REVIEW

Advances in Ferroptosis-Inducing Agents by Targeted Delivery System in Cancer Therapy

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Abstract: Currently, cancer remains one of the most significant threats to human health. Treatment of most cancers remains challenging, despite the implementation of diverse therapies in clinical practice. In recent years, research on the mechanism of ferroptosis has presented novel perspectives for cancer treatment. Ferroptosis is a regulated cell death process caused by lipid peroxidation of membrane unsaturated fatty acids catalyzed by iron ions. The rapid development of bio-nanotechnology has generated considerable interest in exploiting iron-induced cell death as a new therapeutic target against cancer. This article provides a comprehensive overview of recent advancements at the intersection of iron-induced cell death and bionanotechnology. In this respect, the mechanism of iron-induced cell death and its relation to cancer are summarized. Furthermore, the feasibility of a nano-drug delivery system based on iron-induced cell death for cancer treatment is introduced and analyzed. Secondly, strategies for inducing iron-induced cell death using nanodrug delivery technology are discussed, including promoting Fenton reactions, inhibiting glutathione peroxidase 4, reducing low glutathione levels, and inhibiting system Xc$^-$. Additionally, the article explores the potential of combined treatment strategies involving iron-induced cell death and bionanotechnology. Finally, the application prospects and challenges of iron-induced nanoagents for cancer treatment are discussed.

Keywords: cancers, ferroptosis, nano-drug delivery system, target

Introduction

Over the past decade, various malignant tumor treatment methods have been applied in the clinic, including traditional treatment strategies such as surgery, chemotherapy, radiotherapy, and emerging immunotherapy.[1] However, due to the inherent limitations of conventional treatment approaches and the heterogeneity of tumors, their clinical efficacy remains dismal.[2,3] Although immunotherapy has become a promising cancer treatment in recent years, its narrow anti-tumor spectrum, potential toxicity, and autoimmune suppression have greatly limited its clinical application.[4,5] Additionally, drug delivery barriers within solid tumors account for the poor efficacy of tumor immunotherapy.[6,7] Therefore, in the face of the serious threat to human health posed by malignant tumors, there is an urgent need for a safer and more effective treatment approach.

In recent years, emerging biomedical developments and technological innovations have provided more possibilities for effectively treating cancer.[8] An increasing body of literature suggests that inducing iron death in tumor cells represents a potential new anti-tumor strategy.[9,10] Iron is one of the essential elements of the human body. It exists in the form of hemoglobin, myoglobin, and other compounds, and the rest is stored as ferritin in the liver, spleen, and bone marrow.[11,12] Iron is reportedly involved in metabolic processes and various life activities, including oxygen transport, cell respiration, electron transfer, DNA synthesis, and immune regulation.[13,14] The abnormal metabolism of iron leads to many physiological disorders. In this regard, the presence of Fe^{2+} in cells greatly accelerates the lipid peroxidation of

saturated fat.[15] During mitochondrial oxidative phosphorylation, where iron is involved, cells generate both adenosine triphosphate (ATP) and reactive oxygen species (ROS).[16] If the production of ROS surpasses the cellular antioxidant capacity, it can trigger oxidative stress reactions.[17] Consequently, macromolecules like proteins, nucleic acids, and lipids may suffer damage, ultimately leading to cell impairment or death.[18–20] This novel form of regulated cell death is called ferroptosis. In recent years, research on ferroptosis has increased exponentially.[21] It is widely thought that the induction of ferroptosis in tumor cells represents a feasible research direction for tumor treatment.[22,23] The compounds that trigger ferroptosis in tumor cells and the underlying mechanisms leading to this process represent crucial aspects of anti-tumor drug development.[24,25]

With the development of nanotechnology and biomaterials, biological nanotechnology has been widely applied in designing nanomedicine delivery systems.[26,27] This system offers significant advantages in drug delivery, such as improving water solubility, prolonging circulation time, enhancing tumor accumulation, increasing cell uptake, and reducing toxicity.[28–30] Various nanoformulations, such as doxorubicin liposomes (Doxil) and paclitaxel albumin nano-particles (Abraxan), have been applied in clinical practice.[31] Therefore, biological nanotechnology holds significant implications for the delivery of hydrophobic small-molecule anticancer drugs, leading to enhanced treatment efficiency and minimized adverse reactions.[32–34] This concept opens up innovative possibilities for the in vivo delivery of ferroptosis inducers that suffer from poor water solubility, high systemic toxicity, and limited tumor delivery efficiency.[35] As a result, it paves the way for the development of novel, efficient, and low-toxicity cancer therapeutics. Interestingly, nanoformulations can use endogenous substances from tumors as substrates to drive catalytic reactions and regulate their microenvironment to achieve anti-tumor effects.[36,37] They can also enable targeted delivery and controlled release of clinical chemotherapy drugs, achieving site-specific therapy of malignant tumors. In recent years, nanotherapy in the context of ferroptosis has received extensive attention. The synergistic combination of ferroptosis inducers and biological nanotechnology for tumor treatment holds tremendous potential for various applications.[9] This article provides a systematic introduction to the process of ferroptosis, elucidates the mechanism of nanoparticle-induced ferroptosis, and highlights the latest advancements in combined anti-tumor therapy based on ferroptosis.

Ferroptosis and Its Process
Overview of Ferroptosis

In 2003, Dolma et al discovered a new compound called erastin, which could induce RAS mutations and cause tumor cells to die differently from traditional cell apoptosis.[38] In 2008, Yang et al discovered two new compounds (RSL3 and RSL5) that yielded the same effect as erastin and determined that this novel form of cell death could be inhibited by iron chelating agents, ferroamine B methanesulfonate, and antioxidant vitamin E, which captures peroxyl radicals, confirming that this form of cell death is related to intracellular iron and ROS levels.[39,40] The term "Ferroptosis" was coined by Dixon et al in 2012 to describe a specific type of cell death that occurs due to the accumulation of iron and lipid reactive oxygen species.[41,42]

The common forms of cell death include apoptosis, necrosis, necrotic apoptosis, autophagy, pyroptosis, copper death, etc. (1) Apoptosis refers to the autonomous and programmed death of cells controlled by genes to maintain the stability of the internal environment.[43] It involves the activation, expression, and regulation of a series of genes, which is physiological and selective.[44] The main morphological changes include cell atrophy, increased cytoplasmic density, decreased mitochondrial membrane potential (MMP), permeability changes, and the appearance of complete apoptotic bodies.[45] (2) Cell necrosis is cell damage and death caused by extreme physical and chemical factors or severe pathological stimulation and represents an unnatural form of cell death.[46] When apoptosis cannot occur under normal circumstances, necrosis is employed as an alternative mechanism for cell death.[47] (3) Necrotic apoptosis is also a form of programmed cell death (PCD) mediated by various cytokines and pattern recognition receptors (PRR), leading to cytological changes, including swelling, membrane rupture, chromosomal condensation, and the release of damage-related molecular patterns (DAMPs), inflammatory cytokines, and chemokines, mediating extreme inflammatory responses.[48] (4) Autophagy refers to the process of degrading dysfunctional cell components through lysosomes.[49] Its main morphological features include autophagic vacuole accumulation, cytoplasm vacuolization, and the absence of

chromatin condensation.[50] It is well-established that autophagy can degrade and digest damaged and denatured organelles, proteins, nucleic acids, and other biological macromolecules, providing raw materials for cell regeneration and repair and achieving the recycling and utilization of intracellular substances.[51] Autophagy also promotes cellular senescence and cell surface antigen presentation and prevents genomic instability and necrosis, accounting for its key role in preventing cancer, neurodegeneration, cardiomyopathy, diabetes, liver disease, and other diseases.[52] (5) Pyroptosis is a newly discovered mode of programmed cell death, characterized by the continuous expansion of cells until cell membrane rupture, leading to the release of cell contents and then activating a strong inflammatory reaction.[53] Pyroptosis is vital to the body's innate immune response, serving as a crucial defense mechanism against infections and endogenous danger signals.[54] (6) Cuproptosis is caused by the direct combination of Cu^{2+} with the fatty acid component of the citric acid cycle in mitochondrial respiration, inducing the aggregation of fatty acylated proteins and the instability of iron-sulfur proteins, leading to proteotoxic stress and inducing cell death independent of the apoptosis pathway.[55] The manifestation of copper death includes mitochondrial shrinkage and mitochondrial membrane rupture.

