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Ferroptosis in Osteoarthritis: Current Understanding

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Abstract: Osteoarthritis (OA) is a prevalent degenerative disease in elderly people that is characterized by cartilage loss and abrasion, leading to joint pain and dysfunction. The aetiology of OA is complicated and includes abnormal mechanical stress, a mild inflammatory environment, chondrocyte senescence and apoptosis, and changes in chondrocyte metabolism. Ferroptosis is a regulated cell death modality characterized by the excessive accumulation of lipid peroxidation and mitochondrial dysfunction. The role of ferroptosis in OA pathogenesis has aroused researchers' attention in the past two years, and there is mounting evidence indicating that ferroptosis is destructive. However, the impact of ferroptosis on OA and how the regulators of ferroptosis affect OA development are unclear. Here, we reviewed the current understanding of ferroptosis in OA pathogenesis and summarized several drugs and compounds targeting ferroptosis in OA treatment. The accumulation of intracellular iron, the trigger of Fenton reaction, the excessive production of ROS, the peroxidation of PUFA-PLs, and mitochondrial and membrane damage are involved in chondrocyte ferroptosis. System X_c^- and GPX4 are the most important regulators that control ferroptosis. Several compounds, such as DFO and Fer-1, have been proven effective in preventing ferroptosis and slowing OA progression on animal models. Collectively, targeting ferroptosis shows great potential in treating OA.

Keywords: ferroptosis, osteoarthritis, chondrocyte, lipid peroxidation, iron metabolism

Introduction

Osteoarthritis (OA) is a prevalent joint degenerative disease in elderly individuals and is characterized by chronic joint pain and joint dysfunction, imposing a huge burden on life quality and the economy.[1] OA is a heterogenous disease with multiple etiologies, initially recognized as a wear-and-tear disease.[2,3] However, non-loading joints such as those in the hands can also develop OA, indicating that many other mechanisms play important roles in OA, such as inflammation, dysregulation of chondrocyte metabolism and diet-associated dysbiosis.[4–6] The ferroptosis pathway was found to be enriched, and the expression of iron overload-related genes, including FTH1, was elevated in cartilage collected from individuals with hand OA compared to that of healthy donors.[7] Chondrocytes are the only cell type within cartilage, whose state is vital for extracellular matrix (ECM) formation and cartilage metabolism. When catabolism exceeds anabolism, cartilage degeneration occurs and OA develops.[8] Several studies have reported the roles of chondrocyte apoptosis,[9–12] chondrocyte senescence,[13–15] chondrocyte hypertrophy,[16–18] chondrocyte pyroptosis[19–21], and chondrocyte energy metabolism dysfunction[22–24] in the development of OA.

Chondrocyte ferroptosis has garnered researchers' attention in recent years and has been proven to exacerbate cartilage degeneration and the progression of OA. Ferroptosis is a regulated cell death first proposed by Stockwell's team.[25] It is associated with lipid peroxidation and abnormal mitochondrial changes, including morphology, bioenergetics and metabolism.[26] During ferroptosis, morphological alterations include diminished or vanished mitochondrial cristae, as well as rupturing and wrinkling of the mitochondrial outer membrane, resulting in intensified mitochondrial staining.[27] While the cell membrane is breached, the nucleus remains intact, distinguishing this process from other forms of cell death such as apoptosis.[27] Ferroptosis also dynamically regulates key processes of mitochondrial homeostasis such as fission, fusion and mitophagy.[28] Over the past decades, ferroptosis has been shown to participate in various diseases and conditions, such as brain

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injury, Parkinson's disease, heart injury, tumor suppression and immune functions.[29] Recently, the role of ferroptosis in promoting OA development has been reported and treated as a therapeutic target. Increased expression of a disintegrin and metalloproteinase with thrombospondin 5 (ADAMTS5) and matrix metalloproteinase-13 (MMP13) was found in the iron overloaded mice model, indicating that iron overload significantly contributed to cartilage degeneration. A ferroptosis inducer like ferric ammonium citrate (FAC) could increase MMP3 and MMP13 levels in chondrocytes and promote the progression of OA.[30,31] The expression of glutathione peroxidase 4 (GPX4), an inhibitory factor of ferroptosis, was significantly lower in osteoarthritic cartilage than in normal cartilage.[32] Additionally, the knockdown of GPX4 by AAV-Gpx4 shRNA exacerbated OA in posttraumatic OA mouse model.[32] Ferroptosis is closely related to oxidative stress, which is a key factor in OA pathogenesis.[13,14] The Fenton reaction in the ferroptosis process could generate ROS and exacerbate oxidative stress,[33] and the downregulation of GPX4 could enhance the susceptibility of chondrocytes to oxidative stress through the MAPK/NF-κB pathway.[32] Lipid peroxidation has long been associated with OA, and there are increased markers of lipid peroxidation in serum,[34] synovial fluid,[35] osteoarthritic chondrocytes,[36] and synoviocytes.[37] Several compounds, such as DFO,[31,32,38] Fer-1,[32] Icariin,[39] and N-acetyl cysteine (NAC),[40] have been demonstrated to effectively alleviate OA progression by regulating ferroptosis. Therefore, a deeper understanding of the mechanism of ferroptosis in the pathogenesis of OA has potential significance for exploring new drug targets for OA. In this review, we illustrate the impacts of ferroptosis and lipid peroxidation on OA pathogenesis to identify potential treatments targeting ferroptosis in the future.

The Key Processes in Ferroptosis

The initiation of ferroptosis normally included the following processes, the accumulation of intracellular iron, the triggering of Fenton reaction, excessive production of ROS, the integration of polyunsaturated fatty acids (PUFAs) into phospholipids (PLs) and the peroxidation of PUFA-PLs, and finally mitochondrial and membrane damage. They are as follows.

Intracellular Iron Accumulation

Fe^{2+} in food is taken up by enterocytes via divalent metal-ion transporter 1 (DMT1) and secreted into the blood via ferroportin (FPN).[41] Fe^{2+} is oxidized into Fe^{3+} by ferroxidase and hephaestin,[42–44] and Fe^{3+} binds with transferrin (Tf), circulates through the body, and is delivered to multiple organs and tissues.[42] After Tf binds to the transferrin receptor 1 (TfR1) on the cell membrane, Fe^{3+} bounded with Tf is absorbed into cells through receptor-mediated endocytosis.[42] Low pH in the endosomes can release Fe^{3+} from Tf and reduce Fe^{3+} into Fe^{2+}, and then Fe^{2+} in the endosome is released via DMT1.[45] Intracellular iron is primarily bound to ferritin, which consists of ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL) and functions as iron storage.[46,47] The degradation of ferritin through autophagy will trigger labile iron overload and contributes to the initiation of ferroptosis, a process known as ferritinophagy.[48] NCOA4 functions as a ferritinophagy receptor, which interacts with an arginine residue in the C terminal domain of FTH1, leading to selective degradation of ferritin and increased Fe^{2+} level in the cytoplasm.[49] Under normal conditions, only a small amount of free iron forms the labile iron pool and regulates iron homeostasis.[50,51] Fe^{2+} can be released from the cell via SLC40A1 on the plasma membrane. Excessive intracellular iron levels can lead to reactive oxygen species (ROS) generation via the Fenton reaction, which promotes lipid peroxidation and ferroptosis. Mitochondrial iron accounts for 20–50% of the total intracellular iron depending on the cell type,[52] which also contains a free iron pool that participates in the production of mitochondrial ROS.[53,54] Factors that promote iron absorption, inhibit iron storage, or restricting iron efflux will lead to lipid peroxidation and ferroptosis[55] (Figure 1).

