

Ionizing Radiation-Induced Ferroptosis Based on Nanomaterials

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Abstract: Ferroptosis is an iron-dependent form of regulated cell death (RCD), that is associated with peroxidative damage to cellular membranes. A promising therapeutic method is to target ferroptosis. Nanomaterial-induced ferroptosis attracts enormous attention. Nevertheless, there are still certain shortcomings in ferroptosis, such as inadequate triggered immunogenic cell death to suit clinical demands. Various investigations have indicated that ionizing radiation (IR) can further induce ferroptosis. Consequently, it is a potential strategy for cancer therapy that combines nanomaterials and IR to induce ferroptosis. Initially, we discuss various ferroptosis inducers based on nanomaterials in this review. Furthermore, mechanisms of IR-induced ferroptosis are briefly introduced. Ultimately, we assess the feasibility of combining nanomaterials with IR to induce ferroptosis, paving the way for future research.

Keywords: radiation therapy, lipid peroxidation, ROS, nanoparticles, combined therapy

Introduction

Ferroptosis, one of the rare non-apoptotic cell deaths, is an iron-dependent form of RCD induced by peroxidative damages of polyunsaturated-fatty-acid-containing phospholipids (PUFA-PLs) in cellular membranes.¹ Studies have demonstrated that ferroptosis is distinct from other forms of RCD. Ferroptosis cells typically have constricted mitochondria, higher mitochondrial membrane density, and fewer mitochondrial cristae.¹ Mechanistically, cells undergoing ferroptosis is regulated by multiple cellular metabolic pathways such as redox homeostasis,² iron handling,³ and metabolism of amino acids,⁴ lipids⁵ and energy.⁶ Ferroptosis as a critical cell death response is involved in multiple cancer therapies.⁷ As a result, ferroptosis has sparked a wave of interest in recent years as a viable therapeutic approach. Ferroptosis, on the other hand, is dependent on reactive oxygen species (ROS) and lipid peroxidation. Targeting ferroptosis treatment has obstacles because of limited efficiency and selectivity.⁸ For example, ferroptosis-induced immunogenic cell death is insufficient to fulfill clinical requirements.

Various nanomaterials have garnered a great deal of attention as nanotechnology has advanced. The benefits of nanomaterials in terms of biocompatibility, cytotoxicity, targeted delivery characteristics, dispersion throughout the organism, and metabolism are increasingly being revealed.⁹ Consequently, Nanomaterials-induced ferroptosis has gained significant attention. By boosting ROS expression and activating long-chain-fatty-acid CoA ligase 4 (ACSL4) via IR, ferroptosis can be strengthened.¹⁰ In addition, recent studies have discovered that cancer cells can be hypersensitive to radiation by enhancing ferroptosis,¹¹ which can increase the efficacy and indications of IR.¹² In this review, firstly, we discuss various ferroptosis inducers based on nanomaterials. Secondly, mechanisms of IR-induced ferroptosis are briefly introduced. Finally, we evaluate the viability of using nanomaterials in conjunction with IR to induce ferroptosis, opening the door for further investigation.

Ferroptosis Inducer Based on Nanomaterials

Numerous therapeutically authorized drugs and ferroptosis inducers are being studied. These drugs primarily affect ferroptosis via influencing the ferroptosis executive system and defense system, redox and iron balance, and cellular metabolism. Ferroptosis inducers are mainly grouped into three categories: I FINs, which inhibit the activity of SLC7A11 or deplete GSH (Erastin, Sulfasalazine (SAS)), class II FINs that inhibit the activity of GPX4 (RSL3), and Class III FIN (Idebenone), which indirectly depletes CoQ and GPX4 by activating tricosahexaene synthase(SQS).¹ There are several drawbacks of small-molecule ferroptosis inducers, but nanomaterials can improve the accumulation and release of drugs on the tumor microenvironment (TME), hence exerting due to their strong biocompatibility, considerable benefits owing to nano-size effects, and enhanced permeability. Recently, several reviews have discussed the mechanism and application of ferroptosis in nanomedicine.^{13,14} In comparison to small-molecule ferroptosis inducers, nanomaterial-based ferroptosis inducers not only promote water solubility, cell targeting ability, tumor-specific drug accumulation and prolong circulation times in vivo,¹⁵ but also induce ferroptosis by loading and releasing $\text{Fe}^{2+}/\text{Fe}^{3+}$ ions in cells, accelerating Fenton reactions and lipid peroxidation accumulation.^{16,17} Therefore, nanomaterial-based ferroptosis inducers have received a huge amount of attention. The ferroptosis execution system and the ferroptosis defense system are crucial to the rational design of nanomaterial-based ferroptosis inducers (Table 1).

