Review

Oxidative Stress, microRNAs and Long Non-Coding RNAs in Osteoarthritis Pathogenesis: Cross-Talk and Molecular Mechanisms Involved

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Oxidative Stress, microRNAs and Long Non-Coding RNAs in Osteoarthritis Pathogenesis: Cross-Talk and Molecular Mechanisms Involved

Teresa Iantomasi [1,*], Cinzia Aurilia [1], Simone Donati [1], Irene Falsetti [1], Gaia Palmini [2], Roberto Carossino [1], Roberto Zonefrati [2], Francesco Ranaldi [1] and Maria Luisa Brandi [2]

[1] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy
[2] FirmoLab, Fondazione F.I.R.M.O. Onlus and Stabilimento Chimico Farmaceutico Militare (SCFM), 50141 Florence, Italy
* Correspondence: teresa.iantomasi@unifi.it

Abstract: Osteoarthritis (OA) is the most common degenerative joint disease characterized by articular cartilage degradation, synovial inflammation and ligament lesions. Non-coding RNAs (ncRNA) do not encode any protein products and play a fundamental role in regulating the gene expression in several physiological processes, such as in the regulation of cartilage homeostasis. When deregulated, they affect the expression of genes involved in cartilage degradation and synovial inflammation, contributing to the onset and progression of OA. Oxidative stress is also involved in the pathogenesis of OA by contributing to the inflammatory response, degradation of the extracellular matrix and induction of chondrocyte apoptosis. Studies in the literature show a reciprocal relationship between the altered expression of a number of ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), and oxidative stress. The aim of this review is to highlight the role of oxidative stress, miRNAs and lncRNAs and their cross-talk in OA in order to understand the main molecular mechanisms involved and to identify possible targets that may be useful for the identification and development of new diagnostic and therapeutic approaches for this disease.

Keywords: oxidative stress; osteoarthritis; miRNAs; lncRNAs; cartilage degradation

1. Introduction

Osteoarthritis (OA) is a chronic and degenerative disease that affects the joints causing structural disorders to cartilage and surrounding tissues. It mainly affects the elderly and alters their quality of life being one of the main causes of disability [1]. The joints prevalently affected by OA are the hips, ankles, knees, hands, feet, cervical and lumbar spine and temporal and mandibular joint [2,3]. The symptoms of OA develop slowly and get worse over time. Joint pain, stiffness and loss of flexibility, as well as bone spurs and swelling, result from inflammation of the synovium, the soft tissue surrounding the joint [4]. Loss of articular cartilage and subchondral bone, tissue hypertrophy, laxity of tendons and ligaments, and hypervascularization of the synovium occur when the pathology is in an advanced state [5]. Cartilage coats and lubricates bone surfaces at joints and absorbs stresses during movement, and chondrocytes in cartilage regulate the balance of protein metabolism, which is shifted toward catabolism in OA. This induces extracellular matrix (ECM) degradation, resulting in cartilage damage [6,7]. In OA, cartilage integrity is also affected by changes in the levels of lubricin and hyaluronic acid, components of the synovial fluid produced by the synovium to maintain proper cartilage and chondrocyte function [8]. Although OA is a condition due to mechanical stresses, it is also caused by the infiltration of inflammatory cells into the synovial membrane and the consequent production of pro-inflammatory cytokines [9,10]. Risk factors for OA are diverse and include genetics, aging, obesity, gender, joint injury, and some metabolic diseases. In addition, the risk of OA

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is increased in individuals with a genetic predisposition and in older individuals in whom the presence of age-related inflammation leads to changes in ECM components and articular cartilage [11–13]. Moreover, considering that OA is predominantly associated with menopause, women are more likely to develop this pathology compared to men [14]. This can be explained by the lack of estrogen after menopause, which does not stimulate chondrocytes to produce proteoglycans and does not inhibit the production of reactive oxygen species (ROS), the activation of the enzyme inducible nitric oxide synthase (iNOS), and the transcription factor nuclear factor-kappa B (NF-kB) [15,16]. It is well known that the oxidative stress, due to an imbalance between ROS and antioxidants to the detriment of the latter, plays an important role in the onset and progression of OA by inhibiting new cartilage synthesis and the migratory and proliferative capacity of chondrocytes [17]. In addition, activation of NF-kB is critical in OA and upregulates the expression of inflammatory mediators, including iNOS and cyclooxygenase-2 (COX-2), and proteinases involved in cartilage degradation [18].

Obesity is one of the greatest risks for OA; in fact, increased body weight increases stress on weight-bearing joints such as the hips and knees, causing ligament damage. Moreover, adipose tissue produces cytokines that can cause inflammation in and around the joints, leading to failure of ECM components and cartilage degeneration [19,20].

Injury to the joint, along with the resulting increase in inflammatory cytokines in the synovial fluid, are implicated in the development of OA. In fact, joint trauma in the form of fractures, cartilage damage, or ligament tears, even those that occurred many years ago and appear to have healed, are a significant risk factor for OA. People who suffer a joint injury have a much higher risk of developing OA than those who are not injured [21,22].

Some metabolic diseases such as hypertension, type II diabetes and hemochromatosis are risk factors for OA. In particular, individuals with hypertension appear to be more susceptible to OA, as vasoconstriction and subchondral ischemia may trigger cartilage degradation [23,24]. The link between type II diabetes and OA has been demonstrated by the fact that chondrocytes isolated from patients with OA accumulate significantly more glucose than those isolated from healthy donors resulting in excessive production of ROS [25]. In chondrocytes, high glucose levels correlate with an increase in ROS and matrix-degrading enzymes such as metalloproteinases (MMPs). This results in cytokine production, activation of signaling pathways, cartilage degradation, and cell apoptosis [25,26]. Conditions, characterized by an iron overload such as, hemochromatosis, thalassemia, haemophilia but also aging and estrogen deficiency, are related to OA [27,28]. In chondrocytes, large amounts of iron upregulate the expression of MMP-3 and MMP13, leading to cartilage damage, and promote apoptosis by inducing oxidative stress [29,30].

Several pro-inflammatory cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)α, and IL-6, secreted by immune cells influence chondrocyte metabolism and are involved in the development of OA [31,32]. They upregulate the expression of genes that promote the production of nitric oxide (NO) and prostaglandin E2, which increase articular inflammation and injury through activation of MMP expression, chondrocyte apoptosis, and inhibition of collagen and proteoglycan synthesis [33]. Specifically, IL-1β upregulates ROS production and downregulates ROS scavenging enzymes, accelerating cartilage degradation in OA [34]. ROS and cytokines can activate the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway, which may be involved in the pathogenesis of OA by increasing inflammatory mediators and oxidative stress, resulting in ECM degradation and synovial inflammation [35,36]. In addition, stimulation of chondrocytes with pro-inflammatory mediators can also activate the WNT/β-catenin signaling pathway that plays a central role in the progression of OA. Indeed, in OA there is an increase in both mediators and downstream targets of WNT/β-catenin signaling with increased expression of MMPs, A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)4 and ADAMTS5 and subsequent cartilage degradation [37]. ADAMTS4 and ADAMTS5 are highly expressed in OA cartilage and play a critical role in the degradation of aggrecan during the development of OA [38].

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Non-coding RNAs (ncRNAs) are RNAs that are transcribed from DNA but not translated into proteins They are no less important than protein-coding mRNAs and are involved in the regulation of gene expression in several fundamental cellular processes [39]. In particular, they are involved in regulating cartilage homeostasis, which is essential for joint function, by influencing chondrocyte differentiation and proliferation and ECM biosynthesis [40]. When deregulated, they are one of the epigenetic factors that play an important role in contributing to the onset and progression of OA through synovial inflammation, ECM degradation and chondrocyte hypertrophy, senescence, and apoptosis [41,42]. Reciprocal interactions exist between oxidative stress and levels of ncRNAs. Oxidative stress can cause the alteration of several ncRNA expression, and several ncRNAs can affect the intracellular redox state by increasing or inhibiting ROS production [43,44].

This review will focus on the role of oxidative stress, altered expression of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in the pathogenesis of OA, highlighting the cross-talk between them. The aim is to identify molecular targets and pathways that may be useful in identifying new therapeutic approaches to attenuate the progression of OA and/or alleviate its symptoms.

2. Oxidative Stress and Osteoarthritis

Under physiological conditions, chondrocytes, metabolically active cells involved in the synthesis of ECM components such as collagen, glycoproteins, proteoglycans, and hyaluronan, live in an avascular environment. As a result, they are adapted to anaerobic metabolism and receive the oxygen they need for their biological functions from the synovial fluid [45].

ROS production, mainly due to activation of NADPH oxidase (NOX), a resting membrane enzyme complex, is very low in chondrocytes and plays an important role in maintaining cartilage homeostasis and chondrocyte function by modulating apoptotic processes and gene expression as well as ECM metabolism and cytokine synthesis [17,46,47]. Mechanical stress, changes in the partial pressure of oxygen in the synovial fluid, and other factors such as pro-inflammatory cytokines present in the chondrocyte environment can alter chondrocyte metabolism and induce excessive increases in ROS, particularly NO and superoxide anion (O2●-), from which other radicals are generated [48–50]. The increase in ROS, if not counterbalanced by an equal increase in antioxidant systems, creates a state of oxidative stress that induces changes in the biological functions of proteins and affects signaling pathways. This is a critical factor in the development of OA, as high levels of ROS and low levels of antioxidants have been found in human OA joints, cartilage and chondrocytes, causing inflammation and chondrocyte apoptosis [51,52]. In particular, the antioxidant properties of the glutathione (GSH) system and the activity of intracellular redox state related enzymes, such as superoxide dismutase (SOD) and catalase, are reduced in OA [53,54]. On the contrary, pro-inflammatory mediators increase in the synovial fluid of joints with OA and induce ROS production, which in turn stimulates the inflammatory response by regulating the expression of cytokines and interleukins through the activation of c-Jun N-terminal kinases (JNK) in chondrocytes [17,55]. In the mouse temporomandibular joint (TMJ), mechanical stress in the synovial fluid induces ROS production that may contribute to synovial inflammation and OA by activating mitogen-activated protein kinases (MAPKs), particularly extracellular signal-regulated kinases (ERK)1/2. This leads to overexpression of the neutrophil chemoattractant CXCL15/Lungkine in fibroblast-like synoviocytes with consequent recruitment of neutrophils into the joint and amplification of inflammatory processes [56]. ROS reduce cartilage synthesis by limiting the chondrocyte stimulation by growth factors, and do not allow for adequate repair of the injury by reducing the migration and proliferative capacity of chondrocyte precursors within the damaged areas [57,58]. NO is critical for chondrocyte apoptosis through activation of caspase-3 and caspase-9 and crosstalk between iNOS and COX-2, mediated by activation of p38-MAPK and MAPK kinases (MEK1/2) [59,60]. High ROS accumulation activates MAPKs and NF-kB, which regulate genes involved in cartilage metabolism and inflammation, and causes chondrocyte senescence by activating Krüppel-like transcription factor 10, involved in several biological processes including proliferation, apoptosis and differentiation [61–63]. In addition, oxidative stress promotes chondrocyte death and premature senescence through the

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overexpression of caveolin-1 due to the activation of p38-MAPK, NF-kB, and COX-2 expression [64,65]. In contrast, the inhibition of both ROS-stimulated NF-kB and MAPKs pathways delays the progression of TMJ-OA in rats and reduces ECM degradation and chondrocyte apoptosis [66]. In vitro and in vivo studies show that compounds that reduce the levels of ROS help to restore the homeostasis of the ECM and alleviate chondrocyte senescence and cartilage degeneration in OA by inhibiting the ROS-stimulated NF-kB signaling pathway [67–69].

