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REVIEW

Targeting Ferroptosis in Bone-Related Diseases: Facts and Perspectives

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Abstract: Ferroptosis is a new cell fate decision discovered in recent years. Unlike apoptosis, autophagy or pyroptosis, ferroptosis is characterized by iron-dependent lipid peroxidation and mitochondrial morphological changes. Ferroptosis is involved in a variety of physiological and pathological processes. Since its discovery, ferroptosis has been increasingly studied concerning bone-related diseases. In this review, we focus on the latest research progress and prospects, summarize the regulatory mechanisms of ferroptosis, and discuss the role of ferroptosis in the pathogenesis of bone-related diseases, such as osteoporosis (OP), osteoarthritis (OA), rheumatoid arthritis (RA), and osteosarcoma (OS), as well as its therapeutic potential.

Keywords: ferroptosis, cell death, iron accumulation, lipid peroxidation, bone-related diseases

Introduction

Cell fate decision (CFD) is an important mechanism for multicellular organisms to maintain biological stability. Under physiological or pathological conditions, the body maintains homeostasis through different CFDs. Abnormal regulation of CFDs also contributes to a variety of diseases. Currently, known CFDs include apoptosis, necrosis, necroptosis, autophagy, pyroptosis, ferroptosis, cuproptosis, etc.[1] In 2012, Dixon et al found that Ras-selective lethal (RSL) compounds RSL3 and Erastin can induce cell death in RAS mutant cell lines through a unique iron-dependent CFD and termed it Ferroptosis.[2] Unlike other CFDs, ferroptosis cells morphologically exhibit distinctive mitochondrial structural abnormalities, including shrunken mitochondrial, reduced mitochondrial cristae, and increased mitochondrial membrane density.[3] Ferroptosis is mainly due to excessive accumulation of intracellular iron and iron-dependent increase in reactive oxygen species (ROS) and lipid peroxidation, which eventually leads to cell membrane rupture, contents efflux and necrosis-like CFD.[4] Therefore, various molecules and signals related to iron metabolism and peroxidation are critical for regulating ferroptosis.

Ferroptosis has been explored to play important roles in different diseases such as cancers, cardiovascular diseases, and kidney diseases.[5–7] Recent studies have shown that ferroptosis is closely related to bone-related diseases, but the underlying mechanisms still need to be further studied.[8] In the following sections, we focus on the relevant mechanism of ferroptosis and the role of ferroptosis in different bone-related diseases, such as osteoporosis (OP), osteoarthritis (OA), rheumatoid arthritis (RA), and osteosarcoma (OS), aiming to provide a theoretical basis for further research on the pathogenesis and treatment of ferroptosis in bone-related diseases.

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Inducers of Ferroptosis

Iron overload is necessary for the occurrence of ferroptosis. Iron is an essential trace element for the human body and participates in a variety of life processes, such as nucleic acid metabolism, cell cycle and enzyme synthesis, etc. Dietary sources of iron mainly include heme iron and non-heme iron. Non-heme iron can be derived from iron ions or ferritin, etc.[9] Iron ions are usually obtained from food in ferrous (Fe^{2+}) or ferric (Fe^{3+}) form. Fe^{3+} is reduced to Fe^{2+} by different ferrireductases in the intestine such as duodenal cytochrome B (DCYTB), and then Fe^{2+} enters enterocytes via divalent metal transporter 1 (DMT1) on the apical membrane.[10] Ferritin iron and heme iron can enter enterocytes via ferritin receptor and CD91, respectively.[11] In enterocytes, Fe^{2+} not involved in biological processes can be bound to ferritin for storage.[12] As required, Fe^{2+} can leave enterocytes via ferroportin 1 (FPN1) and be oxidized to Fe^{3+} by ferroxidase hephaestin (HEPH) for transport.[9,13] Transferrin (TF) produced from the liver is responsible for transporting Fe^{3+}, and one TF can bind two Fe^{3}+.[14] Fe^{3+}-TF transports to target cells and binds to its receptor transferrin receptor (TFR1), then subsequently transports Fe^{3+} to endosomes.[15] In the acidic environment of endosomes, Fe^{3+} is reduced to Fe^{2+} by metalloreductases such as six transmembrane epithelial antigen of the prostate 3 (STEAP3) and subsequently transported into the cytoplasm via DMT1.[16]

Intracellular Fe^{2+} needs to be strictly regulated. Intracellular Fe^{2+} deficiency restricts various biological processes. Intracellular Fe^{2+} excess leads to the Fenton reaction-excess Fe^{2+} reacts with hydrogen peroxide (H_2O_2).[17] Fenton reaction generates ROS, and iron overload and ROS accumulation can lead to ferroptosis.[18] Excess Fe^{2+} also promotes lipid peroxidation by participating in the catalytic subunit of lipoxygenase (LOX).[10,17] Excess intracellular Fe^{2+} can be oxidized to Fe^{3+} by ferritin and stored as ferritin heavy chain 1 (FTH1) or ferritin light chain (FTL).[19] This iron-binding ferritin can be degraded by nuclear receptor coactivator 4 (NCOA4) and release free iron.[20] Cells can also expel excess Fe^{2+} via FPN1. FPN1 and its regulator hepcidin are essential for iron regulation, and FPN1 is currently the only iron export pathway.[21] Abnormal expression or function of these proteins can lead to increased intracellular labile iron (Figure 1).

Iron-dependent lipid peroxidation is another important process of ferroptosis. Phospholipid (PL) is one of the main components of cell membranes. PLs can bind different fatty acyl chains to their *sn1* and *sn2* sites to increase their diversity.[22] Polyunsaturated fatty acyl (PUFA) can combine with the *sn2* site of PL to form PUFA-PLs after being catalyzed by acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3).[23] *ACSL4* or *LPCAT3* knockout results in a marked reduction in PUFA-PLs production.[24,25] PUFA-PLs can increase the fluidity of cell membranes and maintain the normal physiological function of cells.[26] However, PUFA-PLs are also important substrates of lipid peroxidation. PUFAs contain bis-allylic, which can be easily stripped a hydrogen atom by strong oxidants and form a phospholipid radical (PL•), and subsequently bind to an oxygen molecule to form a phospholipid peroxyl radical (PLOO).[27] Importantly, PLOO• can rob a hydrogen atom from the bis-allylic of another PUFA-PL, leading to the formation of PUFA-PL-OOH and the formation of another PL.[28] The continuous production and accumulation of PUFA-PL-OOH driven by the labile iron pool and ROS will disrupt the integrity of the cell membrane and lead to ferroptosis.[29] LOXs can also drive PUFA-PLs peroxidation and promote ferroptosis.[29]

