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Application of Multifunctional Nanomaterials in Radioprotection of Healthy Tissues

Jiani Xie, Chengyan Wang, Feng Zhao, Zhanjun Gu,* and Yuliang Zhao**

Radiotherapy has been extensively used in clinic for malignant tumors treatment. However, a severe challenge of it is that the ionizing radiation needed to kill tumors inevitably causes damage to surrounding normal tissues. Although some of the molecular radioprotective drugs, such as amifostine, have been used as clinical adjuvants to radio-protect healthy tissues, their shortcomings such as short systemic circulation time and fast biological clearing from the body largely hinder the sustained bioactivity. Recently, with the rapid development of nanotechnology in the biological field, the multifunctional nanomaterials not only establish powerful drug delivery systems to improve the molecular radioprotective drugs' biological availability, but also open a new route to develop neozoic radioprotective agents because some nanoparticles possess intrinsic radioprotective abilities. Therefore, considering these overwhelming superiorities, this review systematically summarizes the advances in healthy tissue radioprotection applications of multifunctional nanomaterials. Furthermore, this review also points out a perspective of nanomaterial designs for radioprotection applications and discusses the challenges and future outlooks of the nanomaterial-mediated radioprotection.

1. Introduction

Radiotherapy, which harnesses high energy ionizing radiation to conquer the tumor cells, is one of the three conventional cancer treatment methods and has been extensively used in clinic. According to statistics, over 50% cancer patients need to treat with radiotherapy either alone or assisted with other therapies.[1,2] However, the high energy ionizing radiation needed for cancer treatment not only kills tumor cells but also inevitably damages surrounding healthy tissues, which causes a severe side effect to body.[3] Therefore, the development of radioprotectors to protect normal tissues against radiation-induced injuries is essential for radiotherapy. Up to now, a lot of radioprotectors have been designed and fabricated, but most of them are organic molecular agents and suffer from the drawbacks of insolubility in water, short circulation in body, and fast metabolism. As a result, their drug efficiencies are discounted.[4–6] Therefore, it is necessary to look for new ways to improve their biological availability or exploit new radioprotectors to substitute them.

With the development of nanobiomedicine, multifunctional nanomaterials provide such a promising platform to overcome aforementioned challenges. It is known that lots of nanomaterials are the good drug delivery systems.[7–9] Thus, they can play the role of carriers to deliver molecular radioprotective drugs into body so as to increase the stability as well as circulation time of the drugs in vivo, and eventually enhance the drugs' bioavailability. As a paradigm, using poly (lactide-co-glycolide) (PLGA) microspheres to encapsulate radioprotective drug can enhance the stability and allow slower release of the drug, which endows the drug-loaded PLGA nanosystem with a greater radioprotective efficacy compared to that of the drug alone.[4] Besides taking nanomaterials as drug carriers to indirectly assist radioprotection, some nanomaterials have been found to have intrinsic radioprotective activities and thus can be directly used as radioprotective agents. For instance, the water-soluble C_{60} fullerene-based nanomaterials with the ability of free-radical scavenging can consume the radiation-induced toxic free radicals, and thus shield the healthy tissues from radiation-induced damages.[10] In this regard, nanoradioprotectors have the potential to act as neozoic radioprotectors to substitute conventional molecular radioprotective drugs. Consequently, the multifunctional nanomaterials manifest a unique superiority in radioprotection applications.

Therefore, in this review, we highlight and discuss the advances in radioprotection applications of multifunctional nanomaterials. We first emphasize the radioprotection of healthy tissues via delivering the molecular radioprotectors by nanocarriers, which encompass organic polymer nanocarriers,

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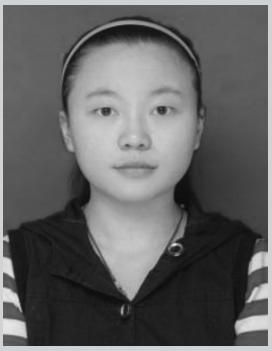
inorganic nanocarriers, as well as nanosize radioprotectors assembled by molecular radioprotective drugs. Then, we highlight the radioprotection of healthy tissues by the nanomaterials with intrinsic radioprotective natures, which involve carbon-based nanoradioprotectors, cerium-based nanoradioprotectors, transition-metal dichalcogenide (TMDC) nanoradioprotectors, and noble metal nanoradioprotectors. In addition, we point out a perspective of nanoradioprotectors designs for radioprotection application. Finally, the challenges and future outlooks in the development of nanoplatforms for radioprotection are discussed. We hope that such a review can help researchers to better grasp the recent progresses of nanomaterial-mediated radioprotection so as to inspire and facilitate more exciting developments in this field.

2. Radioprotection of Healthy Tissues via Delivering the Molecular Radioprotectors by Nanocarriers

Up to date, a lot of molecular radioprotective drugs are developed, and some of them even have been used in the clinic for radioprotection. For instance, the curcumin has the protective function against the harmful effects of radiation via free radical scavenging process.[4] The methylproamine exhibits radioprotective effects through preventing DNA double-strand breaks.[11] The sesamol can act as a radioprotector by enhancing DNA repair.[12] The amifostine, which are widely used in clinical, achieve radioprotection via complicated mechanisms involving induction of cellular hypoxia, free-radical scavenging, as well as DNA protection and repair acceleration.[13] However, the therapeutic efficiency of molecular radioprotectors is unlikely to be fully realized due to their inherent disadvantages such as insolubility in water, adverse effects to body, short distribution half-life, and fast metabolism from the body. Thus, it is in urgent need of assistants to solve these problems. Luckily, the emerging nanotechnology offers a promising platform to combat these limitations, because the nanomaterials with high biocompatibility and drug-load ability can serve as nanocarriers to increase stability, prolong the systemic circulation time, lower the metabolism rate, and achieve controlled release of drugs. Consequently, the nanocarriers enhance the bioavailability of molecular radioprotective drugs and ultimately improve their radioprotective efficacy. In this section, we sum up the research progress of application of nanocarriers in radioprotecion, which covers three aspects involving organic polymer nanocarriers, inorganic nanocarriers, and the nanosize radioprotectors assembled by molecular radioprotective drugs.

2.1. Delivering the Molecular Radioprotectors by Organic Polymer Nanocarriers

Organic polymer nanocarriers are the most widely used carriers for various molecular radioprotectors' delivery due to their biodegradability, particularly PLGA nanocarriers.[4–6,14–26] For example, Souza et al. once used PLGA microspheres to encapsulate radioprotective drug curcumin. This microencapsuation enhanced the stability of curcumin and allowed its slower release so as to offer greater radioprotective efficacy.[4] Pamujula et al. used molecular radioprotective agent amifostine and PLGA to form amifostine nanoparticles.[14] They evaluated the protective ability of the amifostine nanoparticles in inhibition of γ-irradiation-induced injury to mice, which indicated that oral delivery of the amifostine nanoparticles 1 h preirradiation could significantly improve



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the 30 d survival, hemopoietic progenitor cell survival, and jejunal crypt cell survival compared to irradiation alone. Soon after, they adopted the similar oral delivery strategy and demonstrated that the *N*-(2-mercaptoethyl)1,3-diaminopropane (WR-1065)/PLGA nanoparticles could also remarkably reduce the radiation-induced bone marrow suppression and intestinal injury and improve 30 d survival, where WR-1065 was the active metabolite of amifostine and widely used as cytoprotective agent in cancer radiotherapy.[15] Mohamed et al. used PLGA to deliver penicillamine and potassium iodide radioprotective drugs for protecting γ-irradiated mice.[18] The results illustrated that administration of these drug-loaded PLGA nanoparticles could improve drug efficacy in body for longer duration than that of the free drug in equal dose. Besides PLGA, the other nontoxic and biocompatible polymers have also been developed as carriers for the delivery of radioprotective compounds. Take chitosan as an example, chitosan is a natural polysaccharide and is considered as an ideal polymer nanocarrier. Zhou et al. once employed chitosan-based nanocarrier to improve the radioprotective efficacy of ferulic acid (a prototypical radioprotective agent) because this nanosystem presented prolonged drug retention time in blood.[20] Soon afterwards, Kumar et al. took chitosan to fabricate bovine serum albumin (BSA)-green tea polyphenols (TPs)-chitosan nanoparticles (BGCN) for radioprotection (**Figure 1**). TPs have been proved to mitigate radiation-induced injury in multiple studies.[21] According to the experiment results, the 3 d pretreatment of BGCN to mice before irradiation significantly reduced radiation-induced lethality. From the detail tissue analysis, the BGCN increased spleen index, bone-marrow cells, and hematological parameters of irradiated mice. As well, the BGCN could ameliorate the unbalance of endogenous antioxidant systems caused by radiation. Deeper analysis in gene expression level showed that the BGCN mitigated radiation-induced oxidative injury by restoring the redox status via the Nrf2-ERK pathway as well as decreasing Bax expression, respectively. More importantly, the BGCN presented a higher radioprotective efficacy than free TPs. Therefore, the chitosan nanocarrier is also a powerful assistant to improve the radioprotective availability of molecular drugs. In addition, solid lipid nanoparticles (SLNs) have also been used to encapsulate and deliver molecular radioprotective agents. Ahmad et al. employed SLNs to deliver radioprotective drug trans-resveratrol (RVL).[6] The solubility and systemic circulation of RVL could be obviously increased by SLNs delivering. The antioxidant and radioprotective assays presented a significant increase in RVL-encapsulated SLNs treated group compared to that of pure drug treated group.

