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Review Article

Iron and magnetic: new research direction of the ferroptosis-based cancer therapy

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Abstract: Ferroptosis is an iron depend cell death which caused by lipid peroxidation. Abnormal iron metabolism and high intracellular iron content are the characteristics of most cancer cells. Iron is a promoter of cell growth and proliferation. However, iron also could take part in Fenton reaction to produce reactive oxygen species (ROS). The intercellular ROS could induce lipid peroxidation, which is necessary for ferroptosis. Iron metabolism mainly includes three parts: iron uptake, storage and efflux. Therefore, iron metabolism-related genes could regulate intercellular iron content and status, which can be involved ferroptosis. In recent years, the application of nanoparticles in cancer therapy research has become more and more extensive. The iron-based nanoparticles (iron-based NPs) can release ferrous (Fe^{2+}) or ferric (Fe^{3+}) in acidic lysosomes and inducing ferroptosis. Magnetic field is widely used in the targeted concentration of iron-based NPs related disease therapy. Furthermore, multiple studies showed that magnetic fields can inhibit cancer cell proliferation by promoting intracellular ROS production. Herein, we focus on the relationship of between ferroptosis and iron metabolism in cancer cells, the application of nanoparticles and magnetic field in inducing ferroptosis of cancer cells, and trying to provide new ideas for cancer treatment research.

Keywords: Iron metabolism, iron-based nanoparticles, magnetic field, ferroptosis, cancer therapy

Introduction

Cell death is closely related to the development, metabolic and disease of organism. Regulated cell death (RCD) has a significant role in organismal homeostasis in both physiological and pathological settings, excessive or insufficient RCD can cause disease. including autoimmunity, neurodegeneration, even cancer [1]. The RCD contains a variety of forms, including apoptosis, necroptosis, pyroptosis, parthanatos, autosis, ferroptosis [2], and many new forms of RCD were found in succession.

Ferroptosis is a new form of RCD was found and named by the team of Dr. Brent R Stockwell in 2012 [3]. Before Ferroptosis was named, the first ferroptosis inducer was discovered in 2003, when the lab of Stockwell study the killing effect of various chemical compounds on tumor cells, the erastin can trigger a RAS-mutated dependent cell death, and quite different from apoptosis [4]. Ferroptosis was defined as a form of RCD initiated by oxidative perturbations of the intracellular microenvironment that is under constitutive control by GPX4 and can be inhibited by iron chelators and lipophilic antioxidants by The Nomenclature Committee on Cell Death (NCCD) [5]. Multiple physiological and pathological processes are associated with ferroptosis, such as neurodegenerative diseases, neurotoxicity, hepatic and heart ischemia/reperfusion injury, drug-induced hepatotoxicity, acute renal failure, et al. Understanding the molecular mechanisms of ferroptosis may provide some ideas of the diagnosis and treatment of human disease about cell death.

Ferroptosis has the special morphological characteristics compared with other forms of regulated cell death (**Table 1**) [6, 7]. From the morphological changes of cells, the symbols of

Table 1. Comparison of features between apoptosis, autophagy, necroptosis and ferroptosis

		Apoptosis	Autophagy	Necroptosis	Ferroptosis
Morphological features	Cell membrane	Plasma membrane blebbing; rounding-up of the cell	Lack of change	Rupture of plasma membrane	Lack of rupture and blebbing of the plasma membrane; rounding-up of the cell
	Cytoplasm	Retraction of pseudopods; reduction of cellular volume	Accumulation of double-membraned autophagic vacuoles	Cytoplasmic swelling (oncosis); swelling of cytoplasmic organelles	Small mitochondria with condensed mitochondrial membrane densities, reduction or vanishing of mitochondria crista, as well as outer mitochondrial membrane rupture
	Nucleus	Reduction of nuclear volume; nuclear fragmentation; chromatin condensation	Lack of chromatin condensation	Moderate chromatin condensation	Normal nuclear size and lack of chromatin condensation
Biochemical features		Activation of caspases Oligonucleosomal DNA fragmentation Δψm dissipation PS exposure	LC3-I to LC3-II conversion Substrate (e.g., p62) degradation	Drop in ATP levels Activation of RIP1, RIP3, and MLKL Release of DAMPs (e.g., HMGB1) PARP1 hyperactivation	Iron and ROS accumulation Activation of MAPKs Inhibition of system X_c^- with decreased cystine uptake GSH depletion and increased NAPDH oxidation Release of arachidonic acid mediators (e.g., 11-HETE and 15-HETE) Δψm dissipation
Inhibitors		Caspase inhibitors	Autophagy inhibitors (e.g. 3-MA, wortmannin)	Necrostatins (e.g. Nec-1) Necrosulfonamide	Lipophilic antioxidants (e.g. Fer-1, vitamin E) Iron chelators (e.g. DFO, CPX)

Adapted from Xie Y et al. [6] and Cao JY, Dixon SJ [7].

ferroptosis are smaller mitochondria, higher mitochondrial membrane density and often accompanied by reduction/vanishing of mitochondria crista [3, 4, 8].

