From mitochondrial dysregulation to ferroptosis: Exploring new strategies and challenges in radioimmunotherapy (Review)

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Abstract. Ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated immunogenic cell death (ICD). ICD has demonstrated potential to overcome resistance to conventional cancer therapies, enhancing the efficacy of treatments such as chemotherapy, radiotherapy, immunotherapy and photodynamic therapy. Notably, in the context of radiotherapy, ferroptosis serves a key role, particularly when combined with radioimmunotherapy. Mitochondria are central to the regulation of radiation-induced oxidative stress and the remodeling of the immune microenvironment, and they undergo characteristic morphological changes during the ferroptotic process. However, the precise regulatory association between mitochondrial dysfunction and ferroptosis remains incompletely understood, and there is an ongoing debate regarding this complex interaction. The present review aimed to explore the mechanisms through which mitochondria and ferroptosis interact in the context of radiotherapy, with a focus on how ferroptosis exacerbates mitochondrial dysfunction. Additionally, the present review proposed novel strategies leveraging radioimmunotherapy to offer more precise and effective approaches for cancer treatment.

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1. Introduction

Malignant tumors, which are characterized by phenotypic plasticity, metabolic reprogramming and immune evasion, continuously adapt to conventional treatment strategies, highlighting the urgent need for the development of novel and more effective therapeutic approaches (1). Radiotherapy exerts its tumor-killing effects through two main mechanisms: i) Direct DNA damage induced by high-energy radiation; and ii) indirect DNA damage via reactive oxygen species (ROS). Ionizing radiation (IR) releases high-energy photons that disrupt the DNA structure of tumor cells, leading to base modifications and single- or double-strand breaks. These DNA lesions result in cell cycle arrest, apoptosis or necrosis, directly impacting tumor cell survival (2). In addition to DNA damage, IR induces the decomposition of intracellular water, generating substantial hydroxyl radicals (OH·) and other ROS species. IR causes a redox imbalance within cells, which leads to lipid peroxidation, protein denaturation and DNA damage, further disrupting normal cellular processes, particularly mitochondrial function (3). With advancements in computational modeling, image-guided technologies and biochemical agents, radiotherapy has been increasingly optimized and currently demonstrates distinct advantages

in combination with other therapies. While previous studies have primarily focused on the mechanisms underlying DNA damage from radiotherapy (4,5), recent research on tumor hypoxia and metabolic reprogramming has shifted attention toward ROS-induced damage and mitochondrial dysfunction resulting from redox imbalance, which have become key areas of investigation (6,7).

Ferroptosis is a newly identified form of programmed cell death characterized by iron-dependent lipid peroxidation, accompanied by an immunogenic response. This form of cell death is intricately linked to the cellular metabolic state and redox balance, serving a critical role in the regulation of radiotherapy efficacy (8). IR promotes the generation of ROS, which directly damage nucleic acids and lipids in tumor cells, thereby triggering lipid peroxidation and ferroptosis (9). In the context of therapeutic resistance, particularly in chemotherapy, radiotherapy and immunotherapy, tumor cells (and especially those in a mesenchymal state with higher metastatic potential) become more susceptible to ferroptosis due to mitochondrial metabolic alterations dependent on the tumor microenvironment (TME) (10). Ferroptosis emerges as a promising pathway for enhancing radiation sensitivity, facilitated by the combined effects of mitochondrial-mediated redox reactions, lipid peroxidation and dysregulated iron metabolism. This offers notable clinical potential for overcoming resistance to conventional therapies (11,12).

Mitochondria are not only the powerhouse of the cell but also central hubs for redox reactions, iron metabolism and lipid peroxidation (13). Mitochondrial involvement in ferroptosis extends beyond regulating redox imbalance, as they are also crucial in ROS accumulation (14). As a result, mitochondria serve a pivotal role in maintaining intracellular redox equilibrium and are essential for executing ferroptotic cell death. In the context of radiotherapy, mitochondrial dysfunction and redox imbalance further drive ferroptosis, while the immunogenic response triggered by ferroptosis provides new opportunities for enhancing radioimmunotherapy. Ferroptosis is not merely a form of cell death; it elicits an immune response that activates immune cells within the TME, thereby improving the therapeutic efficacy of radiotherapy (15).

Despite these findings, the reciprocal regulatory mechanisms between mitochondria and ferroptosis, as well as the associated immune activation in the context of radiotherapy, remain incompletely understood. As research into the association between mitochondria and ferroptosis advances, targeting mitochondrial ferroptosis may become a key strategy for radiation immunosensitization. The present review explored the mechanisms underlying the interaction between ferroptosis and mitochondria under IR, and discussed the potential for targeting mitochondrial ferroptosis as a strategy for enhancing radioimmunotherapy, aiming to uncover the clinical importance of mitochondrial ferroptosis in radiation-based cancer treatment.

2. Ferroptosis is an ICD induced by IR

The incidence and mortality rates of cancer continue to rise, and radiotherapy, a cornerstone in cancer treatment, has been developed and use in the clinic for >100 years (16). Several common cancer types, including nasopharyngeal carcinoma and esophageal cancer, can be effectively treated with radiotherapy, either as a monotherapy or in combination with chemotherapy, immunotherapy and targeted-therapy (17). However, a subset of patients still experiences recurrence or metastasis, presenting a persistent challenge to the efficacy of clinical radiotherapy. Radiotherapy dosage is a crucial determinant of tumor control rates; however, high radiation doses may lead to significant damage to surrounding normal tissues and organs. Therefore, optimizing the radiation dose, enhancing tumor radiosensitivity and minimizing toxic side effects remain critical challenges yet unresolved in the field of radiotherapy (18,19).

Previous research has indicated that the primary mechanism of tumor cell death induced by radiotherapy is through IR-induced proliferative cell death, which includes apoptosis, autophagy and necrosis (20). However, increasing attention has been paid to the potential role of other forms of regulated cell death (RCD) in radiotherapy's therapeutic effects (21,22). Ferroptosis, a form of radiation-induced cell death, has emerged as an important contributor to tumor response, and exhibits characteristics of ICD, which is intricately linked with radioimmunotherapy (23). The hallmark of ferroptosis is iron-dependent lipid peroxidation, particularly of polyunsaturated fatty acid (PUFA)-phospholipids (PLs), accompanied by characteristic mitochondrial morphological changes such as shrinkage, loss or reduction of mitochondrial cristae and increased mitochondrial membrane density. In the context of radiotherapy, IR induces immune system recognition and activation by releasing specific immune stimulants, such as High Mobility Group Box 1 Protein (HMGB1, a nuclear protein promotes late-stage inflammation), ATP and exposed cell membrane antigens, thus triggering ICD and activating $CD8^+$ T cells. IFN-γ produced by $CD8^+$ T cells can alter the lipid metabolic profile of tumor cells, promoting ferroptosis through an ACSL4-dependent pathway (24).

Notably, ferroptosis exhibits crosstalk with various forms of RCD, particularly under oxidative stress conditions, a hallmark of radiation exposure. NADPH oxidase (NOX), a key regulator of lipid redox signaling, serves dual roles in both apoptotic pathways and ferroptosis initiation through lipid peroxidation induction (25). During bortezomib-induced apoptosis, ACSL4 inactivation may suppress the incorporation of PUFAs into cell membranes, consequently diminishing ferroptotic susceptibility. Furthermore, selective autophagy-mediated GPX4 degradation results in intracellular accumulation of free iron and lipid peroxides, ultimately driving ferroptosis progression (26,27).

Radiation-induced ferroptosis not only interacts with other RCD mechanisms, such as apoptosis and autophagy, to modulate tumor cell radiosensitivity, but also reshapes the TME by enhancing the activation and infiltration of immune cells (28). This immune activation, in turn, further sensitizes the tumor to radiotherapy, especially in radioimmunotherapy strategies (28). Specifically, radiotherapy-induced ferroptosis enhances the uptake of tumor antigens by dendritic cells (DCs), thus boosting tumor-specific T cell responses. Additionally, ferroptosis can modulate the activity of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), thus