Integration of PUFAs into PLs

PUFAs are fatty acids that contain more than one unsaturated bond, such as C=C bonds. Unsaturated C=C bonds grant can be peroxidised. Free PUFAs can be directly synthetized from acetyl-CoA, which is catalysed by acetyl-coenzyme A carboxylase. Then PUFAs are converted into PUFA-CoA by acyl-CoA synthetase long-chain family member 1 (ACSL1) and ACSL4, and they bind to PLs via lysophosphatidylcholine acyltransferase 3 (LPCAT3). The conjunction of PUFAs to PLs is vital, because only when PUFA-PLs are oxidized can they break the membrane, and PUFA-OOH alone has no negative effects (Figure 2).

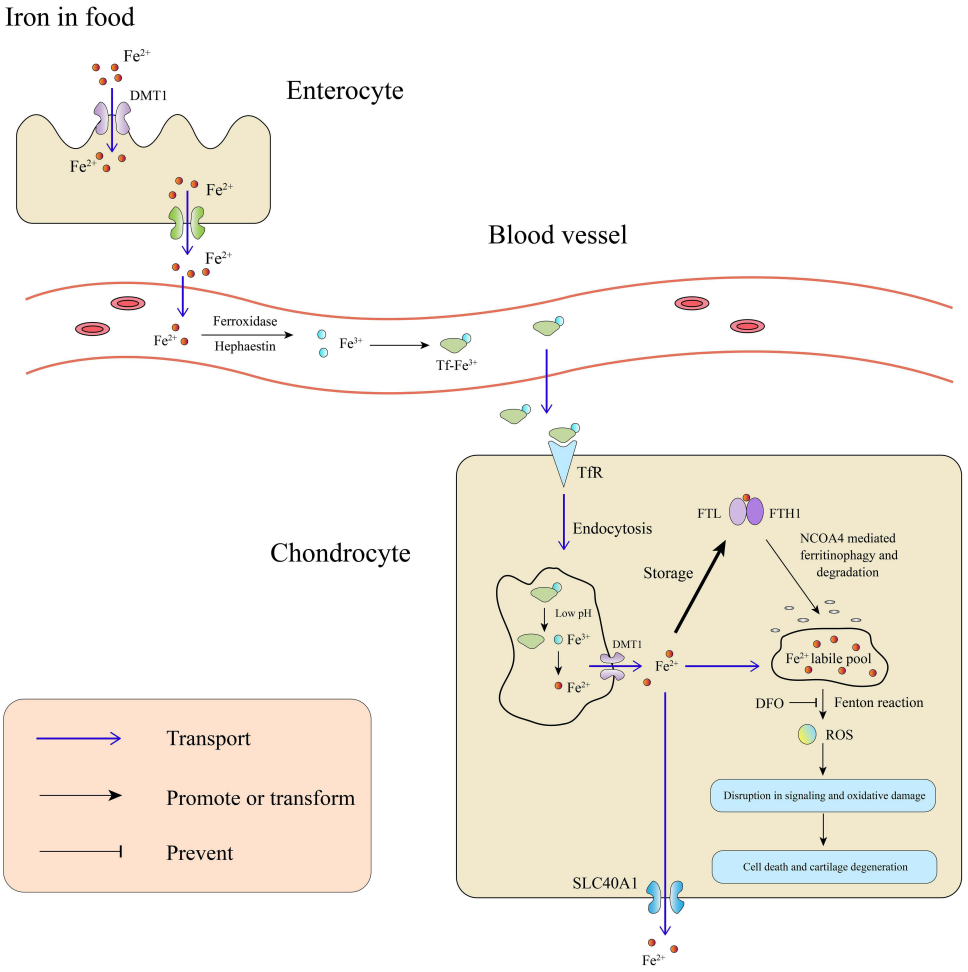

Figure 1 Iron metabolism. Iron in food is taken up by enterocytes in the form of Fe^{2+} via DMT1, and secreted into extracellular fluid via FPN. Fe^{2+} is oxidized into Fe^{3+} through the catalysis of ferroxidase and hephaestin, and binds with Tf, forming the Tf-Fe^{3+} complex. The Tf-Fe^{3+} complex is then circulated to peripheral tissues and cells via blood flow. Tf-Fe^{3+} is recognized by TfR on the cell membrane and taken up by the cell via endocytosis. Low pH in the endosomes can release Fe^{3+} from Tf and reduce Fe^{3+} into Fe^{2+}, and then Fe^{2+} in the endosome is released out via DMT1. The majority of intracellular iron is bound to ferritin, which consists of FTH1 and FTL and functions as iron storage. Only a small amount of free iron forms the labile iron pool and regulates iron homeostasis. Ferritin can be degraded through NCOA4-mediated autophagy named ferritinophagy, leading to increased Fe^{2+} level in the cytoplasm. Fe^{2+} can generate ROS via the Fenton reaction, ultimately resulting in lipid peroxidation. The ROS induce oxidative damage in cell membranes and organelles, as well as disturbances in homeostatic cell signal transduction, including the activation of pro-catabolic MAP kinase (p38 and ERK) signaling and the inhibition of pro-anabolic IGF-1 and BMP7 signaling through the inhibition of PI3K-Akt and Smads, ultimately leading to cell death and cartilage degeneration. DFO can inhibit the free Fe^{2+}-mediated Fenton reaction. Excess Fe^{2+} is excreted from the cell via SLC40A1.

