Cross-link between ferroptosis and nasopharyngeal carcinoma: New approach to radiotherapy sensitization (Review)

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Abstract. Ferroptosis is a recently discovered special type of regulated cell death that is strongly associated with both homeostasis maintenance and cancer development. Previous studies have indicated that a number of small-molecular agents inducing ferroptosis have great potential in the treatment of different types of cancer, including breast, pancreatic, prostate and head and neck cancer. However, the role of ferroptosis in nasopharyngeal carcinoma (NPC) has remained to be fully determined. To the best of our knowledge, no review of the currently available studies on this subject has been published to date. The metabolism and expression of specific genes that regulate ferroptosis may represent a promising radiosensitization target in cancer treatment. The aim of the present review was to describe the cross-link between ferroptosis and NPC and to discuss the potential value of regulators and the possible mechanism underlying the role of ferroptosis in the radiosensitization of NPC, in the hope that linking the mechanism of ferroptosis with the development of NPC will accelerate the development of novel ferroptosis-based targets and radiotherapy strategies in NPC.

Contents

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1. Introduction

Nasopharyngeal carcinoma (NPC), an important type of head and neck cancer, is highly prevalent in East Africa and Asia, particularly in southern China (1,2). Due to the concealed location of NPC, surgical treatment is relatively difficult. According to the National Comprehensive Cancer Network guidelines, radiotherapy (RT) is the primary treatment of choice for NPC (3). RT uses an appropriate intensity of ionizing radiation (IR) to eliminate tumor cells (4,5). IR directly causes DNA damage and indirectly stimulates the production of reactive oxygen species (ROS) in tumor cells (6,7). However, according to statistics, 10-20% of patients with NPC suffer from recurrence after primary RT due to radiation resistance (8). Therefore, there is an urgent requirement to discover novel methods of radiosensitization for patients with resistance to RT.

Ferroptosis, a newly identified type of regulated cell death (RCD), was proposed by Dixon *et al* (9) in 2012. Unlike other types of RCD, ferroptosis is characterized by loss of lipid peroxidation repair ability and the accumulation of redox-active iron (10). Morphologically, the mitochondrial cristae decrease in number or disappear, the outer mitochondrial membrane ruptures and the mitochondrial membrane becomes condensed. Although the mechanism of ferroptosis has yet to be fully elucidated, ferroptosis has a key role in a number human diseases, such as ischemia/reperfusion injury (11), neurodegeneration (12) and various types of cancer, including NPC (13,14). From the perspective of radiosensitization and side effects of RT, the pharmacological modulation of ferroptosis (stimulation or inhibition) may be of significant clinical value.

The aim of the present review article was to discuss the potential molecular mechanisms of ferroptosis and the microRNAs (miRNAs/miRs) regulating ferroptosis in NPC, alongside the potential future directions and clinical value of ferroptosis research in RT for NPC.

