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REVIEW

Nrf2 participates in progression of osteoarthritis through modulating redox balance

Zihan Deng[a, #], Chuan Yang[b, #], Yueqi Chen[a, *]

[a] *Department of Orthopedics, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China.*
[b] *Department of Biomedical Materials Science, Third Military Medical University (Army Medical University), Chongqing, China.*

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Abstract

Osteoarthritis (OA) is one of the most common degenerative joint diseases associated with aging, obesity and joint trauma, and is always associated with pain, joint deformity and dysfunction. Recent studies have shown that OA is closely related to oxidative stress, which serves as a major cause of chronic inflammation in cartilage, leading to irreversible structural changes in the joint. As a transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2) plays an important role in the antioxidant system, which regulates the expression of cytoprotective genes to facilitate the elimination of reactive oxygen species (ROS). In this review, we have summarized the dramatic function of oxidative stress in OA pathology, established a complex regulatory network of Nrf2 in OA progression, and aimed to provide new insights into the treatment of OA.

Keywords: Osteoarthritis, nuclear factor-erythroid 2-related factor, oxidative stress, redox balance, chondrocyte

Introduction

As a common chronic degenerative disease, osteoarthritis (OA) is associated with increasing obesity and global population aging, and has become a major public health burden, currently affecting more than 500 million people worldwide [1]. OA is mainly characterized by pain as the primary clinical manifestation, which gradually affects the stability of joint motion and ultimately leads to the disability, thereby reducing the quality of patient's life. To date, the risk factors that contribute to the development of OA are diverse, including aging, trauma, obesity, as well as mechanical loading and many other factors [2]. Aging is one of the most evident risk factors for the pathogenesis of OA, and studies have shown the presence of a large number of senescent chondrocytes in the cartilage of hip and knee joints in OA patients [3, 4]. Specifically, with the progression of aging, senescent chondrocytes gradually accumulate in OA joints and secrete a variety of senescence-associated secretory phenotypes (SASPs), including various pro-inflammatory cytokines and matrix metalloproteinases (MMPs), which can activate chronic inflammatory responses and induce oxidative stress, thus contributing to the accumulation of reactive oxygen species (ROS) and leading to the disruption of antioxidant enzymes and ROS scavenging systems [5]. ROS are the toxic by-products of aerobic metabolism that are both essential and lethal for cell behavior [6]. On the one hand, ROS are required for cellular signal transduction in many fundamental biological processes, including cell growth and differentiation [7]. On the other hand, ROS can be toxic to DNA, proteins and lipids, leading to severe oxidative damage to cells and even cell death. Recent studies have demonstrated that low-grade chronic inflammation increases ROS accumulation and leads to excessive oxidative stress, which causes abnormal cell metabolism in chondrocytes, thereby accelerating cartilage degradation [8]. Therefore, maintaining oxidant-antioxidant balance and redox homeostasis in OA chondrocytes is essential for

# Zihan Deng and Chuan Yang contributed equally to this work.
* Corresponding author: Yueqi Chen
Mailing address: Department of Orthopedics, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China.
Email: chenyueqi1012@sina.com
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OA treatment and remission.

Nuclear factor-erythroid 2-related factor (Nrf2) is widely recognized as an important component of the antioxidative stress system, which is heavily involved in the cellular defense against multiple pathological stressors and maintains the homeostasis of the intracellular environment. Nrf2 functions cytoprotective roles by modulating the expression of various important genes involved in the scavenging of ROS, reactive nitrogen species (RNS) and electrophiles. Specifically, Nrf2-induced antioxidation is generally achieved by enzymes that regulate the biological synthesis, utilization, and regeneration of the reduced glutathione (GSH). In the process of GSH synthesis, Nrf2 targets three key enzyme genes, including glutamate cysteine ligase catalytic (GCLC), modulator (GCLM) subunits, and glutathione synthetase (GSS). In addition, the redox cycling enzymes thioredoxin, thioredoxin reductase and many other glutathione S-transferases that are responsible for scavenging ROS are also the targets of Nrf2 [9]. Interestingly, Nrf2 also forms a large network of cooperating enzymes in the regulation of basal metabolic processes, mainly including metabolic enzymes involved in the pentose phosphate pathway and fatty acid metabolism, which form a potential bridge between redox and intermediary metabolism [5, 10-12].