Abbreviations: DMT1, divalent metal-ion transporter 1, a protein that assists in transmembrane transport of Fe^{2+}; FPN, ferroportin, a protein that assists in excreting Fe^{2+} from cells; Tf, transferrin, a protein that binds with Fe^{3+} and helps transfer it in the blood; TfR1, transferrin receptor 1, a receptor of Tf-Fe^{3+} complex on the cell membrane of the peripheral cells; FTL, ferritin light chain, a polypeptide chain combined with FTH1 and stores intracellular iron; FTH1, ferritin heavy chain 1, a polypeptide chain combined with FTL and stores intracellular iron; ROS, reactive oxygen species; DFO, deferoxamine, an iron chelator; SLC40A1, solute carrier family 40 member A1, a protein that assists in excreting Fe^{2+} from cells.

Peroxidation of PUFA-PLs

The accumulated PUFA-PLs can be oxidized by Fe^{2+} and endoperoxide compounds such as $FINO_2$. Several Fe^{2+}-dependent enzymes promote the change from PUFA-PL to PUFA-PL-OOH, including lipoxygenases (ALOXs), phosphatidylethanolamine binding protein 1 (PEBP1) and cytochrome p450 oxidoreductase (POR). Additionally, there are several secondary products, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA).[56] 4-HNE and MDA serve as reliable indicators of lipid peroxidation and ferroptosis in various diseases,[57] such as cancer,[58] neurodegenerative disease,[59] cardiac injury[60] acute kidney injury[61] and acute lung injury.[62] The accumulation of PUFA-PL-OOH can cause stiffening of the endoplasmic reticulum (ER) membrane.[63] Mitochondrial ROS can also oxidize PUFA-PLs on mitochondrial membranes, resulting in lipid peroxidation and mitochondrial DNA damage.[64] The mitochondrial membrane is affected by the destructive effect of lipid

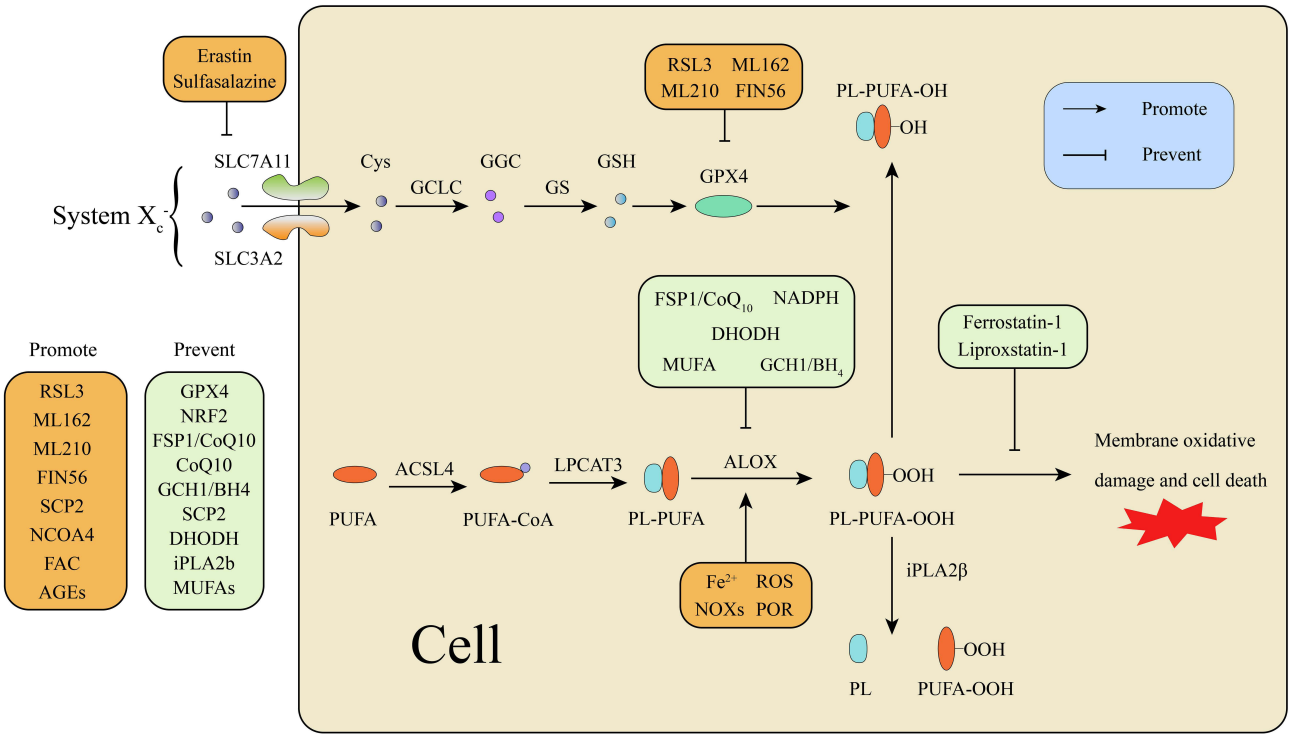

Figure 2 The process of lipid peroxidation and ferroptosis. System X_c^- are composed of two members, SLC7A11 and SLC3A2, which can take up cystine and discharge glutamate from the cell. Intracellular cystine ultimately participates in the synthesis of GPX4, a key negative regulator of ferroptosis. PUFAs are activated by LPCAT3 and ACSL4 and bind to PLs. Then, PUFAs are oxidized into PL-PUFA-OOH by ALOX and oxidants such as Fe^{2+}, ROS, NOXs, and POR. PL-PUFA-OOH ultimately results in membrane oxidative damage and cell death. GPX4 exerts its anti-ferroptotic effect by reducing PL-PUFA-OOH to PL-PUFA-OH. Its activity is inhibited by RSL3, ML162, ML210, and FIN56. Other inhibitors of ferroptosis act by preventing the production of PL-PUFA-OOH, such as FSP1/CoQ_{10}, NADPH, DHODH, MUFA and GCH1/BH_4. Moreover, the peroxidized PUFA-OOH tail can be trimmed from the phospholipid by iPLA2β, which can suppress the negative effects of PL-PUFA-OOH. Erastin and sulfasalazine promote ferroptosis by inhibiting the intake of cysteine through System X_c^-. RSL3, ML162, ML210 and FIN56 promote ferroptosis by inhibiting the activity of GPX4. Fe^{2+}, POS, NOXs, POR promote ferroptosis by stimulating the production of PL-PUFA-OOH. Conversely, FSP1/CoQ_{10}, NADPH, DHODH and GCH1/BH_4 prevent ferroptosis by inhibiting the the production of PL-PUFA-OOH; Finally, Ferrostatin-1 and Liproxstatin-1 prevent ferroptosis by mitigating the detrimental effects of PL-PUFA-OOH on the membrane.