One important characteristic of ferroptosis is the accumulation of lipid peroxidation products, which could be produced by the Fenton reaction. The Fenton reaction is an abbreviation for the chemical reaction which participation by the iron (II or III) and hydrogen peroxide (H_2O_2), which was first described by H. J. H. Fenton in 1989. The Fenton reaction has been widely accepted and is described as follows [9]

$$Fe^{2+} + H_2O_2 = Fe^{3+} + \bullet OH + HO^-$$

$$Fe^{3+} + H_2O_2 = Fe^{2+} + \bullet OOH + H^+$$

Therefore, the iron content and metabolism in the tissue is closely related to the death of cell iron. Iron metabolism is one of the characteristics of cancer cells. Most cancer cells have higher levels of iron and ROS. Therefore, the relationship between iron metabolism and ferroptosis in tumor cells has also been studied in recent years. At the same time, with the development of nanotechnology, the various Iron-based nanomaterials have been used for cancer therapy research which based on Fenton reaction and ferroptosis. Caused by the excellent magnetic targeting properties and biocompatibility, iron-based NPs attracts a lot of attention to the field of magnetic resonance imaging (MRI) [10-12], computed tomography (CT) [13], biosensing [14], photothermal therapy [15], and therapeutic agent delivery [16]. The iron-based NPs can release ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions in acidic lysosomes, and further involved in the intracellular Fenton reaction to produce ROS and induce lipid peroxidation [17]. The magnetic field can provide a target for the localization of iron-based NPs in tumor site [18]. Meanwhile, many studies have shown that magnetic fields can inhibit the proliferation of many cancer cells and tumor growth [19, 20]. More interestingly, both alternating magnetic fields and static magnetic fields can promote intercellular ROS production [21, 22]. This means that regulating iron metabolism, inducing the concentration and internalization of iron-based NPs in cancer cells could induce ferroptosis, and local magnetic field exposure of the tumor can promote this process. This paper focuses on the application of iron metabolism, iron-based NPs and magnetic field in ferroptosis-based cancer therapy, and attempts to explore the application potential for iron and magnetic based ferroptosis studies.

The iron metabolism and ferroptosis

The free intracellular iron can cause lipid peroxidation through the Fenton reaction, which is required for the ferroptosis. The ferroptosis induced by erastin could be inhibited by the iron chelator, such as DFO [3]. The increasing

Table 2. Iron metabolism genes involved in ferroptosis

Gene	Name	Function
TFRC	Transferrin receptor	Imports iron into cells; promotes ferroptosis
HSPB1	Heat shock protein beta 1	Regulates iron uptake and GPX4 abundance; promotes ferroptosis
IRP2/IREB2	Iron-regulatory protein 2	Post-transcriptionally repress ferritin expression and increase TFR1 expression; promotes ferroptosis
DMT1	Divalent metal transporter 1	Transporting ferrous iron; promotes ferroptosis
FTH1	Ferritin heavy chain 1	Store excess intercellular iron; inhibits ferroptosis
NCOA4	Nuclear receptor coactivator 4	Involved in ferritinophagy and control of free iron abundance; promotes ferroptosis
FPN	Ferroportin	mediate iron efflux; inhibits ferroptosis

intracellular iron by the expression change of iron metabolism-related gene and iron treatment promotes ferroptosis [23]. Those results suggest that gene about iron metabolism could mediate process of ferroptosis (**Table 2**).

The iron uptake and ferroptosis

The cell iron uptake from extracellular environment mainly mediated by transferrin and transferrin receptor. The expression of transferrin and transferrin receptor is essential for ferroptosis [8, 24]. The cytotoxicity caused by erastin can be reduced through the knockdown of transferrin receptor. Both immunodepleted transferrin and TFRC RNAi in glutaminolysis free medium can significantly inhibited ferroptosis [23]. The inactivation of HSPB1 has could accelerate the erastin-induced ferrptosis [25]. Meanwhile, the HSPB1 can inhibit the TFRC recycling and suppression the TFRC mediated iron uptake [26, 27]. Iron-regulatory protein 2 (IRP2, also known as IREB2) is a gene acts to regulate iron levels in the cells by regulating the translation and stability of mRNAs that affect iron homeostasis under conditions when iron is depleted. It could inhibit the ubiquitination of transferrin receptor 1 (TfR1) and the divalent metal transporter 1 (DMT1) to upregulate cell iron uptake. It also suppresses the mRNA translation of ferritin and ferroportin (FPN) to increases the labile iron pool [28]. The study of Dixon et al. showed that IRP2 can promote erastin-induced ferroptosis and the inhibition of the IRP2 ubiquitination by FBXL5 knockdown could restrain erastin-induced ferroptosis [3].

