ISSN 2706-6819 Vol.5, Issue 3: 77-82, DOI: 10.25236/IJFM.2023.050314

Iron accumulation in ferroptosis and the role of lipid peroxidation in osteoarthritis

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Abstract: *Ferroptosis is a recently discovered mode of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides, which can reach lethal levels, but this process was found to be inhibited by ferroptosis inhibitor-specific reverse. Osteoarthritis (OA) is the most common degenerative joint disease characterized by complex pathogenesis including mechanical overload, elevated levels of inflammatory mediators, metabolic alterations, and cellular senescence and death. Since iron accumulation and oxidative stress are common pathological features of OA, the role of ferroptosis in OA has been extensively explored. Accumulating evidence indicates that iron homeostasis and lipid peroxidation are closely related to the pathogenesis of OA. This article will focus on the mechanisms of ferroptosis and the role of iron homeostasis and lipid peroxidation in the pathogenesis of OA, summarizing recent evidence.*

Keywords: *ferroptosis; iron accumulation; lipid peroxidation; osteoarthritis*

1. Overview of Ferroptosis and Osteoarthritis

Osteoarthritis (OA) is the most common degenerative joint disease, affecting 7% of the global population [1]. The incidence and prevalence of OA are gradually increasing due to reasons such as population aging, increasing life expectancy, and increasing obesity [2]. OA is a global joint disease whose etiology and pathogenesis are complex and have not yet been clarified, but the key role of cartilage degeneration in OA has been recognized [3]. Chondrocytes, the only cell type in cartilage, are critical for the biogenesis and maintenance of the extracellular matrix consisting of type II collagen (COL2), hyaluronic acid, and chondroitin sulfate proteoglycans [4]. Loss of homeostasis in cartilage contributes to the development of OA when chondrocyte synthetic capacity is overwhelmed by processes that promote matrix degradation.

Oxidative stress plays an important role in OA, leading to joint inflammation and matrix degradation. ROS generation and subsequent lipid peroxidation are related to the antioxidant capacity of chondrocytes and play a key role in cartilage degradation and chondrocyte death [5-7]. Lipid peroxidation, usually leading to the formation of lipid hydroperoxide, occurs under oxidative stress. In recent years, a newly identified form of regulated cell death, ferroptosis, has been reported to be implicated in OA pathogenesis, characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels. Yao et al[8] first pointed out that chondrocytes undergo ferroptosis under conditions of inflammation and iron overload, ferroptosis contributes to the progression of OA in vivo, promotes the expression of matrix metalloproteinase (MMP)-13, and simultaneously inhibits the expression of chondrocytes cultured in vitro Expression of COL2 in . Miao et al. [9] found that iron accumulates in cartilage and synovial fluid during OA progression, and biomarkers of the peroxidative defense system, including glutathione peroxidase (GPX) 4 (GPX4) and glutathione peroxidase (GPX4) Expression of glutathione (GSH) levels) was reduced in these patient samples. In addition, as a characteristic change of ferroptosis, morphological changes of mitochondria in OA cartilage were also observed by transmission electron microscopy, indicating that ferroptosis is closely related to OA.

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2. Main features of ferroptosis

Ferroptosis differs from apoptosis, autophagy, and necrosis in terms of cell morphology, biochemistry, and genetics. Ferroptotic cells are morphologically characterized by mitochondrial ultrastructural abnormalities, including reduced mitochondrial volume, increased mitochondrial membrane density, and loss of mitochondrial cristae in ferroptotic cells, as demonstrated by electron microscopy [10]. Iron accumulation and lipid peroxidation are increasingly recognized as central mediators of ferroptosis. The subsequent formation of lipid hydroperoxides and the reduction of antioxidant systems directly lead to ferroptosis [11]. Furthermore, a genetic network distinct from other modes of cell death controls ferroptosis.

