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Mechanism and Research Progress of Mitochondrial Quality Control in Osteoarthritis

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Abstract

Osteoarthritis (OA) is a chronic disease characterized by degenerative lesions of articular cartilage, which is characterized by cartilage degeneration, bone redundancy formation and synovial inflammation. Recent studies have found that mitochondrial dysfunction is closely related to the development of OA. Mitochondrial quality control (MQC) mechanisms, including mitochondrial biogenesis, mitochondrial dynamics and mitochondrial autophagy, are essential for maintaining mitochondrial function. Therefore, targeted regulation of mitochondrial quality control is a promising therapeutic strategy. This article reviews the mechanism of MQC and its relationship with OA, as well as the research progress of targeting and regulating MQC to prevent and treat OA, aiming to provide a theoretical basis for the pathogenesis and preventive strategies of OA.

Keywords: osteoarthritis, mitochondrial quality control, mitochondrial biogenesis, mitochondrial autophagy, mitochondrial dynamics

1. Introduction

Osteoarthritis (OA) is a chronic bone and joint disease with articular cartilage degeneration as the main pathological feature, and its onset is closely related to various risk factors such as age, gender, obesity, and joint trauma. The main pathological features of the disease include progressive cartilage degeneration, osteophyte formation, and synovial inflammation, and its high disability rate seriously impairs the quality of life of patients. As of 2016, epidemiological surveys show that there are more than 14 million patients with symptomatic OA in the United States, and more than 50% of confirmed patients are under the age of 65. The prevalence of OA is expected to continue to rise as the global population agesing [1]. The pathophysiological mechanism of OA is complex, and the current early clinical intervention strategy is mainly focused on pain management, while joint replacement surgery should be considered in advanced cases. Recent studies have shown that mitochondrial homeostasis imbalance plays a key regulatory role in the pathological process of OA [2]-[4]. Mitochondrial dysfunction can lead to abnormal accumulation of reactive oxygen species (ROS) and trigger oxidative stress, which in turn promotes chondrocyte apoptosis and extracellular matrix (ECM) degradation, and ultimately accelerates the process of articular cartilage damage. Mitochondrial quality control (MQC) systems, including mitochondrial biogenesis, mitochondrial kinetic homeostasis, and mitophagy, have been shown to improve OA cartilage damage by maintaining mitochondrial homeostasis.

2. The Role of Mitochondrial Quality Control in the Pathogenesis of Osteoarthritis

2.1 The Role of Mitochondrial Biogenesis in the Pathogenesis of Osteoarthritis

Mitochondrial biogenesis is a biological process in which cells maintain cellular homeostasis by generating new mitochondria from existing mitochondria in response to changes in energy requirements induced by developmental signals and environmental stress. Peroxisome proliferator activated receptor γ γ coactivator 1α (PGC-1α), as a key transcriptional coactivator, can synergistically regulate the expression and functional activity of multiple nuclear transcription factors, including nuclearrespiratory factor 1 (NRF-1), nuclearrespiratory factor 2 (NRF-2) α and estrogen related receptor alpha (ERRα). Among them, NRF1/2 can specifically promote the expression of mitochondrial proteins encoded by the nuclear genome and Mitochondrial transcription factor A (TFAM), thereby stimulating mtDNA replication and repairing damaged mtDNA, and ensuring cellular energy metabolism needs and internal environment homeostasis by promoting mitochondrial production [5]. The activation of PGC-1α is

mainly dependent on upstream regulatory mechanisms: adenosine monophosphate-activated protein kinase (AMPK)-mediated phosphorylation [6] and sirtuin (SIRT) family-mediated deacetylation [7].

Recent studies have shown that mitochondrial biogenesis defects exist in OA chondrocytes, which are closely related to the decrease in AMPK and SIRT activity, and the decrease in the expression of PGC-1α and downstream molecules. Activation of AMPK, SIRT1 and SIRT3 can increase the expression and activity of PGC-1α, reverse the damage to mitochondrial biosynthesis, maintain the stability of mitochondrial quantity and quality, and alleviate OA cartilage damage [8]-[12]. It has been suggested that activation of AMPK-PGC1α signaling pathway-mediated mitochondrial biogenesis can alleviate neuroinflammation and improve mechanical allodynia in OA rats [13], QIU[10] was also pointed out that the activation of the AMPK-SIRT1 signaling pathway can restore the impaired mitochondrial function and alleviate OA by inhibiting the degeneration of OA articular cartilage. In addition, SIRT3 activates and enhances mitochondrial biogenesis induced by AMPK, restores mitochondrial homeostasis and reduces apoptosis, limiting the progression of aging-related OA mice [14]. Inhibition of mitochondrial biogenesis mediated by the AMPK-SIRT1-PGC-1α pathway leads to increased oxidative stress and apoptosis in chondrocytes, while the expression of MMP-13 accelerates cartilage degradation [12]. In addition, enhancing the mitochondrial biogenesis process by up-regulating PGC1-α and NRF2 can reduce the expression of matrix metallopeptidase (MMP) in OA mouse chondrocytes, inhibit ECM degradation, and alleviate arthritis response [15]; Similarly, it has been shown that upregulation of PGC-1α expression can maintain proteoglycan homeostasis and prevent mitochondrial dysfunction-induced degeneration of articular cartilage in OA mice [16]. In conclusion, these studies not only showed that there was a decrease in mitochondrial biogenesis in OA chondrocytes, but also showed that the activation of PGC-1α pathway would increase mitochondrial biogenesis in OA chondrocytes, and repair the damaged mitochondria in OA chondrocytes by regulating mitochondrial function and promoting mtDNA production, thereby exerting a certain cartilage protective effect, which has certain significance for limiting or even reversing the progression of OA.