2. Molecular mechanism of ferroptosis in cancer

Research has revealed three critical pathways involved in ferroptosis, which are the iron metabolism pathway, the polyunsaturated fatty acid (PUFA) metabolism pathway and the phospholipid hydroperoxidase glutathione peroxidase (GPX)4 metabolism pathway (Fig. 1) (15). Iron metabolism is a redox reaction of iron in the cytoplasm. During this process, ferric iron (Fe^{3+}) is absorbed into the cytoplasm via transferrin and is then rapidly transformed into ferrous iron (Fe^{2+}) and stored as ferritin or in the labile iron pool; however, Fe^{2+} is released due to the destruction of ferritin via ferritinophagy, a process mediated by nuclear receptor coactivator 4 (14,16). Finally, excessive Fe^{2+} is oxidized through the Fenton reaction by PUFA-containing phospholipids (PUFA-PL), generating a large amount of ROS and subsequently resulting in ferroptosis (17). PUFA-PL is the stress form of PUFA acetylated by acyl-CoA synthetase and activated by acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3, and it represents the main lipid source of ROS (18,19). ROS are a group of molecules with partially reduced oxygen, including free radicals (HO• and RO•), peroxides (H_2O_2 and ROOH) and superoxide ($O2•^-$), which cause cell death by damaging DNA, RNA and lipid molecules (20). Therefore, PUFA metabolism has an oxidative role in ferroptosis. GPX4 metabolism is key for antagonizing lipid ROS due to the fact that GPX4 is able to catalyze the decomposition of H_2O_2 and complex lipid peroxides (21). Yang *et al* (22) reported that GPX4 is able to convert reduced glutathione (GSH) to oxidized glutathione (GSSG), leading to weakened Ras-selective lethal small molecule 3 (RSL3)- and erastin-induced ferroptosis. Mechanistically, several molecules are involved in GPX4 metabolism in ferroptosis. Among those, system Xc^- and GPX4 are considered as the main regulators of GPX4 metabolism, negatively regulating ferroptosis (23). System Xc^- is a membrane Na^+-dependent cysteine-glutamate transporter, which is a disulphide-linked heterodimer composed of a light-chain subunit [solute carrier (SLC)7A11] and a heavy-chain subunit (SLC3A2) (24). Cysteine and glutamate are important elements in GSH synthesis, and GSH generation and maintenance are key to preventing oxidative damage due to lack of GPX4 (25). In addition, the mitochondrion is the most important organelle involved in ferroptosis, as the energy and electron transfer provided by the electron transfer chain are necessary in the process of ferroptosis (26). Mitochondrial voltage-dependent anion channels (VDACs), the transmembrane channels for transporting ion and metabolites, are widely distributed on the outer mitochondrial membrane (27). It was previously demonstrated that erastin is able to target VDAC2 on the outer mitochondrial membrane, resulting in lipid ROS release and slowing down the oxidation of NADH (28). NADH is mainly involved in material and energy metabolism in cells, which supplies the energy required for ATP synthesis through the oxidative phosphorylation process and for the conversion of GSSH to GSH (14,29). Therefore, VDACs and NADPH oxidase (NOX) are crucial positive regulators that promote ferroptosis, and altering outer mitochondrial membrane permeability by antitumor drugs may be a novel approach to tumor treatment. In summary, ferroptosis is a non-apoptotic type of cell death that is involved in several complex regulatory and three intersecting metabolic pathways.

3. Potential role of ferroptosis in NPC radiosensitization

RT-induced ferroptosis. A number of pharmacological studies have attempted to promote ferroptosis through various methods to improve the efficacy of RT (30,31). However, to date, the association between ferroptosis and RT has not been studied in depth. IR randomly causes oxidative damage in all intercellular spaces, including lipid membranes, and ferroptosis is caused by the accumulation of toxic lipid peroxidation products (31). Therefore, there may be an interesting connection between ferroptosis and IR. According to various studies, RT affects the four key regulators of ferroptosis, namely ROS, SLC7A11, ACSL4 and GPX4 (Fig. 2). Among those, ROS is considered the most important factor implicated in ferroptosis caused by RT. Ye *et al* (32) reported that IR acting synergistically with ferroptosis inducers increased ROS levels, leading to lipid oxidation in an *in vitro* study using the HT-1080 human fibrosarcoma cell line. However, regarding the expression of SLC7A11, the conclusions have been controversial among studies. An *in vitro* study involving the irradiation of ovarian cancer, melanoma and human fibrosarcoma cells demonstrated that the ataxia-telangiectasia mutated gene (ATM) activated by RT and IFN derived from activated $CD8^+$ T cells synergistically inhibited the expression of SLC7A11 (30). However, Lei *et al* (33) indicated that IR markedly induced the expression of SLC7A11, GPX4 and ACSL4. Subsequently, the expression of SLC7A11 was considered as an adaptive response (34) and it likely involves activating transcription factor 4 and/or the transcription factor NF-E2-related factor 2 (NRF2), both of which are known to regulate SLC7A11 transcription and are largely activated by IR (35-37). Therefore, it appears that RT is able to either repress or activate SLC7A11 expression, depending on the conditions. Mechanistically, there are three pathways involved in RT-induced ferroptosis (30-33). First, RT is able to induce oxidative stress and then produce a large amount of ROS, leading to lipid peroxidation. In addition, RT may promote PUFA-PL biosynthesis by upregulating ACSL4 expression. Furthermore, RT also promotes GPX4-mediated ferroptosis through DNA damage and inhibition of GSH production. Taken together, these results indicated that the specific mechanisms of RT-induced ferroptosis require to be further explored and inducing ferroptosis to eliminate the radiation resistance of tumor cells may be a direction worthy of further investigation. These findings indicate the potential therapeutic value of targeting ferroptosis to enhance the radiosensitivity of NPC.