2.2. Delivering the Radioprotectors by Inorganic Nanocarriers

In recent years, inorganic nanocarriers are gradually used in radioprotective agents' delivery.[27–32] For instance, Schweitzer et al. once used silica nanoparticles to load and deliver melanin (a naturally occurring pigment that has radioprotective properties) for radioprotection. It polymerized melanin precursors onto the silica nanoparticles to synthetize melanin-covered nanoparticles (MNs). The MNs minified hematologic toxicity of mice treated by external beam radiation therapy or radioimmunotherapy, and had no protection effect on tumor.[27] Chandrasekharan et al. took silver nanoparticles (SNs) to delivery glycyrrhizic acid (GLY, a radioprotector) for protection against ionizing radiation. An effective radiation protection effect could be observed in the irradiated mice treated by SN-GLY in either preirradiation or postirradiation conditions.[28,30,31] As well, they further employed SN to transmit 6-palmitoyl ascorbic acid-2-glucoside (PAsAG, a radioprotective agent) for radiation protection. The SN-PAsAG also presented a positive radioprotective response under in vitro, ex vivo, as well as in vivo scenarios of radiation exposure.[29] Lately, Xie et al. adopted D-α-tocopherol polyethylene glycol 1000 succinate (TPGS)-functionalized bamboo charcoal nanoparticles (BCNPs) (TPGS-BCNPs) to deliver the radioprotector curcumin for radioprotection of normal cells.[32] The TPGS-BCNPs@curcumin obviously diminished the radiation-induced DNA break in human umbilical vein endothelial

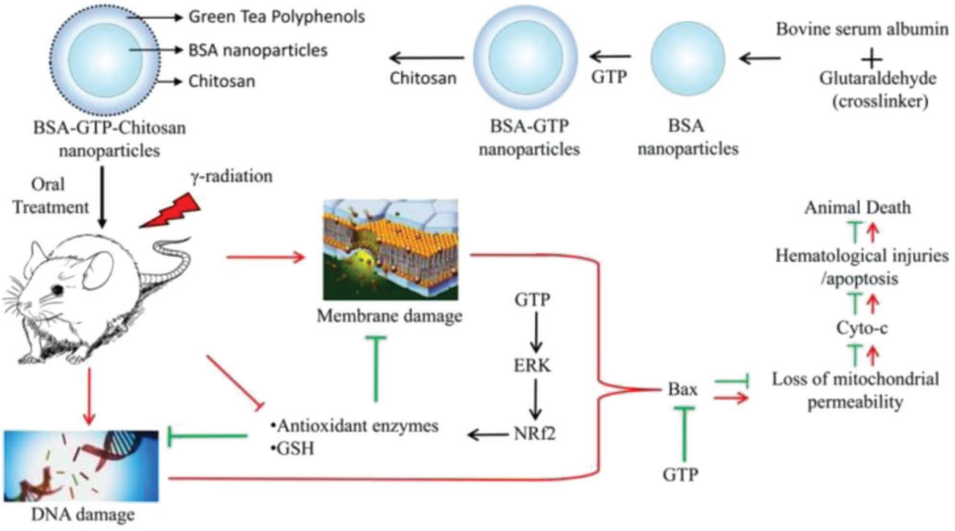

Figure 1. Scheme of the BGCN for radioprotection. Adapted with permission.[21] Copyright 2016, American Chemical Society.

cells (HUVECs) and thus exhibited a good efficiency in radiation protection. Therefore, inorganic nanocarriers are also the promising platforms for improving the bioavailability of molecular radioprotectors.

2.3. Nanosize Radioprotectors Assembled by Molecular Radioprotectors

In addition to loading the molecular radioprotective drugs onto nanocarriers, assembling the radioprotective compounds into nanosize particles is another effective avenue to overcome their defect of low bioavailability.[33–40] For example, Adhikari and Arora formulated silymarin (a radioprotective agent) into nanoemulsion to improve its bioavailability and therapeutic efficacy.[35] The nanosilymarin exhibited promising radioprotective potential in shielding γ-radiation-induced oxidative damage to human embryonic kidney cells. For another example, melanin has been proved to possess radioprotective activity. Rageh et al. prepared melanin manoparticles (MNPs) for radioprotection. The MNPs could powerfully protect hematopoietic tissues of mice from γ-radiation-induced damage.[36] Most recently, they further indicated that MNPs could reduce DNA damage, restore superoxide dismutase (SOD) antioxidase activity, and decrease harmful malondialdehyde (MDA) production in the irradiated mice.[40] In addition, Yazdi et al. provided biogenic selenium nanoparticles (SeNPs) to irradiated mice in a scheduled oral way to reduce the side effect of radiation. The toxicity of elemental Se (Se^0) at nanosize is smaller than that of selenate (Se^{+2}) or selenite (Se^{+4}) ions. The experimental results showed that SeNPs supplementation could enhance both neutrophils and lymphocytes counts especially of mice exposed to 2 Gy and 4 Gy radiation.[34]

In a word, either loading molecular radioprotective agents in nanocarriers or assembling the agents into nanosize particles can effectively improve the agents' bioavailability and ultimately enhance their radioprotective activity.

3. Radioprotection of Healthy Tissues by Nanoradioprotectors

Thanks to the multifunctional properties of nanomaterials, in addition to using them as carriers to indirectly assist molecular radioprotectors for radioprotection, researchers gradually find that some of the nanomaterials also have the radioprotective natures and can directly act as radioprotective drugs (also known as nanoradioprotectors). These nanoradioprotectors have the irreplaceable superiority including longer systemic circulation and lower the rate of metabolism compared to molecular radioprotectors, and thus have the potential to become the neozoic radioprotective drugs.

3.1. Radioprotective Principle of Nanoradioprotectors

When mentioning the radiation protection principle, we should first understand the damage rationale of radiation to tissues. It is generally believed that the high-energy ionizing radiations damage the cells via both the direct and indirect action. In the direct action, the ionizing radiations directly interact with DNA and lead to DNA damage. In the indirect action, the radiations first interact with water molecule and produce excessive amounts of reactive oxygen species (ROS, a class of free radicals), such as superoxide ($\bullet O_2^-$), hydrogen radical (•H), and hydroxyl radical (•OH). Then, these ROS will cause strong damage to cellular macromolecules (such as DNA, RNA, proteins, and membrane) and other cellular components, disrupt cellular structures, and eventually induce cell dysfunction and mortality.[41–44] Because normal tissues contain 80% water, the major radiation damage is attributed to the ROS generated by the radiolysis of water.[43,45] Therefore, the commonest design principle of nanoradioprotectors for radioprotection is based on a free-radical scavenging process, which utilizes the nanomaterials with free-radical scavenging ability to consume radiation-induced ROS and thus reduce the damage of these free-radicals to cells.

3.2. The Common Nanoradioprotectors for Radioprotection

The ensuing discussion focuses on the advancements of common nanoradioprotectors, including carbon-based nanoradioprotectors, cerium-based nanoradioprotectors, TMDC nanoradioprotectors, and noble metal nanoradioprotectors (**Figure 2**).