PUFA-PL Synthesis and Peroxidation

Lipid peroxidation is a common feature of ferroptosis. Nanomaterials cause ferroptosis predominantly by accelerating PUFA oxidation and esterification¹⁸ and rewriting lipid metabolism.¹⁹ Additionally, ferroptosis was studied by stimulating the synthesis of polyunsaturated ether phospholipids (PUFA-ePLs) as a substrate for lipid peroxidation.²⁰

Iron Metabolism

Due to the formation of iron-mediated ROS via the Fenton reaction, iron metabolism plays a crucial role in ferroptosis.²¹ Iron-based nanoparticles (NPs) and non-iron-based nanoparticles are the two primary categories of nanomaterials used to induce ferroptosis (NNPs). NPs were developed to induce ferroptosis by regulating the intracellular iron, utilizing iron oxide nanoparticles,²⁰ amorphous nanometallic glasses²² and metal organic frameworks (MOFs). In order to directly release ferrous/ferric ions and trigger ferroptosis, Chen et al created the Fe_3O_4 -PLGA-Ce6 nanosystem. This system undergoes the Fenton reaction with intracellular excess hydrogen peroxide.²³ Additionally, some NPs-induced ferroptosis is intimately connected to lysosomal dysfunction. They primarily employ redox processes, denaturation of lysosomal biomolecules, and physical interactions to treat lysosomal impairment, which eventually culminates in ferroptosis.¹³ Additionally, Some NPs-induced ferroptosis is intimately connected to lysosomal dysfunction. They primarily employ redox processes, denaturation of lysosomal biomolecules, and physical interactions to treat lysosomal impairment, which eventually culminates in ferroptosis.²⁴ By indirectly boosting intracellular iron and controlling genes or proteins involved in iron metabolism, NNPs can alter cellular iron metabolism. By completely exploiting endogenous iron stored in endo-lysosomes and an artificial intracellular favorable feedback loop, Xiong et al established a nano-activator to induce ferroptosis.²⁵

Mitochondrial Metabolism

Mitochondria are the primary site of intracellular iron utilization and a major source of cellular ROS.²⁶ Nanomaterials can stimulate mitochondrial metabolism in a multitude of ways to induce ferroptosis. One of the key mechanisms of nanomaterials-induced ferroptosis is Mitochondria iron overload. Superparamagnetic iron oxide nanoparticles (SPION) were degraded to free ferrous iron in lysosomes and subsequently entered into mitochondria, leading to mitochondrial iron overload, and finally mitochondrial lipid peroxidation accumulation, causing ferroptosis.¹⁶ Mitochondrial membrane anchored oxidation/reduction response and Fenton-Reaction-Accelerable magnetic nanophotosensitizer complex self-assemblies loading sorafenib (CSO-SS-Cy7-Hex/SPION/Srfrn) were constructed, which can anchor to the mitochondrial membrane to induces ferroptosis.²⁷ Other investigations have discovered that ferroptosis can be induced by affecting mitochondrial metabolism by upregulating mitochondrial voltage-dependent anion channel (VDAC) proteins.²⁸ Simultaneously, the research reveals that mitochondrial morphological deformations promote mitochondrial collapse,