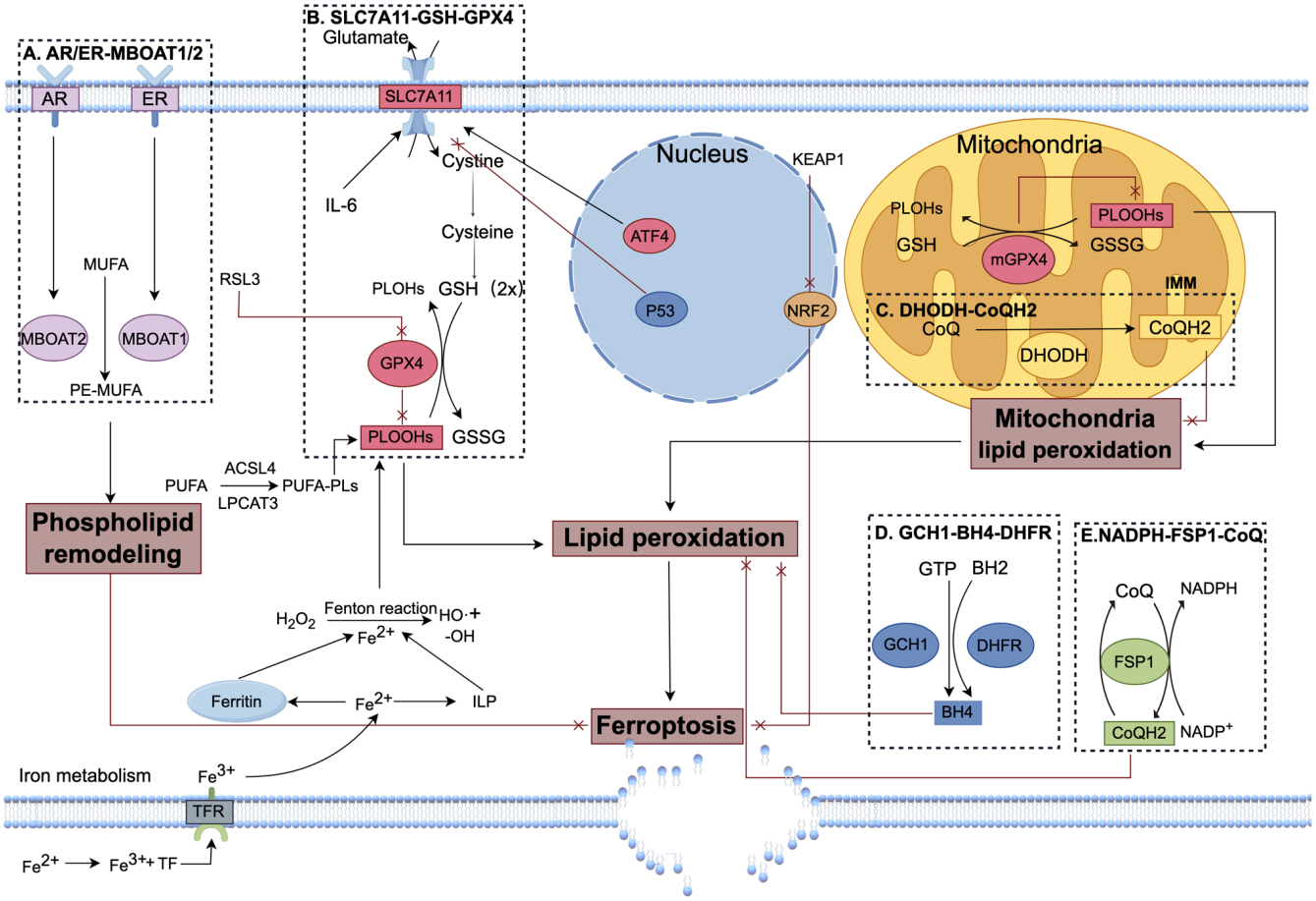

Figure 1. Regulatory network of the ferroptosis defense system. (A) AR/ER-MBOAT1/2: Regulated by ER and AR signaling, MBOAT1/2 inhibits ferroptosis via phospholipid remodeling in a GPX4-independent manner. (B) SLC7A11-GSH-GPX4: The cytoplasmic and mitochondrial GPX4 axis, mediated by GSH, prevents ferroptosis primarily through the inhibition of PLOOH formation. (C) DHODH-CoQH2: The electrons generated from DHODH concurrently reduce CoQ to CoQH2, which in conjunction with mGPX4, effectively prevents lipid peroxidation and inhibits ferroptosis. (D) GCH1-BH4-DHFR: BH4 participates in CoQ synthesis and the REDOX cycle via DHFR, protecting PUFA-PL from oxidative degradation and consequently preventing RSL3-induced ferroptosis. (E) NADPH-FSP1-CoQ: Hydrogen provided by NAD(P)H reduces CoQ to its reduced form CoQH2, which functions as a lipophilic antioxidant to inhibit lipid peroxidation and thereby prevent ferroptosis. The figure was created using Figdraw (www.figdraw.com, ID: UITOP08066). ER, estrogen receptor; AR, androgen receptor; MBOAT, membrane bound O-acyltransferase; GPX4, glutathione peroxidase 4; SLC7A11, Solute Carrier Family 7 Member 11; GSH, glutathione; PLOOH, phospholipid hydroperoxide; DHODH, dihydroorotate dehydrogenase; BH4, tetrahydrobiopterin; PUFA-PL, polyunsaturated fatty acid-phospholipid; NADPH; nicotinamide adenine dinucleotide phosphate.

reshaping the immune landscape of the TME and preventing immune escape (29).

Research into the regulatory pathways of ferroptosis has identified several defense systems with distinct subcellular localizations, including Solute Carrier Family 7 Member 11 (SLC7A11, an antiporter that imports cystine for glutathione synthesis)-glutathione (GSH)-glutathione peroxidase 4 (GPX4), NAD(P)H-FSP1-CoQ, GCH1-BH4-DHFR, sex hormone-MBOAT1/2 and mitochondrial-localized dihydroorotate dehydrogenase (DHODH)-CoQH$_2$ (30). These defense systems regulate key processes such as iron metabolism, redox balance and lipid peroxidation in different cellular compartments, collectively maintaining cellular homeostasis (Fig. 1). When these defense mechanisms are disrupted, cells become more vulnerable to ferroptosis, particularly metabolically active tumor cells (31). Inhibiting key antioxidant enzymes and iron homeostasis regulators can significantly enhance the efficacy of radiotherapy. Consequently, targeting the ferroptosis defense systems has emerged as an effective strategy for radiosensitization in malignant tumors.

3. Mitochondrial involvement in IR-induced cellular damage

Mitochondria are dynamic organelles with a double-membrane structure, serving a pivotal role in maintaining cellular homeostasis through multiple pathways, including the kallikrein system, the unfolded protein response, autophagy and various metabolic processes (32). However, common mitochondrial defects in tumor cells can significantly alter energy production, shifting from oxidative phosphorylation (OXPHOS) to a more simplified, oxygen-independent glycolysis pathway, in order to meet the high metabolic demands of rapid proliferation and the hypoxic, acidic microenvironment typical of tumors (33). These mitochondrial defects also downregulate the mitochondrial apoptosis pathway, a key factor that enables tumor cells to sustain their malignant phenotype and develop resistance to radiation. IR induces serious damage to the mitochondrial membrane, altering its permeability and leading to mitochondrial swelling, vacuolization and fragmentation of the cristae. The damage impairs the electron transport chain

(ETC) and results in ROS accumulation (34). The dysfunction of mitochondria caused by IR can be further amplified through mitochondrial fusion and fission processes, which help dilute the damaged mitochondria. This leads to the genetic transmission of oxidative stress damage within the cell, causing side effects, exacerbating instability in both mitochondrial and nuclear DNA (35). In response to IR, tumor cells compensate by increasing the number of mitochondria and activating repair mechanisms to offset declines in mitochondrial respiratory efficiency, partially restoring mitochondrial function after IR-induced damage (36). However, this compensatory response leads to sustained ROS production, excessive depletion of mitochondrial antioxidants such as manganese superoxide dismutase and coenzyme Q, which further aggravates mitochondrial damage and generates more ROS, creating a vicious cycle that increases the risk of cell death (37).

In a microenvironment with persistently high ROS levels, tumor cells undergo long-term damage, leading to cellular senescence after repeated irradiation and exacerbating secondary radiation damage (38). Mitochondria play a critical role in cellular metabolic plasticity and regulate various forms of RCD, including ferroptosis, following radiation injury. Irreversible mitochondrial outer membrane permeabilization (MOMP) results in the release of pro-apoptotic factors such as cytochrome *c* from the intermembrane space into the cytoplasm, which activates the caspase-9-dependent intrinsic apoptosis pathway (39). Furthermore, mitochondrial DNA (mtDNA) released into the cytoplasm is recognized by cyclic GMP-AMP synthase (cGAS), which activates the cGAS-STING inflammatory pathway, triggering pyroptosis and inhibiting mitochondrial autophagy, thereby exacerbating mitochondrial damage (40). In addition to acting as a cytoplasmic DNA sensor that activates innate immune responses, cGAS also contains a mitochondrial targeting sequence, enabling its localization to the mitochondrial outer membrane (OMM), where it plays a protective role against ferroptosis (41). As IR intensifies its effects on mitochondrial function in tumor cells, structural and metabolic alterations in mitochondria significantly enhance ferroptosis, supporting the potential of ferroptosis in radioimmunotherapy strategies.

Mitophagy, a selective form of macroautophagy that induces the degradation of dysfunctional and damaged mitochondria via the autophagy pathway. Mitophagy serves a key role in maintaining cellular homeostasis (42). Protein disulfide isomerase (PDI), an enzyme primarily located in the endoplasmic reticulum (ER), mediates disulfide bond formation and is often highly expressed in tumor tissues, where its elevated levels correlate with increased pathological grading (43). In colorectal cancer (CRC) cells subjected to radiation-induced ER stress, PDI not only inhibits autophagy initiation by activating the GRP78-mTOR pathway but also competes with LC3II for binding to the mitochondrial autophagy receptor PHB2, thereby regulating the mitophagy process and reducing radiation sensitivity (44). Specifically, PDI plays a critical role in balancing ferroptosis and mitophagy. During ferroptosis, PDI modulates cellular iron homeostasis and redox reactions by influencing antioxidant activity. Additionally, through its dual localization in both the ER and mitochondria, PDI regulates the ER stress response and impacts mitophagy initiation by interacting with PHB2 (44). Through these mechanisms, PDI not only suppresses autophagy initiation but also plays a pivotal role in regulating ferroptosis.

