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REVIEW

The Multifaceted Protective Role of Nuclear Factor Erythroid 2-Related Factor 2 in Osteoarthritis: Regulation of Oxidative Stress and Inflammation

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Abstract: Osteoarthritis (OA) is a chronic degenerative joint disease characterized by the degradation of joint cartilage, subchondral bone sclerosis, synovitis, and structural changes in the joint. Recent research has highlighted the role of various genes in the pathogenesis and progression of OA, with nuclear factor erythroid 2-related factor 2 (NRF2) emerging as a critical player. NRF2, a vital transcription factor, plays a key role in regulating the OA microenvironment and slowing the disease's progression. It modulates the expression of several antioxidant enzymes, such as Heme oxygenase-1 (HO-1) and NAD(P)H oxidoreductase 1 (NQO1), among others, which help reduce oxidative stress. Furthermore, NRF2 inhibits the nuclear factor kappa-B (NF-κB) signaling pathway, thereby decreasing inflammation, joint pain, and the breakdown of cartilage extracellular matrix, while also mitigating cell aging and death. This review discusses NRF2's impact on oxidative stress, inflammation, cell aging, and various cell death modes (such as apoptosis, necroptosis, and ferroptosis) in OA-affected chondrocytes. The role of NRF2 in OA macrophages, and synovial fibroblasts was also discussed. It also covers NRF2's role in preserving the cartilage extracellular matrix and alleviating joint pain. The purpose of this review is to provide a comprehensive understanding of NRF2's protective mechanisms in OA, highlighting its potential as a therapeutic target and underscoring its significance in the development of novel treatment strategies for OA.

Keywords: nuclear factor erythroid 2-related factor 2, osteoarthritis, chondrocytes, inflammation, oxidative stress

Introduction

Osteoarthritis (OA) is a widespread chronic degenerative disease that affects over 22% of the global population aged 40 and above, imposing a significant economic burden on both families and society.[1,2] It primarily impacts the knees, hips, and ankles, with the joint microenvironment typically characterized by oxidative stress and inflammation. These conditions lead to cartilage destruction, subchondral bone sclerosis, and synovitis.[3] Currently, treatment for early to mid-stage OA focuses on conservative methods, such as anti-inflammatory medications and pain relief, due to the absence of drugs capable of reversing OA's progression. Although various drugs targeting OA pathology, like anakinra and adalimumab for synovitis, have been developed, they often yield unsatisfactory results.[4] This may stem from OA's complex nature involving multiple joint components, where single-target treatments are insufficient. Hence, ongoing research into more effective therapeutic options is essential.

The onset and progression of OA are driven by complex interactions among various cell types, including chondrocytes, synovial fibroblasts, osteoclasts, macrophages and so on. Chondrocytes, the primary cell type in cartilage, maintain the balance of the cartilage matrix. In the microenvironment of OA, chondrocytes undergo pathological phenotypic

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changes, leading to increased matrix degradation and chondrocyte apoptosis, resulting in cartilage degeneration.[5] Synovial fibroblasts, which secrete synovial fluid to lubricate joints in normal conditions. However, there will be a large amount of production of inflammatory cytokines in OA, leading to synovitis and accelerating cartilage degradation.[6] Osteoclasts are involved in bone resorption, and during the progression of OA, subchondral bone loss drives increased bone remodeling and the overactivation of osteoclasts, which induces the catabolism of articular cartilage and promotes the development of OA.[7,8] Inflammatory Macrophages drive the inflammatory response by secreting inflammatory mediators, which not only accelerate cartilage destruction but also affect the degradation of other joint structures.[9] Therefore, regulating multiple cell types, including chondrocytes, synovial fibroblasts, immune cells, and osteocytes, is crucial for inhibiting the progression of OA.

Discovered in 1994, the transcription factor NF-E2 p45-related factor 2 (NRF2), encoded by NFE2L2, belongs to the human CNC basic leucine zipper transcription factor family.[10] NRF2 regulates over 250 genes containing enhancer sequences in their promoter regions, known as antioxidant response elements (ARE). These genes contribute to a synergistic enzyme network responsible for various biochemical processes, including biotransformation reactions, antioxidant metabolism, and the metabolism of carbohydrates, lipids, and proteins.[11] Through this network, NRF2 coordinates comprehensive responses to diverse stressors, maintaining cellular stability. Kelch-like ECH-associated protein 1 (Keap1), an inhibitor of NRF2,[12] also functions as an E3 ubiquitin ligase substrate adapter,[13–15] targeting NRF2 for rapid degradation under non-stress conditions. Under oxidative stress, the highly reactive cysteine residues of KEAP1, when modified by electrophilic molecules, prevent the degradation of NRF2, leading to its accumulation and nuclear translocation. This process triggers dimerization with small MaF proteins, inducing the expression of ARE genes.[16,17] These genes encode proteins that perform antioxidant, detoxifying, and anti-inflammatory functions, offering broad cellular protection. The NRF2-Keap1 axis plays a vital role in preventing diseases characterized by oxidative stress and inflammation, including metabolic, inflammatory, autoimmune disorders, and diseases affecting various organs and systems.[16,18] NRF2 plays an important regulatory role in OA chondrocytes, osteoclasts, Synovial fibroblasts, and macrophages.[9,19–21] NRF2 can inhibit the activation of the NF-κB signaling pathway, thereby suppressing inflammation factors and matrix metalloproteinases (MMPs) in OA chondrocytes, synovial fibroblasts, and macrophages. Additionally, NRF2 regulates the expression of antioxidant-related genes, such as HO-1 and NQO1, reducing oxidative stress levels in the OA microenvironment and thereby decreasing synovial inflammation and protecting the cartilage matrix. Furthermore, NRF2 can inhibit the expression of RANKL factors, thereby suppressing osteoclast activity and maintaining bone homeostasis in the OA environment. This review highlights recent advancements in NRF2 research within the context of OA, offering fresh perspectives for developing novel therapeutics to mitigate the disease.

