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Review Article

Ferroptosis In Orthopedic Diseases: A Novel Therapeutic Target In Osteoarthritis And Bone Degeneration

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ABSTRACT

Ferroptosis represents an iron-dependent mechanism of regulated cellular demise, distinguished by significant iron accumulation, lipid peroxidation, oxidative stress, reduced glutathione levels, and diminished glutathione peroxidase 4 (GPX4) function. Accumulating data points to the crucial involvement of ferroptosis in the etiology and evolution of multiple orthopedic ailments, including osteoarthritis, osteoporosis, osteonecrosis, intervertebral disk degeneration, and deficient fracture healing. Ferroptosis in osteoarthritis accelerates chondrocyte mortality, extracellular matrix disintegration, and cartilage damage through augmented oxidative stress and lipid peroxidation. In the context of osteoporosis, iron deposition intensifies oxidative stress, facilitates the demise of osteoblasts, and heightens osteoclast activity, resulting in continuous bone loss. Likewise, ferroptosis is linked to osteocyte impairment in osteonecrosis and the loss of nucleus pulposus cells in intervertebral disk degeneration, while excessive oxidative stress could obstruct fracture repair. Strategies for treating ferroptosis involve the use of iron chelators, ferroptosis inhibitors, antioxidants, the activation of GPX4, and the engagement of the NRF2 pathway. Investigational drugs like deferoxamine, ferrostatin-1, liproxstatin-1, melatonin, vitamin E, N-acetylcysteine, and selenium have exhibited potential safeguarding effects. Nonetheless, insufficient human clinical data, unclear long-term safety, the lack of targeted biomarkers, and obstacles in drug administration continue to pose substantial difficulties. More clinical research is needed to determine the treatment potential of ferroptosis modulation in orthopedic ailments.

INTRODUCTION

Musculoskeletal ailments are a primary source of disability worldwide. Disorders like osteoarthritis,

osteoporosis, intervertebral disk degeneration, and osteonecrosis profoundly influence mobility and life quality. Aging, inflammation, obesity, and mechanical strain are established factors to these

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ailments; nevertheless, mounting data indicates that cell death driven by oxidative stress is essential in the progression of the diseases.¹ Ferroptosis is a specific mode of regulated cell death that is contingent upon iron and is both visually and biochemically dissimilar to apoptosis, necrosis, pyroptosis, and autophagy. It was first discovered in 2012 by Scott J. Dixon and his team. The defining features of ferroptosis consist of intracellular iron accumulation, elevated lipid peroxidation, mitochondrial diminishment, and a decline in antioxidant protection. It causes the mortality of chondrocytes, osteoblasts, osteocytes, and nucleus pulposus cells in orthopedic tissues, expediting the decline of cartilage, loss of bone, and tissue integrity. As a result, the control of ferroptosis has been identified as a viable treatment target in musculoskeletal illnesses.²

WHAT IS FERROPTOSIS?

Ferroptosis constitutes an iron-dependent mechanism of orchestrated cell death resulting from an overaccumulation of lipid hydroperoxides. Significant attributes consist of excessive iron, lipid oxidation, a proliferation of reactive oxygen species, GPX4 inhibition, glutathione scarcity, decreased mitochondrial function, heightened membrane density, and cell membrane impairment. Unlike apoptosis, ferroptosis is characterized by the absence of caspase activation and DNA fragmentation.³

MOLECULAR MECHANISM OF FERROPTOSIS

A. Iron Metabolism

The metabolism of iron is the principal trigger and contributor to the process of ferroptosis. The main iron-transport protein in plasma is transferrin, which attaches to circulating ferric iron (Fe^{3+}). The transferrin-iron complex binds to the

transferrin receptor 1 (TfR1) on the cell surface, leading to its internalization via receptor-mediated endocytosis. Enzymes known as ferrireductases, such as six-transmembrane epithelial antigen of the prostate 3 (STEAP3), facilitate the reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) in the endosomal compartment. The released Fe^{2+} is integrated into the intracellular labile iron pool, which acts as an accessible reservoir of redox-active iron. An excess of ferrous iron promotes the Fenton reaction, during which Fe^{2+} combines with hydrogen peroxide (H_2O_2) to produce highly reactive hydroxyl radicals ($\cdot\text{OH}$). The presence of hydroxyl radicals promotes the peroxidation of polyunsaturated fatty acids (PUFAs) in the phospholipids of cellular membranes, causing an increase in detrimental lipid peroxides.⁴ In the end, the antioxidant protective mechanism was surpassed, preventing the effective detoxification of lipid peroxides and culminating in ferroptosis, a controlled iron-dependent cell death distinguished by oxidative damage to lipid membranes.

