Journal of Biomed Research

Zhang Y, et al., J Biomed Res. 2026;7(1):13-16.

Mini Review

Molecular network regulation and precision therapy frontiers in osteoarthritis: from ferroptosis to autophagy metabolic reprogramming

Yue Zhang[1–5,#,*], Huichang Zhang[1,#], Xiaoying Zhu[1,2,#], Bohong Gao[1,#], Kamel Meguellati[6,*], Cibo Huang[7,8,*]

[1]Shenzhen Futian Hospital for Rheumatic Diseases, Shenzhen, Guangdong, China

[2]Department of Rheumatology and Immunology, The First Clinical College of Harbin Medical University, Harbin, China

[3]Shenzhen Weilan Translational Institute of Biomicromolecules Research, Shenzhen, Guangdong, China

[4]Hezhou Dongrong Yao Medicine Research Institute, Joint Institute of Shenzhen University and Hezhou Hospital for Traditional Chinese Medicine, Hezhou, Guangxi, China

[5]Integrated Chinese and Western Medicine Research Institute, TORAMI Avatar Longevity and Healthcare Hub, Zheng He Hospital, Changsha, Hunan, China

[6]College of Pharmacy, Jinan University, Guangzhou, China

[7]Department of Rheumatology, Immunology and Gerontology, South-China Hospital of Shenzhen University, Shenzhen, China

[8]Department of Rheumatology and Immunology, National Center of Gerontology, Beijing Hospital, Beijing, China

[#]Contributed equally

*Author for correspondence: Email: humanoids101@163.com, kameljilin@yahoo.fr, huangcibo1208@139.com

Abstract

Osteoarthritis (OA), the most prevalent degenerative joint disease, involves intricate molecular interactions across joint tissues. This review highlights advancements in understanding OA pathogenesis, focusing on the ferroptosis-autophagy axis and the therapeutic potential of Coenzyme Q10 (CoQ10). By integrating and reviewing multi-omics technologies, novel diagnostic tools, and targeted therapies, this review underscores the shift toward precision medicine in OA management.

Keywords: Osteoarthritis, Ferroptosis, Metabolic reprogramming, CoQ10

Introduction

So far, we have no cure for osteoarthritis (OA)—the most common disease of the joints, affecting over 500 million individuals globally, a chronic degenerative joint pathology with a global prevalence of 22.9% in individuals aged 40 and over, characterized by progressive cartilage degradation, synovitis, and subchondral bone remodeling [1–4]. Traditional therapies focus on symptom management, but recent insights into molecular mechanisms—particularly ferroptosis and metabolic reprogramming—have redefined therapeutic strategies [5–9]. This review synthesizes advances in OA pathogenesis, diagnostic innovations, and the multi-target role of CoQ10, emphasizing its potential in precision medicine [10].

Pathogenesis of Osteoarthritis: A Multidimensional Perspective

Dynamic tissue imbalance and molecular drivers

OA progression involves cross-talk among cartilage, synovium, and subchondral bone [6,11,12]. These cells secrete IL-6 and MMP-13, perpetuating a pro-inflammatory microenvironment [13]. Mechanical stress and its link to ATP synthesis via mitochondrial oxidants in articular cartilage indicates abnormal mechanical stress can impair chondrocyte mechanosensitivity [14]. Furthermore, Ji *et al.* [15] used single-cell RNA sequencing to uncover the progression of human osteoarthritis and Zhang *et al.* [16] suggested that reprogramming of the mitochondrial respiratory complex, particularly targeting the SIRT3-COX4I2 axis, might be a strategy to slow OA progression.

Diagnostic innovations

OA diagnostic innovations emerge for early detection. The application of artificial intelligence (AI) to magnetic resonance imaging (MRI) with high-resolution T2 mapping predicts cartilage degeneration years in advance [17]. Additionally, we previously reported that a high-fat diet accelerates osteoarthritis and is associated with a distinct plasma metabolite signature, with AI playing

an empowering role in this context [18]. Furthermore, Roemer *et al.* [19] analyzed the association of knee OA structural phenotypes with progression risk through a secondary analysis from the Foundation for National Institutes of Health Osteoarthritis Biomarkers study (FNIH).