4. Mitochondrial redox states regulate ferroptosis

Functionally intact and structurally complete mitochondria are crucial in defending against ferroptosis through various metabolic and antioxidant pathways (45). On the OMM, voltage-dependent anion channels (VDAC) 2/3, iron transporter proteins Mfrn1/Mfrn2, the mitochondrial permeability transition pore and the mitochondrial Ca^{2+} uniporter facilitate the physiological uptake of Fe^{2+}, maintaining a labile iron pool (46). Mitochondrial ferritin (FtMt) plays a pivotal role in regulating iron metabolism within the mitochondrial matrix. It is involved in the synthesis of iron-sulfur (Fe/S) cluster proteins, such as NADH dehydrogenase, cytochrome *c* and succinate dehydrogenase, thereby maintaining ATP production and preventing the accumulation of mitochondrial ROS (mtROS) (47). FtMt also regulates the availability of free iron in mitochondria, mitigating iron overload, oxidative stress and ferroptosis under conditions such as cerebral ischemia-reperfusion and IR injury. The Fe/S cluster proteins mitoNEET and frataxin on the OMM are similarly essential for maintaining mitochondrial iron metabolism balance and inhibiting ferroptosis. In addition to iron metabolism, cellular energy metabolic pathways, including the tricarboxylic acid cycle (TCA) and OXPHOS, as well as associated regulatory factors such as NADPH, GSH and AMPK, all play critical roles in ferroptosis regulation (48). For example, the mitochondrial transmembrane protein MTCH1 stabilizes the mitochondrial OXPHOS cycle and mtROS levels; its deficiency activates pro-ferroptotic retrograde signaling involving the FoxO1-GPX4 axis, which synergistically enhances the antitumor activity of ferroptosis-inducing agents such as sorafenib (49).

Mitochondrial cysteine metabolism also plays a central role in ferroptosis regulation. The cysteine desulfurase complex NFS1-ISD11 provides sulfur for Fe-S cluster formation and promotes GSH synthesis, thus upregulating the activity of the GSH-GPX4 antioxidant system (50). The hereditary inactivation of fumarase, a key enzyme in the TCA cycle, induces ferroptosis by downregulating GPX4 activity in conditions such as smooth muscle tumors and renal cell carcinoma (51). NADPH, which is critical for GSH conversion in the mitochondrial TCA cycle, is catalyzed by $NADP^+$-dependent isocitrate dehydrogenase (IDH), and its cytoplasmic source can be provided by the reversible oxidative decarboxylation of malate to pyruvate catalyzed by malic enzyme 1 (ME1). NADPH not only drives ATP release through coupling with OXPHOS but also maintains the GSH cycle across various metabolic pathways, thus counteracting mitochondrial lipid peroxidation and reducing susceptibility to ferroptosis (51).

The ETC complexes (complexes I-IV) and ATP synthase (complex V) stimulate ATP synthesis through phosphocreatine and activate the AMPK signaling pathway. Inhibiting acetyl-CoA carboxylase phosphorylation and PUFA synthesis also negatively regulates mitochondrial ferroptosis, exerting similar effects to those of the LKB1-AMPK axis (52). Similarly, enzymes targeting mitochondrial CoQ reduction, such as DHODH and G3P dehydrogenase 2 (GPD2), inhibit mitochondrial lipid peroxidation and ferroptosis by reducing

CoQ to $CoQH_2$ (53). GPD2 further synergizes with mtGPX4, leading to the acetylation of mtGPX4 and contributing to cadmium-induced renal cell ferroptosis (54). The role of mitochondrial supercomplexes formation and its regulatory factor COX7A2L in ferroptosis sensitivity has also been confirmed (55). COX7A2L deficiency induces mitochondrial metabolic reprogramming, enhancing glutamine (GLN) metabolism, cell proliferation and oxidative defense against ferroptosis (56). Furthermore, several regulatory factors that are localized in or translocated to mitochondria after activation also serve a key role in mitochondrial ferroptosis. Mitochondrial inner membrane-localized PDK4 inhibits ferroptosis by blocking pyruvate dehydrogenase-dependent pyruvate oxidation and fatty acid synthesis. However, the roles of AMPK and PDK4 in ferroptosis are cell-type-dependent, with complex interactions between energy status and ferroptosis induced by different activators (57). The mitochondrial metabolic enzyme PCK2 phosphorylates ACSL4 and promotes ACSL4-associated PL remodeling in tumor cells. Cancer stem cells promote PCK2 ubiquitination and degradation, thus maintaining membrane PLs in a ferroptosis-tolerant state (58). Activated by PLC kinase, monocarboxylate transporter 1 (MCT1) translocates to the mitochondrial surface, mediating lactate uptake, promoting ATP production and inactivating AMPK, which increases the expression of sterol regulatory element-binding protein 1, stearoyl-CoA desaturase 1 and the end products monounsaturated fatty acids, thereby contributing to ferroptosis resistance (59). Furthermore, lithium carbonate-induced MCT1 translocation and Ca^{2+} release activate LA oxidation in mitochondria, reactivating LA-suppressive $CD8^+$ T effector cells (60). Mitochondria serve a key role in cysteine deprivation-induced (CDI) ferroptosis, which is distinct from GPX4 inhibition-induced ferroptosis, with the TCA cycle and amino acid metabolism pathways closely linked to CDI ferroptosis (61). GLN, a key respiratory substrate for energy production and lipid synthesis in tumor cells, is degraded by mitochondrial glutaminases (GLS) 1/2. Due to their similar amino acid sequences encoded by unrelated genes, reduction of GLS2, rather than GLS1, through genetic or pharmacological mechanisms, inhibits CDI ferroptosis. Aminooxyacetate inhibits the conversion of GLN to α-ketoglutarate, rescuing CDI ferroptosis in tumor cells (61).

Mitochondria-associated ER membranes (MAMs) are highly dynamic and tightly interconnected structures between the mitochondria and the ER. MAMs serve as a platform for Ca^{2+} signaling between the two organelles and serve a vital role in regulating mitochondrial ferroptosis signaling (62). Mitochondrial microsomal glutathione S-transferase 1 limits lipid peroxidation and ferroptosis by binding to and downregulating ALOX5 activity (63). The calcium-sensitive receptor chaperone protein σ1R mediates the inhibitory effect of the kinase inhibitor CGI1746 on ferroptosis. CGI1746 also slows the Ca^{2+} transport rate within MAMs, disrupting the ferroptosis process (64). The IP3R-GRP75-VDAC1 axis is a key regulatory pathway for the dynamic changes in MAMs, and its inhibition leads to the accumulation of PUFA-containing triacylglycerols, conferring resistance to ferroptosis (65). Mitofusin-2 (Mfn-2), originating from both the mitochondrial membrane and the ER surface, mediates physical and biochemical interactions between the mitochondria and the ER. Mfn-2 serves a key role in mitochondrial fusion and stabilizing mitochondrial-ER contact sites (66). Mfn-2 interacts with the ER-resident protein inositol-requiring enzyme 1α (IRE1α) to participate in arsenic-induced ferroptosis, while IRE1α also influences ferroptosis sensitivity by regulating GSH synthesis (67). Deficiency in the autophagy regulator WIPI4 increases the localization of ATG2 to mitochondria and MAMs, which enhances the transfer of phosphatidylserine within MAMs and the ATG2-dependent synthesis of mitochondrial phosphatidylethanolamine (PE) by phosphatidylserine decarboxylase (PISD), ultimately triggering mitochondrial membrane lipid peroxidation and ferroptosis (68). Inhibition of PISD protects cells from ferroptosis induced by WIPI4 depletion and other inducers, suggesting that PE synthesis in mitochondria may represent a general early step in ferroptosis (69).

The regulatory role of mitochondrial metabolic pathways in ferroptosis varies across different tumor types (70). For instance, abnormal NADPH production and regulation may result in notable differences in ferroptotic effects across malignancies (71). Enzymes involved in NADPH production, such as IDH and ME1, exhibit mutations or deletions in different cancer types, leading to an imbalance in the antioxidant system (72). Specifically, in cholangiocarcinoma, IDH1 mutations promote ferroptosis by lowering GPX4 expression and accelerating GSH depletion (73). In synovial sarcoma, ME1 deficiency alters the mitochondrial NADPH-dependent antioxidant system, increasing susceptibility to ferroptosis induced by ACXT-3102 (74). MAMs also display different ferroptosis sensitivities under various treatments within the same tissue type. mtROS activate the PERK pathway, suppress Mfn-2 expression and cause MAM dysfunction, contributing to arsenic-induced ferroptosis in liver cells. Upregulation of PERK-c fragment expression in MAMs can trigger alcoholic liver ferroptosis, a process inhibited by quercetin (75). Thus, research into mitochondrial metabolic pathways and MAMs regulatory mechanisms across tumor types could offer novel insights into their susceptibility and resistance to ferroptosis, providing potential therapeutic targets for clinical treatment.

Overall, the regulatory role of mitochondria in ferroptosis encompasses iron metabolism, energy metabolism, antioxidant regulation and transmembrane signaling with the ER. These pathways and mechanisms exhibit marked variability across different tumor types. A deeper understanding of these differences could provide personalized therapeutic strategies for ferroptosis-related anticancer treatments.

