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REVIEW ARTICLE

Targeting ferroptosis: A novel therapeutic avenue in osteoarthritis and bone degeneration

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Abstract

Osteoarthritis (OA) and bone degeneration are progressive musculoskeletal disorders that compromise joint function, cause chronic pain, and reduce quality of life in aging populations. While current therapeutic approaches aim to manage symptoms, there remains a significant unmet need for disease-modifying treatments. Ferroptosis, a distinct iron-dependent form of regulated cell death characterized by lipid peroxidation, has emerged as a crucial pathological mechanism in multiple degenerative diseases. Recent advances suggest that ferroptosis contributes to chondrocyte death, subchondral bone remodeling, and the inflammatory milieu observed in OA and other bone degenerative conditions. This review consolidates current knowledge on the molecular mechanisms linking ferroptosis to bone tissue pathology, highlights key regulatory pathways involved, and discusses emerging therapeutic interventions aimed at modulating ferroptotic activity. We also explore the potential of ferroptosis-targeting agents as novel disease-modifying drugs in OA and bone degeneration, and outline future research directions and translational implications.

1. Introduction

Osteoarthritis, the most prevalent form of arthritis, is characterized by the progressive degradation of articular cartilage, subchondral bone sclerosis, osteophyte formation, and synovial inflammation (Chen et al., 2017). Despite its multifactorial etiology including mechanical, genetic, metabolic, and inflammatory components. The recent evidence has pointed to ferroptosis as a critical contributor to OA pathogenesis. Similarly, bone degenerative diseases such as osteoporosis and avascular necrosis show pathological hallmarks that may be partially driven by oxidative stress and ferroptotic cell death (C. Zhang et al., 2023). Ferroptosis differs fundamentally from apoptosis, necrosis, and autophagy in its requirement for iron and accumulation of lipid peroxides, which cause oxidative damage and compromise cellular membrane integrity (Endale et al., 2023). The discovery of this cell death pathway provides a new dimension in understanding bone pathology and opens novel avenues for therapeutic targeting.

2. Molecular Mechanisms of Ferroptosis in Bone Cells

Ferroptosis is initiated when the balance between lipid peroxide generation and antioxidant defenses of glutathione (GSH) and glutathione peroxidase 4 (GPX4) is disrupted (Forcina and Dixon, 2019; Kuang et al., 2020). In bone and cartilage cells, excess free iron catalyzes the Fenton reaction, generating reactive oxygen species (ROS) that oxidize membrane polyunsaturated fatty acids (PUFAs) (Zhang et al., 2022). The inactivation of GPX4 impairs cellular ability to detoxify lipid peroxides, resulting in oxidative stress and ferroptotic cell death (Latunde-Dada, 2017). In chondrocytes, this oxidative burden disrupts cartilage matrix homeostasis, decreases the expression of collagen type II and aggrecan, and increases matrix metalloproteinases (MMPs), accelerating cartilage breakdown. Additionally, osteoblasts and osteocytes exposed to iron overload exhibit reduced viability and bone-forming capacity (H. Zhang et al., 2023), further supporting ferroptosis' involvement in bone degeneration (Figure 1).

3. Ferroptosis and Subchondral Bone Remodeling

Subchondral bone plays a central role in the development and progression of OA. The early phase of OA is often marked by increased bone turnover, leading to trabecular bone loss followed by sclerosis (Tamimi et al., 2020). Ferroptosis may contribute to this abnormal bone remodeling through its impact on osteoblasts, osteoclasts, and bone marrow stromal cells (Yan et al., 2022). In particular, osteoclasts is responsible

