-AuNPs, which could target integrin that overexpressed in cancer cells, trafficking to lysosomes by integrins. It demonstrated that RGD/P-AuNPs enhanced the radiosensitization as well as inhibited the radiation-induced invasion in breast cancer cell lines. Moreover, Stefančíková group reported label-free gadolinium-based nanoparticles (GdBN) [219], which were high-Z NPs that could enhance the radiosensitizing efficacy in cancer cells. The cell organelles co-localization confirmed that GdBN NPs mainly localized in the lysosome (Fig. 5B-5G), and amplified gamma rays-induced cellular mortality. GdBNs, likewise, reported by their group after two years, could potentiate radiation-induced cell killing [220]. GdBNs that were localized in the cytoplasm, without penetrating into the cell nucleus and damaging DNA, could also efficiently intensify the radiosensitization of cancer cells.

In addition, some lysosomes-related radiosensitizers have been used in BNCT. T-Gal-B-Cy3@MSN was designed by the Lai group [221], which was based on mesoporous silica nanoparticles (MSNs) and then modified with Cy3 (fluorescent dye) as well as galactose (Gal), loading with o-carborane. The targeting and uptake experiments showed that T-Gal-B-Cy3@MSNs were located in endosomes and lysosomes after endocytosis in cells.

3.4.3. *Lysosomes-targeted particle RT, especially BNCT*

As shown for ER-targeted BNCT, porphyrin–polyamine conjugates para-carborane clusters also demonstrate preference for localizing in the lysosomes of human glioma T98G cells(Fig. 5H-5K) [196]. The conjugation of boron nanoparticles with porphyrins enables penetration into A549 human lung adenocarcinoma cells, diffuse cytoplasmic staining, and high accumulation in lysosomes [222]. Additionally, The water-soluble nido–carboranylporphyrin 5 (H(2)OCP) is internalized by human glioblastoma T98G cells in culture, demonstrating a subcellular preference for lysosomal localization [223]. Similarly, carboranylporphyrins effectively deliver therapeutic amounts of boron to T98G cells, predominantly localizing within the cell lysosomes [224].

3.5. *Other organelles-targeted RT*

Since the PM, Golgi apparatus, peroxisome [45], and so on also make a difference in cancer RT, they could be studied as targets for sensitization of RT.

3.5.1. *PM-targeted RT*

The PM constantly consists of a phospholipid bilayer structure in which thousands of lipid and protein species are inhomogeneously distributed [225]. Moreover, PM is also an important organelle to sense the extracellular environment as well as participates in signaling pathways [226]. However, the lipid composition of cancer cell PM changes in diverse diseases [227], so the PM can hopefully become a fresh target of cancer therapy.

The researches demonstrated that PM-targeted photosensitizers had been used in studies of PDT, especially the nanoparticles [228]. Notably, the membrane proteins, like Hsp70 [229], could determine the radiosensitizing effect of cancer cells. Furthermore, Hu et al. analyzed boron-containing inhibitors targeting the upregulated prostate-specific membrane antigen (PSMA), a cell surface glycoprotein overexpressed in cancerous cells, for BNCT [230]. Similarly, the efficacy of boron-containing PSMA inhibitors has also been demonstrated, highlighting their potential utility in BNCT [231].

3.5.2. *Golgi apparatus (GA)-targeted RT*

GA is the hub of intracellular trafficking [232], so the alterations in the structure are expected to influence the homeostasis of cellular lipids and proteins [233]. What's more, the integrity of the GA plays a significant role in multiple signaling pathways [234]. Reports showed that Golgi protein glycosylation abnormalities are in connection with the occurrence and metastasis of cancers [233,235]. Thereby, it conceivably supplies the GA with an opportunity for specific radiosensitization.

Studies have shown that enzymatic reaction enables efficient GA targeting. For instance, thiophosphopeptides, as reported by Tan et al. [232], target the GA instantly as well as kill cancer cells selectively. Additionally, the prodrug based on chondroitin sulfate was found to locate at GA and the relevant nanoparticles could enhance the effect of chemotherapy [234] and photodynamic immunotherapy [236]. As discussed earlier in Section 3.3.3, porphyrin–polyamine conjugates featuring para-carborane clusters exhibit a marked preference for localization in the GA of human glioma T98G cells [196]. Thereby, it is foreseen that GA will become an effective target for tumor therapy and is also expected to be applied with radiosensitization.

Furthermore, the peroxisomes are expected to be a radiosensitizing target as well [237], according to their effective role in regulating cancer initiation and progression [238]. Although research on these organelles remains scarce, there is an urgent need to explore their working mechanisms and to provide further rationale for the development of other organelle-localized radiosensitizers.