In terms of morphological and biochemical characteristics, ferroptosis is different from other forms of cell death. Morphologically, ferroptosis is characterized by mitochondrial contraction and increased mitochondrial membrane density.[56,57] Unlike other cell death types, there is no cell swelling or membrane rupture, and no changes in the nucleus or chromatin contraction are observed. Biochemically, ferroptosis involves the aggregation of reactive oxygen species and iron ions, activation of the mitogen-activated protein kinase (MAPK) system, reduced cystine uptake, depletion of glutathione, and inhibition of system Xc^-, among others.[58,59] At the gene level, ferroptosis is mainly regulated by specific genes, including Ribosome L8 (RPL8), iron response element binding protein (IREB2), ATP synthase F0 complex subunit C3 (ATP5G3), tritetrapeptide repeat domain 35 (TTC35), citrate synthase (CS), acyl-coenzyme A synthase family member 2 (ACSF2), and metabolic and storage genes such as transferrin receptor protein 1 (TFRC), iron-sulfur cluster assembly enzyme (ISCU), ferritin heavy chain 1 (FTH1), ferritin light chain (FTL), and solute carrier family 11 member 2 (SLC11A2).[60]

The Process of Ferroptosis

It is well-established that lipoxygenase and ROS can oxidize the polyunsaturated fatty acid (PUFA) chain on the cell membrane lipid to form lipid peroxide (L-OOH). In the presence of iron, lipid peroxides turn into toxic lipid free radicals, resulting in the fragmentation of polyunsaturated fatty acids of cell membrane lipids and cell death.[61] The glutathione-dependent lipid repair enzyme glutathione peroxidase 4 (GPX4) can prevent the development of this process by reducing the iron-dependent lipid peroxidation into highly active lipid free radicals, thereby reducing the accumulation of lipid reactive oxygen species (L-ROS).[62] The synthesis of GSH requires cystine-glutamate reverse transporter system (system Xc^-, an important antioxidant that imports cystine (Cys2) into the cell), while the Xc^- transporter transports glutamate out of the cell.[63] The inhibition of system Xc^- transporter function reduces glutathione (GSH levels in cells, inhibits GSH-dependent GPX4 enzyme activity, and increases the iron content in cells, leading to the accumulation of L-ROS and ferroptosis.

Regulation of Intracellular Biochemical Processes on Ferroptosis

Ferroptosis refers to the process whereby excessive iron in cells participates in the Fenton reaction, which leads to the production of highly active hydroxyl radicals, promotes the peroxidation of PUFA, induces the production of many lipid reactive oxygen species, and leads to cell death.[64] The excessive production of reactive oxygen species, the massive accumulation of iron ions, and lipid peroxidation are the three major characteristics of ferroptosis. These key aspects highlight the central role of lipid metabolism, iron metabolism, and amino acid metabolism in driving the occurrence of ferroptosis. However, it should be borne in mind that other pathways and processes can also regulate this form of cell death.

Lipid Metabolism

The essential reaction substrates for lipid peroxidation, a central process in ferroptosis, are provided by fatty acids. Among fatty acids, polyunsaturated fatty acids (PUFAs), particularly arachidonic acid and adrenic acid found in

phosphatidylethanolamine (PE) and phosphatidylcholine (PC) are the preferred targets for lipid peroxidation.[65,66] This process affects the cell membrane's function by disrupting the lipid bilayer. Free PUFA can be converted within cells to polyunsaturated fatty acids coenzyme A (PUFA CoA) catalyzed by long-chain acyl-coenzyme A synthetase 4 (ACSL4).[67] Subsequently, PUFA CoA enters the endoplasmic reticulum phospholipids via lysophosphatidylcholine acyltransferase 3 (LPCAT3), leading to the generation of polyunsaturated fatty acid phospholipids (PUFA PLs). Under the dual influence of reactive oxygen species and lipoxygenase, these PUFA PLs undergo oxidation, forming peroxidized PUFA PLs. This process destroys the lipid bilayer membrane, affecting membrane function, and ultimately triggers ferroptosis.[68] In contrast, monounsaturated fatty acid (MUFA), like Saturated fat palmitate (SFA) through stearoyl CoA desaturase-1 (SCD1), are incorporated into phospholipids in a manner dependent on ACSL3. This incorporation interferes with the formation of PUFA phospholipids and protects cells from iron-induced apoptosis.[69]

During lipid peroxidation, intracellular lipid peroxidation products primarily accumulate through non-enzymatic and enzymatic lipid peroxidation. During the non-enzymatic autooxidation process, free ferrous reacts with hydrogen peroxide (H_2O_2) to produce triiron and hydroxyl radicals (•OH) through the Fenton reaction.[70] On the other hand, the enzymatic mechanism of Lipid peroxidation involves the involvement of NADPH oxidase (NOX) and Lipoxygenase (LOXs), which are closely linked to the imbalance of lipid oxidation metabolism.[71] Overexpression of NADPH oxidase (NOX) can lead to NADPH depletion, causing a rapid increase in oxidative free radicals in cells and significantly enhancing the cell's susceptibility to ferroptosis.[72] Several pathways, including peptidyl peptidase 4 (DPP4) and p53 pathway, Arachidonic acid and Protein kinase C pathway, and HIPPO signal pathway, have been found to regulate NOX function.[73] Lipoxygenase (LOX) is a group of non-heme iron-containing enzymes. In the ferroptosis pathway, LOX is crucial in peroxidizing the plasma membrane and promoting ferroptosis in tumor cells.[74] Among the LOX family members, LOX5, LOX12, and LOX15 have been established to significantly impact lipid metabolism.[75]

Iron Metabolism

Ferroptosis primarily occurs due to abnormal cell iron metabolism, especially excess iron. Transferrin (TF) is a glycoprotein with a molecular weight of 76 kDa, responsible for tightly and reversibly binding to iron in the blood, facilitating its transport to various tissues and organs.[76] The binding of transferrin to iron is pH-dependent.[77] At pH 7.4, transferrin efficiently binds with Fe^{3+}, but under acidic pH conditions, they separate, releasing iron from TF.[78] On the cell surface, TF interacts with Fe^{3+} to form a total iron-transferrin (Tf) complex, which then binds to the Transferrin receptor (TFR) and enters the endosome via endocytosis.[79] Within the acidic endosomes, Fe^{3+} separates from TF. Simultaneously, iron oxidoreductase 3 (STEAP3) reduces Fe^{3+} to Fe^{2+}, which is transported to the cytoplasm by the divalent metal ion transporter 1 (DMT1).[80] The TF-TFR complex releases Fe^{3+} and returns to the cell surface through exocytosis. Iron in cells can be stored in two ways: either stored harmlessly in Ferritin or forming an unstable iron pool in the form of free $Fe.^{2+}$[81] Ferritin is a cytoplasmic iron storage protein comprising Ferritin heavy chain 1 (FTH1) and Ferritin light chain (FTL) subunits.[82] FTH1 exhibits iron oxidase activity, converting excess Fe^{2+} to Fe^{3+}, while FTL allows for Fe^{3+} storage.[83] Fe^{2+} is mainly excreted from the cell membrane by the solute carrier family 40 member 1 (SLC40A1) or can be expelled as Ferritin via exosomes.[84] The protein prominin 2 promotes the formation of polyvesicles and exosomes, facilitating iron excretion from cells and maintaining the dynamic equilibrium of intracellular iron levels.[85] Furthermore, Nuclear receptor coactivator 4 (NCOA4) selectively recognizes ferritin within cells and transports it to lysosomes for degradation, releasing free $Fe.^{2+}$[86] This process is known as ferritinophagy, a special type of autophagy involved in the regulation of iron levels within cells.

Finally, the instability and heightened reactivity of excess Fe^{2+} results in the Fenton reaction, generating highly reactive hydroxyl radicals.[87] These radicals directly interact with polyunsaturated fatty acids present in the cell membrane, leading to a substantial production of lipid reactive oxygen species and cell ferroptosis.

Amino Acid Metabolism

Cells experiencing ferroptosis usually exhibit an imbalance between the antioxidant defense system and lipid peroxidation.[88] The cellular stability of cells may be compromised when the intracellular antioxidant defense system fails to sufficiently limit the extent of lipid peroxidation. The GSH-GPX4 antioxidant system plays a pivotal role in the

ferroptosis process.[89] GSH, serving as the substrate of GPX4, is a vital component of the intracellular antioxidant system and a critical factor influencing the occurrence of ferroptosis.[90] GSH synthesis relies on amino acid metabolism, where the specific transporter cystine/glutamate reverse transporter (system Xc$^-$) facilitates the entry and exit of amino acids.[91] Comprising SLC7A11 and SLC3A2, system Xc$^-$ transports glutamic acid out of cells while importing cystine into cells.[92] Once inside the cell, cystine is oxidized to cysteine, which, under the influence of glutamate cysteine ligase and glutathione synthetase, combines with glycine to produce glutathione (GSH).[93] Glutathione exists in two forms: oxidized and reduced, and Glutathione reductase catalyzes their interconversion, enabling them to regulate the intracellular oxidative balance.[94] GSH serves as a cofactor for GPX4, allowing GPX4 to reduce hydrogen peroxide or peroxidized PUFA PLs to water and alcohol, respectively. This action inhibits the process of lipid peroxidation within cells and consequently hinders the occurrence of ferroptosis.[95]

When there is an increase in extracellular glutamate, or specific inhibitors hinder the function of the cystine-glutamate reverse transporter system, the transport of cystine and glutamate into cells becomes impaired, resulting in reduced intracellular GSH synthesis.[96] Since GSH is a crucial antioxidant in cells, its reduction leads to the accumulation of a large number of lipid reactive oxygen species, consequently promoting the occurrence of ferroptosis and causing cell death. GPX4 is a significant marker of ferroptosis and one of the GSH peroxidases. It is a Selenoprotein, and its functionality depends on the selenium level in the body.[97] When selenium is deficient, the catalytic activity of GPX4 can decrease dramatically, up to 1000 times.[97] Research has indicated that both the iron inducer Erastin and RSL3 can inhibit the activity of GPX4. Erastin may promote ferroptosis by depleting the GPX4 substrate GSH, while RSL3 directly inhibits the activity of GPX4.[39] Consequently, the inactivation or reduction of GPX4 becomes a crucial factor in promoting tumor cell death, which is also an important condition for inducing ferroptosis in tumor cells.

