Recent progress on metal-based nanomaterials for cancer radiosensitization

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Abstract

Radiotherapy is a mainstay treatment for malignant tumors in clinical. However, enhancing radiation damage to tumor cells meanwhile sparing normal tissues is still a great challenge in radiotherapy. Nanomaterials with high atomic number (Z) values are promising radiosensitizers by promoting the radiation energy deposition in irradiated tumor cells, thus enhancing the therapeutic ratio of radiotherapy. In this review, we described the mechanisms of high-Z element radiosensitizers and systematically summarized the recent progress on metal-based nanomaterials, including high-Z metal nanoparticles, metal-organic frameworks (MOFs) and other high-Z-containing nanomaterials. Finally, further potential and challenges in this field were discussed.

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Comprehensive Summary

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Keywords

Radiotherapy | Nanoradiosensitizers | High-Z metal | Energy deposition | Nanomaterial

Contents

1. Introduction

As the first-line clinical management of malignant tumors, approximately 50% of cancer patients receive radiotherapy (RT),[1-3]which is usually used as an adjuvant treatment modality prior to surgery to shrink the tumor, or postoperative prevention of residual tumor recurrence.[4] Radiotherapy mainly uses X-rays to kill cancer cells. The high-energy radiation can directly cause DNA damage, or react with water molecule to produce reactive oxygen species (ROS), indirectly damage DNA. The accumulated DNA breaks ultimately induce tumor cell necrosis or apoptosis.[5-6]Despite radiotherapy has made some progress in suppressing tumor growth, tumor cells often show innate or acquired resistance to ionizing radiation. For example, the soft tumor tissues have low energy absorption coefficient, which usually requires a high radiation dosage and cause unavoidable damage to neighboring normal tissues, thus reducing the long-term life quality of patients.[7-8] In addition, the hypoxic tumor microenvironment, strong antioxidant system in tumor cells and enhanced DNA damage response are not conducive to effective DNA damage, which greatly reduce radiotherapy efficiency and ultimately result in treatment failure.[9-12] Thus, it is crucial to explore effective strategies for enhancing cancer radiotherapy.

Currently, impressive advances have been made in radiosensitizers for boosting tumor radiosensitivity. Especially, due to the intrinsic radiosensitive activities, chemical inertness, and good biocompatibility, high-Z element-containing nanomaterials are promising radiosensitizers and have been successfully employed for improving the RT therapeutic efficacy.[13-15] High-Z radiosensitizers possess high X-ray coefficient, which is significantly higher than that of tumor soft tissue. When tumor cells are exposed to high-energy radiation, high-Z atoms are excited by high-energy elements to collide due to the larger electron density. A large number of secondary charged particles and radiated photons are released, including Photoelectrons, Compton electrons and Auger electrons, which make a major contribution to energy conversion and deposition in the irradiated tumor tissues.[16] The dose-enhancing effect amplifies the damage of DNA directly, or producing more ROS by dissociating water to enhance the radiation sensitivity of cancer cells. Previously, many researchers have focused on the noble metal nanoparticles with intrinsic radiosensitive activities and good biocompatibility, particularly gold nanoparticles (Au NPs)-mediated radiosensitization. With the rapid development of nanotechnology, a large number of multifunctional high-Z element-containing nanomaterials with synthetic tenability and drug loading capacity are continuously reported, which broaden the horizon of this field and accelerate the development of metal-based radiosensitizers. In this review, we highlight the progress of metal-based nanoradiosensitizers. Based on the structures, we divide these nanoradiosentizers into three categories, namely, high-Z metal nanoparticles, metal-organic frameworks (MOFs), and other high-Z-containing nanomaterials. Finally, we further discuss the current challenges of metal-based nanoradiosentizers. We hope that this review article can help researchers understand the latest progress of metal-based nanoradiosensitizers and encourage all of us to make new breakthroughs in this field in the future work.

2. High-Z metal nanoparticles for radiosensitization

So far, many high-Z metal nanoparticles have been used as radiosensitizers to improve the efficacy of RT

through a rationale of energy deposition. They possess good chemical stability, low toxicity and morphological diversity. Several investigations about various high-Z metal nanoparticles have been made to improve the radiosensitivity of tumor cells (Table. 1), including metal nanoparticles of Au,[17-35]Hf,[14, 36] Pt,[37]Bi,[38-43] Ir, [44-46]Gd,[47-53] Ta,[54]Ga,[49, 55] and Te,[55, 56] etc.