NRF2 Signaling Pathway in Osteoarthritis, Research Progress

The Role of NRF2 in Chondrocytes

Cartilage destruction stands as a significant pathology in OA. Inflammation and oxidative stress impede the synthesis of the extracellular matrix in chondrocytes, promoting cellular aging and death, which includes apoptosis, necroptosis, and ferroptosis, thus compromising joint cartilage integrity and exacerbating joint pain. NRF2 demonstrates efficacy in suppressing inflammation within chondrocytes by interacting with the NF-κB signaling pathway. Additionally, it orchestrates the expression of various antioxidant enzymes such as HO-1 and NQO1, thus mitigating oxidative stress. As shown in Figure 1, anti-inflammatory and antioxidant properties of NRF2 offer protective mechanisms for compromising' extracellular matrix, inhibiting cellular aging and death. Subsequent sections delve into a comprehensive analysis of NRF2's effects on chondrocytes.

Inflammation Inhibition

The inflammatory response plays a pivotal role in OA pathogenesis. The NF-κB signaling pathway emerges as a crucial player in OA inflammation.[22] Stimulated by Interleukin-1β (IL-1β), IκB kinase (IKK) is activated through a series of membrane-proximal events. The phosphorylated IκBs subsequently induce the release of NF-κB, leading to its nuclear translocation and activation of gene transcription, ultimately triggering inflammatory responses.[23] This process impedes

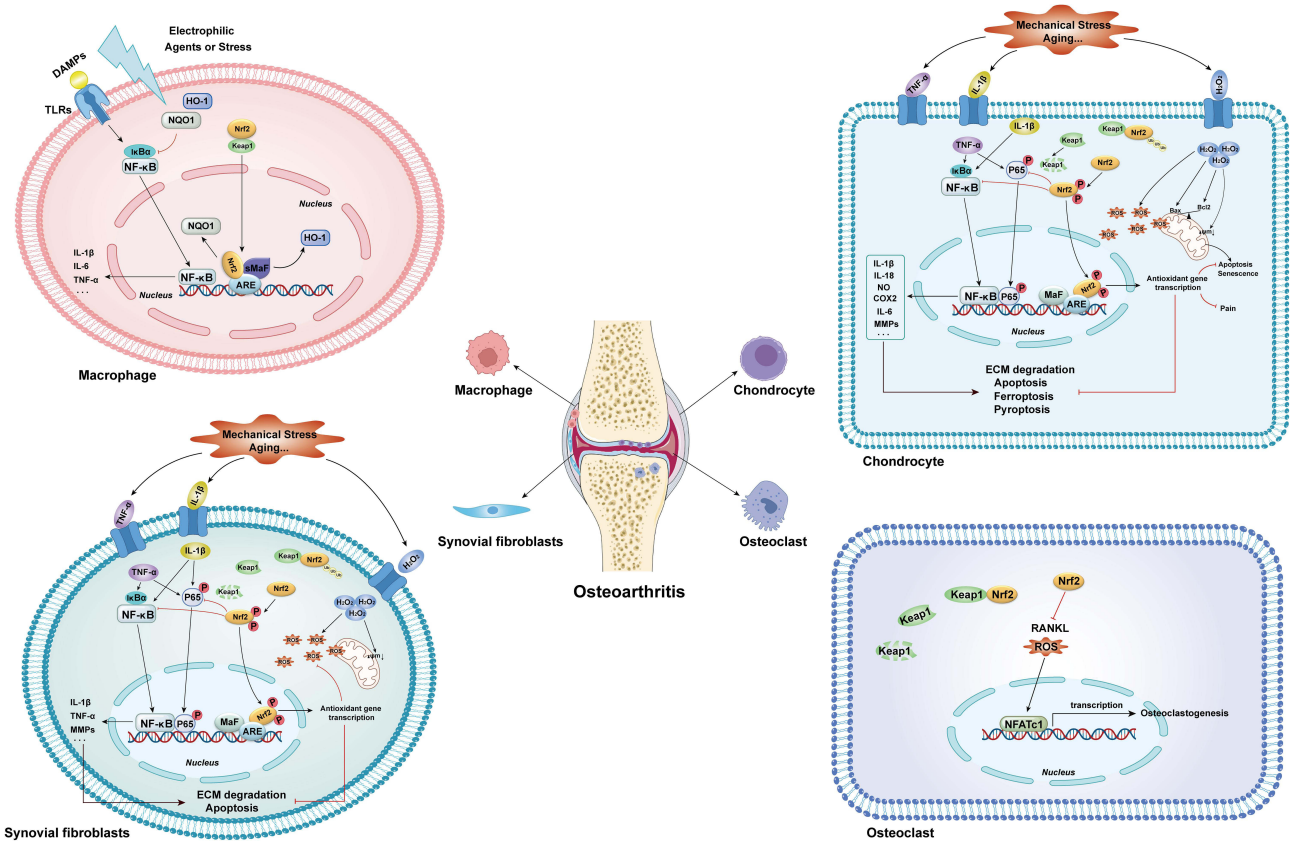

Figure 1 The mechanism of NRF2 in regulating chondrocytes, osteoclasts, synovial fibroblasts, and macrophages in OA.