Others

In addition to iron ion metabolism, lipid metabolism, and amino acid metabolism, ferroptosis is regulated by other regulatory factors, including ferroptosis suppressor protein 1 (FSP1), NRF2, p53, and mitochondria.[98,99]

Fsp1

FSP1 is a recently discovered significant regulatory protein crucial in ferroptosis inhibition. Initially known as mitochondrial apoptosis-inducing factor 2, it was renamed FSP1 in 2019 to highlight its unique function in preventing cell ferroptosis.[100] FSP1 functions as the Oxidoreductase of Coenzyme Q10 (CoQ10).[101] Its N-terminal undergoes lipid modification through myristoylation, promoting FSP1's localization to the plasma membrane that enables FSP1 to facilitate NADH-dependent CoQ reduction on the plasma membrane, inhibiting CoQ10 activity.[102] Ultimately, through the FSP1-CoQ10-NAD(P)H pathway, which runs parallel to the classic glutathione (GSH) - GPX4 pathway, FSP1 hinders phospholipid peroxidation and ferroptosis by interfering with MDM2-MDMX.[103]

Nrf2

Nuclear factor E2-related factor 2 (NRF2) is a key regulatory factor in the endogenous antioxidant defense system of cells.[104] It controls the expression of antioxidant and electrophilic stress genes and maintains cellular metabolism, redox, and protein homeostasis balance. NRF2 can reportedly induce the expression of numerous protective and detoxifying genes and is widely thought to act as a negative regulator of ferroptosis.[105,106] In hepatoma cell lines, upregulation of NRF2 was found to promote the expression of antioxidant genes, such as heme oxygenase-1 and quinone oxidoreductase 1, leading to the inhibition of ferroptosis.[107] Conversely, downregulation of NRF2 can accelerate ferroptosis induced by substances like erastin or Sorafenib.[25] The NRF2 target genes not only regulate the key process of iron metabolism but also control the catabolism of foreign organisms and reactive aldehydes, as well as the synthesis of GSH and regeneration of nicotinamide adenine dinucleotide phosphate (NADPH), making it a versatile regulator of cellular resistance to iron degradation.[108,109]

P53

The transcription factor p53 plays a crucial role in inhibiting tumor cell growth. In recent years, its involvement in ferroptosis has become a new research hotspot. Studies indicate that p53 exhibits a dual role in regulating ferroptosis.[110]

On one hand, it can promote the occurrence of ferroptosis by inhibiting the expression of solute vector family 7 member 11 (SLC7A11) or by promoting the expression of spermidine/spermine N1 acetyltransferase 1 (SAT1) and glutaminase 2 (GLS2).[111] On the other hand, it can inhibit ferroptosis by inhibiting dipeptidyl peptidase 4 (DPP4) activity or by promoting the expression of cell cyclin-dependent kinase inhibitor 1A (CDKN1A/p21).[112]

Vdac

Voltage-dependent anion channel (VDAC) is an ion channel in the outer mitochondrial membrane that mediates and controls molecular and ion exchange between mitochondria and the cytoplasm.[113] Yagoda et al revealed that cells activated by the mitosis-activated protein kinase pathway (RAS-RAF-MEK pathway) could bind with certain ligands of VDAC, resulting in increased sensitivity to erastin.[114] Erastin can prevent and reverse the blocking of VDAC by free Tubulin in the cytoplasm in vivo and in vitro, thus opening VDAC and leading to non-apoptotic cell death.[115] VDAC can be upregulated in response to the RAS-RAF-MEK pathway, leading to mitochondrial dysfunction and ROS accumulation.[116] Additionally, drugs can alter the permeability of VDAC, resulting in disrupted mitochondrial metabolism, leading to an influx of substances into the mitochondria and excessive ROS production.[117]

The Mechanism of Tumor Cell Ferroptosis Mediated by Nanoparticles

With the rapid advancement of nanotechnology and biomaterials, loading ferroptosis inducers onto nanocarriers is feasible, offering significant advantages.[62,118] It enhances the accumulation and controlled release of ferroptosis inducers at tumor sites, effectively reducing the toxicity of drug delivery systems, overcoming drug resistance in tumor cells, and notably enhancing the ferroptosis effect on tumor cells. Ferroptosis can be induced by various drugs and strategies that lead to the accumulation of reactive oxygen species and lipid peroxides within cells. To achieve efficient ferroptosis induction in tumor cells, novel nanopreparations adopt the following strategies: (1) Increasing the content of intracellular iron ions to trigger the Fenton reaction, thereby elevating ROS levels.[119] (2) Inhibiting system Xc^- activity to reduce glutathione (GSH) synthesis or suppressing GPX-4 to increase intracellular ROS and lipid peroxide accumulation.[120] (3) Exogenously regulating Lipid peroxidation in tumor cells.[121] By employing these ferroptosis-induction strategies, researchers have significantly improved the efficacy of tumor treatment, offering the potential for developing new, efficient, and low-toxicity nano agents (Figure 1).