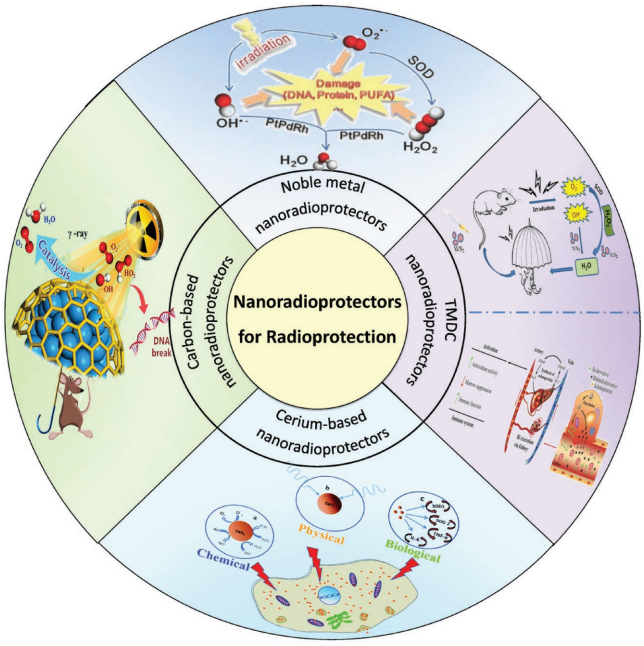

Figure 2. Scheme of the general nanoradioprotectors for radioprotection. Carbon-based nanoradioprotectors: Adapted with permission.[70] Copyright 2017, Tsinghua University Press and Springer-Verlag GmbH Germany, part of Springer Nature. Cerium-based nanoradioprotectors: Adapted with permission.[82] Copyright 2016, the Royal Society of Chemistry. TMDC nanoradioprotectors: 1) WS_2 nanoparticles. Adapted with permission.[91] Copyright 2017, American Chemical Society. 2) Bi_2Se_3 nanoparticles. Adapted with permission.[94] Copyright 2017, Wiley-VCH. Noble metal nanoradioprotectors: Adapted with permission.[97] Copyright 2018, Wiley-VCH.

3.2.1. Carbon-Based Nanoradioprotectors

Carbon-based nanomaterials have been extensively studied for radiation protection. Here, we divide the general carbon-based nanoradioprotectors into three types: (1) C_{60} fullerene-based nanoradioprotectors; (2) graphene-based and carbon nanotube (CNT)-based nanoradioprotectors; and (3) other new emerging carbon-based nanoradioprotectors. Next, we detailedly introduce the radioprotective mechanisms and radioprotection applications of them.

3.2.1.1. C_{60} Fullerene-Based Nanoradioprotectors: Fullerenes are a family of molecules that consist of carbon atoms, such as C_{20}, C_{60}, C_{70}, and C_{84}. C_{60} fullerene, which was discovered in 1985, is one of the most frequently investigated members.[46–48] Among the C_{60} fullerene-based materials, water-soluble C_{60} fullerene derivatives are paid a considerable attention to be used as potential radioprotectors in the radioprotection field due to their ROS scavenging ability. The effective ROS scavenging activity of them is on account of the fact that they possess a lot of π-conjugated bonds and a low-energy lowest unoccupied molecular orbital, which makes it easy for them to accept and react with free radicals.[49] Up to date, a lot of works about the radioprotection ability of water-soluble C_{60} derivatives have been reported, and most of the studies are focused on the water-soluble fullerenols and dendro[C_{60}]fullerene-1 (DF-1). Therefore, the main fullerene-based nanoradioprotectors we review here will concentrate on these two kinds of nanomaterials. Meanwhile, the other water-soluble C_{60} fullerene derivatives for radiation protection will be simply introduced here.

The water-soluble fullerenols have high electron affinity, free radical attached activity, reactivity for nucleophilic substituents, as well as polarity of the molecule, and thus meet the requirements of good radioprotectors.[49] Therefore, they get the wide interest for radioprotection application.[10,50–56] Zhao et al. studied the radioprotection effects of fullerenols $C_{60}(OH)_x$ (where x = 18–22) on ^{60}Co γ-ray-exposed stylonychia mytilus cells.[50] Importantly, the effectiveness of radiation protection depended on both the γ-ray dose and fullerenols concentration. Under the relatively low doses of γ-ray and low concentration of fullerenols (0.10 mg mL^{-1}), the fullerenols could increase the surviving fraction, improve the SOD and catalase (CAT) activities, and diminish the harmful lipid peroxidation products of MDA as well as lipofusion (LIP) of the radiated stylonychia mytilus cells, and thus showed an effective protection response. However, at the condition of high doses of γ-ray and high concentration of fullerenols (0.25 mg mL^{-1}), little protection effect was observed. Trajkovic et al. reported the radioprotective efficiency of fullerenol $C_{60}(OH)_{24}$ in whole-body irradiated mice.[51] The experimental results indicated that the radioprotective efficiency of $C_{60}(OH)_{24}$ also depended on its concentration. The $C_{60}(OH)_{24}$ of 100 mg kg^{-1} intraperitoneally (i.p.) given half-hour before irradiation displayed good radioprotective effect in irradiated mice. Whereas in a dose of 10 mg kg^{-1}, the $C_{60}(OH)_{24}$ had little protection and even aggravated harmful effect of irradiation. Therefore, the $C_{60}(OH)_{24}$ can behave as an effective radioprotector under suitable radiation dose and concentration. After that, Bogdanović et al. used $C_{60}(OH)_{24}$ for protecting the human erythroleukemia cell line from X-ray-induced damage.[53] Pretreatment of the cells by $C_{60}(OH)_{24}$ before irradiation significantly decreases the cell death caused by X-ray. Moreover, the $C_{60}(OH)_{24}$ was also able to enhance the antioxidative enzyme activity of SOD and glutathione peroxidase (GPX) and to decrease the levels of γ-glutamyltransferase (GGT) in irradiated cells. Later, Cai et al. further demonstrated that chronic pretreatment of mice with $C_{60}(OH)_{24}$ could protect against γ-radiation-induced immune dysfunction, oxidative damage, and mitochondrial dysfunction so as to reduce the radiation-induced mortality.[10] Attributed to the plenty of radioprotection investigations of these water-soluble fullerenols, researchers attempted to compare the radioprotective efficacy between them and amifostine (amifostine is the Food and Drug Administration-approved radioprotector) to further envision the clinical application prospect of the fullerenols-based radioprotectors.[52,54] As a representative paradigm, Trajkovic et al. compared the efficacy of $C_{60}(OH)_{24}$ and amifostine in shield of rats from radiation injury via evaluating the tissue-protective effects.[52] Under the condition of 100 mg kg^{-1} i.p. of $C_{60}(OH)_{24}$ and 300 mg kg^{-1} i.p. of amifostine 0.5 h before 7 Gy X-ray, the results of hematological studies indicated that $C_{60}(OH)_{24}$ was better than amifostine in prevention X-ray-induced white cell count (granulocytes and lymphocytes) reduction. Moreover, pathohistology investigations showed that $C_{60}(OH)_{24}$ was more effective than amifostine in protection of the spleen, lung, and small intestine, while amifostine had better radioprotective effects on the heart, liver, and kidney compared to $C_{60}(OH)_{24}$. Therefore, the radioprotective efficacy of $C_{60}(OH)_{24}$ in irradiated rats is comparable to that of amifostine, which makes the $C_{60}(OH)_{24}$ a potentially valuable candidate for radioprotection.

DF-1 is another C_{60} fullerene derivative, which contains 18 carboxylic groups for enhancing its water solubility.[48,57] It is also a hot fullerene-based nanoradioprotector. For example, Daroczi et al. assessed the radioprotection response of DF-1 in the zebrafish (Danio rerio) embryos model by monitoring survival, morphology, and organ functions.[48] DF-1 (100 μmol L^{-1}) showed an effective attenuation of overall and organ-specific ionizing radiation-induced toxicity when added with 3 h before or up to 15 min after radiation treatment. Also, the radioprotection degree provided by 100 μmol L^{-1} of DF-1 was comparable to that of 4 mmol L^{-1} of amifostine. More interestingly, the DF-1 remarkably mitigated the dorsal curvature of the body axis caused by radiation-induced defective midline development and attenuated the radiation-induced nerve cell injury. Furthermore, the DF-1 could also reduce radiation-induced renal function defects, which restored the impaired excretory function in the irradiated zebrafish embryos. Later, Theriot et al. manifested the protective properties of DF-1 to radiosensitive mammalian cells, which confirmed that DF-1 powerfully protected against several harmful effects of irradiation to mammalian cells including the oxidative stress, DNA damage, as well as cell death.[58] Consequently, the DF-1 is promising to serve as a radioprotector.