Data from the literature show that the balance between MAPKs and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) is a very important factor in the pathogenesis of OA, and oxidative stress regulates these signaling pathways a different way in chondrocytes [62]. In these cells, excessive ROS production not only activates MAPKs but also inhibits PI3K/Akt activity, which is critical for cell survival, differentiation and matrix synthesis [62,70,71]. Oxidative stress has also been shown to reduce the PI3K/Akt pathway in human chondrocytes through overexpression of phosphatase and tensin homologue of chromosome 10 (PTEN), a negative regulator of this signaling pathway [71]. In addition, hydrogen peroxide (H_2O_2) induces apoptosis and activates autophagy in human chondrocytes by inhibiting the classical PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway [72]. Megakarioblastic leukemia 1, a transcriptional coactivator involved in several inflammatory processes, is overexpressed in H_2O_2-treated chondrocytes from osteoarthritic rats, and its inhibition attenuates inflammation and cell apoptosis through Twist-related protein 1-mediated activation of the PI3K/AKT signaling pathway [73]. In fact, PI3k/Akt activation also reverses the induction of apoptosis and matrix degradation in primary rat chondrocytes treated with sodium nitroprusside, which promotes ROS production and mimics the progression of OA [74]. However, some studies show that H_2O_2 treatment induces apoptosis by activating MAPK and PI3K/Akt in chondrocytes [75,76]. Withaferin A, a steroidal lactone that represents the principal constituent of Withania somnifera, also known as Indian ginseng, causes oxidative stress and the consequent loss of collagen and up-regulation of COX-2 expression by activating PI3K/Akt, p38 MAPK, and JNK pathways in rabbit articular chondrocytes [77].

Stimulation of chondrocytes with IL-1β, a key cytokine released during the onset of OA, mimics OA in vitro and represents a model of cartilage inflammation. It has been shown that IL-1β activates NOX and induces ROS production, oxidative stress, chondrocyte apoptosis, and ECM degradation in mouse OA chondrocytes [78]. IL-1β-induced oxidative stress activates both PI3K/Akt and/or NF-kB/MAPKs and promotes ECM degradation and inflammatory response in human chondrosarcoma SW1353 cell line and primary mouse chondrocytes [79–81]. In addition, in rat chondrocytes, IL-1β induces apoptosis and cartilage degeneration, and reduces viability through oxidative stress and the consequent activation of NF-kB and over-expression of hypoxia-inducible factor (HIF)2α, an important catabolic mediator regulated by NF-kB in OA progression [82,83]. Upregulation of NF-kB and hypoxia-inducible factor 2 alpha (HIF2α) is also involved in IL-1β-mediated downregulation of the expression of cartilage-specific genes, such as SRY-box transcription factor 9 (SOX9) and collagen type II alpha 1 chain (Col2a1) [69,82].

ROS induce cartilage damage by down-regulating the expression of the transcriptional factor, nuclear factor erythroid-2 related factor (Nrf2), with the function of regulating the cellular oxidative stress response, and OH-1 gene involved in the regulation of cellular functions, such as proliferation and inflammation [84,85]. In animal models of OA and IL-1β-stimulated chondrocytes, inhibition of Nrf2/OH-1 associated with NF-kB activation due to oxidative stress may be responsible for chondrocyte apoptosis and OA progression [86,87]. Murine chondrocytes stimulated with tert-butyl hydroperoxide (tBHP) show increased levels of ROS, decreased nuclear translocation of Nrf2, and inhibition of Nrf2/HO-1, resulting in mitochondrial dysfunction and apoptosis [88,89]. For this, the activation of Nrf2 and the HO-1 signaling pathways is very important for preserving the chondrocyte homeostasis and cartilage integrity [85,90,91], and alleviating OA in rats [92]. In fact, it has been shown that enhancement of the Nrf2/HO-1 signaling pathway and/or inhibition of PI3K/AKT/NF-κB and MAPK pathways promotes the antioxidant capacity of chondrocytes, protects cartilage from degradation, and alleviates OA in rats. [70,78,93–95].

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It has been shown that there is a relationship between oxidative stress and a decrease in cartilage ECM, considering that ROS inhibit the production of proteoglycans induced by insulin-like growth factor-1 through the activation of ERKs and the inhibition of PI3K/Akt. Furthermore, H_2O_2 reduces proteoglycan biosynthesis through the reduction of ATP levels in chondrocytes [61,96]. High levels of ROS upregulate the activity and expression of MMPs [97,98], and this leads to degradation of the ECM and destruction of cartilage [78,99]. H_2O_2 degrades collagen type II (Col2) and increases expression of MMP3 and MMP13 in human chondrocytes [72], and oxidative stress, through activation of p38 MAPK and JNK, upregulates expression of MMP-13 and ADAMTS5 [78]. The latter mediates aggrecan cleavage and is the main aggrecanase associated with OA pathogenesis considering that, when it is overexpressed, represents a crucial risk factor in the degeneration of joints [100].

Cytokines also promote cartilage destruction through the production of ROS, the activation of NF-kB and the subsequent overexpression of MMPs [101,102]. In fact, in human OA chondrocytes, IL-1β increases MMP-1, MMP-13 and ADAMTS4 levels by activating NOX4, an isoform of NOX whose deficiency reduces OA severity in a mouse model of OA [103,104]. However, in addition to NOX activation, inhibition of the transcriptional factor forkhead O (FOXO), which regulates the expression of antioxidant enzymes, is also involved in the increased expression of MMP13 and decreased expression of aggrecan [105].

Age, obesity, and vitamin D levels may be partly responsible for the development of OA through changes in the redox state of the synovial fluid [106]. In particular, vitamin D deficiency is strongly associated with oxidative stress and increased MMP activity in patients with knee OA [107] It also promotes the development of age-related spontaneous knee OA in mice [108]. Hyaluronic acid injections with vitamin D reduce oxidative stress in synovial fluid, decrease knee pain, and improve knee function in OA patients with vitamin D insufficiency [106]. Administration of exogenous 1,25(OH)2D3 to mice stimulates chondrocyte proliferation and ECM synthesis and reduces chondrocyte differentiation and ECM degradation by activating sirtuin 1 (Sirt1), a class III protein deacetylase, and reducing oxidative stress. This prevents chondrocyte senescence and knee OA development and progression [108]. Indeed, Sirt1 is involved in the regulation of many biological processes, including inflammation and oxidative stress, and low levels of its expression in chondrocytes correlate with OA [109,110].

Iron is a trace element that regulates several biological processes in humans. Its excess causes oxidative stress, an increase in chondrocyte apoptosis, and the overexpression of metalloproteinases, inducing cartilage damage that can be alleviated by the activation of Nrf2/HO-1 [111,112]. Ferroptosis, a novel form of iron-regulated cell death characterized by high levels of ROS and lipid peroxidation, contributes to the pathogenesis of OA, as chondrocytes undergo ferroptosis under conditions of inflammation and iron overload. Iron has been shown to accumulate in cartilage and synovial fluid, while markers of the peroxidation defence system, such as glutathione peroxidase 4 (GPX4) and GSH levels, decrease as OA progresses [113]. Ferroptosis increases oxidative stress and the expression of NOX1, HIF2α, and MMPs, while it inhibits the expression of Col2 in chondrocytes [114,115]. In fact, oxidative stress/NF-kB/HIF2α signaling pathway is involved in the chondrocytes ferroptosis and cartilage degeneration by increasing the expression of MMP3 and MMP13 [114]. The oxidative stress-related HIF-1α pathway also plays a key role in iron homeostasis and OA, and gut microbiota attenuate ferroptosis-dependent OA by specifically reducing oxidative stress and HIF1α levels [116].

Data from the literature have shown that under conditions of iron overload, ROS generation can downregulate Col2 expression and upregulate MMPs expression also by inhibiting Nrf2/HO-1 and GPX4/cysteine/glutamate exchanger signaling pathways [117]. GPXs are involved in the antioxidant response and play a very important role in the pathogenesis of OA. However, high levels of GPX1 have been found in OA patients and this upregulation can be explained by attributing to it a compensatory role against the oxidative stress that occurs during the onset and progression of OA [118].

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The inflammasome, a multimeric protein complex, is activated by numerous stimuli, including ROS and NF-kB, resulting in the maturation and secretion of IL-18 and IL-1β, which exacerbate the inflammatory response [44,119]. In addition to oxidative stress, cartilage biopsies and chondrocytes from patients with OA have been shown to have increased levels of ILs and inflammasome components such as nucleotide-binding oligomerisation-like receptor family pyrin domain-containing 3 (NLRP3), apoptosis-associated speck-like protein, caspase-1 and cleaved caspase-1 [120]. Increased expression of NLRP3, associated with downregulation of the Nrf2/OH-1 pathway, has also been reported in the rat OA model [121], and H_2O_2 treatment of rat primary chondrocytes promotes NLRP3 activation and cleavage of gasdermin D, with consequent increases in pro-inflammatory mediators and MMPs [122]. During the onset and progression of OA synovitis, ROS contribute to the induction of the inflammatory phenotype (M1) of macrophages [123], whose high infiltration present in human OA synovium contributes to the progression of this pathology through the ROS/NLRP3 signaling pathway [124]. Among the adipokines that are implicated in the pathogenesis of OA, leptin activates the NLRP3 inflammasome through activation of NOX4 and subsequent ROS production [120].