Iron Ion-Based Fenton Reaction Induces Ferroptosis

It is now understood that the process of tumor cell ferroptosis is dependent on the presence of iron, with a significant increase in ferrous ion (Fe^{2+}) levels observed during ferroptosis. The elevated Fe^{2+} triggers the Fenton reaction [$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + (OH)^- + \bullet OH$], generating toxic hydroxyl radicals that react with polyunsaturated fatty acids in cells, resulting in the production of lipid peroxides and inducing ferroptosis. However, the concentration of hydrogen peroxide and iron ions in tumor cells is generally low, making it less effective in inducing ferroptosis.[122] To address this, researchers have devised various nanotherapy strategies to trigger Fenton reactions in tumor cells. One strategy involves delivering high-performance nanocatalysts based on nanodrug delivery systems or directly delivering reactants of Fenton reactions, such as iron ions and H_2O_2 (Table 1). For instance, Xu et al[123] designed a highly efficient and multifunctional nano drug delivery system by encapsulating Piperine nano MOF within a pH-sensitive lipid layer and modifying it with transferrin (Tf-LipoMof@PL) (Figure 2). This system regulates intracellular iron by using iron-containing MOF and transferrin, while Piperine, an inducer of ferroptosis, provides H_2O_2. Combining these two triggers the Fenton reaction, increasing intracellular ROS and inducing cell ferroptosis. In vitro and in vivo experiments demonstrated that Tf-LipoMof@PL had a highly effective cytotoxic effect, with the Tf-LipoMof@PL group showing the strongest anti-tumor effect. Furthermore, due to their strong hydrophobicity, good biological stability, and low toxicity, Ferrocene and its derivatives can act as stable sources of Fe^{2+} and catalyze the Fenton reaction. Lin et al successfully prepared amphiphilic polymer nanoparticles with selective release of doxorubicin (mPEG-b-PPLGFc@Dox).[124] When entering the body, mPEG-b-PPLGFc@Dox undergoes oxidation by endogenous H_2O_2, leading to a hydrophilic-to-hydrophobic transition of hydrophobic Ferrocene molecules and releasing Dox. This process disrupts the redox balance and increases H_2O_2. Additionally, the Fe^{2+} from Ferrocene can transform H_2O_2 into hydroxyl radicals ($\bullet OH$), subsequently inducing
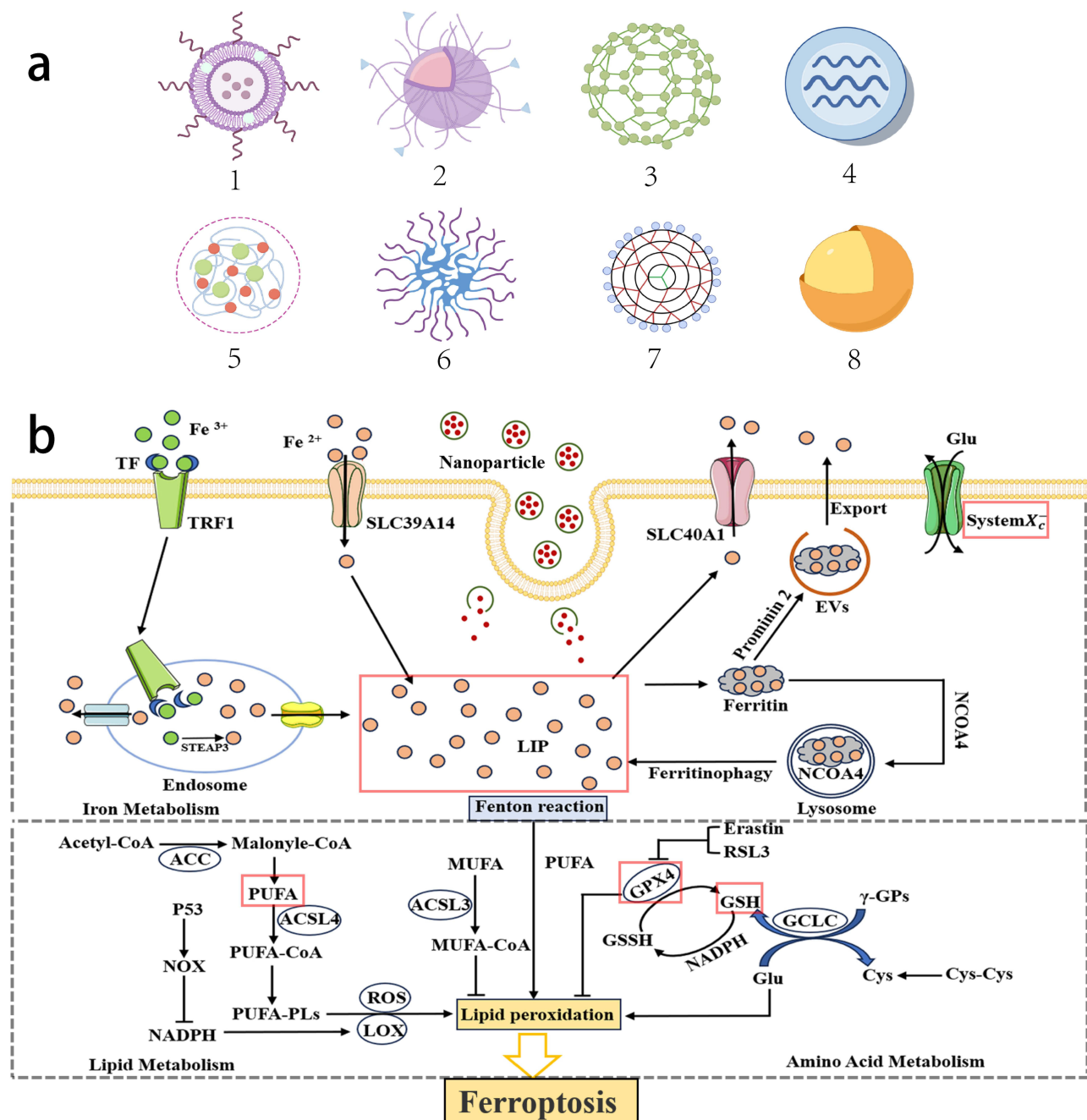
Figure 1 The occurrence and regulatory mechanisms of ferroptosis and the targets of nanoparticles intervention. (**a**) The schematic diagram of various nano delivery system carrier. (a-1) Nanoliposome. (a-2) Solid lipid nanoparticle. (a-3) Metal Organic Framework. (a-4) Exosome. (a-5) Hydrogel. (a-6) Polymeric micelle. (a-7) Dendrimer. (a-8) Gold nanoparticle. (**b**) The core network of ferroptosis regulation is roughly divided into three pathways. The first pathway involves iron metabolism, including iron import and export, storage or overload. The second pathway involves lipid metabolism including long-chain fatty acid CoA ligase 3/4 (ACSL3/4), and other enzymes. The third pathway involves amino acid metabolism, including the system Xc^-/GSH/GPX4 pathway.

ferroptosis. To improve the utilization of iron sources and enhance the induction of Lipid peroxidation in cells,[125] FeOCl nanosheets functionalized with unsaturated phospholipids and polyacrylic acid (FeOCl@PAA-Lip) were prepared by He et al.[126] These nanosheets enter tumor cells through endocytosis, reacting with H_2O_2 in tumor cells to generate •OH via the Fenton reaction. The •OH attacks the unsaturated phospholipids on the FeOCl@PAA-Lip, converting them into phospholipid free radicals (L •) and lipid peroxidation free radicals (LOO •), effectively avoiding their annihilation. The FeOCl@PAA-Lip particles exhibit good dispersion and physiological stability. Apart from organic nanocatalytic

Table 1 Nanoparticles for Ferroptosis in Tumor Cells

Nanoparticle	Contents	Tumor Targeting Mechanism	The in vitro/vivo Efficiency	References
Tf-LipoMof@PL	Piperine	Triggers the Fenton reaction, increasing intracellular ROS and inducing cell ferroptosis.	Highly efficient and multifunctional nano drug delivery system	[123]
mPEG-b-PPLGFc@Dox	DOX	To improve the utilization of iron sources and enhance the induction of Lipid peroxidation in cells.	Satisfactory tumor suppression effects	[124]
FeOCl@PAA-Lip	-	These nanosheets enter tumor cells through endocytosis, reacting with H_2O_2 in tumor cells to generate •OH via the Fenton reaction.	It can more effectively inhibit tumor growth, and the tumor suppression rate can reach 73.3%	[125,126]
Fe_3O_4-PEI@HA-RSL3	RSL3	Hyaluronic acid and magnetic field	Inhibiting the expression of Lactoferrin, FACL4, GPX4, and Ferrin protein in Huh 7 cancer cells	[128]
MIL-101(Fe)@sor NPs	Sorafenib	Inhibition of GPX-4 activity induces ferroptosis.	Notably promote lipid ROS accumulation and accelerate ferroptosis occurrence in HCC.	[129]
AMSNs	DOX	Reduction of glutathione level induces ferroptosis.	Reduction of glutathione level induces ferroptosis	[130]
MMSNs@SO	Sorafenib	Degraded in the tumor microenvironment due to the breakage of - Mn-O -, leading to glutathione depletion in cells.	GSH content rapidly decreased in HCC cells, and the synthesis of GSH was inhibited upon incubation	[131]
PCDF	Cinnamaldehyde	Increasing ROS levels and consuming glutathione through thiol Michael addition reaction, ultimately inducing iron apoptosis	Significant and sustained tumor suppression	[132]
Her2-ANs@CDDP	Cisplatin	Overcome cisplatin drug resistance by consuming intracellular GSH and inducing ferroptosis,	Promising application potential in treating chemotherapy-insensitive tumors	[133]
Erastin@FA-exo	Erastin	Inhibitory system- activity induces ferroptosis	Enabled the rapid and massive accumulation of Erastin in triple-negative breast cancer cells	[134]
E/M@FA-LPs	Erastin	Inhibitory system- activity induces ferroptosis	Exhibited a potent killing effect on tumor cells.	[135]

medicines based on iron ions, inorganic nanocatalytic medicines using iron ions, such as Fe_2O_3 and Fe_3O_4, are also essential components of nanotherapy strategies.[127]