Abbreviation, OA, Osteoarthritis; NRF2, nuclear factor erythroid 2-related factor 2; DAMPs, Damage-associated molecular patterns; TLRs, Toll-like receptors; HO-1, Heme Oxygenase-1; NQO1, NAD(P)H,quinone oxidoreductase 1; NF-κB, nuclear factor kappa-B; IkBα, Inhibitor of Nuclear Factor kappa-B alpha; Keap1, kelch-like ECH-associated protein 1; ARE, antioxidant response element; sMaF, small MaF; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor Alpha; Ub, Ubiquitination; H_2O_2, hydrogen peroxide; P-P65, Human phosphorylated nuclear transcription factor P65; ROS, Reactive Oxygen Species; Bax, BCL2 Associated X protein; Bcl2, B-cell lymphoma-2; $\Delta\Psi m$ represents Mitochondrial membrane potential; IL-18, interleukin-18; NO, Nitric Oxide; COX2, Cyclooxygenase-2; MMPs, matrix metalloproteinases; ECM, Extracellular matrix; RANKL, Receptor Activator of Nuclear Factor-κ B Ligand; NFATc1, Nuclear Factor Of Activated T-Cells, Cytoplasmic 1.

collagen and proteoglycan production in chondrocytes and activates MMPs and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS), ultimately fostering cartilage degradation.

Augmenting NRF2 nuclear translocation effectively suppresses the NF-κB pathway, thereby mitigating inflammation within chondrocytes and safeguarding joint integrity.[24–27] As shown in Table 1, Itaconate,[28] Oxymatrine,[29] Phillygenin,[30] Orientin,[31] Stevioside,[32] Suramin,[33] Chrysophanol,[34] Tangeretin,[35] Chicoric acid,[36] Linalool,[37] Ginkgolide C,[38] Asiaticoside,[39] Corynoline,[40] Rhoifolin,[41] Procyanidin B2,[42] Maltol,[43] Lycopene,[44] Betulin,[45] Limonin,[46] Xanthohumol,[47] 18β-Glycyrrhetinic acid,[48] moracin,[49] Nomilin,[50] hesperetin,[51] Akebia Saponin D,[52] Sinomenine,[53] Sinapic acid,[54] Monascin,[55] Sauchinone[56] and Piceatannol[57] have been shown to have the ability to enhance the movement of the NRF2 into the cell nucleus, which in turn inhibits the NF-κB pathway. The mechanism by which NRF2 inhibits the NF-κB signaling pathway can be divided into the following parts. NRF2 suppresses NF-κB activation by increasing the expression of antioxidant enzymes such as HO-1 and NQO1. Additionally, NRF2 indirectly inhibits the nuclear translocation of phosphorylated p65 by modulating the intracellular environment and reducing the level of phosphorylated p65. Furthermore, NRF2 can compete with NF-κB for binding to certain transcription factors and nuclear receptors, thereby reducing NF-κB activity. This inhibition subsequently suppresses downstream pro-inflammatory factors and MMPs while concurrently enhancing the expression of Collagen II and Aggrecan, ultimately preserving cartilage.

Oxidative Stress

Oxidative stress represents a pivotal factor driving age-associated diseases, including OA. An imbalance between Reactive Oxygen Species (ROS) production and the antioxidant capacity of joint cells, such as chondrocytes, constitutes

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Table 1 Activation of NRF2 Inhibits Inflammation and Catabolism in Chondrocytes by Suppressing the NF-κB Signaling Pathway

Regulators	Cell Type and Source	Concentration	NRF2/NF-κB axis	Biological Actions	Author (year)
Itaconate	IL-1β-treated mouse chondrocytes	120, 250 and 500 μM	Nucleus, NRF2↑, P65↓ Whole cell, HO-1↑, NQO1↑, p-p65↓, IkBα↑, STING↓	iNOS↓, COX2↓, TNF-α↓, IL-6↓, PGE2↓, NO↓, Aggrecan↑, Collagen II↑, MMP13↓, ADAMTS5↓	Ni et al, 2022[28]
Oxymatrine	IL-1β-treated mouse chondrocytes	1, 2, 4 and 8 μM	Nucleus, NRF2↑, HO-1↑, P65↓Cytoplasm, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, Nitrite↓, PGE2↓, Collagen II↑, Aggrecan↑, LDH↓, JC-1↓, ADAMTS5↓, MMP13↓	Zhou et al, 2023[29]
Phillygenin	IL-1β-treated mouse chondrocyte	5, 10, 20, 40 μM	Cytoplasm, IkBα↑Nucleus, NRF2↑, HO-1↑, P65↓	iNOS, IL-6, Ptgs2, TNF-α, COX2, Nitrite, PGE2, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓, DCF↓, JC-1↓	Zhang et al, 2023[30]
Orientin	IL-1β-treated mouse cchondrocytes	10, 25, 50 μM	Nucleus, NRF2↑, p65↓Cytoplasm, HO-1↑ Whole cell, p-p65/ p65↓, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Aggrecan↑, Collagen II↑, MMP13↓, ADAMTS5↓	Xia et al, 2023[31]
Stevioside	IL-1β-treated mouse chondrocytes	10, 20, 40 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, Nitrite↓, PGE2↓, Collagen II↑, Aggrecan↑, ADAMTS4↓, MMP13↓	Wu et al, 2023[32]
Suramin	IL-1β-treated mini-pigs chondrocytes	5, 10 μM	Whole cell, NRF2↑, p-p65/ p65↓	iNOS↓, IL-6↓, IL-8↓, TNF-α↓, COX2↓, Nitrite↓, PGE2↓, SOX9↑, Collagen II↑, Aggrecan↑, ADAMTS4↓, ADAMTS5↓, MMP3↓, MMP13↓	Shen et al, 2023[33]
Chrysophanol	IL-1β-treated mouse chondrocytes	10, 20, 40 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, NQO1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS4↓, MMP13↓	Lu et al, 2023[34]
Tangeretin	IL-1β-treated mouse chondrocytes	5, 10, 20 μM	Nucleus, NRF2↑, p65↓Cytoplasm, HO-1↑ Whole cell, NRF2↑, p-p65/ p65↓, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Shi et al, 2022[35]
Chicoric acid	TNF-α-treated human chondrocytes	5, 10, 20 μM	Nucleus, NRF2↑, p65↓ Whole cell, HO-1↑, p-p65/ p65↓, pIkBα/IkBα↓	iNOS↓, IL-1β↓, IL-12↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP3↓, MMP9↓, MMP13↓	Qu et al, 2022[36]
Linalool	IL-1β-treated mouse chondrocytes	100, 200, 400 μM	Nucleus, NRF2↑, p65↓Cytoplasm, HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Miao et al, 2022[37]
Ginkgolide C	H_2O_2-treated rat chondrocytes	7.5, 15, 30 μM	Nucleus, NRF2↑, p65↓ytoplasm, NRF2↓, p-IkBα↓, IkBα↑hole cell, NRF2↑, HO-1↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, ADAMTS4↓, MMP3↓, MMP13↓, ROS↓, Bax↓, Cleaved Caspase-3↓, Bcl-2↑	Ma et al, 2022[38]
Asiaticoside	TBHP-treated mouse chondrocytes	25, 50, 100 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, IkBα↑	Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓, Bax↓, Cleaved Caspase-3↓, BCL2↑	Luo, et al, 2022[39]
Corynoline	IL-1β-treated mouse chondrocytes	2, 4 μM	Nucleus, NRF2↑, p65↓ Whole cell, NRF2↑, HO-1↑, p-p65/p65↓, p-IkBα/ IkBα↓	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, ROS↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP3↓, MMP13↓	Li et al, 2022[40]
Rhoifolin	IL-1β-treated rat chondrocytes	10, 20 μM	Nucleus, NRF2↑, p65↓ Whole cell, HO-1↑, IkBα↑	IL-6↓, TNF-α↓, COX2↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP3↓, MMP13↓	Chen et al, 2022[41]
Procyanidin B2	IL-1β-treated rat chondrocytes	20, 40 μM	Nucleus, NRF2↑, p65↓ Whole cell, HO-1↑, p-p65/p65↓, IkBα↑	IL-6↓, IL-8↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP3↓, MMP10↓, MMP13↓	Cai et al, 2022[42]
Maltol	IL-1β-treated mouse chondrocytes	25, 50, 100 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Zhu et al, 2021[43]
Lycopene	IL-1β-treated mouse chondrocytes	0.5, 2.5, 5 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Zhan et al, 2021[44]