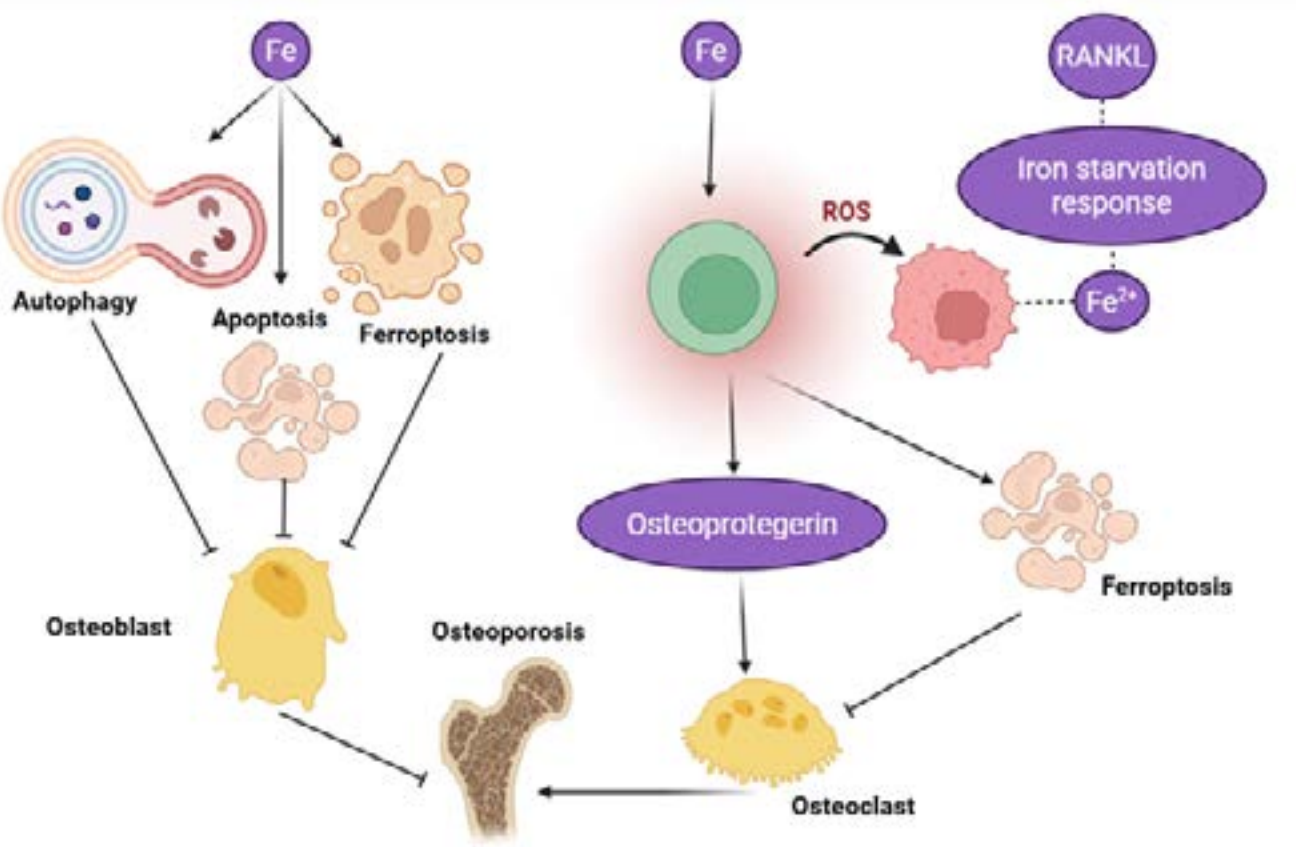

Figure 1: Ferroptosis and its Implications in Osteoarthritis and Bone Degeneration. The diagram illustrates the role of iron (Fe) in regulating various forms of cell death—autophagy, apoptosis, and ferroptosis—and its subsequent impact on osteoblast and osteoclast function. Excess iron induces oxidative stress through reactive oxygen species (ROS), contributing to cell damage and ferroptosis. In osteoblasts, ferroptosis, apoptosis, and autophagy impair bone formation and promote osteoporosis. On the osteoclast side, iron-mediated ROS production influences osteoprotegerin expression, which normally inhibits osteoclast differentiation. Disruption of this regulation promotes osteoclast activity and bone resorption. Additionally, the RANKL-induced iron starvation response contributes to ferroptosis in osteoclasts. Overall, iron dysregulation and ferroptosis contribute significantly to bone degeneration and osteoarthritis pathophysiology.

Table 1: Key Regulators and Molecular Events in Ferroptosis Related to OA and Bone Degeneration

Component	Function	Implication in OA/Bone Degeneration
GPX4	Antioxidant enzyme that detoxifies lipid peroxides	Downregulated in OA cartilage, promoting chondrocyte ferroptosis
Iron (Fe2+/Fe3+)	Cofactor in ROS generation via Fenton reaction	Elevated in synovial fluid and subchondral bone, induces oxidative damage
ACSL4	Facilitates PUFA incorporation into phospholipids	Upregulated in damaged chondrocytes, sensitizes to ferroptosis
TfR1	Mediates cellular iron uptake	Overexpressed in OA tissues, increases intracellular iron load
FPN	Iron exporter	Decreased expression leads to iron accumulation in osteoblasts

for bone resorption. It may be differentially affected by iron metabolism and lipid peroxidation, influencing the delicate balance of bone homeostasis. Dysregulation in iron transporters such as transferrin receptor (TfR1) and ferroportin (FPN) in bone cells alters intracellular iron levels, exacerbating susceptibility to ferroptosis (Ru et al., 2024). Targeting these pathways may thus offer therapeutic benefit in restoring subchondral bone integrity