Inhibition of GPX-4 Activity Induces Ferroptosis

GPX-4 is a crucial regulator of ferroptosis, a process characterized by iron-dependent lipid peroxidation and reactive oxygen species generation. GPX-4 catalyzes the conversion of R-OOH to R-OH, effectively preventing the production of iron-dependent lipid ROS and inhibiting ferroptosis. In recent years, nanotherapy approaches that target GPX-4 activity have been harnessed to induce ferroptosis, involving the targeted delivery of GPX-4 small molecule inhibitors and the rational design of nanocarrier materials with GPX-4 inhibitory function. One such inhibitor is RSL3, which directly targets GPX4 to trigger ferroptosis. By inhibiting the expression of GPX4, RSL3 disrupts cysteine and glutamate ester transporters, ultimately leading to cell ferroptosis (Table 1). Liang et al developed magnetic Fe_3O_4 nanocubes loaded with the small molecule ferroptosis inducer RSL3, modified with Polyethyleneimine (PEI) and Hyaluronic acid (HA) (Fe_3O_4-PEI@HA-RSL3).[128] This drug delivery system actively targets tumor cells using an external magnetic field in combination with HA-CD44. Cell experiments revealed that Fe_3O_4-PEI@HA-RSL3 nanoparticles effectively suppressed the proliferation of liver cancer cells without harming normal liver cells. An increase in the concentration of Fe_3O_4-PEI @HA-RSL3 nanoparticles was found to activate the ferroptosis signal transduction pathway by inhibiting the expression of Lactoferrin, FACL4, GPX4, and Ferrin protein in Huh 7 cancer cells, leading to an enhanced formation of ROS.
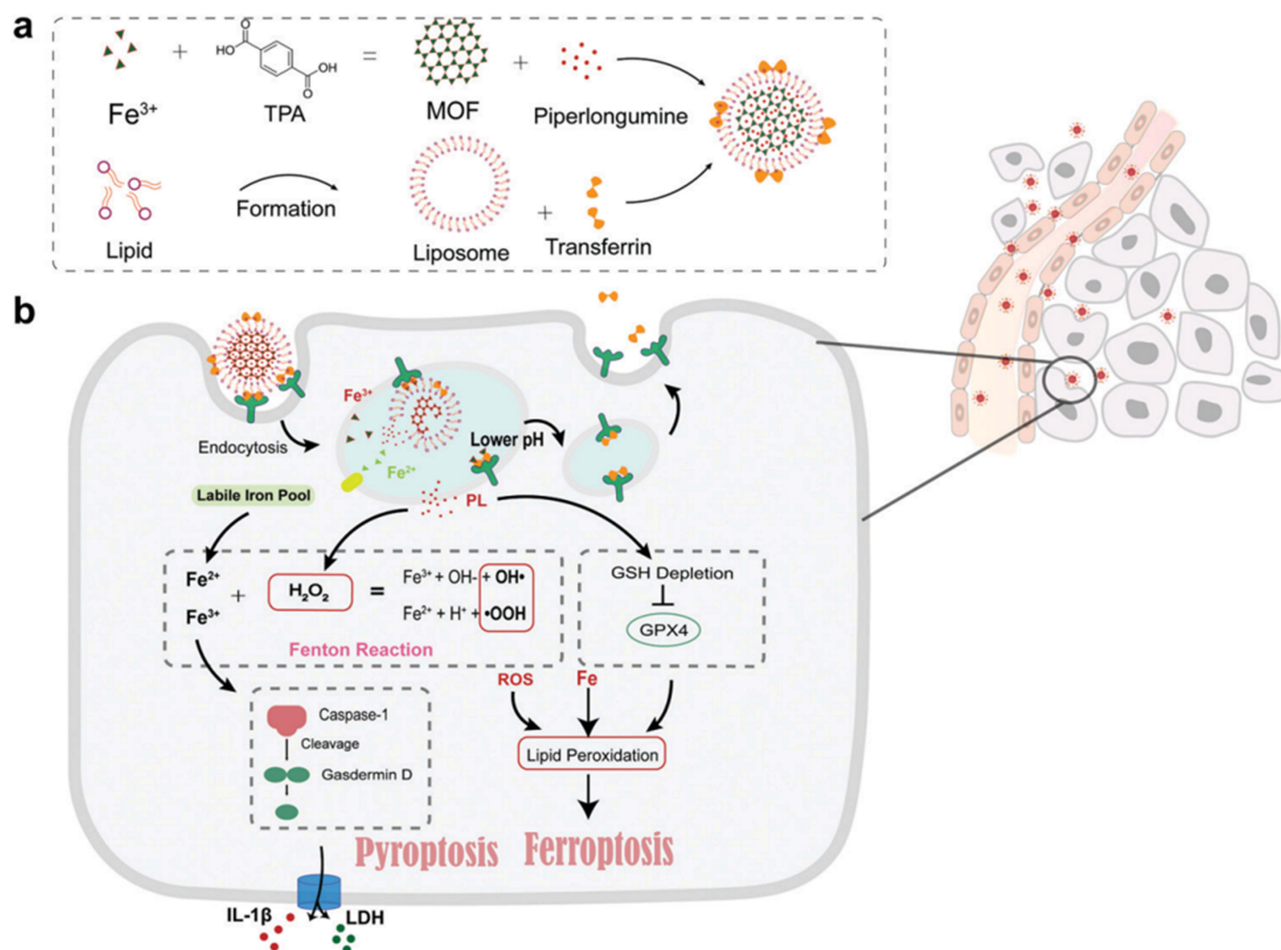
Figure 2 Formation of the Tf-LipoMof@PL nanoparticles (**a**) and the illustration of the mechanism of the nanoparticles (**b**). Reprinted with permission of the Royal Society of Chemistry from Xu R, Yang J, Qian Y, et al. Ferroptosis/pyroptosis dual-inductive combinational anti-cancer therapy achieved by transferrin decorated nanoMOF. *Nanoscale Horiz*. 2021;6(4):348–356; permission conveyed through Copyright Clearance Center, Inc.[123]

Sorafenib, another agent, has been reported to inhibit GPX4 activity by reducing GSH synthesis and inhibiting the activity of the SLC7A11 transporter, thus promoting ROS and lipid peroxide accumulation and inducing ferroptosis to achieve a therapeutic effect. Studies have demonstrated that Manganese dioxide nanoparticles loaded with Sorafenib effectively deplete GSH in cells, resulting in reduced GPX4 activity, enhanced lipid ROS accumulation, and the induction of ferroptosis in hepatocellular carcinoma (HCC). Iron nanoparticles loaded with Sorafenib (MIL-101(Fe) @sor NPs) significantly inhibit tumor growth, reduce GPX-4 expression levels, and exhibit negligible long-term toxicity.[131] When MIL-101(Fe)@sor NPs and iRGD peptide are combined, they notably promote lipid ROS accumulation and accelerate ferroptosis occurrence in HCC.[129]

Reduction of Glutathione Level Induces Ferroptosis

Glutathione, composed of glutamic acid, cysteine, and glycine, exerts antioxidant effects and regulates cellular redox balance. The elevated expression of GSH in tumor cells, typically 7–10 times higher than normal cells, poses challenges to various cancer treatment strategies, given that GSH also acts as a cofactor of GPX-4.[136] Consequently, depleting GSH can disrupt the redox balance in tumor cells, making it a targeted strategy for tumor treatment (Table 1). Wang et al reported manganese-doped silicon nanoparticles (AMSNs) modified with arginine to consume intracellular GSH.[130] The arginine (Arg) ligands on AMSNs' outer surface allowed tumor targeting after intravenous administration. AMSNs contained a manganese oxygen bond (- Mn-O -) sensitive to the tumor microenvironment rich in GSH. Upon breaking one molecule of - Mn-O -, two molecules of GSH were consumed, demonstrating efficient GSH clearance ability and

facilitating ferroptosis induction. Similarly, Tang et al developed manganese-doped mesoporous silica nanoparticles loaded with Sorafenib by a one-pot method (MMSNs@SO).[131] MMSNs@SO degraded in the tumor microenvironment due to the breakage of - Mn-O -, leading to glutathione depletion in cells. Additionally, the degradation of MMSNs released Sorafenib, dysregulating the function of the Xc⁻ transport system. As a result, GSH content rapidly decreased in HCC cells, and the synthesis of GSH was inhibited upon incubation with MMSNs@SO. Another approach designed by Zhang et al involved constructing nanoparticles (PCDF) with doxorubicin and Fe^{3+}, combined with a ROS-sensitive ligand (TCA) binding cinnamaldehyde (CA).[132] PCDF internalized by tumor cells released CA upon exposure to intracellular ROS, increasing ROS levels and consuming glutathione through thiol Michael addition reaction, ultimately inducing iron apoptosis and leading to significant and sustained tumor suppression in in vivo experiments. Moreover, He et al designed anti-HER2-modified arsenic nanosheets loaded with cisplatin (Her2-ANs@CDDP).[133] These nanosheets could overcome cisplatin drug resistance by consuming intracellular GSH and inducing ferroptosis, thus showing promising application potential in treating chemotherapy-insensitive tumors and expanding the usage of arsenic in solid tumor treatment.

Inhibitory System Xc⁻ Activity Induces Ferroptosis

Current evidence suggests that the intracellular cysteine concentration is closely related to the initial step of glutathione production, which is regulated by the membrane Na^+-dependent cysteine-glutamic acid exchange transporter known as system Xc⁻. This transporter is responsible for transporting glutamic acid out of the cell and NADPH into the cell. Intracellular cystine is further converted into cysteine, which promotes GSH synthesis. Thus, downregulation of system Xc⁻ expression can reduce intracellular cysteine concentration, limiting GSH synthesis efficiency, which increases the level of intracellular ROS and the accumulation of lipid peroxides, ultimately inducing ferroptosis. Erastin, an inhibitor of system Xc⁻, induces cell ferroptosis by inhibiting its activity, activating P53, and acting on voltage-dependent anion channels, highlighting its significance as an important anti-tumor strategy. Exosomes are microbubbles secreted by cells that effectively transfer internal substances to surrounding cells through interactions between rich adhesion proteins and cell membranes. However, Erastin faces challenges due to its poor water solubility and low bioavailability. To overcome these issues, Yu et al[134] designed a system to load Erastin into FA-modified exosomes (erastin@FA-exo), which enabled the rapid and massive accumulation of Erastin in triple-negative breast cancer cells, significantly increasing ROS production and GSH consumption in cells. Similarly, Gai et al developed a nanodelivery system based on folate-modified liposomes (FA-LP) to co-deliver MT1DP (a lncRNA) and Erastin (E/M@FA-LPs).[135] In vitro and in vivo experiments demonstrated that E/M@FA-LPs exhibited a potent killing effect on tumor cells (Table 1).