Betulin	IL-1β-treated mouse chondrocytes	25, 50, 100 μM	Nucleus, NRF2↑, p65↓ Cytoplasm, HO-1↑, IkBα↑ Whole cell, HO-1↑, p-p65/p65↓, p-IkBα↓	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Ren et al, 2021[45]
Limonin	IL-1β-treated mouse chondrocytes	15, 30, 60 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Jin et al, 2021[46]
Xanthohumol	IL-1β-treated mouse chondrocytes	10, 25, 50 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Chen et al, 2021[47]
18β-Glycyrrhetinic acid	IL-1β-treated mouse chondrocytes	10, 25, 50 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Chen et al, 2021[48]
moracin	IL-1β-treated rat chondrocytes	5, 10, 15 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Zhou et al, 2020[49]
Nomilin	IL-1β-treated mouse chondrocytes	5, 10 μM	Nucleus, p65↓ Cytoplasm, IkBα↑ Whole cell, NRF2↑, HO-1↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Xue et al, 2020[50]
hesperetin	IL-1β-treated human chondrocytes	10, 20, 40 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Lin et al, 2020[51]
Akebia Saponin D	IL-1β-treated mouse chondrocytes	50, 100, 200 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Gu et al, 2020[52]
Sinomenine	IL-1β-treated mouse chondrocytes	6.25, 12.5, 25 μM	Nucleus, NRF2↑, p-p65/ p65↓Cytoplasm, HO-1↑, p-IkBα/IkBα↓	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitric oxide↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP3↓, MMP13↓	Wu et al, 2019[53]
Sinapic acid	IL-1β-treated human chondrocytes	40, 80, 160 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP9↓, MMP13↓	Li et al, 2018[54]
Monascin	IL-1β-treated mouse chondrocytes	5, 10, 15 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Collagen II↑, Aggrecan↑, ADAMTS5↓, MMP13↓	Zheng et al, 2018[55]
Sauchinone	IL-1β-treated mouse chondrocytes	1, 3, 10 μM	Nucleus, NRF2↑, p65↓ Cytoplasm,HO-1↑, p-IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Aggrecan↑, Collagen II↑, ADAMTS5↓, MMP3↓, MMP13↓	Wu et al, 2018[56]
Piceatannol	IL-1β-treated human chondrocytes	1, 5, 10 μM	Nucleus, NRF2↑, p65↓Cytoplasm,HO-1↑, IkBα↑	iNOS↓, IL-6↓, TNF-α↓, COX2↓, PGE2↓, Nitrite↓, Aggrecan↑, Collagen II↑, ADAMTS5↓, MMP13↓	Tang et al, 2017[57]

Abbreviations: NRF2, Nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-B; P65, nuclear transcription factor P65; HO-1, heme oxygenase-1; NQO-1, NAD (P)H,quinone oxidoreductase 1; P-P65, phosphorylated nuclear transcription factor P65; IKBα, Inhibitor of KB alpha; STING, Stimulator of Interferon Genes; iNOS, inducible nitric oxide synthase; COX2, Cyclooxygenase-2; TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin-6; PGE2, Prostaglandin E2; NO, Nitric Oxide; MMP13, matrix metallopeptidase 13; ADAMTS5, A Disintegrin And Metalloproteinase With Thrombospondin 5; LDH, Lactate Dehydrogenase; JC-1, 5,5,6-chloromethyl2,6-bis (ethylamino) triphenylene; Ptgs2, prostaglandin-endoperoxide synthase 2; DCF, Dichlorofluorescein; ADAMTS4, A Disintegrin And Metalloproteinase With Thrombospondin 4; IL-8, Interleukin 8; SOX9, SRY-related high-mobility group box 9; MMP3, matrix metallopeptidase 3; IL-12, Interleukin-12; MMP9, Matrix metalloproteinase 9; ROS, Reactive Oxygen Species; Bax, BCL2 Associated X protein; BCL2, B-cell lymphoma-2; MMP10, matrix metallopeptidase 10.