5. IR-induced mitochondrial metabolic reprogramming regulates ferroptosis

IR induces ferroptosis in tumor cells through multiple mechanisms, which is closely tied to mitochondrial metabolic reprogramming (15). Upon exposure to IR, mitochondria in tumor cells undergo shrinkage and vacuolization, while key components of the cysteine/glutamate antiporter system (system XC-), including SLC3A2 and SLC7A11, are significantly downregulated. This downregulation reduces the synthesis of mtGPX4, thereby weakening the mitochondria's ability to counter lipid peroxidation (76). IR also enhances tumor cell glucose and GLN metabolism, dose-dependently increasing ROS production, which leads to mitochondrial

energy stress. In addition, IR upregulates the expression of the iron transporter SLC39A14 and the key enzyme ACSL4, which is involved in PUFA-PLs metabolism, thus inducing lipid peroxidation (77). Furthermore, a reduction in mitochondrial membrane potential and the proteolytic cleavage of PTEN-induced kinase 1 (PINK1) by the inner membrane protease, presenilin-associated rhomboid-like protease, leads to the stabilization of full-length PINK1 on the OMM. This stabilization recruits the E3 ubiquitin ligase Parkin from the cytoplasm, promoting the ubiquitination of OMM proteins, including VDAC1 and mitochondrial fusion proteins, Mfn-1/2. p62 is subsequently recruited to the mitochondrial surface, initiating mitophagy (78). Lipid droplets (LDs), which serve as cellular organelles for fatty acid storage, are degraded by lysosomes via autophagy under radiation stress, increasing the release of free fatty acids (FFAs) and the risk of lipid peroxidation (79). IR also induces an increase in LD volume and their proximity to mitochondria, eventually forming mitochondrial-LD complexes that facilitate fatty acid transfer to mitochondria (80,81). Key components of this process, such as the LD-anchor protein PLIN5 and carnitine palmitoyltransferase 1, help mitigate lipid accumulation in LDs, thus enhancing mitochondrial fatty acid oxidation (FAO) and the risk of ferroptosis (82). Through the PINK1/Parkin-mediated mitophagy pathway, damaged mitochondrial-LD complexes are engulfed and degraded by lysosomes, and the released FFAs further accelerate the ferroptosis process (83). Additionally, the PINK1/Parkin pathway promotes the ubiquitin-mediated degradation of the mitochondrial iron transporters SLC25A37 and SLC25A28, which enhances mitochondrial sensitivity to ferroptosis. Inhibition of this pathway leads to disrupted mitochondrial iron-dependent immune metabolic function (84).

Hypoxic microenvironments markedly diminish the radiosensitivity of tumor cells and are a major factor contributing to radiation resistance (85). Hypoxia induces the expression of BCL2-interacting protein 3 (BNIP3), which integrates into and anchors to the OMM. By competitively binding to the BH3 domain and activating the PI3K pathway, BNIP3 promotes the initiation of mitophagy (86). Under hypoxic conditions, ROS production increases, promoting the formation of PUFA-PLs through the hypoxia inducible factors (HIFs)-hypoxia inducible lipid droplet associated (HILPDA) axis. The LD-associated protein HILPDA remodels the cellular lipidome, particularly altering the levels of mitochondrial cardiolipin (CL). The HILPDA-CLS1 axis further enhances the accumulation of CL, which promotes mitophagy induced by IR (87). Therefore, mitophagy-dependent ferroptosis may represent a key pathway for enhancing radiosensitivity in hypoxic solid tumors. Furthermore, IR activates multiple signaling pathways that regulate mitochondrial metabolic reprogramming and ferroptosis. These pathways, including AMPK/NF-κB, JAK2/STAT3 and PI3K/Akt/mTOR, activate the reprogramming of mitochondrial glycolysis and lipid metabolism, thereby enhancing ferroptosis susceptibility (3).

Mitochondrial activity-driven innate and adaptive immune responses also serve a key role in the IR-mediated enhancement of ferroptosis sensitivity in tumor cells (15). Upon IR exposure, the mitochondrial metabolism of immune cells, such as T cells, monocytes, macrophages and B cells, becomes increasingly reliant on FAO as a substrate. This metabolic shift serves as a critical endogenous trigger for T cell exhaustion (88). Elevation of FAO leads to mitochondrial depolarization, impaired biosynthesis and excessive ROS production, thereby inducing oxidative stress. Furthermore, FAO inhibits the proteasomal degradation of HIF1α, mediating the glycolytic reprogramming of precursor exhausted T cells. This reprogramming drives their transcriptional and metabolic transformation into terminally exhausted T cells (89).

The newly identified metabolic reprogramming and autophagy pathways offer valuable insights into how modulation of mitochondrial function and ferroptosis mechanisms can enhance the efficacy of clinical radiotherapy for radiation-resistant tumors. These findings potentially provide novel therapeutic targets and sensitization strategies for radioimmunotherapy (Fig. 2).

6. Mitochondrial metabolic reprogramming regulates antitumor immune responses

Mitochondrial dysfunction in various cell types, including tumor cells and immune cells within the TME, serves a pivotal role in tumor progression and immune evasion (90). Specifically, during T cell activation, naïve T cells undergo a metabolic shift from OXPHOS and FAO to aerobic glycolysis and fatty acid synthesis. During this mitochondrial reprogramming, mitochondria accumulate beneath the activated T cell receptor clusters, promoting mitochondrial fission and concurrent relaxation of the inner membrane cristae. This process stimulates mitochondrial activity, including increased production of mtROS and ATP synthesis (91). This metabolic transition is essential for T cell activation and supports their short-term immune responses. However, as T cells differentiate into memory T cells or Tregs, mitochondrial metabolism gradually shifts back to OXPHOS and FAO to support cell survival, maintain cellular phenotype and ensure immune tolerance or immunosuppressive functions (76). In the TME, tumor-infiltrating T cells exposed to chronic hypoxia environments sustained mitochondrial dysfunction due to aberrant activation of the Akt1-PGC1α signaling pathway, leading to persistent mitochondrial damage. This metabolic dysfunction weakens T cell anti-tumor immunity, inhibits cytokine secretion and ultimately facilitates tumor immune evasion (92). Similarly, the immune response of natural killer (NK) cells is significantly influenced by mitochondrial metabolic alterations. During NK cell activation, glycolytic capacity and basal OXPHOS rates increase remarkably. However, in the transition to memory NK cells, damaged mitochondria are removed via mitophagy-related proteins such as BNIP3(L), thereby reducing mtROS production and supporting the formation of memory NK cells (93). By contrast, within a hypoxic TME, tumor-infiltrating NK cells exhibit severe mitochondrial fragmentation, which impairs their tumor-killing capacity and immune surveillance function, thus promoting tumor immune evasion (94). Furthermore, mitochondrial metabolic states profoundly impact macrophage polarization and function within the TME. Upon M1 polarization, macrophages shift their mitochondrial metabolism from OXPHOS to aerobic glycolysis, accompanied by increased mitochondrial fission and elevated mtROS production. By contrast, M2 polarization