Crosstalk between ferroptosis and other types of RT-induced cell death. As described in the previous section, the major cellular effect triggered by RT is to damage DNA and induce ROS generation in cells. With regard to signaling, there appear to be interactions between ferroptosis and other types of radiation-induced cell death. RT damages DNA in the nucleus and, thus, activates ATM (38). ATM is the major regulator of the first step in DNA damage response sensing (39). ATM activation is able to sensitize AMP-activated protein kinase, which promotes Beclin 1 (BECN1)-mediated autophagy, while

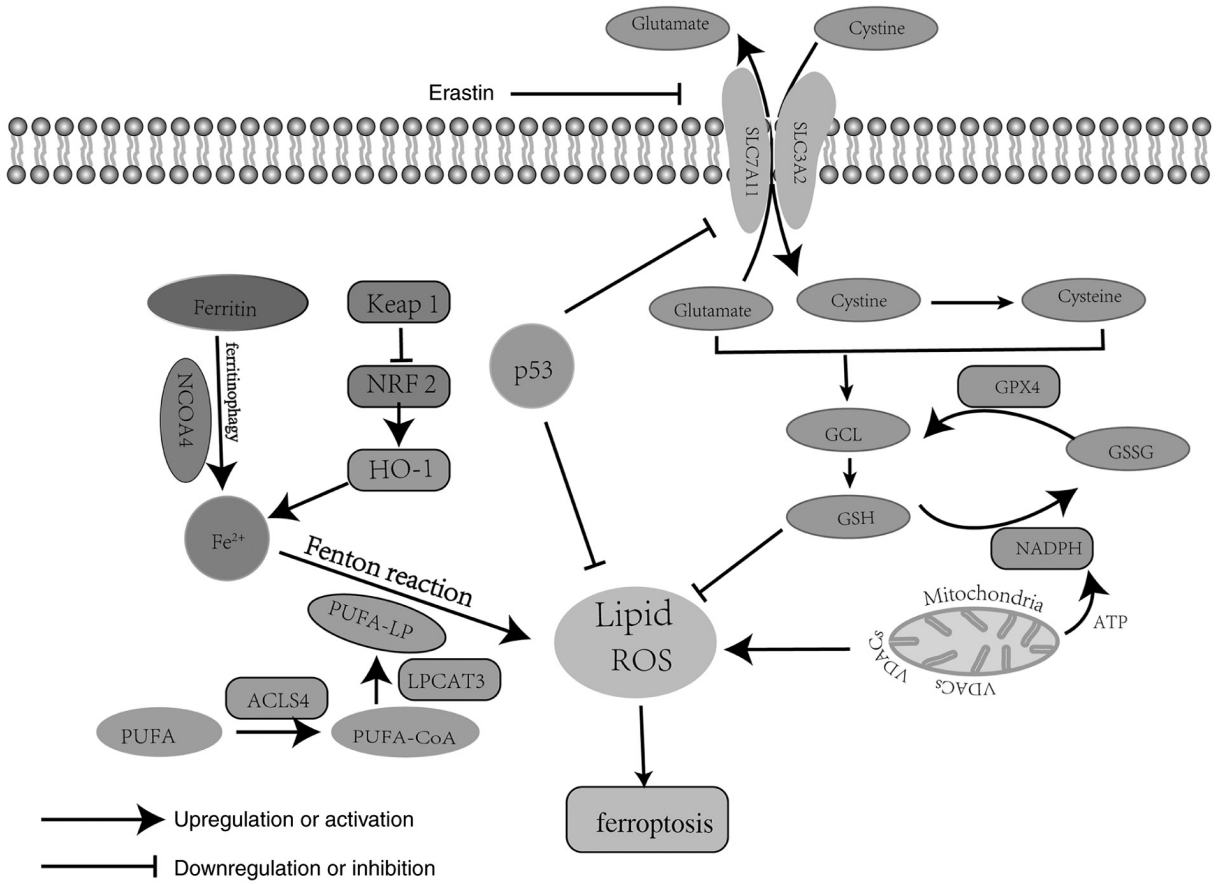

Figure 1. Molecular mechanism of ferroptosis in cancer. The iron metabolism, PUFA metabolism and GPX4 metabolism pathways are involved in the process of ferroptosis. System Xc^- and GPX4 are significant regulators of ferroptosis. Erastin is able to trigger ferroptosis by inhibiting the function of system Xc^-. Mitochondria are also able to promote ferroptosis by enhancing ROS generation. ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; GCL, glutamate-cysteine ligase; GSH, glutathione; NCOA4, nuclear receptor coactivator 4; NADPH, nicotinamide adenine dinucleotide phosphate hydride; NRF2, nuclear factor E2-related factor 2; KEAP1, Kelch-like ECH-associated protein 1; HO-1, heme oxygenase 1; PUFA, polyunsaturated fatty acid.

at the same time ferroptosis is promoted through regulating the ATM/GPX4 axis (31,40). A previous study indicated that RT is able to directly induce tumor cell necroptosis, which displays a certain overlap with apoptosis (41). The intrinsic apoptotic pathway is initiated by identifying double-strand breaks (DSBs) if DNA repair is not successful (42). Of note, ROS accumulation is able to prevent DNA repair and promote ferroptosis (7). In brief, multiple lines of evidence suggest that there is a close association between ferroptosis and other types of RT-induced cell death, particularly apoptosis, necroptosis and autophagic cell death.

4. Targeting ferroptosis to sensitize NPC to RT