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a significant component of OA progression.[58] Consequently, alleviating oxidative stress within cartilage can substantially attenuate OA progression. Activation of the NRF2/ARE signaling pathway manifests protective effects against OA pathogenesis by upregulating antioxidant factors such as HO-1, NQO1, Glutathione (GSH), Glutathione Peroxidase (GPx), and Superoxide Dismutase (SOD), thereby suppressing oxidative stress in chondrocytes.[59] As shown in Table 2, Fibroblast growth factor 9,[60] Curcumin,[61] catalase,[61] Ellagic acid,[62] Allicin,[63] Sulforaphane,[63] Lycopene[63] and Cudratricusxanthone O[64] can activate NRF2 in chondrocytes, thereby activating antioxidant enzymes such as HO-1, SOD, and GPx, effectively reducing oxidative stress levels in OA chondrocytes.

Regulation of Cartilage Matrix Synthesis

Notably, Sex-determining Region Y (SRY)-box 9 (SOX9) serves as an indispensable transcription factor for chondrocyte lineage differentiation during embryonic development and postnatally in the growth plate and articular chondrocytes.[65] Additionally, SOX9 acts as a major driver behind osmolarity-determined chondrogenic differentiation capacity of progenitor cells,[66] wherein osmolarity enhances cartilage Extracellular Matrix (ECM) marker expression while specifically affecting ADAMTS4 and ADAMTS5.[67] One pivotal function of NRF2 could be to maintain sufficiently high SOX9 expression in articular cartilage throughout aging, thereby mediating ADAMTS suppression to protect cartilage integrity, consequently delaying OA onset.[68]

Senescence

Age governs NRF2 homeostasis in human articular chondrocytes, with NRF2 protein levels notably lower in older adult chondrocytes (approximately 0.59 fold; $P = 0.034$) and OA chondrocytes compared to younger cells.[69] In OA cartilage, oxidative stress presence upregulates aging-related factors such as Tumor Protein p53 (p53) and Cyclin-Dependent Kinase Inhibitor 2A (p16INK4a), promoting senescence in chondrocytes. The NRF2 signaling pathway regulates the expression of various antioxidant enzymes to inhibit chondrocyte aging. As shown in Table 3, Theaflavin,[70] Itaconate,[28] Procyanidin B2,[42] and S-allyl cysteine[71] effectively activate the NRF2 signaling pathway, thereby inhibiting aging in OA chondrocytes.

Apoptosis

Inflammatory environments (such as high IL-1β) and oxidative stress can induce apoptosis in chondrocytes.[75,76] NRF2 activation in OA chondrocytes can counteract these effects by inhibiting IL-1β-induced mitochondrial dysfunction, Reactive Oxygen Species (ROS) production, and apoptosis.[19] Overexpression of NRF2 upregulates the expression of anti-apoptotic factors, downregulates pro-apoptotic proteins, and activates Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) and its downstream factors, such as ETS-Like Transcription Factor 1 (ELK1), Ribosomal Protein S6 Kinase, 70 kDa (P70S6K), and 90 kDa Ribosomal S6 Kinase (P90RSK).[19] Moreover, NRF2 indirectly impacts chondrocyte apoptosis and senescence by controlling the expression of glyoxalase I, an enzyme responsible for detoxifying methylglyoxal.[77]

Pyroptosis

Pyroptosis is a type of proinflammatory programmed cell death that is triggered by inflammasomes, which is strongly correlated with OA progression.[78] It is also reported that activation of the NRF2 signaling pathway may alleviate the progression of OA by suppressing the NOD-like Receptor Protein 3 (NLRP3) inflammasome in primary mouse chondrocytes.[79] As shown in Table 4, Cardamonin,[80] Ginkgolide C,[81] Licochalcone A,[79] Loratadine,[82] Bisdemethoxycurcumin,[83] Cucurbitacin B[84] effectively inhibit pyroptosis in OA chondrocytes by activating the NRF2 signaling pathway.

Ferroptosis

Ferroptosis, characterized by excessive lipid peroxidation and iron accumulation, is a nonapoptotic cell death process that plays a significant role in the progression of OA.[85] The NRF2-ARE system can inhibit or repair lipid peroxidation damage through multiple pathways, thus reducing chondrocytes ferroptosis.[86,87] Firstly, key synthesizing enzyme genes of the GSH-GPx4 pathway are positively regulated by NRF2, such as enzymes promoting GSH biosynthesis (glutamate-cysteine ligase, GSH synthetase, and Solute Carrier Family 7 Member A11 (SLC7A11)), GSH reductase, and GPx4.[85] NRF2 can also activate the thioredoxin system to compensate for the GSH system.[88] Moreover, NRF2 is a central control factor for the expression of NQO1 under steady and stress conditions.[89] NQO1, a homodimeric flavoenzyme, can