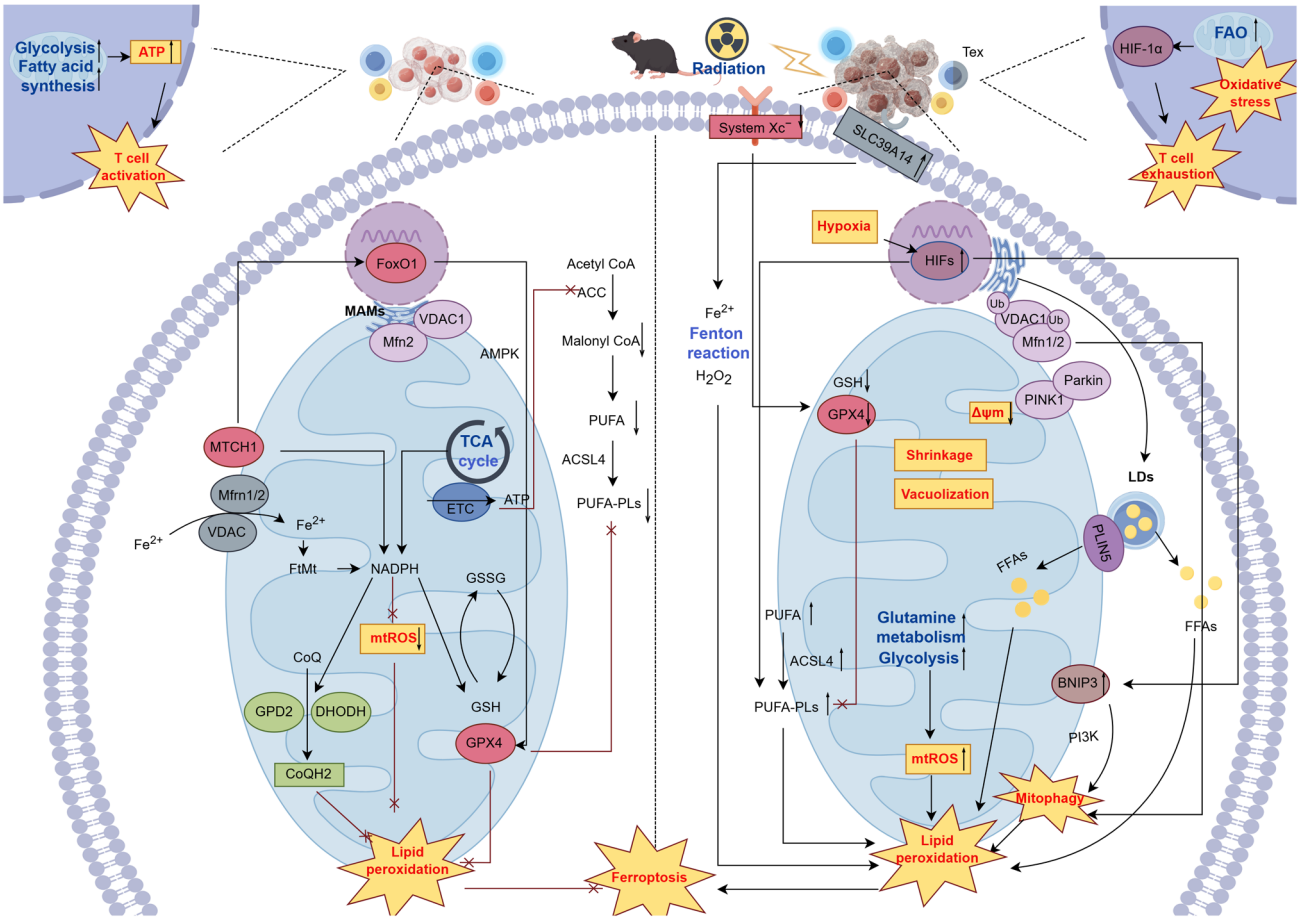

Figure 2. Ionizing radiation-induced remodeling of mitochondrial metabolism regulates ferroptosis. IR augments glucose and glutamine metabolism, consequently elevating ROS production and inducing mitochondrial oxidative stress. The upregulation of ACSL4 expression, autophagic degradation of LDs and PINK1/Parkin-mediated mitophagy result in increased FFA levels, thereby promoting lipid peroxidation. In immune cells, mitochondrial metabolism shifts towards fatty acid oxidation, a critical pathway that contributes to excessive mitochondrial ROS generation and T-cell exhaustion. The figure was created using Figdraw (www.figdraw.com; ID: TIAIY1fbaa). ACSL4, acyl-CoA synthetase long-chain family member 4; LDs, lipid droplets; FFA, free fatty acid; ROS, reactive oxygen species.

is characterized by enhanced mitochondrial fusion, increased OXPHOS and FAO (95). These metabolic reprogramming processes not only govern macrophage polarization but also directly regulate their immune functions and responses to tumor progression. Therefore, dynamic alterations in mitochondrial metabolic states and morphology have a direct impact on immune cell polarization and immune efficacy within the TME, serving a crucial role in tumor immune evasion (Fig. 3).

IR-induced mitochondrial stress triggers the release of mtDNA into the cytoplasm and extracellular space, where it functions as a damage-associated molecular pattern (DAMP) that activates pattern recognition receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs). This activation sets off a cascade of innate immune signaling (27). Notably, NLRP3 recognizes cytosolic mtDNA, initiating caspase-1 activation, and promoting the cleavage and maturation of the inflammatory cytokines IL-1 and IL-18. These cytokines recruit T lymphocytes, macrophages and neutrophils, thereby amplifying the immune response (96). In normal cells, caspase-dependent mitophagy serves to mitigate immune signaling induced by mtDNA by clearing damaged mitochondria. However, under pathological conditions, impaired mitophagy or caspase-dependent mtDNA release may convert immunologically silent cell death into ICD. In the absence of caspases, MOMP activates the mtDNA-STING pathway, initiating antitumor immune responses (97). IR also upregulates the expression of mitochondrial fission protein 1 Drp1, contributing to mitochondrial dysfunction and subsequent mtDNA release. This extracellular mtDNA activates immune cells via the cGAS-STING and TLR9-NF-κB pathways, modulating the polarization and function of immune cells, including T lymphocytes, macrophages and DCs (98). Thus, IR-induced ICD and released mtDNA serves a dual role in tumor immune evasion and activation. On one hand, mtDNA enhances the host's antitumor immune response by stimulating immune reactions. On the other hand, IR-induced ICD may also foster tumor immune evasion. Therefore, IR not only activates immune responses through mtDNA release but also modulates immune evasion via mitophagy regulation (99).

ROS serve a pivotal role in tumorigenesis, particularly in the inflammatory TME, where they contribute to the formation of immune-suppressive environments (100). Elevated ROS levels inhibit the formation of TCR-antigen peptide-MHC complexes on the surface of infiltrating T cells, thereby impairing T cell activation and facilitating tumor immune escape (101).

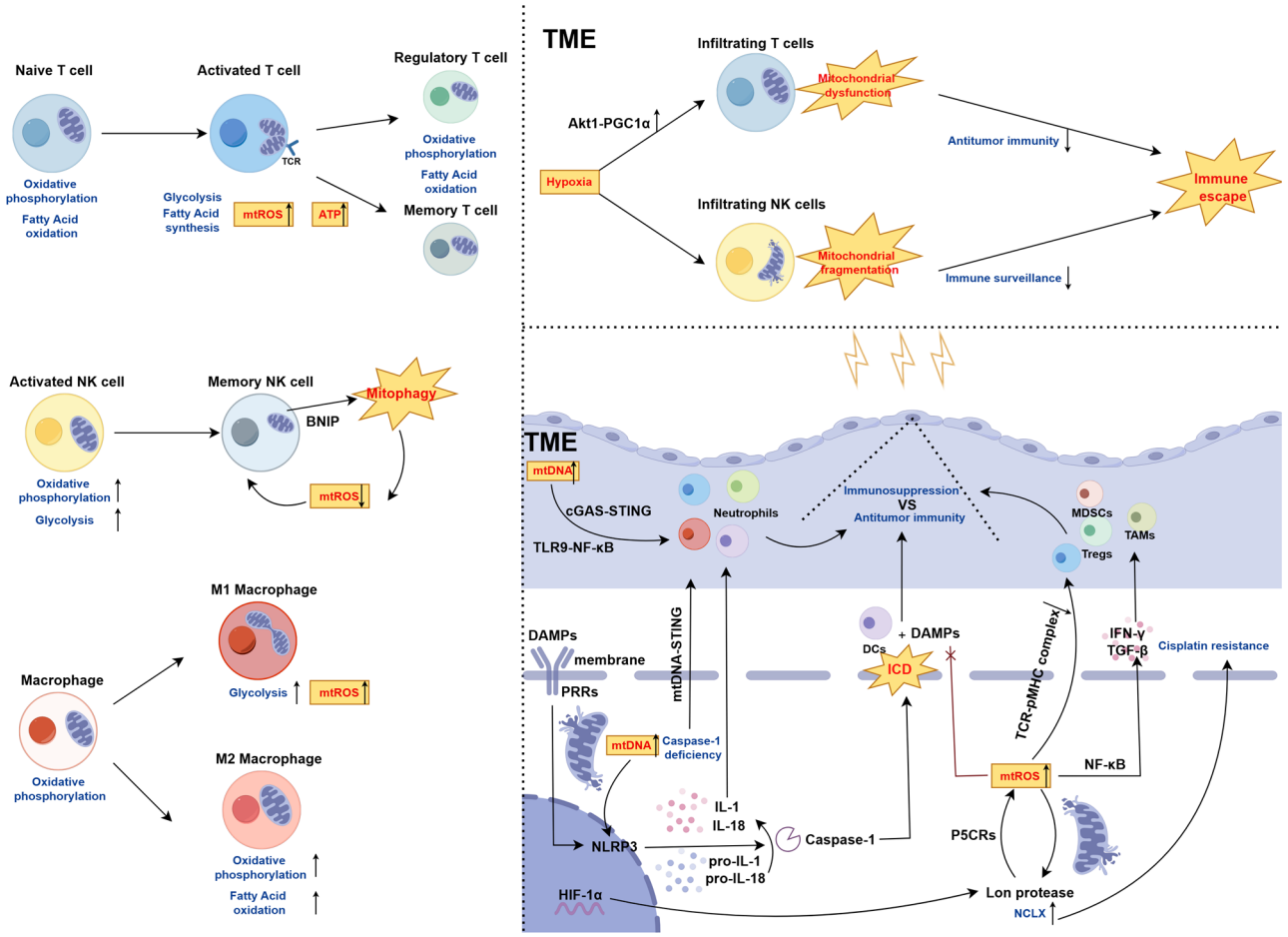

Figure 3. Mitochondrial metabolic reprogramming modulates anti-tumor immune responses. In the context of ionizing radiation, the mitochondrial metabolic state of immune cells such as T cells, NK cells and macrophages within the tumor microenvironment undergoes alterations. These changes include shifts between oxidative phosphorylation and glycolysis, the production and impact of mtROS, and the immune response triggered by the release of mtDNA; such modifications facilitate tumor immune evasion. The key role of mitochondrial morphology and function in modulating immune cell activity and the tumor immune response is thereby emphasized. The figure was created using Figdraw (www.figdraw.com; ID: IOSPS4b55e). NK, natural killer; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species.