An association between oxidative stress and epigenetic DNA methylation changes in OA has been reported in the literature. Upregulation of DNA methyltransferase and subsequent suppression of peroxisome proliferator-activated receptor-gamma, a transcription factor that protects chondrocytes for its antioxidant and anti-inflammatory properties, occurs in knee cartilage of OA mice. The inhibition of these effects prevents ROS increase and antioxidant decrease in IL-1β -stimulated chondrocytes both in vivo and in vitro [125]. In OA cartilage, increased expression of the methyltransferase SET-1A promotes methylation of the promoters of iNOs, COX-2, resulting in upregulation of these enzymes [126]. On the contrary, the increase in partially methylated CpG sites in the SOD-2 promoter may be involved in the downregulation of SOD expression during OA progression [54]. In addition, in IL-1β-stimulated chondrocytes, upregulation of the non-histone chromatin structural protein, high mobility group A1, which is involved in the modification of DNA structure, has been shown to exacerbate oxidative stress damage and the inflammatory response [127,128].

3. miRNA and Osteoarthritis

miRNAs are small ncRNA molecules consisting of approximately 22 nucleotides of intragenic origin, mostly from introns, or intergenic origin. According to the canonical pathway, miRNAs derive from a primary transcript (pri-miRNA) that is cleaved by Drosha in the nucleus to yield the miRNA precursor (pre-miRNA). The pre-miRNA is transferred to the cytoplasm where it is cleaved by Dicer, releasing the mature miRNA [129]. By binding to the complementary sequence located in the 3'-untranslated regions of mRNA, miRNAs degrade mRNA or inhibit its translation, resulting in decreased gene expression [130]. Then, miRNAs affect biological processes and signaling pathways that contribute to the regulation of cell cycle, proliferation, differentiation, and death [131]. Contribution of miRNAs to OA pathology has been demonstrated using genetically engineered animal models. Specifically, it was shown that chondrocyte proliferation and differentiation are decreased and increased, respectively, in mice deficient in Dicer, an enzyme involved in miRNA biogenesis. The result is altered cartilage formation [132]. In addition, mice that lack miRNA-204/-211 are more likely to develop OA, and the disease is much more severe [133,134]. In fact, these two homologous miRNAs can maintain joint homeostasis and prevent OA development through regulation of mesenchymal progenitor cell proliferation and differentiation [134]. Then, altered expression of specific miRNAs may contribute to the progression of OA by affecting chondrocyte function and increasing inflammation through the production of pro-inflammatory mediators such as cytokines and ROS. It may also promote cartilage degradation by increasing MMP expression [135]. Furthermore, miRNAs can be used as potential markers for OA, as a large number of differentially expressed miRNAs have been identified in the serum of OA patients.

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An increase in the levels of miRNA-345-5p and miRNA-132-3p and a decrease in the levels of miRNA-127-3p and miRNA-382-5p were found in a rat model of OA and in human primary synovial cells stimulated with lipopolysaccharide (LPS), to mimic OA [136]. There is also an increase in the levels of both miRNA-122 and miRNA-451 in rat OA cartilage; however, in IL-1β-stimulated rat chondrocytes, the role of these two miRNAs is opposite, as miRNA-122 reduces the effect of IL-1 β, whereas miRNA-451 increases it [137]. High levels of miRNA-203 and low levels of estrogen receptor α are detected in postmenopausal rats with consequent inflammation and cartilage destruction [138]. In contrast, downregulation of miRNA-4287, miRNA-142-3p, miRNA-18a-3p and miRNA-130a, induces inflammatory response, cartilage damage and chondrocyte apoptosis in model of mouse OA [139–142].

In human OA, the downregulation of several miRNAs contributes to the development and progression of OA by increasing the production of pro-inflammatory mediators and/or increasing the expression of proteases, such as ADAMTS4/5 and MMP3/13, involved in the ECM degradation. Reduced expression of miRNA-130a, miRNA-149, miRNA-373, miRNA-24-3p increases the expression of cytokines such as TNFα, IL1β, IL-8 and IL-6, leading to inflammation [142–145]. In cartilage tissues of OA patients, decreased miR-149 levels are accompanied by an increase in the expression of vascular cell adhesion molecule-1 VCAM-1 and phosphoprotein kinase B (pAKT), and this could promote inflammation and apoptosis through activation of the PI3K/Akt signaling pathway as demonstrated in cartilage of mice with OA [146]. In IL-1β-stimulated human chondrocyte cell line CHON-001, downregulation of miRNA-24-3p correlates with upregulation of B-cell leukemia 2-like 12 and causes apoptosis, inflammation and cartilage degradation due to increased ADAMTS5 and MMP13 [145]. miRNA-92a-3p and miRNA-497-5p are low expressed in human cartilage [147,148]. In particular, in human IL-1β-stimulated chondrocytes, the decrease in miRNA-92-3p causes activation of NF-kB and MAPKs resulting in an increase in ADAMTS4/5 [147]. The reduced expression of miR-497-5p found in human OA cartilage is associated with decreased expression of cartilage matrix molecules, collagen II and aggrecan and increased expression of MMP13 and ADAMTS4 through Wnt/β-catenin signaling pathway [148]. In addition, the expression of Wnt1 inducible signaling pathway protein 1 (WISP1), a product of the Wnt/β-catenin signaling pathway, is upregulated and associated with the downregulation of miRNA-128-3p in cartilage from OA patients. The WISP1 overexpression induces inhibition of chondrocyte proliferation, apoptosis, ECM degradation and production of proinflammatory cytokines, by the activation of PI3K/Akt/NF-κB pathway [149]. In OA synovial fluid, the reduced expression of miRNA-140 and miRNA-199 is associated with an increase in MMP3, leading to cartilage destruction [150]. The decrease in miRNA-548d-5p has been found in human OA cartilage and promotes excessive inflammatory cytokine release, altered ECM deposition, inhibition of cell growth and enhanced apoptosis by increasing specificity protein 1 (S1P) expression in the IL-1β-stimulated human chondrocyte cell line C28/I2 [151]. During the progression of human OA, downregulation of miRNA-140-5p expression in cartilage progenitor/stem cells is associated with altered differentiation, increased apoptosis, and decreased proliferation through activation of Jagged1/Notch signaling [152]. In human OA tissues, downregulation of miRNA-379-5p increases the expression of Y-box binding protein 1 and also activates the PI3K/Akt pathway, resulting in decreased chondrocyte proliferation and expression of ECM-related proteins, collagen II, and aggrecan [153]. The reduced expression of miRNA-382-3p is also involved in the development of OA through the upregulation of connexin 43 (CX43) and the consequent increase in the expression of Toll-like receptor 4 (TLR4), myeloid differentiation primary response 88 (MyD88) and NF-κB [154]. It has been shown that the downregulation of miRNA-99a expression, observed in the severe spine of OA patients, in the in vivo human OA rat model and in in vitro OA-like chondrocyte model, is responsible for the increased apoptosis and ECM degradation by overexpression of Frizzled 8, a positive regulator of Wnt/β-catenin pathways [155]. Moreover, in human OA cartilage and IL-1β-stimulated chondrocytes, the decrease in expression of miRNA-33b-3p correlates with the increase in expression of DNA methyltransferase 3A reducing cell proliferation and causing apoptosis and cartilage ECM degradation [156]. Downregulation of miRNA-320a

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promotes inflammatory response and apoptosis and inhibits chondrocyte proliferation rate by increasing DAZ Associated Protein 1 and MAPKs expression in an in vitro human chondrogenic HC-A cells OA model [157]. In human OA increased levels of miRNA-381a-3p and miRNA-454 promote the release of IL-6 and IL-8 through the activation of the transcription factor NF-kB by decreasing the expression of the inhibitor kappa B-alpha (IkBα) and stanniocalcin-1, respectively [158,159]. Stimulation of primary human articular chondrocytes with TNFα or IL-1β induces increased levels of miRNA-760, which is significantly elevated in human OA tissues along with decreased levels of heparin-binding EGF-like growth factor and increased cartilage degeneration [160]. Conversely, in mouse TNFα-treated chondrocytes, there is a decrease in miRNA-145, whose downregulation in human OA cartilage plays an important role in OA pathogenesis by activating MAPK kinase 4 [161].

High levels of miRNA-146a contribute to the pathogenesis of human OA, and the application of mechanical pressure upregulates miRNA-146a expression, which causes apoptosis by increasing vascular endothelial growth factor (VEGF) and inhibiting Smad4 in human chondrocytes [162]. miRNA-146a-5p is also upregulated in human OA cartilage, leading to increased inflammation and cartilage degeneration [163]. Upregulation of miRNA-182-5p and miRNA-34a in human OA chondrocytes, in addition to inhibiting cell proliferation and increasing apoptosis, induces cartilage degradation by reducing the expression of fibroblast growth factor 9, which regulates bone remodeling [164], and Sirt1 [165], respectively. Indeed, Sirt1 regulates ECM metabolism and its reduced expression, resulting in ECM degradation, is also associated with miRNA-122 increase detected in human OA cartilage [166]. miRNA-195 is significantly overexpressed in human OA cartilage. It has been shown that upregulation of this miRNA causes cartilage destruction by downregulating parathyroid hormone-related protein, which increases the expression of MMP-13 and Col X in human chondrocytes stimulated with IL-1β [167].

Table 1 summarises the effects and targets of the major differentially expressed miRNAs associated with the development and progression of human OA.