2.1. Gold (Au)-based metal NPs

Au nanoparticles (Au NPs) are commonly researched radiosensitizers. In recent years, there has been a rapid development in the research on radiation sensitization of Au NPs. The regulation of the size, structure and surface modification of nanoparticles can optimize the efficiency of radiation sensitization and tumor treatment to varying degrees. For example, Coulter et al. prepared polystyrene-supported gold nanoparticles (AuNP@PS) for increasing its stability in physiological conditions. Compared with free Au NPs, the composite AuNP@PS showed enhanced radiation efficiency at a dose of 4 Gy, which proved the radiation enhancement of the polymer support material.[27] Wang et al. modified ultra-small gold nanoparticles with a tumor microenvironment (TME)-responsive multifunctional peptide (Tat-R-EK) *via* the Au-S bonds between gold and thiol groups from cysteine on Tat peptide. The Au NPs exhibited good stability and cathepsin B-responsive release of Tat-modified gold nanoparticles, leading to selectively targeting tumor cells. Such a formation improved radiotherapy efficiency by enhancing DNA damage. Moreover, it was easily cleared by the kidney profiting from the ultra-small size.[26] Liu et al. reported an acid-triggered gold nanoparticles (GNPs) aggregation strategy for RT enhancement. GNPs were modified with two peptides grafting 2, 3-Dimethylmaleic anhydride, termed as GNPs-A and GNPs-B, respectively. When arriving at the acidic tumor microenvironment (pH 6.5), the negatively charged GNPs-B was reversed to a positive charge state, and formed a larger GNPs aggregate with the negatively charged GNPs-A through electrostatic interaction, which promoted GNPs to effectively accumulate at the tumor tissue and meanwhile improved its*in vivo* photoacoustic imaging ability. More importantly, the sensitizer enhancement ratio (SER) value of the GNPs aggregation (1.73) in MCF-7 cells was much higher than that of single GNPs (1.16), greatly improved the radiosensitive efficiency.[28] In addition, Yang et al. prepared a GSH-responsive Au-MnO Janus nanovesicle (JNP Ve) by being self-assembled with a NIR-II dye IR1061. JNP Ve could be degraded into small Au NPs and manganese ion (Mn^{2+}) in response to GSH, which not only allowed for deep penetration of Au NPs but also produced more ROS through Mn^{2+}-mediated Fenton-like reaction, significantly enhancing RT efficacy. Meanwhile, the quenched IR1061 fluorescence was restored for image-guided tumor detection.[20] As a typical example, Song et al. observed that a multifunctional photocatalytic driven dandelion nanosystem composed of plasma amorphous TiO_2 components and Au nanorods could significantly enhance the radiotherapy effect due to the heterogeneous structure of electron-hole pairs, which enhanced drug accumulation through autonomous navigation.[18]

2.2. Bismuth (Bi)-based metal NPs

Bi-based nanoparticles are one of the hottest materials in radiotherapy. For example, Zhao et al. provided a representative example that met both radiosensitization and biosafety requirements. Ultra-small BiOI quantum dots (QDs) were synthesized *via* a simple two-step method. Under X-ray irradiation, BiOI QDs with high-Z element could also generate *OH by decomposing overexpressed hydrogen peroxide (H_2O_2) for radiation enhancement. In addition, BiOI QDs showed good biocompatibility, which were rapidly cleared by renal metabolic pathway and showed low accumulation in liver and spleen.[41] Chen et al. synthesized plasmonic Bi/Bi_2O_3-x by in situ fabrication of Bi_2O_3-x on Bi*via* a hydrothermal method and modified with the folate for tumor targeting. The oxygen vacancy defects allowed Bi/Bi_2O_3-x to absorb near-infrared light for combined photothermal therapy and radiotherapy. Moreover, Bi/Bi_2O_3-x showed excellent photoacoustic imaging ability for deep tissues.[39] Zhang et al. recently reported a biomimetic RT sensitization platform by combining cyanobacterial and 2D bismuthine. Upon the 660 nm laser and X-ray irradiation, cyanobacteria could produce oxygen *via*photosynthesis to relieve hypoxia in tumor tissue, further amplifying Bi-mediated radiation sensitization.[40] Recently, bacteria with excellent tumor targeting have attracted wide attention and are used as drug delivery carriers due to the easy surface modification. As a representative example, Zhang et al. developed a Bi_2S_3 nanoparticles-loaded engineered Escherichia coli MG1655 (Bac@BNP).