The iron storage and ferroptosis

The excess intracellular iron mainly stores in ferritin for most cell. The downregulation of ferritin increases the labile iron pool and increasing intracellular oxidative stress [29, 30]. Downregulation of ferritin increases the sensitivity of breast cancer cells to the chemotherapeutic agents doxorubicin [31], the heavy chain ferritin siRNA can increase killing effect of carmustine to breast cancer cell [32]. Ferritin can autophagic degradation by ferritinophagy to maintaining homeostasis when iron depletion. The Ferritinophagy mainly mediated by nuclear receptor coactivator 4 (NCOA4).

The ferritinophagy was acticated in the initiation of ferroptosis [33], and promote intercellular ROS accumulation by releasing the iron to LIP. Different from autophagy, ferritinophagy mediated by NCOA4 don't need autophagic vacuoles, it can be done directly in lysosomes, but this process could inhibit by the inhibitor of autophagy. The suppression of ferritin degradation by the inhibition of NCOA4 could reduce ferroptosis, while NCOA4 overexpression could promote ferroptosis.

Induction to ferroptosis by erastin was shown to cause a time-dependent LIP increase, a process that is blocked by bafilomycin A1 (BafA1), a potent inhibitor of autophagy [34]. Meanwhile, the endogenous ferritin heavy chain 1 (FTH1) was increased during ferroptosis. Wan SY et al. studies show that overexpression of FTH1 enhanced ferritinophagy during the ferroptosis caused by erastin [34]. The regulation of ferritinopathy and the switch to ferroptosis during pathological conditions leads to cell death and this could also be beneficial therapeutically in the pathophysiology of cancer progression.

In HCT116, A549 and MIA PaCa-2 cell lines synthetic lethal screen, specificity towards oncogenic RASV12 transformed tumor cells was