Exogenous Regulation of Lipid Peroxidation of Tumor Cells Induces Ferroptosis

Lipid peroxides primarily originate from PUFAs produced by membrane phospholipids under oxidative stimulation. Supplementing exogenous lipids can enhance the accumulation of lipid peroxides within cells. Researchers conducted screenings of various unsaturated fatty acids and discovered that oral administration of conjugated linolenic acid effectively induces ferroptosis in triple-negative breast cancer cells, demonstrating its potent activity.[137] This finding supports the possibility of using exogenous lipid supplementation to induce ferroptosis for cancer treatment, providing the foothold for the design of relevant nanodrug delivery systems. Zhou et al developed a nano drug delivery system based on a Fenton-like reaction. They modified the surface of iron oxide nanoparticles with hydrophobic peroxidized linoleic acid (LAHP) and hydrophilic oligomers.[138] In an acidic tumor microenvironment, metastable iron(II) oxide and ferric tetroxide release Fe^{2+} on demand. Subsequently, the release of Fe^{2+} and LAHP significantly generates singlet oxygen ($^1O_2$). These LAHP-modified iron oxide nanoparticles induce ferroptosis of tumor cells by producing tumor-specific ROS. Moreover, Gao et al designed polymer micelles with modified unsaturated lipid side chains, encapsulating the ferroptosis inducer RSL3.[139] Notably, modifying the unsaturated fatty acid side chain enhanced the level of lipid peroxidation in vivo and synergistically induced ferroptosis.

Combined Treatment Scheme Based on Ferroptosis

The combination of two or more therapies has been found to enhance their interaction and produce significant super-additive ("1+1>2") therapeutic effects.[140] As a result, tumor therapy has gradually shifted towards multimodal

Table 2 Combination Therapy Regimens Based on Ferroptosis

Nanoparticle	Contents	Combination Regimens	Tumor Targeting Mechanism	References
mPEG-b-PPLGFc@Dox	DOX	Ferroptosis combined with chemotherapy	Fenton reaction	[124]
DOX/ ART@LiMOFs	DOX/ART	Ferroptosis combined with chemotherapy	Providing ferrous ions and inducing ART to carry out redox reactions in cells, producing ROS to trigger Lipid peroxidation and induce ferroptosis.	[144]
Bi_2Te_3 NPs	Bi_2Te_3	Ferroptosis combined with optical therapy	Reduction of glutathione level induces ferroptosis	[145]
BMP	iFSP1/Ce6	Ferroptosis combined with photodynamic therapy	Reduction of glutathione level induces ferroptosis	[146]
Fe-TiO$_2$ NDs	TiO$_2$	Ferroptosis combined with acoustic dynamic therapy	Fenton reaction	[147]
HSA-Ce6- IrO2	Ce6	Ferroptosis combined with acoustic dynamic therapy	Reduction of glutathione level induces ferroptosis	[148]
PIOC@CM NPs	Fe_3O_4/Ce6	Ferroptosis combined with acoustic dynamic therapy	Reduction of glutathione level induces ferroptosis	[149]
IRP NPs	IR780/RSL-3	Ferroptosis combined with acoustic dynamic therapy	Activity in the antioxidant system and induces ferroptosis of tumor cells.	[22]
CBD NPs	Cannabidiol/Poly	Combined immunotherapy for ferroptosis	Inhibiting distant tumors, reducing the burden of metastatic tumors	[150]

approaches with flexible and adjustable advantages. Numerous studies have demonstrated that compared to single treatment strategies, combining multiple therapies offers distinct advantages in clinical cancer treatment, including efficient synergistic effects,[141] reduced adverse reactions,[142] and addressing drug resistance.[143] In recent years, the development of nano-drug delivery technology has provided a versatile platform for co-loading two or more drugs, opening up promising possibilities for combined tumor therapy. This paper reviews the latest research progress on combining ferroptosis with chemotherapy, phototherapy, sonodynamic therapy, immunotherapy, hunger therapy, and other therapies based on nanotechnology. These advancements present a new nano-combined delivery approach for effective cancer treatment (Table 2 and Figure 3).

Ferroptosis Combined with Chemotherapy

Chemotherapy (CT) is a crucial cancer treatment method, often indicated for managing tumor recurrence and metastasis.[151,152] However, most anti-tumor chemotherapy drugs suffer from drawbacks like poor water solubility, low specificity, and severe organ toxicity, which limit their clinical use.[153] Using nanodrug delivery systems to load chemotherapy drugs has significantly improved drug delivery efficiency and therapeutic effectiveness.[154] Nevertheless, the efficacy of single-drug chemotherapy remains poor for most tumors. Hence, combining chemotherapy with other therapies has become a prominent trend in tumor treatment. Doxorubicin (DOX) is a common chemotherapy drug often combined with ferroptosis therapy. DOX typically induces cell apoptosis through a gene-regulated process involving complex signal transduction within cells.[155] However, this slow process leads to weak inhibitory effects on tumors. Additionally, tumor cells often develop resistance to apoptosis-inducing drugs by enhancing gene mutations. Long-term exposure to apoptosis inducers can also invalidate apoptosis mechanisms. DNA damage reactions further contribute to resistance, undermining the efficacy of chemotherapy drugs. To address these challenges, Lin et al synthesized amphiphilic polymer nanoparticles
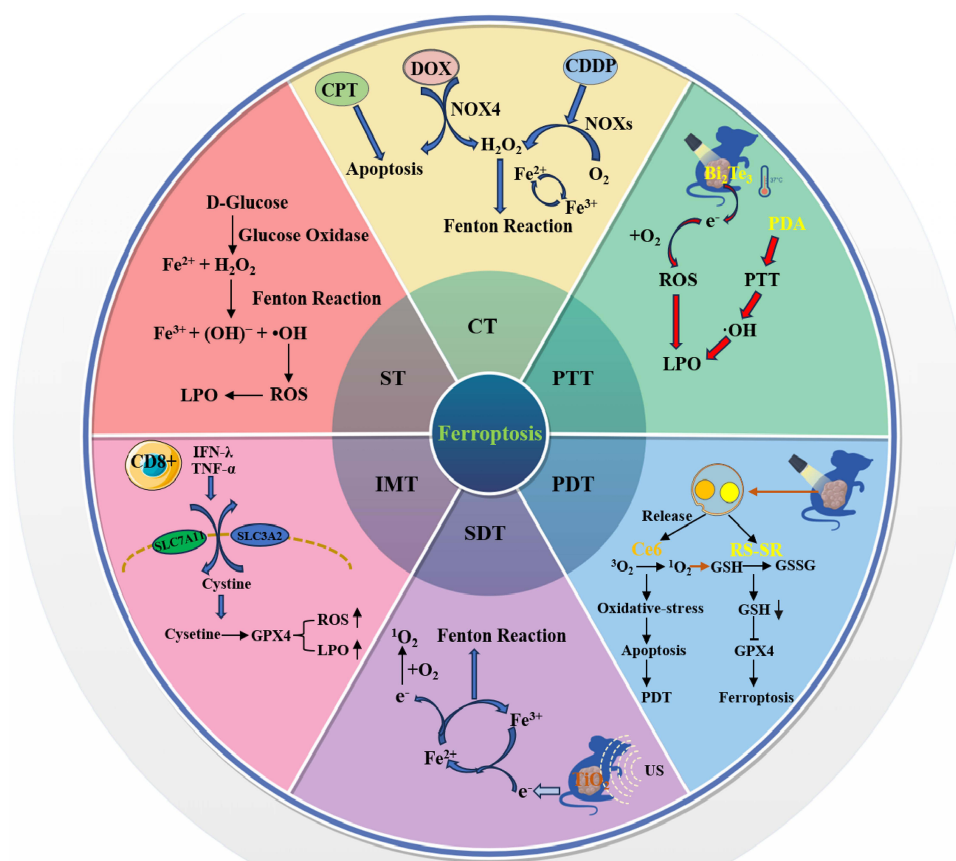
Figure 3 Multimodal therapy based on ferroptosis mechanism.
Abbreviations: CT, Chemotherapy; PTT, Photothermal therapy; PDT, Photodynamic therapy; SDT, Sonodynamic therapy; IMT, immunotherapy; ST, Starvation therapy.

that can be oxidized by ROS and selectively release DOX (mPEG-b-PPLGFc@Dox).[124] When these nanoparticles enter tumor cells and undergo oxidation by endogenous H_2O_2, Fe (II) ions and DOX are released, and Fe(II) derived from Ferrocene triggers the Fenton reaction, generating ·OH and inducing ferroptosis. Furthermore, DOX stimulates cancer cells to produce more H_2O_2, leading to significant apoptosis. In vivo anti-tumor experiments with mPEG-b-PPLGFc@Dox demonstrated lower systemic toxicity and higher combined treatment efficiency of chemotherapy and ferroptosis, effectively inducing tumor cell death and inhibiting tumor growth in mice with volumes of approximately 200 mm^3. Similarly, Celia Nieto et al developed a method to simultaneously load Fe^{3+} and DOX by examining the adsorption of PDA NPs on Fe^{3+} under different pH conditions (PD NPs@Fe/DOX).[156] This approach led to a synergistic therapeutic effect of ferroptosis and DOX chemotherapy, significantly reducing the viability of breast cancer cells without affecting the survival rate of normal cells to the same extent. In another study, Ji et al designed a tumor-selective nanoreactor (DOX) based on MOF/ART@LiMOFs, where Artesunate (ART) and DOX were wrapped in the porous structure of MOF and coated with a lipid bilayer on the surface.[144] LiMOFs exhibited excellent pH response, and in an acidic tumor cell environment, they self-degraded, providing ferrous ions and inducing ART to carry out redox reactions in cells, producing ROS to trigger Lipid peroxidation and induce ferroptosis. Simultaneously, DOX slowly permeated outward, activating the apoptotic pathway and achieving a binding function of cell apoptosis and iron apoptosis. Apart from doxorubicin, other chemotherapy drugs like cisplatin (DDP)[157,158] and camptothecin (CPT)[159] are also often used in combination with ferroptosis to enhance tumor treatment.