mtROS regulate immune cell phenotypes and functions, thus supporting the establishment of an immune-suppressive TME (102). For instance, HIF-1α-induced mitochondrial Lon protease promotes mtROS production through interaction with pyrroline-5-carboxylate reductase (P5CRs), which in turn activates the NF-κB pathway, leading to the secretion of immune-suppressive cytokines such as IFN-γ and TGF-β by tumor cells (103). In addition, mtROS can further enhance Lon protease expression, activate the mitochondrial Na^+/Ca^{2+} exchanger and regulate mitochondrial calcium efflux, thus improving tumor cell resistance to cisplatin (24). The central role of mtROS in immune evasion underscores the importance of understanding the complex regulatory mechanisms between mtROS and immune cell activation in the TME. It is crucial for enhancing radioimmunotherapy through mitochondrial ferroptosis sensitization. Tumor-associated fibroblasts amplify oxidative stress in surrounding monocytes, promoting their differentiation into MDSCs, which in turn inhibit $CD8^+$ T cell proliferation (104). Elevated ROS levels, through pathways involving HIF-1α and Lon protease, contribute to the generation of immune-suppressive cells such as MDSCs, tumor-associated macrophages (TAMs) and Tregs, thereby further promoting immune suppression (105). ROS also alter the immunogenicity of antigen peptides in antigen-presenting cells, affecting the interaction between damage-associated molecular patterns (DAMPs) and DC receptors, thus inhibiting antitumor immunity triggered by ICD. Conversely, in the antitumor immune response, activated T lymphocytes and NK cells utilize ROS to recruit neutrophils and macrophages, thereby enhancing tumor cell killing. In reduced GSH-deficient Tregs, abnormal serine metabolism leads to oxidative stress, which downregulates Foxp3 expression and impairs the immune-suppressive function of Tregs (106). Therefore, the levels and sustained production of ROS in both tumor cells and immune cell subsets are critical factors in determining the occurrence of ICD and its capacity to induce effective antitumor immunity.

Macrophages are key immune cells within the TME, serving a crucial role in maintaining immune homeostasis during tumor progression. Tumor cells remodel the surrounding and distal microenvironments by secreting tumor-derived factors that activate monocytes and macrophages in circulation or local tissues, thereby accelerating tumor progression (107,108). While mtROS were once regarded as harmful byproducts of

mitochondrial metabolism, recent research underscores their signaling roles in preventing excessive immune responses, particularly in regulating macrophage immune functions (109). A previous study has shown that mitochondrial Lon protease expression is elevated in M2-type macrophages, suggesting that, during tumorigenesis, macrophages regulate Lon expression through multiple signals to induce mtROS generation, thereby serving a critical role in the differentiation of TAMs (110).

7. Ferroptosis crosslink radiotherapy with antitumor immunity

Radiotherapy enhances antitumor immunity through multiple mechanisms, notably inducing tumor ICD, which activates adaptive anti-tumor immune responses. IR promotes the release of double-stranded DNA (dsDNA) from the nucleus, leading to its accumulation in tumor-derived exosomes and increasing OMM permeability, thereby exposing mtDNA in the cytoplasm (111). As potent mediators, dsDNA and mtDNA initiate the cGAS-STING pathway, upregulating IFN I transcription, which activates the innate immune system, promotes T-cell activation and suppresses tumor growth. Additionally, IR induces the expression of MHC class I molecules and tumor-associated antigens on tumor cell surfaces, while increasing the exposure of calreticulin, HMGB1 and ATP, expanding the antigen pool for presentation. This further enhances tumor immunogenicity and promotes immune responses within the TME (112). Furthermore, IR stimulates the release of inflammatory mediators and chemokines, such as CXCL9, CXCL10 and CXCL11, from tumor and stromal cells. These factors increase the infiltration of DCs, macrophages and T cells, triggering both local and systemic antitumor immune responses (113). These immune-enhancing mechanisms suggest that radiotherapy not only exerts direct cytotoxic effects on tumor cells but also significantly activates the host immune system by reshaping the TME. When combined with anti-PD-L1 immunotherapy, IR further reduces the accumulation of MDSCs in the TME, creating a more inflammatory environment and effectively reversing immunosuppression (114).

However, under certain dosing schedules and time gradients, radiotherapy may also induce immunosuppressive effects (115). These effects, driven by alterations in the tumor hypoxic microenvironment, particularly metabolic reprogramming and expansion of immune-suppressive cells such as Tregs, may impair therapeutic efficacy and promote tumor immune escape. IR can activate the GPR81/mTOR/HIF-1α/STAT3 pathway by enhancing tumor cell glycolysis, which in turn promotes MDSC activation in the TME (116). Additionally, tumor metabolic reprogramming increases mitochondrial FAO, providing ATP through mitochondrial catabolism, thus facilitating tumor cell radioresistance. FAO upregulates CD47 transcription via the citrate-acetyl-CoA-RelA pathway, further contributing to immunosuppression by protecting radioresistant tumor cells from macrophage-mediated attack (116). The sustained activation of HIF-1α by IR not only maintains the hypoxic microenvironment but also drives macrophage subtypes (such as Macro-HK2, Macro-HSP and Macro-MT) toward a pro-angiogenic phenotype. These macrophages secrete additional chemokines, which recruit immunosuppressive neutrophils after radiotherapy (117).

Under conventional fractionated radiotherapy, sufficient radiotoxicity depletes circulating peripheral blood monocytes and induces tumor cells to secrete Gal-1, which promotes T-cell apoptosis (118). Tumor cells subjected to repeated irradiation induce chronic expression of FN I and IFN-γ, upregulating PD-L1 and IDO, leading to T-cell exhaustion. This process is further enhanced by the IR-activated cGAS-STING signaling pathway, which mobilizes Tregs and MDSCs while inhibiting effector T-cell function (119). In local radiotherapy, IR upregulates the secretion of CCL2 and CCL5, recruiting monocytes and activating Tregs in a TNF-α-dependent manner, further diminishing the therapeutic effect of radiotherapy (120). In later stages of radiotherapy, the proportion of terminally exhausted CD8+ T cells increases, along with upregulated exhaustion markers such as Pdcd1, Lag3 and Tigit. This is accompanied by a limited maturation of DCs, impairing their ability to activate $CD4^+$/$CD8^+$ T cells and exacerbating T-cell dysfunction (121).

Although radiotherapy combined with anti-PD-1 antibodies enhances tumor control via a $CD8^+$ T-cell-dependent mechanism in certain therapeutic regimens, low-dose fractionated radiotherapy (such as 2 Gy x10) may inhibit IFN-γ expression in tumor-specific $CD8^+$ T cells within draining LNs. This effect is closely linked to radiation-induced lymphopenia and the immunosuppressive TME (122). In localized radiotherapy, selective lymph node irradiation (which is effective in addressing subclinical lymph node micrometastases) may contribute to an immunosuppressive TME when combined with anti-CTLA-4 antibodies. This combination upregulates PD-L1 expression, leading to T-cell exhaustion and radioresistance (123).

Among the immunomodulatory mechanisms of radiotherapy, ferroptosis has emerged as a critical effector pathway. Ferroptosis is not only a form of cell death but also a potential mechanism through which radiotherapy induces ICD, thereby activating antitumor immunity (124). IR induces ICD, prompting activated $CD8^+$ T cells in the TME to release IFN-γ. This process inhibits system XC-(SLC3A2 and SLC7A11) expression, reduces cysteine uptake by tumor cells and impairs the chelation of GSH-cisplatin complexes, thus diminishing the ferroptotic defense system and potentially reversing cisplatin-based chemoresistance (125). Furthermore, IR remodels the lipid profile of tumor cells, increasing the incorporation of linoleic acid into C16- and C18-acyl PLs in an ACSL4-dependent manner, thereby inducing ferroptosis (126). IFN-γ secreted by Th1, NK and NKT cells can further promote ferroptosis by interacting with specific fatty acids in the TME, thereby enhancing antitumor immunity (127). This suggests a complex interplay between ferroptosis, radiotherapy and immune responses, presenting novel therapeutic targets for radioimmunotherapy strategies. Within tumor cells, DNA damage sensors (including ATRIP, Rad24p, γH2AX, NBS1, BRCA1/2, Ku70/80 and RNA polymerases) recognize radiation-induced damage signals and recruit core DNA damage response kinases ATM, ATR and DNA-dependent protein kinase (DNA-PK) to DNA break sites, initiating repair mechanisms (128). Previous research has shown that IR-activated ATM kinase, together with IFN-γ, synergistically suppresses

SLC7A11 expression and cysteine uptake, promoting lipid peroxidation and ferroptosis, thus enhancing $CD8^+$ T-cell-mediated antitumor immunity (129,130). This highlights the dual role of ATM in radiation biology. Inhibition of ferroptosis diminishes the efficacy of immune checkpoint inhibitors (ICIs) in combination with radiotherapy, while inactivation of SLC7A11 enhances the synergistic effects of ICIs and IR (131). Additionally, resistance to ferroptosis mediated by lysosomal exocytosis pathways has been negatively correlated with the efficacy of tumor radioimmunotherapy. Although previous studies suggest that tumor-derived $CD8^+$ T cells exhibit elevated levels of lipid peroxidation within the TME, thereby increasing their susceptibility to ferroptosis (an important factor influencing radiotherapy efficacy), the exact mechanism by which DC function and antitumor immunity are influenced by radiotherapy-induced ferroptosis warrants further investigation (132-134). Ferroptosis in immune cell subsets can also modulate immune responses within the TME. Tumor cells damaged by radiation typically exhibit dysregulated lipid metabolism, while tumor-infiltrating T cells accumulate lipids in a CD36 receptor-dependent manner, increasing intracellular oxidized low-density lipoprotein levels, which induces lipid peroxidation and ferroptosis. Inhibition of CD36 reduces ferroptosis in $CD8^+$ T cells, preserves antitumor immunity while maintaining radiation-induced damage and enhances the efficacy of immune checkpoint blockade (135). Activation of the ER stress response factor X-box binding protein 1 (XBP1) in DCs inhibits T cell-DC interactions by driving abnormal lipid accumulation. Silencing XBP1 improves the antitumor and immune-stimulatory functions of DCs, suggesting that targeting the ER stress response could enhance antitumor immunity and promote ferroptosis in tumor cells (136).