Inhibitors of Ferroptosis

Under physiological conditions, cells can neutralize lipid peroxidation in time to prevent overload. Glutathione peroxidase 4 (GPX4) belongs to the glutathione peroxidase (GPXs) family and is the main detoxifying enzyme of PL-OOH. GPX4 can convert PL-OOH to non-toxic phospholipid alcohol (PL-OH) and simultaneously convert glutathione (GSH) to glutathione disulfide (GSSG).[30] GSH is an important cofactor for the lipid peroxidation detoxification of GPX4, which is inhibited when GSH biosynthesis is reduced.[31] GSH is composed of glutamate, glycine and cysteine, of which cysteine needs to be ingested extracellular and is the rate-limiting precursor for GSH biosynthesis.[32] Intracellular cysteine acquisition depends on cystine/glutamate reverse transporter (System X_C-), whose core components are light chain subunit solute carrier family 7 member 11 (SLC7A11) and heavy chain subunit solute carrier family 3 member 2 (SLC3A2). SLC7A11 can exchange intracellular glutamate and extracellular cystine in a 1:1 ratio.[33] Cystine that enters cells can be reduced to cysteine and participate in GSH synthesis.[34] Up to this, GSH biosynthesis and GSH-dependent PL-OOH detoxification of GPX4 constitute the main ferroptosis defense system: SLC7A11-GSH-GPX4 axis and inhibition of SLC7A11-GSH-GPX4 axis will lead to ferroptosis. For example, Dixon et al found that RSL3 and Erastin lead to intracellular PL-OOH overload and ferroptosis by inhibiting GPX4 and system X_C-, respectively.[2]

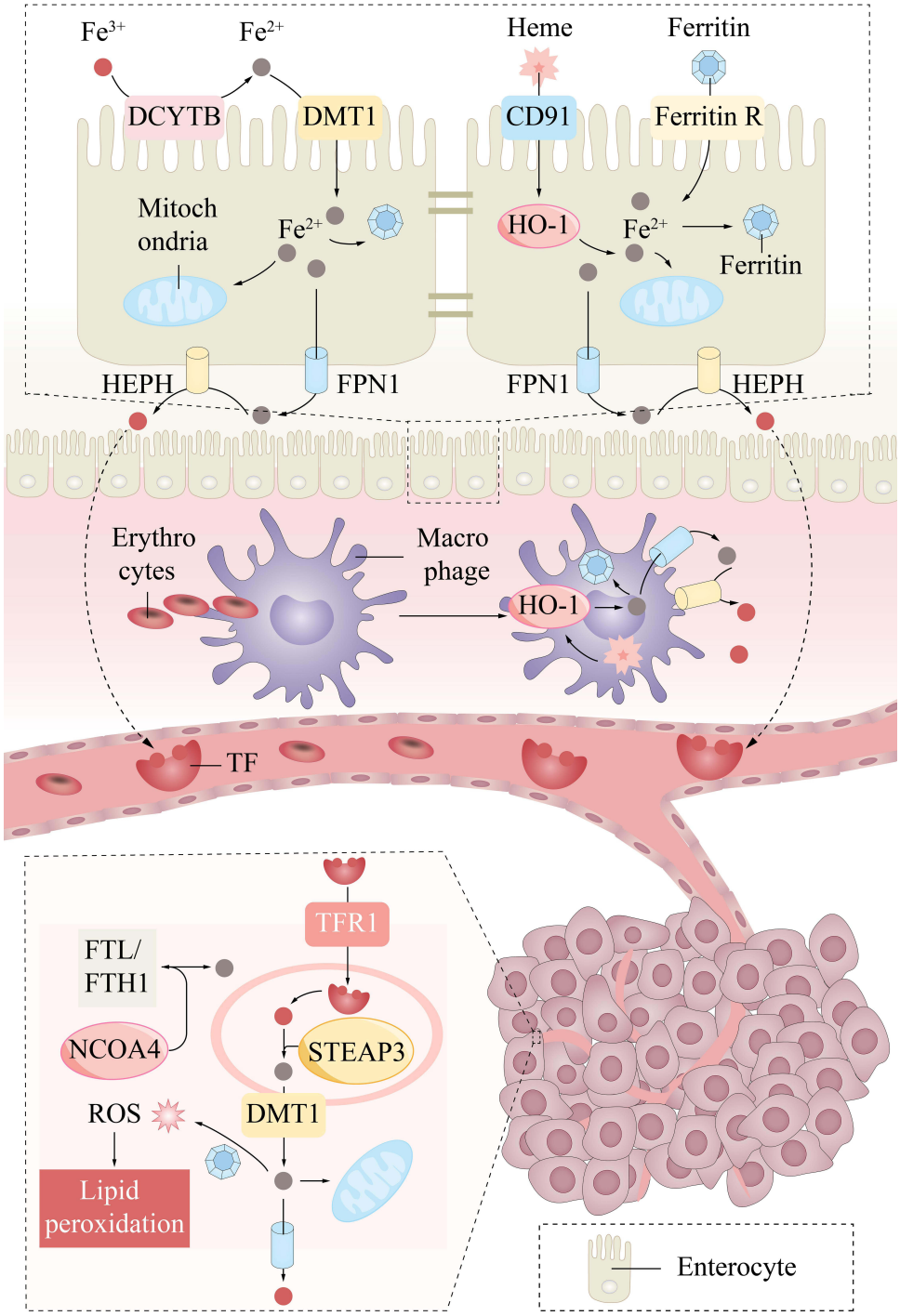

Figure 1 Iron transport and ferroptosis. Iron from different sources is converted to Fe^{3+} in enterocytes or macrophages and transported by transferrin to target cells. Intracellular iron overload can promote ferroptosis by increasing ROS and lipid peroxidation through the Fenton reaction.

Abbreviations: DCYTB, duodenal cytochrome B; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; HEPH, hephaestin; HO-1, heme oxygenase-1; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; STEAP3, six transmembrane epithelial antigen of the prostate 3; TF, transferrin; TFR1, transferrin receptor 1.

In addition to SLC7A11-GSH-GPX4 axis, cells are able to inhibit ferroptosis through parallel pathways. Ubiquitin (UQ, coenzyme Q_{10}, CoQ_{10}) is a lipophilic molecule that is widely presented in various cells. CoQ_{10} is mainly synthesized in mitochondria, has redox activity, and is participated in electron transport in the mitochondrial respiratory chain.[35] CoQ_{10} can be cycled in both oxidized and partially/fully reduced states, and its fully reduced form ubiquinol ($CoQ_{10}H_2$) has strong

antioxidant properties, which can consume lipophilic free radicals and inhibit ferroptosis. Ferroptosis suppressor protein 1 (FSP1) is a ubiquitin reductase that can deplete NAD(P)H and reduce CoQ_{10} to $CoQ_{10}H2$.[36] FSP1 structurally has a characteristic N-terminal canonical myristoylation motif, which may aid in the localization of FSP1 to the plasma membrane.[36] Alterations in this motif can lead to aberrant FSP1 plasma membrane targeting and abnormal FSP1 function. FSP1-$CoQ_{10}H_2$ axis forms a ferroptosis defense system parallel to SLC7A11-GSH-GPX4 axis by continuously reducing CoQ_{10} to $CoQ_{10}H_2$ and directly consuming lipid free radicals. Bersuker et al demonstrated that FSP1 is parallel to GXP4 to defend ferroptosis. FSP1 KO cells showed no change in GSH levels but increased lipid peroxidation. GPX4 KO H460 cells could maintain normal growth through FSP1, while GPX4 KO/FSP1 KO H460 cells could induce severe ferroptosis.[37] Doll et al found that FSP1 overexpression attenuated GPX4 KO-induced lipid peroxidation.[38]