Ferroptosis-Autophagy Axis and Its Core Regulatory Networks

Studies of the ferroptosis-autophagy axis and its core regulatory networks explore the mechanisms and potential therapeutic applications of this axis. Yi *et al.* [20] investigated novel pH-responsive lipid nanoparticles delivering UA-mediated mitophagy and ferroptosis for osteoarthritis treatment. Jiang *et al.* [21] reviewed the mechanisms, biology, and role of ferroptosis in disease. Li *et al.* [22] demonstrated that mitochondria transplantation could transiently rescue cerebellar neurodegeneration by improving mitochondrial function and reducing mitophagy in mice. Chen *et al.* [23] showed that mitochondrial transplantation could rescue neuronal cells from ferroptosis.

Ferroptosis in OA pathogenesis

Several key molecules, including GPX4 and FSP1, inhibit ferroptosis. Ferroptosis is implicated in various diseases. Recent studies have explored the mechanisms of ferroptosis in disease models including OA, a common joint disorder characterized by cartilage degradation and chondrocyte death, particularly of interest to societies like China with increasing burden of elderly population with OA. Lv *et al.* [24] used single-cell RNA-seq analysis to identify a ferroptotic chondrocyte cluster and revealed TRPV1 as an anti-ferroptotic target in osteoarthritis. Wang *et al.* [25] found that mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. Dixon *et al.* [5] first introduced the term ferroptosis to describe a novel form of non-apoptotic cell death and identified ferrostatin 1 as the first specific inhibitor of ferroptosis. Doll *et al.* [26] demonstrated that ACSL4 shapes cellular lipid composition and dictates ferroptosis sensitivity. Ernster & Dallner [27] discussed the biochemical, physiological, and medical aspects of ubiquinone function. Fang *et al.* [28] provided an overview of the molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Lian *et al.* [29] found that histone H3K27 demethylase UTX compromises articular chondrocyte anabolism and aggravates osteoarthritic degeneration.

Autophagy in OA

Autophagy plays a complex role in osteoarthritis (OA), depending on the stage of disease. In early OA, AMPK/ULK1 activation enhanced autophagic flux, helping clear damaged mitochondria. However, in late OA, overactivation of mTORC1 signaling contributes to disease progression and reduces autophagosome-lysosome fusion efficiency [30]. SIRT1 directly activates autophagy in human chondrocytes [31], while targeting the SIRT3-COX4I2 axis can reprogram mitochondrial respiratory chain complexes and attenuate OA progression [16]. Additionally, autophagy defects may cause cartilage damage during joint aging in mouse models [13]. Recent advances, such as AI-driven drug design and 3D-bioprinted joint models, offer novel solutions for drug screening and therapy development. CoQ10 has its role in mitigating mitochondrial damage through autophagy promotion [23].

Critical interaction nodes

NCOA4-mediated ferritinophagy axis

Interaction nodes in cellular processes regulate iron homeostasis and oxidative stress responses. The selective autophagy receptor NCOA4 coordinates iron homeostasis through ferritinophagy [32], a process that directs ferritin complexes to lysosomal degradation. The NCOA4-mediated ferritinophagy axis plays a key role in directing ferritin complexes to lysosomal degradation, thereby influencing iron levels and contributing to ferroptosis [33]. The p62/SQSTM1-Keap1-Nrf2 axis acts as a molecular rheostat, organizing antioxidant responses to electrophilic stress through phase-separated condensates. Additionally, the HIFs regulatory machinery, particularly HIF-2α, is involved in skeletal growth and osteoarthritis development through transcriptional regulation of endochondral ossification [34]. Mechanistic insights reveal that V-ATPase assembly factor TMEM9B stabilizes V0-V1 domain interactions, with its deficiency leading to lysosomal alkalinization and ferroptosis in renal tubular cells [35]. These findings highlight the complex interplay between autophagy, iron metabolism, and redox signaling in cellular homeostasis and disease.