Ferroptosis Combined with Optical Therapy

Optical therapy encompasses photodynamic therapy and photothermal therapy. Photothermal therapy (PTT) employs photothermal agents to harness energy from external light sources, typically near-infrared light, and convert it into heat,

raising the surrounding environment's temperature and inducing cancer cell death.[160] PTT offers several advantages, including low invasiveness, high spatiotemporal accuracy, and low biological toxicity. When tissue reaches 41°C, cells upregulate heat shock proteins (HSPs) to resist initial heat damage. At temperatures exceeding 42°C, irreversible tissue damage and cell necrosis occur. Additionally, at 46–52°C, microvascular thrombosis and ischemia can arise. Beyond 60°C, protein denaturation and plasma membrane damage cause rapid cell death.[161] The insufficient blood supply in tumor tissue results in lower heat resistance than normal tissue, making photothermal therapy an appropriate approach for treating solid tumors.[162] PTT typically uses near-infrared light ranging from 650 nm to 900 nm as the light source since tissue absorption in this range is weak, resulting in deep tissue penetration and minimal tissue damage.[163] However, the heterogeneity of tumors and the low efficiency of deep tissue photothermal conversion have limited the efficacy of single photothermal therapy in eradicating tumors.[164] Therefore, combining multiple drugs or treatment modes to construct a multimodal collaborative treatment system is important to improve treatment effectiveness and reduce chemotherapy drug toxicity.[165] Jiang et al[145] synthesized Bi_2Te_3 NPs with high-performance photothermal electrocatalytic effects through hydrothermal reactions. Under near-infrared light irradiation (808 nm and 1064 nm), Bi_2Te_3 NPs induced PTT temperatures to increase to 55.6°C and 63.3°C, respectively, effectively inhibiting the expression of MTH1. The temperature changes caused by heating and cooling led to Bi_2Te_3 NPs generating free charges and electron transfer, generating ROS, damaging heat shock proteins, reducing the heat tolerance of tumor cells, and synergistically enhancing PTT. Moreover, the hole (H^+) with strong oxidizing capacity on $B_{i2}Te_3$ NPs can oxidize GSH to GSSG, leading to GSH depletion, further improving the ROS level, and ultimately reducing Glutathione peroxidase 4 activity, inducing ferroptosis of tumor cells. In vivo anti-tumor results showed that Bi_2Te_3 NPs exhibited significant tumor inhibitory effects in both ectopic and in situ eye tumor models. Among the reported PTT materials, the polymer polydopamine (PDA) is an excellent photothermal conversion material with biocompatibility. Additionally, its molecular structure's high content of primary and secondary amines and catechol (3,4-dihydroxybenzene) provides it with high adhesion and excellent drug release ability. Researches[166,167] prepared (PDA)-hemin PEG ferrocene (Fc) (PHPF) nanomotors and Fe_3O_4@PDA-HCPT (10-hydroxycamptothecin) NPs, and in vivo and in vitro experiments demonstrated that the combination of photothermal ferroptosis and photothermal chemotherapy ferroptosis significantly inhibited tumor growth, making nanoparticles a promising cancer treatment strategy.

Photodynamic therapy (PDT) is a non-invasive and highly selective treatment method.[168] Its principle involves sending a specific photosensitizer (PS) to an excited state, and the excited state photosensitizer transmits energy to the surrounding oxygen, generating reactive oxygen species, including singlet oxygen, which exerts toxicity on surrounding tissues and cells.[169] PDT has been widely used in treating tumors such as esophageal cancer and skin cancer.[170] Although PDT offers many advantages, the tumor site's hypoxic microenvironment often limits its ability to produce $^1O_2$ due to the large amount of O_2 involved in its production process. Simultaneously, PDT's characteristic consumption of O_2 further exacerbates hypoxia at the tumor site, inhibiting its therapeutic effect.[171] Generally, ferroptosis requires two factors, ROS production and GSH depletion. Therefore, there may be some interaction and mutual promotion between ferroptosis and PDT.[172] Zhao et al[173] found that the highly active $^1O_2$ produced by PDT can stimulate ferroptosis by consuming GSH. In vivo anti-tumor experiments showed that the novel metal-organic framework loaded with Chlorin e6 (Ce6) significantly inhibited tumor growth through PDT-induced ferroptosis. However, ferroptosis induced by PDT (mainly to promote GSH depletion) may be inhibited by iron droop inhibitor protein 1 (FSP1). To overcome this limitation, researchers used the light-responsive nanocomposite self-assembled by BODIPY-modified PAMAM (BMP) to stably encapsulate the FSP1 inhibitor (iFSP1) and Ce6.[146] This nanosystem can promote intracellular transmission, penetration, and accumulation of the iron death inducer in tumors under light radiation. Both in vitro and in vivo, they demonstrated a high ability to trigger ferroptosis and immunogenic cell death (ICD).

Ferroptosis Combined with Acoustic Dynamic Therapy

Sonodynamic therapy (SDT) was first proposed by the Japanese scientist Yumita as a tumor treatment strategy that combines low-frequency focused ultrasound irradiation with sound-sensitive substances.[174,175] Traditional sound sensitizers mainly originate from photosensitive substances, known as photosensitizers, which possess special porphyrin rings, anthracene rings, and other structures that respond well to light and sound.[176] When stimulated by radiation, they can

rapidly produce highly oxidizing substances such as reactive oxygen species to kill tumor cells. The main chemical dynamic process in which ferroptosis occurs is the Fenton reaction. Research has shown that Fenton catalysis can be mediated by external energy stimulation. For instance, light Fenton relies on a reaction solution of metal ions, where ultraviolet light stimulates and guides ions to generate redox reactions, producing H_2O_2 and adjusting the iron valence, thus initiating an electron exchange process.[177,178] Similarly, ultrasound can mediate Fenton catalysis, and the sound energy addresses the unevenness of light irradiation, resulting in more comprehensive energy conduction. Bai et al[147] synthesized Fe-doped TiO_2 nanoparticles (Fe TiO_2 NDs) through a thermal decomposition strategy, which can serve as a sound-sensitive agent for the combined treatment of tumors with SDT and CDT. The experimental results indicate that with increased Fe doping, the Fenton reaction of Fe TiO_2 NDs becomes more pronounced. However, to optimize the balance between US irradiation and Fenton reaction-induced ROS generation, the authors chose Fe TiO_2 NDs with a Fe: Ti feed ratio of 1:4 for subsequent experiments. Upon intravenous injection, Fe TiO_2 NDs efficiently accumulate in tumors and exert significant anti-tumor therapeutic effects through the combined action of SDT and CDT. Moreover, due to the extremely small size of Fe TiO_2 NDs (average size 2.49 ± 0.74 nm), they can be excreted from the body, and their long-term toxicity to mice can be disregarded. Therefore, incorporating metal ions into TiO2 nanostructures boosts the production of reactive oxygen species by ultrasound-triggered nanodroplets and confers Fenton catalytic capabilities to generate ROS from endogenous H_2O_2 within tumors. This offers promising prospects for the application of combined sonodynamic therapy and catalytic therapy in cancer treatment. This offers promising prospects for the application of combined sonodynamic therapy and catalytic therapy (SDT/CDT) in cancer treatment. Similarly, Hu et al[148] designed iron (Fe) and manganese (Mn) co-doped zinc oxide nanosensitizers, which can synergistically induce ferroptosis in addition to the sono-Fenton catalysis mediated by nano SDT. Nie et al[179] synthesized HSA-Ce6 IrO_2 (HCIr) nanoclusters using a mild biomineralization method. HCIr produces a large amount of $^1O_2$ under US stimulation, promoting the accumulation of lipid peroxidation (LPO) in cells. Additionally, HCI can consume GSH by accelerating the conversion of Ir (IV) to Ir (III), inhibiting GPX4 activity, thus enhancing SDT-induced ferroptosis. Zhu et al[149] combined biomimetic technology with SDT and ferroptosis to construct multifunctional cancer homologous targeting biomimetic nanoparticles encapsulating Fe_3O_4 and Ce6 (PIOC@CMNPs) as a nanosound sensitizer. The unique tumor-specific surface antigen on the C6 cell membrane (CM) of gliomas endows PIOC@CMNPs with innate immune escape and homologous cell targeting advantages, enabling targeted delivery to tumor tissue. Under ultrasound irradiation, the reduction of ROS and the consumption of GSH lead to the loss of GPX4 activity, promoting SDT and ferroptosis to kill glioma C6 cells. Mitochondria are potential therapeutic targets crucial in regulating tumor cell death and metabolism. Wang et al[22] proposed a new mitochondrial targeting nanosystem ("Mito Bob") for SDT promoted by ferroptosis. The sound-sensitive agent IR780 and the ferroptosis activator RSL-3 are encapsulated in biocompatible PLGA nanoparticles to form "Mito Bob" (IRP NPs). IR780 mediates mitochondrial targeting of SDT in this nanosystem, while RSL-3 inhibits GPX4 activity in the antioxidant system and induces ferroptosis of tumor cells, thereby altering tumor metabolism and enhancing the sensitivity of tumor cells to SDT-induced apoptosis. Additionally, the good biosafety of IRP NPs makes them more valuable for clinical applications.