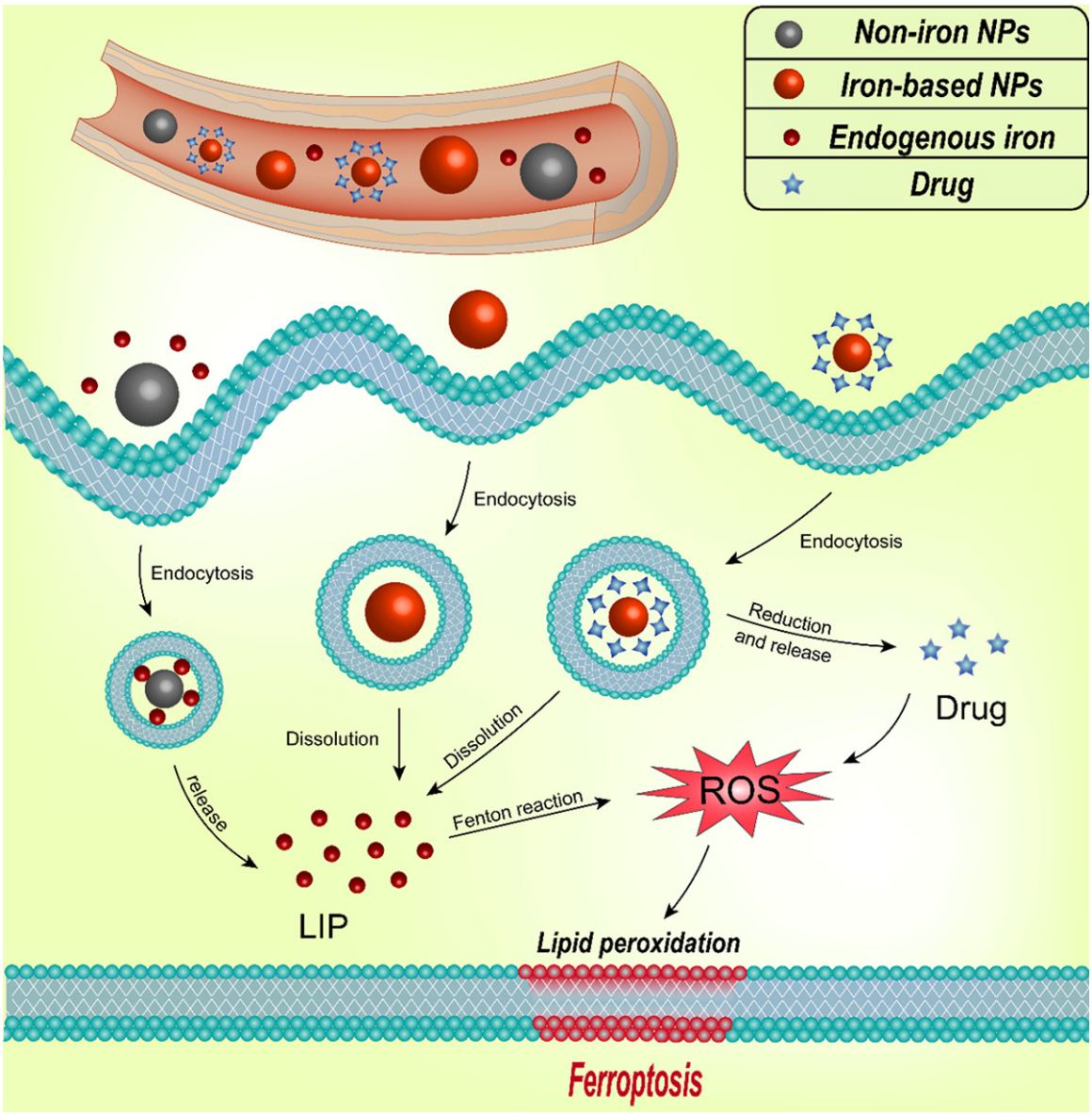

Figure 1. Mechanism of the iron-based NPs and Non-iron NPs for ferroptosis-based cancer therapy. The Non-iron NPs can loaded endogenous iron and the iron-based NPs can release iron in lysosome after endocytosis, which can be involved in the Fenton reaction to produce ROS and induce ferroptosis. The drugs carried by nanoparticles can facilitate the production of ROS, which caused by excess iron. Adapted from Shen ZY, et al. [17].

ensured as these cells exhibit elevated iron levels through increased expression of transferrin receptor 1 and downregulation of the iron storage protein ferritin [8]. Knockdown of the ferritinophagy-specific nuclear receptor coactivator 4 significantly decreases the ferroptotic response to erastin in human pancreas carcinoma cells (PANC1) and HT-1080 [35].

Iron efflux and ferroptosis

Ferroportin (FPN) is the only known iron efflux pump in vertebrates. Decreased expression of FPN and iron efflux are characteristic of most cancer cells. Dramatically, the S Ma et al. studies show that expression of FPN is decreased after treatment with siramesine or in combination with lapatinib in the human breast cancer cell lines MCF-7 and ZR-75-1. Meanwhile, knockdown of FPN resulted in increased ROS and ferroptosis after siramesine and lapatinib treatment, contrary to the effect of FPN overexpression [36]. The Erastin induced ferroptosis in neuroblastoma and SH-SY5Y cells, could promoted by knockdown of FPN. After the treatment of erastin, the expression of Fpn gene and

protein in SH-SY5Y cells has been significate reduction [37]. Those results suggested that the decrease of FPN expression can significantly increase iron-dependent lipid ROS accumulation, which can accelerate the rate of ferroptosis inducer. Therefore, FPN could be a potential therapeutic target site for ferroptosis based cancer therapy.

The genes that indirectly regulate iron metabolism and ferroptosis

In addition to the conventional iron metabolism related genes could participate in the process of ferroptosis by regulating the intracellular iron content, there are also many genes that affect the status and distribution of intercellular iron in an indirect way. Sun X study's shows that heat shock protein β-1 (HSPB1) could reduce intercellular iron to prevent cell ferroptosis. HSPB1 knockdown could promote the anti-tumor effect of erastin *in vivo* [25]. Heme oxygenase-1 has always been considered relevant to iron availability, also could regulate ferroptosis by affecting intercellular iron status or as an antioxidant [38]. The activation of nuclear factor (erythroid-derived 2)-like 2 (NRF2) which proved to have the ability to up-regulate heme oxygenase 1 and ferritin, could inhibit ferroptosis [39] Frataxin is a mitochondrial protein that is seemed to be involved in assembly of iron-sulfur clusters. Frataxin dysfunction leads to the accumulation of mitochondrial iron, and the production of ROS and oxidative stress [40]. Liver-specific knockout of frataxin impairs mitochondrial function and promotes the development of liver tumors in mice [41]. H_2S acts as the second messenger in the cell. It is closely related to the iron metabolism and intercellular iron status. Cystathionine b-synthase (CBS) catalyzes the transsulfuration pathway and participate in the regulation of intracellular H_2S synthesis. The team of Qian ZM found that CBS knockout (CBS-/-) mice significant increase in iron contented with severe tissue damages in the liver [42]. The condition is very similar to hemochromatosis, which the diseases accompanied by normal cell ferroptosis. The deregulation of miRNAs is entangled with the tumor, it also participates in the regulation of cancer cell's iron phenotype [43]. The miRNA-210 has proved to inhibit the expression of TfR1, and but instead of decreased uptake of transferrin-bound iron [44]. Furthermore, some aminoferrocence-based therapies also could increase intercellular iron content and enhancing ferroptosis [45, 46].