RT currently remains the first choice of treatment for NPC. However, radiation resistance has come to represent a serious problem, as tumor cells are not sensitive to other forms of death, including apoptosis. Therefore, inducing ferroptosis of tumor cells may represent a good target for the radiosensitization of NPC. RT causes DNA DSBs in tumor cells. Furthermore, a large number of ROS are produced during the process of ferroptosis, which makes it difficult to repair the DNA double strand, thus further accelerating cell death (43). Acquired radioresistance is currently a long-standing challenge in RT for NPC. In view of this fact, the landing points for investigating the therapeutic relevance of ferroptosis in RT include the following: i) Whether the regulators of ferroptosis modulate radiosensitivity in NPC; and ii) how to target the regulators in NPC. These points are discussed below.

Iron. As the term suggests, the occurrence of ferroptosis requires high levels of intracellular iron (9). In the process of ferroptosis, numerous ROS-forming or -decomposing enzymes (cytochrome P450, xanthine oxidase, lipoxygenase, NOX, mitochondrial complex I and III, catalase and peroxidases) are iron-dependent (44,45). Imbalances in iron metabolism in cells lead to iron overload and ROS accumulation, resulting in Fenton oxidation reaction on the lipid membrane and, eventually, ferroptosis (46). Therefore, iron is able to amplify the production of ROS in ferroptosis (47,48). The conversion process between Fe^{3+} and Fe^{2+} is accompanied by the generation of energy, which benefits cellular energy metabolism (49). Similarly, it was demonstrated that reducing the level of intracellular iron via the tumor suppressor gene 3-hydroxybutyrate dehydrogenase type 2 inhibited the proliferation and metastasis of NPC cells (50). Furthermore, Xu *et al* (51) indicated that itraconazole was able to reduce the activity of NPC stem cells by increasing the concentration of intracellular iron in lysosomes and lipid peroxides. Therefore, the disruption of intracellular iron balance may affect NPC cell survival and