2.2 Role of Mitochondrial Dynamics in the Pathogenesis of Osteoarthritis

The process by which mitochondria maintain the overall morphology of a mitochondrial population through continuous fusion and division is called mitochondrial dynamics. The equilibrium transition between fusion and division determines the overall morphology of mitochondrial populations, which in turn controls their shape, number, size, and function to meet intracellular energy and metabolic requirements [17]. The outer mitochondrial membrane is mediated by mitochondrial fusion protein 1 (Mfn1) and mitofusin 2 (Mfn2), while the fusion of the inner membrane is regulated by optic atrophy protein 1 (OPA1) [18] . Mitochondrial division is mainly mediated by dynamin-related protein 1 (Drp1), which first binds to the receptor protein mitochondrial fission factor and mitochondrial fission protein 1 (FIS1) on the outer mitochondrial membrane [19] , and then oligomerizes Drp1 and forms a helical and circular structure in a GTP-dependent manner, splitting the original mitochondria into two smaller mitochondria through enhanced contraction [20].

Accumulating evidence suggests that excessive mitochondrial division and inhibition of fusion are associated with the progression of OA, and that by promoting fusion and inhibiting division, mitochondrial kinetic balance can be remodeled to improve its dysfunction, thereby enhancing the ability to resist oxidative stress and apoptosis, and ultimately improving OA disease [21], [22]. Ansari et al. [23] reported that ERK1/2 accelerated OA chondrocyte apoptosis by activating DRP1-mediated mitochondrial fission, and that the use of Mdivi-1 to inhibit Drp1-dependent mitochondrial fission reversed mitochondrial dysfunction and reduced chondrocyte apoptosis, delaying OA progression. Another study showed that TBK1 improved mitochondrial dynamics by inhibiting DRP1-mediated mitochondrial fission and significantly attenuated OA chondrocyte apoptosis and cartilage degradation [24]. On the other hand, mitochondrial fusion disorders can also promote the development of OA. Studies have shown that OPA1-deficient mice exhibit age-dependent osteoarthritis, suggesting that OPA1-mediated regulation of mitochondrial dynamics is essential for maintaining cartilage metabolic homeostasis [25]. At the same time, overexpression of Mfn2 to enhance the mitochondrial fusion process can accelerate the cartilage differentiation of chondrogenitor cells/stem cells, promote chondrogenesis, and improve cartilage injury in OA rats through the Notch2 pathway [26]. Yao et al. [27] found that FGF-18 promoted OPA1 and MFN2-mediated mitochondrial fusion by activating the PI3K-AKT signaling pathway, which reduced ROS production and improved mitochondrial function, effectively attenuated the occurrence of chondrocyte apoptosis in the posttraumatic OA rat model, and alleviated cartilage degradation by increasing type II collagen and inhibiting the expression of MMP13. These studies suggest that enhanced mitochondrial fusion can reverse mitochondrial dysfunction in OA chondrocytes and may be a potential target for the treatment of OA oxidative stress injury and chondrocyte apoptosis. Therefore, re-establishing the balance between mitochondrial fusion and fission is key to maintaining mitochondrial health and exerting therapeutic effects.

2.3 The Role of Mitophagy in the Pathogenesis of Osteoarthritis

When cells are subjected to deleterious stimuli and mitochondrial damage occurs, the process of maintaining mitochondrial homeostasis by selectively removing damaged or depolarized mitochondria is known as mitophagy [28]. In mammals, the classical mitophagy pathway is divided into ubiquitin-dependent pathways and non-ubiquitin-dependent pathways [29]. The PTENinduced putative kinase 1 (PINK1)-Parkin signaling pathway is the most common ubiquitin-dependent mitophagy pathway, which promotes mitophagy mainly through extensive ubiquitination of mitochondrial surface proteins. The mitochondrial membrane potential is depolarized in response to stress, which promotes the recruitment of PINK1 on the outer mitochondrial membrane, and then PINK1 phosphorylation activates Parkin, which promotes the binding of Parkin to the damaged mitochondria [30] and exposes its E3 ligase active site, thereby promoting the ubiquitination of the substrate molecule. Damaged mitochondria are encapsulated in autophagosomes to form mitochondrial autophagosomes, which are eventually degraded by lysosomes. Non-ubiquitin-dependent mitophagy triggers mitochondria-autophagosomal membrane fusion primarily through autophagy receptors on the outer mitochondrial membrane (eg, FUNDC1, NIX, and BNIP3) binding to the autophagy protein LC3 in a non-ubiquitination-dependent pathway, and ultimately through lysosomal targeted clearance of damaged mitochondria [31]. In addition, mitophagy can occur through non-classical pathways, including AMPK, SIRT3, and mammalian target of rapamycin (mTOR). Impaired mitophagy leads to the accumulation of dysfunctional mitochondria and further exacerbates cell damage.