B. Lipid Peroxidation

Lipid peroxidation, a key phenomenon in ferroptosis, is chiefly connected to polyunsaturated fatty acids (PUFAs), which are very prone to oxidative injury owing to their numerous double bonds. At the outset, Acyl-CoA synthetase long-chain family member 4 (ACSL4) initiates the activation of free polyunsaturated fatty acids (PUFAs) and transforms them into PUFA-CoA derivatives.⁵ Lysophosphatidylcholine acyltransferase 3 (LPCAT3) then catalyzes the esterification of these activated fatty acids into membrane phospholipids. Lipoxygenases (LOXs) oxidize phospholipids rich in polyunsaturated fatty acids (PUFAs) to produce lipid hydroperoxides. An overabundance of these oxidized lipids undermines the structural soundness and operational capacity of cellular membranes,



culminating in membrane breakdown and cell mortality. If these lipid peroxides are not eradicated by antioxidant defenses, membrane deterioration ensues, resulting in ferroptosis cell death.^{6,7}

C. Antioxidant Defence

The principal cellular protective mechanism against ferroptosis is the System Xc glutathione (GSH)–glutathione peroxidase 4 (GPX4) antioxidant pathway. The exchange of intracellular glutamate for extracellular cystine is mediated by System Xc⁻, which functions as a cystine/glutamate antiporter. Cysteine, serving as

the rate-limiting precursor for the production of glutathione (GSH), the principal intracellular antioxidant, is formed through the reduction of cystine inside the cell.⁸ GPX4, a selenoenzyme, safeguards cells by converting dangerous lipid hydroperoxides into harmless lipid alcohols and requires glutathione as a cofactor. Membrane stability is upheld, cell longevity is supported, and the formation of lipid reactive oxygen species (ROS) is thwarted. Conversely, if GPX4 action is hindered or System Xc⁻ is repressed, levels of glutathione decline and lipid hydroperoxides cannot be neutralized.^{9,10}

BIOMARKERS OF FERROPTOSIS

Table -1

Biomarker	Role
GPX4	Decreased
ACSL4	Increased
Lipid ROS	Increased
MDA	Increased
4-HNE	Increased
Fe ²⁺	Increased
Ferritin	Altered
SLC7A11	Decreased
PTGS2	Increased

FERROPTOSIS IN OSTEOARTHRITIS

Osteoarthritis (OA) is a chronic joint ailment that advances gradually, distinguished by the degradation of extracellular matrix integrity and articular cartilage. Current research suggests that ferroptosis substantially influences the advancement of OA through the induction of chondrocyte mortality and the breakdown of cartilage.¹⁸ In osteoarthritis, there is an elevated production of pro-inflammatory cytokines, notably interleukin-1 β (IL-1 β), in response to inflammatory stimuli.¹¹ This amplifies the generation of reactive oxygen species (ROS) and

interferes with cellular iron balance. The accumulation of iron leads to excessive lipid peroxidation, which in turn exacerbates oxidative stress and lowers the activity of glutathione peroxidase 4 (GPX4). The development of lipid peroxides leads to the ferroptosis of chondrocytes, which are the key cells tasked with sustaining cartilage equilibrium. Osteoarthritis advances as cartilage is incrementally damaged owing to the loss of chondrocytes, which hastens the disintegration of collagen and proteoglycans in the extracellular matrix.^{12,13.}

EFFECTS ON CHONDROCYTES



Ferroptosis impedes chondrocyte operations and the stability of the extracellular matrix, causing cartilage degeneration. It elevates the expression of matrix-degrading enzymes including matrix metalloproteinase-13 (MMP-13) and a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5), while diminishing the formation of type II collagen, a crucial structural part of articular cartilage.^{16,20} The extracellular matrix slowly vanishes as a consequence of the escalating activity of these enzymes, promoting the disintegration of proteoglycans and collagen. Ferroptosis obstructs the conservation and repair of cartilage while reducing chondrocyte viability. In conclusion, these degenerative modifications expedite the progression of osteoarthritis by the erosion of cartilage.^{16,21}