4. Role of Ferroptosis in Inflammatory Microenvironment

Inflammation is a key driver of joint degeneration in OA. Recent findings reveal that ferroptotic cells release damage-associated molecular patterns (DAMPs), including HMGB1, which can activate pattern recognition receptors on synovial macrophages and perpetuate local inflammation (Valentí et al., 2023; Wen et al., 2019). Furthermore, iron

Table 2: Therapeutic Strategies Targeting Ferroptosis in OA and Bone Degeneration

Agent	Mechanism	Therapeutic Role
Ferrostatin-1	Lipid ROS scavenger	Reduces chondrocyte ferroptosis and cartilage damage in models
Deferoxamine	Iron chelation	Protects osteoblasts from iron-induced cytotoxicity
Liproxstatin-1	Lipid peroxide inhibitor	Inhibits ferroptosis and inflammation in OA models
N-acetylcysteine	GSH precursor	Enhances antioxidant capacity, restores redox balance
Nrf2 activators	Induces cellular defense genes	Mitigates oxidative stress and promotes chondrocyte survival

accumulation in synovial tissues amplifies pro-inflammatory cytokine production, including IL-1β and TNF-α, which further promote cartilage catabolism and synovial hyperplasia (Cai et al., 2022; Jing et al., 2021). These observations suggest a vicious cycle in which inflammation and ferroptosis mutually reinforce each other, exacerbating tissue damage. Thus, inhibiting ferroptosis may not only preserve structural integrity but also attenuate synovitis and inflammation in OA.

5. Therapeutic Targeting of Ferroptosis in OA and Bone Degeneration

Pharmacological inhibition of ferroptosis has gained interest as a therapeutic approach in degenerative diseases. Ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 have shown protective effects in preclinical models of cartilage injury and bone loss (Cheng et al., 2024; Xu et al., 2023). These agents act by scavenging lipid ROS or enhancing GPX4 activity. Moreover, iron chelators such as deferoxamine reduce iron-induced oxidative stress and protect against chondrocyte and osteoblast ferroptosis (Wang et al., 2022). Nutritional antioxidants (e.g., vitamin E, N-acetylcysteine) and upregulation of Nrf2 signaling also represent promising strategies. Given their diverse mechanisms, combination therapies targeting multiple ferroptotic regulators may yield synergistic benefits. Importantly, the specificity, bioavailability, and safety of these agents must be carefully evaluated in translational and clinical studies.

6. Challenges and Future Directions

Despite promising data, several challenges remain in the clinical translation of ferroptosis-targeted therapies. First, the heterogeneity of OA and bone degenerative diseases necessitates precise stratification of patients based on ferroptotic markers. Second, long-term inhibition of ferroptosis may disrupt physiological iron homeostasis and antioxidant responses, leading to unintended effects. Therefore, context-dependent modulation rather than broad suppression of ferroptosis is crucial. Future research should focus on identifying specific biomarkers of ferroptosis in synovial fluid and serum, validating imaging techniques to track ferroptosis in vivo, and developing tissue-targeted delivery systems for ferroptosis inhibitors.

7. Conclusion

Ferroptosis represents a novel and promising therapeutic target in osteoarthritis and bone degeneration. By elucidating the mechanisms underlying iron-dependent lipid peroxidation and their impact on cartilage and bone integrity, new strategies can be developed to modify disease progression. The development of ferroptosis-targeted interventions, guided by robust biomarkers and patient-specific approaches, has the potential to transform the management of these debilitating musculoskeletal disorders.

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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Author contribution

Conceptualization: S.N, Data curation, Investigation: S.P, V.M.R. Writing—review and editing: S.N. All authors have read and agreed to the published version of the manuscript

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Reference

1. Cai, C., Hu, W., Chu, T., 2022. Interplay Between Iron Overload and Osteoarthritis: Clinical Significance and Cellular Mechanisms. Front. Cell Dev. Biol. 9. https://doi.org/10.3389/fcell.2021.817104
2. Chen, D., Shen, J., Zhao, W., Wang, T., Han, L., Hamilton, J.L., Im, H.-J., 2017. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res. 5, 16044. https://doi.org/10.1038/boneres.2016.44
3. Cheng, B., Zhang, J., Shen, Q., Sun, Z., Luo, Y., Hu, Y., 2024. Liproxstatin-1 alleviates cartilage degradation by inhibiting