Table I The Identified Nanomaterials for Inducing Ferroptosis

Compound	Mechanism	In vivo	Reference
Fe ₃ O ₄ -PLGA-Ce6	Increase intracellular Fe ²⁺ and accumulation of ROS	√	[28]
DPA-r-GMA-BA	Delivery system releasing RSL-3	√	[33]
SRF@Hb-Ce6	Delivery system releasing SRF	√	[61]
SRF @Fe ^{III} -TA	Increase intracellular Fe ²⁺ and inhibition of GPX4	√	[62]
NFER Nanodrug	GPX4 inhibition and lipid peroxidation accumulation	√	[63]
FCS/GCS	Increase ROS, lipid peroxidation accumulation and GPX4 inhibition	√	[64]
ZnP@DHA/PyroFe	Increase ROS	√	[65]
ipGdIO-Dox	Increase intracellular Fe ²⁺ and ROS	√	[66]
SPIONCs	Increase lipid peroxidation	√	[53]
PPy-FePO-Gox-PVA	Increase intracellular Fe ²⁺ and H ₂ O ₂	√	[35]
PFTT@CM	Increase intracellular Fe ³⁺	√	[67]
ZVI-NP	Increase mitochondria dysfunction, and lipid peroxidation	√	[47]
CSO-SS-Cy7-Hex/SPION/Srfrn	Increase intracellular Fe ²⁺ and Fe ³⁺	√	[27]
Tf-LipoMof@PL	Increase intracellular iron and Delivery system releasing Piperlongumine	√	[68]
Pa-M/Ti-NCs	Increase intracellular Fe ²⁺ and H ₂ O ₂	√	[69]
The high-performance pyrite nanozyme	Increase intracellular iron and H ₂ O ₂	√	[70]
Fe ₃ O ₄ -PLGA-Ce6	Increase intracellular Fe ²⁺ and Fe ³⁺	√	[23]
TA-Fe/ART@ZIF	Increase intracellular Fe ²⁺	√	[71]
Malt-PEG-Abz@RSL3	Delivery system releasing RSL-3	√	[72]
NMIL-100@GOx@C	Increase intracellular Fe ²⁺ and H ₂ O ₂	√	[73]
DBCO-8ArmPEG-SS-DHA @RSL3	Delivery system releasing RSL-3, Increase intracellular Fe ²⁺ and GPX4 inhibition	√	[74]
AMSNs	The inactivation of GPX4	√	[75]
macDNA-Fe/PMCS	Increase ROS and on-demand GSH-consuming ability	√	[76]
ACC@DOX-Fe ²⁺ -CaSi-PAMAM-FA/mPEG	Increase intracellular Fe ²⁺ and H ₂ O ₂	√	[77]
FesiRNAPNPs	Increase intracellular Fe ²⁺ and interfere with tumor energy metabolism	√	[78]
⁶⁴ CaCO ₃ -PEG	Increase intracellular Fe ²⁺ and ROS	√	[79]
Fc-NLC(F)@PC	Increase intracellular Fe ²⁺ and lipid peroxidation, the inactivation of GPX4 and mitochondrial dysfunction	√	[80]
FTG/L&SMD	Increase intracellular Fe ²⁺ , H ₂ O ₂ and GPX4 inhibition	√	[81]
ChA CQDs	The inactivation of GPX4	√	[82]
RSL3@COF-Fc (2b)	Increase intracellular Fe ²⁺ and GPX4 inhibition	√	[83]

(Continued)

Table I (Continued).

Compound	Mechanism	In vivo	Reference
FGLC	Increase intracellular Fe ²⁺ and ROS and consume reduced glutathione	√	[84]
Fe ₃ O ₄ @PGL NPs	Increase intracellular Fe ²⁺ and ROS	√	[85]
UCNP	Increase intracellular Fe ³⁺ and Fe ²⁺	√	[86]
DOX-TAF@FN	Increase intracellular Fe ³⁺ and Fe ²⁺	√	[87]
GNPIPI2MA	Deplete GSH and disrupted intracellular redox status	√	[88]
DMSN/Fe ₃ O ₄ -Mn@CB-839	Decompose H ₂ O ₂ , deplete GSH and block the endogenous synthesis of GSH	√	[89]

which can eventually lead to ferroptosis.²⁹ Therefore, nanomaterials that directly target mitochondria can boost ferroptosis efficiency even more.