Various pathways-mediated mitophagy have been widely reported in OA. A large number of studies have shown that mitophagy is defective in OA chondrocytes, and mitophagy, as a protective self-regulatory mechanism, can maintain cellular homeostasis by selectively degrading aged or damaged mitochondria, and inhibit ECM degradation, reduce chondrocyte senescence and apoptosis to alleviate OA cartilage damage and delay the development of OA [32],[33], therefore, it is considered an effective target for the treatment of OA [34]-[36], therefore, it is considered an effective target for the treatment of OA [37], while the protective effect against ECM degradation disappears after antagonizing SIRT3 [38]-[40]. In addition, studies have shown that 17β-estradiol can promote the expression of p-AMPK and SIRT1 and inhibit the expression of p-mTOR in OA chondrocytes, suggesting that 7β-estradiol regulates the level of mitophagy in chondrocytes through the AMPK/mTOR signaling pathway to maintain chondrocyte homeostasis [41]. It has been found that HIF-1α can alleviate mitochondrial dysfunction and chondrocyte apoptosis stimulated by hypoxia by promoting mitophagy, and alleviate OA-related inflammation and cartilage damage [42], [43], and the mechanism may be related to the activation of BNIP3L-mediated mitophagy by HIF-1α under hypoxic conditions. In addition, FUNDC1-mediated mitophagy also plays a therapeutic role in ameliorating OA cartilage degeneration, and in vivo knockdown of FUNDC1 will reduce mitophagy and exacerbate mitochondrial dysfunction, aggravate chondrocyte degeneration and OA progression [44], [45]. However, it has also been noted that the level of mitophagy in OA chondrocytes is elevated, and SHIN et al. [46] found that the autophagy-related proteins LC3 and p62 were significantly up-regulated in OA rat chondrocytes induced by sodium iodoacetate, and the expression of Pink1 and Parkin proteins in OA was also increased. This suggests that the difference in the level of autophagy in OA may be related to the establishment methods of different animal models and the stage of OA disease, and the compensatory enhancement of mitophagy in early OA can clear the dysfunctional mitochondria and delay cartilage degeneration. However, the abnormal activation of mitophagy may also lead to the non-selective removal of normal mitochondria, which further induces intracellular energy and metabolism abnormalities and aggravates chondrocyte damage.

3. Targeted Regulation of Mitochondrial Quality Control by Traditional Chinese Medicine to Prevent and Treat Osteoarthritis

3.1 Traditional Chinese Medicine Targets the Regulation of Mitochondrial Biogenesis and Prevents Osteoarthritis

The dysfunction of mitochondrial biogenesis mediated by the AMPK/SIRT/PGC-1a pathway in chondrocytes is related to the occurrence and development of OA, making it an ideal target for OA management. Some drugs and bioactive ingredients have been shown to target and activate the AMPK/SIRT/PGC-1a-related signaling pathway to promote chondrocyte mitochondrial biogenesis, which has potential therapeutic value in improving cartilage damage. For example, apple proanthocyanidins can improve mitochondrial and cellular homeostasis by promoting PGC-1α-induced mitochondrial biogenesis in OA chondrocytes and prevent mitochondrial dysfunction-induced articular cartilage degeneration in OA models [16]. In addition, apple proanthocyanidins also ameliorate synovial inflammation of OA and inhibit OA progression by promoting cell proliferation and hyaluronic acid production [47]. Puerarin has also been shown to enhance chondrocyte mitochondrial biogenesis and alleviate mitochondrial dysfunction through the AMPK/PGC-1α signaling pathway, and has a protective effect on mechanical hyperalgesia and cartilage injury in OA rats [48]. In addition, puerarin has been found to inhibit the activation of the NF-κB pathway by regulating the level of NRF2, reducing the expression of inflammatory cytokines and

cartilage destruction [49]. Dimethyl fumarate has also been shown to alleviate pain-related behaviors in rat OA models by activating Nrf2-induced mitochondrial biogenesis, and to exert chondroprotective effects by inhibiting type II collagen degradation [50] . In addition, Ma et al. [51] found that ginsenoside Rg3 inhibits mitochondrial dysfunction by activating the SIRT1/PGC-1α/SIRT3 pathway and reduces the production of IL-8 and MMP-9, suggesting that ginsenoside Rg3 may improve inflammation and cartilage degeneration in OA patients. These studies have shown that the main regulators of mitochondrial biogenesis can enhance the mitochondrial function of OA chondrocytes by targeting and up-regulating, which has certain limitations and therapeutic effects on the progression of OA.