FERROPTOSIS IN OSTEOPOROSIS

The persistent physiological activity of bone remodelling demands a precise harmony between osteoblasts responsible for forming new bone and osteoclasts tasked with dismantling old bone. The presence of excessive iron disturbs this equilibrium, leading to a reduction in new bone synthesis by inducing osteoblast mortality and hindering their performance. An overabundance of iron increases oxidative stress through the production of reactive oxygen species, which aggravates bone cell impairment and enhances osteoclast formation and activity.^{14, 15, 24} The advancement of bone loss is attributed to both augmented osteoclastic resorption and reduced osteoblastic synthesis of bone. Thus, a reduction in bone mineral density occurs, undermining bone architecture and eventually contributing to the emergence and development of osteoporosis.

FERROPTOSIS IN OSTEONECROSIS

The phenomenon of ferroptosis in bone tissue arises from steroid-induced osteonecrosis, connected to alterations in iron metabolism,

vascular impairment, and increased oxidative stress. Impaired vascular function leads to decreased blood flow and worsens oxidative harm, whereas surplus iron accumulation heightens the synthesis of reactive oxygen species and lipid peroxidation.¹⁵ These modifications stimulate osteocyte ferroptosis, culminating in the progressive necrosis of bone and the death of bone cells. Addressing ferroptosis pathways might represent a viable treatment option for steroid-induced osteonecrosis, given that experimental findings suggest that regulating ferroptosis could mitigate osteocyte damage and bone necrosis.

FERROPTOSIS IN INTERVERTEBRAL DISC DEGENERATION

The hallmark indicators of intervertebral disk degeneration are extracellular matrix breakdown, ongoing inflammation, and the mortality of nucleus pulposus cells. The presence of iron in nucleus pulposus cells leads to ferroptosis through the elevation of oxidative stress and the stimulation of excessive lipid peroxidation. Inflammatory reactions intensify damage to disk tissue, while the reduction of these cells disturbs the equilibrium of the extracellular matrix and hastens its disintegration. Thus, ferroptosis and iron-related oxidative stress are pivotal in the development of intervertebral disk degeneration.^{15,29}

FERROPTOSIS IN FRACTURE HEALING

In the early phases of bone repair, managing reactive oxygen species (ROS) levels is helpful for cellular signalling and tissue regeneration. In contrast, significant oxidative stress can trigger ferroptosis, resulting in increased osteoblast apoptosis and a decline in bone synthesis. Furthermore, ferroptosis might reduce angiogenesis, which would constrain the delivery of blood and critical nutrients necessary for tissue



recovery. Thus, suboptimal fracture healing is ultimately attributed to decreased osteoblast longevity and inadequate vascularization, hindering the process of bone reconstruction.^{16,30}

THERAPEUTIC TARGETS

A. Iron Chelators

By reducing the intracellular labile iron reservoir, iron chelation provides an effective treatment option for averting ferroptosis. By chelating surplus iron, deferoxamine (DFO) diminishes the formation of reactive oxygen species (ROS) and lipid peroxidation induced by iron. DFO could safeguard bone cells and facilitate bone repair by diminishing oxidative stress and obstructing ferroptosis.

B. Ferroptosis Inhibitors

Musculoskeletal tissues could be safeguarded against oxidative harm by the direct regulation of ferroptosis. Ferrostatin-1 serves as a ferroptosis inhibitor that reduces cartilage degeneration, protects chondrocytes against ferroptotic cell death, and suppresses lipid peroxidation. Likewise, liproxstatin-1 functions as a robust ferroptosis inhibitor that reduces oxidative cellular harm, fosters GPX4-mediated antioxidant defense, and limits the accumulation of lipid peroxides.