It has been well studied that the Nrf2 protein consists of seven functional domains, including Neh2, Neh4, Neh5, Neh7, Neh6, Neh1, and Neh3 from the N-terminus to the C-terminus. Among these functional domains, Neh2 and Neh6 affect Nrf2 stability, with the Neh2 domain responsible for Keap1-mediated Nrf2 degradation, and Neh6 involved in the negative modulation of Nrf2 via the serine-rich domain [13]. Neh3 could recruit the chromo-ATPase/helicase DNA-binding protein, and Neh4 and Neh5 form the transactivation domain to recruit CREB-binding protein (CBP), which participates in Nrf2-dependent transcriptional activation of genes with the ARE sequence in the promoter [14]. The Neh1 domain promotes Nrf2 heterodimerization with small musculoaponeurotic fibrosarcoma (Maf) proteins to achieve DNA binding [15, 16]. In addition, Neh1 interacts with the ubiquitin-conjugating enzyme UbcM2, which enhances the transcriptional activity of endogenous of Nrf2 [17]. The Neh7 domain binds and interacts with the retinoid X receptor alpha (RXRα), which is a repressor of Nrf2 [18]. Recent studies have demonstrated that Nrf2 plays a critical role in numerous common human diseases associated with oxidative stress, such as type 2 diabetes and cardiovascular disease. In fact, Hinoi *et al*. and Solomon *et al*. found that appropriate Nrf2 activity is also essential for chondrocyte differentiation and maturation and cartilage metabolism [19, 20]. In addition, Nrf2 was also found to modulate osteoclastogenesis in bone resorption and remodeling, further demonstrating the key role of Nrf2 in bone homeostasis [21]. Therefore, we summarized the underlying mechanisms by which Nrf2 regulates oxidative stress in OA and aimed to develop novel biopharmaceuticals for the treatment of OA.

Pathogenesis of OA

OA, the most common chronic joint disease with increasing incidence in an aging and increasingly obese population, is a major cause of disability in the elderly and has a significant impact on socioeconomic costs [22-24]. In recent years, researchers have increasingly focused on the important role of articular cartilage in the progression of OA. Articular cartilage, a specialized dense connective tissue, is composed of chondrocytes and extracellular matrix, and has avascular and alymphatic properties that affect its natural ability to self-repair [22, 23]. Articular cartilage covers the load-bearing surface of the bone to form a smooth articular contact surface that absorbs external mechanical pressures or stimuli to achieve painless joint motion [24].

OA is a degenerative change that disrupts the dynamic balance between joint tissue destruction and repair, resulting in the loss of normal physiological joint function [25]. The complex pathogenesis of this disease involves several aspects, such as increased inflammatory components, mechanical overload, and metabolic disorders, which gradually contribute to structural changes in the articular and periarticular tissues, specifically leading to apoptosis of chondrocytes and progressive degeneration of articular cartilage [22, 26-29]. Chondrocytes in OA are activated by various factors that lead to cartilage degradation, such as high mechanical stress, erosion of a large number of pro-inflammatory cytokines, imbalanced oxidative stress, and senescence, among others, leading to the disruption of joint homeostasis and further inducing the production of matrix-degrading enzymes, resulting in bone metabolic disorders and aberrant inflammatory osteolysis [30-32]. Initially, alterations in chondrocyte function in OA cause progressive cartilage degradation and destruction, which may be accompanied by persistent secondary inflammation [33]. As cartilage degeneration progresses, osteoclast-mediated bone resorption is abnormally accelerated, leading to bone cysts and sclerotic bone formation. In addition, cartilage and bone loss disrupts bone matrix homeostasis and triggers compensatory osteoblast-mediated bone remodeling. In advanced disease, deeper cartilage fissures are followed by osteoblast oversynthesis, leading to osteophyte formation at the joint margins, expansion of the calcified cartilage zone, and periarticular fibrosis [22, 34].