The iron-based NPs related tumor therapy and ferroptosis

In recent years, more and more nanoparticle research in the direction of cancer treatment. Moreover, the most research was based on the iron-based NPs, cause by the special physical and chemical properties of nanostructures, such as active targeting et al. Due to the magnetic field targeting, the concentration of nanoparticles could be significantly improving in the tumor site, and the reduce the side effects on other tissue.

The iron in iron-based NPs can be released as ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions in acidic lysosomes. Moreover, the pH in most tumor cells is more acidic than normal cell. Owing to the poor perfusion under hypoxic condition and increased anaerobic glycolysis, the tumor tissue is overall acidic [47]. Previous studies have shown that the extracellular pH values approaching 6.0 in the human and animal tumours [48]. This means that the iron-based NPs releases ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions in the tumor site is more pronounced than at the normal tissue. Released iron can participate in the Fenton reaction and induce ferroptosis of tumor cell. Therefore, there are many types of nanoparticles used as inducers of ferroptosis in the study of cancer therapy (**Figure 1**).

Iron oxide NPs

The iron oxide nanoparticles (IO NPs) alone has anti-cancer effect by inducing cell ferroptosis [17]. By studying the PLGA-coated Fe_3O_4 nanoparticles and the pure PLGA nanoparticles on MCF-7, Zhang XD and Mei L determined that the iron core rather than the nanoparticle structure caused endoplasmic reticulum stress and mitochondrial damage [49].

Ferumoxytol is an intravenous preparation as iron supplementation in patients with renal insufficiency and approved by the U.S. Food and Drug Administration (FDA) [50, 51]. Zanganeh et al. study focus on the intrinsic therapeutic effect of ferumoxytol on the growth of early mammary cancers, and lung cancer metastases in liver and lungs [52]. The research

showed that adenocarcinoma cells caspase-3 activity has significantly increased from co-incubated with ferumoxytol and macrophages, and macrophages exposed to ferumoxytol displayed increased mRNA associated with pro-inflammatory Th1-type responses in vitro. In their previous study, the M1 macrophage subtype has been shown can induce a Fenton reaction in cancer cell. Furthermore, the growth of subcutaneous adenocarcinomas in mice has been significantly inhibited by ferumoxytol and accompanied by an increased presence of pro-inflammatory M1 macrophages in the tumor tissues which detect by Fluorescence-activated cell sorting (FACS) and histopathology studies. Therefore, the ferumoxytol could trigger the ferroptosis in cancer cell by inducing tumor-associated macrophage (TAM) transformation to M1 subtype.

Chemotherapeutic agents -loaded iron-based NPs

Combining iron-based NPs with conventional chemotherapeutic agents are currently one of the main research methods about cancer therapy. The most current method is to modify the drug into nanoparticles to make it a whole, and using the iron-induced ferroptosis enhances the therapeutic effect of conventional drugs.

Zhu XL et al. found that the DOX-Cit/CuS@Fe_3O_4 nanoparticle could show higher cytotoxicity than DOX at the same concentration in MCF-7 cells. DOX-Cit/CuS@Fe_3O_4 nanoparticle could rapidly increase intracellular ROS levels under of 980 nm laser irradiation [53]. Sorafenib has been used as anti-cancer drugs in clinical for Liver cancer, kidney cancer and osteosarcoma et al. It has also been identified as a ferroptosis inducer. Zhang L et al. studies found that Sorafenib-modified iron-based NPs is more effective at inhibiting proliferation and inducing death of HepG2 cells in vitro than sorafenib alone [54]. The intracellular ROS generation plays a critical role in therapeutic effects of cisplatin [55, 56]. The cisplatin-loaded iron-based NPs has been designed by Ma et al. to study its anticancer efficacy. Human ovarian carcinoma A2780 cells (cisplatin-sensitive) and cisplatin-resistant A2780DDP cells (denoted ACP) has been used to testing the anticancer efficacy of designed IO NPs in Ma P et al. study [57]. The results showed that the A2780 and ACP cells death could be significant increasing by the treatment of Cisplatin-Loaded IO NPs than Cisplatin alone which can be blocked by iron chelator and ROS scavenger. Caused the Cisplatin mediates activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which triggers oxygen (O_2) to superoxide radical ($O_2^{\bullet-}$) and its downstream H_2O_2. Through the Fenton reaction, H_2O_2 could be catalyzed by Fe^{2+}/Fe^{3+} which released from IO NPs to the toxic hydroxyl radicals (•OH), which cause oxidative damages to lipids, proteins, and DNA. The result is also demonstrated tumor site-specific conversion of ROS generation induced by released cisplatin and Fe^{2+}/Fe^{3+} from iron-oxide nanocarriers with cisplatin(IV) prodrugs for enhanced anticancer activity but minimized systemic toxicity. Interestingly, the IC50 (half maximal inhibitory concentration) values of carboplatin, oxaliplatin, doxorubicin, and artesunate in A2780 and ACP cells showed a significant decrease with iron treatment.