GTP cyclohydrolase-1 (GCH1)-tetrahydrobiopterin (BH_4) is another ferroptosis defense axis. BH_4 is an important cofactor with strong antioxidant properties, which can directly reduce lipid peroxidation and promote the synthesis of CoQ_10.[39] GCH1 is the rate-limiting enzyme that catalyzes GTP to BH4.[40] Several studies have demonstrated that GCH1-BH4 axis prevents ferroptosis through lipid remodeling (Figure 2).[39,41–43]

Regulation of Ferroptosis

p53 Pathway

p53 is an important tumor suppressor gene involved in various CFDs such as apoptosis, senescence, mitotic catastrophe and ferroptosis.[1] p53 plays a dual role in ferroptosis, possibly related to the level of stress. p53 promotes cell survival

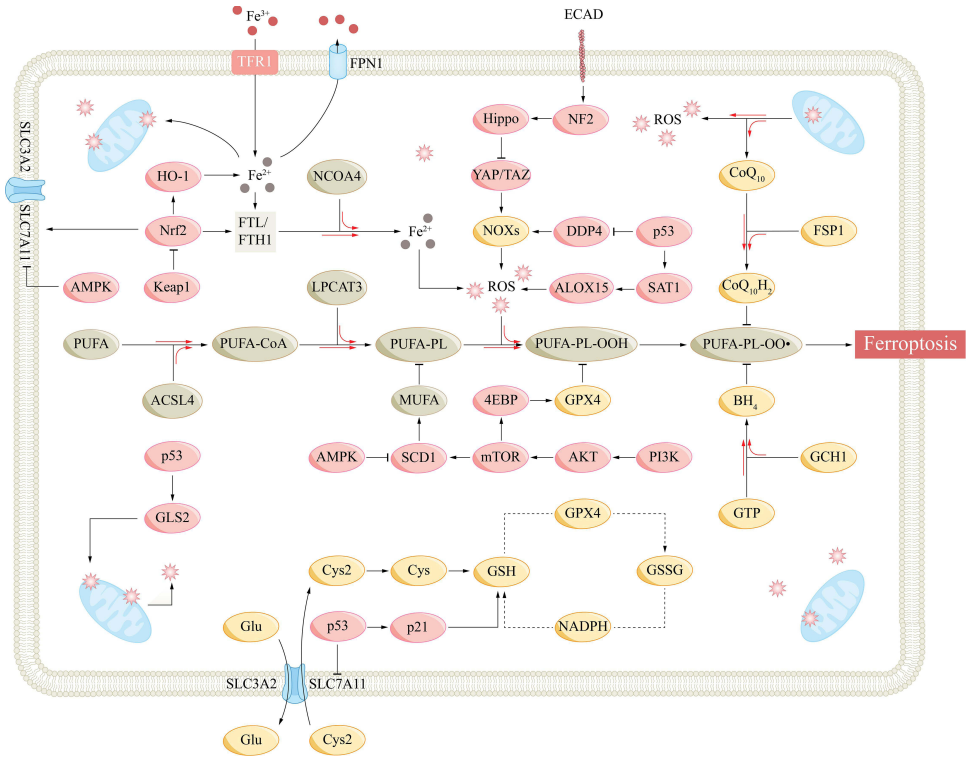

Figure 2 Mechanisms and important regulatory signaling pathways of ferroptosis.

Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX15, arachidonate lipoxygenase 15; AMPK, AMP-activated protein kinase; Akt, protein kinase B; BH_4, tetrahydrobiopterin; CoQ10, coenzyme Q10; Cys, cysteine; Cys2, cysteine; DDP4, dipeptidyl peptidase-4; ECAD, E-cadherin; 4EBP, eukaryotic initiation factor 4E-binding proteins; FPN1, ferroportin 1; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GCH1, GTP cyclohydrolase-1; GLS2, glutaminase 2; Glu, glutamate; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; HO-1, heme oxygenase-1; Keap1, Kelch-like ECH-associated protein 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acyl; NCOA4, nuclear receptor coactivator 4; NF2, neurofibromatosis 2; NOX, NADPH oxidase; Nrf2, nuclear factor E2-related factor 2; PI3K, phosphatidylinositol-3 kinase; PL, phospholipid; PLOO, phospholipid peroxyl radical; PUFA, polyunsaturated fatty acyl; ROS, reactive oxygen species; SAT1, spermidine/spermine N1-acetyltransferase 1; SCD1, stearoyl-CoA desaturase-1; SLC7A11, subunit solute carrier family 7 member 11; TAZ, WW domain-containing transcription regulator protein 1; TFR1, transferrin receptor 1; YAP, yes-associated protein 1.

under low levels of stress and induces various cell fate decisions such as ferroptosis under high levels of stress. SLC7A11 is a target of p53, and several studies have shown that p53 can inhibit SLC7A11 expression and GSH biosynthesis and promote ferroptosis, which is an effective way to induce tumor cell death.[44–46] The acetylation-defective mutant of p53, $p53^{3KR}$, which has three arginine residues K117R, K161R and K162R, can precisely inhibit SLC711A and do not involve in other CFDs.[47] p53 can also promote the expression of arachidonate lipoxygenase 15 (ALOX15) and induce ACSL4-independent lipid peroxidation through p53-spermidine/spermine N1-acetyltransferase 1 (SAT1)-ALOX15 axis.[48] p53 can also promote the transcription of glutaminase 2 (GLS2) and promote ferroptosis.[49] GLS2 is involved in glutaminolysis, converting glutamate to α-ketoglutarate and increasing lipid ROS. GLS2 also enhanced GSH and antioxidant functions, but it was not sufficient to counteract the promotion of lipid ROS.[50]

p53 exerts an anti-ferroptosis effect through p21 promoting and dipeptidyl peptidase-4 (DDP4) reducing.[51] p21 regulates the cell cycle and is involved in CFDs such as senescence and mitotic catastrophe.[1] p53 can promote p21 transcription, increase GSH production, and delay ferroptosis.[52] p53 can bind to DDP4 and promote nuclear accumulation, inhibiting its function. p53 inhibition can lead DDP4 inter the plasma membrane and combine with NADPH oxidase 1 (NOX1) to promote lipid peroxidation and ferroptosis.[53]