Apart from the two former hot C_{60} fullerene-based nanoradioprotectors, some of the other C_{60} fullerene derivatives also have been evaluated for radiation protection. For example, hydrated C_{60} fullerene (C_{60}HyFn), a water soluble and highly stable donor–acceptor complex of the C_{60} with H_2O molecules with a formula of $C_{60}@\{H_2O\}_n$ (n = 22–24), presented a

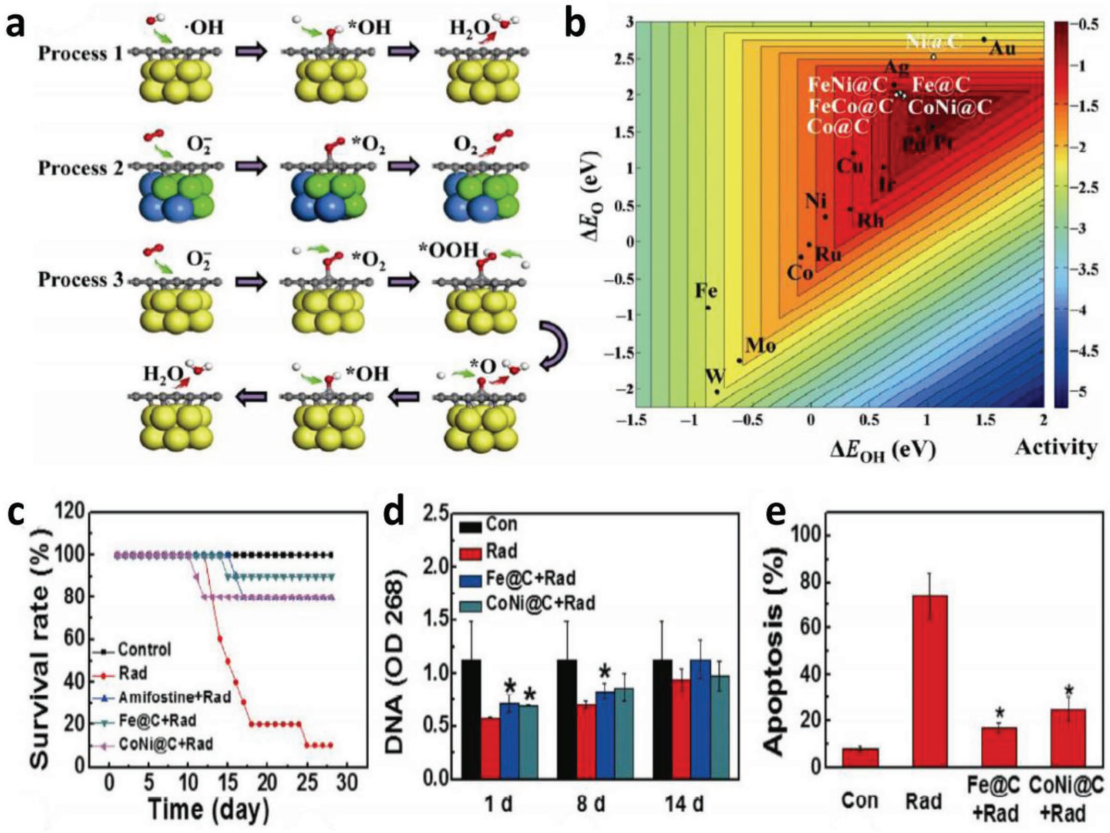

Figure 3. The graphene-encapsulated metal nanoshields for radioprotection. a,b) The simulation of catalytic processes of graphene-encapsulated metal nanoshields by density functional theory. c) Survival rates of mice after different treatments. d) Total DNA of bone marrow of mice after different treatments. e) Cell apoptosis ratio in intestine tissue sections of mice after different treatments. Adapted with permission.[70] Copyright 2017, Tsinghua University Press and Springer-Verlag GmbH Germany, part of Springer Nature.

positive radioprotective response under in vitro and in vivo conditions.[59] The C_{60}HyFn in concentrations range from 10^{-7} to 10^{-6} M could significantly reduce the oxidative damage of nucleic acids caused by X-ray irradiation. In animal experiments, administration of 1 mg kg^{-1} dosage of C_{60}HyFn before a full-spread lethal dose of irradiation remarkably prolonged the life span of the mice. Collectively, the C_{60}HyFn substantially diminishes the deleterious effects of ionizing radiation and manifests a good radioprotective effect.

3.2.1.2. Graphene-Based and CNT-Based Nanoradioprotectors: Graphene-based and CNT-based nanomaterials have already been widely reported that they can serve as free radical scavengers because of their unique chemical structures.[60–67] Thus, they are also the promising radioprotective agents in occupational and therapeutic settings. For instance, Tour et al. published a patent titled "Radiation Protection Using Single Wall Carbon Nanotube Derivatives."[68] In the typical in vitro assay, the single wall carbon nanotube (SWCNT) derivatives could improve the survival of irradiated rat small intestine crypt cells. Moreover, from the in vivo experiment, the SWCNT derivatives reduced radiation-caused severe curly up of zebrafish. Qiao et al. confirmed the effective radioprotective ability of low concentration graphene oxide (GO) (10 μg mL^{-1}).[69] They employed the normal human fibroblast cells as a model system. The results confirmed that GO could effectively remove ROS and reduce X-ray-induced DNA damage and apoptosis of fibroblast cells under the experimental condition of 10 μg mL^{-1} GO and 1.25 Gy X-ray. Most recently, Wang et al. reported the single-layer graphene-encapsulated Fe and CoNi nanoshields (Fe@C and CoNi@C) for radioprotection.[70] The detailed protection principle was illustrated as follows: the graphene-encapsulated metal nanohybrids with extraordinary electrocatalytic activity could powerfully catalyze the processes of scavenging •OH, HO_2•, and $•O_2^-$ species via an electronic transfer mechanism between the single-layer graphene and metal core, thus providing a route to consume excessive toxic ROS generated by high-energy ionizing radiation and ultimately realizing radiation protection. The cyclic voltammograms of Fe@C and CoNi@C-modified glassy carbon electrode (GCE) presented a sharp increase in reduction current density compared to the unmodified GCE with negligible reduction current density in the O_2-, H_2O_2-, and O_3-saturated atmosphere, which proved the superior catalytic activity of Fe@C and CoNi@C in these reduction reactions and thus could effectively convert oxygen-free radicals into O_2 and H_2O. Meanwhile, As shown in **Figure 3**a,b, the quantum chemical calculations of the catalytic processes by density functional theory further offered atomic-level insights into the free radicals scavenging processes. The cellular level assays demonstrated that the Fe@C and CoNi@C

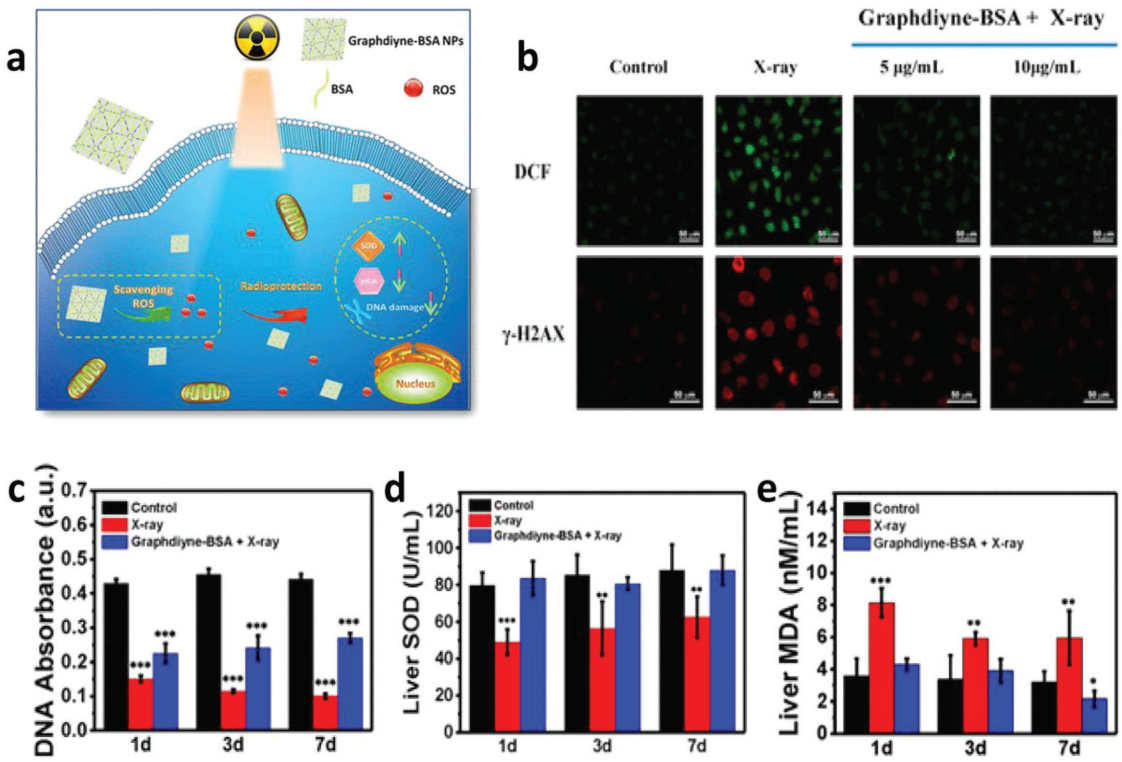

Figure 4. The graphdiyne-BSA nanoparticles for radioprotection. a) The scheme of graphdiyne-BSA nanoparticles for radioprotection. b) Fluorescence images of the intracellular ROS generation and DNA damage in HUVECs after different treatments. c) Total DNA of bone marrow of mice after different treatments. d) SOD levels of liver of mice after different treatments. e) MDA levels in the liver of mice after different treatments. Adapted with permission.[72] Copyright 2018, American Chemical Society.