Table 1. Major differentially expressed miRNAs in human osteoarthritis (OA) and their major targets and effects.

miRNA	Targets	Effects	Human Model/cell type	Ref.
miRNA-149 (-)	TAK1/NF-kB (+)	Inflammation	OA chondrocytes	[143]
	VCAM-1 (+) p-Akt (+)	Apoptosis Inflammation	OA cartilage	[146]
miRNA-130a (-)	TNFα (+)	Inflammation	OA chondrocytes	[142]
miRNA-373 (-)	P2X7R (+)	Inflammation Proliferation (-)	OA chondrocytes	[144]
miRNA-24-3p (-)	BCL2L12 (+)	Inflammation ECM degradation	IL-1β-stimulated CHON-001 cells	[145]
miRNA-92a-3p	NF-kB (+) MAPKs (+)	ECM degradation	IL-1β-stimulated chondrocytes	[147]
miRNA-497-5p (-)	Wnt/β-catenin (+)	ECM degradation	IL-1β-stimulated chondrocytes	[148]
miRNA-128-3p	WISP1 (+)	Inflammation ECM degradation, Apoptosis Proliferation (-)	OA cartilage IL-1β-stimulated C28/I2 cells	[149]
miRNA-140 (-)	MMP3 (+)	ECM degradation	OA synovial fluid	[150]
miRNA-190 (-)	MMP3 (+)	ECM degradation	OA synovial fluid	[150]
miRNA-548d-5p (-)	S1P (+)	Inflammation	IL-1β-stimulated C28/I2 cells	[151]

 doi:10.20944/preprints202506.0240.v1

		ECM degradation, Apoptosis Proliferation (-)		
miRNA-140-5p (-)	Jagged1/Notch (+)	Differentiation alteration Apoptosis Proliferation (-)	CPSC from OA cartilage	[152]
miRNA-379-5p (-)	YBX1 (+) PI3K/AKT (+)	Proliferation (-) Expression of ECM proteins (-)	OA cartilage	[153]
miRNA-382-3p (-)	CX43 (+) TR4/MyD88/ NF-κB (+)	Inflammation ECM degradation	IL-1β-stimulated NHAC-kn	[154]
miRNA-99a (-)	Frizzled 8 (+)	ECM degradation Apoptosis	Cytokine-stimulated SW1353 cells	[155]
miRNA-33b-3p (-)	DNMT3A (+)	ECM degradation Apoptosis Proliferation (-)	OA cartilage IL-1β-stimulated chondrocytes	[156]
miRNA-320a (-)	DAZAP1 (+) MAPKs (+)	Inflammation Apoptosis Proliferation (-)	IL-1β-stimulated HC-A cells	[157]
miRNA-381a-3p (+)	IkBα (-) NF-kB (+)	Inflammation ECM degradation	OA cartilage and synovium	[158]
miRNA-454 (+)	Stanniocalcin-1 (-) NF-kB (+)	ECM degradation	OA Synovial Fibroblast-like cells	[159]
miRNA-760 (+)	HBEGF (-)	ECM degradation	OA cartilage	[160]
miRNA-145 (-)	MKK4 (+)	ECM degradation	OA cartilage	[161]
miRNA-146a (+)	VEGF (+) Smad4 (-)	Apoptosis	Mechanically stressed chondrocytes	[162]
miRNA-146a-5p (+)	NF-kB (+)	Inflammation ECM degradation	OA cartilage	[163]
miRNA-182-5p (+)	FGF9 (-)	ECM degradation Apoptosis Proliferation (-)	OA chondrocytes	[164]
miRNA-34a (+)	Sirt1 (-)	ECM degradation Apoptosis Proliferation (-)	OA chondrocytes	[165]
miRNA-122 (+)	Sirt1 (-)	ECM degradation	OA cartilage	[166]
miRNA-195 (+)	PTHrP (-)	ECM degradation	OA cartilage	[167]

Abbreviations: TAK1, Transforming growth factor-β activated kinase 1; NF-kB, Nuclear factor kappa B; VCAM-1, Vascular cell adhesion molecule-1; p-Akt, Phosphoprotein kinase B; TNFα, Tumor necrosis factor α; MMP, metalloproteinase; IL-1β, interleukin-1β P2X7R, Purinergic P2X7 receptor; BCL2L12, B cell leukemia 2-like 12; PDP1, phosphatase catalytic subunit 1; SP1, specificity protein 1; IkBα, inhibitor kappa B-alpha; HBEGF, heparin-binding EGF-like growth factor; MKK4, mitogen-activated protein kinase kinase 4; VEGF, vascular endothelial growth factor; DAZAP1, DAZ associated protein 1; MAPKs, mitogen-activated protein kinases; CPSC, cartilage progenitor/stem cells; YBX1, Y-box binding protein 1; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; CX43, Connexin 43; TLR4/MyD88/NF-κB, Toll-like receptor 4/Myeloid differentiation primary response 88/NF-kB; NHAC-kn, normal human articular chondrocytes-knee; FGF9, Fibroblast growth factor 9; Sirt1, Sirtuin-1; DNMT3A, DNA methyltransferase 3A; PTHrP, Pathyroid hormone-related protein; WISP1, Wnt-1 inducible signalling pathway protein 1. (-) Downregulated (+) Upregulated.

4. Cross-Talk Between Oxidative Stress and miRNAs in Osteoarthritis

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Several miRNAs have been shown to regulate the redox state of cells under different pathological conditions by modulating signaling pathways involved in ROS and antioxidant production [168]. Various miRNAs are able to regulate the intracellular redox state by inhibiting the Nrf2 repressor, Kelch-like ECH-associated protein 1 [169,170]. In contrast, some miRNAs alter the intracellular redox state and induce oxidative stress by regulating genes involved in ROS production [171]. Oxidative stress may also be involved in altering miRNA expression levels by activating transcription factors such as p53, NF-kB, c-jun, FOXO, and HIF, or by causing epigenetic changes in miRNA gene methylation or post-translational histone modifications [172]. Thus, there is a close and reciprocal relationship between oxidative stress and miRNA expression, as demonstrated by a large body of experimental evidence [44,173]. The presence of oxidative stress and an altered miRNA profile in OA suggests that a mutual interaction between miRNA and ROS production may also exist in this disease.

The involvement of oxidative stress in the modulation of miRNA expression in OA has been demonstrated by stimulating human chondrocytes with H_2O_2, which increases $\bullet O^{2-}$ levels, or with compounds capable of inducing oxidative stress. Indeed, in H_2O_2-treated human IL-1β-stimulated chondrocytes there is a significant decrease in miRNA-93-5p and an increase in miRNA-449c-5p and miRNA-1207-5p, whereas miRNA-637 and miRNA-4763-3p do not change [174]. In particular, the downregulation of miRNA-93-5p by activating MAPK kinase kinase (MAP3K8) increases the expression of pro-inflammatory cytokines, MMPs and ADAMTS-4/5, and reduces the expression of Col2a1 and SOX9 resulting in cartilage degradation [174]. Conversely, miRNA-93-5p also upregulates oxidative stress, as reduction of this miRNA increases the expression of COX-2 and iNOS in H_2O_2-treated human Il-1β-stimulated chondrocytes [174]. ROS-induced changes in miRNA-34a-5p/Sirt1/p53 may be involved in developing OA. In fact, the oxidative stress induced by tBHP upregulates the expression of miRNA-34a-5p, which causes joint degeneration by increasing apoptosis and inflammatory processes in the HC-OA chondrocyte line derived from human cartilage of OA patients. Upregulation of miRNA-34a-5p is associated with decreased expression of Sirt1, which leads to inhibition of acetyl-p53 deacetylation and increase in p53-mediated apoptosis [175]. The relationship between miRNA-9 overexpression detected in OA cartilage and oxidative stress has been demonstrated in human primary chondrocytes and C28/I2 human chondrocyte cell line [176]. Indeed, in H_2O_2-treated C28/I2 cells, an increase in miRNA-9 associated with a decrease in Sirt1 mediates oxidative stress-induced damage in OA [176]. Furthermore, in H_2O_2-treated C28/I2 cells, there is an upregulation of miRNA-195 and a consequent decreased expression of IKKα, an inhibitor of NF-kB, which induces activation of the NF-kB pathway, resulting in increased apoptotic processes [177]. In IL-1β-stimulated C28/I2 cells, decreased expression of mechanosensitive miRNA-222-3p promotes the production of ROS and pro-inflammatory mediators, ECM degradation, and apoptosis through increased expression of disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), which is involved in cartilage degeneration [178].

Adipokines, which together with miRNAs and oxidative stress are involved in synovitis and cartilage destruction in OA, induce oxidative stress by up-regulating the expression of miRNA-34a, miRNA-146a and miRNA181a and subsequent activation of NF-kB in human OA synovial fibroblasts [179]. In addition, in human OA chondrocytes, visfatin also increases miRNA-34a and miRNA-181a that promote oxidative stress and apoptosis through NF-kB activation [180]. Treatment of human OA chondrocytes with H_2O_2 induces oxidative stress and promotes an increase in miRNA-34a and a decrease in miRNA-146a, demonstrating the responsiveness of these miRNA to oxidative stress and confirming their role in the development and progression of OA [181]. In addition to apoptosis and reduced cell viability, H_2O_2 in human OA chondrocytes promotes increased expression of the antioxidant enzymes, catalase (CAT), SOD2, and GPX, and the transcription factor, Nrf2, a regulator of the cellular redox state [181]. In particular, Nrf2 and SOD2 are targets of miRNA-146; therefore, it is likely that the downregulation of miRNA-146 expression induced by H_2O_2 and associated with an increase in Nrf2 and SOD2 represents a form of defence to protect chondrocytes from the damaging effects of ROS [181–183]. The decrease of miRNA-146 due to oxidative stress in human OA

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chondrocytes contradicts other data showing an upregulation of this miRNA in OA cartilage and in IL-1β-stimulated chondrocytes [184]. Even in rat OA chondrocytes, miRNA-146a is elevated and causes ROS production by inhibiting Nrf2 expression. In fact, melatonin, by downregulating miRNA-146a, increases Nrf2/HO-1 protein expression, reduces ROS production and ECM degradation in rat OA chondrocytes [185]. Downregulation of Nrf2 associated with oxidative stress, inflammation and apoptosis is also correlated with an increase in miRNA-1323 in LPS-stimulated human OA chondrocytes. In fact, inhibition of this miRNA activates the Nrf2-OH-1 pathway, downregulates ROS levels, and increases the activity of SOD and CAT [186]. miRNAs 34a, 146a and 181a are also involved in the modulation of chondrocyte metabolism by hydrostatic pressure (HP), which regulates cartilage homeostasis in a force-, intensity-, and duration-dependent manner [187]. Their increase is involved in ROS production and upregulation of SOD and Nrf2 expression in human OA chondrocytes exposed to static continuous HP (10 MPa) for 3 h. The authors speculate that the increase in SOD and Nrf2 is due to the ability of these altered miRNA to inhibit Sirt1, which regulates the expression of various antioxidant genes [187]. Furthermore, these miRNAs have been shown to mediate oxidative stress, apoptosis, and upregulation of MMP13 and ADAMTS-5 through the involvement of Wnt/β-catenin in HP (10 MPa) treated OA chondrocytes [187].

In human OA cartilage, the upregulation of miRNA-505-3p causes ROS production, apoptosis, overexpression of MMP3 and COX-2, downregulation of Col2, and mitochondrial dysfunction by decreasing the expression of Sirt3, a mitochondrial sirtuin that plays an important role in regulating oxidative stress by deacetylating compounds involved in mechanisms leading to ROS production or detoxification [188,189]. On the contrary, decreased expression of miRNA-26a and miRNA-26b detected in human OA cartilage and chondrocytes promotes the cartilage degradation and ROS production by increasing MMP and COX-2 expression. This effect is mediated by upregulating the expression of karyopherin subunit alpha 3 (KPNA3), which is involved in p65 translocation to the nucleus and then in NF-kB activation [190,191].