Bac@BNP could effectively accumulate at tumor tissues and released Bi_2S_3nanoparticles in response to the matrix metalloproteinase-2 (MMP-2). The produced cytolysin A (ClyA) protein by Bac could regulate the cell cycle, accompanied with the radiosensitization effect of Bi_2S_3 for enhanced tumor radiotherapy (Figure 1A).[38] Therefore, nanomaterials with Bi manifest the great hope for radiosensitization.

2.3. Gadolinium (Gd)-based metal NPs

Similar to gold, metal nanomaterials with Gd have been developed to promote radiosensitization. For example, by using the virus-like silica (V-Si) as the template, Zhang et al. constructed a biodegradable Gd-based hollow virus-like nanoparticle loaded with second near-infrared dye ICG and then modified with cyclic RGD peptide (R&HV-Gd@ICG). The Gd-based nanoparticles showed excellent tumor targeting capability and enhanced RT efficacy by producing numerous ROS and serious DNA damage. Otherwise, its fluorescent imaging capability allowed tumors to be visualized, which was of significance in breast conservation surgery.[57] In addition, Zhang et al. synthesized a RVG29-modified gadolinium-based biodegradable nanocapsule for NIR-II FI/MRI-guided glioblastoma (GBM) treatment, with PLGA as the carrier loading Gd_2O_3: Nd^{3+} nanodots, MnO_2 and chemotherapy drug TMZ. After the nanocapsule crossed the blood brain barrier and aggregated to tumor tissue owing to the RVG29 peptide, the high-Z-based nanocapsule released TMZ and produced O_2 in response to pH for enhanced radio-chemotherapy and remarkably inhibited the growth of the tumors.[47] As a paradigm, Xie et al. developed an ultrafine gadolinium-carbon quantum dots (Gd@Cdots) *via* a hydrothermal method, which had minimal Gd leakage and low toxicity due to the biological inertness of carbon and rapid clearance from body. Moreover, Gd@Cdots could produce hydroxyl radical in H1299 cells under X-ray irradiation due to the photoelectric effect of Gd and surface catalytic effect of carbon.[51] Consequently, Gd-based metal nanoparticles can be envisioned to a certain extent as the effective radiosensitizers to support RT.

2.4. Iridium (Ir)-based metal NPs

Iridium (Ir, Z = 77) with high stability and high biocompatibility has hold much attention in RT field over recent decades. For instance, Liu et al. successfully synthesized Ir nanocrystals (IrNCs) *via* a chemical reduction and were encapsulated with PEG-modified liposomes for preventing being toxified by thiol biomolecules. According to the photoacoustic images *in vivo* , Ir@liposome showed better accumulation and retention ability compared with Ir NPs. Moreover, IrNCs showed catalase-mimicking activity upon NIR laser to relieve tumor hypoxia, combined with the radiosensitization of high-Z element Ir, greatly improved the efficacy of radiotherapy.[46] Xu et al. also reported an ultra-small Ir nanocrystals of < 5 nm, which was decorated with RGD and TAT peptides for double targeting of tumor cell membrane and cell nucleus. It had been demonstrated that the high-Z element Ir effectively accumulated in the nucleus and produced extensive DNA damage under X-rays in 4T1 cells, indicating the amazing sensitization effect. Fortunately, Ir nanocrystals was not only a good radiotherapy sensitizer, but also had good photothermal conversion ability, which provides great potential for photothermal synergistic therapy (Figure 1B).[45]