are helpful in removing ROS, reducing ionizing radiation-induced DNA damage, and improving the survival rates of irradiated CHO healthy cells. In the animal experiments, the Fe@C and CoNi@C could enhance the survival rates and total bone marrow DNA in irradiated C57BL/6 mice (Figure 3c,d), and decrease the cell apoptosis in intestine tissue (Figure 3e). All these results manifested the excellent radiation shielding effects of the Fe@C and CoNi@C.

3.2.1.3. Other New Emerging Carbon-Based Nanoradioprotectors: Recently, some new emerging carbon-based nanoparticles are also investigated for radioprotection, such as BCNPs and graphdiyne nanoparticle. BCNPs, as the natural carbon nanomaterials, possess the unparalleled superiorities including low cost, easy preparation, and relative low toxicity compared to the man-made nanomaterials.[71] Similar to some carbon materials, BCNPs are also confirmed to have free radical scavenging activity and can be used as the radioprotectors.[32] Xie et al. successfully prepared the TPGS-BCNPs and applied them in radioprotection of normal cells.[32] The TPGS-BCNPs could effectively decrease the radiation-induced intracellular ROS level and DNA damage in HUVECs, exhibiting the potential for radioprotection. In another study, a new emerging carbon networks nanomaterial graphdiyne nanoparticle was investigated in radiation protection (**Figure 4**a).[72] The graphdiyne is consisted of strong π-conjugated structure and highly reactive diacetylenic linkages. This unique structure endows the graphdiyne with high free-radicals scavenging activity, because the delocalized conjugated π-system is benefit to capture the electrons and thus easy to react with free radicals. Therefore, the graphdiyne can be used as a free-radicals scavenger and applied in radioprotection. In a typical cell experiment, the as-prepared BSA-modified graphdiyne nanoparticles (graphdiyne-BSA NPs) could powerfully reduce the radiation-induced intracellular ROS and protect DNA from the radiation-induced break in HUVECs, which are reflected by the lower fluorescence signals of 2′,7′-dichlorofluorescein (DCF) and γ-H2AX in graphdiyne-BSA NPs + X-ray-treated group compared to that of X-ray group, respectively (Figure 4b). In addition, the animal experiments indicated that the graphdiyne-BSA NPs could decrease the radiation-induced bone marrow DNA damage, and recover SOD and MDA of radiation-injured mice into normal levels (Figure 4c–e). Therefore, the graphdiyne-BSA NPs hold great promise to be used as the radioprotectors.

Having all these studies in mind, we summarize the radioprotective applications of the representative carbon-based nanomaterials in **Table 1**.

3.2.2. Cerium-Based Nanoradioprotectors

Cerium, a lanthanide element with 4f electrons, has received great attention in the fields of physics, chemistry, biology, as well as materials science.[73] Over the past decade, researchers find that the cerium-based nanoparticles can also protect normal tissue from radiation injury and thus put a lot of effort

Table 1. A list of representative carbon-based nanomaterials used for radioprotection.

Carbon-based nanomaterials	Experimental systems	Evaluative indicators of radioprotection	Radiation type	Ref.
$C_{60}(OH)_x$, (where $x = 18–22$)	Stylonychia mytilus cells	The survival of cells. The activity of SOD, CAT, MDA, and LIP of cells.	^{60}Co γ-ray (22.57 GBq)	[50]
$C_{60}(OH)_{24}$	Male adult white mice	The mean lethal times (LT50) of irradiated mice and the mean lethal dose of X-rays.	X-ray (8 MV)	[51]
$C_{60}(OH)_{24}$	Male adult Wister rats	The survival of rats.	X-rays (8 MV)	[52]
		The blood cell count including (granulocytes and lymphocytes).		
		The pathohistology of the main organs including the lung, heart, liver, kidney, small intestine, and spleen.		
$C_{60}(OH)_{24}$	Human erythroleukemia cell line	The survival rates of cells.	X-rays (10 MV)	[53]
		The activity of GGT, SOD, and GPX.		
$C_{60}(OH)_{24}$	Male ICR mice	The survival of mice. The immune dysfunction, oxidative damage, and mitochondrial dysfunction.	^{60}Co γ-irradiation	[10]
$C_{60}(OH)_{24}$	Male Wistar rats	The survival of mice.	X-rays (8 MeV)	[54]
		The pathohistology of the main organs including the lung, heart, liver, kidney, small intestine, and spleen.		
DF-1	Zebrafish embryos	The survival, morphology, and physiology of zebrafish embryos.	^{137}Cs radiation	[48]
DF-1	Mammalian cells	The oxidative stress, DNA damage, as well as cell death.	^{137}Cs γ- ray	[58]
C_{60}HyFn	Male white Kv:SHK mice	The oxidative damage of DNA in vitro.	X-ray	[59]
		The life span of the mice		
SWCNT	Rat small intestine crypt cells and zebrafish	The survival rates of cells.	γ-ray	[68]
		The growth and morphology of zebrafish		
GO	Fibroblast cells	The cytotoxicity, genotoxicity, γ-H2AX expression, intracellular ROS assay, apoptosis, and micronucleus assay of cells.	X-ray	[69]
Fe@C and CoNi@C	CHO-K1 and H460 cells, C57BL/6 mice, and human lymphocytes	The survival, intracellular ROS assay, micronucleus assay, and DNA damage assay in cells.	γ-radiation using ^{137}Cs (662 keV, 3600 Ci)	[70]
		The chromosomal aberration assay of human lymphocytes.		
		The survival rates, hematology analysis, biochemistry analysis, bone marrow total DNA, bone marrow nucleated cells, cell apoptosis of intestine tissue, SOD, and GSH levels in mice.		
TPGS-BCNPs	HUVECs	The intracellular ROS assay and DNA damage assay in cells.	X-ray	[32]
Graphdiyne-BSA	HUVECs and BALB/c male mice	The cell viability, intracellular ROS assay, and DNA damage assay in cells.	X-ray	[72]
		The total bone marrow DNA, SOD, and MDA levels in mice.		

to study the radioprotection of them.[74] The radioprotective activity of cerium-based nanoparticles derives from their ability of participating the redox coupled reactions. In detail, there are mixed-valence states of cerium (4+) and cerium (3+) on the surface of cerium-based nanoparticles, which are induced by the oxygen vacancies. Through converting the valence state from cerium (3+) to cerium (4+), the cerium-based nanoparticle can react with the free radicals produced by irradiation, and thus diminish the irradiation-induced oxidative damage to cells.[75,76] In recent years, various radioprotection applications of cerium-based nanoparticles can be searched.[75,77–84] For example, Tarnuzzer et al. designed a vacancy engineered cerium oxide nanoparticle and used it for cells radioprotection.[75] Interestingly, the cerium oxide nanoparticle presented almost 99% protection to normal cells but no protection to tumor cells under the same concentration, which endowed the cerium oxide nanoparticle with great potential for protecting normal tissue in cancer radiotherapy. Colon et al. reported that cerium oxide nanoparticles could prevent the onset of pneumonitis caused by radiation.[78] The cell experiments showed that the cerium oxide nanoparticles significantly improved the viability of irradiated normal lung fibroblast cells. The animal studies indicated that the lungs of mice in the radiation alone group presented visible pneumonitis with massive macrophage invasion, but the lungs of mice in radiation + cerium oxide nanoparticles group showed no visible pneumonitis. Soon afterward, they further demonstrated that cerium oxide nanoparticles could combat the radiation-induced gastrointestinal epithelium damage, which not only protected normal human colon cells from radiation-induced cell death, but also reduced terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)- and caspase 3-positive cells of the colonic crypt from irradiated mice.[79] Recently, Popov et al. comprehensively studied the radioprotective action and mechanism of ultrasmall citrate-stabilized