Low expression of miRNA-485-3p is linked to upregulation of the Notch 2 target in human OA cartilage, and downregulation of this miRNA increases oxidative stress, apoptosis, inflammation, and ECM degradation by activating Notch2 and NF-kB signaling in human LPS-treated SW1353 and CHON-001 chondrocyte cell lines [192]. Indeed, Notch signaling is involved in the pathogenesis of OA and can regulate oxidative stress by increasing ROS production or decreasing antioxidant systems. However, oxidative stress can also modulate the Notch signaling pathway [3,193]. miRNA-27 is decreased in human OA cartilage and causes oxidative stress, increased expression of MMPs and decreased activity of antioxidant enzymes such as SOD and GPX in IL-1β-stimulated human chondrocytes through upregulation of TLR4, a molecule upstream of NF-κB activation [194]. The decrease in miRNA-127-5p also increases the expression of TLR4, which causes oxidative stress, apoptosis, inflammation, and ECM degradation in human OA cartilage [195]. Downregulation of miRNA-24-3p by upregulation of cathepsin B promotes oxidative stress, apoptosis and inflammation in human OA cartilage and in CHON-001 chondrocyte cell line stimulated with IL-1β [196]. Decreased miRNA-197-3p causes oxidative stress, inflammation and cartilage degradation by increasing SOX5 in human OA cartilage and in IL-1β-stimulated C28/I2 cells chondrocytes [197].

High levels of miRNA-181-5p in human OA chondrocytes and IL-1β-stimulated SW1353 cell line cause oxidative stress and cellular damage by downregulating selenocysteine insertion sequence-binding protein 2 (SBP2), a regulator of antioxidant selenoprotein expression, and the antioxidant enzyme GPX [198]. In human and rat chondrocyte models of OA, miRNA-181b is upregulated and is involved in the development of ferroptosis by downregulating the solute carrier family 7 member 11 (SLC7A11), a ferroptosis protective protein [199]. The downregulated expression of miRNA-1 in human OA cartilage and IL-β1-stimulated human OA chondrocytes contributes to the increase in ferroptosis through upregulation of CX43 accompanied by enrichment of intracellular ROS and decrease in GPX4 and SLC7A11 [200].

The upregulation of miRNA-375 detected in mouse OA models causes oxidative stress, apoptosis, and ECM degradation associated with an increase in some MMPs and a decrease in SOD

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through downregulation of JAK2/STAT3 signaling pathway. Knockdown of miRNA-375 and subsequent activation of the JAK2/STAT3 pathway increases the ability of chondrocytes to counteract oxidative stress and maintain ECM homeostasis to prevent OA [201]. In fact, activation of the JAK2/STAT3 pathway by attenuating oxidative stress and apoptosis has been shown to reduce chondrocyte damage in rabbit models of OA in vivo and in vitro [202]. Treatment of the murine chondrogenic ATDC5 cell line with LPS promotes oxidative stress, apoptosis and inflammation by up-regulating miRNA-486-5p and down-regulating its target, Nrf1. This factor is considered a therapeutic target for OA, as inhibition of MIRNA-486-5p increases Nrf1 and alleviates oxidative stress and related damage [203]. The expression of miRNA-203a-3p is decreased in OA knee tissue [204], and in the in vitro and the in vivo rat models of OA [205]. In these models, decreased miRNA-203a-3p induces oxidative stress as well as ECM degradation, apoptosis and pyroptosis of chondrocytes by activating the MyD88/NF-κB pathway [205]. Table 2 shows the targets and effects of the principal microRNA related to oxidative stress in OA.

Table 2. Main miRNAs involved in the cross-talk with oxidative stress in osteoarthritis (OA).

miRNA	Targets	Effects	Model/cell type	Ref.
miRNA-93-5p (-)	MAP3K8 (+) iNOS (+) COX2 (+)	Inflammation ECM degradation Oxidative stress	Human chondrocytes treated with H_2O_2 and stimulated with Il-1β	[174]
miRNA-34a-5p (+)	Sirt1/p53 (-)	Inflammation Apoptosis	tBHP-treated HC-OA cells	[175]
miRNA-9 (+)	Sirt1 (-)	Cartilage damage	H_2O_2-treated human chondrocytes H_2O_2-treated C28/I2 cells	[176]
miRNA-195 (+)	IKKα (-) NF-kB (+)	Apoptosis	H_2O_2-treated C28/I2 cells	[177]
miRNA-222-3p (-)	ADAM10 (+)	Inflammation ECM degradation Apoptosis Oxidative stress	IL-1β-stimulated C28/I2 cells	[178]
miRNA-34a (+) miRNA-146a (+) miRNA-181a (+)	NF-kB (+)	Inflammation Apoptosis Proliferation (-) Oxidative stress	Adipokines-stimulated human OA synoviocytes	[179]
	Sirt1 (-) Nrf2 (+) SOD2 (+) Wnt/β-catenin (+)	Oxidative stress Apoptosis ECM degradation	HP-stimulated human OA chondrocytes	[187]
miRNA-34a (+) miRNA-181a (+)	NF-kB (+)	Oxidative stress Apoptosis	Visfatin-stimulated human OA chondrocytes	[180]
miRNA-34a (+) miRNA-146a (-)	Nrf2 (+) SOD2 (+) CAT (+) GPX (+)	Apoptosis Cell viability (-)	H_2O_2-treated human chondrocytes	[181]
miRNA-146a (+)	Nrf2/HO-1 (-)	Oxidative stress ECM degradation	Rat OA chondrocytes	[185]
miRNA-1323 (+)	Nrf2/OH1 (-)	Inflammation Apoptosis Oxidative stress	LPS-stimulated human OA chondrocytes	[186]
miRNA-505-3p (+)	Sirt3 (-)	Inflammation Oxidative stress	Human OA cartilage	[188]

 doi:10.20944/preprints202506.0240.v1

		Apoptosis ECM degradation		
miRNA-26a (-)	KPNA3 (+)	Oxidative stress	Human OA cartilage and chondrocytes	[190]
miRNA-26b (-)	NF-kB (+)	ECM degradation		[191]
miRNA-485-3p (-)	Notch2 (+) NF-kB (+)	Oxidative stress, Inflammation ECM degradation, Apoptosis	Human OA cartilage LPS-stimulated SW1353 and CHON-001 cells	[192]
miRNA-27 (-)	TLR4 (+) NF-kB (+)	Oxidative stress ECM degradation	IL-1β-stimulated chondrocytes	[194]
miRNA-127-5p (-)	TLR4 (+)	Oxidative stress, Inflammation ECM degradation Apoptosis	Human OA cartilage	[195]
miRNA-24-3p (-)	CTSB (+)	Oxidative stress Apoptosis Inflammation	Human OA cartilage IL-1β-stimulated CHON-001 cells	[196]
miRNA-197-3p (-)	SOX5 (+)	Oxidative stress, Inflammation ECM degradation Apoptosis	Human OA cartilage IL-1β-stimulated C28/I2 cells	[197]
miRNA-181-5p (+)	SBP2 (-) GPX (-)	Oxidative stress Cartilage damage	Human OA chondrocytes IL-1β-stimulated SW1353 cells	[198]
miRNA-181b (+)	SLC7A11 (-)	Oxidative stress Ferroptosis	Human and rat chondrocyte models of OA	[199]
miRNA-1 (-)	CX43 (+) SLC7A11 (-) GPX (-)	Oxidative stress, Ferroptosis	Human OA cartilage and IL-1β-stimulated human chondrocytes	[200]
miRNA-375 (+)	JAK2/STAT3 (-)	Oxidative stress Apoptosis ECM degradation	Mouse OA models	[201]
miRNA-486-5p (+)	Nrf1 (-)	Oxidative stress Apoptosis Inflammation	LPS-stimulated ATDC5 cells	[203]
miRNA-203-3p (-)	MYD88/NF-kB (+)	Oxidative stress Apoptosis ECM degradation Pyroptosis	*In vitro* and *in vivo* rat models of OA	[205]

Abbreviations: MAP3K8, mitogen-activated protein kinases kinase kinase; iNOS, inducible nitric oxide synthase; COX2, cyclooxygenase; Sirt, sirtuin; tBHP, tert-butyl hydroperoxide; IKKα, inhibitory Kappa B Kinase α; NF-kB, nuclear factor kappa B; ADAM10, disintegrin and metalloprotease domain-containing protein 10; Nrf2/HO-1, nuclear factor erythroid 2-related factor 2/Heme Ossigenasi-1; SOD, superoxide dismutase; CAT, catalase; HP, hydrostatic pressure; KPNA3, karyopherin subunit alpha 3; TLR4, Toll-like receptor 4; CTSB, cathepsin B; SOX5, SRY-box transcription factor 5; SBP2, selenocysteine insertion sequence-binding protein 2; GPX, glutatione peroxidase; SLC7A11, ferroptosis protective protein, solute carrier family 7 member 11; CX43, connexin 43; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transduction; MYD88, myeloid differentiation primary response 88; LPS, lipopolysaccharide; IL-1β, interleukin-1β. (-) Downregulated; (+) Upregulated.

5. lncRNAs and Osteoartrithis

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lncRNAs are molecules of more than 200 nucleotides in length. They can be intergenic, antisense, exonic, intronic, or derived from 5′/3′ untranslational regions and adopt complex structures to facilitate their interactions with DNA, RNA, and proteins [206]. Due to their diverse biogenesis, lncRNAs are involved in a wide variety of biological processes, such as chromatin remodeling, transcriptional regulation, and the regulation of the integrity and function of the nuclear body [207–209]. Since a number of lncRNAs are exported to the cytoplasm, they play an important role in the regulation of mRNA stability, turnover and translation, and in the modulation of post-translational modifications [210,211]. Finally, by binding to nucleic acids (RNA and DNA) or proteins, lncRNAs play an important role in the modulation of gene expression and/or regulation of signaling pathways, such as the NF-kB and p53 pathways [212,213]. For this, lncRNAs regulate various physiological processes such as inflammation, cytokine expression, glucose and cholesterol metabolism, and cellular signal transduction [214–217]. lncRNAs can also affect the role of miRNAs, and the effect of lncRNAs on miRNA is twofold: they can sequester miRNAs, thereby inhibiting their function, or they can be precursors of miRNAs. However, the stability of lncRNAs can also be affected by interaction with specific miRNAs [218].