Keap1-Nrf2-HO-1 Pathway

Nuclear factor E2-related factor 2 (Nrf2) is an important transcription factor for cellular antioxidant regulation, and Kelch-like ECH-associated protein 1 (Keap1) is a major negative regulator of Nrf2.[54] Under physiological conditions, Keap1 binds and inactivates Nrf2, maintaining intracellular Nrf2 at low levels. Under oxidative stress conditions or when Keap1 is artificially inhibited (such as p62), Nrf2 is released from Keap1.[55] Nrf2 then translocates to the nucleus and binds to the antioxidant response element (ARE), activating various downstream antioxidant pathways to maintain intracellular redox homeostasis. Nrf2 regulates ferroptosis at multiple steps. Nrf2 controls FTL/FTH1 expression and regulates intracellular free iron concentration.[56] SLC7A11 is also regulated by Nrf2, which can promote cystine uptake and GSH synthesis.[57] Nrf2 also promotes ferroptosis SLC7A11-GSH-GPX4 defense axis by inducing GPX4 synthesis.[58] Nrf2 promotes NADPH regeneration and plays an antioxidant role.[59]

Heme oxygenase-1 (HO-1), as one of the key downstream of Nrf2, possesses some features of Nrf2, and Nrf2-HO-1 axis can promote the production of GPX4 and NADPH.[60] However, HO-1 can degrade hemosiderin to biliverdin, CO, and $Fe2^{+}$, resulting in an increase in free iron and may promote ferroptosis.[61] Tang et al found that elevated HO-1 promoted ferroptosis in retinal pigment epithelium cells.[62]

AMPK Pathway

AMP-activated protein kinase (AMPK) is an important sensor and regulator of cellular energy balance. AMPK can sense the intracellular AMP-ATP ratio and is activated in response to the elevation of AMP.[63] Activated AMPK promotes complex downstream pathways, reducing ATP consumption and increasing ATP production to restore AMP-ATP balance and maintain cell physiological function. AMPK also regulates mitochondrial biosynthesis, dynamics, and mitophagy.[64] Due to the complexity and phosphorylation activation level of the downstream targets, AMPK may promote or inhibit ferroptosis. Song et al found that AMPK promotes phosphorylation of downstream BECN1 (beclin 1) at S90 and S93, which combines with SLC7A11 to inhibit system X_C- and promote ferroptosis.[65] AMPK can also inhibit stearoyl-CoA desaturase-1 (SCD1), an enzyme that catalyzes the production of monounsaturated fatty acyl (MUFA), which can replace PUFA and inhibit ferroptosis.[66,67] Several studies have shown that AMPK can induce the activation and nuclear translocation of Nrf2, promote cellular antioxidant function and inhibit ferroptosis.[68,69] Lee et al found that AMPK activation inhibited acetyl-CoA carboxylases 1 (ACC1).[70] ACC1 is involved in de novo lipid synthesis, and its inhibition reduces PUFA biosynthesis and inhibits ferroptosis.[71] Contrary conclusions confirm the complexity of AMPK reticular pathways. Based on the importance of AMPK in mitochondria, further studies are needed to explore the specific role of AMPK in ferroptosis.

Hippo Pathway

Studies have shown that increasing the density of individual cells that are sensitive to ferroptosis increases their ferroptosis resistance, and this alteration is closely related to cell–cell contact and activation of Hippo pathway.[72–74] Hippo pathway is regulated by cell–cell contact, physical and biochemical signals, and controls a variety of biological processes such as cell proliferation, CFDs, and organ size.[75] Hippo pathway consists of several core components, which constitute signal modules to regulate the downstream effector transcription coregulators Yes-associated protein 1 (YAP)/WW domain-containing transcription regulator protein 1 (TAZ).[76] Hippo pathway inhibition leads to the dephosphorylation and nuclear translocation of YAP/TAZ, which subsequently binds to TEA-domain transcription factor (TEAD) and promotes cell proliferation; high cell density activates Hippo pathway, leading to phosphorylation and inhibition of YAP/TAZ, inhibiting cell proliferation, promoting apoptosis, and controlling organ size.[77] Several stages of ferroptosis, such as TFR1, ACSL4 and NOX2/4, are regulated by Hippo pathway.[74,78–80] Studies have shown that overexpression of E-cadherin in mesothelioma and renal cell carcinoma mediates cell–cell contact and neurofibromatosis 2 (NF2) activation, leading to Hippo pathway activation and YAP/TAZ inhibition, promoting ferroptosis.[72,81] Therefore, YAP/TAZ-TEAD complex is an important target for regulating ferroptosis. Furthermore, the role of specific components in the core cascade of Hippo pathway in ferroptosis remains to be elucidated.

PI3K-Akt-mTOR Pathway

Phosphatidylinositol-3 kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin (mTOR) pathway plays an important role in cell survival, proliferation and other physiological processes.[82] PI3K-Akt-mTOR pathway is frequently abnormal in cancer, and activating mutations in *PI3K* or inactivation of tumor suppressor *phosphatase and tensin homolog deleted on chromosome 10 (PTEN)* can confer ferroptosis resistance in tumor cells.[27,83] Further studies showed that PI3K-Akt-mTOR pathway inhibited lipid peroxidation and promoted GPX4 expression. Sterol regulatory element-binding protein 1 (SREBP-1) is a key transcription factor involved in lipogenesis, and SCD1 is its important target. PI3K-Akt-mTOR pathway promotes SREBP-1 transcription and SCD1 expression, leading to an increased MUFA and inhibition of PUFA-PL-OOH.[84–86] In addition, Zhang et al showed that mTORC1 can activate eukaryotic initiation factor 4E (eIF4E)-binding proteins (4EBPs) to promote GPX4 synthesis.[87] Taken together, targeting PI3K-Akt-mTOR pathway or SCD1 will contribute to the regulation of ferroptosis (Table 1 and Figure 2).