3.2 Traditional Chinese Medicine Targets the Regulation of Mitochondrial Dynamics in the Prevention and Treatment of Osteoarthritis

Excessive mitochondrial fission and weakened fusion in chondrocytes are involved in the pathogenesis of OA, and excessive mitochondrial fission leads to reduced ATP production, impaired calcium regulation and redox balance, and restoring this balance helps to restore cell function and delay OA cartilage damage. In recent years, relevant studies have pointed out that some drugs and bioactive components can regulate mitochondrial function by targeting mitochondrial dynamics, which can delay the progression of OA to a certain extent. Nod [52], as the main active ingredient of Angelica sinensis, may alleviate inflammation and improve cartilage degradation by regulating the mitochondrial Drp1/ROS/NLRP3 axis, and reverse the pathological changes of subchondral bone in OA. The expression of MMP13 decreased, the content of type II collagen increased, and the levels of NLRP3 inflammasome, COX2, IL-1β, TNF-α and ROS decreased after Nod intervention, indicating that Nod may alleviate oxidative stress and ECM degradation by inhibiting excessive mitochondrial fission, and has the potential to treat OA. Wang et al. [53] found that irisin exhibits multiple protective effects against OA by regulating mitochondrial integrity and autophagy. Irisin up-regulated the expression of Mfn1 and reduced the expression level of Drp1, up-regulated the expression of autophagy markers, PINK1 and Parkin, and increased the expression of PGC-1α and Tfam, indicating that irisin could enhance mitochondrial function by promoting mitochondrial biogenesis, kinetics and autophagy, and attenuate OA articular cartilage damage by inhibiting chondrocyte oxidative stress and ECM destruction. Another study showed that Schizandra B promoted the expression of mitochondrial fusion proteins MFN1, MFN2, and OPA1 and inhibited the increase in DRP1 expression, improved mitochondrial membrane potential damage and maintained mitochondrial activity by balancing the mitochondrial fusion and fission process, and exerted a protective effect on LPS-induced chondrocyte injury [54] found that irisin exhibits multiple protective effects against OA by regulating mitochondrial integrity and autophagy. Irisin up-regulated the expression of Mfn1 and reduced the expression level of Drp1, up-regulated the expression of autophagy markers, PINK1 and Parkin, and increased the expression of PGC-1α and Tfam, indicating that irisin could enhance mitochondrial function by promoting mitochondrial biogenesis, kinetics and autophagy, and attenuate OA articular cartilage damage by inhibiting chondrocyte oxidative stress and ECM destruction. Another study showed that Schizandra B promoted the expression of mitochondrial fusion proteins MFN1, MFN2, and OPA1 and inhibited the increase in DRP1 expression, improved mitochondrial membrane potential damage and maintained mitochondrial activity by balancing the mitochondrial fusion and fission process, and exerted a protective effect on LPS-induced chondrocyte injury [27],[55]. Studies have pointed out that FGF18 can restore mitochondrial morphology and function, reduce ROS production and apoptosis, and alleviate cartilage degradation by increasing type II collagen deposition and inhibiting MMP13 expression. FGF19 upregulates the expression of Mfn1, Mfn2, Opa1 and PGC-1α through the AMPKα/PGC-1α/SIRT1 axis, enhances the mitochondrial biogenesis and fusion levels of chondrocytes to stabilize mitochondrial morphology, thereby playing a positive role in chondrocyte metabolism. These studies suggest that targeted modulation of mitochondrial dynamics can exert a protective effect on OA chondrocytes and is a potential strategy for the treatment of OA.

3.3 Traditional Chinese Medicine Targets the Regulation of Mitophagy Level in the Prevention and Treatment of Osteoarthritis

Enhancing mitophagy removes damaged mitochondria to improve mitochondrial function and reduce oxidative stress and inflammation levels. By activating PINK1/Parkin or down-regulating PI3K/AKT/mTOR, it can effectively activate the occurrence of mitophagy in chondrocytes, thereby inhibiting chondrocyte apoptosis and ECM degradation in OA. Jin et al. [56] found that curcumin could improve mitochondrial function damage and maintain ECM stability by promoting AMPK/PINK1/Parkin-mediated mitophagy, and maintain ECM stability to exert anti-OA effects. In addition, β-hydroxybutyrate can also activate this pathway to alleviate apoptosis, senescence, inflammatory factor secretion, and ECM degradation in OA chondrocytes [57]. Protocatechaldehyde was found to alleviate OA chondrocyte senescence by activating the PINK1/Parkin pathway, ultimately reducing chondrodegeneration [58]. Protocatechaldehyde was found to alleviate OA chondrocyte senescence by activating

the PINK1/Parkin pathway, ultimately reducing chondrodegeneration [59]. In addition, electroacupuncture also plays a role in the adjuvant treatment of anti-cartilage injury. XING et al. [60] showed that electroacupuncture can activate mitophagy in OA rabbit chondrocytes, remove damaged mitochondria and restore mitochondrial homeostasis, and this regulation may be achieved by upregulating the Pink1-Parki signaling pathway. Pioglitazone has also been shown to act as a PPARγ agonist to improve mitochondrial function by restoring Pink1/Parkin-dependent mitophagy and inhibiting chondrocyte ferroptosis to delay the progression of OA [61]. It can be seen that mitophagy mediated by the PINK1-Parkin pathway can help improve the pathological damage of OA cartilage and play a protective role. In addition, Lu et al. [62]. It can be seen that mitophagy mediated by the PINK1-Parkin pathway can help improve the pathological damage of OA cartilage and play a protective role. In addition, Lu et al. [63]. Based on the above findings, specific regulation of the MI3K/AKT/mTOR pathway-mediated mitophagy process in OA chondrocytes can effectively restore cellular homeostasis and inhibit OA joint degeneration.