Under physiological conditions, lncRNAs preserve cartilage homeostasis, promote chondrocyte proliferation, inhibit chondrocyte apoptosis and induce cartilage regeneration [219–221]. During the onset and development of OA, the expression of lncRNAs may be dysregulated and thus participate in the pathogenesis and progression of OA [222]. This is supported by the fact that the lncRNA alteration can increase the expression of MMP3, MMP9, ADAMTS5, bone morphogenic protein 2 and VEGF, resulting in degradation, hypertrophic remodeling and vascular invasion of cartilage [223,224]. The downregulation of LncRNA maternally expressed gene 3 (MEG3) in human OA cartilage is associated with an increase in VEGF, which promotes angiogenesis and contributes to progressive joint damage [225]. Furthermore, reduced expression of MEG3 is involved in OA progression via the miRNA16/SMAD7 axis in cartilage of the OA rat model [226] and is associated with high levels of miRNA-34a, decreased Klotho, fibroblast growth factor 23 and Bcl2 and increased Bax, transforming growth factor beta 1 and caspases in LPS-stimulated C28/I2 cells, reducing mineralisation and increasing ECM degradation and apoptosis [227].

The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) may be involved in the development of OA, as its upregulation increases ADAMTS5 expression and cartilage destruction by miRNA-145 downregulation in human OA cartilage [228]. Suppression of MALAT1 attenuates OA progression by downregulating MyD88 protein levels through upregulation of miRNA-212-5p in the rat model [229] and by reducing NF-kB and Wnt signalling in OA mouse chondrocytes [230]. It has also been shown in the OA mouse model that overexpression of miRNA124-3p may mediate the reduction of cartilage damage in OA by impairing the stability of MALAT1 [231]. Other literature data suggest that in human OA cartilage MALAT1 overexpression is associated with a decrease in miRNA-150-5p and a consequent increase in AKT3 expression, and promotes proliferation and inhibits apoptosis and cartilage destruction through the miRNA-150-5p/AKT3 axis in IL-1β-stimulated human and rat chondrocytes [232]. Furthermore, in LPS-treated human chondrocytes, high levels of MALAT1 downregulate miRNA-146a expression with subsequent activation of the PI3K/AKT/mTOR signaling pathway, resulting in the inhibition of inflammation and apoptosis [233]. Activation of the PI3K/AKT/mTOR pathway and decreased apoptosis and increased proliferation of chondrocytes has also been attributed to high levels of lncRNA homeobox (HOX) A11 antisense (HOXA11-AS) and low levels of miRNA-506-3p found in human OA cartilage and chondrocytes [234].

Overexpression of HOX transcript antisense RNA (HOTAIR), another major lncRNA involved in OA progression, causes inflammation, cell damage and apoptosis by reducing miRNA-17-3p, in LPS-stimulated C28/I2 chondrocytes [235], and miRNA-130a-3p in human OA cartilage [236]. High levels of HOTAIR promote cartilage degradation by downregulating miRNA-17-5p, increasing α-1,2-fucosyltransferase 2 (FUT2) and activating the Wnt/β-catenin pathway in IL-1β-stimulated human chondrocytes [237]. Indeed, overexpression of HOTAIR downregulates the expression of Wnt

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inhibitory factor 1, a key inhibitor of Wnt/β-catenin, and activates the Wnt signaling pathway leading to cartilage degradation in OA [238]. The HOTAIR upregulation has been found also in OA human peripheral blood mononuclear cell (PBMC) and promotes the inflammation response by reducing the expression of PTEN and adiponectin and increasing the phosphorylation and subsequent activation of PI3K and AKT in human OA chondrocytes [239]. In the rat knee OA model, elevation of the lncRNA HOTAIR upregulates serum IL-1β and TNFα levels and p38 expression and phosphorylation in tissue cartilage, resulting in cartilage inflammation and ECM degradation [240]. HOTAIR expression is regulated by the lncRNA, p50-associated cyclooxygenase 2-extragenic RNA (PACER), whose levels are inversely related to those of HOTAIR [241]. In fact, decreased PACER expression has been found in the blood of OA patients and increases pro-inflammatory mediators and decreases anti-inflammatory mediators in a human OA model cell line [242].

The lncRNA ENST00000512512.1, called human insulin-like growth factor binding protein-7-OT (IGFBP7-OT), and the lncRNA EGFR long non-coding downstream RNA (ELDR) are overexpressed in human OA cartilage and chondrocytes [243,244]. Upregulation of IGFBP7-OT accelerates OA progression by reducing methylation of the IGFBP7 promoter, resulting in the overexpression of IGFBP7, apoptosis and reduced chondrocyte viability [243]. High levels of ELDR promote chondrocyte senescence and cartilage degradation by increasing the expression of the Indian hedgehog signaling molecule, involved in OA progression, by regulating histone modifications of the promoter region [244].

In human OA cartilage and IL-1β-stimulated chondrocytes, the overexpressed lncRNA minichromosome maintenance complex component 3 associated protein antisense 1 (MCM3AP-AS1) is involved in cell apoptosis and ECM degradation by inhibiting the expression of miRNA-149-5p with consequent activation of Notch1 [245].

In IL-1β-stimulated mouse chondrocytes-like ATDC5 cells, the LncRNA plasmacytoma variant translocation 1 (PVT1) overexpression reduces proliferation and increases apoptosis and ECM degradation through the downregulation of miRNA-497 and consequent activation of AKT3 [246]. In human OA synovial fluid and tissue, high levels of PVT1 are associated with low levels of the lncRNA, growth arrest-specific 5 (GAS5), and this combination promotes LPS-induced apoptosis in OA chondrocytes [247]. However, GAS5 has been shown to be upregulated in human OA serum, cartilage and chondrocytes, promoting apoptosis and inhibiting proliferation by down-regulating miRNA-137 [248]. In addition, the upregulation of GAS5 leads to ECM degradation, inflammation and apoptosis, but in contrast it increases the anti-apoptotic factor Bcl2 through the downregulation of miRNA-34a [249].

LncRNA X-inactive specific transcript (Xist) is overexpressed in human OA synovial tissue and fibroblasts, together with downregulation of miRNA-150-5p and upregulation of vascular cell adhesion protein 1 and the monocyte marker CD11b, suggesting high monocyte infiltration in inflamed synovial tissue [250]. Xist is also increased in human OA cartilage and is associated with OA progression by increasing FUT1 expression through binding to TATA-box binding protein-associated factor 15 [251].

Overexpression of the lncRNA TM1-3P, found in IL-1β-stimulated human synovial fibroblasts, causes inflammation and ECM degradation through downregulation of miRNA-144-3p and subsequent upregulation of the transcription factor one cut homeobox 2 [252].

With regard to lncRNA H19, the literature is conflicting, linking its role in human OA progression to both up- and down-regulation (253-255). Specifically, overexpression of H19 decreases miRNA-130 and miRNA-106a-5p levels, promoting apoptotic and inflammatory processes [253,254], whereas low levels of H19 increase miRNA-106b-5p expression and decrease tissue inhibitor of metalloproteinases 2, causing cartilage damage and decreasing proliferation and migration of chondrocytes [255].

In human OA cartilage, upregulation of the lncRNA KCNQ1 overlapping transcript 1, also known as KCNQ1OT1, causes inflammation and ECM degradation by decreasing miRNA-211-5p and increasing transcription factor 4 expression [256]. In addition, in the serum of OA patients, it is

 doi:10.20944/preprints202506.0240.v1

involved in the development of OA by inhibiting miRNA-1202 and increasing the expression of E26 transcription factor-1, which regulates many cartilage genes such as those of MMPs [257]. There are also contrasting data for KCNQ1OT1 showing that downregulation of this lncRNA promotes ECM degradation by increasing miRNA-126-5p and subsequently decreasing the transcriptional repressor GATA binding 1 in human OA cartilage [258].

Upregulation of lncRNA LINC01094 and lncRNA actin filament-associated protein 1 (AFAP1-AS1) occurs in human OA cartilage. LINC01094 induces apoptosis by decreasing miRNA-577 and increasing metal-regulatory transcription factor 1, whereas AFAP1-AS1 increases MMP-13 expression and promotes cartilage destruction by suppressing miRNA-512-3p [259,260]. In human OA cartilage and in IL-1β-stimulated human CHON-001 chondrocytes, high levels of the lncRNA LINC00958 and low levels of miRNA-214-3p induce apoptosis and inflammation and reduce cell viability by increasing the expression of forkhead box M1 [261].

High levels of the lncRNA nuclear enriched abundant transcript 1 (NEAT1) promote apoptosis, inflammation, cartilage degradation and cell death through the downregulation of miRNA-181c and the decrease in miRNA-543 levels associated with the upregulation of phospholipase A2 group IVA expression involved in OA development [262,263]. The increase in NEAT1 expression is associated with an increase in miRNA-377-3p and stimulation of endoplasmic reticulum stress in cartilage of the OA mouse model [264], and with an upregulation of miRNA-378 in LPS-induced rat OA chondrocytes [265]. However, contrasting data show that low levels of NEAT1 are associated with upregulation of miRNA-374b-5p, leading to apoptosis and production of pro-inflammatory mediators through downregulation of post-GPI attachment to protein 1 (PGAP1) expression in human OA cartilage and in LPS-stimulated chondrocytes [266]. In the latter cells, the decrease of the lncRNA LEMD1 antisense RNA 1 (LEMD1-AS1) also causes the downregulation of PGAP1 expression, but through the increase in miRNA-944 expression, promoting apoptosis and inflammation [267].

Increasing the lncRNA bladder cancer associated transcript 1 (BLACAT1) promotes apoptosis and ECM degradation through downregulation of miRNA-149-5p and subsequent activation of 3-hydroxy-3-methylglutaryl-CoA reductase in IL-1β-stimulated human chondrocytes [268].