4. Conclusion and outlook

In recent years, advancements in biomedicine and precision medicine have led to the emergence of various organelle-targeted radiosensitizers, encompassing both inorganic and organic species. This review focuses on four major organelles, including the nucleus, mitochondria, ER and lysosomes, and briefly outlines their characteristics and apoptosis-regulating pathways to reveal the potential and distinct characteristics of different suborganelle targets. Meanwhile, possible strategies for organelle-targeted delivery systems and design ideas for organelle-targeted radiosensitization are explored based on the unique features of various organelles. Organelle-targeted radiosensitizers can regulate the local subcellular microenvironment in different ways, including ROS, cell cycle blockade, DNA damage, and tissue DNA damage repair [239]. Therefore, by rationally designing various systems, radiation resistance can be effectively overcome, therapeutic efficacy improved, and metastatic [240] as well as side effects reduced.

While RT remains the most effective cytotoxic therapy for localized solid cancers, it faces limitations such as low radiation penetration, damage to normal cells, and tumor resistance. New RT methods such as BNCT have increased tumor control and reduced the killing of surrounding normal tissues. However, BNCT still faces challenges such as insufficient boron accumulation and short retention time, which limits its efficacy. New boron compounds with different tumor accumulation strategies have been developed, some of which exhibit organelle targeting selectivity, significantly enhancing the therapeutic effect of BNCT on tumors while preserving the normal surrounding tissues and organs. Recently, a series of radiosensitizers that selectively aggregate to specific organelles within cancer cells have been developed continuously. These radiosensitizers are crucial for RT to precisely target and reduce the side effects of normal tissue damage, overcome radiation resistance, improve the sensitivity and effectiveness of RT, maintain the effective value of radiation energy for a long time, and reduce the number of RT sessions, thus maximizing the effect of RT. This review aims to elucidate the research progress and future development direction for organelle-targeted radiosensitizers, in the hope of providing clues for better design of radiosensitizers in clinical cancer treatment.

Although research on organelle targeting has made significant progress, there are still several challenges that need to be addressed. These include unclear regulatory mechanisms of cellular pathways, poor transmembrane effects of targeting, and small delivery capacity. The current challenges in this field can be summarized as follows: 1) The molecular pathogenesis of tumors remains unclear, and more in-depth research is needed to understand abnormal cellular signaling pathways and molecular regulatory factors in cancer, especially regarding potential intrinsic molecular regulatory mechanisms and the development of new molecular targets. 2) Targeting specific organelles remains elusive, as ideal targets are lacking, and many barriers to translocation to organelles still exist. The emphasis tends to concentrate on a single aspect or channel, neglecting the need for a comprehensive assessment and analysis of the entire process. Further research into organelle targeting mechanisms is necessary to explore effective targeting strategies. 3) The complexities of the *in vivo* TME, physiological barriers, systemic circulation, immune responses, and biodistribution issues should be noted. Most organelle-targeted radiosensitizers currently consist of heavy metals and nano and organic materials [199,241], which may not have ideal biocompatibility and utilization. 4) The efficacy and safety of organelle-targeted RT are insufficiently studied. Issues such as substance clearance and retention time in the blood require long-term follow-up studies on safety and treatment efficacy [242]. Establishing experimental primate models is crucial for clinical translation. 5) The results are difficult to truly reflect organelle targeting, including the impact of the animal model's enhanced permeability and retention (EPR) effect, variations in organelle distribution observed within *in vitro* cell lines (such as the nucleus), and the complexities involved in assessing organelle targeting through techniques like confocal fluorescent labeling. Overcoming these challenges is crucial for the clinical implementation of organelle-targeted radiosensitization. Innovative approaches such as intratumoral injection and in-situ hydrogel delivery may offer potential solutions. Leveraging the established clinical utility of nano-radiosensitizers, they provide a valuable reference for the development of organelle-targeting nanoparticles. Expanding beyond the initial focus on tumor targeting, these nanoparticles should progress towards spanning tumor cell membranes and precisely positioning themselves within subcellular structures. Critical factors to address include further functionalization of nanoparticles to enhance organelle targeting, seamless integration of advanced delivery systems, preclinical models that faithfully replicate human physiology, and a rigorous assessment of safety and toxicity concerns.

In conclusion, organelle-targeted radiosensitizing strategies are extremely helpful for precision medicine in cancer treatments, which will be very significant for the development of new organelle-targeted substances, therapeutic integration, and novel RT methods. It is believed that in the future, organelle-targeted RT with high targeting, high sensitization efficiency, low biotoxicity and safety will have a great potential and revolutionary impact in the field of cancer treatments.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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