4. Summary and Prospect

Recent studies have shown that mitochondrial homeostasis imbalance is of great significance in the pathogenesis of OA. In addition, the specific mechanism of PGC-1α pathway to promote mitochondrial biogenesis in chondrocytes and improve cartilage injury, the effect of mitochondrial fission degree on mitochondrial kinetic imbalance, the role of the balance between mitochondrial fusion and fission in mitochondrial homeostasis, and the precise regulation of mitochondrial autophagy homeostasis are still unclear and need to be further explored. In addition, some drugs and bioactive components have been found to effectively restore chondrocyte homeostasis and inhibit the pathological progression of OA by targeting the homeostasis of MQC, however, most of the above conclusions are based on animal models or in vitro cell models induced by acute injury, which are different from the chronic and progressive disease characteristics of OA in clinical practice. Second, there may be potential side effects associated with therapeutic strategies that target MQC. For example, activating mitophagy levels may lead to non-selective clearance of normal mitochondria, exacerbating energy metabolism disorders; Targeted MQC regulation may lack specificity, resulting in a difficult balance between efficacy and side effects. We believe that further exploration of the interaction mechanism between MQCs can effectively reveal the role it plays in cartilage protection, and at the same time, a targeted delivery system can be developed to improve the precision of treatment, providing new ideas for the prevention and treatment of OA.

References

[1] Vina, E. R., & Kwoh, C. K. (2018). Epidemiology of osteoarthritis: Literature update. *Current Opinion in Rheumatology, 30*(2), 160–167. https://doi.org/10.1097/BOR.0000000000000479

[2] Mao, X., Fu, P., Wang, L., et al. (2020). Mitochondria: Potential targets for osteoarthritis. *Frontiers in Medicine, 7*, 581402. https://doi.org/10.3389/fmed.2020.581402

[3] Bolduc, J. A., Collins, J. A., & Loeser, R. F. (2019). Reactive oxygen species, aging and articular cartilage homeostasis. *Free Radical Biology and Medicine, 132*, 73–82. https://doi.org/10.1016/j.freeradbiomed.2018.08.038

[4] Early, J. O., Fagan, L. E., Curtis, A. M., et al. (2021). Mitochondria in injury, inflammation and disease of articular skeletal joints. *Frontiers in Immunology, 12*, 695257. https://doi.org/10.3389/fimmu.2021.695257

[5] Kang, C., & Li, Ji, L. (2012). Role of PGC-1α signaling in skeletal muscle health and disease. *Annals of the New York Academy of Sciences, 1271*(1), 110–117. https://doi.org/10.1111/j.1749-6632.2012.06738.x

[6] Yao, Q., Wu, X., Tao, C., et al. (2023). Osteoarthritis: Pathogenic signaling pathways and therapeutic targets. *Signal Transduction and Targeted Therapy, 8*(1), 56. https://doi.org/10.1038/s41392-023-01330-w

[7] Cantó, C., & Auwerx, J. (2009). PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Current Opinion in Lipidology, 20*(2), 98–105. https://doi.org/10.1097/MOL.0b013e328328d0a4

[8] Yang, Q., Shi, Y., Jin, T., et al. (2022). Advanced glycation end products induced mitochondrial dysfunction of chondrocytes through repression of AMPKα-SIRT1-PGC-1α pathway. *Pharmacology, 107*(5–6), 298–307. https://doi.org/10.1159/000521720

[9] Wang, Y., Zhao, X., Lotz, M., et al. (2015). Mitochondrial biogenesis is impaired in osteoarthritis chondrocytes but reversible via peroxisome proliferator–activated receptor γ coactivator 1α. *Arthritis & Rheumatology, 67*(8), 2141–2153. https://doi.org/10.1002/art.39182

[10] Qiu, L., Luo, Y., & Chen, X. (2018). Quercetin attenuates mitochondrial dysfunction and biogenesis via upregulated AMPK/SIRT1 signaling pathway in OA rats. *Biomedicine & Pharmacotherapy, 103*, 1585–1591.

https://doi.org/10.1016/j.biopha.2018.05.003

[11] De la Rosa, A., Olaso-Gonzalez, G., Garcia-Dominguez, E., et al. (2022). Glucosamine supplementation improves physical performance in trained mice. *Medicine and Science in Sports and Exercise, 54*(3), 466–474. https://doi.org/10.1249/MSS.0000000000002821

[12] Ma, C. H., Chiu, Y. C., Wu, C. H., et al. (2018). Homocysteine causes dysfunction of chondrocytes and oxidative stress through repression of SIRT1/AMPK pathway: A possible link between hyperhomocysteinemia and osteoarthritis. *Redox Biology, 15*, 504–512. https://doi.org/10.1016/j.redox.2018.01.010

[13] Sun, J., Song, F. H., Wu, J. Y., et al. (2022). Sestrin2 overexpression attenuates osteoarthritis pain via induction of AMPK/PGC-1α-mediated mitochondrial biogenesis and suppression of neuroinflammation. *Brain, Behavior, and Immunity, 102*, 53–70. https://doi.org/10.1016/j.bbi.2022.02.015