Reduction inhibitors/oxide -tethered iron-based NPs

Since the release of iron from iron-based NPs can increase intracellular ROS levels, the oxides or reducing inhibitors can synergize with iron in cells. Many studies focus on the modifying oxides on iron-based NPs to promote ferroptosis caused by nanoparticle ingestion.

Ascorbic acid, known an antioxidant, is able to produce endogenous H_2O_2 to result in the oxidative stress by the generation of ROS [58]. The combination of Ascorbic acid with iron oxide particles was used as a new source of ROS manipulating anticancer drugs. This nanoparticle was ionized in acidic tumors and released iron, which in turn induced localized Fenton reaction. The rate of OH• generation using free Fe^{2+} ions was found to be faster than Fe^{2+} on the surface of Fe_3O_4 nanoparticles [59, 60].

β-lapachone (β-lap), a novel anticancer drug, has shown considerable cancer specificity by selectively increasing reactive oxygen species (ROS) stress in cancer cells. A 10-fold increase in ROS stress was detected in β-lap-exposed cells pretreated with iron oxide nanoparticle over those treated with β-lap alone in A549 non-small cell lung carcinoma (NSCLC) cells, which also correlates with significantly increased cell death [61].

Zhou et al. have designed an activatable singlet oxygen ($^1O_2$)-generating system for specific cancer therapy under tumor acidic pH environment through engineering the reaction between linoleic acid hydroperoxide (LAHP) and catalytic iron (II) ions. LAHP is one of the primary products of lipid peroxidation, which is associated with several diseases by decomposition into ROS and $^1O_2$ in the presence of Fe^{2+} through the Russell mechanism. The iron could release from nanoparticle under tumor acidic pH environment, and LAHP can react with Fe^{2+} to produce $^1O_2$, which is much more efficient than Fenton reaction without LAHP participation. The result showed that IO-LAHP nanoparticles are able to induce efficient cancer cell death in U87MG cells through tumor-specific $^1O_2$ generation and subsequent ROS mediated mechanism, and the tumor growth has been significant inhibited *in vivo* [62].

No iron-based NPs

There are also special cases in which non-iron nanoparticles can induce cancer cells ferroptosis. Sung EK et al. studies show that ultrasmall αMSH-PEG-C' dots could suppress tumor growth, the function could be reserved liproxstatin-1, which has been determined as an inhibitor of ferroptosis. Their results also demonstrated that αMSH-PEG-C' dots could induce nutrient-deprived cancer cells ferroptosis, while the generally cancer cells are resistant to it. In this study, the anti-cancer ability of αMSH-PEG-C' dots come from its promotion of iron uptake of cancer cell [63]. Ou WJ et al. designed a Low-Density Lipoprotein Docosahexaenoic Acid Nanoparticles (LDL-DHA NPs) and found that it could induce hepatoma cells death selectively and inhibit orthotopic liver tumors growth *in vivo*. This anti-cancer effect is accompanied by lipid peroxidation with the iron-dependent characteristics of ferroptosis [64].

By the way, even besides iron, other particles such as silver, gold, and FeOx-MSNs22 were reported to produce OH• from H_2O_2 in the acidic lysosomes. But the drawback of these studies is that these nanoparticles only produced OH• at the surface via a heterogeneous reaction and unable to treat the cancer cells using the endogenous H_2O_2.

The iron-based NPs has been used as contrast agents for magnetic resonance imaging (MRI) in clinical [65]. Therefore, its security has a certain guarantee of cancer therapy. Furthermore, iron-based NPs can be easily for targeted concentration in tumor sites due to their special physicochemical properties. It cannot be ignored that function and magnetic-targeting efficiency of nanoparticle is closely related to iron-particle size. Guo XM et al. found that smaller Fe_3O_4 nanoparticles are easier internalized by cells, while larger Fe_3O_4 nanoparticles are easier to accumulate in the tumor [66].

In addition to releasing iron to increase the intracellular ROS level, the iron-based NPs can also participate in intercellular redox metabolism as a "nanozyme" [67, 68]. Ultrasmall Fe_3O_4 nanoparticles could be described as an inorganic nanozyme and can participate in intercellular redox metabolism as a Fenton reaction catalyst in the mildly acidic microenvironment of tumor [69]. Huo MF et al. has designed a nanoparticle constructed from glucose oxidase (GOD), synthetic ultrasmall Fe_3O_4 nanoparticle, and dendritic MSN combinations to investigate the role and mechanism of GOD and ultrasmall Fe_3O_4 nanoparticles on tumors [70]. Their result shows that GOD-Fe_3O_4@DMSNs nanocatalysts (GFD NCs) could induce death of 4T1 and U87 cells *in vitro* and inhibit tumor growth *in vivo* accompanied by elevated levels of intracellular ROS.