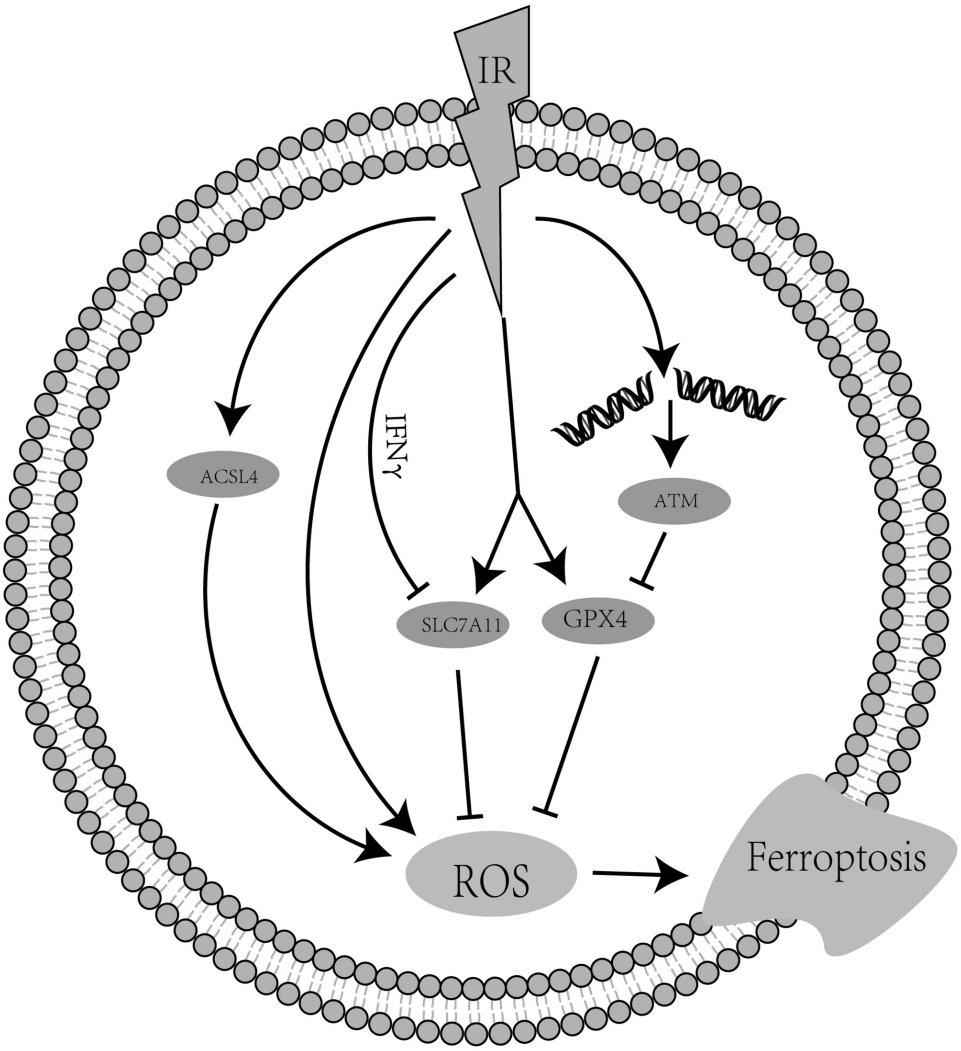

Figure 2. Mechanisms of radiotherapy-induced ferroptosis. IR upregulates the expression of ACSL4, GPX4, SLC7A11 and directly or indirectly increases ROS production. IR combined with IFN-γ inhibits SLC7A11. DNA double-strand breaks induced by IR are able to activate ATM and then inhibit GPX4. ACSL4 and ROS promote lipid peroxidation and lead to ferroptosis. ACSL4, acyl-CoA synthetase long chain family member 4; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier 7A11; ATM, ataxia-telangiectasia mutated; ROS, reactive oxygen species; IR, ionizing radiation.

proliferation (52). Of note, an *in vivo* study suggested that long-term treatment with iron-containing water improved the efficiency of RT for glioma in rats via ferroptosis (53). This method may also be applied to RT for NPC. When ferritin is degraded via ferritinophagy, it releases iron and promotes ferroptosis (54,55). Previous studies suggested that transferrin and its receptor promote ferroptotic cell death, whereas iron chelators inhibit this type of cell death (56-58). Serum ferritin is the best single marker reflecting iron stores *in vivo* (59). Compared with that of healthy individuals, the serum ferritin level of patients with undifferentiated NPC was reported to be higher (60). It was previously indicated that serum ferritin levels may be valuable for predicting distant metastasis in patients with NPC following standard intensity-modulated RT and chemotherapy (61). Lactotransferrin (LTF), a member of the transferrin family, may negatively regulate the development and metastasis of NPC *in vivo* (62). It has been reported that LTF is highly expressed in NPC cells and overexpression of LTF inhibited the proliferation of NPC cells by modulating the MAPK/AKT pathway, which is an essential pathway for tumor radiosensitization (63-66). Therefore, this may be a viable strategy for promoting radiosensitization of NPC through disrupting iron metabolism.