C. Antioxidants

Compounds like melatonin, vitamin E, N-acetylcysteine, and coenzyme Q10 may defend cells against ferroptosis by diminishing oxidative stress and surplus ROS generation. These agents curtail lipid oxidation and avert the formation of

toxic lipid peroxides in cellular membranes. Thus, antioxidant therapy might inhibit ferroptotic cell mortality and safeguard musculoskeletal tissues against oxidative harm.^{17,25}

D. GPX4 Activation

Glutathione peroxidase 4 (GPX4) is a significant antioxidant enzyme that prevents ferroptosis by reducing toxic lipid hydroperoxides. By augmenting GPX4 activity, cells can be safeguarded against ferroptotic mortality and the rise of lipid peroxides. Examples of potential methods include selenium supplementation, pharmacological modifications of GPX4 activity, and gene therapy procedures designed to augment GPX4 expression or function.¹⁹

E. NRF2 Activation

NRF2, known as nuclear factor erythroid 2-related factor 2, is a crucial transcription factor that regulates cellular antioxidant defense mechanisms. When NRF2 is activated, there is an increased expression of antioxidant and cytoprotective genes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and solute carrier family 7 member 11 (SLC7A11). The heightened activity of SLC7A11 facilitates cystine absorption and glutathione synthesis, which bolsters GPX4 performance and diminishes lipid peroxidation. Thus, the stimulation of the NRF2-driven antioxidant pathway may avert ferroptosis and provide a viable therapy option for musculoskeletal ailments.²²

CURRENT EXPERIMENTAL DRUGS

Table -2

Drug	Mechanism	Disease
Ferrostatin-1	Lipid ROS inhibitor	Osteoarthritis
Liproxstatin-1	Ferroptosis inhibitor	OA, IVDD



Deferoxamine	Iron chelator	Osteoporosis
Melatonin	Antioxidant	OA
Vitamin E	Lipid antioxidant	OA
N-acetylcysteine	Restores glutathione	Bone degeneration
Selenium	GPX4 activation	Osteoporosis

CHALLENGES

The role of ferroptosis in musculoskeletal conditions is becoming increasingly clear, but its practical application is hindered by several obstacles. At present, human clinical studies remain few, and the bulk of the data is sourced from in vitro and animal experimentation. Ongoing research is focused on the long-term safety and probable negative effects of ferroptosis inhibitors.²³ At now, there are no recognized, specific biomarkers for the clinical identification and observation of ferroptosis. Another major impediment is the transportation of medications to tissues that are poorly supplied with blood, like bone and cartilage. Medications aimed targeting ferroptosis should thus be transitioned into clinical settings through supplementary clinical studies and refined drug delivery systems.²⁶

FUTURE PERSPECTIVES

Future investigations ought to focus on translating knowledge connected to ferroptosis into effective treatment solutions for musculoskeletal disorders. The performance and safety of ferroptosis inhibitors in ailments like osteoarthritis and osteoporosis should be examined via rigorously structured clinical trials. Methods of drug delivery utilizing targeted nanoparticles could augment the administration of therapeutic drugs to bone and cartilage. The discovery of dependable circulating biomarkers may enhance the early detection and surveillance of ferroptosis-related disorders. Techniques for gene editing that focus on significant ferroptosis regulatory pathways,

including NRF2, SLC7A11, and GPX4, may present innovative therapy possibilities. In addition, the amalgamation of ferroptosis inhibition with regenerative medical approaches, including tissue engineering and stem cell therapy, may yield superior clinical results and foster tissue regeneration.²⁷

CONCLUSION

A variety of orthopedic conditions, such as osteoarthritis, osteoporosis, osteonecrosis, intervertebral disk degeneration, and suboptimal fracture healing, have been connected to ferroptosis. The demise of chondrocytes, osteoblasts, and osteocytes is induced by dysregulated iron metabolism, lipid peroxidation, oxidative stress, and a reduction in GPX4, resulting in gradual tissue decline. Experimental results suggest that the pharmacological inhibition of ferroptosis by the use of iron chelators, lipid peroxidation inhibitors, antioxidants, and activators of GPX4 or NRF2 can diminish tissue damage and bolster the integrity of bone and cartilage. Although the outcomes seem optimistic, rigorously designed human studies are required to validate safety, effectiveness, and the most effective treatment strategies before they can be integrated into ordinary clinical practice. Thus, addressing ferroptosis provides a unique and promising treatment avenue for orthopedic ailments.

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