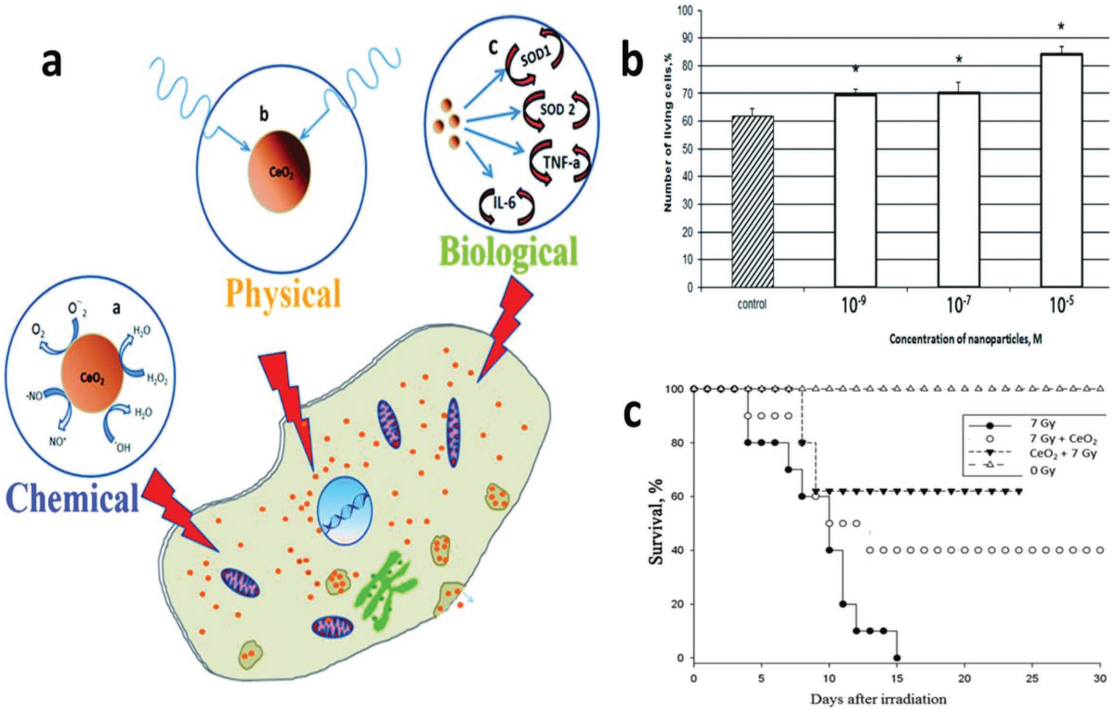

Figure 5. The citrate-stabilized cerium oxide nanoparticles for radioprotection. a) The scheme of the radioprotective mechanisms of citrate-stabilized cerium oxide nanoparticles. b) The cell viability of primary fibroblasts after different treatments. c) The survival rate of mice after different treatments. Adapted with permission.[82] Copyright 2016, the Royal Society of Chemistry.

cerium oxide nanoparticle both in cell and animal models.[82] As illustrated in **Figure 5**a, the radioprotective activities of this nanoparticle mainly covered three aspects. First, this nanoparticle could efficiently inactivate the •OH and hydrogen peroxide generated by X-ray irradiation via chemical protective approach. Second, this nanoparticle performed a shielding function to ionizing radiation through physical protective path. Third, this nanoparticle could regulate some antioxidant enzymes as well as proinflammatory cytokines in vivo from biological protective route. As a result, the ultrasmall citrate-stabilized cerium oxide nanoparticle remarkably decreased the apoptosis of mouse fibroblasts in vitro as well as the death of mice caused by X-ray radiation (Figure 5b,c).

Attributed to the positive radioprotective response of cerium-based nanoparticles, researchers attempt to optimize the physical or chemical parameters of them so as to further enhancing their radioprotective efficiency. As a paradigm, although the cerium-based nanoparticles without surface modification exhibit good radioprotective effects, their nakedness or weakly protection from surfactants may still weaken their bioavailability to a certain extent. Based on this issue, Li et al. adopted surface modifiers to further enhancing stability, reducing cytotoxicity, and improving bioavailability of the cerium-based nanoparticles.[80] They employed PEGylated ceria nanoparticles for radioprotecting human normal liver cells (L-02). It showed that the PEGylated ceria nanoparticles had a higher radioprotective ability compared to the naked ceria nanoparticles. Therefore, optimizing the physicochemical parameters of cerium-based nanoparticle is significant to further improve their radioprotection efficiency.

3.2.3. TMDC Nanoradioprotectors

TMDC is one kind of the hottest research nanomaterial over the last few decades.[85–88] Its chemical formula is MX_2, where M represents a transition metal from Group IVB – VIII (such as Mo and W), and X refers a chalcogen atom (including S, Se, and Te). The 3D structure of TMDC is consisted of a hexagonal layer of M sandwiched between the two layers of X. Together with the topological insulators (such as Bi_2Se_3), over 40 types of TMDCs can be searched.[87] Attributing to their special chemical structure and multifunctional properties, they are extensively applied in many fields such as the energy storage, optoelectronics, sensors, transistors, catalysis, and biomedicine.[88,89]

Interestingly, researchers recently observed that some of the TMDCs are available to be applied in radioprotection via various mechanisms (shown in **Table 2**). As the most representative example, Zhang et al. successfully used the cysteine-modified MoS_2 nanodots for radiation protection through the extraordinary catalytic activities of MoS_2 nanodots (**Figure 6**a).[90] The as-prepared MoS_2 nanodots had highly catalytic abilities toward hydrogen peroxide and oxygen reduction reactions, bringing about many free electron transfers. The endogenous catalytic properties endowed the MoS_2 nanodots with the potential to eliminate the free radicals in vivo, which decreased the normal tissues damage caused by the radiation-induced toxic free radicals and thus achieved radioprotection. As shown in Figure 6b, viabilities of 3T3/A31 cells treated with the MoS_2 nanodots under γ-rays were significantly higher than that of cells treated with γ-rays alone, reflecting the powerful radioprotective behaviors of the MoS_2 nanodots in vitro. Meanwhile, the surviving

Table 2. A list of representative TMDCs used for radioprotection.

Materials	Modification	Radioprotective mechanisms	Injection mode	Radiation types	Ref.
MoS_2	Cysteine	Catalytic activity of the MoS_2 nanoparticles to scavenge the free radicals in vivo	Intraperitoneal injection	γ-rays	[90]
WS_2	Cysteine	Catalytic activity of the WS_2 nanoparticles to scavenge the free radicals in vivo	Intraperitoneal injection	γ-rays	[91]
WSe_2	Cysteine	Catalytic activity of the WSe_2 nanoparticles to scavenge the free radicals in vivo	Intraperitoneal injection	γ-rays	[92]
Bi_2Se_3	PVP	Catalytic activity of the Bi_2Se_3 nanoparticles to scavenge the free radicals in vivo	Intraperitoneal injection	γ-rays	[93]
Bi_2Se_3	PVP, Sec	The synthesis of selenoprotein by the traces of Se released from the PVP-Bi_2Se_3@Sec nanoparticles	Intratumorally injection	X-ray	[94]

fractions of the radiation-injured mice injected with MoS_2 nanodots were improved compared to that of without MoS_2 nanodots, clearly demonstrating the in vivo radiation protection effects of the MoS_2 nanodots (Figure 6c). Moreover, MoS_2 nanodots can effectively decrease bone marrow DNA damage from high-energy γ-rays, and almost recover the SOD and MDA back to normal levels 7 d after treatment. These results further exhibited the ability of MoS_2 nanodots on repair of radiation-induced damage. Consequently, the as-prepared MoS_2 nanodots with extraordinary catalytic activities can be used as the nanoradioprotectors for radiation protection. Similar to MoS_2, other TMDCs including WS_2, WSe_2, and Bi_2Se_3 also have been confirmed to possess the strongly catalytic abilities to scavenge the free radicals and thus have been applied in protection against ionizing radiation.[91–93]