NRF2. NRF2 is considered as a main regulator of the antioxidant response in ferroptosis, as a number of its downstream target genes are responsible for preventing redox imbalance in cancer cells (67). Qiang *et al* (68) indicated that NRF2 serves a protective role in ferroptosis-mediated ischemia/reperfusion-induced acute lung injury by regulating SLC7A11 and activating STAT3. P62 may promote this process by preventing NRF2 degradation and then increasing NRF2 nuclear accumulation through inhibiting kelch-like ECH-associated protein 1 (KEAP1), which is able to regulate the expression of NRF2 via the ubiquitin-proteasome route (69,70). NRF2 was observed to be markedly upregulated in NPC tissues and may serve as an unfavorable prognostic biomarker in patients with NPC (71). An *in vitro* study suggested that NRF2 gene knockout enhanced the radiosensitivity of NPC cells, whereas silencing KEAP1 inhibited the radiosensitivity of NPC cells (72). In addition, Zhang *et al* (73) reported that lowering NRF2 levels and promoting ROS production

sensitized NPC cells to RT. Huang *et al* (71) indicated that NRF2 expression was upregulated through the Raf kinase inhibitor protein/miR-450b-5p/NRF2/NAD(P)H:quinone oxidoreductase 1 axis, which improved the radioresistance of NPC. Another study also demonstrated that NRF2 promoted the proliferation of Epstein-Barr virus (EBV)-transformed B cells through the EBV-related proteins LMP1 and 2A and AKT signaling, which indicated that NRF2 may represent a potential molecular target for EBV-related diseases, including NPC (74).

GSH. GSH is able to protect lipid membranes by scavenging ROS (75). Under normal physiological conditions, the concentration of GSSG is 10-100 times lower compared with that of GSH; however, under conditions of severe oxidative stress, GSH is transformed into GSSG (76). GSH is an important cofactor of GPX4 and its biosynthesis is accomplished with the help of system Xc^- (77). The functions of GSH include inactivation of dangerous endogenous compounds and/or detoxification of exogenous compounds through the action of GPXs and GSH-S-transferases (78). Xu *et al* (51) demonstrated that NPC spheroids displayed a certain degree of ferroptosis resistance due to increased GSH levels. The metabolism of free radicals is disrupted and the effectiveness of the antioxidant defense system decreases significantly in patients with NPC. GSH has been indicated to have an antiapoptotic role in response to radiation via decreasing ROS production and inhibiting the MAPK pathway in NPC cells (79).

Fanconi anemia group D2 protein (FANCD2). FANCD2, a negative regulator of ferroptosis, is able to repair DNA damage as a nuclear protein in bone marrow stromal cells (80). Knockout of FANCD2 may influence iron and GPX4 metabolism. In addition, an *in vitro* and *in vivo* study revealed that FANCD2 silencing enhanced the sensitivity of NPC cells to ionizing radiation (81). Recent results have demonstrated that FANCD2 expression is associated with the prognosis of NPC (82). Therefore, FANCD2 may be an effective target for radiosensitization, as well as a prognostic and diagnostic marker of NPC.

Heme oxygenase 1 (HO-1). HO-1 may be regulated by NRF2 and endoplasmic reticulum-associated protein degradation and has a dual role in ferroptosis (10). On the one hand, increased expression of HO-1 may increase intracellular iron levels; on the other hand, HO-1 was able to attenuate erastin-induced ferroptosis in renal epithelial cells (83,84). A study on the association between NPC and HO-1 suggested that patients with low expression levels of HO-1 were more sensitive to RT compared with those with high expression levels of HO-1 (85). The results suggested that HO-1 may be a useful indicator for identifying patients with RT-sensitive NPC. Therefore, HO-1, as a regulator of ferroptosis, may also be an important target for radiosensitization.

p53. p53, a key tumor suppressor gene, is activated under different stress stimuli, including IR. p53 is able to transcriptionally inhibit SLC7A11 expression to impair cysteine import, ultimately promoting ferroptosis (86). p533KR, an acetylation-defective p53 mutant, is highly effective in repressing the expression of SLC711A, but not that of other already known p53 target genes (cell cycle-, apoptosis- or senescence-related genes) (87). However, it has also been reported that p53 may inhibit ferroptosis by the transcriptional activation of cyclin-dependent kinase (CDK) inhibitor 1A/p21 or inhibition of dipeptidyl-peptidase 4 activity (88). Therefore, p53 appears to have a dual role in ferroptosis. Previous studies have indicated that p53 also has a key role in regulating the occurrence and development of NPC, particularly in terms of its radiosensitivity. Wang *et al* (89) reported that activating the p53 signaling pathway via overexpressing miR-372 enhanced the radiosensitivity of NPC. Furthermore, a clinical study suggested that recombinant human adenovirus p53 promoted radiosensitivity in patients with recurrent NPC (90).