chondrocyte ferroptosis in the temporomandibular joint. Biol. Cell 116. https://doi.org/10.1111/boc.202300042
4. Endale, H.T., Tesfaye, W., Mengstie, T.A., 2023. ROS induced lipid peroxidation and their role in ferroptosis. Front. Cell Dev. Biol. 11. https://doi.org/10.3389/fcell.2023.1226044
5. Forcina, G.C., Dixon, S.J., 2019. GPX4 at the Crossroads of Lipid Homeostasis and Ferroptosis. Proteomics 19. https://doi.org/10.1002/pmic.201800311
6. Jing, X., Du, T., Li, T., Yang, X., Wang, G., Liu, X., Jiang, Z., Cui, X., 2021. The detrimental effect of iron on OA chondrocytes: Importance of pro-inflammatory cytokines induced iron influx and oxidative stress. J. Cell. Mol. Med. 25, 5671–5680. https://doi.org/10.1111/jcmm.16581
7. Kuang, F., Liu, J., Tang, D., Kang, R., 2020. Oxidative Damage and Antioxidant Defense in Ferroptosis. Front. Cell Dev. Biol. 8. https://doi.org/10.3389/fcell.2020.586578
8. Latunde-Dada, G.O., 2017. Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy. Biochim. Biophys. Acta - Gen. Subj. 1861, 1893–1900. https://doi.org/10.1016/j.bbagen.2017.05.019
9. Ru, Q., Li, Y., Chen, L., Wu, Y., Min, J., Wang, F., 2024. Iron homeostasis and ferroptosis in human diseases: mechanisms and therapeutic prospects. Signal Transduct. Target. Ther. 9, 271. https://doi.org/10.1038/s41392-024-01969-z
10. Tamimi, I., Cortes, A.R.G., Sánchez-Siles, J.-M., Ackerman, J.L., González-Quevedo, D., García, Á., Yaghoubi, F., Abdallah, M.-N., Eimar, H., Alsheghri, A., Laurenti, M., Al-Subaei, A., Guerado, E., García-de-Quevedo, D., Tamimi, F., 2020. Composition and characteristics of trabecular bone in osteoporosis and osteoarthritis. Bone 140, 115558. https://doi.org/10.1016/j.bone.2020.115558
11. Valentí, V., Capdevila, L., Ruiz, I., Ramos, J., Badía, J., Blázquez, S., Villuendas, Ó., Pérez, C., Fernández-Sender, L., Córdoba, M., Alonso-Villaverde, C., 2023. Variation of Plasma Damage-Associated Molecular Patterns in Patients with Advanced Solid Tumors after Standard of Care Systemic Treatment. Cancer Invest. 41, 821–829. https://doi.org/10.1080/07357907.2023.2283458
12. Wang, W., Jing, X., Du, T., Ren, J., Liu, X., Chen, F., Shao, Y., Sun, S., Yang, G., Cui, X., 2022. Iron overload promotes intervertebral disc degeneration via inducing oxidative stress and ferroptosis in endplate chondrocytes. Free Radic. Biol. Med. 190, 234–246. https://doi.org/10.1016/j.freeradbiomed.2022.08.018
13. Wen, Q., Liu, J., Kang, R., Zhou, B., Tang, D., 2019. The release and activity of HMGB1 in ferroptosis. Biochem. Biophys. Res. Commun. 510, 278–283. https://doi.org/10.1016/j.bbrc.2019.01.090
14. Xu, W., Zhang, B., Xi, C., Qin, Y., Lin, X., Wang, B., Kong, P., Yan, J., 2023. Ferroptosis Plays a Role in Human Chondrocyte of Osteoarthritis Induced by IL-1β In Vitro. Cartilage 14, 455–466. https://doi.org/10.1177/19476035221142011
15. Yan, C., Zhang, J., An, F., Wang, J., Shi, Y., Yuan, L., Lv, D., Zhao, Y., Wang, Y., 2022. Research Progress of Ferroptosis Regulatory Network and Bone Remodeling in Osteoporosis. Front. Public Heal. 10. https://doi.org/10.3389/fpubh.2022.910675
16. Zhang, C., Li, H., Li, J., Hu, J., Yang, K., Tao, L., 2023. Oxidative stress: A common pathological state in a high-risk population for osteoporosis. Biomed. Pharmacother. 163, 114834. https://doi.org/10.1016/j.biopha.2023.114834
17. Zhang, H., Wang, A., Li, G., Zhai, Q., Huang, Z., Wang, X., Cao, Z., Liu, L., Liu, G., Chen, B., Zhu, K., Xu, Ying, Xu, Youjia, 2023. Osteoporotic bone loss from excess iron accumulation is driven by NOX4-triggered ferroptosis in osteoblasts. Free Radic. Biol. Med. 198, 123–136. https://doi.org/10.1016/j.freeradbiomed.2023.01.026
18. Zhang, S., Xu, J., Si, H., Wu, Y., Zhou, S., Shen, B., 2022. The Role Played by Ferroptosis in Osteoarthritis: Evidence Based on Iron Dyshomeostasis and Lipid Peroxidation. Antioxidants 11, 1668. https://doi.org/10.3390/antiox11091668