Abbreviations: SLC7A11, solute carrier family 7 member 11; GPX4, Glutathione peroxidase 4; PUFA, Polyunsaturated fatty acid; Cys, cysteine; GCLC, glutamate-cysteine ligase catalytic subunit, which transforms cysteine into GGC; GGC, γ-glutamylcysteine, direct precursor of GSH; GS, glutamylcysteine synthase; GSH, glutathione; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PL, phospholipid; PL-PUFA, the conjunction of PUFAs to PLs; PL-PUFA -OH, the oxidized PL-PUFA; PL-PUFA-OOH, the peroxidized PL-PUFA; ALOXs, lipoxygenases; ROS, reactive oxygen species; POR, cytochrome P450 oxidoreductase; RSL3, RAS-selective-lethal-3; FIN56, ferroptosis-Inducer-56; FSP1, ferroptosis suppressor protein 1; CoQ_{10}, coenzyme Q10; NADPH, nicotinamide adenine dinucleotide phosphate; DHODH, dihydroorotate dehydrogenase; MUFA, monounsaturated fatty acid; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin; iPLA2b, phospholipase A2 group VI.

peroxidation products, leading to mitochondrial dysfunction.[55] However, the mechanisms through which lipid peroxides break the membranes and cause cell death are still unknown (Figure 2).

Negative Regulators of Ferroptosis

System X_c^- and GPX4 are the most important regulators that control ferroptosis. Several typical ferroptosis inducers, including erastin and sulfasalazine, exert their effects by inhibiting ferroptosis.[65] Located on the cell membrane, system X_c^- is composed of two members, solute carrier family 7 member 11 (SLC7A11) and SLC3A2. System X_c^- functions by taking up cystine and discharging glutamate from the cell.[66] Cystine and glutamate are used to synthesize GSH and GPX4. GPX4 is a GSH-dependent enzyme and is central to ferroptosis regulation by reducing reactive PUFA-PL-OOH to nonreactive and nonlethal PUFA-PL-OH.[65] The reduction of GSH can inactivate GPX4 and trigger Fe^{2+} for the Fenton reaction, leading to the accumulation of lipid peroxides and ferroptosis.[67] Genetic inactivation of GPX4 can induce lipid peroxidation and nonapoptotic cell death,[68] which is called ferroptosis. The overexpression of the light chain of system X_c^- protects cells from this nonapoptotic cell death.[69] Moreover, nuclear factor erythroid 2-related factor 2 (NRF2), an important transcriptional regulator of anti-ferroptotic genes such as GPX4 and System X_c^-, can prevent lipid peroxidation and the accumulation of free iron.[70] As a stress-inducible transcription factor, NRF2 translocates to the nucleus to

promote the transcription of antioxidant response element (ARE)-containing gene, most of which are responsible for preventing lipid peroxidation and ferroptosis.[70] NRF2 also maintains cellular iron homeostasis by controlling HERC2 (E3 ubiquitin ligase for NCOA4 and FBXL5) and VAMP8 (mediates autophagosome-lysosome fusion).[71]

There are other regulators that counteract ferroptosis and are independent of GPX4, such as ferroptosis suppressor protein 1 (FSP1)/ coenzyme Q10 (CoQ_{10}), dihydroorotate dehydrogenase (DHODH), and GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4). CoQ_{10} acts as an another endogenous mechanism against lipid peroxidation in addition to GPX4. FSP1 is responsible for regenerating CoQ_{10} by using nicotinamide adenine dinucleotide phosphate (NADPH).[72] iFSP1 was reported to competitively inhibit FSP1 enzyme activity[73] and 3-phenylquinazolinones (icFSP1) was newly identified to inhibit FSP1 by triggering subcellular relocalization of FSP1 from the membrane before ferroptosis induction.[74] CoQ_{10} protects against lipid peroxidation by being oxidized as a substitute for PUFA-PL. The amino acid oxidase interleukin-4-induced-1 (IL4i1), first recognized as a response to IL-4 in B cells, generates indole-3-pyruvate (In3Py), which prevents ferroptosis by clearing radicals and manipulating the relevant gene expression that alleviates ferroptosis.[75] GCH1 can generate the antioxidant BH4, whose functions are similar to CoQ_{10} in preventing lipid peroxidation.[76] In addition, GCH1 can restore the level of decreased CoQ_{10}, and eliminate PUFA-PLs, which are the precursors of PUFA-PL-OOHs and lead to ferroptosis.[77] DHODH was recognized as a mitochondrial inhibitor of ferroptosis that reduces ubiquinone to ubiquinol in mitochondria.[78] The depletion of DHODH results in excessive lipid peroxidation and ferroptosis in tumor cells.[78] High expression of DHODH or GCH1 endows cells with resistance to ferroptosis, while cells with low expression are more vulnerable to ferroptosis. Brequinar, a DHODH inhibitor, can suppress $GPX4^{low}$ tumor growth by inducing ferroptosis. When combined with sulfasalazine treatment, it can induce ferroptosis and suppress $GPX4^{high}$ tumor growth.[79,80] Moreover, phospholipase A2 group VI (iPLA2b) can suppress p53-related ferroptosis by trimming oxidized PUFA tails from PLs, and PUFA-OOH alone has no effect on ferroptosis.[81] Monounsaturated fatty acids (MUFAs) also show anti-ferroptotic effects in an ACSL3-dependent manner.[82]

Factors Aggravating Ferroptosis

The accumulation of intracellular iron could trigger ferroptosis, as we have mentioned above. Several factors promote ferroptosis by directly or indirectly inhibiting GPX4, including RAS-selective-lethal-3 (RSL3),[83] ML162, ML210 and ferroptosis-inducing-56 (FIN56) and so forth.[84,85] FINO2 accelerates ferroptosis by triggering the peroxidation of PUFA-PLs. SCP2 promotes chondrocyte ferroptosis by mediating the transport of cytoplasmic lipid hydroperoxides to mitochondria.[86] Nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy could control cellular iron levels,[87] and overexpression of NCOA4 promoted chondrocyte ferroptosis and aggravated posttraumatic OA.[88] Ferric ammonium citrate (FAC), a typical inducer of ferroptosis, could upregulate the expression of MMP-3, MMP-13, and ADAMTS-5 in chondrocytes by increasing intracellular iron and ROS levels.[30] Advanced glycation end products (AGEs) promote chondrocyte ferroptosis and OA progression by decreasing GSH expression and increasing intracellular ROS levels.[89]