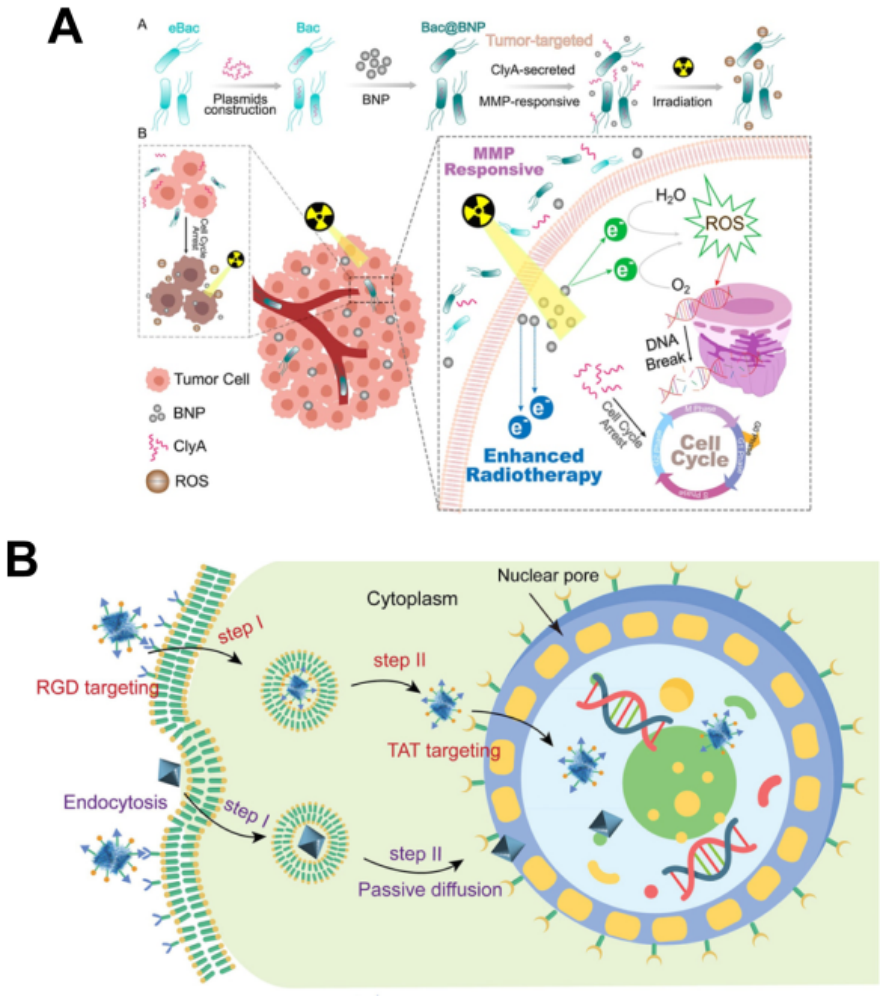


Figure 1 (A) Mechanism diagram of Bac@BNP-mediated radiosensitization. Reprinted with permission,[38] Copyright 2022, American Chemical Society. (B) Illustration of tumor cell membrane and cell nucleus dual-targeting process of Ir-R/T NCs. Reprinted with permission,[45] Copyright 2019, Wiley-VCH.

Table 1 High-Z metal nanoparticles for radiosensitization

Element	Size (nm)	Shape
Au Au Au Au Au Au	4.0-6.3 110 4.5 ± 0.7 < 5.5 28.2 Length: 93, Diameter: 16	Nanocluster Nanostar Spherical Sphe
Bi	150	Nanosheet
Bi	100	Spherical
Bi	3	Spherical
Bi	200	Layered Nanosheet
Bi	190	Spherical
Gd	140	Spherical surrounded by nanospike
Gd	3	Spherical
Gd	84	Nanocapsule
Gd	< 5	Spherical
Pt	6.64 ± 1.3	Spherical

Element	Size (nm)	Shape
Ir	< 5	Octahedral
Ir	3.3	Spherical
Te	180	Nanosword
Ga	110	Spherical
Hf	213.2 ± 15.8	Lamellar
Ta	70	Spherical