Table 1 Several Regulators of Ferroptosis

	Regulator	Mechanism	References
Inducer	p53	Inhibiting SLC7A11 expression and GSH biosynthesis	[44–47]
		Promoting ALOX15 expression and lipid peroxidation	[48]
		Promoting GLS2 transcription, converting glutamate to α-ketoglutarate, and increasing ROS	[49]
	HO-1	Degrading hemosiderin and producing Fe^{2+}	[61]
	AMPK	Inhibiting system X_C-	[65]
		Inhibiting SCD1, reducing MUFA production to promote PUFA	[66,67]
	Hippo	Promoting NOX2/4 expression	[79,80]
Inhibitor	p53	Promoting p21 transcription and increasing GSH production	[52]
		Inhibiting the binding of DDP4 to NOX1	[53]
	Nrf2	Promoting FTL/FTH1 expression	[56]
		Promoting SLC7A11 and GPX4 synthesis	[57,58]
	HO-1	Promoting GPX4 and NADPH production	[60]
	AMPK	Inducing Nrf2 activation and promoting antioxidant function	[68,69]
		Inhibiting ACC1 and reducing PUFA biosynthesis	[71]
	mTOR	Promoting SCD1 expression, leading to increased MUFA and PUFA substitution	[85]
		Promoting GPX4 synthesis	[87]

Abbreviations: ACC1, acetyl-CoA carboxylases 1; ALOX15, arachidonate lipoxygenase 15; AMPK, AMP-activated protein kinase; DDP4, dipeptidyl peptidase-4; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GLS2, glutaminase 2; GPX4, glutathione peroxidase 4; GSH, glutathione; HO-1, heme oxygenase-1; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acyl; NOX, NADPH oxidase; Nrf2, nuclear factor E2-related factor 2; PUFA, polyunsaturated fatty acyl; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase-1; SLC7A11, subunit solute carrier family 7 member 11.

Ferroptosis and Osteoporosis

Bone is an important tissue of the human body, which plays roles in the movement, protection of internal organs and endocrine regulation, etc.[88] Bone cells are mainly composed of osteocytes, osteoblasts (OB), and osteoclasts (OC).[89] Osteocytes are the major cells of bones, and more than 90% of adult bone cells are osteocytes.[90] OBs, which are derived from mesenchymal stem cells (MSC), are cells that produce bone matrix and dominate bone-forming.[91] Osteocytes can considered to be fully differentiated OBs.[92] OCs are derived from monocyte/macrophage lineage of hematopoietic cells and contain abundant mitochondria and lysosomes and can lead to bone-resorbing.[93] The homeostasis of OCs and OBs promotes the balance of bone-resorbing and bone-forming, promotes bone-remodeling, and makes bone a dynamic tissue to maintain its normal function.[94]

Osteoporosis (OP) is a common metabolic bone disease. Due to abnormal OBs-OCs homeostasis, bone-forming is weakened and bone-resorbing is enhanced, resulting in decreased bone mass, increased bone brittleness, and poor healing ability after fracture.[95] According to the causes, OP is divided into primary, secondary and idiopathic. Primary OP mainly includes senile OP (SOP) and postmenopausal OP (PMOP), while secondary OP is usually diabetic OP (DOP) or glucocorticoid-induced OP (GIOP).[96] Many studies indicate an association between ferroptosis and OP. An in vitro study confirmed the inhibitory effect of iron on bone-remodeling. Co-cultured iron-containing body fluids with hydroxyapatite crystals, the calcium concentration of hydroxyapatite significantly decreased as the iron concentration increased.[97] In addition, iron overload produces a large number of ROS through the Fenton reaction, which affects bone metabolism and has different effects on OBs, OCs and osteocytes.[98]

Bone marrow-derived mesenchymal stem cells (BMSCs) are an important source of OBs. BMSCs are stem cells with the ability to differentiate into OBs, chondrocytes, and adipocytes, and other cells.[99] Runt-related transcription factor 2 (Runx2) is an important transcription factor regulating BMSCs differentiation into OBs. Activation of Runx2 and expression of osteocalcin (OCN) and alkaline phosphatase (ALP) promote osteogenic differentiation.[100] Iron overload increased the expression of ferritin in BMSCs in an iron dose-dependent manner, decreased the expression of Runx2, OCN, and ALP, and inhibited the osteogenic differentiation of BMSCs.[101] Lan et al found that quercetin inhibited BMSCs ferroptosis and promoted the expression of Runx2 and ALP and osteogenic differentiation by inhibiting the PI3K-Akt-mTOR pathway.[102] For mature osteoblasts, ferroptosis can lead to phenotypic and functional inhibition of OBs, which has been demonstrated in vivo and in vitro.[103,104] Several studies showed the ability of Nrf2-GPX4, Nrf2-HO-1, AMPK-SIRT1 and other pathways to regulate OB ferroptosis and promote bone-forming.[105–107] Tian et al found that ferric ion treatment could promote the increase of ferroptosis indicator NOX4 in MC3T3-E1 cells and also apoptosis indicators: increased caspase-3 and Bax and decreased Bcl-2.[108]

Osteoclast differentiation requires the activation of the receptor activator of the nuclear factor-κB (RANK)-RANKL pathway. RANKL is produced by OBs and binds to RANK on the surface of osteoclast precursor cells, promotes the differentiation of osteoclast precursor cells into OCs, and also inhibits OCs apoptosis.[109] Studies have indicated that iron overload can promote RANKL expression and promote osteoclast differentiation.[110,111] Ni et al found that, due to the decreased activity of aconitase, RANKL activation can lead to the increase of TFR1 and the NOCA4-induced ferritinophagy of FTH1, increase the free iron content in OCs and Fenton reaction, which may be one of the regulations to inhibit the overproduction of OCs.[112] However, under hypoxic conditions, the activation of hypoxia-inducible factors (HIF-1α) inhibits FTH1 ferritinophagy and OCs ferroptosis, and inhibition of HIF-1α can induce OCs ferroptosis and alleviate OP.[112] Thus, hypoxic environments, such as medullary cavities and growth plates, would contribute to the resistance of osteoclasts to ferroptosis, and targeting HIF-1α may be a potential therapeutic direction of OP. In addition, postmenopausal estrogen deficiency leading to reduced inhibition of estrogen on HIF-1α and activation of OCs may be one of the causes of PMOP.[113]

Compared to OBs and OCs, there have been rare studies on ferroptosis associated with osteocytes in the context of osteoporosis. However, as the most abundant cells in bone, osteocyte ferroptosis undoubtedly plays a role in the pathogenesis of OP. DOP is closely related to abnormal glucolipid homeostasis, and the deposition of glucolipid metabolites was observed in the bone tissue of DOP. Yang et al found that the type 2 diabetes microenvironment promotes the transcription of HO-1 through Nrf2/c-Jun as well as GPX4 reduction and the occurrence of osteocyte ferroptosis, which promotes DOP.[114] In addition, inhibition of osteocyte ferroptosis with ferrostatin-1 (Fer-1) or iron chelator desferrioxamine (DFO) can rescue DOP. In addition, Yang et al found that iron overload can induce osteocyte apoptosis and subsequently promote increased