It is noteworthy that hypertrophic chondrocytes exhibit increased synthetic activity during the repair process, producing numerous pro-inflammatory mediators and stromal degradation products that act on the adjacent synovium to facilitate proliferation and inflammatory responses, accompanied by tissue hypertrophy and angiogenesis [22, 35]. Insights into the pathophysiology of the disease indicate that mutations or errors in the gene expression of matrix molecules and certain factors that modulate the synthesis of matrix components may lead to chondrocyte hypertrophy and dysfunction, resulting in chondrodysplasia at a relatively early age [34]. Furthermore, chondrocytes located near load-bearing regions are more likely to acquire this altered phenotype, and susceptibility to OA also increases with age. In the middle and late phases of OA, various cell types (including chondrocytes,

osteoclasts, osteoblasts, and immune cells, *etc*.) may be involved in the pathogenesis, and all of them may exhibit abnormal gene expression and disruption of the oxido-antioxidant balance, ultimately leading to OA predisposition in the elderly population [5].

Dramatic role of oxidative stress in OA pathology

Over the past few decades, numerous studies have demonstrated that oxidative stress plays an integral role in the pathogenesis of several age-related diseases, including cardiovascular, bone, renal, and neurodegenerative diseases [36]. Furthermore, increased oxidative stress and decreased mitochondrial antioxidant capacity affect physiological cellular signaling pathways, which may contribute to senescence through progressive loss of cellular integrity and disruption of tissue homeostasis [37, 38]. In the context of OA, there is a growing consensus that oxidative stress is a driver of an imbalance between catabolic and anabolic signals in cartilage, which progressively induces bone matrix degradation as the disease progresses, leading to aberrant inflammatory osteolysis [39].

ROS, consisting of superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH), among others, are by-products of normal cellular metabolism that are generated in electron transport chain reactions and are primarily responsible for transferring electrons to molecular oxygen in the mitochondria [40]. This process is limited by the oxidoreductase $p66^{Shc}$, which translocates to mitochondria in response to exogenous signals such as growth factor deprivation, oxidative stress, and ultraviolet radiation [40, 41]. ROS in mitochondria can cause oxidative stress and is a predominant regulator of cellular senescence, inducing multiple genes to facilitate mitochondrial dysfunction, swelling and apoptosis associated with aging, as well as triggering senescence or dedifferentiation of chondrocytes [42]. Additionally, some ROS are produced by non-mitochondrial pathways, namely NADPH oxidase (NOX) or dual oxidase (DUOX), which exist in discrete regions of plasma or endosomal membranes. And NOX enzymes can regulate downstream signals for cell activation, differentiation, proliferation, and apoptosis in healthy cells, whereas they are responsible for confining H_2O_2 to specific cellular microdomains and preventing its diffusion into the cytoplasm, thereby blocking abnormal signaling [43, 44]. It has been reported that ROS (such as H_2O_2 and $O_2^{\cdot -}$) and RNS [including $\cdot$NO and peroxynitrite ($ONOO^-$)] play an important role in regulating chondrocyte function, disrupting cartilage homeostasis, and inducing the progression of osteoarthritis [45-47].

In chondrocytes, osteoblasts, and osteoclasts of OA, aberrant ROS signaling is often accompanied by a spatiotemporal progression of damage from the articular surface to the subchondral bone. Yudoh *et al*. found that the antioxidant capacity in the degenerated cartilage region of OA patients was dramatically lower than that in the intact cartilage region, indicating that oxidative damage was increased in degenerated cartilage compared with normal cartilage [48]. Interestingly, based on *in vitro* experiments, H_2O_2-cultured chondrocytes had shorter telomere length. In addition, studies have shown that when OA cartilage tissue is treated with H_2O_2, glycosaminoglycans (GAGs), a long linear polysaccharide that can attach to the articular surface with lubricating and protective effects, are gradually reduced in a time-dependent manner. Nevertheless, the use of antioxidants has been confirmed to reverse the above effects, limiting the loss of GAGs and maintaining telomere length [49]. In fact, ROS exert a significant effect on the dynamic balance of osteoclast-mediated bone resorption and osteoblast-mediated bone remodeling under physiological conditions, which is conducive to maintaining bone integrity. However, abnormal levels of ROS can negatively regulate mitochondrial function and lead to changes in signal transduction pathways and gene expression, which may induce chondrocyte apoptosis and senescence, ultimately contributing to cartilage degeneration, as well as alterations in subchondral bone and bone remodeling processes [5].