Table 2 Metal-based metal-organic frameworks for radiosensitization

Element	Size (nm)	Surface modification	Responsiveness	Cell line/model	X-ray dose	Refs
Hf	100	-	-	MC38	1 Gy	[70]
Hf	212.9 ± 4.2	αCD47	-	CT26	2 Gy	[71]
Hf	80-150	PEG	-	4T1	6 Gy	[72]
Hf Hf	190 98.1 ± 4.1	cGAMP -	High phosphate -	MC38 MC38	2 Gy 2 Gy	[75] [76]
Hf	100	-	-	MC38	2 Gy	[77]
Hf	95 ± 18	-	-	KYSE 150	6 Gy	[68]
Hf	100	PEG	-	HeLa	4 Gy	[69]
Hf	100	CPG	-	MC38	1 Gy	[78]
Hf	72	-	-	SQ20B	1 Gy	[79]
Hf	44 ± 14	DDR inhibitors	-	4T1	4 Gy	[80]
Zr	62	QU	PH	A549	8 Gy	[87]
Zr Zr Th Bi	80 250 80 109 ± 5	AuNPs AuNPs - -	High phosphate - - -	U87MG MDA-MB-231 CT26 TRAMP-C2	8 Gy 8 Gy 2 Gy 1 Gy	[88] [89] [93] [94]
Ln	250	-	-	HeLa	4 Gy	[95]

3. Metal-Organic Frameworks

Nanoscale metal organic frameworks (nMOFs) represent a class of hybrid materials assembled from tunable metal clusters and functional organic bridging ligands. Over the past decade, nMOFs have emerged as a new type of material that proposed for biomedical applications due to the synthetic tenability, simple synthesis process, high porosity, large surface area and good biocompatibility.[58-62]Notably, high-Z-based nMOFs have shown potential antitumor ability by increasing local radiation dose deposition and generating highly cytotoxic ROS upon x-ray irradiation. Compared to traditional metal-based nanoradiosensitizer (e.g., Au、Bi_2S_3 and HfO_2), nMOFs present several advantages including the improved drug loading capacity and good biodegradability, which have emerged as a promising radiosensitizer platform. Table 2 summarized the combination of different metal ions to form different nMOFs for radiosensitization. Herein, we took the most popular nMOFs containing the metal element (hafnium, zirconium, lanthanide) as paradigms to describe a series of coordination frameworks of metal-based radiosensitizers for improving the efficiency of radiotherapy.

3.1. Hafnium (Hf)-based nMOFs

In recent years, hafnium-based nanoscale metal-organic frameworks (Hf-nMOFs) have received great attention in the radiosensitization field owing to their excellent X-ray conversion and energy absorption ability.[63-67] For example, Cheng et al. reported a Hf-based MOF (UiO-66-NH_2(Hf)) of about 100 nm

for achieving radiosensitization, which showed a good anti-tumor effect*in vitro* and *in vivo* by increasing the X-ray absorption in tumor cells.[68] Despite the success of radiotherapy, the single sensitizing effect is still not satisfactory. Multimode combined therapy has become a popular trend in recent years. As showed in Figure 2A, Bu et al. prepared the Fe^{3+}-functionalized Hf-nMOFs (Hf-BPY-Fe) for providing the full-process radiation sensitivity by magnifying *OH formation to obtain better radiotherapy efficiency.[69]Specifically, Hf^{4+} in Hf-BPY-Fe (Hf-nMOFs) could produce substantial amounts of high-energy electrons when received high-energy radiation, which could convert H_2O to *OH partially and, besides, formed an environment of electron enrichment. The electron enrichment environment created by nMOFs could accelerate the reduction of Fe^{3+} to Fe^{2+}, which further promoted the generation of *OH in the process of Fenton reaction to effectively destroy DNA molecules. The RT enhancement mechanism of this Hf-nMOFs was illustrated in Figure 2B. In general, this work realized CDT and RT synergistic therapy. In addition, there were lots of works using the strategy that combined a method based on radiotherapy and photodynamic therapy (RT-RDT), which could significantly decrease the tumor cell survival and delay tumor growth.[70-77] As a representative example, Lin et al. prepared a novel nMOF (Hf-DBBF-Ir) as an in situ cancer vaccine by rationally integrating high-Z metal Hf_6 secondary building units and photosensitizing ligands DBBF-Ir and meanwhile loading immune adjuvant CpG *via* electrostatic interactions.[78] Mechanistically, after intratumoral administration, the Hf clusters could effectively absorb X-ray to generate *OH through radiolysis and transferred energy to adjacent photosensitizing ligands to generate $^1O_2$, resulting in the release of tumor associated antigens, danger-associated molecular patterns and CpG for antigen presenting cells (APCs) upon X-ray irradiation. In general, this strategy of using RT-RDT effectively activated systemic antitumor immunity through Hf-nMOFs and promoted tumor elimination. For another example, Lu et al. constructed Hf-based nMOFs composed of Hf clusters and DBP or TBP-based photosensitizer ligands for RT-RDT therapy, which could efficiently eradicate primary and distant tumors under a low dose of X-rays when combined with checkpoint blockade agent (IDOi).[79] In addition, Sun et al. prepared two DNA damage repair (DDR) inhibitors-loaded nMOF (TB@Hf-BDC-PEG), which restored the sensitivity of tumor cells to radiotherapy and improved the apoptosis rate of tumor cells *via*Hf-mediated ROS enhancement and the block of DNA damage repair pathway of tumor.[80]