In addition to the catalytic approaches of TMDCs for protecting healthy tissues against ionizing radiation, Du et al. recently reported another new radioprotective mechanism of Bi_2Se_3 for radioprotection.[94] They designed and constructed the poly(vinylpyrrolidone) (PVP) and selenocysteine (Sec)-modified Bi_2Se_3 nanoparticles (PVP-Bi_2Se_3@Sec NPs). Specially, the traces of Se that released from the PVP-Bi_2Se_3@Sec NPs in tumor tissue and entered the blood circulation system could increase the immune function, because the Se was able to be translated into selenoprotein and then catalyzed a series of electron-transfer reactions for antioxidant defense and redox regulation (**Figure 7**). After treating the radiation-injured mice with PVP-Bi_2Se_3@Sec NPs, the expressions of all cytokines (cytokines are the essential components of the innate immune responses) in serum were recovered, indicating that the PVP-Bi_2Se_3@Sec NPs could recover the cytokine-mediated immune function so as to reduce the side effects caused by X-ray radiation. Additionally, the SOD activity of the irradiated mice recovered to normal level 3 d after administration of PVP-Bi_2Se_3@Sec NPs. The glutathione peroxidase (GSH-Px) activity could sustain in higher level until 7th day in X-ray+PVP-Bi_2Se_3@Sec NPs treatment group. The white blood cell (WBC) level of X-ray+PVP-Bi_2Se_3@Sec NPs treatment group gradually rose up to the level of control group

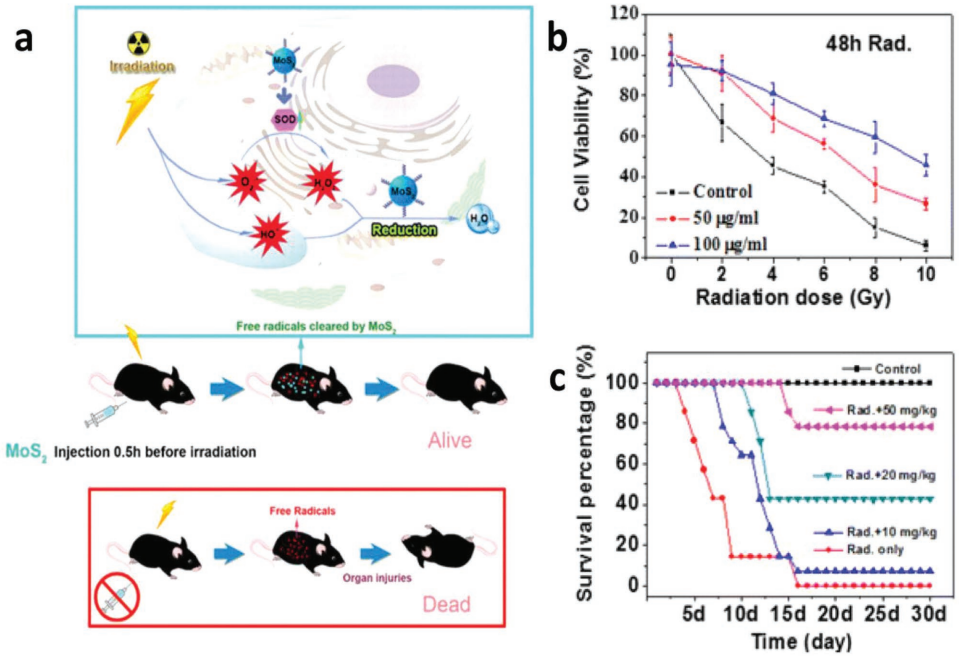

Figure 6. The cysteine-protected MoS_2 nanodots for radioprotection. a) The scheme of the radioprotective action of cysteine-protected MoS_2 nanodots. b) The cell viability of A31 cells after different treatments. c) The survival rate of mice after different treatments. Adapted with permission.[90] Copyright 2016, American Chemical Society.

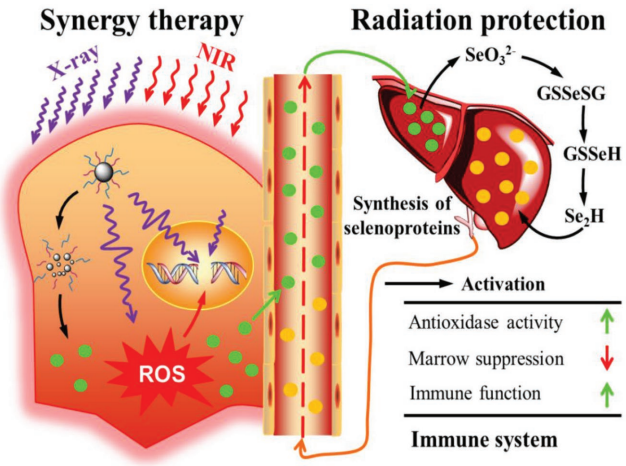

Figure 7. The scheme of the radioprotective mechanisms of PVP-Bi_2Se_3@Sec nanoparticles. Adapted with permission.[94] Copyright 2017, Wiley-VCH.

after 3 d. The marrow DNA level in X-ray+PVP-Bi_2Se_3@Sec NPs group presented unobvious downtrend. These results further manifested the powerfully radiation protection performance of PVP-Bi_2Se_3@Sec NPs.

3.2.4. Noble Metal Nanoradioprotectors

Recently, noble metal nanoradioprotectors including silver (Ag) and platinum (Pt) are gaining interest in the radioprotection field. For example, Chandrasekharan and Nair evaluated the ability of SN to protect against ionizing radiation using the Swiss albino mice.[28] The comet assay demonstrated that postirradiation addition of SN to cells could enhance the cellular DNA repair in blood leukocytes. The in vivo results indicated that the postirradiation administration of SN also increased the cellular DNA repair process and reduced the micronucleus formation. Shortly afterward, they studied the radioprotective ability of SN in preirradiation conditions.[30] The radiation was exposed to the Swiss albino mice after administration of SN in 1 h. It could be observed that the SN decreased the radiation-induced injury in peripheral blood leucocytes, spleen cells, and bone marrow cells of mice via comet assay. Meanwhile, the SN reduced the micronucleus formation as well as chromosomal aberrations. Therefore, the SN exhibited high radiation protection efficiency both in preirradiation and postirradiation conditions. Later, they further certified the potential of SN for the radioprotection of hemopoietic and gastrointestinal system in preirradiation conditions.[31] Administration of SN before γ-radiation exposure could minimize the radiation-induced WBC depletion, improve the bone marrow cellularity, enhance the endogenous spleen colony formation, reduce the radiation-induced consumption of cellular antioxidants as well as lipid peroxidation, and decrease the radiation-induced damage in villus and crypt structure of the intestine. Consequently, these works demonstrate the potential of Ag-based nanoparticles to serve as the nanoradioprotectors for radiation protection.

As early as 2008, Hamasaki et al. had suggested that ultrasmall Pt nanoparticles also had the ability to scavenge •OH and $\bullet O_2^-$, which significantly protected HeLa cells from ROS damage-induced cell death.[95] Recently, Xu et al. further demonstrated that ultrasmall Pt clusters could reduce radiation-induced injuries both in cell and animal models via scavenging free radicals, which could not only decrease the DNA injury in irradiated cells, but also recover the SOD activities and bone marrow DNA level and improve the survival rate of irradiated mice.[96] Most recently, Wang et al. proposed a polyvinyl pyrrolidone-protected PtPdRh nanocube with a simple one-pot synthesis route for radiation protection via catalytic mechanism (**Figure 8**).[97] The ternary PtPdRh nanocubes exhibited a better

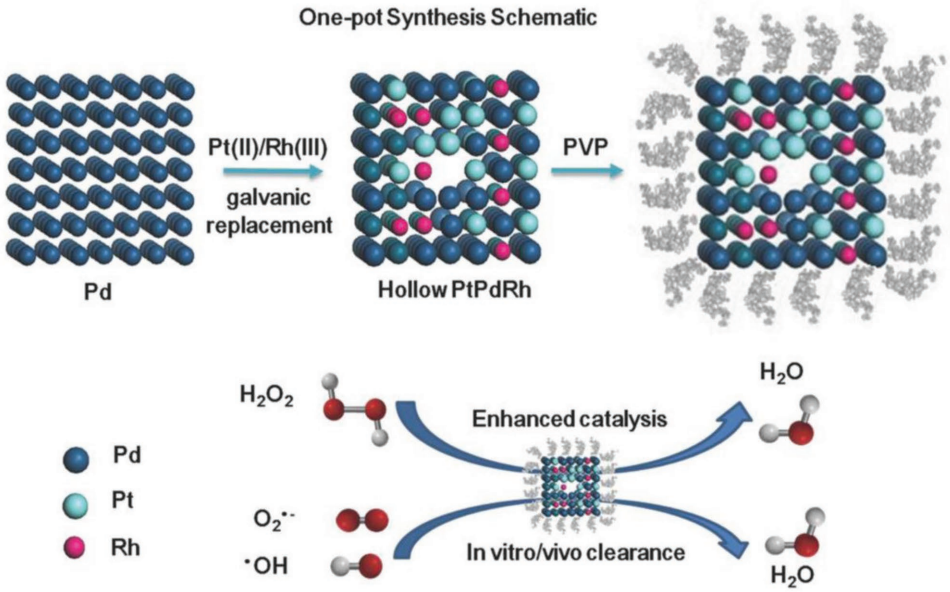

Figure 8. The scheme of the synthetic route and radioprotective mechanisms of PtPdRh nanocubes. Adapted with permission.[97] Copyright 2018, Wiley-VCH.