Table 2 The Antioxidant and Anti-Chondrocyte Apoptotic Effects of NRF2

Regulators	Cell Type and Source	NRF2 Signaling Pathway	Anti-oxidative Actions	Mitochondrial Dysfunction	Anti-apoptotic Actions	Author (year)
Fibroblast growth factor 9	TBHP-treated mouse chondrocytes	Nucleus, NRF2↑	DHE↓, HO-1↑, C-CASP3↓, Cyt-C↓, SOD2↑, CAT↑	Mito ROS↓, JC-1 intensity (Aggrega-tes/Monomers)↑	TUNEL positive cells↓, BAX↓, BCL2↑	Pan et al, 2023[60]
Curcumin and catalase	IL-1β-treated rat chondrocytes	NRF2↑	ROS↓, Lipid ROS↓, MDA↓, HO-1↑, SOD1↑, SOD2↑, Catalase↑,	JC-1 Monomers↓	BAX↓, BCL2↑	Chen et al, 2023[61]
Ellagic acid	IL-1β-treated human chondro-cytes	Nucleus, NRF2↑Keap1↓	HO-1↑, NQO1↑, SOD1↑, SOD2↑	JC-1 intensity (Aggregates/ Monomers)↑		Zhu et al, 2022[62]
Allicin or Sulforaphane or Lycopene	H_2O_2-treated human chondro-cytes	p-NRF2↑, NRF2↑, Keap1↓	GPX1↑, GPX3↑, GPX4↑, SOD1↑, CAT↑, GST↑		Apoptosis ratio↓	Yang et al, 2020[63]
Cudratricusxanthone O	H_2O_2-treated human chondro-cytes	Nucleus, NRF2↑,HO-1↑ Cytoplasm: NRF2↓, HO-1↑	ROS↓, HO-1↑, SOD↑, CAT↑		AnnexinV↓, Caspase 3/7↑, BAX↓, BCL2↑, Caspase 3↑	Kim et al, 2020[64]

Abbreviations: TBHP, t-butylhydroperoxide; DHE, Dihydroethidium; C-CASP3, Caspase-3; Cyt-C, Cytochrome C; SOD2, Superoxide Dismutase 2; CAT, Catalase; Mito ROS, mitochondrial reactive oxygen species; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay; MDA, Malondialdehyde; SOD1, Superoxide Dismutase 1; GPX1, Glutathione peroxidase 1; GPX3, Glutathione peroxidase 3; GPX4, Glutathione peroxidase 4; GST, glutathione S-transferase; SOD, Superoxide Dismutase.

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Table 3 The Role of NRF2 in Regulating Chondrocyte Senescence

Regulators	Cell Type and Source	NRF2 Signaling Pathway	Anti-senescence Actions	Author (year)
Sirt 6	IL-1β-treated human chondrocytes	Nucleus, NRF2↑ Whole cell, Keap1↓, HO-1↑	SA-β-Gal↓, p16↓, p53↓, p21↓	Mao et al, 2024[72]
Patchouli Alcohol	D-galactose-treated mouse chondrocytes	Nucleus, NRF2↑ Whole cell, HO-1↑	SA-β-Gal↓, p53↓, p21↓	Chen et al, 2022[73]
Procyanidin B2	IL-1β-treated rat chondrocytes	Nucleus, NRF2↑ Whole cell, HO-1↑	SA-β-Gal↓, apoptosis ratio↓, BCL2↑, Bax↓, Caspase 3↓, p16↓, p21↓	Cai et al, 2022[42]
Theaflavin	TBHP-treated mouse chondrocytes	Nucleus, NRF2↑ Whole cell, HO-1↑	SA-β-Gal↓, Cleaved caspase 3↓, p16INK4a↓	Xu et al, 2021[70]
S-allyl cysteine	TBHP-treated mouse chondrocytes	Nucleus, NRF2↑ Whole cell, HO-1↑	SA-β-Gal↓, p21↓, p16INK4a↓, TUNEL positive cells↓, CASP3↓, Bax↓, BCL2↑	Shao et al, 2020[71]
Pinitol	TNF-α-treated human chondrocytes	Nucleus, NRF2↑	SA-β-Gal↓, GO/G1 phase↓, LDH release↓, Telomerase activity↑, p21↓, p53↓	Lou et al, 2020[74]

Abbreviations: Sirt 6, Sirtuin 6; SA-β-Gal, senescence-associated β-galactosidase; p53, Tumor Protein p53; p21, P21 One of the mitotic inhibitors (antigen); p16, MTS (multiple tumor suppressor 1); p16INK4a, Cyclin-Dependent Kinase Inhibitor 2A.

Table 4 Activation of NRF2 Inhibit Chondrocyte Pyroptosis

Regulators	Cell Type and Source	NRF2 Signaling Pathway	Anti-inflammasome Actions	Author (year)
Cardamonin	IL-1β-treated human chondrocytes	NRF2↑, NQO-1↑	NLRP3↓, Caspase 1↓, ASC↓	Jiang et al, 2021[80]
Ginkgolide C	ATDC5 cell line	NRF2↑, NOQ1↑, Keap1↓	p-IRE1a/IRE1a↓, TXNIP↓, NLPR3↓, ASC↓, Caspase1↓, GSDMD-N↓	Jia et al, 2024[81]
Licochalcone A	IL-1β-treated mouse chondrocytes	Nucleus, NRF2↑Cytoplasm, HO-1↑	NLRP3↓, Cle-GSDMD/GSDMD↓, Cle-caspase1 /Pro-caspase1↓, ASC↓, IL-1β↓, IL-18↓	Yan et al, 2020[79]
Loratadine	AGEs-treated human chondro-cytes	NRF2↑	NLRP3↓, ASC↓, P10↓, IL-1β↓, IL-18↓	Gao et al, 2020[82]
Bisdemethoxycurcumin	TBHP-treated ATDC5 cell line	NRF2↑, HO-1↑	NLRP3↓, GSDMD↓, Caspase1↓, IL-1β↓	Jin et al, 2024[83]

Abbreviations: NLRP3, NOD-like receptor protein 3; ASC, apoptosis-associated speck-like protein; p-IRE1α/IRE1α, Phosphorylation-Inositol-requiring enzyme 1α/Inositol-requiring enzyme 1α; TXNIP, thioredoxin-interactingprotein; GSDMD-N, the cleaved N-terminal end of gasdermin D; Cle-GSDMD/GSDMD, cleaved-gasdermin D/gasdermin D; AGEs, Advanced glycation end-products; P10, caspase-9 p10 Protein.