3.2. Zirconium (Zr)-based nMOFs

Zirconium (Zr)-based nMOFs have received great attention in recent years.[81-85] It is noteworthy that it has also shown great potential in the field of radiotherapy sensitization.[86] Meng et al. prepared Zr-MOF through the coordination of Zr^{2+} and 1, 4-benzenedicarboxylic acid and loaded with quercetin (QU) (Zr-MOF-QU). Under tumor acid microenvironment, Zr-MOF was degraded, releasing Zr^{2+}, 1, 4-benzenedicarboxylic acid and QU. 1,4-benzenedicarboxylic acid could inactive carbonic anhydrase IX by binding to the active site of Zn^{2+} to relieve tumor hypoxia, which cooperated with QU for a dual radiosensitization effects and thus improved the efficiency of radiotherapy (Figure 2C).[87] A hybrid nanomaterial based on Zr-based MOF and Au NPs reported by Chen et al. significantly inhibited tumor growth with minimal systemic toxicity, opening up a new prospect for the next generation of therapeutic nanomaterials.[88]Zr-cluster and Au NPs as radiosensitizers had high X-ray attenuation coefficients. More importantly, the combined application of Zr and Au exerted the catalase-Like activity to alleviate the hypoxic tumor microenvironment by catalyzing the conversion of tumor metabolite H_2O_2 to O_2, which facilitated O_2-dependent radiotherapy. Tian et al. also reported core/satellite-like UiO-66/Au NPs nanohybrids for improving the RT efficiency in the hypoxic triple negative breast cancer by dual CA IX inhibition strategy. [89] Once the nanohybrid entered tumor cells, the UiO-66 matrix were decomposed by the high concentration of phosphate, releasing p-phthalic acid, the building skeleton of the UiO-66 MOF, to inhibit CA IX. Meanwhile, the Au NPs not only could enhance the radiosensitivity of tumor cells but also effectively load CA IX antisense oligonucleotide (ASO) *via* Au-S bond to knockdown CA IX. These previously integrated functional parts cooperated with each other and played an excellent RT effect in the hypoxic tumor bearing animal model.

3.3. Other types of metal-based nMOFs

A considerable number of nMOFs based on other metal elements have been proven to have effective ra-

diosensitization or synergistic killer effect for single or multifunctional radiotherapy.[90-92] Thorium (Th) is a radioactive metal element. Lin et al. reported a high-Z Th-based nMOF with photosensitizing ligands, which could promote radiation damage of tumors *via* RT-RDT. Th-MOFs with high X-ray attenuation efficiency promoted energy deposition and leaded to more active oxygen generation, thus inducing significantly cell apoptosis and inhibiting tumor growth.[93] Bismuth (Bi) as a radiosensitizer is also an ideal metal for building nMOFs because of the strong absorption of X-rays. Lin et al. reported a Bi-based nanoscale metal-organic framework.[94] Bismuth metal-constructed nMOFs were expected to adsorb more X-rays for enhancing the effect of RD-RDT and triggering stronger local immune activation, which cooperated with CBI for systemic tumor elimination. The lanthanides-based radiosensitizer not only has natural high-Z metal but also good biocompatibility because of the redox stability of Ln^{3+} ions, which is widely used in biomedicine. Lanthanides can interact with X-ray radiation, and their photoelectric effect and Compton effect effectively improve the radiotherapy efficiency. Chen et al. designed lanthanide coordination nMOFs as X-ray responsive radiosensitizers for cancer therapy, and they could increase intracellular ROS level according to the experimental data showed.[95]