It is well known that ROS production and clearance in cells are in a state of dynamic equilibrium under physiological conditions, thus maintaining the homeostasis of the internal environment in the cytoplasm. One caveat is that there are some scavenging systems that can be used to detoxify ROS, consisting of catalase, SOD, as well as GSH peroxidase and reductase, *etc* [45]. As a dimeric cytosolic enzyme, SOD1 binds copper and zinc (Cu/Zn-SOD), while SOD2 is a mitochondrial homotetramer binding one manganese ion per subunit (Mn-SOD). Both enzymes are responsible for the conversion of superoxide to H_2O_2 and diatomic oxygen. And catalase, composed of a tetrameric protein, is able to convert H_2O_2 to H_2O and gaseous O_2. Moreover, in the cytosol, the GSH peroxidase and GSH reductase system maintains the reducing environment in cells. When ROS production escapes the antioxidant systems and mechanisms, cells are adversely affected by oxidative stress and become susceptible to activation of apoptotic pathways. ROS-mediated damage can often be reversed by repair, replacement, degradation, or sequestration of the damaged macromolecules, but in some cases the stress can be sustained, driving mitochondrial and cell death or mutagenesis [40, 41]. The biological effects of ROS in all cell types are due to hyperperoxidation, protein carbonylation, direct DNA damage, telomere shortening, epigenetic changes in gene expression and failure of DNA repair, alterations in receptor and metabolic pathways, and autophagy. However, the sources of ROS may differ in different cell types and may depend on the functional and metabolic state of the cell type.

Nrf2 and redox balance during OA progression

Aging is known to be an important pathogenic factor in OA, and Nrf2 may play an indispensable role in inhibiting cellular aging through the antioxidant system. Research has shown that the activity of Nrf2 gradually decreases

during the aging process of human fibroblasts. As expected, silencing of Nrf2 is able to induce premature aging, while pharmacological activation of Nrf2 can increase cell lifespan, suggesting that inhibition of Nrf2 signaling in the context of oxidative stress is able to facilitate premature cell aging [50]. Currently, numerous comprehensive studies have demonstrated that the role of the Nrf2 transcription factor plays an essential role in maintaining cartilage homeostasis and regulating redox balance in OA. Antioxidant and detoxification enzymes such as heme oxygenase 1 (HO-1), sulfiredoxin (Srx), thioredoxin reductase (TrxR), peroxiredoxins (Prxs), catalase, SODs, glutathione peroxidase (GPx), and NADPH:quinone oxidoreductase 1 (NQO1) can be significantly regulated and induced by Nrf2. Therefore, maintaining the stability of Nrf2 physiological function exerts an essential effect in maintaining cellular redox homeostasis [51]. Recent studies have confirmed that activation of Nrf2 can reduce IL-1β-induced ROS production in chondrocytes, further suggesting that Nrf2 is an important determinant of antioxidant response [52, 53]. According to the study by Wang *et al*., the level of Nrf2 protein was decreased in human OA chondrocytes compared with healthy chondrocytes [54]. Interestingly, other studies have confirmed that Nrf2 protein levels are increased in OA cartilage and synovium compared to normal individuals [52, 53]. Furthermore, Khan *et al*. proposed that Nrf2 gene expression is dramatically elevated in severely injured OA cartilage compared to uninjured samples from the same OA joint [53].

Recently, Nrf2 has been shown to play an important role in maintaining cartilage homeostasis *in vivo*. Notably, Wruck *et al*. have found and confirmed that in the mouse model of rheumatoid arthritis, Nrf2 knockout mice exhibited higher levels of oxidative stress and more severe articular cartilage damage, compared to wild-type mice [55]. Furthermore, according to Cai *et al*., Nrf2 knockout mice exhibited a more severe OA phenotype compared to wild-type mice in both post-traumatic OA models and inflammatory OA models [56]. Meanwhile, histone deacetylation inhibitors (TSAs) have been shown to ameliorate the progression of OA in the above two mouse models via TSA-induced acetylation and Nrf2 activation pathways. In chondrocytes, downstream antioxidant mediators (such as HO-1) are activated by acetylation-induced Nrf2 and lead to the upregulation of its expression, which is related to the reduction of matrix metalloproteinase expression [56]. HO-1 is considered to be an important downstream target of Nrf2, and recent evidence has indicated that knockout of Bach1, which is a transcriptional suppressor factor of HO-1, can alleviate the severity of age-related OA and surgically induced OA in mice [57]. *In vitro* studies have shown that articular chondrocytes of Bach1 knockout mice have higher levels of SOD2 protein, which is a key superoxide detoxifying antioxidant. The level of SOD2 was found to decrease in Bach1 knockout cells after HO-1 gene expression was silenced, indicating that the expression of SOD2 is dependent on HO-1. In addition, Takada *et al*. demonstrated that TBHP-induced chondrocyte apoptosis was enhanced when HO-1 expression was silenced, further demonstrating that HO-1 has an essential effect in the dynamic redox balance of cartilage (Figure 1) [57].