catalytic property of H_2O_2 decomposition than Pt and PtPd counterparts, which effectively scavenged ROS and showed the positive responses in the important radioprotective indicators, such as cell viability, mice survival rate, DNA damage repair, and antioxidant enzyme activity. As a result, Pt-based nanoparticles are also the promising agents of radioprotection.

3.3. A Perspective of Nanoradioprotectors Designs for Radioprotection Application

Radiation-induced damage can be likened to a chain reaction range from molecular to cell and eventually to tissue. Thus, radioprotective processes can be accomplished through multiform mechanisms at molecular, physiological-biochemical, and organic levels.[98] In recent years, numerous radioprotective mechanisms have been proposed. However, up to date, the design mechanism for almost all of the nanoradioprotectors is still limited to free-radical scavenging. Therefore, we want to introduce some of the other promising radioprotective mechanisms to inspire researchers to design and fabricate nanoradioprotectors with new radioprotective approaches. For example, DNA is the major target of ionizing radiation induced damage of a cell. All the DNA lesions (involving DNA single-strand breaks, DNA double-strand breaks, base damages, and sugar damages) may lead to mutagenicity, function alteration, or death of cells.[43,99] Researchers have devoted great efforts to repair radiation-damaged DNA for radioprotection, such as direct DNA-lesion reversal, mismatch repair, single-strand break repair, base excision repair, nucleotide excision repair, DNA inter strand cross link repair, nonhomologous end joining, and homologous recombination.[100] Herein, we can exploit the nanomaterials with these DNA repair functions to use as radioprotectors. For another example, It has been reported that hypoxic tissue is insensitive to radiation damage and thus the biological effect of radiation is decreased under the condition of hypoxia.[101] Hence, the radioprotective effect will be created if there is a medicine that can provide temporary hypoxic condition in a tissue or cell system. As a representative paradigm, the hypoxia inducible factor HIF1α (a transcriptional factor) is up-regulated when hypoxic condition is formed. Based on this fact, it is easy to understand why the HIF1α level in tumor is higher than that of normal tissue, because the tumor microenvironment is significantly hypoxic. Therefore, it can also increase the concentration of HIF1α in normal tissue to mediate adaptive responses to hypoxia and enhance radioprotection effect.[99,102,103] We thus can design the nanomaterials with HIF1α enhancement ability to induce suitable hypoxia response in normal tissues to block the damage at primary stage of radiotherapy and eventually achieve radioprotection. In addition, inhibiting the death signaling pathways of normal cell is another way to offset the radiation-induced toxicity in vivo. For example, p53 is an important mediator of stress response. It has been indicted that a massive cell loss appeared in radiosensitive tissues after ionizing radiation because of the activation of p53-dependent apoptotic pathway.[104,105] Thereby, inhibiting p53 will block the apoptotic pathway, inhibit cell death, and provide valid radioprotective effects. Moreover, mitogen-activated protein kinase (MAPK) pathway is important to control fundamental cellular process. The MAPK superfamily (including the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK) can mediate ionizing radiation-stimulated multiple signal transduction pathways.[106] As a result, the nanomaterials that have the ability to regulate these radiation-related signaling pathways also have the potential to be developed as radioprotectors. Consequently, plenty of new promising approaches are worth taking into account to design and fabricate nanoradioprotectors, which are beneficial to promote the prosperous development of nanotechnology for radioprotection applications.

4. Conclusion and Outlooks

The development of multifunctional nanomaterials for radioprotection is of great significance. This review sums up the recent advances of harnessing multifunctional nanomaterials for radioprotection, which mainly involve using nanomaterial as drug delivery system to increase the bioavailability of molecular radioprotective drugs, and developing the nanomaterials with intrinsic radioprotective activities as new radioprotectors. Note that despite the fact that important progresses and achievements have been obtained in corresponding studies, the investigations of nanomaterials for radioprotection are still at their early stage, and the challenges still exist and need to be addressed to promote the advances of this field.

(1) *The biosafety and biodistribution of nanomaterials*. It is known that the biosafety and biodistribution data of nanomaterials have guiding significance for their biological application. Taking graphene-based and CNT-based nanomaterials as examples, although the reports of graphene-based and CNT-based nanoradioprotectors can be searched, there are still limited papers about possible radioprotective properties of them, which may be ascribed to the toxicity of these materials induced by the factors of concentration, synthesis methods, impurities, size, and so on.[47] For instance, Qiao et al. indicated that only at relatively low concentrations of 10 μg mL^{-1}, the GO could be used as an effective radioprotector. At a higher concentration of 100 and 500 μg mL^{-1}, the GO would lead to DNA damage and cell death.[69] For another example, Kostarelos indicated that the long and rigid CNTs should be avoided when applying in vivo, and the chemical functionalization of CNT needed be optimized to ensure its sufficient dispersibility, individualization, as well as excretion rates to avoid tissue accumulation.[107] Therefore, if the graphene-based nanomaterials and CNTs are desirous to apply in radioprotection, plenty of physical and chemical parameters of them should be optimized to satisfy its acceptable biosafety for future application.

Moreover, although a large number of toxicity and biodistribution studies of nanomaterials have been reported, most biosafety evaluations of them are short-term. The investigations on the long-term biosafety of nanomaterials in vivo are still insufficient. Therefore, it is important to examine the long-term biosafety of nanomaterials in vivo so as to guide their clinical utility.

(2) *Improving radioprotective efficiency by optimizing the physicochemical parameters of nanomaterials*. The radioprotective efficiency of nanoradioprotectors is associated with many physicochemical properties of nanomaterials, such as the shape, size, and surface functional modification. For instance, as mentioned above, it has been shown that the ceria nanoparticles modified with PEG had a higher radioprotective ability compared to naked ceria nanoparticles.[80] Therefore, the efforts are needed to compare the radioprotective efficacy of radioprotectors with different physicochemical parameter to obtain the optimal conditions.

(3) *Promoting the development of new type of nanoradioprotectors*. Some nanomaterials have been proved to possess free radical scavenging activities, but have not yet been applied for radioprotection, such as $Gd@C_{82}$-based nanoparticles.[108,109] As well, a few nanomaterials have been mentioned that possess the potential for radioprotection, but wider radioprotective applications of them can be explored. For instance, $GdEuVO_4$ nanoparticles have once been reported to display a strong radioprotective effect in the irradiation of rats.[110] We can further explore their radioprotective responses in other cell or animal models. Therefore, there is still large space to develop and apply the new type of nanoradioprotectors.

(4) *Deeper explanation of the mechanisms of nanoradioprotection*. Although there have been plenty of papers about nanomaterial-induced radioprotection, most of them focus on exhibiting the radioprotective phenomenon, and the corresponding radioprotective mechanisms are not deep discussed. Therefore, it is desired to deeply understand radioprotective mechanisms of nanoradioprotectors.

(5) *Establishment of evaluation standards for radioprotection*. A large number of evaluating indicators can be found for estimating the effects of radioprotectors, such as the survival of cells or animals, DNA damage level, antioxidase activity, and pathohistology of the main organs. However, integration of all the evaluating indicators into a systematic evaluation standard is still not achieved. Therefore, further efforts are required to establish the evaluation criteria for radioprotection.

(6) *Promoting the clinical translation of nanoradioprotectors*. Up to date, there are still too many literatures but too few clinic nanoradioprotectors. Therefore, it needs to spare no effort to promote the clinical translation of nanoradioprotectors.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

multifunctional nanomaterials, nanocarriers, nanoradioprotectors, radioprotection, radioprotective mechanisms

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