Dysregulated expression of lncRNAs belonging to the small nucleolar RNA host gene (SNHG) family may be associated with the progression and development of OA. For example, SNHG12, SNHG14 and SNHG16 are overexpressed in human OA cartilage and promote OA progression by reducing chondrocyte viability and increasing inflammatory response, apoptosis and ECM degradation through the inhibition of miRNA-16-5p, miRNA-137, and miRNA-373-3p, respectively [269–271]. Reduced expression of SNHG1, SNHG5, SNHG7 and SNHG15 has been found in human OA cartilage, affecting chondrocyte viability, proliferation, apoptosis and migration. In particular, low levels of SNHG1 induce metabolic dysfunction by upregulating levels of MMPs, ADAMTS4/5 and pro-inflammatory mediators, and downregulating collagen II and aggrecan through the activation of miRNA-16-5p-mediated p38 MAPK and NF-κB pathways in IL-1β-stimulated human chondrocytes [272]. Downregulation of SNHG5 is associated with high levels of miRNA-26a and low levels of SOX2, with a consequent reduction in chondrocyte proliferation and migration [299]. Furthermore, low levels of SNHG5 promote apoptosis by increasing miRNA-10-5p and decreasing histone H3 family 3B [274], and promote apoptosis, inhibition of viability and increase in ADAMTS5 and MMP-13 levels by upregulating miRNA-181a-5p and downregulating transforming growth factor beta receptor 3 in an IL-β-stimulated human chondrocyte cell line [275]. Downregulation of SNHG7 in OA causes inflammation, apoptosis and antiproliferative effects through upregulation of miRNA-34a-5p and miRNA-214-5p and downregulation of the synovial apoptosis inhibitor 1 and peroxisome proliferator-activated receptor gamma coactivator 1-beta pathway, respectively [276,277]. In addition, the low levels of SNHG7 contribute to inflammation and apoptosis in OA through the overexpression of miRNA-324-3p, the downregulation of dual-specificity phosphatase 1 and consequent activation of the p38 MAPK signalling pathway [278]. In IL-β-stimulated human chondrocytes, SNGH15 are low and induce apoptosis and ECM degradation and reduce the

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proliferation by increasing the expression of miRNA-141-3p and decreasing the expression of Bcl2-like protein 13 [279]. Furthermore, SNGH15 downregulation is also associated with low levels of Krüppel-like factor 4, which is involved in the regulation of proliferation, differentiation and apoptosis, and high levels of miRNA-7 in human OA knee cartilage and in IL-β-stimulated chondrocytes [280]. Low levels of SNHG9 and high levels of miRNA-34a have been found in synovial fluid and chondrocytes from OA patients, leading to an increase in apoptotic processes [281].

The LncRNA OPA interacting protein 5 antisense RNA 1 (OIP5-AS1) is downregulated in human OA cartilage and IL-1β-stimulated human chondrocytes and is associated with increased apoptosis, inflammation and ECM degradation and decreased proliferation and viability through overexpression of miRNA-338-3p [282], and through overexpression of miRNA-29b-3p and downregulation of progranulin via activation of the PI3K/AKT pathway [283]. The lncRNA WDR11 divergent transcript (lncRNA WDR11-AS1) has been shown to be downregulated in human OA cartilage and cytokine-stimulated chondrocytes and is associated with increased polyadenylate binding protein 1 and ECM degradation [284]. Human OA synovial fluid and chondrocytes show low levels of lncRNA PMS2L2 and upregulation of miRNA-34a expression, resulting in reduced chondrocyte proliferation [285].

In cartilage and synovial tissue of the OA rat model and in IL-1β-stimulated mouse chondrocyte-like ADTC5 cells, the lncRNA colorectal neoplasia differentially expressed (CRNDE) is downregulated, causing cartilage damage, inflammation and apoptosis by decreasing the expression of dapper antagonist of catenin-1 [286]. Table 3 summarises the effects and targets of major differentially expressed lncRNAs associated with human OA.

Table 3. Major differentially expressed lncRNAs in human osteoarthritis (OA) and their major targets and effects.

lncRNA	Targets	Effects	Model/cell type	Ref.
MEG3 (-)	VEGF (+)	Angiogenesis	OA cartilage	[225]
	miRNA34a (+) Kloto (-), FGF23 (-), Bcl2 (-), Bax (+), caspases (+)	Mineralisation (-) ECM degradation Inflammation Apoptosis	LPS-stimulated C28/I2 cells	[227]
MALAT1 (+)	miRNA-145 (-) ADAMTS5 (+)	ECM degradation	OA cartilage IL-β-stimulated chondrocytes	[228]
	miRNA-150-5p (-) AKT3 (+)	Proliferation Apoptosis (-) ECM degradation (-)	OA cartilage IL-β-stimulated chondrocytes	[232]
	miRNA-146a (-) PI3K/AKT/mTOR (+)	Inflammation (-) Apoptosis (-)	LPS-stimulated chondrocytes	[233]
HOXA11-AS (+)	miRNA-506-3p (-) PI3K/AKT/mTOR (+)	Proliferation Apoptosis (-)	OA cartilage and chondrocytes	[234]
HOTAIR (+)	miRNA-17-3p (-)	Inflammation Apoptosis Cell damage	LPS-stimulated C28/I2 cells	[235]
	miRNA-130a-3p (-)		OA cartilage and chondrocytes	[236]
	miRNA-17-5p (-) FUT2 (+),	ECM degradation	IL-β-stimulated chondrocytes	[237] [238]

 doi:10.20944/preprints202506.0240.v1

	WIF-1 (-), Wnt/β-catenin (+)		OA chondrocytes	
	Adiponectin (-)	Inflammation		[239]
	PTEN (-), PI3K/AKT (+)		OA PBMC and chondrocytes	
PACER (-)	HOTAIR (+)	Inflammation	OA blood and OA cell model	[241] [242]
IGFBP7-OT (+)	*IGFBT* promoter methylation (-)	Inflammation Apoptosis Cell viability (-)	OA cartilage and chondrocytes	[243]
ELDR (+)	Indian hedgehog signaling molecule (+)	ECM degradation Chondrocyte senescence	OA cartilage and chondrocytes	[244]
MCM3AP-AS1 (+)	miRNA-149-5p (-) Notch1 (+)	ECM degradation Apoptosis	OA cartilage IL-β-stimulated chondrocytes	[245]
PVT1 (+)	GAS5 (-)	Apoptosis	OA synovial fluid LPS-stimulated HC-OA cells	[247]
GAS5 (+)	miRNA-137 (-)	Apoptosis Proliferation (-)	OA serum, cartilage and chondrocytes	[248]
	miRNA-34a (-) Bcl2 (+)	ECM degradation Inflammation Apoptosis	OA chondrocytes	[249]
Xist (+)	miRNA-150-5p (-) VCAM1 (+) CD11b (+)	Monocyte infiltration	OA synovial tissue and fibroblasts	[250]
	FUT1 (+), TAF15 (+)	OA progression	OA cartilage	[251]
TM1-3P (+)	miRNA-144-3p (-) ONECUT2 (+)	ECM degradation Inflammation	IL-β-stimulated synovial fibroblasts	[252]
H19 (+)	miRNA-130 (-)	Inflammation Apoptosis	OA cartilage IL-β-stimulated chondrocytes	[253]
	miRNA-106a-5p (-)	Inflammation Apoptosis	LPS-stimulated C28/I2 cells	[254]
H19 (-)	miRNA-106b-5p (+) TIMP2 (-) MMP3 (+) ADAMTS5 (+)	ECM degradation Proliferation (-) Migration (-)	IL-β-stimulated chondrocytes	[255]
KCNQ1OT1 (+)	miRNA-211-5p (-) TCF4 (+)	Inflammation ECM degradation	OA cartilage LPS-stimulated C28/I2 cells	[256]
	miRNA-1202 (-) ETS1 (+)	Inflammation ECM degradation	OA serum	[257]
KCNQ1OT1 (-)	miRNA-126-5p (+) TRPS1 (-)	ECM degradation	OA cartilage	[258]
LINC01094 (+)	miRNA-577 (-)	Apoptosis	OA cartilage	[259]

 doi:10.20944/preprints202506.0240.v1

	MTF1 (+)		LPS-stimulated chondrocytes	
AFAP1-AS1 (-)	miRNA-512-3p (-) MMP13 (+)	ECM degradation	OA cartilage	[260]
LINC00958 (+)	miRNA-214-3p (-) FOXM1 (+)	Inflammation Apoptosis Cell viability (-)	IL-β-stimulated CHON-001	[261]
NEAT1 (+)	miRNA-181c (-) miRNA-543 (-), PLA2G4A (+)	Inflammation Apoptosis ECM degradation	OA cartilage and chondrocytes	[262] [263]
NEAT1 (-)	miRNA-374b-5p (+) PGAP1 (-)	Inflammation Apoptosis	OA cartilage LPS-stimulated chondrocytes	[266]
LEMD1-AS1 (-)	miRNA-944 (+) PGAP1 (-)	Inflammation Apoptosis	OA cartilage LPS-stimulated chondrocytes	[267]
BLACAT1 (+)	miRNA-149-5p (-) HMGCR (+)	ECM degradation Apoptosis	IL-β-stimulated chondrocytes	[268]
SNHG12 (+)	miRNA-16-5p (-)	Inflammation Apoptosis ECM degradation	OA cartilage	[269]
SNHG14 (+)	miRNA-137 (-)	Inflammation Apoptosis ECM degradation Cell viability (-)	OA cartilage	[270]
SNHG16 (+)	miRNA-373-3p (-)	Inflammation Apoptosis ECM degradation Cell viability	OA cartilage	[271]
SNHG1 (-)	miRNA-16-5p (+) p38 MAPK/NF-kB (+)	Inflammation Apoptosis ECM degradation	IL-β-stimulated chondrocytes	[272]
SNHG5 (-)	miRNA-26a (+) SOX2 (-)	Proliferation (-) Migration (-)	OA cartilage	[273]
	miRNA-10-5p (+) H3F3B (-)	Apoptosis Proliferation (-)	IL-β-stimulated chondrocytes	[274]
	miRNA-181a-5p (+) TGFβR3 (-)	Apoptosis (+) ECM degradation	IL-β-stimulated C20/A4 cells	[275]
SNHG7 (-)	miRNA-34a-5p (+) SYVN1 (-)	Inflammation Apoptosis Proliferation (-)	IL-β-stimulated chondrocytes	[276]
	miRNA-214-5p (+) PPARGC1B (-)	Inflammation Apoptosis Proliferation (-)	IL-β-stimulated chondrocytes	[277]
	miRNA-324-3p (+)	Inflammation		[278]

 doi:10.20944/preprints202506.0240.v1

	DUSP1 (-) P38 MAPK (+)	Apoptosis	IL-β-stimulated chondrocytes	
SNHG15 (-)	miRNA-141-3p (+) Bcl2-L-13 (-)	Inflammation Apoptosis Proliferation (-)	IL-β-stimulated chondrocytes	[279]
	miRNA-7 (+) KLF4 (-)	Proliferation (-) Apoptosis	OA cartilage IL-β-stimulated chondrocytes	[280]
SNHG9 (-)	miRNA-34a (+)	Apoptosis	OA synovial fluid and chondrocytes	[281]
OIP5-AS1 (-)	miRNA-338-3p (+) PI3K/AKT (+)	Inflammation Apoptosis ECM degradation	IL-β-stimulated chondrocytes	[282]
	miRNA29b-3p (+) progranulin (-)	Proliferation (-) Cell viability (-)		[283]
WDR11-AS1 (-)	PABPC1 (+)	ECM degradation	OA cartilage cytokine-stimulated chondrocytes	[284]
PMS2L2	miRNA-34a (+)	Proliferation (-)	OA synovial fluid and chondrocytes	[285]