2.1 Iron homeostasis and ferroptosis

Systemic iron homeostasis is maintained by balancing iron supply, utilization, and loss. Iron is mainly used for erythropoiesis, iron enters the circulatory system through reticuloendothelial macrophages, reticuloendothelial macrophages recycle iron from aged red blood cells and duodenal small intestinal cells at a rate of 20-25 mg per day, duodenal Cells absorb 1–2 mg of dietary iron per day [12]. Absorbed iron is transported into enterocytes by the divalent metal ion transporter 1 (DMT1) [13], and then exported to the blood by ferroportin (FPN), which works with the ferroxidase hephaestine, The latter oxidizes ferrous (Fe2+) to ferric (Fe3+), binding transferrin (Tf) [14,15]. Tf-bound iron circulates throughout the body, delivering iron to peripheral tissues. The loss rate of iron is 1 mg per day, mainly through epithelial cell shedding and body fluid loss. Hepcidin, a key regulator of systemic iron homeostasis, is a small circulating peptide mainly produced by hepatocytes that binds to FPN on enterocytes, macrophages, and other cells, triggering FPN degradation and blocking iron export. [16]

In the circulation, Tf-bound Fe3+ is taken up by cells through receptor-mediated endocytosis after Tf binds to the membrane protein transferrin receptor (TfR) 1 (TfR1) [17]. In the transferrin cycle, iron bound to transferrin (Tf) binds to the transferrin receptor (Tfr1), the complex is taken up by receptor-mediated endocytosis, iron is released from Tf by endosomal acidification, Delivery to cytoplasmic metal transporter 1 (Dmt1)2–4 via a bivalent transporter. Tf carries ferric iron (Fe3+), while Dmt1 is selective for ferrous (Fe2+)4. The major erythrocyte ferrous reductase of Tf recycling endosomes is Steap3 [18]. Then, Fe2+ endosomes are imported into the cytoplasm through DMT1. Most intracellular iron is bound to ferritin, an iron storage protein complex consisting of ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1) [19]. Small amounts of unbound iron include labile iron pools that play a role in regulating iron homeostasis [20]. FPN-mediated iron efflux works in conjunction with the multi-copper iron oxidase hephaestine, which oxidizes Fe2+ to iron3+, which binds Tf.

Excess iron can lead to ROS generation through the Fenton reaction and activation of iron-containing enzymes (such as lipoxygenase) that promote lipid peroxidation and lead to ferroptosis. Thus, ferroptosis is promoted by increasing iron uptake, decreasing iron storage, or limiting iron efflux, and iron chelators can therefore prevent ferroptosis. Feng et al. [21] detected ferroptotic cells using an anti-3F3 iron optical membrane antibody (3F3-FMA) and found that 3F3-FMA is a TfR1 antigen; thus, they concluded that TfR1 accumulation on the cell surface is a feature of ferroptosis. In a study of baicalin-induced ferroptosis in vitro and in vivo, Kong et al. [22] found higher levels of intracellular chelated iron after FTH1 overexpression in bladder cancer cells, suggesting that baicalin-induced ferroptosis is accelerated by downregulating FTH1 expression. Bao et al. [23] found a ferroptosis phenotype in the brains of Alzheimer's disease (AD) model mice, in which ferroptosis was induced by downregulation of FPN expression. In contrast, FPN overexpression in the hippocampus partially attenuated iron mortality and improved memory impairment in AD model mice. Indeed, directly increasing exogenous iron supply, for example via ferric ammonium citrate (FAC), enhanced erastin-induced ferroptosis, while iron chelators such as deferoxamine (DFO) suppressed ferroptosis, thereby reducing iron overload.