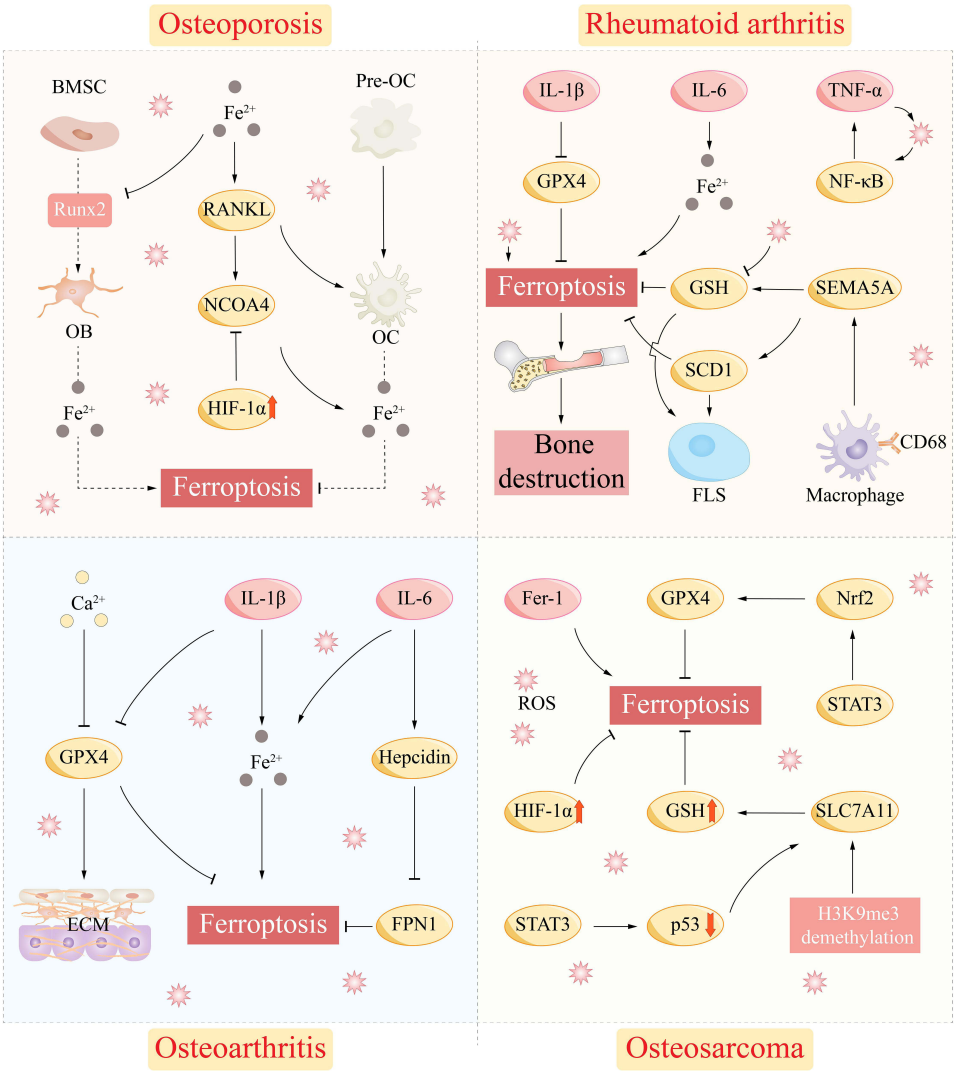

Figure 3 Ferroptosis is involved in the pathogenesis of various bone-related diseases, such as osteoporosis, osteoarthritis, rheumatoid arthritis, and osteosarcoma.
Abbreviations: BMSC, bone marrow-derived mesenchymal stem cell; ECM, extracellular matrix; Fer-1, ferrostatin-1; FLS, fibroblast-like synoviocyte; FPN1, ferroportin 1; GPX4, glutathione peroxidase 4; GSH, glutathione; HIF-1α, hypoxia-inducible factors; Nrf2, nuclear factor E2-related factor 2; OB, osteoblast; OC, osteoclast; RANKL, receptor activator of the nuclear factor-κB ligand; ROS, reactive oxygen species; Runx2, Runt-related transcription factor 2; SCD1, stearoyl-CoA desaturase-1; SEMA5A, semaphorin 5A; SLC7A11, subunit solute carrier family 7 member 11; STAT3, signal transducer and activator of transcription 3.

secretion of osteocytic RANKL, increasing osteoclast activation and leading to OP.[111] In summary, iron overload and ferroptosis significantly promote bone-resorbing and reduce bone-forming. How to reduce osteoblasts and osteocytes ferroptosis or promote osteoclasts ferroptosis should be a focus of future research on osteoporosis (Figure 3).

Ferroptosis and Osteoarthritis

Osteoarthritis (OA) is a common degenerative disease that can cause pain, dysfunction, and deformity. The main mechanisms of OA are cartilage degeneration, cartilage extracellular matrix degradation, synovium inflammation, and subchondral bone sclerosis and hyperplasia.[115] The progressive degeneration of cartilage plays an important role in the progression of OA. Chondrocytes are the only cell type in cartilage and can produce extracellular matrix (ECM).[116] ECM is mainly composed of water, collagen and proteoglycans, which encapsulates chondrocytes and forms a closed environment.[117] This closed environment lacks nerves and blood vessels, so the repair capacity of chondrocytes is poor.

Chondrocyte ferroptosis plays a role in the pathogenesis of OA. Genome-wide RNA-Seq data and several studies have shown a marked reduction of GPX4 in OA cartilage.[118–120] The decrease of SLC3A2 in OA cartilage has also been

reported.[121] Miao et al found that endochondral GPX4 and SLC3A2 were reduced in OA patients, and Fer-1 and DFO can inhibit chondrocyte ferroptosis and OA. Besides, GPX4 inhibition also promoted ECM degradation through the MAPK/NF-κB pathway.[118] Yan et al found that Erastin promoted chondrocyte ferroptosis and inhibited the expression of type II collagen (the major collagen protein in the ECM). Fer-1 reversed this process and activated the Nrf2-GPX4 and Nrf2-HO-1 pathways.[122] Activation of the Nrf2-GPX4 pathway can ameliorate Erastin-induced ferroptosis in OA chondrocytes.[119] In another study, metformin reversed Erastin-induced ferroptosis and p53 pathway activation in OA chondrocytes.[123] The AMPK pathway is also involved in the regulation of chondrocyte activity and OA.[124] Baicalein promotes the stability of AMPK and nuclear translocation of Nrf2, activates the AMPKα-Nrf2-HO-1 pathway, and alleviates the progression of OA.[125] Zhou et al found that in addition to mediating chondrocyte CFDs such as apoptosis and autophagy, HIF-2α inhibited SLC7A11 and GPX4 and promoted lipid peroxidation to mediate chondrocyte ferroptosis.[126] D-mannose inhibited HIF-2α and attenuated the above process and OA progression.