GPX4 Dependent Systems

The SLC7A11-GSH-GPX4 axis constitutes GPX4 dependent systems against ferroptosis. SLC7A11 is the critical transporter subunit in the glutamate-cystine reverse transporter (system Xc-), which is the primary route for intracellular cysteine to be obtained.³⁰ Intracellular cysteine is largely responsible for GSH synthesis, and GSH peroxidases 4 (GPX4) plays an essential role in converting GSH into oxidized glutathione disulfide (GSSG) to inhibit ferroptosis.³¹ Inhibition of system Xc-³² and GPX4³³ and depletion of intracellular GSH³⁴ are the chief mechanisms by which nanomaterials for inducing ferroptosis regulate GPX4 dependent systems to induce ferroptosis.

Other Mechanisms

FSP1, which is recruited to the plasma membrane as an oxidoreductase, lowers coenzyme Q₁₀ (CoQ10), preventing the growth of lipid peroxides.³⁵ To amplify ferroptosis, a ferroptosis-driven nanomaterial is intended to disrupt a GPX4- and GSH-independent ferroptosis regulation the FSP1-CoQ10-NADPH pathway.³⁶

Mechanisms of Ferroptosis Induced by Radiotherapy

The crux of ferroptosis execution is regulating the balance between the ferroptosis execution system and the ferroptosis defense system. Cells conduct ferroptosis when the ferroptosis execution system exceeds the ferroptosis defense system. PUFA-PLs synthesis and peroxidation,³⁷ iron metabolism,³⁸ and mitochondrial metabolism⁷ constitute the ferroptosis execution system. The ferroptosis defense system mostly consists of GPX4 dependent and GPX4 non-dependent systems. The ferroptosis defense system is heavily reliant on the solute carrier family 7 member 11-glutathione (SLC7A11)-GSH-GPX4 axis.³⁹ The ferroptosis inhibitory protein 1 (FSP1)-CoQ10 pathway,³⁵ dihydroorotate dehydrogenase (DHODH)-dihydrobiquinone (CoQH2) pathway,⁴⁰ and GTP cyclohydrolase-1 (GCH1)-tetrahydrobiopterin (BH4) pathway⁴¹ constitute the ferroptosis defense system. Specifically, IR predominantly induces ferroptosis via the parallel mechanisms listed below (Figure 1).

1. IR not only causes excess ROS formation by initiating radiolysis of cellular water and stimulating oxidative enzymes, altering mitochondrial structure or function, but also induces ACSL4-catalyzed PUFA production of PUFA-CoA, which is subsequently stimulated by LPCAT3 to generate PUFA-PLs. ROS and PUFA-PLs collaborate together to peroxide PUFA-PLs and induce ferroptosis.¹
2. The insertion of multi-PUFA into phospholipids of membrane components can be promoted via IR by upregulating the expression of ACSL4 to construct PUFA-PLs, which is subsequently mediated by ALOX to undergo lipid peroxidation and induce ferroptosis.⁴²