The role of granulocytes in ferroptosis within the TME is still under extensive investigation. Granulocytes isolated from mouse glioma models have been shown to transfer myeloperoxidase to tumor cells via cytoplasmic vesicles, thereby inducing lipid peroxidation products and triggering ferroptosis in tumor cells (137). Granulocytic myeloid-derived suppressor cells (G-MDSCs) in the TME are highly sensitive to ferroptosis. They release oxidized lipids that suppress T-cell activity, thereby contributing to immune evasion. Beyond G-MDSCs, T-cell subsets may also undergo ferroptosis under different environmental conditions (138,139). In Treg cells, the deletion of GPX4 following TCR signaling leads to lipid peroxidation and ferroptosis, which inhibits tumor growth and enhances antitumor immunity (140). By contrast, the deletion of GPX4 in $CD8^+$ T cells results in the failure of antigen-stimulated T-cell proliferation, attributed to the rapid accumulation of membrane lipid peroxides and ferroptosis within the cells. Furthermore, the suppression of GPX4 expression in naïve $CD4^+$ T cells prevents the generation of follicular helper T (Tfh) cells and impedes germinal center responses, limiting antibody production (141). Although T-cell proliferation *in vitro* depends on system XC-, this transporter is not an essential factor for T-cell proliferation or primary/memory immune responses *in vivo*, with cysteine's role potentially compensated by other mechanisms. Ferroptotic cells release surface-exposed oxidized lipid species, such as SAPE-OOH, which deliver key phagocytic signals, enhancing macrophage-mediated phagocytosis via TLR2 (142). However, the regulatory mechanisms of SAPE-OOH and the immunogenicity of the TLR pathway remain incompletely understood. Therefore, the composition of the TME serves a decisive role in determining whether ferroptosis induces immune suppression or activation. Before utilizing ferroptosis induction as a strategy to sensitize radioimmunotherapy, targeted therapies for specific immune cell populations may be required.

8. Targeting mitochondrial ferroptosis as a radioimmunotherapy sensitization strategy

Inducing mitochondrial ferroptosis has emerged as a promising approach to enhance tumor radiosensitivity in hypoxic microenvironments (143). IR-induced incomplete MOMP is a critical factor contributing to radiation resistance. This process leads to the upregulation of phosphorylayed-eIF2α and ATF4, which exacerbates tumor radioresistance (144). Liposomal formulations containing metformin and 2-deoxyglucose, by targeting ATF4, effectively reverse radioresistance in CRC, preventing T lymphocyte exhaustion and enhancing the efficacy of fractionated radiotherapy through ferroptosis sensitization (145). PGC1α, a key regulator of mitochondrial metabolism, is recognized by DNA-PK under IR conditions, promoting its ubiquitination and degradation. This contributes to radioresistance in glioma subtypes. Therefore, the use of the PGC1α activator ZLM005 can reactivate mitochondrial ROS (mtROS) production and upregulate various forms of cell death, including ferroptosis, thereby enhancing radiosensitivity (146). Additionally, subcellular-targeted nanostructures, including DHODH inhibitors such as QSSP, can enhance radiosensitivity by disrupting the ferroptotic defense system. The mitochondria-targeted ferroptosis inducer IR780-SPhF, which exhibits specific GSH-responsive properties, induces mitochondrial redox imbalance, offering a novel treatment strategy for breast cancer (147). Tubastatin A inhibits GPX4 enzyme activity in a concentration- and time-dependent manner, synergistically enhancing ferroptosis and sensitizing breast cancer cells to radiotherapy (148).

Apart from targeting the ferroptosis defense system, regulating the concentration of metal ions such as Fe^{2+} within mitochondria serves a key role in enhancing ferroptosis-mediated radiosensitization (48). In nasopharyngeal carcinoma, previous research has demonstrated that nanocarriers targeting circular (circ) RNA circADARB1 can elevate intracellular iron ion concentrations, thereby promoting radiotherapy-induced ferroptosis and increasing radiosensitivity. Self-assembled pH-sensitive superparamagnetic iron oxide nanoclusters enhance mitochondrial-localized ferroptosis and apoptosis, synergistically sensitizing tumors to radiotherapy (149). Cationic nanometal-organic frameworks such as Th-Ir-DBB/digoxin, developed for ICD-induced ferroptosis, utilize mitochondrial targeting and cholesterol depletion to enhance the antitumor efficacy of radiotherapy-radiodynamic therapy (150).

In the era of radioimmunotherapy, radiation resistance and immune suppression within the TME often limit the effectiveness of radiation-induced antitumor immune responses. Ferroptosis has emerged as an effective strategy to enhance antitumor immunity in this context (Fig. 4) (151). Targeting macrophage membrane-coated biomimetic nanoparticles

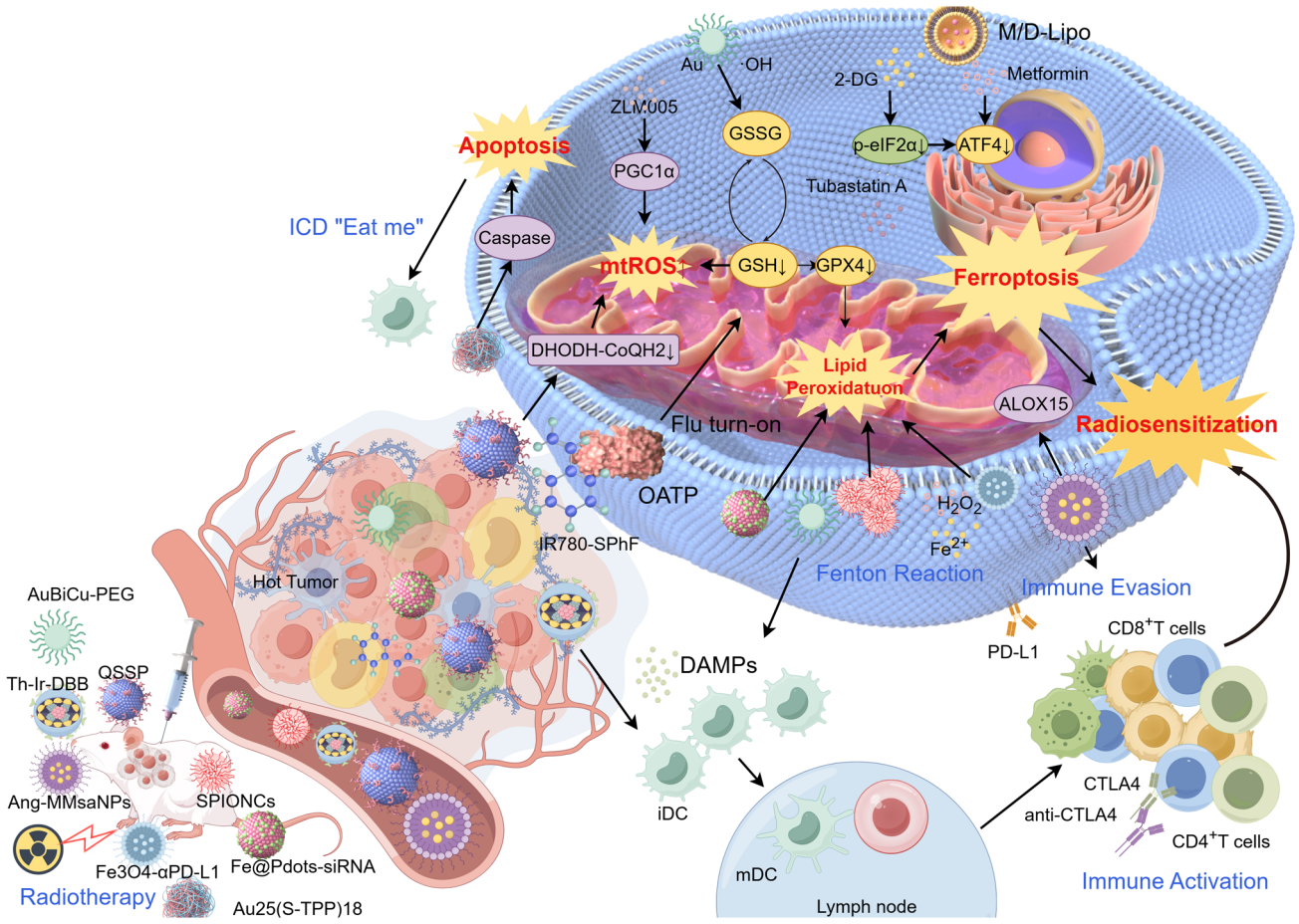

Figure 4. Strategies for radioimmunosensitization targeting mitochondrial ferroptosis. Modulating ferroptosis defense mechanisms, including the ATF4 and PGC1α pathways, as well as regulating mitochondrial Ca^{2+} levels, represent effective approaches to enhance radiotherapy efficacy. By targeting immunogenic cell death associated with ferroptosis through advanced nanotechnologies such as biomimetic nanoparticles, nMOFs and trimetallic nanoparticles, the synergistic effects of ferroptosis in radioimmunotherapy can be harnessed to augment immune responses and overcome tumor immune evasion. The figure was created using Figdraw (www.figdraw.com; ID: PAWUTb4f45).ATF4, activating transcription factor 4; nMOFs, nano-metal-organic frameworks.