[14] Chen, L. Y., Wang, Y., Terkeltaub, R., et al. (2018). Activation of AMPK-SIRT3 signaling is chondroprotective by preserving mitochondrial DNA integrity and function. *Osteoarthritis and Cartilage, 26*(11), 1539–1550. https://doi.org/10.1016/j.joca.2018.07.004

[15] Ajmal, I., Farooq, M. A., Abbas, S. Q., et al. (2022). Isoprenaline and salbutamol inhibit pyroptosis and promote mitochondrial biogenesis in arthritic chondrocytes by downregulating β-arrestin and GRK2. *Frontiers in Pharmacology, 13*, 996321. https://doi.org/10.3389/fphar.2022.996321

[16] Masuda, I., Koike, M., Nakashima, S., et al. (2018). Apple procyanidins promote mitochondrial biogenesis and proteoglycan biosynthesis in chondrocytes. *Scientific Reports, 8*(1), 7229. https://doi.org/10.1038/s41598-018-25348-1

[17] Jin, J. Y., Wei, X. X., Zhi, X. L., et al. (2021). Drp1-dependent mitochondrial fission in cardiovascular disease. *Acta Pharmacologica Sinica, 42*(5), 655–664. https://doi.org/10.1038/s41401-020-00518-y

[18] Tilokani, L., Nagashima, S., Paupe, V., et al. (2018). Mitochondrial dynamics: Overview of molecular mechanisms. *Essays in Biochemistry, 62*(3), 341–360. https://doi.org/10.1042/EBC20170104

[19] Hu, C., Huang, Y., & Li, L. (2017). Drp1-dependent mitochondrial fission plays critical roles in physiological and pathological progresses in mammals. *International Journal of Molecular Sciences, 18*(1), 144. https://doi.org/10.3390/ijms18010144

[20] Basu, K., Lajoie, D., Aumentado-Armstrong, T., et al. (2017). Molecular mechanism of DRP1 assembly studied in vitro by cryo-electron microscopy. *PLOS ONE, 12*(6), e0179397. https://doi.org/10.1371/journal.pone.0179397

[21] Court, A. C., Vega-Letter, A. M., Parra-Crisóstomo, E., et al. (2024). Mitochondrial transfer balances cell redox, energy and metabolic homeostasis in the osteoarthritic chondrocyte preserving cartilage integrity. *Theranostics, 14*(17), 6471–6486. https://doi.org/10.7150/thno.96723

[22] Shi, G., Lan, S., Zhang, Q., et al. (2025). Molybdenum nanodots act as antioxidants for photothermal therapy osteoarthritis. *Biomaterials, 315*, 122909. https://doi.org/10.1016/j.biomaterials.2024.122909

[23] Ansari, M. Y., Novak, K., & Haqqi, T. M. (2022). ERK1/2-mediated activation of DRP1 regulates mitochondrial dynamics and apoptosis in chondrocytes. *Osteoarthritis and Cartilage, 30*(2), 315–328. https://doi.org/10.1016/j.joca.2021.11.003

[24] Hu, S., Mamun, A. A., Shaw, J., et al. (2023). TBK1-medicated DRP1 phosphorylation orchestrates mitochondrial dynamics and autophagy activation in osteoarthritis. *Acta Pharmacologica Sinica, 44*(3), 610–621. https://doi.org/10.1038/s41401-022-00967-7

[25] Risbud, M., Madhu, V., Hernandez-Meadows, M., et al. (2024). The loss of OPA1 accelerates intervertebral disc degeneration and osteoarthritis in aged mice. https://doi.org/10.21203/rs.3.rs-3950044/v1

[26] Moqbel, S. A. A., Zeng, R., Ma, D., et al. (2022). The effect of mitochondrial fusion on chondrogenic differentiation of cartilage progenitor/stem cells via Notch2 signal pathway. *Stem Cell Research & Therapy*, *13*(1), 127. https://doi.org/10.1186/s13287-022-02758-7

[27] Yao, X., Zhang, J., Jing, X., et al. (2019). Fibroblast growth factor 18 exerts anti-osteoarthritic effects through PI3K-AKT signaling and mitochondrial fusion and fission. *Pharmacological Research, 139*, 314–324. https://doi.org/10.1016/j.phrs.2018.09.026

[28] Tolkovsky, A. M. (2009). Mitophagy. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*,

1793(9), 1508–1515. https://doi.org/10.1016/j.bbamcr.2009.03.002

[29] Youle, R. J., & Narendra, D. P. (2011). Mechanisms of mitophagy. *Nature Reviews Molecular Cell Biology*, *12*(1), 9–14. https://doi.org/10.1038/nrm3028

[30] Okatsu, K., Uno, M., Koyano, F., et al. (2013). A dimeric PINK1-containing complex on depolarized mitochondria stimulates Parkin recruitment. *Journal of Biological Chemistry, 288*(51), 36372–36384. https://doi.org/10.1074/jbc.M113.509653

[31] Sun, K., Jing, X., Guo, J., et al. (2021). Mitophagy in degenerative joint diseases. *Autophagy, 17*(9), 2082–2092. https://doi.org/10.1080/15548627.2020.1822097