Excessive mechanical stimulation is a contributing factor to OA. Piezo1 is an important mechanically-sensitive ion channel in vertebrates and is involved in iron metabolism.[127] Wang et al found that excessive mechanical stimulation activated piezo1 channels and increased Ca^{2+} influx, leading to GSH reduction and GPX4 inhibition, promoting chondrocyte ferroptosis and OA. In addition, FSP1 and CoQ_{10} can inhibit ferroptosis in parallel with GPX4, indicating that piezo1 induces chondrocyte ferroptosis mainly by inhibiting the SLC7A11-GSH-GPX4 axis.[128]

Synovium inflammation is also an important factor in the progression of OA. Various inflammatory mediators such as TNF-α, IL-1β, IL-6, cyclooxygenase-2 (COX-2) and NO can promote cartilage injury, and some inflammatory mediators are associated with chondrocytes ferroptosis, such as IL-1β and IL-6.[129] Gong et al found that IL-1β played a role in intracellular iron overload, GPX4 inhibition, and ROS production. Cardamonin and DFO could rescue IL-1β-induced chondrocyte ferroptosis and OA through the p53-SLC7A11-GPX4 axis.[130] IL-6 can induce chondrocyte ferroptosis by up-regulating hepcidin to inhibit intracellular iron export, increase ROS, and reduce GPX4 activity.[131] In intervertebral disc degeneration, miR-10a-5p can inhibit IL-6 and reduce chondrocyte ferroptosis.[131]

Overall, ferroptosis plays an important role in the pathogenesis of OA, but the specific mechanism still needs to be clarified. Targeting inhibition of chondrocyte ferroptosis, especially the GSH-GPX4 axis, is one of the potential therapeutic directions for OA (Figure 3).

Ferroptosis and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common autoimmune disease. RA is characterized by immune cell infiltration and synovial fibroblast proliferation, leading to the destruction of cartilage and bone, forming aggressive arthritis.[132]

Ferroptosis is closely related to the pathogenesis of RA. Compared with healthy people, the synovial iron content of RA and OA patients is higher, especially in RA patients.[133] Infiltrating immune cells produce various proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, which improve hepcidin expression and change the glycosylation pattern of transferrin, promote intracellular iron storage and reduce hemoglobin levels.[134,135] This may lead to a redistribution of iron in the body, leading to iron deposition in the synovium but iron deficiency anemia in RA patients. Etanercept reversed iron deficiency anemia in RA by down-regulating hepcidin expression.[136] In addition, RA patients also showed elevated ROS levels and lipid peroxidation in the synovium.[137,138] Importantly, ROS is a key factor to promote the progression of RA. ROS stimulates the continuous production of TNF-α through the NF-κB pathway, forming a ROS/TNF-α positive feedback.[138]

Fibroblast-like synoviocytes (FLSs) are important cells in RA, which can produce cytokines and promote neovascularization and matrix degradation to promote RA progression.[139] It has been mentioned that iron overload and excessive ROS can promote OC differentiation and bone resorption, as well as chondrocyte ferroptosis and type II collagen destruction.[140,141] In this case, FLSs ensure normal survival and proliferation through their resistance to ferroptosis. Although ROS was increased in RA FLSs, SLC7A11, GPX4, FTH1 were increased and ACSL4 was decreased, resulting in an increase in free iron and antioxidant/oxidative capacity.[142] Wu et al found that in collagen-induced arthritis (CIA), TNF promotes SLC7A11 expression and GSH biosynthesis in FLSs, increasing ferroptosis resistance.[143] In addition, macrophages showed a protective effect against ferroptosis to FLSs when treated with RSL3.[143] Cheng et al found that increased Semaphorin 5A (SEMA5A) produced by synovial $CD68^{+}$ macrophages in RA patients promoted GPX4 and

SCD1 expression through the PI3K-Akt-mTOR pathway and inhibited lipid peroxidation and ferroptosis of FLSs.[144] Due to the resistance of FLS to ferroptosis and the redistribution of iron, iron supplementation in RA patients with iron deficiency anemia may lead to exacerbation of RA.[145]

Targeting ferroptosis has already shown positive effects in RA. Icariin can promote the SLC7A11-GSH-GPX4 axis to alleviate ferroptosis and lipopolysaccharide-induced synovitis.[146] Several studies anticipated that activation of the FSP1-$CoQ_{10}H2$ axis might help to suppress ROS/TNF-α positive feedback and attenuate RA.[138,147] Galectin-1 derived peptide 3 (G1dP3) showed an inhibitory effect on FLS cell line MH7A cells. G1dP3 promotes ferroptosis of MH7A cells by activating the p53-SLC7A11 axis, and the knockout of p53 abolished the inhibitory effect of G1dP3 on MH7A cells.[148] Xiang et al identified SLC2A3 as a possible marker of RA. RSL3 could cause SLC2A3, SLC7A11, GPX4, and FTH1 inhibition in RA FLSs and promote ferroptosis.[149] The combination of TNF blocker etanercept and ferroptosis inducer imidazole ketone erastin can promote FLS ferroptosis and alleviate CIA.[143] Glycine, an important component of GSH, also promotes the expression of S-adenosylmethionine (SAM). SAM promoted the *GPX4* promoter methylation and inhibited *GPX4* expression. A study showed that both glycine and SAM treatment can promote ferroptosis of FLS cells and improve CIA.[142] Glycine also inhibited FTH1 expression and increased intracellular free iron in FLSs. Transient receptor potential melastatin 7 (TRPM7) is highly permeable to Ca^{2+} and Mg^{2+}, and TRPM7 channel activation promotes intracellular Ca^{2+} and ROS accumulation.[150,151] Zhou et al found that TRPM7 channel is elevated in RA patients and adjuvant arthritis (AA) and promotes chondrocyte ferroptosis via the PKCα-NOX4 axis to promote RA and AA.[152] Although studies on osteoblastic ferroptosis in RA are still lacking, there is no doubt that FLS, OCs and chondrocytes have different sensitivity to ferroptosis in RA. A large number of studies are still needed to explore the unique mechanisms of ferroptosis in different cells in arthritis and provide guidance for more specific targeted therapies for RA (Figure 3).

Ferroptosis and Osteosarcoma

Osteosarcoma (OS), a familiar primary malignant bone tumor, originated from primitive mesenchymal cells and is aggressive and prone to lung metastasis.[153] At present, the treatment of OS includes surgery, radiotherapy, chemotherapy, neoadjuvant chemotherapy, etc. However, the treatment effect of metastatic, recurrent and drug-resistant OS is not satisfactory.[154] Inducing tumor cell death and inhibiting tumor cell proliferation is an important part of cancer treatment.[155] Targeted induction of ferroptosis in tumor cells has brought new opportunities for the treatment of OS.