Based on accumulating evidence, various types of compounds with antioxidant properties, such as licochalcone A, pterostilbene, resveratroland, wogonin, and 6-gingero, etc., have been identified to play anti-inflammatory as well as cartilage protective roles in the joint of OA via activation of Nrf2 signaling pathways (Table 1). In light of these findings, it is reasonable to speculate that Nrf2 signaling pathways contribute to the maintenance of redox balance and modulation of chondrocyte homeostasis in the process of OA, but the exact signaling pathways responsible for these effects are not fully understood at present. According to the results of Khan *et al*., Nrf2 can modulate IL-1β-induced ROS production by stimulating the ERK MAP kinase pathway, thereby promoting the anti-apoptotic effect, which further elucidates that the regulation of Nrf2-controlled signaling pathways may have an important effect in attenuating oxidation and apoptosis of human OA chondrocytes [53]. Additionally, the in-depth study of Nrf2 has not yet identified any clinical drugs targeting OA, but a variety of new clinical drugs have been developed for the treatment of other diseases. For example, based on a randomized, double-blind, placebo-controlled phase 3 clinical trial (CARDINAL), the Nrf2 activator bardoxolone methyl was approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic kidney disease (CKD) caused by Alport syndrome [58]. Another Nrf2 activator, dimethyl fumarate, can induce upregulation of antioxidant gene expression, and is therefore also approved by the FDA and the European Medicines Agency as a first-line therapy for adult patients with relapsing-remitting MS (RMSS) [59]. However, activation of Nrf2 has been shown to play a double-edged role in cancer. On the one hand, Nrf2 can prevent cancer progression caused by oxidative stress; on the other hand, specific activation of Nrf2 in various cancers can promote cancer cell proliferation as well as induce chemo- and radioresistance of cancer cells [60]. Therefore, potential therapeutic strategies that precisely target Nrf2-regulated pathways may be of clinical value in ameliorating the progression of OA, and much remains to be done.

Conclusion and future perspectives

Accumulating evidence suggests that OA is not only a chronic injury disease limited to the joints, but also a comprehensive and degenerative disease involving multiple systems. There is increasing evidence that oxidative stress plays a dramatic role in age-related changes in articular cartilage, disrupting cartilage homeostasis and contributing to the development of OA. Aging, inflammation, and mechanical loading are capable of inducing oxidative stress and promoting ROS production that damages proteins and DNA, resulting in mitochondrial dysfunction, disruption of cell signaling, and alterations in epigenetic gene expression. Therefore, high levels of ROS signaling pathways and altered Nrf2 activity may facilitate chondrocyte apoptosis along with cartilage degradation and