BECN1. BECN1, a key regulator of autophagy, is able to block the activity of system Xc^- via combining with SLC7A11 to promote ferroptosis in cancer cells (91,92). A randomized controlled trial indicated that BECN1 and hypoxia-inducible factor (HIF)-1α expression exhibited a positive association and that HIF-1α-associated high BECN1 expression promoted NPC cell survival after chemoradiotherapy (93). Of note, another previous study suggested that increasing HIF-1α stability promoted radiosensitivity in NPC (94). Therefore, there appears to be a close association among BECN1, HIF-1α and radiosensitivity in NPC.

5. miRNAs regulating ferroptosis

The major function of miRNAs is to bind to the 3'-untranslated region of target mRNAs and subsequently inhibit their expression (95). Previous studies have revealed that miRNAs have an important role in the regulation of ferroptosis. miR-182-5p and miR-324-3p were demonstrated to promote ferroptosis via targeting GPX4 in ischemia/reperfusion-induced renal injury and lung adenocarcinoma (96,97). miR-17-92 and miR-424-5p abrogated erastin- and RSL3-induced ferroptosis through targeting ACSL4 in human umbilical vein endothelial cells and ovarian cancer cells (98,99). In radioresistant cells, miR-7-5p restrained ferroptosis through downregulating mitoferrin and subsequently reducing iron levels (100). Furthermore, miR-9 and miR-137 promoted ferroptosis via reducing intracellular GSH levels; miR-9 inhibited the synthesis of GSH and miR-137 suppressed the expression of SLC1A5, which is a component of system Xc^- (101,102). To date, several studies have demonstrated that miRNAs regulating ferroptosis are associated with the proliferation, invasion, migration and apoptosis of NPC cells, particularly in terms of radiosensitivity regulation (Table I). For instance, miR-214 and miR-182-5p were indicated to contribute to radioresistance in NPC by regulating LTF and BNIP3 expression (103,104). However, miR-124 and miR-9 may promote radiosensitivity of NPC via targeting programmed cell death protein 6 (PDCD6) and suppressing the expression of junctional adhesion molecule A (JAMA) (105-107). Hu *et al* (108) indicated that miR-214 enhanced radiosensitivity of colorectal cancer via inhibition of autophagy-related 12-mediated autophagy. Based on the results reported to date, miR-214 is considered to act as an oncogene in NPC, which is able to promote the proliferation of NPC cells and inhibit

Table I. Summary of miRNAs regulating ferroptosis in NPC.

miRNA	Target of ferroptosis	Function in NPC	Target gene/pathway in NPC	(Refs.)
miR-214	TFR1 TP53	Proliferation (+); Apoptosis (-)	WWOX, PTEN, Bim, Bax, LTF	(115)
miR-182-5p	GPX4	Apoptosis (-)	BNIP3	(96)
miR-124	Fe^{2+}	Proliferation (-); Apoptosis (+); Invasion (-)	Wnt, PDCD6, JAMA, Foxq1, NF-κB	(116)
miR-9	GSH	Proliferation (-); Apoptosis (+); Invasion (-)	MDK, PDK/AKT, CXCR4, GSH	(101)
miR-424-5p	ACSL4	Proliferation (-); Apoptosis (+); Invasion (-)	AKT3	(99)
miR-7-5p	Fe^{2+}	Apoptosis (-)	ENO2	(100)
miR-324-3p	GPX4	Proliferation (-); Apoptosis (+); Invasion (-)	WNT2B, GLI3	(97)

(-) was used to indicate inhibition and (+) was used for promotion. miRNA/miR, microRNA; NPC, nasopharyngeal carcinoma; WWOX, WW domain-containing oxidoreductase; LTF, lactotransferrin; BNIP3, Bcl-2/adenovirus E1B 19kDa interacting protein 3; PDCD6, programmed cell death 6; MDK, midkine; ENO2, hypermethylation of the enolase gene.