Coenzyme Q10: A Multi-Target Therapeutic Agent

Mechanisms of action

It possesses antioxidant properties that neutralize lipid peroxyl radicals [36] and enhances mitochondrial optimization by restoring Complex I/III activity and increasing ATP production [37]. CoQ10-loaded nanoparticles have shown efficacy in improving OA by modulating inflammation and mitochondrial dynamics [38]. Additionally, CoQ10 performs epigenetic modulation [23]. Research indicates associations between CoQ10 status, oxidative stress, and muscle strength/endurance in OA patients [38]. CoQ10 also prevents interleukin-1 beta-induced inflammatory responses by inhibiting MAPK signaling pathways in rat articular chondrocytes [10]. Furthermore, Bersuker *et al.* [39] highlighted the role of CoQ oxidoreductase FSP1 in acting parallel to GPX4 to inhibit ferroptosis.

Synergistic therapeutic strategies

Research explores synergistic therapies combining autophagy-targeted nanoparticles with ferroptosis or apoptosis approaches. Coenzyme Q10 (CoQ10) shows promise when combined with emerging therapies such as Liproxstatin-1, potentially increasing cartilage thickness. Research indicates that PLGA nanoparticles enhance intra-articular CoQ10 retention compared to free drug administration. Na *et al.* [40] demonstrated that CoQ10 encapsulated in micelles effectively alleviates osteoarthritis by inhibiting inflammatory cell death. These findings align with studies on reactive oxygen species-induced lipid peroxidation mechanisms in apoptosis, autophagy, and ferroptosis [41], further supported by Raizner's [42] review of CoQ10's biological functions.

Challenges and Future Directions

Current limitations and emerging solutions

CoQ10 faces limitations in systemic absorption due to its high lipophilicity, which affects its bioavailability [37]. However, emerging solutions such as 3D-bioprinted joint models offer high-throughput drug screening capabilities, like organ-on-a-chip

technology. Additionally, AI-driven drug design has shown promise in identifying FSP1 agonists with high hit rates through virtual screening [43]. Recent advancements also include the development of injectable biomimetic conjugates based on nanoarchitectonics, which show potential for cartilage protection and therapy in degenerative osteoarthritis [44].

Conclusion

The ferroptosis-autophagy axis and metabolic reprogramming emerge as central to OA pathogenesis. CoQ10, with its multi-target actions, represents a promising therapeutic candidate. Future research must address bioavailability challenges and leverage technologies like AI, micro physiological systems, robots, digital-twin and 3D modeling to advance quantitative personalized OA therapies.