Application potential of magnetic field in ferroptosis-based cancer therapy

The magnetic field often plays a guiding role in the process of iron-based NPs induce ferroptosis, allowing nanoparticles to be enriched in the tumor site. In some special structure of nanoparticle treatment, the magnetic field can also change the arrangement of nanoparticles in the body to promote the local release of the drug. They build two types nanoparticle as enzyme and substrate, the nanoparticle could merge and forced to interact with the generated nanocompartment during the external magnetic field loading [71].

In some studies, the magnetic field can be used as a stirrer of nanoparticles to promote the production of ROS in tumor cells. The Flanagan SW et al. showed that the magnetic field can heat the IO NPs, lead the hyperthermia in tumor area, and the ROS production to suppress the proliferation of pancreatic cancer cells (PANC-1

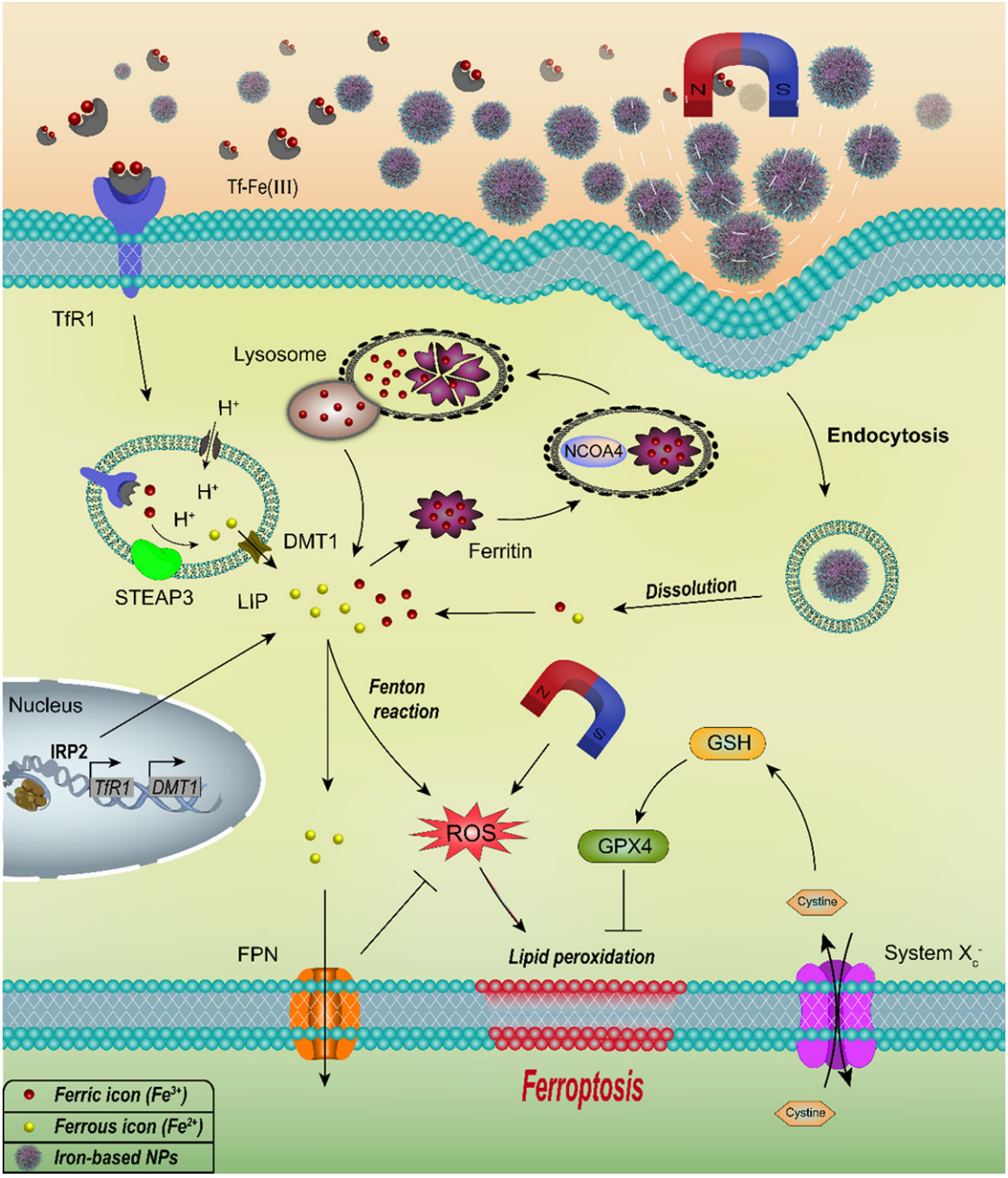

Figure 2. The mechanism of iron metabolism, iron-based NPs and magnetic field in the ferroptosis-based cancer therapy. Iron metabolism affects ferroptosis by regulating cellular iron uptake (TfR1, DMT1, IRP2), storage (Ferritin, NCOA4), and efflux (FPN). Iron-based NPs could release ferrous (Fe^{2+}) or ferric (Fe^{3+}) in acidic lysosomes. Excess intercellular iron can cause lipid peroxidation by participating in Fenton reaction, which is necessary for ferroptosis. The magnetic field can be used to concentrate iron-based NPs in the tumor site, meanwhile magnetic field can directly promote the intracellular ROS production.

and BxPC-3 cells) and reduced tumor volumes. In this process, ROS is not only produced by the release of Fe from the nanoparticles, but also be induced via hyperthermia [72, 73]. Furthermore, numerous studies have shown that the magnetic field itself can also inhibit tumor cell proliferation by promoting intracellular ROS production. Magnetic field treatment can in-

crease the concentration, viability and longevity of paramagnetic intercellular free radicals, and changes the conformation and activity of oxidative balance related enzymes. These changes may lead to a series of subsequent changes in oxidative stress levels even cell death [74].

Sabo J et al. found that after 1.0 T strong magnetic field treatment for 72 h, the rat leukemia HL-60 cell's metabolic activity has been significate inhibited. This phenomenon probably due to the strong magnetic field induced intracellular ROS increase, then ROS destroyed the cell's metabolic process, thus making it metabolic activity is inhibited [22]. Spyridopoulou K et al. found that both the static magnetic field and the rotating magnetic field can inhibit the activity of human colon cancer HT29 cells, and the inhibition is positively correlated with the magnetic field strength. Interestingly, during this experiment they also found that the magnetic field promoted the absorption of nanoparticles by the cells [75]. The research of Hajipour VB et al. shows that the 5, 10, 15 and 20 mT magnetic field can promote the accumulation of iron in MCF-7 and HFF cells, increase of production of ROS, inhibit its cellular activity and has a synergistic effect with doxorubicin [76]. At the same time, previous research in our laboratory showed that high statics magnetic field can promote iron uptake in osteosarcoma cell line MG63 (unpublish). This means that the magnetic field has great potential and application value in the study of cancer therapy based on ferroptosis.