Evidence of Ferroptosis in OA

Iron Metabolism in OA

Iron accumulation and dysfunction in iron homeostasis have been observed in OA patients. The iron concentration in the synovial fluid of osteoarthritic joints was markedly higher than that in healthy joints,[90] and another study revealed that the iron concentration in synovial fluid has positive correlation with OA severity.[32] The iron concentration in synovial fluid was increased in OA patients, but not in rheumatoid arthritis (RA) patients.[31] Iron deposition was also found in the osteoarthritic synovium, and more Fe^{3+}, Fe^{2+} and total iron deposition were found in osteoarthritic cartilage than in normal cartilage.[91] Serum ferritin and iron are indicators of the iron store level in total body, and serum ferritin levels were positively correlated with OA severity.[92,93] Increased serum ferritin levels were independent of age, sex, C-reactive protein levels, and body mass index.[93] Patients with hereditary haemochromatosis, whose body iron content is over-loaded, suffer from OA more frequently than healthy individuals.[94] The negative effects of iron overload (IO) were shown in an IO model by Jing et al,[31] and significant cartilage degeneration and subchondral bone destruction, and higher Osteoarthritis Research Society International (OARSI) scores were observed in the IO group, compared with the control

group. In addition, increased a ADAMTS5 and MMP13 expression was found in the IO group, indicating that iron overload contributed greatly to cartilage degeneration.[31] Moreover, Wu et al[95] proposed that proper iron intake was beneficial for slowing OA development, while both excessive and a lack of iron intake may increase the risk of OA. Nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy has been identified as a crucial mechanism for regulating cellular iron levels.[87] The JNK-JUN-NCOA4 axis contributes to chondrocyte ferroptosis and aggravates OA through ferritinophagy[88] (Figure 1).

Lipid Peroxidation in OA

4-HNE and MDA, two markers of oxidative stress and lipid peroxidation, are closely linked to OA development. Increased levels of 4-HNE and MDA were found in osteoarthritic synovial cells compared with normal synovial cells.[37] Additionally, higher levels of 4-HNE were found in the osteoarthritic synovial fluids.[96] Moreover, MDA and 4-HNE levels in OA cartilage were measured by immunostaining, revealing increased fluorescence intensity in the OA patient groups.[97] In animal models, higher levels of 4-HNE were found in the cartilage and synovial fluid of the surgery-induced OA dog model, and intraarticular administration of 4-HNE led to cartilage destruction and increased the expression of MMP13, ADAMTS5, and cyclooxygenase-2 (COX2) in dogs.[98] In addition to surgically induced OA models, monosodium iodoacetate (MIA)-induced OA models have also presented the evidence of lipid peroxidation.[99,100] These results support the role of lipid peroxidation in contributing to cartilage degeneration and OA development.

Ferric citrate (FAC), a ferroptosis inducer, increased MMP3 and MMP13 levels in chondrocytes, promoted chondrocyte apoptosis,[31] induced lipid ROS accumulation, and altered the expression of ferroptosis-related proteins including SLC7A11, GPX4, P53, NRF2-ARE and ACSL4.[101] FAC reduced intracellular calcium storage and promoted iron accumulation. Furthermore, FAC reduced the expression of MMP-13 and promoted the expression of FTH1 and FTL.[102] Erastin, another typical ferroptosis inducer, increased the expression of MMP13 and decreased the expression of type II collagen. Additionally, ferrostatin-1 (Fer-1) can protect chondrocytes from ferroptosis and ameliorate OA progression in an animal model.[101]

Changes in Key Ferroptosis Factors in OA

Decreased GPX4 and increased MDA levels were found in ACLT-induced osteoarthritic cartilage[103] and in the serum of Freund's adjuvant-induced OA rats.[104] Additionally, reduced GSH levels were found in the cartilage of the medial meniscus resection OA model[105], in the plasma of MIA-induced OA rats[99,100] and in the serum of OA patients.[106]

The loss of GPX4 is vital for OA pathogenesis. The expression of GPX4 in OA cartilage was markedly lower than that in undamaged cartilage.[32] GPX4 downregulation not only rendered chondrocytes more vulnerable to oxidative stress but also exacerbated cartilage degeneration via the MAPK/NF-κB pathway.[32] Moreover, the depletion of GPX4 by AAV-Gpx4 shRNA accelerated OA progression in posttraumatic OA mouse model.[32] The same result was obtained by conditional knockout of GPX4 in mouse cartilage in another study.[107] These findings indicated that OA development was accompanied by the loss of GPX4, which in turn promoted and exacerbated OA.

OA pathogenesis is closely related to mechanical overload and cartilage abrasion. Piezo1, a Ca^{2+} channel, is a mechanical sensor in OA that promotes cartilage degeneration and exacerbates OA development.[108–111] Therefore, another study investigated the relationship between Piezo1 and ferroptosis and concluded that inhibiting Piezo1 can increase GPX4 expression, alleviate the ferroptosis and attenuate the severity of OA. Further experiments revealed that Piezo1 affected GPX4 expression through Ca^{2+} influx.[107] However, transient receptor potential vanilloid 1 (TRPV1), another ion channel, inhibited ferroptosis by promoting GPX4 expression, and its anti-ferroptotic effect was markedly reduced in the $GPX4^{+/-}$ OA mouse model.[112] Liu et al[113] proposed that GPX4 was regulated by heat shock protein family A member 5 (HSPA5) and the RNA-binding protein SND1. HSPA5 directly binds to GPX4 and increases GPX4 expression. SND1 promotes GPX4 degradation by binding with HSPA5 at the 3′UTR and destabilizing HSPA5 mRNA.[113]

CoQ_{10} is another ferroptosis inhibitor that is independent of GPX4. Similar to GPX4, CoQ_{10} also exerts great potential in ameliorating OA. The administration of CoQ_{10} can ameliorate OA progression in GPX4-knockout mice.[107] CoQ_{10} alleviated cartilage degradation and pain in the MIA-induced OA rat model by regulating the production of nitric

oxide and inflammatory factors, including iNOS, IL-6, IL-1β, IL-15, MMP-13, RAGE and nitrotyrosine.[114] CoQ_{10} encapsulated in micelles slowed MIA-induced OA in rats by inhibiting inflammatory cell death. The inflammatory cell death markers pMLKL, RIP1 and RIP3 were markedly reduced in the synovium after CoQ_{10}-micelle administration.[115] Moreover, CoQ_{10} reduced IL-1β-induced inflammation by interfering with the MAPK signaling in rat chondrocytes.[116] These findings suggested a protective role of CoQ_{10} in OA.