catalyze the reduction of quinones to hydroquinones in a single-step, two-electron reduction reaction; it also plays a significant role in protecting endogenous antioxidants by maintaining the reduced forms of ubiquinone and α-tocopheryl quinone. NRF2 can also regulate the detoxification of lipid peroxidation downstream products, such as by transcriptionally activating the expression of the aldo-keto reductase family (AKR1C1-3) and the aldehyde dehydrogenase family (ALDH3A1).[86,87] Finally, NRF2 promotes the expression of ferritin and Ferroportin 1 to store or export free iron, thus reducing intracellular iron accumulation and preventing the occurrence of ferroptosis.[90] Targeting NRF2 activation could effectively inhibit ferroptosis in chondrocytes. As shown in Table 5, Gamma-oryzanol,[91] Baicalein,[92] Curcumin,[93] and Deferoxamine[94] effectively inhibit cartilage cell ferroptosis by activating the NRF2 signaling pathway.

The Role of NRF2 in Macrophages

Macrophages are primarily classified into M1 and M2 types, where M1 macrophages are pro-inflammatory and M2 macrophages are anti-inflammatory.[95] In the OA microenvironment, synovial macrophages predominantly differentiate into the M1 type, secreting large amounts of inflammatory cytokines, thereby damaging cartilage and exacerbating the progression of OA. In contrast, M2 macrophages can promote the repair of cartilage.[96] Thus, effectively regulating

Table 5 Activation of NRF2 Inhibits Chondrocyte Ferroptosis

Regulators	Cell Type and Source	NRF2 Signaling Pathway	Anti-ferroptosis Actions	Author (year)
Gamma-oryzanol	IL-1β-treated rat chondrocytes	Nucleus, NRF2↑Cytoplasm, HO-1↑	GPX4↑, SLC7A11↑, GSH↑, HO-1↑, MDA↓, Lipid ROS↓	Dai et al, 2024[91]
Baicalein	IL-1β-treated mouse chondro-cytes	NRF2↑, Keap1↓	Intra-cellular iron ↓, HO-1↑, Lipid ROS↓, mitochondrial damage↓	Wan et al, 2023[92]
Curcumin	Erastin-treated mouse chondro-cytes	NRF2↑	Intra-cellular iron ↓, MDA↓, SOD↑, GSH-Px↑, ACSL4↓, SLC7A11↑, GPX4↑, FTH1↑, TFR1↓	Zhou et al, 2023[93]
Deferoxamine	IL-1β-treated mouse chondro-cytes	NRF2↑	Intra-cellular iron ↓, HO-1↑, NQO1↑, ACSL4↓, LOX15↓, LPCAT3↓, p53↓, MDA↓, Lipid ROS↓, mitochondrial damage↓	Guo et al, 2022[94]

Abbreviations: SLC7A11, Solute Carrier Family 7 Member 11; GSH, L-Glutathione; GSH-Px, Glutathione Peroxidase; ACSL4, Acyl-CoA synthetase long-chain family member 4; FTH1, Ferritin Heavy Chain 1; TFR1, Transferrin Receptor 1; LOX15, Lipoxygenase 15; LPCAT3, Lysophosphatidylcholine Acyltransferase 3.

macrophage polarization is a crucial strategy for alleviating OA. Notably, NRF2 can effectively inhibit the differentiation of macrophages into the M1 type and promote differentiation into the M2 type.[9] STUB1, also known as CHIP, is a chaperone-dependent E3 ubiquitin ligase that can ubiquitinate NRF2, thus inhibiting its function.[97] The research team led by Zheng Wang demonstrated that silencing STUB1 reduces NRF2 ubiquitination, thereby promoting macrophage differentiation into the M2 type and inhibiting the progression of OA. Another research team showed that TRPV1-evoked Ca(2+) influx promoted the phosphorylation of calcium/calmodulin-dependent protein kinase II (CaMKII) and facilitated the nuclear localization of NRF2, ultimately resulting in the inhibition of M1 macrophage polarization.[98] These results prove that NRF2 is a key target for regulating macrophage polarization. Regarding the mechanism, NRF2 may inhibit M1 macrophage differentiation by promoting the expression of HO-1, thereby inhibiting the NF-κB signaling pathway. NRF2 may promote M2 macrophage differentiation through the Transforming Growth Factor-beta/SMAD (TGF-β/SMAD) and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathways.[9] Besides regulating macrophage polarization, NRF2 can also directly block the transcription of pro-inflammatory cytokines, thereby inhibiting the inflammatory response of macrophages.[99] In summary, the activation of NRF2 can inhibit inflammatory macrophages, promote the differentiation of macrophages into a reparative type, and thus effectively protect cartilage and inhibit the progression of OA.

The Role of NRF2 in Synovial Fibroblasts

In the inflammatory microenvironment of OA, macrophages and synovial fibroblasts in the synovium are often in an activated inflammatory state. Activated synovial fibroblasts produce a large amount of inflammatory cytokines (such as IL-1β, Tumor Necrosis Factor-α (TNF-α)), metabolic degradation factors (such as MMPs and ADAMTS), and ROS. These factors further activate the synovial inflammation and damage cartilage. Therefore, inhibiting synovial inflammation is crucial for alleviating OA. The activation of NRF2 is vital for inhibiting the activation of inflammatory synovial fibroblasts. NRF2 activators such as oltipraz can inhibit the hyperactivation of human fibroblasts.[21] Carnosine can activate NRF2 and HO-1 expression, effectively inhibiting MMPs and ROS levels in inflammatory synovial fibroblasts and protecting the mitochondrial membrane potential.[100] The dihydroartemisinin derivative DC32 can also effectively activates the NRF2 signaling pathway, and concurrently inhibits the NF-κB signaling pathway, thereby effectively suppressing synovial inflammation.[101] These results indicate that NRF2 is a key target for inhibiting synovial inflammation, thus protecting cartilage.