Combined Immunotherapy for Ferroptosis

In recent years, there has been growing interest in using immunotherapy (IMT) as an innovative approach to cancer treatment.[180] Specifically, the use of PD-1 antibodies has gained FDA approval for clinical treatment.[181] At the same time, researchers have been exploring the potential of ferroptosis, a process that regulates intracellular lipid and oxygen metabolism and is associated with immune response, as a complementary method to enhance cancer treatment outcomes.[182] Traditional tumor immunotherapy primarily focuses on four approaches:[183] immunomodulatory therapy, immune checkpoint blockade therapy, adoptive immunotherapy, and tumor vaccine immunotherapy. However, these therapies still face certain limitations, including effectiveness being limited to a small group of patients,[184] potential adverse reactions, and low efficiency due to insufficient immunogenicity of tumor cells.[185] The combination of immunotherapy with ferroptosis has emerged as a promising and effective strategy for cancer treatment. Ferroptosis can effectively inhibit tumor growth and increase the immunogenicity of tumor cells. When ferroptosis occurs, tumor cells release tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs), which induce the

maturation and antigen presentation of dendritic cells (DCs). This, in turn, initiates a T-cell-mediated anti-tumor immune response.[186,187] Ferroptosis also triggers immunogenic cell death (ICD) in tumor cells, activating T-cell immune responses.[188–190] The release of interferon-gamma (IFN-γ) further enhances the immune response and inhibits tumor growth by reducing cystine uptake by tumor cells, leading to the inhibition of GSH synthesis and promoting ferroptosis.[191,192]

Researchers[150] have conducted experiments using ferroptosis inducer Cannabidiol nanoparticles (CBD NPs) and the immune enhancer Poly (I: C) (CP nanoparticles) delivered via a Pluronic F127 thermosensitive injection hydrogel. The study demonstrated that CBD NPs promote ferroptosis in tumor cells and induce lipid peroxidation and ferroptosis. Additionally, CP nanoparticles enhance the immune response, inhibiting distant tumors, reducing the burden of metastatic tumors, and improving the survival rate in a lung metastasis mouse model. This approach of combining CP nanoparticles to induce tumor ferroptosis and immune activation proves to be a promising strategy for controlling tumor development. Researchers such as Chin[193] and Wang et al[194] have observed similar successful designs and conclusions. Furthermore, using an FSP1 inhibitor (iFSP1) in mice has shown increased numbers of DCs, macrophages, and T cells in tumors. This novel finding suggests that iFSP1 can cooperate with various immunotherapies to improve the survival rate in mice with liver cancer, presenting a new avenue for the combined application of ferroptosis and immunotherapy in cancer treatment.[195]

Combination of Ferroptosis and Hunger Therapy

Organisms possess an inherent enzyme called glucose oxidase (GOx), which efficiently catalyzes the conversion of β-D-glucose into gluconic acid and H_2O_2. Subsequently, the H_2O_2 interacts with Fe^{2+} to induce ferroptosis in tumor cells. Tumor growth relies on glucose to generate ATP for energy, but GOx can deplete a substantial amount of glucose within the tumor, cutting off the nutrient supply and impeding the growth of tumor blood vessels, a process referred to as "hunger therapy" for tumors.[196] Wan et al[197] introduced a nanoreactor utilizing an iron metal-organic framework (MOF) and glucose oxidase (GOx) modified cancer cell membrane coating. Upon reaching the tumor site, the high levels of GSH trigger the reduction of Fe^{3+}, leading to the collapse of the MOF structure and releasing Fe^{2+}. Simultaneously, GOx catalyzes glucose oxidation to generate H_2O_2. The interaction between H_2O_2 and Fe^{2+} via the Fenton reaction produces hydroxyl radicals (· OH), achieving a combined effect of ferroptosis and "starvation therapy"(ST).

Ferroptosis Combined with Multiple Treatment Strategies

Due to tumor heterogeneity, the induction of ferroptosis in combination with other monotherapies has not yet achieved the desired therapeutic effect. Researchers have explored multi-functional nanoplatforms to combine multiple treatment methods with ferroptosis, aiming to achieve a synergistic and enhanced tumor treatment effect. Liang et al[198] constructed a novel TME activated metal organic framework by involving Fe & Cu ions bridged by disulfide bonds (FCSP@DOX MOFs). FCSP@DOX MOFs could accumulate in the tumor site through the EPR effect and break disulfide linkers in the TME of overexpressed GSH, consuming GSH. This nanoparticle not only inhibits GPX4 expression and induces ferroptosis, but also simultaneously releases Fe^{3+}, Cu^{2+} and DOX. The release of double ions serves as a catalyst for the Fenton reaction of overexpressed H_2O_2, whereas DOX can induce chemotherapy by inhibiting topoisomerase II and additionally enhance the therapeutic impact of ferroptosis through the production of H_2O_2. Meanwhile, due to the inherent photothermal property of the released Cu^{2+} and FCSP MOFs, more ROS could be generated through the acceleration of Fenton reaction. This system is specifically activated in TME, achieving a synergistic therapeutic effect based on ferroptosis through chemodynamic/photothermal/chemo therapy. In another recent study, Wang et al[199] reported a NIR-triggered and ROS-boosted nanoplatform [MnO$_2$-SOR-Ce6@PDA-PEGFA (MSCPF)] for enhancing the chemo/PDT/PTT synergistic therapy of sorafenib (SOR/SRF) in HCC treatment. MSCPF could generate excessive ROS to alleviate tumor hypoxia, and the production of ROS further enhances Ce6-mediated PDT and PDA-mediated PTT. In vitro and in vivo experiments have shown that MSCPF could inhibit P-gp expression and induce ferroptosis through the inactivation of GPX4 and SLC7A11, ultimately enhancing the synergistic therapeutic effect of ferroptosis in HCC treatment. In this research, the constructed MSCPF not only demonstrates great potential as a multifunctional nanoplatform to improve the efficiency of HCC treatment and reduce drug resistance, but also provides new ideas for loading

other anti-tumor drugs and synergistic PTT/PDT therapy of other types of tumors. These combinations have shown relatively efficient anti-tumor treatment outcomes, presenting advantages over single therapies. The development of multi-strategy synergistic anti-tumor therapy based on ferroptosis holds great promise and significance. However, these novel combined multi-strategy therapies still have certain drawbacks and potential risks that hinder their further clinical application. Challenges include the complexity of nanocomposite systems, difficulty in achieving industrial production, accurate calculation of synergistic effects between multiple therapies, and concerns about drug toxicity and side effects resulting from the combination of different drugs or methods.

Summary and Outlook

Ferroptosis is a novel cell death mechanism induced by iron-dependent lipid peroxides that has garnered increasing attention in tumor biology and anti-tumor treatment as a novel target for cancer therapy. Nanotechnology and emerging nanomaterials have provided a foundation for delivering ferroptosis inducers and combining them with multiple therapies, capitalizing on their unique advantages. This review summarizes the latest research on nanotechnology-induced tumor ferroptosis and highlights the design of nanotherapy methods based on ferroptosis inducers and their combined applications with other treatments. Albeit significant progress has been made in cancer treatment based on ferroptosis, the clinical implementation of ferroptosis-based nanotherapy remains challenging. It is essential to further study the potential differences in this non-apoptotic cell death mode between animals and humans. Additionally, research on potential adverse reactions of ferroptosis inducers is crucial to ensure tumor-specific ferroptosis induction while avoiding off-target toxicity to normal tissues. The design of combined nanotherapy schemes based on ferroptosis requires careful evaluation of potential superimposed toxicity and industrial feasibility. Thus, more research is needed to deepen our understanding and exploration of ferroptosis, considering various factors, to design safe and effective nano preparations capable of inducing ferroptosis.

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Disclosure

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