Drugs Targeting Ferroptosis and Lipid Peroxidation in OA Treatment

In recent years, numerous compounds have been reported to be effective in preventing ferroptosis and slowing the progression of OA. Various iron chelators can be used in the treatment of iron overload. Among these, DFP, DFX, and DFO are significant. Each of these chelators has its own set of advantages and disadvantages. DFO, a nontoxic parenteral iron chelator, has been clinically approved and has shown efficacy in long-term iron chelation therapy. DFP, an oral iron chelator, could serve as a viable option for patients who have not responded to DFO or DFX. DFX has fewer gastrointestinal side effects and is more friendly to patients with high gastrointestinal sensitivity.[117,118] Patients taking DFP commonly experience gastrointestinal symptoms and agranulocytosis as the most prevalent adverse events.[119] Adverse events associated with DFO include growth retardation, skin reactions, ocular and auditory issues, allergic reactions, and bone abnormalities. Moreover, high doses have been linked to the observation of pulmonary and neurological disorders.[120] Intraarticular administration of deferoxamine (DFO) or Fer-1 twice per week for eight continuous weeks can attenuate OA development by preventing chondrocyte ferroptosis in ACLT-induced OA mouse models.[32] In addition, DFO abrogated the increase in the expression of MMP-13 and MMP-3 induced by interleukin-1beta (IL-1β).[31] Another study confirmed that DFO inhibited TNF-α, IL-1β, and type X collagen expression.[38] Lactoferrin, a naturally occurring iron chelator, can inhibit IL-1β-induced prostaglandin E2 (PGE2) production and COX2 expression in human osteoarthritic chondrocytes.[121]

Apart from iron chelators mentioned above, numerous compounds have shown efficacy in treating OA by affecting ferroptosis. Quercetin alleviated mitochondrial dysfunction by upregulating the AMPK/SIRT1 signaling pathway in OA rats.[105,122] Cashew nut administration reduced pain-like behavior and reversed cartilage damage in MIA-induced rats. In addition, cashew nuts showed antioxidant effects and could inhibit lipid peroxidation by restoring GSH, catalase and GPX levels.[123] Zinc protected chondrosarcoma cells from oxidative stress and slowed MIA-induced OA progression through Nrf2-mediated changes in antioxidants, cytokines and MMP.[106] D-mannose can protect chondrocytes by reducing the sensitivity to ferroptosis and preventing OA development.[103] The administration of collagen type III restored serum levels of MDA and GSH and ameliorated MIA-induced osteoarthritic radiographic images and histopathological changes in the joints.[100] Platelet-rich plasma (PRP) reduced serum lipid peroxides, GSH and glutathione S-transferase (GST) levels in MIA-induced osteoarthritic rats, suppressed joint inflammation and oxidative stress and ameliorated OA progression.[124] Astaxanthin retarded OA progression by inhibiting ferroptosis in chondrocytes.[125] Biochanin A protected osteoarthritic chondrocytes from iron overload by inhibiting TfR1, promoting FPN and regulating the System xc-/GPX4 axis.[126] Theaflavin-3,3′-digallate attenuated erastin-induced chondrocyte ferroptosis by regulating the NRF2/GPX4 pathway in OA.[127] Icariin promoted synovial cell survival after lipopolysaccharide (LPS) treatment by inhibiting ferroptosis via enhancing the SLC7A11/GPX4 signaling.[39,128] One recent study reported that lipoxin A4 mitigates the progression of knee OA in rats by counteracting ferroptosis through the activation of the ESR2/LPAR3/Nrf2 axis in synovial fibroblast-like synoviocytes.[129] Capsiate, a metabolite produced by the gut microbiota, suppressed the expression of HIF-1α and reduced ferroptosis-relative OA progression by activating SLC2A1.[130] Cardamonin mitigates chondrocyte inflammation and cartilage degradation in OA by suppressing ferroptosis through the p53 pathway.[131] Curcumin counteracts erastin-induced chondrocyte ferroptosis by increasing the expression of Nrf2.[132] Baicalein restricts the progression of OA by suppressing ferroptosis in chondrocytes through the AMPK/Nrf2/HO-1 signaling pathway.[133] Forkhead box O3 modulates ECM and ameliorates the progression of OA by inhibiting ferroptosis through the inactivation of NF-κB/MAPK signaling.[134] P21, an indicator of aging, resists ferroptosis in osteoarthritic chondrocytes by regulating the stability of GPX4. P21 significantly influenced the recruitment of GPX4 to the linear ubiquitin chain assembly complex (LUBAC) and regulated the level of M1-linked ubiquitination of GPX4. P21 knockdown aggravated cartilage degradation in DMM-induced OA mouse models.[135] Vitamin K2 attenuates OA by inhibiting ferroptosis and

ECM degradation through activating GPX4 and increasing intracellular GSH content.[136] Sarsasapogenin reduced chondrocyte ferroptosis and alleviated OA progression through the promotion of YAP1.[137,138] Another study showed that quercetin inhibited inflammation and apoptosis in chondrocytes and modulated synovial macrophage polarization to the M2 phenotype.[139] Vitamin E acted as an antioxidant and reduced the cartilage matrix degradation induced by H_2O_2 by inhibiting lipid peroxidation in chondrocytes.[36] N-acetyl cysteine (NAC) reversed the H_2O_2-induced GSH reduction[40] and IL-1β mediated enhancement of ADAMTS-5, MMP-3, and MMP-13 expression.[140] BAPTA-AM, a calcium chelator, can ameliorate iron overload-induced cartilage degeneration and mitochondrial dysfunction in chondrocytes.[30] FAC treatment markedly promoted the expression of MMPs and chondrocyte apoptosis, which could be reversed by BAPTA-AM. Moreover, BAPTA-AM suppressed iron influx into chondrocytes and reduced downstream ROS generation and mitochondrial dysfunction.[30] The efficacy of reducing Ca^{2+} influx in countering ferroptosis was also confirmed by knocking out the Ca^{2+} channel Piezo1.[107] Epigallocatechin-3-gallate (EGCG) and selenomethionine (SeMet) can efficiently synthesize polyphenol-based nanodrugs in aqueous media. These EGCG-based nanodrugs effectively reduce GPX4 inactivation, abnormal Fe^{2+} accumulation, and lipid peroxidation induced by oxidative stress, ultimately attenuating cartilage degradation in DMM-induced OA mouse models[141] (Table 1).