Inhibition of Osteoclastogenesis

Osteoclasts impact the development and progression of OA through various mechanisms.[7,8] In OA, increased osteoclast activity leads to bone loss, particularly in the subchondral bone, which in turn results in subchondral bone sclerosis and

osteophyte formation. Additionally, osteoclasts are activated in the inflammatory environment of arthritis and can secrete inflammatory factors and enzymes, which promote local inflammation. Therefore, inhibiting osteoclast activity is crucial for slowing the progression of OA. The activation of the NRF2/HO-1 signaling pathway can effectively inhibit nuclear factor-κB ligand (RANKL)-induced osteoclast formation and extracellular matrix (ECM) degradation.[102]

Pain

Pain is a prominent symptom of OA.[103] The types of pain associated with OA are still debated. Nerve damage, inflammation, and damaged joint tissues might be the causes of OA pain.[104] Pharmacologic treatment of OA pain relies primarily on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioids.[103] NSAIDs are not effective in alleviating OA pain, and opioids have multiple side effects, such as nausea and dizziness.[105] Therefore, new treatment options are needed. The activation of NRF2 can alleviate pain behaviors in rats with OA. The activation of NRF2 nuclear transcription can enhance the synthesis of peroxidase enzymes, such as GSH, NQO1, and glutathione S-transferase (GST), leading to a subsequent reduction in the initial pain experienced in OA.[106–108]

Antioxidants Combined with Nanospheres

NRF2 activators such as Oltipraz, curcumin, and resveratrol suffer from poor water solubility, which significantly impacts their biological activity. With advancements in nanotechnology, issues such as poor drug solubility and rapid degradation can be effectively addressed. Hengfeng Yuan's team encapsulated the NRF2 activator Oltipraz in ROS-responsive nanoparticles, which, compared to standalone nanoparticles, could effectively activate the NRF2/HO-1 signaling pathway, thereby exhibiting ROS scavenging and anti-apoptotic properties in chondrocytes.[109] A bioactive gel based on gallen gum (GG-CD@ARC) encapsulated with the antioxidant arctiin was developed to alleviate the progression of OA by effectively activating NRF2.[110] Another study demonstrated that antioxidant arbutin-loaded gelatin methacryloyl-liposome (GM-Lipo@ARB) microspheres were developed to activate the NRF2 signaling pathway, reduce oxidative stress in OA cartilage, and thus alleviate OA.[111] Therefore, combining antioxidants with nanotechnology to more efficiently activate the NRF2 signaling pathway could more effectively inhibit the progression of OA.

Conclusion and Prospects

As a transcription factor, NRF2 can affect OA chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. NRF2 inhibits inflammation in OA chondrocytes by suppressing the NF-κB signaling pathway, promotes the expression of various antioxidant enzymes such as HO-1 and NQO1, thus inhibiting oxidative stress, protecting the cartilage extracellular matrix, reducing aging and death of chondrocytes (including apoptosis, ferroptosis, and pyroptosis), and alleviating joint pain. Additionally, NRF2 can inhibit the differentiation of synovial macrophages into the M1 type and promote differentiation into the M2 type, thus creating an environment conducive to cartilage repair. The activation of NRF2 can also inhibit inflammatory synovial fibroblasts, thereby reducing their secretion of pro-inflammatory cytokines and metabolic degradation factors, and protecting the cartilage. NRF2 also inhibits the formation of osteoclasts, thus maintaining the morphology of the subchondral bone. Various drugs have proven effective in alleviating the progression of OA by activating NRF2. Furthermore, the development of nanotechnology can be well integrated with NRF2 activators, activating NRF2 through prolonged drug release, thereby effectively alleviating OA.

Given the protective role of NRF2, researchers should actively explore compounds or drugs that effectively activate NRF2. The specific molecular mechanisms of NRF2 in OA, including its regulatory effects on chondrocytes, synovial fibroblasts, osteoclasts, and macrophages, require further in-depth research. These studies will help to elucidate how NRF2 influences the progression of OA through its antioxidant and anti-inflammatory pathways. Additionally, utilizing gene editing technologies, such as CRISPR-Cas9, to directly regulate NRF2 gene expression has emerged as a novel therapeutic strategy.

While NRF2 exhibits various benefits, current research on NRF2 still faces several challenges and difficulties. Most of the NRF2 activators developed so far lack high selectivity, and while activating the antioxidant pathway, they may also activate other signaling pathways, such as glycolysis and mitochondrial function, leading to unintended biological effects.[112,113] Furthermore, although NRF2 activators may show positive effects in the short term, the safety and side

effects of long-term use still require further investigation. Additionally, while nanocarriers can enhance the efficacy of NRF2 activators, their drug-loading efficiency and sustained-release properties need further improvement. Finally, although NRF2 shows great potential in laboratory studies, translating this potential into clinical applications remains challenging. Currently, clinical research on NRF2 activators in OA remains in its early stages. Most studies are focused on preclinical models, and there are still relatively few clinical trials specifically targeting OA with NRF2 activators. The safety and efficacy of these compounds in long-term human use are still under investigation.

In summary, activation of NRF2 can effectively regulate the function of chondrocytes, synovial macrophages, synovial fibroblasts, and osteoclasts, thereby effectively inhibiting synovial inflammation, protecting cartilage and subchondral bone, alleviating joint pain, and serving as a potential target for treating OA. However, researchers still need to overcome issues of selectivity and safety, as well as challenges related to drug delivery, to achieve clinical application of NRF2 activators. Addressing these challenges will open new prospects for the treatment of OA.

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Disclosure

The authors report no conflicts of interest in this work.

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