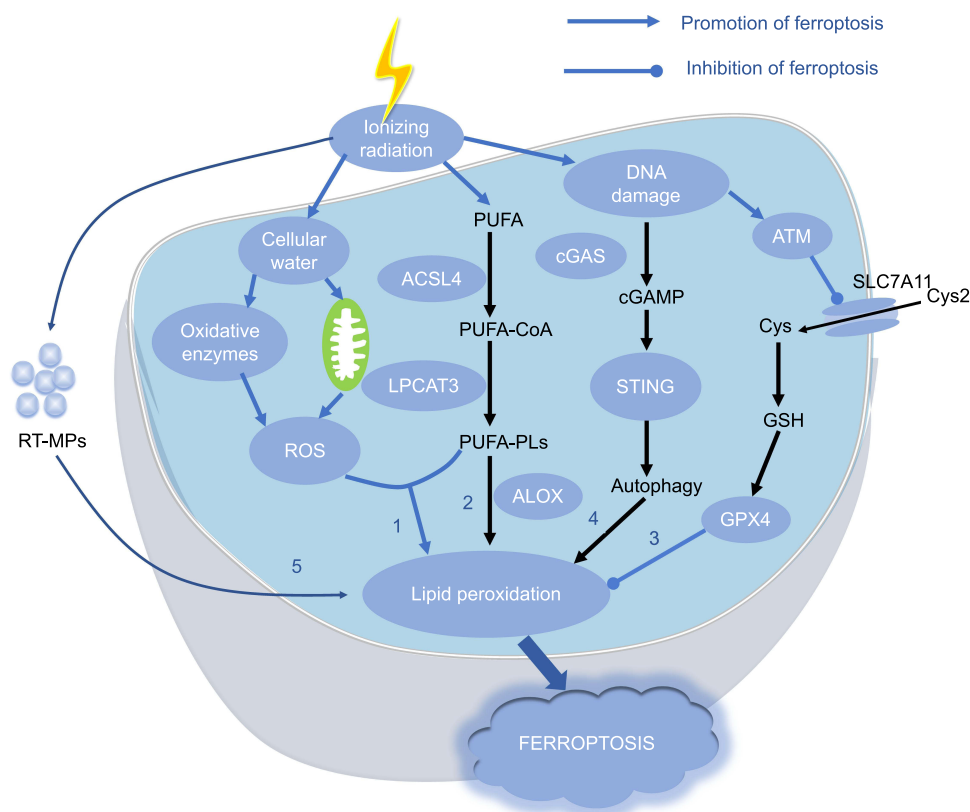


Figure 1 Mechanisms of ferroptosis induced by IR. It mainly affects ferroptosis through 5 pathways. 1: IR not only causes excess ROS to induce ferroptosis by triggering radiolysis of cellular water and stimulating oxidative, altering mitochondrial structure or function. 2: IR can mediate lipid peroxidation and induce ferroptosis by upregulating the expression of ACSL4. 3: IR induced DNA damage, inhibited the expression of SLC7A11, weakened the ferroptosis defense system mediated by the SLC7A11-GSH-GPX4 signaling axis, and further promoted ferroptosis. 4: IR-induced DNA breakage activates the cGAS-STING1 pathway, leading to autophagy-dependent ferroptosis via lipid peroxidation. 5: IR, primarily by causing ferroptosis, can promote the production of tumor cell-released particles (RT-MPs), reverse the tumor microenvironment, increase antitumor effects, and mediate bystander effects (RIBE).

3. IR induces DNA damage, which activates ATM, inhibiting the production of SLC7A11, a crucial component of the cystine/glutamate transporter. It can continuously deplete GSH and inhibit GPX4, weakening the SLC7A11-GSH-GPX4 signaling axis-mediated ferroptosis defense system and further promoting ferroptosis.¹²
4. IR-induced DNA breakage and subsequent activation of the DNA sensor cyclic GMP-AMP synthase (cGAS) signal activates the cGAS-STING1 pathway, leading to autophagy-dependent ferroptosis via lipid peroxidation.³⁸
5. IR can contribute to the production of tumor cell release particles (RT-MPs), which reverses the tumor microenvironment, increases antitumor effects, and mediates bystander effects (RIBE) in tumor cells essentially by triggering ferroptosis.⁴³

Combined Ferroptosis-Driven Nanomaterials and Ionizing Radiation

Some studies have revealed that inducing ferroptosis is closely related to TME. Interferon- γ (IFN- γ) secreted by CD8⁺ cytotoxic T cells augment lipid peroxidation and ferroptosis through downregulating SLC7A11 expression.⁴⁴ Nanomaterials may be used to transport therapeutic radioisotopes into malignancies, according to several studies.⁴⁵ In recent investigations, nanoparticles operate as radio-sensitizers, depositing radiation energy and improving the therapeutic impact.⁴⁶ A novel nanomaterial leads to ferroptosis by generating mitochondria dysfunction, intracellular oxidative stress, and lipid peroxidation, and a technique to synergistically reprogram TME is developed.⁴⁷ Nonetheless, this therapy still has certain shortcomings in that induced immunogenic cell death is insufficient to fulfill clinical demands. Radiation therapy (RT) induces tumor-cell ferroptosis, whereas