Studies showed that Sulfasalazine, Tirapazamine and miRNA-1297-5p can promote OS cell ferroptosis by inhibiting SLC7A11-GSH-GPX4 axis.[156–158] KDM4A knockdown inhibited H3K9me3 demethylation in *SLC7A11* promoter region and reduced SLC7A11 expression in OS cells.[159] Baicalin can bind to Nrf2 and promote Nrf2 degradation, inducing MG63 and 143B ferroptosis through the Nrf2-SLC7A11-GPX4 axis.[160] RNA sequencing analysis revealed that zoledronic acid upregulated P450 oxidoreductase (POR), leading to excessive ROS and lipid peroxidation in OS cells.[161] Lv et al found that β-Phenethyl isothiocyanate (PEITC) can promote multiple CFDs in OS cells, such as apoptosis, autophagy and ferroptosis.[162] PEITC can promote the increase of intracellular free iron and ROS and the decrease of GSH, which may be related to the activation of mitogen-activated protein kinase (MAPK) signaling.[163] EF24, an antitumor compound, has been shown to induce tumor cell death in osteosarcoma cell line U2os and Saos-2.[164] This process is inhibited by Fer-1 but not by inhibitors of apoptosis, autophagy, or necroptosis. Further study found EF24 promotes *HMOX1* and HO-1 expression and inhibits GPX4 expression, improving ROS accumulation and lipid peroxidation.

As an important tumor suppressor, p53 regulates multiple CFDs. p53 is frequently inactivated in osteosarcoma, leading to resistance of OS cells to apoptosis and ferroptosis.[165] Studies have shown that p53 regulates typical and atypical ferroptosis, and p53-SLC7A11 binding is the primary mechanism. Mutation or inactivation of p53 can inhibit p53-SLC7A11 binding and ferroptosis in OS cells.[166] p53 also regulates cellular ROS, iron and lipids. Flavonoids bavachin can inhibit signal transducer and activator of transcription 3 (STAT3) phosphorylation, promote p53 and inhibit SLC7A11 expression through STAT3-p53-SLC7A11 axis. In addition, bavachin increased intracellular free iron and inhibited the proliferation of OS cell lines MG63 and HOS. DFO and Fer-1 reversed bavachin-induced ferroptosis.[44] STAT3 phosphorylation inhibition also impaired Nrf2-GPX4 axis to promote OS cell ferroptosis and increase the

sensitivity to cisplatin.[167] Fanconi anemia complementation group D2 (FANCD2) can inhibit JAK2-STAT3 pathway and ferroptosis and promote temozolomide resistance in OS cells.[168] Hypoxia is a characteristic of solid tumors such as osteosarcoma and is closely related to drug resistance.[169] An ultrasound-activatable DOX-Fe(VI)@HMS-HE-PEG (DFHHP) nanomedicine developed based on reoxygenation and ferroptosis has been confirmed to induce apoptosis and ferroptosis in hypoxic Saos-2 cells and promote doxorubicin chemotherapy efficacy by inhibiting HIF-1α, MDR1, P-pg, GSH, GPX4 and promoting Fenton reaction.[170]

Overall, ferroptosis as an emerging CFD provides a strong direction for the treatment of OS, but more studies are still needed to explore the specific role of ferroptosis in OS cells and how to reduce the side effects on normal cells. Some studies have identified several genes associated with OS ferroptosis by bioinformatics analysis, which may provide research directions for this purpose (Figure 3).[171–175]

Conclusion

As a novel CFD, ferroptosis is tightly regulated at different levels and is involved in the pathogenesis of many diseases. Since its discovery in 2012, ferroptosis has been increasingly investigated in bone-related diseases. In this manuscript, we summarize the main regulatory mechanisms of ferroptosis and its role in bone-related diseases. In general, ferroptosis plays an important role in a variety of bone-related diseases such as OP, OA, RA and OS. The different responses of different cells to ferroptosis, such as OBs, OCs, BMSCs, chondrocytes, FLSs and osteosarcoma cells, lead to the pathological progression of various bone-related diseases. Interfering with the ferroptosis pathway in these cells shows great clinical potential in the treatment of bone-related diseases. However, current studies still remain many gaps. Some progress has been made in the application of ferroptosis inhibitors or inducers, ferroptosis inhibitors such as FSP-1, Fer-1, and DFO have shown therapeutic potential in bone-related diseases, but most of these studies remain in animal or in vitro experiments, and relevant clinical studies are still lacking.[118,138,176] Because different cells (OBs, OCs, BMSCs, chondrocytes, FLSs, OS cells) have different tolerance to ferroptosis, ferroptosis is a double-edged sword in bone-related diseases. Clinical studies are needed to explore how to use ferroptosis inducers or inhibitors in specific bone-related diseases. In addition, ferroptosis and other CFDs such as apoptosis and autophagy constitute cell fate regulatory networks, more studies are needed to explore their interactions in bone-related diseases. Finally, iron is also an essential element for normal cells. How to specifically target ferroptosis in bone-related diseases while reducing the damage to normal cells and organs is also a challenge for subsequent research.

In conclusion, ferroptosis is closely related to bone-related diseases such as osteoporosis, osteoarthritis, rheumatoid arthritis, and osteosarcoma. An in-depth study of ferroptosis-related regulatory mechanisms will provide new targets for the diagnosis and treatment of bone-related diseases.

Abbreviations

ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX15, arachidonate lipoxygenase 15; AMPK, AMP-activated protein kinase; Akt, protein kinase B; BH_4, tetrahydrobiopterin; BMSC, bone marrow-derived mesenchymal stem cell; CoQ10, coenzyme Q10; Cys, cysteine; Cys2, cysteine; DCYTB, duodenal cytochrome B; DDP4, dipeptidyl peptidase-4; DMT1, divalent metal transporter 1; ECAD, E-cadherin; ECM, extracellular matrix; 4EBP, eukaryotic initiation factor 4E-binding proteins; Fer-1, ferrostatin-1; FLS, fibroblast-like synoviocyte; FPN1, ferroportin 1; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GCH1, GTP cyclohydrolase-1; GLS2, glutaminase 2; Glu, glutamate; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; HEPH, hephaestin; HIF-1α, hypoxia-inducible factors; HO-1, heme oxygenase-1; Keap1, Kelch-like ECH-associated protein 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; mTOR, mammalian target of rapamycin; MUFA, mono-unsaturated fatty acyl; NCOA4, nuclear receptor coactivator 4; NF2, neurofibromatosis 2; NOX, NADPH oxidase; Nrf2, nuclear factor E2-related factor 2; OB, osteoblast; OC, osteoclast; PI3K, phosphatidylinositol-3 kinase; PL, phospholipid; PLOO•, phospholipid peroxyl radical; PUFA, polyunsaturated fatty acyl; RANKL, receptor activator of the nuclear factor-κB ligand; ROS, reactive oxygen species; Runx2, Runt-related transcription factor 2; SAT1, spermidine/spermine N1-acetyltransferase 1; SCD1, stearoyl-CoA desaturase-1; SEMA5A, semaphorin 5A; SLC7A11, subunit solute carrier family 7 member 11; STAT3, signal transducer and activator of transcription 3; STEAP3, six transmembrane epithelial

antigen of the prostate 3; TAZ, WW domain-containing transcription regulator protein 1; TF, transferrin; TFR1, transferrin receptor 1; YAP, yes-associated protein 1.

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