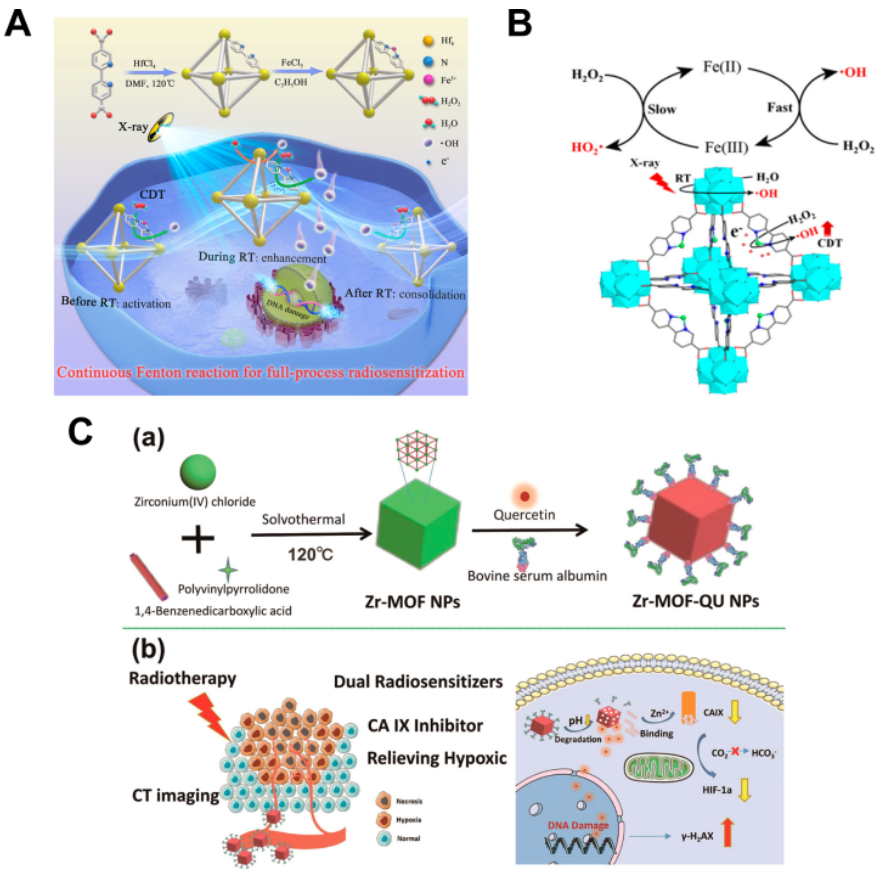


Figure 2 (A, B) Illustration of the synthesis process and full-processradiosensitization mechanism of Hf-nMOFs. Reprinted with permission,[69] Copyright 2020, American Chemical Society. (C) Illustration of the radioenhancement effect of Zr-MOF-QU NPs. Reprinted with permission,[87] Copyright 2019, American Chemical Society.

4. Other high-Z-containing nanomaterials

Metal-phenolic networks (MPNs) are emerging versatile nanomaterials, which are constructed *via* the coordination between phenolic ligands and metal ions. As discussed, in view of the great advantages of

metal elements in radiotherapy, a large number of MPNs based on metal elements (e.g., Hafnium, Platinum, Gadolinium) have been prepared to improve therapeutic benefits for radiotherapy.[39, 96] Dai et al. have done a lot of excellent works in this field. For example, an oxygen-enriched X-ray nanoprocessor based on the Hf-polyphenols coordination (Hb@Hf-Ce6) was developed for improving the therapeutic effect of RT-RDT, enhancing oxygen enrichment in tumor microenvironment and promoting antitumor immune responses when combined with PD-1 immune checkpoint blockade. Given the high-Z metal of Hf not only could promote radiation dose enhancement, but also exhibited superior photoelectric effect, which could be used as favorable light source for RDT. Consequently, abundant ROS was generated and resulted in tumor regression.[97] Pt-based MPN has also been designed as a platform for relieving tumor hypoxia, which has made good achievements in the field of RT and sonodynamic therapy (SDT). In a nutshell, low-intensity pulsed ultrasound (LIPUS) was performed before radiotherapy to regulate hypoxia levels. Then the prepared PP18-Pt NPs based on the assembly of the PEG-polyphenols encapsulated with radiosensitizers Pt and the sonosensitizer PEG-purpurin 18 were administrated. The radiosensitizer and sonosensitizer were activated *via* controllable LIPUS and RT, producing high concentrations of ROS to kill tumor cells accurately as displayed in Figure 3A.[98] Besides, based on the robust metal-phenolic coordination of $NaGdF_4$:Nd@$NaLuF_4$ and Mn^{2+}, they also successfully fabricated a novel lanthanide-doped MPN (DSPM). As shown in Figure 3B, the released radiosensitizer and Mn^{2+} in response to pH sensitized tumor cells to X-ray and promoted STING pathway activation to overcome the radioresistance caused by the immunosuppressive microenvironment after DSPM internalized into cells.[99]