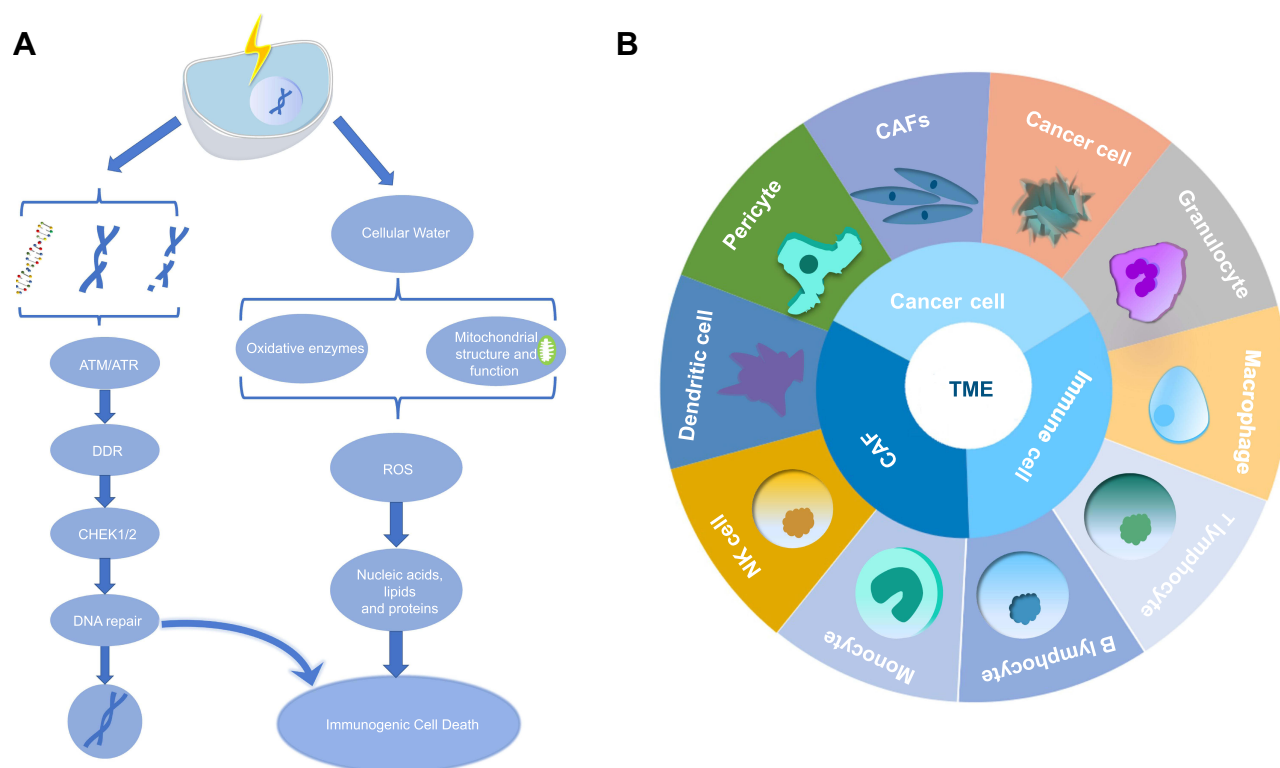


Figure 2 (A) IR possesses direct and indirect impacts on cellular function. Base damage, SSBs, and DSBs are only a couple of minor types of DNA damage that IR may induce. In addition, IR causes radiolysis of cellular water, activates oxidative enzymes, and modifies mitochondrial structure or function to yield ROS. **(B)** TME is composed of different cell populations, such as tumor cells, immune cells, and CAFs, each of which reacts differently to radiation. Granulocytes and monocytes are particularly vulnerable to radiation, while B cells, T cells, NK cells, macrophages, and dendritic cells react differently.