enables immune camouflage to evade phagocytosis by the mononuclear phagocyte system, damaging mitochondria and inducing ferroptosis in glioblastoma cells (152). The mitochondrial-targeting synthetic cluster Au25(S-TPP)18 inhibits the thioredoxin reductase system, enhancing mtROS production. This cluster exhibits potent radiosensitizing effects, induces a bystander effect and activates the immune response (153). Tri-metallic nanoparticles (AuBiCu-PEG NPs) with dual enzymatic activities not only promote ICD induced by radiotherapy and enhance antitumor immunity, but also effectively reverse radiation-induced PD-L1 upregulation. These NPs suppress tumor immune evasion, reshape the immune microenvironment and synergistically sensitize radiotherapy through X-ray deposition, hypoxia alleviation and the induction of ferroptosis and cuproptosis (154). Fe3O4-αPD-L1 nanoprobes, when combined with radiotherapy, specifically target MDSCs, modulating lipid and amino acid metabolism, particularly unsaturated fatty acids and antioxidant metabolites associated with ferroptosis. This approach reprograms the tumor immune-suppressive microenvironment, promoting both local and systemic antitumor immune responses (155). Equally important, iron-containing hyaluronic acid (HA) NPs, which internalize by high-affinity interactions with overexpressed CD44 receptors through HA, generate lipid ROS. When combined with radiotherapy, these nanoparticles induce both mitochondrial apoptosis and ferroptosis (156). Additionally, CSM nanoparticles loaded with single-atom nanocatalysts (SAzyme), and manganese carbon monoxide enhance FLASH radioimmunotherapy by inducing ferroptosis through multiple pathways, including GSH depletion and $CD8^+$ T-cell infiltration (157). Other ferroptosis-inducing NPs, such as BZAMH NPs, 8HSA8 NPs, Au/CuNDs and Cu2WS4-PEG, also serve crucial roles in sensitization of radioimmunotherapy (158).

Radiopharmaceutical therapy (RPT), or targeted radionuclide therapy, directly treats malignant tumors by delivering radioactive atoms (β- or α-particles) to the tumor site (159). Compared with X-ray-mediated IR, RPT allows for precise delivery of radiation to cancer cells or the TME, maximizing tumor cell killing while sparing surrounding healthy tissues (160). For instance, 3-nm monocrystalline iron NPs (iRGD-bcc-USINP), when combined with a PD-L1 blocking agent, target ferroptosis and synergistically exert antitumor immune effects. However, ultra-small NPs (<6 nm) demonstrate poor tumor accumulation (161). Particle size-optimized NPs, assembled with radiopharmaceuticals such as USINP-131I-aPD-L1, promote ROS production and enhance ferroptosis induced by USINP, activating immune pathways and synergizing with PD-L1 blockade to enhance

antitumor immune responses. Furthermore, the 124I-P/C@CMLvs system, combined with PET imaging tracer, can synergistically enhance ferroptosis and necroptosis, inducing lung cancer regression and improving the efficacy of anti-PD-L1 immunotherapy (162).

In addition to enhancing radiotherapy, mitochondrial ferroptosis can also sensitize emerging tumor treatments, such as photothermal therapy (PTT), photodynamic therapy (PDT), and sonodynamic therapy (SDT) (163). The IR780/Ce@EGCG/APT nanoreactor, by combining ferroptosis with PTT, improves the immune-suppressive microenvironment in breast cancer and activates systemic immune responses, leading to long-term immune memory. Mitochondria-specific type I PDT mediated by organic NIR-II photosensitizers (TPEQM-DMA) and two-photon nanosensitizers (IR-g-C3N4) disrupt the lipid repair system, resulting in mitochondrial dysfunction and induction of both apoptosis and ferroptosis, providing an effective phototherapy strategy for hypoxic tumors (164). Furthermore, the mitochondria-specific organic-metal ultrasound sensitizer IRCur-Pt enhances the synergistic effect of ferroptosis and SDT, further activating immune pathways. Pancreatic cancer-specific antibody NRP2-guided MOFs@COF nanocarriers target and disrupt mitochondrial and ER homeostasis, inducing autophagy-dependent ferroptosis while sensitizing chemotherapy and SDT (165). In summary, inducing mitochondrial ferroptosis through the disruption of iron ion homeostasis and peroxidation intervention has emerged as an effective strategy to improve the radiosensitivity of malignant tumors and enhance the efficacy of radioimmunotherapy.

9. Conclusions and perspectives

The present review summarized the research advancements in novel radioimmunotherapy strategies, focusing on the transition from 'ferroptosis' to 'mitochondrial dysfunction'. Ferroptosis, a form of RCD, has recently been implicated in tumor resistance to radiotherapy. Inducing ferroptosis by modulating iron metabolism and redox imbalance has emerged as a promising strategy to enhance the efficacy of radiotherapy [Table SI (166-276)]. Concurrently, radiation-induced mitochondrial dysfunction serves as a critical pathway for ICD in tumor cells. Radiotherapy-ICIs has shown considerable therapeutic benefits in clinical studies across various cancer types. These studies underscore the complex interplay between ferroptosis and mitochondrial dysfunction in tumor treatment responses, highlighting the potential of combination strategies that integrate radiotherapy, immunotherapy and ferroptosis modulation.

Although the potential of ferroptosis and mitochondrial dysfunction in enhancing radioimmunotherapy is becoming increasingly apparent, the research presently described demonstrates several unresolved paradoxes in the regulation of ferroptosis. Specifically, i) in hepatocytes, while mtROS-activated PERK signaling promotes arsenite-induced ferroptosis by downregulating Mfn-2 and impairing MAMs function, its cleaved C-terminal fragment paradoxically exerts protective effects against alcoholic hepatocyte ferroptosis (75); ii) the complex role of cGAS-STING in either promoting cell death (via pyroptosis) (40) or supporting cell survival (by suppressing ferroptosis) (41); iii) the TME presents even more complex dichotomies: Although hypoxia generally diminishes radiosensitivity, hypoxia-induced BNIP3 protein can stimulate mitophagy and elevate ROS production, mechanisms known to potentiate ferroptosis and consequently improve radiation response (86); and iv) radiation-enhanced FAO exhibits dual effects: While increasing tumor cell vulnerability to ferroptosis, it simultaneously induces T cell exhaustion, ultimately attenuating anti-tumor immunity and compromising radioimmunotherapy efficacy (88).

The current research still faces other challenges. First, the immunogenicity of ferroptosis in different contexts remains unclear. Second, whether DAMPs are released during ferroptosis, and how these DAMPs mediate immune responses within the TME, require further investigation. Additionally, the interactions between various cell death pathways and the optimization of drugs that either promote or inhibit ferroptosis are critical issues that need to be addressed. Resolving these questions will help clarify the precise role of ferroptosis in the TME and provide new insights for cancer treatment.

These challenges collectively indicate that the current understanding remains incomplete regarding the molecular mechanisms of ferroptosis are not fully understood, particularly in terms of its heterogeneous effects across different tumor types and subcellular organelles, which warrants further exploration [Table SII (277-430)] such as the impact of TME factors (oxidative stress, hypoxia and lipid metabolism) on ferroptosis susceptibility and the precise mechanisms by which ferroptosis synergizes with radioimmunotherapy, including the efficacy of radioimmunotherapy combined with ferroptosis modulation may vary significantly depending on the clinical context. Therefore, accurately assessing patient responses and resistance mechanisms remains a key area of research. Furthermore, while the combination of ICIs and radiotherapy has shown promise, the interactions between immune-related side effects and radiotherapy-induced toxicity have not been thoroughly evaluated. Balancing therapeutic efficacy with safety and optimizing treatment regimens remains a major challenge in clinical applications.

Future research should focus on several pivotal areas. First, a deeper exploration of the molecular mechanisms underpinning ferroptosis and mitochondrial dysfunction, particularly their roles within different TMEs, is essential. By utilizing molecular targeting technologies, the development of novel drugs or small molecule modulators that specifically induce ferroptosis or restore mitochondrial function could offer new strategies to enhance radiotherapy efficacy. Second, there is a need for the advancement of immune monitoring techniques, particularly those aimed at precisely assessing the association between immune system responses and tumor cell death. This will provide the foundation for personalized treatment strategies. Furthermore, combining modern gene-editing technologies with immunotherapeutic approaches to overcome the current resistance to radiotherapy will be a major focus of future research.

In conclusion, the combination of radiotherapy and immunotherapy holds significant promise in cancer treatment. However, to achieve widespread clinical application, several mechanistic and clinical challenges must be overcome. Future research will deepen the current understanding of the

interactions between ferroptosis, mitochondrial dysfunction and immunotherapy. Based on these insights, more precise and safer treatment regimens will be developed, offering patients with cancer a broader range of therapeutic options.

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Authors' contributions

TW, XZ and XY conceived the study and wrote the manuscript. AZ, YF, KC, HT, ZT and PZ conducted literature search/selection and data extraction. XH and LY revised and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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