2.2 Lipid peroxidation and ferroptosis

Ayala et al. [24] summarized lipid peroxidation as the process by which oxidizing agents such as free radicals or ROS attack lipids containing carbon-carbon double bonds, especially polyunsaturated fatty acids (PUFAs). Overall, lipid peroxidation involves three steps: initiation, propagation and termination. Once lipid peroxidation begins, the chain reaction continues until a terminating product is produced. The major primary product of lipid peroxidation is lipid hydroperoxide, and the major secondary products are malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [25]. Due to its high reactivity

ISSN 2706-6819 Vol.5, Issue 3: 77-82, DOI: 10.25236/IJFM.2023.050314

and reliability, MDA is a commonly used clinical biomarker of oxidative stress. 4-HNE is currently considered to be a major bioactive marker of lipid peroxidation and a signaling molecule involved in the regulation of stress-sensitive transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2) in the regulation of cell proliferation, differentiation, and death. In ferroptosis, MDA and 4-HNE are reliable markers of oxidative stress-induced lipid peroxidation in cancer, AD and acute lung injury [26]

In general, ferroptosis is triggered when lipid peroxidation production exceeds the antioxidant buffer capacity of the cellular antioxidant system. At least three antioxidant systems control ferroptosis: the cystine/GSH/GPX4 axis, the ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) axis, and cyclohydrolase 1/tetrahydrobiopterin/dihydrofolate reduction enzyme axis. The cystine/glutathione/GPX4 axis is the most commonly targeted pathway that triggers the ferroptosis cascade [27]. Cystine is the raw material for GSH synthesis, and the cystine/glutamate anti-transport system Xc− on the cell membrane usually mediates the exchange of extracellular cystine and intracellular glutamate. GPX4 is a GSH-dependent enzyme that converts reduced GSH to oxidized glutathione (GSSG) and simultaneously reduces lipid hydroperoxides to the corresponding lipid alcohols or free hydrogen peroxide (H2O2) [28]. Disruption of C−-mediated cystine uptake by System X or depletion of glutathione leads to inactivation of GPX4, allowing accumulation of lipid peroxides and thus triggering ferroptosis. FSP1 is localized in the plasma membrane and acts as an NAD(P)H-dependent oxidoreductase that can reduce CoQ10 and capture lipid peroxyl radicals, thereby inhibiting lipid peroxidation and ferroptosis [29].

Downregulation of antioxidant system activation has been reported to be associated with ferroptosis. In studying a genetically engineered mouse model, Badgley et al. [30] reported that deletion of solute carrier family 7, member 11 (SLC7A11, systemic xc− subunit) induced ferroptosis in tumor cells, with median survival compared with vehicle treatment Rate doubled, and mice treated with the antioxidant N-acetylcysteine (NAC) exhibited a recovery from baseline survival and abolished tumor responses, supporting a link to cystine metabolism. [31] found that inhibition of GPX4 by DL-buthionine-S, R-sulfoximine (BSO, a GSH-depleting reagent) sensitized cells to death induced by 12 different compounds, whereas cDNA overexpression Activation of GPX4 rescued cells from lethality induced by these compounds, suggesting that ferroptosis is mediated through a GPX4-regulated pathway. Bersuker et al. [32] studied hundreds of cancer cell lines and found that FSP1 expression was positively correlated with ferroptotic defense, and that FSP1 suppressed ferroptosis by reducing CoQ10 levels in cultured lung cancer cells and mice bearing tumor xenografts.

Potential link between ferroptosis and osteoarthritis

3. Potential link between iron homeostasis and osteoarthritis

3.1 Potential association between iron homeostasis and osteoarthritis

Sun et al. comprehensively evaluated iron homeostasis disturbance in clinical hemophilic arthropathy and hereditary hemochromatosis arthropathy [33]. Iron accumulation and associated disturbances of iron homeostasis have been identified in patients with primary OA. Yazar et al. [34] found that iron ion levels in synovial fluid at the OA site were significantly increased in OA patients compared with healthy subjects. In addition, iron deposition has also been found in the synovium of OA patients [35]. In the circulatory system, serum iron and ferritin are indicators of the level of systemic iron stores. A Mendelian two-sample randomization analysis showed that serum iron was positively associated with an increased risk of unspecified OA in men [36], and a similar association was found in women with OA. In performing a genome-wide association study and pathway analysis, Liu et al. [37] reported that the iron ion transport pathway was significantly associated with knee osteoarthritis in African Americans. Nugzar et al. [38] evaluated the correlation between serum ferritin levels assessed by arthroscopic examination and the severity of cartilage damage in patients with knee OA and found that serum ferritin levels increased with the severity of cartilage damage, these results are consistent with Age, sex, body mass index, and C-reactive protein levels were not correlated, suggesting that ferritin may be actively involved in the progression of cartilage damage in patients with symptomatic knee OA. Kennish et al. [39] found that higher serum ferritin levels were positively associated with Kellgren-Lawrence stage worsening in the general OA population, especially in OA men.