ferroptosis inducers boost radiation effectiveness.⁴⁸ When IR is paired with ferroptosis inducers, antitumor immune responses are strengthened even more.⁴⁸

External beam radiotherapy (EBRT) and internal radioisotope therapy (RIT) are composed of RT.⁴⁶ RT utilizes IR to induce cell death directly through DNA double-strand breaks.⁴⁹ IR induces cellular effects in both direct and indirect ways (Figure 2A). On the one hand, IR induces various type of DNA damages namely base damage, single-strand breaks (SSBs) and double-strand breaks (DSBs).⁵⁰ DNA damage response (DDR) induced by ATM and ATR detection activates downstream checkpoint kinase 1/2 (CHEK1/2) to cause cell cycle arrest and encourage repair of the damaged DNA. If the damage cannot be fully repaired, the cell will initiate the apoptotic program.^{1,42} IR generate ROS by eliciting radiolysis of cellular water, activating oxidative enzymes and altering mitochondrial structure or function.¹ Then ROS reaches a specific dose and can attack nucleic acids, lipids and proteins to induce ferroptosis. Specialized cells react differently to IR. TME, which is made up of several cells comprising tumor cells, immune cells, and cancer-associated fibroblasts (CAFs) determines how tumor cells respond to IR (Figure 2B).⁵¹ Monocytes and granulocytes, for instance, are extremely susceptible to radiation, whereas B cells, T cells, NK cells, macrophages, and dendritic cells (DCs), which have effective DNA repair and DDR capabilities, respond differently to radiation.⁵⁰ Ferroptosis is one of the multiple deaths brought on by IR, which also releases TAAs and DAMPs, enhances antigen presentation, prompts DC activation, and subsequently enhances T cell activation. IR induces immunogenic cell death (ICD) including ferroptosis, then releases damage-associated molecular patterns (DAMPs) to facilitate the proliferation of CD8⁺ T cells through antigen cross-presentation from DCs.⁴⁹

Jiang et al developed photosynthetic microcapsules (PMCs) powered by external near infrared photons. X-rays have the potential to efficiently generate oxidative radicals and construct micro oxygen factory in the body. Nanomaterial PMCs triggered by NIR-II laser irradiation may create a hyperoxia microenvironment in malignancy via controlled photosynthesis. The combination of X-rays and hyperoxia was discovered to cause Radiation-hyperoxia-induced lipid peroxidation (RHILP),

which interferes with Fe²⁺ metabolism in cells, inhibits GPX4 production, and consumes GSH, ultimately leading to ferroptosis. Combining IR with nanomaterials can create an oxygen-rich microenvironment in the tumor and boost the therapeutic use of radiation by triggering ferroptosis, according to this study.⁵² Li et al reported superparamagnetic iron oxide nanoclusters (SPIONCs) that can release more iron ions on TME, and stimulate more hydrogen peroxide when exposed to X-rays. Ultimately, ferroptosis ensued because IR and NPs exacerbated generation of hydroxyl radicals and tumor lipid peroxidation.⁵³ Additionally, this analysis demonstrated that SPIONCs have no effect on the level of blood biochemical and normal kidney and liver function and has the potential for clinical translation.⁵³ In addition, certain studies have employed nanomaterials as radionuclide carriers to supply sufficient tumor-targeted delivery and improve effect of radionuclide therapy. Chen et al utilized the therapeutic radionuclide iodine-131(¹³¹I) to label HSA-CAT nanoreactors (NRs), and dramatically attenuate tumor hypoxia, hence boosting the therapeutic efficacy of radionuclide ¹³¹I.⁵⁴ Shi et al designed a nano-radiopharmaceutical (¹⁷⁷Lu-SPN-GIP) that displayed greater tumor-killing impact than conventional RT and considerably improved therapeutic outcomes.⁵⁵ Consequently, combining nanomaterials-induced ferroptosis and ionizing radiation will be a viable approach. Because it can improve stability, cell uptake rate and tumor site retention time. Rational design of ionizing radiation-induced ferroptosis based on nanomaterials can not only improve the outcomes of conventional RT, but also enhance ferroptosis therapy, providing better antitumor effects than systemic approaches.