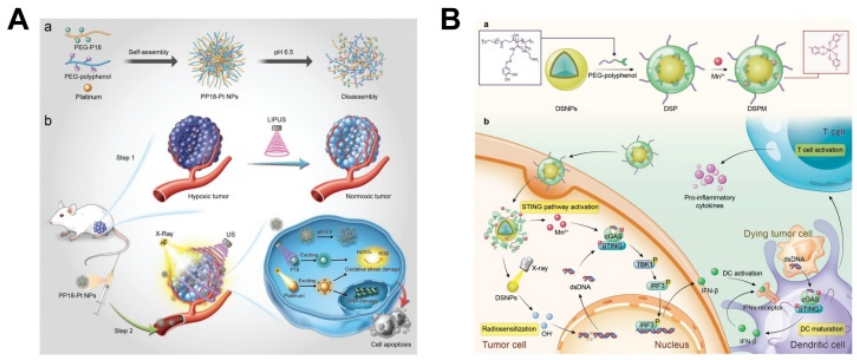
Figure 3 (A) Illustration of the PP18-Pt NPs mediated radiotherapy enhancement. Reprinted with permission,[98] Copyright 2022, Wiley-VCH. (B) Illustration of the radiosensitization and immunomodulation effect of lanthanide-doped MPN. Reprinted with permission,[99] Copyright 2022, Wiley-VCH.

5. Conclusions and Perspectives

In conclusion, the unique properties of nanomaterials, such as the high surface area, stability, and tunability bring opportunities for traditional radiotherapy. Especially, metal-based nanomaterials with the intrinsic radiosensitive activities and chemical inertness in cellular systems exhibit good radiosensitization effects and can be applied to sensitize tumor cells to radiotherapy. The particle size, shape, and surface functionalization of metal-based nanomaterials are well manipulated with the vigorous development of nanotechnology. Therefore, nanoradiosensitizers can be easily synthesized with desirable size and functional modification.[100] More importantly, profiting from the unique advantages of nano-structure, nanomaterials possess favorable pharmacokinetics profiles and can effectively delivery metal-based radiosensitizers to tumor tissue *via* the active targeting or the enhanced permeability and retention (EPR) effect mediated passive targeting. Currently, many high-Z nanomaterials have entered clinical trials for cancer radiosensitization.[101-103] In particular, the HfO_2nanoparticles NBTXR3 showed encouraging radiological and pathologic responses in patients with soft tissue sarcoma in clinical trial.[104-106] Therefore, metal-based nanomaterials are promising radiosensitizers to improve the radiotherapeutic outcome and decrease the side effects, which accelerate the development of nanoradiosensitizers.

Despite the current some achievements, there are still some challenges for metal-based nanoradiosensitizers, such as the potential toxicity of nanoradiosensitizers containing heavy or toxic metals due to the inefficient elimination from body. Compared with small molecule drugs, nanoradiosensitizer has a longer circulation time in the body and is not easy to degrade. Thus, the biocompatibility and long term toxicity of nanoradiosensitizers must be comprehensively investigated before applied to the clinic. Moreover, nanoradiosensitizer lack targeting specificity. In the further, radiosensitizers with highly effective and low toxicity are expected to be exploited for radiotherapy. In conclusion, metal-based nanomaterials are promising radiosensitizers, and more techniques need to be introduced to accelerate the development of metal-based nanoradiosensitization for low dose radiotherapy in clinic.

Acknowledgement



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Metal-based nanomaterials amplify the damage of DNA directly, or produce more ROS by dissociating water to enhance th