[32] Ye, H., Cai, T., Shen, Y., et al. (2024). MST1 knockdown inhibits osteoarthritis progression through Parkin-mediated mitophagy and Nrf2/NF-κB signalling pathway. *Journal of Cellular and Molecular Medicine, 28*(11), e18476. https://doi.org/10.1111/jcmm.18476

[33] Li, W., Zhong, Y., Lin, Z., et al. (2024). Forsythoside A mitigates osteoarthritis and inhibits chondrocyte senescence by promoting mitophagy and suppressing NLRP3 inflammasome via the Nrf2 pathway. *Phytomedicine, 135*, 156052. https://doi.org/10.1016/j.phymed.2024.156052

[34] Kong, X., Ning, C., Liang, Z., et al. (2024). Koumine inhibits IL-1β-induced chondrocyte inflammation and ameliorates extracellular matrix degradation in osteoarthritic cartilage through activation of PINK1/Parkin-mediated mitochondrial autophagy. *Biomedicine & Pharmacotherapy, 173*, 116273. https://doi.org/10.1016/j.biopha.2024.116273

[35] D'Amico, D., Olmer, M., Fouassier, A. M., et al. (2022). Urolithin A improves mitochondrial health, reduces cartilage degeneration, and alleviates pain in osteoarthritis. *Aging Cell, 21*(8), e13662. https://doi.org/10.1111/acel.13662

[36] Liu, L., Zhang, W., Liu, T., et al. (2023). The physiological metabolite α-ketoglutarate ameliorates osteoarthritis by regulating mitophagy and oxidative stress. *Redox Biology, 62*, 102663. https://doi.org/10.1016/j.redox.2023.102663

[37] Shi, P. B., Du, M. M., Yu, P., et al. (2025). Yanghe decoction alleviates osteoarthritis by AMPK-SIRT3 positive feedback loop-mediated mitochondrial autophagy. *Journal of Ethnopharmacology, 341*, 119294. https://doi.org/10.1016/j.jep.2024.119294

[38] Xin, R., Xu, Y., Long, D., et al. (2022). Mitochonic acid-5 inhibits reactive oxygen species production and improves human chondrocyte survival by upregulating SIRT3-mediated, Parkin-dependent mitophagy. *Frontiers in Pharmacology, 13*, 911716. https://doi.org/10.3389/fphar.2022.911716

[39] Xia, X., Liu, Y., Lu, Y., et al. (2023). Retuning mitochondrial apoptosis/mitophagy balance via SIRT3-energized and microenvironment-modulated hydrogel microspheres to impede osteoarthritis. *Advanced Healthcare Materials, 12*(32), e2302475. https://doi.org/10.1002/adhm.202302475

[40] Wang, C., Yang, Y., Zhang, Y., et al. (2018). Protective effects of metformin against osteoarthritis through upregulation of SIRT3-mediated PINK1/Parkin-dependent mitophagy in primary chondrocytes. *BioScience Trends, 12*(6), 605–612. https://doi.org/10.5582/bst.2018.01263

[41] Mei, R., Lou, P., You, G., et al. (2021). 17β-Estradiol induces mitophagy upregulation to protect chondrocytes via the SIRT1-mediated AMPK/mTOR signaling pathway. *Frontiers in Endocrinology, 11*, 615250. https://doi.org/10.3389/fendo.2020.615250

[42] Yang, J., Zhou, Z., Ding, X., et al. (2024). Gubi Zhitong formula alleviates osteoarthritis in vitro and in vivo via regulating BNIP3L-mediated mitophagy. *Phytomedicine, 128*, 155279. https://doi.org/10.1016/j.phymed.2023.155279

[43] Hu, S., Zhang, C., Ni, L., et al. (2020). Stabilization of HIF-1α alleviates osteoarthritis via enhancing mitophagy. *Cell Death & Disease, 11*(6), 481. https://doi.org/10.1038/s41419-020-2680-0

[44] Fang, G., Wen, X., Jiang, Z., et al. (2023). FUNDC1/PFKP-mediated mitophagy induced by KD025 ameliorates cartilage degeneration in osteoarthritis. *Molecular Therapy, 31*(12), 3594–3612. https://doi.org/10.1016/j.ymthe.2023.10.016

[45] Ye, H., Li, D., Wei, X., et al. (2023). Focused low-intensity pulsed ultrasound alleviates osteoarthritis via restoring impaired FUNDC1-mediated mitophagy. *iScience, 26*(10), 107772. https://doi.org/10.1016/j.isci.2023.107772

[46] Shin, H. J., Park, H., Shin, N., et al. (2019). Pink1-mediated chondrocytic mitophagy contributes to cartilage degeneration in osteoarthritis. *Journal of Clinical Medicine, 8*(11), 1849. https://doi.org/10.3390/jcm8111849

[47] Kobayashi, M., Harada, S., Fujimoto, N., et al. (2022). Apple polyphenols exhibit chondroprotective changes of synovium and prevent knee osteoarthritis. *Biochemical and Biophysical Research Communications, 614*, 120–124. https://doi.org/10.1016/j.bbrc.2022.05.016