References

1. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012 Jun;64(6):1697–707.
2. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010 Aug;26(3):355–69.
3. Ye ZZ, Zhang ZY, Li ZG, Huang CB, Zhang Y. Toward wiping out osteoarthritis in China: research highlights. Chin Med J (Engl). 2020 Apr 20;133(8):883–5.
4. Boer CG. Osteoarthritis year in review 2024: Genetics, genomics, and epigenetics. Osteoarthritis Cartilage. 2025 Jan;33(1):50–7.
5. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012 May 25;149(5):1060–72.
6. Huang C, Zhang Z, Chen Y, Zhang Y, Xing D, Zhao L, et al. Development and formulation of the classification criteria for osteoarthritis. Ann Transl Med. 2020 Sep;8(17):1068.
7. Zhang Y, Chen H, Huang C. Optimizing health-span: advances in stem cell medicine and longevity research. Med Rev (2021). 2023 Oct 10;3(4):351–5.
8. Zhang S, Xu J, Si H, Wu Y, Zhou S, Shen B. The Role Played by Ferroptosis in Osteoarthritis: Evidence Based on Iron Dyshomeostasis and Lipid Peroxidation. Antioxidants (Basel). 2022 Aug 27;11(9):1668.
9. Gao B, Yin Z, Zhang Y. Exploring novel therapeutic avenues for arthritis precision medicine: The potential of mTOR-SIRT1, NRF2, GPX4 ferroptosis-and autophagy-related pathways and emerging technologies. Current Rheumatology Research. 2024 Oct 11;4(1):28–32.
10. Li X, Guo Y, Huang S, He M, Liu Q, Chen W, et al. Coenzyme Q10 Prevents the Interleukin-1 Beta Induced Inflammatory Response via Inhibition of MAPK Signaling Pathways in Rat Articular Chondrocytes. Drug Dev Res. 2017 Dec;78(8):403–10.
11. Pal B, Endisha H, Zhang Y, Kapoor M. mTOR: a potential therapeutic target in osteoarthritis? Drugs R D. 2015 Mar;15(1):27–36.
12. Rego-Pérez I, Durán-Sotuela A, Ramos-Louro P, Blanco FJ. Mitochondrial Genetics and Epigenetics in Osteoarthritis. Front Genet. 2020 Jan 17;10:1335.
13. Caramés B, Olmer M, Kiosses WB, Lotz MK. The relationship of autophagy defects to cartilage damage during joint aging in a mouse model. Arthritis Rheumatol. 2015 Jun;67(6):1568–76.
14. Wolff KJ, Ramakrishnan PS, Brouillette MJ, Journot BJ, McKinley TO, Buckwalter JA, et al. Mechanical stress and ATP synthesis are coupled by mitochondrial oxidants in articular cartilage. J Orthop Res. 2013 Feb;31(2):191–6.
15. Ji Q, Zheng Y, Zhang G, Hu Y, Fan X, Hou Y, et al. Single-cell RNA-seq analysis reveals the progression of human osteoarthritis. Ann Rheum Dis. 2019 Jan;78(1):100–10.
16. Zhang Y, Vasheghani F, Li YH, Blati M, Simeone K, Fahmi H, et al. Cartilage-specific deletion of mTOR upregulates autophagy and protects mice from osteoarthritis. Ann Rheum Dis. 2015 Jul;74(7):1432–40.
17. Calivà F, Namiri NK, Dubreuil M, Pedoia V, Ozhinsky E, Majumdar S. Studying osteoarthritis with artificial intelligence applied to magnetic resonance imaging. Nat Rev Rheumatol. 2022 Feb;18(2):112–21.
18. Datta P, Zhang Y, Parousis A, Sharma A, Rossomacha E, Endisha H, et al. High-fat diet-induced acceleration of osteoarthritis is associated with a distinct and sustained plasma metabolite signature. Sci Rep. 2017 Aug 15;7(1):8205.
19. Roemer FW, Collins JE, Neogi T, Crema MD, Guermazi A. Association of knee OA structural phenotypes to risk for progression: a secondary analysis from the Foundation for National Institutes of Health Osteoarthritis Biomarkers study (FNIH). Osteoarthritis Cartilage. 2020 Sep;28(9):1220–8.
20. Yi G, Li M, Zhou J, Li J, Song X, Li S, et al. Novel pH-responsive lipid nanoparticles deliver UA-mediated mitophagy and ferroptosis for osteoarthritis treatment. Mater Today Bio. 2025 Mar 21;32:101697.
21. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021 Apr;22(4):266–82.
22. Li SJ, Zheng QW, Zheng J, Zhang JB, Liu H, Tie JJ, et al. Mitochondria transplantation transiently rescues cerebellar neurodegeneration improving mitochondrial function and reducing mitophagy in mice. Nat Commun. 2025 Mar 22;16(1):2839.
23. Chen T, Majerníková N, Marmolejo-Garza A, Trombetta-Lima M, Sabogal-Guáqueta AM, Zhang Y, et al. Mitochondrial transplantation rescues neuronal cells from ferroptosis. Free Radic Biol Med. 2023 Nov 1;208:62–72.
24. Lv Z, Han J, Li J, Guo H, Fei Y, Sun Z, et al. Single cell RNA-seq analysis identifies ferroptotic chondrocyte cluster and reveals TRPV1 as an anti-ferroptotic target in osteoarthritis. EBioMedicine. 2022 Oct; 84:104258.
25. Wang S, Li W, Zhang P, Wang Z, Ma X, Liu C, et al. Mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. J Adv Res. 2022 Nov;41:63–75.
26. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017 Jan;13(1):91–8.
27. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995 May 24;1271(1):195–204.
28. Fang X, Ardehali H, Min J, Wang F. The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nat Rev Cardiol. 2023 Jan;20(1):7–23.
29. Lian WS, Wu RW, Ko JY, Chen YS, Wang SY, Yu CP, et al. Histone H3K27 demethylase UTX compromises articular chondrocyte anabolism and aggravates osteoarthritic degeneration. Cell Death Dis. 2022 Jun 8;13(6):538.
30. Zhang Y, Vasheghani F, Li YH, Blati M, Simeone K, Fahmi H, et