Table 1 Compounds Targets Ferroptosis or Lipid Peroxidation in the Treatment of OA on Animal Models or in vitro Cultured Chondrocytes

Compounds	Relation to ferroptosis	Effects on OA phenotypes	References
Ferrostatin-1	Inhibiting chondrocyte ferroptosis.	Attenuating the progression of OA in ACLT-induced OA mouse models.	[32]
Deferoxamine	Iron chelator which can reduce intracellular iron level.	Reversing the increased expression of MMP-3 and MMP-13 induced by IL-1β; Inhibiting IL-1β, TNF-α, and type X collagen expression.	[31,38]
Lactoferrin	Iron chelator which can reduce intracellular iron level.	Inhibiting IL-1β-induced COX2 expression and PGE2 production in human osteoarthritic chondrocytes.	[121]
Quercetin	Reducing the ROS levels and alleviating mitochondrial dysfunction; promoting SLC7A11 expression and GSH and GPX4 production.	Attenuating oxidative stress-induced rat chondrocyte apoptosis and retarded the progression of OA in a rat model; modulating synovial macrophages polarization to M2 macrophage and inhibiting inflammation.	[105,122,138,139]
Cashew nuts	Inhibiting lipid peroxidation by restoring GSH, catalase and GPX levels.	Reducing pain-like behavior and reversed cartilage damage in MIA-induced rat models.	[123]
D-mannose	Reducing the sensitivity of chondrocytes to ferroptosis.	Preventing the progression of OA.	[103]
Collagen type III	Restoring the serum levels of MDA, GSH.	Ameliorating MIA-induced osteoarthritic radiographic images and histopathological changes of the joints.	[100]
Platelet-rich plasma	Reducing serum lipid peroxides, GSH and glutathione S-transferase (GST) levels.	Suppressing joint inflammation and oxidative stress and ameliorating the progression of OA.	[124]
Astaxanthin	Inhibiting ferroptosis and regulating mitochondrial function.	Retarding the progression of OA.	[125]
Biochanin A	Protecting chondrocytes from iron overload by inhibiting TfR1, promoting FPN and regulating NRF2/System xc-/GPX4 axis.	Not mentioned.	[126]
Theaflavin-3,3′-Digallate	Attenuating erastin-induced chondrocyte ferroptosis by regulating NRF2/GPX4 pathway.	Alleviating in vivo cartilage damage related to chondrocyte ferroptosis.	[127]
Icariin	Suppressing ferroptosis via the Xc^-/GPX4 axis.	Promoting synovial cells survival under LPS treatment.	[39,128]

(*Continued*)

Table 1 (Continued).

Compounds	Relation to ferroptosis	Effects on OA phenotypes	References
Vitamin E	Inhibiting lipid peroxidation in the chondrocyte.	Reducing cartilage matrix degradation induced by H_2O_2.	[36]
N-acetyl cysteine	Reversing GSH reduction induced by H_2O_2.	Reducing MMP-3, MMP-13, and ADAMTS-5 expression.	[40,140]
BAPTA-AM	Suppressing iron influx into chondrocytes and inhibiting the downstream ROS production and mitochondrial dysfunction.	Reducing the production of MMPs induced by FAC and retarding cartilage degeneration.	[30]
Cardamonin	Promoting the expression of GPX4.	Mitigating chondrocyte inflammation and cartilage degradation.	[131]
Curcumin	Inhibiting chondrocyte ferroptosis by activating the Nrf2 signaling pathway.	Ameliorating the progression of OA.	[132]
Baicalein	Suppressing ferroptosis in chondrocytes through the AMPK/ Nrf2/ HO-1 signaling pathway.	Ameliorating the progression of OA.	[133]
Forkhead box O3	Inhibiting ferroptosis through the inactivation of NF-κB/MAPK signaling.	Modulating ECM metabolism to mitigate the progression of OA.	[134]
P21	Regulating the stability of GPX.	P21 knockdown aggravated cartilage degradation in DMM-induced OA mouse models.	[135]
Vitamin K2	Activating GPX4, increasing intracellular GSH content and the GSH/GSSG ratio, reducing MDA content, and rescuing chondrocyte ferroptosis.	Increasing cartilage thickness and reducing pain and the OARSI score.	[136]
EGCG-SeMet nanodrugs	Reducing GPX4 inactivation, abnormal Fe^{2+} accumulation, and lipid peroxidation induced by oxidative stress.	Attenuating cartilage degradation in DMM-induced OA mouse models.	[141]
Sarsasapogenin	Reducing chondrocyte ferroptosis through the promotion of YAP1.	Ameliorating the progression of OA in rats.	[137]
Lipoxin A4	Counteracting ferroptosis through the activation of the ESR2//LPAR3/Nrf2 axis in synovial fibroblast-like synoviocytes.	Ameliorating the progression of OA in rats.	[129]
Capsiate	Inhibiting ferroptosis.	Ameliorating the progression of OA in mice.	[130]

Discussions

Ferroptosis is related to an iron-dependent cell death characterized by chondrocyte dysfunction and lipid peroxidation.[142] It has been more than ten years since ferroptosis was first identified by Stockwell's team, and oxidative stress and lipid peroxidation have long been confirmed in osteoarthritic chondrocytes and synoviocytes. However, in the last two years, the role of lipid peroxidation and ferroptosis has started to be reconsidered and focused on OA. Lipid peroxidation, as shown by MDA levels, and 4-HNE-mediated downregulation of antioxidant system, as shown by GSH and GPX expression levels, establish the relationship between ferroptosis and OA. Changes in osteoarthritic cartilage in iron-overload models and iron accumulation and lipid peroxidation in OA models have been observed, and ferroptosis inhibitors can restore cartilage homeostasis. These findings indicate that ferroptosis is tightly linked to OA.

Two main pathways that control ferroptosis, the System X_c^- /cystine/GSH/GPX4 pathway and the FSP1/CoQ_{10} pathway, are related to OA, and the depletion of GPX4 can accelerate OA progression while supplementation with CoQ_{10} can relieve OA development. Many related findings support that ferroptosis is a negative biological process in chondrocytes and promotes OA progression. However, there are still some contradictory findings about ferroptosis and lipid peroxidation in OA. One study indicated a significant decrease in GPX4 expression within the cartilage of 55 OA patients compared to undamaged cartilage.[32] However, another study reported that GPX expression and its activity increased dose and time-dependently in IL-1β-treated bovine chondrocytes.[143] IL-1β result in a transient accumulation of H_2O_2 within the mitochondria, leading to subsequent damage to the mitochondria. The reason for the different changes in GPX expression in the two studies may be due to the different phases of OA. The acute inflammatory changes induced by

IL-1β in chondrocytes may not fully represent the natural pathogenesis of OA, which is chronic cartilage abrasion. IL-1β prompts an elevation in GPX4 expression to combat oxidative stress, potentially serving as a self-protective mechanism for chondrocytes. However, in the chronic and natural process of OA onset, GPX4 content decreases, ultimately contributes to an increase in ferroptosis and cartilage degeneration. Another study showed that intraarticular injection of sulfasalazine, a system X_c^- inhibitor, reduced GSH levels in chondrocytes and mitigated cartilage damage and knee swelling in a surgery induced rat OA model.[144] Moreover, OA patients exhibited markedly increased activity of glutathione transforming enzymes and all antioxidant enzymes in synovial fluid compared with the control groups.[145] The reason for the seemingly contradictory role of ferroptosis in OA pathogenesis is unclear, and different stages of OA may account for these differences. Specifically, in the preliminary OA stage, the elevated expression of antioxidant enzymes in OA patients may be attributed to a response to increased levels of these enzymes. This increase in antioxidants serves as a compensatory mechanism to prevent cartilage destruction. However, in the end stage of OA, these antioxidants may be overwhelmed by large amounts of ROS and oxidative stress.[146]