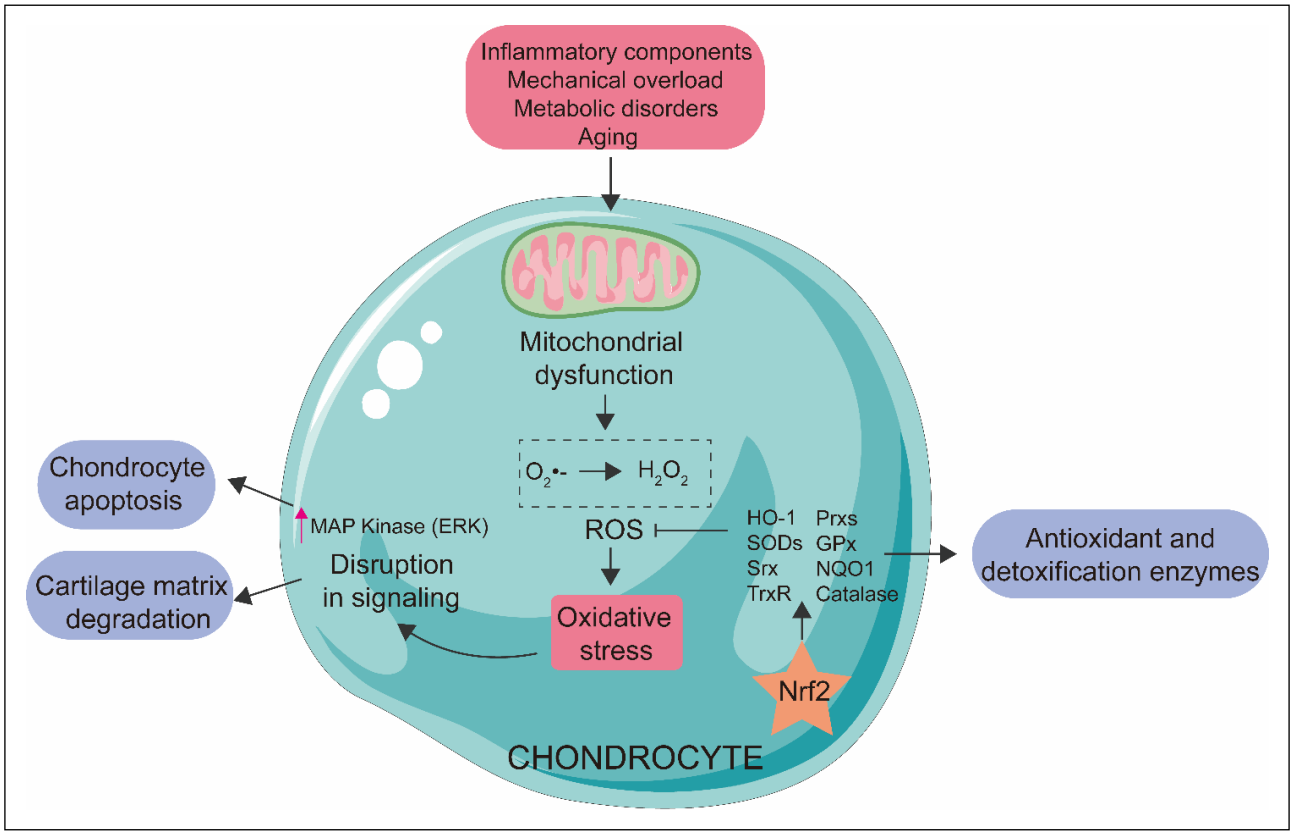

Figure 1. Nrf2 modulates oxidative stress in OA. Various negative stimuli, including inflammatory components, mechanical overload, metabolic disorders and aging, impair the function of the electron transport chain, leading to mitochondrial dysfunction. Then, the ROS system is activated, inducing oxidative stress, which affects cell signaling through the MAP kinase pathway, ultimately contributing to chondrocyte apoptosis and cartilage matrix degradation. Nrf2 is able to modulate antioxidant and detoxification enzymes such as heme oxygenase 1 (HO-1), sulfiredoxin (Srx), thioredoxin reductase (TrxR), peroxiredoxins (Prxs), catalase, SODs, glutathione peroxidase (GPx), and NADPH: quinone oxidoreductase 1 (NQO1), which inhibits the ROS system and thus reduces oxidative stress, further maintaining chondrocyte redox homeostasis and preventing progression of OA.

Table 1. Treatment with bioactive agents with antioxidant activity for OA by targeting Nrf2.

Bioactive agents	Targets	Related signaling pathway	Ref.
Licochalcone A	Nrf2	NF-κB	[53]
Pterostilbene	Nrf2	ERK and NF-κB	[54]
Resveratroland	Nrf2	NF-κB and HO-1	[55]
Wogonin	Nrf2	ERK, HO-1, SOD2, and NQO1	[56]
6-gingero	Nrf2	NF-κB and MAPK	[57]

induce chondrocyte hypertrophy and subchondral bone dysfunction. In addition, decreased Nrf2 activity may be the result of a failure in its homeostatic post-translational regulation and/or altered epigenetic and transcriptional regulatory mechanisms. A large body of experimental evidence indicates that Nrf2 plays a central and complex role in bone integrity, and many functions remain to be elucidated. Treatment methods that increase Nrf2 activity may counteract oxidative stress in OA, thereby effectively limiting cartilage degradation and bone resorption, while restoring the dynamic balance of Nrf2 may induce normalization of bone resorption and remodeling. Thus, the study of the effect of chondrocytes and Nrf2 in OA would be a promising research area for the development of a potential therapeutic strategy for the treatment of OA.

Declarations

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