Conclusions and Perspectives

Ferroptosis inducer based on nanomaterials may not only directly induce cell ferroptosis, but also operate as radio-sensitizers to attenuate the radio-resistance of cancer cells, and at the same time serve as targeted transport vehicles. It has the capacity to effectively limit tumor growth by enhancing immune responses further and observing a long-term immunological memory impact.⁵⁶ Nanomaterial-based ferroptosis inducers have also been suggested as contrast agents for T1-weighted magnetic resonance imaging.⁵⁷

Moreover, there are several issues with nanomaterials that have not yet been resolved. Nanomaterial-based ferroptosis inducers must also have minimal adverse effects, strong anticancer properties, biocompatibility, superior pharmacokinetics, and features for targeted distribution.⁵⁸ We must first take into account the biosafety of nanomaterials. The linked organs may be harmed or toxicated by iron produced from nanomaterials.⁵⁹ Second, it is apparent that multiple cancer forms differ in their susceptibility to radiation. Exist any unique variations in nanomaterials for clinical usages? Finally, can nanomaterial stability and biodegradability satisfy pharmacokinetics within the therapeutic window?⁵⁹ Phagocytes may readily target nanomaterials, which hinders their ability to execute their intended objectives. Although the therapeutic efficacy of radionuclides for treatment is raised by incorporating them into nanomaterials, a significant barrier is their delayed elimination.⁶⁰ The elevated levels of ROS in tumor cells have a variety of functional implications that, like a “double-edged sword”, cause ferroptosis. The susceptibility to ferroptosis and IR varies among people, cell types, and developmental stages, which is noteworthy.¹⁴ Therefore, more research is needed to determine if ionizing radiation and nanomaterial-induced ferroptosis are safe when used together in preclinical trials. IR combined with nanomaterial-induced ferroptosis can enhance immunogenicity and further support antitumor immune responses. Immune checkpoint inhibition facilitates the activation of systemic antitumor immune responses. An innovative concept for the therapy of cancer in the future is provided by coupled nanomaterial-induced ferroptosis and IR.

Abbreviations

RCD, regulated cell death; IR, ionizing radiation; PUFA-PLs, polyunsaturated-fatty-acid-containing phospholipids; ROS, reactive oxygen species; ACSL4, long-chain-fatty-acid CoA ligase 4; TME, the tumor microenvironment; PUFA-ePLs, polyunsaturated ether phospholipids; NPs, iron-based nanoparticles; NNPs, non-iron-based nanoparticles; MOFs, metal organic frameworks; GPX4, GSH peroxidases 4; CoQ10, coenzyme Q₁₀; SLC7A11, The solute carrier family 7 member 11-glutathione; FSP1, The ferroptosis inhibitory protein 1; DHODH, dihydroorotate dehydrogenase (DHODH); CoQH2, dihydroubiquione; GCH1, GTP cyclohydrolase-1; BH4, tetrahydrobiopterin; cGAS, the DNA sensor cyclic GMP-AMP synthase; IFN- γ , Interferon- γ ; RT, Radiation therapy; EBRT, External beam radiotherapy; RIT, internal radioisotope therapy; SSBs, single-strand breaks; DSBs, double-strand breaks; DDR, DNA damage response; CHEK1/2, checkpoint kinase 1/2; CAFs, cancer-associated fibroblasts; DCs, dendritic cells; ICD, immunogenic cell death; DAMPs,

damage-associated molecular patterns; SPION, Superparamagnetic iron oxide nanoparticles; VDAC, voltage-dependent anion channel; PMCs, photosynthetic microcapsules; RHILP, radiation-hyperoxia-induced lipid peroxidation; SPIONCs, superparamagnetic iron oxide nanoclusters; NRs, nanoreactors.

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Disclosure

The authors report no conflicts of interest in this work.

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