Although ferroptosis can lead to chondrocyte loss and death, it is not always a bad thing in OA. That is, the ferroptosis of normal chondrocytes promotes the progression of OA, while the ferroptosis of senescent cells may help alleviate OA. During the early stages of OA, ferroptosis of chondrocytes results in reduced synthesis of the cartilage matrix and increased cartilage degradation. However, in the late stages of OA, the detrimental impact of senescent chondrocytes outweighs the supportive role of cartilage matrix synthesis by normal chondrocytes. During this phase, ferroptosis may act as a senolytic which can eliminate senescent chondrocytes and preventing further progression of OA. Cellular senescence in chondrocytes contributes greatly to OA pathogenesis.[16,147–149] Selective elimination of senescent cells in a posttraumatic OA mouse model could ameliorate OA progression,[150] while intraarticular injection of senescent fibroblasts induced OA-like changes in mice.[151,152] Senescent cells are characterized by cell cycle arrest, resistance to apoptosis and continuous senescence-associated secretory phenotype (SASP) secretion[153]. Moreover, senescent chondrocytes were reported to be tolerant to ferroptosis in one recent study.[154] This resistance to ferroptosis may be attributed to the upregulation of membrane protein excitatory amino acid transporter protein 1 (EAAT1), which increases cellular glutamate levels and activates the glutathione system to resist ferroptosis. The administration of a UCPH-101, a specific inhibitor of EAAT1, or EAAT1-siRNA transfection largely increased the sensitivity of senescent chondrocytes to ferroptosis.[154] Intraarticular administration of UCPH-101, eliminated senescent chondrocytes from cartilage, and markedly delayed the progression of OA.[154] However, in addition to targeting senescence by inducing ferroptosis, ferroptosis inhibitors can also be effective in eliminating senescence. For example, quercetin can inhibit ferroptosis as mentioned previously. In fact, quercetin was one of the first discovered senolytics which is a group of drugs that selectively eliminate senescent cells.[147,155] Certainly, clearing senescent chondrocytes by selectively inducing ferroptosis in these cells is effective, whereas chondrocytes ferroptosis is collectively detrimental to OA pathogenesis.

There are also limitations of the current research on ferroptosis in OA. These studies mainly focused on chondrocyte ferroptosis but ignored other tissues in osteoarthritic joints, such as the synovium, infrapatellar fat pad and subchondral bone. As a highly heterogeneous cartilage degenerative disease, the etiology of OA can be very complicated.[156] Although chondrocytes are the predominant cells in cartilage, other tissues and cells also affect cartilage degeneration.[8] For example, regulated fibroblast growth factor (FGF) signaling is a vital for the homeostasis of cartilage, and abnormal FGF signaling contributes to the development of OA.[157] Osteoblast dysregulation also plays an important role in OA pathogenesis.[158] Senescent fibroblast-like synoviocytes greatly contribute to the inflammatory environment of the joint and can promote chondrocyte senescence by secreting SASP factors.[159] Moreover, synovial inflammation significantly contributes to OA pathogenesis, and the degree of synovitis is related to OA severity.[160,161] Macrophages are the main cells that contribute to synovial inflammatory environment, exacerbating OA and accelerating joint degeneration. M1 macrophages exert proinflammatory effects, while M2 macrophages exert anti-inflammatory effects.[162] This evidence indicates the role of other tissues and cells in the joint in regulating OA pathogenesis. Increased levels of 4-HNE and MDA were observed in osteoarthritic synovial cells and synovial fluid, suggesting that lipid peroxidation occurred in these tissues and cells apart from chondrocytes. Whether lipid peroxidation and ferroptosis in these cells affect OA pathogenesis remains unclear, and whether there is any crosstalk between these cells and chondrocytes further study. Future research should evaluate the role of ferroptosis in the entire joint cavity environment, especially synovial cells and

macrophages, to determine how it affects their metabolites and the interactions between cells, ultimately impacting the progression of OA. Additionally, conducting more comprehensive and detailed animal experiments, especially large animal experiments such as those involving dogs and monkeys, would be beneficial for evaluating the therapeutic effects and potential side effects of ferroptosis regulators in the treatment of OA.

Conclusions

The role of ferroptosis and lipid peroxidation in OA pathogenesis and development has gradually aroused the interest of researchers in recent years. Several drugs targeting ferroptosis have achieved preliminary progress in OA animal models. However, there is still a long way to go before we clearly understand how ferroptosis works and its regulation in osteoarthritic chondrocytes. In conclusion, targeting ferroptosis shows potential in the prevention and treatment of OA.

Abbreviations

OA, Osteoarthritis; ECM, extracellular matrix; GPX4, Glutathione peroxidase 4; DMT1, divalent metal-ion transporter 1; FPN, ferroportin; Tf, transferrin; TfR1, transferrin receptor 1; FTL, ferritin light chain; FTH1, ferritin heavy chain 1; ROS, reactive oxygen species; PUFA, Polyunsaturated fatty acid; ACSL1, acyl-CoA synthetase long-chain family member 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; PL, phospholipid; ALOXs, lipoxygenases; PEBP1, phosphatidylethanolamine binding protein 1; POR, phosphatidylethanolamine binding protein 1; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; ER, endoplasmic reticulum; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; RSL3, RAS-selective-lethal-3; FIN56, Ferroptosis-Inducer-56; FSP1, ferroptosis suppressor protein 1; CoQ_{10}, Coenzyme Q10; DHODH, dihydroorotate dehydrogenase; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin; NADPH, nicotinamide adenine dinucleotide phosphate; IL4i1, interleukin-4-induced-1; In3Py, indole-3-pyruvate; iPLA2b, phospholipase A2 group VI; MUFA, Monounsaturated fatty acid; RA, rheumatoid arthritis; OARSI, Osteoarthritis Research Society International; ADAMTS5, a disintegrin and metalloproteinase with thrombospondin 5; MMP13, matrix metalloproteinase-13; COX2, cyclooxygenase-2; MIA, monosodium iodoacetate; FAC, Ferric citrate; Fer-1, ferrostatin-1; TRPV1, transient receptor potential vanilloid 1; HSPA5, heat shock protein family A member 5; DFO, deferoxamine; IL-1β, interleukin-1beta; PGE2, prostaglandin E2; PRP, platelet-rich plasma; GST, glutathione S-transferase; LPS, lipopolysaccharide; NAC, N-acetyl cysteine; SASP, Senescence-associated secretory phenotype; EAAT1, excitatory amino acid transporter protein 1; FGF, fibroblast growth factor.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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