apoptosis by targeting BAX, LTF, Bcl-2-like protein 11, WW domain-containing oxidoreductase and phosphatase and tensin homolog (109-112). The expression levels of miR-214 were indicated to be upregulated in NPC, particularly in metastasis-prone NPC tissues compared with those in normal nasopharyngeal epithelial tissues (112). Therefore, miR-214 may serve as a potential novel diagnostic and RT sensitization biomarker for NPC. miR-124 has been detected in copious amounts in the brain and it may participate in the pathogenesis of several disorders. Deng *et al* (113) suggested that miR-124 was able to radiosensitize glioblastoma multiforme cells by targeting CDK4. In addition, miR-124 has been reported to be downregulated in NPC (114). miR-124 may enhance cell radiosensitivity by targeting JAMA and PDCD6 (105). Current research suggested that miR-124 is able to suppress stem-like properties and enhance radiosensitivity in NPC cells by directly targeting JAMA (106). These results may provide novel insight into the molecular mechanisms underlying RT failure in NPC and enable the design of novel therapeutic approaches (115,116).

6. Potential value of ferroptosis inducers for NPC radiosensitization

To date, a number of small-molecule compounds have been confirmed to induce ferroptosis, which are expected to be developed into novel antitumor small-molecule drugs. According to the different targets of small-molecule compounds, ferroptosis inducers may be divided into four categories as follows: i) Inhibition of system Xc^-; ii) inhibition of GPX4 activity; iii) degradation of GPX4 and coenzyme Q10; and iv) induction of lipid peroxide production (18). In NPC, ferroptosis may be induced by disulfiram/copper, itraconazole attenuates, cephalosporin antibiotics and cucurbitacin B (13,51,117,118). Among those, itraconazole is able to sequester iron in lysosomes, thereby causing ferroptosis and reversing the radiation resistance of NPC spheres. Therefore, whether ferroptosis inducers exert radiosensitizing effects and their potential value in RT for NPC warrants further investigation. An *in vitro* study indicated that the ferroptosis inducers imidazole ketone erastin and RSL3 act synergistically with radiation to promote ferroptotic cell death in a variety of tumor cell lines (32). In addition, another study suggested that erastin enhances the radiosensitivity of HeLa and NCI-H1975 adenocarcinoma cells via GSH depletion (119). Therefore, ferroptosis inducers may reduce the GSH concentration to enhance the radiosensitivity of radioresistant tumors, including NPC. A recent study indicated that the ferroptosis inducer erastin is able to trigger autophagy by increasing intracellular iron levels (120). Of note, a large number of studies have indicated that the activation of cytotoxic autophagy is able to enhance the sensitivity of tumor cells to RT (121). Therefore, the application of ferroptosis inducers to induce cytotoxic autophagy in NPC cells may be a promising method for radiosensitization.

7. Conclusions and future perspectives

The role of ferroptosis, a relatively newly identified type of cell death, has not been extensively investigated in NPC to date. The aim of the present review was to discuss the molecular mechanisms of ferroptosis in cancer. The metabolism of iron, PUFA and GPX4 have key roles in ferroptosis and there is a potential utility for the modulation of ferroptosis in the radiosensitization of NPC (51,122). Of note, the core regulators of ferroptosis, including miRNAs, serve important functions in RT for NPC. Radiation-resistant cells have been suggested to be more susceptible to ferroptosis due to their metabolic characteristics and cellular signaling pathways (123). Therefore, ferroptosis inducers may be of value in the radiosensitization of NPC. Itraconazole is a promising ferroptosis inducer for radiosensitization of NPC, which may reverse the radioresistance of

NPC spheroids (51). In brief, targeting ferroptosis may provide a novel strategy to improve RT sensitivity of NPC.

However, several issues remain to be addressed, including elucidating the exact mechanism of action of ferroptosis, determining the possible association between autophagy and ferroptosis in the radiosensitization of NPC, determining how to use nanotechnology materials to target ferroptosis regulators in NPC to enhance RT sensitivity and discovering additional ferroptosis inducers and regulatory genes. These questions must be addressed and successfully resolved before ferroptosis may be applied in the clinical setting.

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Authors' contributions

HLL mainly took charge of researching the literature and writing the manuscript; XSH had a guiding role in the review and was involved in revising the manuscript critically for important intellectual content; NHD and JXX provided ideas in the revision process. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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