al. Cartilage-specific deletion of mTOR upregulates autophagy and protects mice from osteoarthritis. Ann Rheum Dis. 2015 Jul;74(7):1432–40.

31. Sacitharan PK, Bou-Gharios G, Edwards JR. SIRT1 directly activates autophagy in human chondrocytes. Cell Death Discov. 2020 May 29; 6:41.
32. Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. Nature. 2014 May 1;509(7498):105–9.
33. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ 3rd, et al. Autophagy promotes ferroptosis by degradation of ferritin. Autophagy. 2016 Aug 2;12(8):1425–8.
34. Saito T, Fukai A, Mabuchi A, Ikeda T, Yano F, Ohba S, et al. Transcriptional regulation of endochondral ossification by HIF-2alpha during skeletal growth and osteoarthritis development. Nat Med. 2010 Jun;16(6):678–86.
35. Jung YS, Stratton SA, Lee SH, Kim MJ, Jun S, Zhang J, Zheng B, Cervantes CL, Cha JH, Barton MC, Park JI. TMEM9-v-ATPase Activates Wnt/β-Catenin Signaling Via APC Lysosomal Degradation for Liver Regeneration and Tumorigenesis. Hepatology. 2021 Feb;73(2):776–94.
36. Fladerer JP, Grollitsch S. Comparison of Coenzyme Q10 (Ubiquinone) and Reduced Coenzyme Q10 (Ubiquinol) as Supplement to Prevent Cardiovascular Disease and Reduce Cardiovascular Mortality. Curr Cardiol Rep. 2023 Dec;25(12):1759–67.
37. Barcelos IP, Haas RH. CoQ10 and Aging. Biology (Basel). 2019 May 11;8(2):28.
38. Chang PS, Yen CH, Huang YY, Chiu CJ, Lin PT. Associations between Coenzyme Q10 Status, Oxidative Stress, and Muscle Strength and Endurance in Patients with Osteoarthritis. Antioxidants (Basel). 2020 Dec 14;9(12):1275.
39. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019 Nov;575(7784):688–92.
40. Na HS, Woo JS, Kim JH, Lee JS, Um IG, Cho KH, et al. Coenzyme Q10 encapsulated in micelles ameliorates osteoarthritis by inhibiting inflammatory cell death. PLoS One. 2022 Jun 24;17(6):e0270351.
41. Su LJ, Zhang JH, Gomez H, Murugan R, Hong X, Xu D, et al. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. Oxid Med Cell Longev. 2019 Oct 13;2019:5080843.
42. Raizner AE. Coenzyme Q_{10}. Methodist Debakey Cardiovasc J. 2019 Jul-Sep;15(3):185–91.
43. Watt FE. Osteoarthritis biomarkers: year in review. Osteoarthritis Cartilage. 2018 Mar;26(3):312–8.
44. Bi J, Zhang L, Zhang P, Xu S, Liu Y, Zhang X, et al. Nanoarchitectonics of Injectable Biomimetic Conjugates for Cartilage Protection and Therapy Based on Degenerative Osteoarthritis Progression. Biomater Res. 2024 Sep 10;28:0075.