Conclusions and prospective

Ferroptosis is essentially destroying the intracellular redox balance by the ROS accumulation. Most of the previous studies about ferroptosis focused on how to maintain or destroy the intercellular redox balance by regulating "reduction part" of the redox balance, such as System X_c^-, Glutathione peroxidase 4 (GPX4), glutathione metabolism and dysregulation of lipid metabolism et al. [77-81]. The role of iron in ferroptosis mainly focused on "oxidation part". The intercellular iron status affects the production of ROS. Abnormal iron metabolism is characteristic of most tumor cells [82]. The overexpression of genes related to iron uptake and the low expression of genes related to iron efflux lead to a much higher intercellular iron content of most cancer cells than normal cells [83, 84]. At the same time, the iron content of the LIP in cancer cells is much higher than that in normal cells. The Fenton reaction involved in iron is one of the main pathways to intracellular ROS production. Therefore, cancer cells have higher levels of ROS, and the redox balance is also more fragile [82]. As a new form of cell death and closely related to intracellular redox balance, ferroptosis introduces iron from the field of nutrition to the cancer therapy. In addition to regulating iron metabolism in cells to induce cancer cells ferroptosis, put the cancer cell in a special high-iron environment is another way to make it ferroptosis. With the development of nanotechnology and the special physical and chemical properties of nanomaterials, the various nanoparticle has also been widely used in the research of cancer treatment. At the same time, iron-based NPs could ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions in acidic lysosomes and increase ROS levels in tumor cells rapidly. This suggests that iron-based NPs has great potential for the ferroptosis based cancer therapy. Due to the tendency towards iron-based NPs to concentrate in the tumor site under the action of a magnetic field, the magnetic field is widely used in tumor therapy research as drugs "guide". The magnetic field not only can play a role in the targeted concentration of nanoparticles, but also promotes the production of ROS in cells (**Figure 2**). Therefore, iron metabolism, iron-based NPs and magnetic field can mutual assistance in ferroptosis-based cancer therapy.

In the future, the research of ferroptosis through the iron metabolism and iron preparations will provide more extensive research ideas of cancer therapy. The used of iron-based NPs combination with other chemotherapeutics have great potential for future research. Furthermore, the magnetic field not only serves as a guide in the ferroptosis-based cancer therapy to have a wide application prospect, but also its own influence on the process of ferroptosis deserves further exploration.

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