Furthermore, iron intake appears to be associated with OA progression. They concluded that adequate iron intake is desirable for the prevention of OA progression, whereas excess or deficient iron

ISSN 2706-6819 Vol.5, Issue 3: 77-82, DOI: 10.25236/IJFM.2023.050314

intake increases the risk of OA progression.

3.2 Potential link between lipid peroxidation and osteoarthritis

The level of oxidative stress, represented by MDA and 4-HNE, is closely related to OA progression. In 2003, Grigolo et al. [40] evaluated the degree of lipid peroxidation in synoviocytes of OA patients and controls by colorimetric assay, and found that the levels of MDA and 4-HNE in synoviocytes of OA group were compared with those of control group Increase. They hypothesized that this peroxidative process might be due to the action of nitric oxide (NO) secreted by chondrocytes, leading to elevated free radical levels in OA. Elevated levels of 4-HNE have also been found in the synovial fluid of OA patients [41]. Furthermore, Shah et al. performed immunohistochemical staining and detected MDA and 4-HNE in OA tissues as well as weak immunostaining of the cartilage surface in normal cartilage sections. Gavriilidis et al. also found that the level of MDA in OA cartilage was higher than that in control cartilage when measuring thiobarbituric acid-reactive substances.[42]

Downregulation of antioxidant system activity has been detected in OA patients. Regan et al. [43] detected decreased levels of GSH and GSSG in the synovial fluid of 27 OA patients and 12 patients who underwent arthroscopic examination of macroscopically intact cartilage knees. Maneesh et al. [44] found that the plasma levels of GSH and GPX were decreased in OA patients compared with healthy controls. Miao et al. found decreased levels of GPX, GSH and GSH/GSSG in OA cartilage.

Vitamin E is a well-known lipophilic antioxidant that reduces cellular lipid peroxide levels and prevents ferroptosis [45]. Notably, vitamin E levels were inversely associated with OA progression. Specifically, Sutipornpalangkul et al. [46] found that the vitamin E concentration in the synovial fluid of 32 patients was inversely correlated with the severity of primary knee OA, suggesting that oxidative stress increases with the clinical severity of OA. A similar study later confirmed this result. With regard to the therapeutic effect of vitamin E supplementation, Bhattacharya et al. [47] conducted a cohort study in which they estimated 40 healthy individuals (control group) and 40 OA patients aged 50–70 before and after 3 months of vitamin E supplementation. Antioxidant enzymes (such as GPX and MDA in plasma) levels; patients were divided into group I (no supplementation) and group II (200 mg/day vitamin E supplementation). Compared with the control group, OA patients without vitamin E supplementation had decreased GPX and increased MDA levels, and OA patients with vitamin E supplementation had significantly increased GPX levels.

4. Summary and Outlook

In conclusion, since ferroptosis is involved in the progression of OA, regulation of iron homeostasis and control of lipid peroxidation offer therapeutic options for OA. The iron chelator DFO and the antioxidants Fer-1 and CoQ10 showed significant anti-OA effects both in vitro and in vivo. There are few studies on the mechanism of ferroptosis in OA. This article reviews the concept and characteristics of ferroptosis, explores the possible mechanism of ferroptosis in OA, and further provides help for the prevention and treatment of OA. As a newly discovered type of cell death, ferroptosis is closely related to OA. May play an important role in the occurrence and development of OA. The regulation mechanism of OA ferroptosis and effective methods to regulate ferroptosis need to be explored urgently, so as to provide a theoretical basis for the prevention and treatment of OA.

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