Abbreviations: FGF23, fibroblast growth factor 23; LPS, lipopolysaccharide; ADAMTS5, disintegrin and metalloproteinase with thrombospondin motifs 5; IL-1β, interleukin-1β; PI3K/Akt/mTor, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; FUT, α-1,2-fucosyltransferase; WIF-1, Wnt inhibitory factor 1; PTEN, phosphatase and tensin homologue of chromosome 10; HC-OA cells, human Chondrocyte-Osteoarthritis cells; VCAM-1, Vascular cell adhesion molecule-1; TAF15, TATA-box binding protein-associated factor 15; ONECUT2, transcription factor one cut homeobox 2; TIMP2, tissue inhibitor of metalloproteinases 2; MMP, metalloproteinase; TCF4, transcription factor 4; ETS1, E26 transcription factor-1; TRPS1, transcriptional repressor GATA binding 1; MTF1, metal-regulatory transcription factor 1; PLA2G4A, phospholipase A2 group IVA; PGAP1, post-GPI attachment to protein 1; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; p38 MAPK, p38 mitogen-activated protein kinase; NF-kB, Nuclear factor kappa B; SOX2, SRY-box transcription factor 2; H3F3B, histone H3 family 3B; TGFβR3, transforming growth factor beta receptor 3; SYVN1, synovial apoptosis inhibitor 1; PPARGC1B, peroxisome proliferator-activated receptor gamma coactivator 1-beta; DUSP1, dual-specificity phosphatase 1; Bcl2-L-13, Bcl2-like protein 13; KLF4, Krüppel-like factor 4; PABPC1, polyadenylate binding protein 1. (-) Downregulated; (+) Upregulated.

6. Cross-Talk Between Oxidative Stress and lncRNAs in Osteoarthritis

An association between altered lncRNA expression and oxidative stress by modulating transcription factors has been demonstrated in several pathologies [43]. Some lncRNAs are able to affect the antioxidant transcription factor Nrf2 signalling pathway [287,288] and it has been shown that decreased expression of lncRNA NR024118 is associated with oxidative stress, apoptosis and inflammation by activating NF-κB expression levels and inhibiting Nrf2 signalling pathways in LPS-treated ATDC5 chondrocytes. In fact, in these cells, NR024118 overexpression attenuates the production of ROS and inflammatory cytokines, and inhibits and promotes the activation of NF-kB and Nrf2 pathways, respectively [289].

The expression of the lncRNA zinc finger NFX1-type containing 1 antisense 1 (ZFAS1) is also reduced in human OA cartilage, and the downregulation of this lncRNA increases ROS levels, decreases the activity of antioxidant enzymes SOD and catalase, and causes apoptosis and inflammation through the upregulation of miRNA-1323 and consequent decrease in Nrf2 and HO-1 protein levels in LPS-treated chondrocytes [186].

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In IL-1β-stimulated human chondrocytes, NEAT1_2 is significantly decreased in association with the onset of oxidative stress due to the inhibition of Nfr2, SOD1 and SOD2 expression and the upregulation of iNOS expression, promoting apoptosis and cartilage degradation [290].

The increase in HOTAIR expression promotes oxidative stress, as evidenced by high levels of ROS and malondialdehyde and low levels of SOD activity, and causes the production of pro-inflammatory factors, MMPs and ADAM10 through the downregulation of miRNA-222-3p in IL-1β-treated C28/I2 chondrocytes [178].

In human OA chondrocytes, there is an increase in lncRNA CIR accompanied by downregulation of miRNA-130a, upregulation of B-cell lymphoma 2 interacting mediators of cell death and accumulation of ROS. Furthermore, high ROS levels increase the expression of lncRNA CIR in H_2O_2-treated human chondrocytes, suggesting a reciprocal interaction between oxidative stress and lncRNA CIR overexpression [291].

H_2O_2 treatment of C28/I2 chondrocytes downregulates SNHG1 expression, upregulates miRNA-195 levels and induces apoptosis and an inflammatory state through NF-kB activation and the production of pro-inflammatory mediators. Conversely, a significant increase in the production of ROS is induced by the knockdown of SNHG1 [177].

The lncRNA LOC727924, also known as LINC02203, is upregulated in human OA cartilage and chondrocytes and is involved in the progression of OA by increasing intracellular ROS, apoptosis, inflammation and ECM degradation through the downregulation of miRNA-26a and the consequent upregulation of KPNA3. The immunosuppressive and anti-inflammatory vasoactive intestinal peptide reduces LOC727924 levels and the accumulation of ROS, in addition to improving chondrocyte function [191].

In the synovial fluid of OA patients, MEG3downregulation is associated with the increase in miRNA-885-5p and the consequent decrease in SLC7A11 and GPX4, and is ultimately involved in chondrocyte ferroptosis. In fact, in human CHON-001chondrocytes, overexpression of MEG3 reduces erastin-induced ferroptosis by downregulating miRNA-885-5p and upregulating SLC7A11 and GPX4 [292].

GAS5 expression increases in fibroblast-like synoviocytes (FLS) from OA patients and in IL-1β-stimulated FLS. In these treated cells, upregulation of GAS5 is associated with reduced expression of SLC7A11, GPX4, Nrf2 and HO-1 and low activity of SOD, and increased levels of long-chain fatty acid CoA ligase 4, an important enzyme involved in the ferroptosis pathway, ROS and p53. This implies a reduced viability and antioxidant capacity leading to cell death, oxidative stress, inflammation and ferroptosis which are mediated by the downregulation of miRNA-205 [293].

In IL-1β-stimulated human chondrocytes and OA cartilage tissue, the decrease in SNHG7 is associated with an increase in miRNA-485-5p, resulting in ROS production and the downregulation of ferroptosis suppressor protein 1, a glutathione-independent ferroptosis inhibitor molecule [294]. The targets and effects of the major lncRNAs related to oxidative stress in OA are shown in Table 4.

Table 4. Main lncRNAs involved in the cross-talk with oxidative stress in osteoarthritis (OA).

lncRNA	Targets	Effects	Model/cell type	Ref.
NR024118 (-)	NF-kB (+) Nrf2 (-)	Oxidative stress Inflammation Apoptosis	LPS-stimulated ATDC5 cells	[289]
ZFAS1 (-)	miRNA-1323 (+) Nrf2/HO-1 (-) SOD (-) CAT (-)	ROS production Inflammation Apoptosis	LPS-stimulated human chondrocytes	[186]
NEAT1-2 (-)	Nrf2 (-) SOD1(-) SOD2 (-) iNOS (+)	Oxidative stress Apoptosis ECM degradation	IL-β-stimulated human chondrocytes	[290]

 doi:10.20944/preprints202506.0240.v1

HOTAIR (+)	miRNA-222-3p (-) SOD (-) MMPs (+) ADAM10 (+)	ROS production Inflammation ECM degradation	IL-β-stimulated C28/I2 cells	[178]
CIR (+)	miRNA-130a (-) Bim (+)	ROS production ECM degradation Apoptosis	Human OA chondrocytes H_2O_2-treated human chondrocytes	[291]
SNHG1 (-)	miRNA-195 (+) NF-kB (+)	Inflammation (+) Apoptosis (+) ROS production	H_2O_2-treated C28/I2 cells C28/I2 cells	[177]
LOC727924 (+)	miRNA-26a (-) KPNA3 (+)	ROS production Inflammation Apoptosis ECM degradation	Human OA chondrocytes	[191]
MEG3 (-)	miRNA-885-5p (+) SLC7A11 (-) GPX4 (-)	Ferroptosis	Synovial OA fluid	[292]
GAS5 (+)	miRNA-205 (-) SLC7A11 (-) GPX4(-) Nrf2/HO-1 (-) ACSL4 (+) P53 (+)	ROS production Cell viability (-) Inflammation Ferroptosis	IL-1β-stimulated OA FLS	[293]
SNHG7 (-)	miRNA-485-5p (+) FSP1 (-+)	ROS production Ferroptosis	IL-β-stimulated human chondrocytes	[294]

Abbreviations: Nrf2/HO-1, nuclear factor erythroid 2-related factor /Hemoxygenase 1; LPS, lipopolysaccharide; NF-kB, Nuclear factor kappa B; SOD, superoxide dismutase; CAT, catalase; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; MMPs, metalloproteinases; ADAM10, A disintegrin and metalloproteinase domain-containing protein 10; Bim, B-cell lymphoma 2 interacting mediators of cell death; IL-1β, interleukin-1β; KPNA3, karyopherin subunit alpha 3; SLC7A11, solute carrier family 7 member 11; GPX4, selenoprotein glutathione peroxidase 4; ACSL4, long-chain fatty acid CoA ligase 4; FSP1, ferroptosis suppressor protein 1. (-) Downregulated; (+) Upregulated.

7. Conclusions

OA causes joint degeneration, pain and reduced physical activity, which negatively impact quality of life. This review reports on the main mechanisms involved in the role of oxidative stress, as well as the most important dysregulated miRNAs and lncRNAs in the pathogenesis of OA. Furthermore, the cross-talk between oxidative stress and these ncRNAs has been discussed. In particular, the dysregulation of several miRNAs and lncRNAs has been shown to be associated with ROS production, and oxidative stress may be responsible for the altered expression of these ncRNAs. Importantly, many oxidative stress-related lncRNAs interact with miRNAs, making the role of oxidative stress in OA pathogenesis more complex. Identifying the molecular mechanisms and pathways involved in the intricate interaction between oxidative stress, miRNAs and lncRNAs in OA may help to identify therapeutic targets to restore the normal expression of these ncRNAs by inhibiting oxidative stress, or to restore the physiological redox state by normalising the levels of miRNAs and lncRNAs. In this sense, it is desirable in the future to stimulate the development of drugs that can inhibit the loss of cartilage homeostasis and/or reduce the progression of osteoarthritic pathology.

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