[48] Wang, L., Shan, H., Wang, B., et al. (2018). Puerarin attenuates osteoarthritis via upregulating AMP-activated protein kinase/proliferator-activated receptor-γ coactivator-1 signaling pathway in osteoarthritis rats. *Pharmacology, 102*(3–4), 117–125. https://doi.org/10.1159/000490418

[49] Chen, X., Huang, C., Sun, H., et al. (2021). Puerarin suppresses inflammation and ECM degradation through Nrf2/HO-1 axis in chondrocytes and alleviates pain symptom in osteoarthritic mice. *Food & Function, 12*(5), 2075–2089. https://doi.org/10.1039/D0FO03076G

[50] Gao, S. J., Li, D. Y., Liu, D. Q., et al. (2022). Dimethyl fumarate attenuates pain behaviors in osteoarthritis rats via induction of Nrf2-mediated mitochondrial biogenesis. *Molecular Pain, 18*, 17448069221124920. https://doi.org/10.1177/17448069221124920

[51] Ma, C. H., Chou, W. C., Wu, C. H., et al. (2021). Ginsenoside Rg3 attenuates TNF-α-induced damage in chondrocytes through regulating SIRT1-mediated anti-apoptotic and anti-inflammatory mechanisms. *Antioxidants, 10*(12), 1972. https://doi.org/10.3390/antiox10121972

[52] Yi, N., Mi, Y., Xu, X., et al. (2022). Nodakenin attenuates cartilage degradation and inflammatory responses in a mice model of knee osteoarthritis by regulating mitochondrial Drp1/ROS/NLRP3 axis. *International Immunopharmacology, 113*, 109349. https://doi.org/10.1016/j.intimp.2022.109349

[53] Wang, F. S., Kuo, C. W., Ko, J. Y., et al. (2020). Irisin mitigates oxidative stress, chondrocyte dysfunction and osteoarthritis development through regulating mitochondrial integrity and autophagy. *Antioxidants, 9*(9), 810. https://doi.org/10.3390/antiox9090810

[54] Hu, F., Hu, W., & Xu, H. (2024). Schisandrin B alleviates LPS induced mitochondrial damage in C28I2 cells. *The Journal of Membrane Biology, 257*(1–2), 107–114. https://doi.org/10.1007/s00232-023-00299-5

[55] Kan, S., Pi, C., Zhang, L., et al. (2023). FGF19 increases mitochondrial biogenesis and fusion in chondrocytes via the AMPKα-p38/MAPK pathway. *Cell Communication and Signaling, 21*(1), 55. https://doi.org/10.1186/s12964-023-01069-5

[56] Jin, Z., Chang, B., Wei, Y., et al. (2022). Curcumin exerts chondroprotective effects against osteoarthritis by promoting AMPK/PINK1/Parkin-mediated mitophagy. *Biomedicine & Pharmacotherapy, 151*, 113092. https://doi.org/10.1016/j.biopha.2022.113092

[57] Zhuang, H., Ren, X., Zhang, Y., et al. (2024). β-Hydroxybutyrate enhances chondrocyte mitophagy and reduces cartilage degeneration in osteoarthritis via the HCAR2/AMPK/PINK1/Parkin pathway. *Aging Cell*, *23*(11), e14294. https://doi.org/10.1111/acel.14294

[58] Jie, L., Shi, X., Kang, J., et al. (2024). Protocatechuic aldehyde attenuates chondrocyte senescence via the regulation of PTEN-induced kinase 1/Parkin-mediated mitochondrial autophagy. *International Journal of Immunopathology and Pharmacology, 38*, 03946320241271724. https://doi.org/10.1177/03946320241271724

[59] Deng, Z., Long, D., Li, C., et al. (2024). IRF1-mediated upregulation of PARP12 promotes cartilage degradation by inhibiting PINK1/Parkin dependent mitophagy through ISG15 attenuating ubiquitylation and SUMOylation of MFN1/2. *Bone Research, 12*(1), 63. https://doi.org/10.1038/s41413-024-00363-3

[60] Xing, L., Chen, X., Guo, C., et al. (2023). Electroacupuncture exerts chondroprotective effect in knee osteoarthritis of rabbits through the mitophagy pathway. *Journal of Pain Research, 16*, 2871–2882. https://doi.org/10.2147/JPR.S416242

[61] Xue, X., Dai, T., Chen, J., et al. (2023). PPARγ activation suppresses chondrocyte ferroptosis through mitophagy in osteoarthritis. *Journal of Orthopaedic Surgery and Research, 18*(1), 620. https://doi.org/10.1186/s13018-023-04092-x

[62] Lu, R., He, Z., Zhang, W., et al. (2022). Oroxin B alleviates osteoarthritis through anti-inflammation and inhibition of PI3K/AKT/mTOR signaling pathway and enhancement of autophagy. *Frontiers in Endocrinology, 13*, 1060721. https://doi.org/10.3389/fendo.2022.1060721

[63] He, J., & He, J. (2023). Baicalin mitigated IL-1β-induced osteoarthritis chondrocytes damage through

activating mitophagy. *Chemical Biology & Drug Design, 101*(6), 1322–1334. https://doi.org/10.1111/cbdd.14215