The Involvement of MicroRNAs in Osteoarthritis and Recent Developments: A Narrative Review

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ABSTRACT

Background: Osteoarthritis (OA) is the most common chronic joint disease and it may progressively cause disability and compromise quality of life. Lately, the role of miRNAs in the pathogenesis of OA has drawn a lot of attention. miRNAs are small, single-stranded, non-coding molecules of RNA which regulate gene expression at post-transcriptional level. The dysregulation of the expression of several miRNAs affects pathways involved in OA pathogenesis. Objective: The purpose of this article is to review the literature on the involvement of miRNAs in the pathogenesis of OA and the implications on its diagnosis and treatment. Materials and Methods: An extensive electronic literature search was conducted by two researchers from January 2008 to August 2017. Titles and abstracts of papers were screened by the authors for further inclusion in the present work. Finally, full texts of the selected articles were retrieved. Results: Abnormally expressed miRNAs enhance the production of cartilage degrading enzymes, inhibit the expression of cartilage matrix components, increase the production of proinflammatory cytokines, facilitate chondrocyte apoptosis, suppress autophagy in chondrocytes and are involved in pain-related pathways. miRNAs are also incorporated in extracellular membranous vesicles such as exosomes and participate in the intercellular communication in osteoarthritic joints. Conclusion: Ongoing research on miRNAs has potential implications in the diagnosis and treatment of OA. Their different levels in peripheral blood and synovial fluid between OA patients and healthy population makes them candidates for being used as biomarkers of the disease, while targeting miRNAs may be a novel therapeutic strategy in OA.

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LIST OF ABBREVIATIONS

Abbreviation Explanation
miRNAs Micro RNAs
Osteoarthritis OA
mRNA Messenger RNA
INTRODUCTION

Osteoarthritis (OA) is the most common chronic arthropathy and is characterised by failure of damaged cartilage to repair itself, synovial inflammation and changes in the subchondral bone. Increased production of cartilage-degrading enzymes (Matrix Metalloproteinases, aggrecanases) by articular chondrocytes, insufficient synthesis of cartilage matrix components (collagen type II, aggrecan) and increased chondrocyte apoptosis lead to gradual cartilage loss. Pain and stiffness are the main clinical features of OA. Loss of movement and function are features of more severe disease, resulting in a worse quality of life.\(^1\)

The etiology of OA is complex and not fully understood yet. It involves genetic and environmental factors, such as joint injury, obesity and aging.\(^2\) According to epidemiological and family-based genetic studies, genetic factors seem to be responsible for a significant proportion of OA susceptibility. Heritability has been estimated to be 39-79% depending on the affected joint, gender and severity of diseases. In addition, these studies have shown that OA is a complex polygenic disorder – multiple risk loci contribute to OA heritability, each of which accounts for a small proportion of it.\(^3\)

During the last decade, large Genome Wide Association Studies (GWAS) have identified 17 genetic loci for OA,\(^4\)-\(^14\) but these risk loci do not fully account for OA heritability. Epigenetic modifications may be responsible for OA heritability that remains unexplained by OA genetics. Epigenetics include heritable mechanisms, such as DNA methylation, histone modifications and microRNAs, which regulate gene expression without changes to the DNA sequences.\(^15\)-\(^16\) MicroRNAs (miRNAs) have attracted a lot of attention lately, since they have the potential to be used as biomarkers or as novel therapeutic agents. Numerous studies have shown that miRNA expression is altered in OA and these alterations possibly contribute to OA pathogenesis. The purpose of this article is to review the literature on the role of miRNAs in the pathogenesis of OA and its implications on diagnosis and treatment of this disorder.
MicroRNAs

MicroRNAs (miRNAs) are small, single-stranded, non-coding RNAs, consisting of 20-25 nucleotides, whose role is post-transcriptional regulation of gene expression. MiRNAs are partially complementary and bind to the 3'-Untranslated Region (3'-UTR) of their target messenger RNA (mRNA). They then inhibit the translation of their target mRNA or cause its degradation. Thus, miRNAs inhibit the expression of their target gene at post-transcriptional level. Concerning the synthesis of miRNAs, primary miRNA is transcribed in the nucleus from its gene (Figure 1). Afterwards, ribonuclease Drosha and protein DGCR8 process the primary miRNA to precursor miRNA. The precursor miRNA is transferred to the cytoplasm and ribonuclease Dicer processes it to mature miRNA. The passenger strand of the miRNA is ejected and degraded and the other strand – the mature miRNA – is loaded to protein Argonaute (Ago). The mature miRNA interacts with proteins Ago and GW182, binds to its target mRNA and inhibits its translation. MiRNAs are encoded by DNA sequences which are found in the genome either as separate miRNA genes or within the introns of other genes. Over 3% of human genes have been found to contain miRNA-coding sequences, while the expression of 40-90% of human protein-coding genes is regulated by miRNAs. Apart from binding to their target mRNAs and inhibiting their translation, miRNAs may be packaged and transferred extracellularly by three different ways: (a) incorporated in extracellular membranous vesicles (exosomes, shedding vesicles and apoptotic vesicles), (b) bound to lipoproteins, like High Density Lipoprotein (HDL), and (c) bound to RNA-binding proteins, like Argonaute-2 and nucleophosmin-1. These miRNAs are secreted via exocytosis, they may be received by other cells via endocytosis and regulate their gene expression. Thus, miRNAs participate in intercellular communication.

The Role of MicroRNAs in OA

A remarkable number of studies have been published during the last few years about the expression of different miRNAs in osteoarthritic cartilage and subchondral bone. Most of these studies examine the expression of miRNAs targeting genes known to participate in the pathogenesis of OA. For this purpose, we have summarized in Table 1 the miRNAs found to be dysregulated in OA and their target genes.

miR-140 in OA

One of the most studied miRNAs in OA is miRNA-140 (miR-140). The expression of miR-140 in chondrocytes increases during their differentiation, suggesting that it is probably a regulator of the differentiation of these cells. In osteoarthritic cartilage the expression of miR-140 is reduced in comparison to healthy cartilage. Target genes of miR-140 include ADAMTS5 (ADAM Metallopeptidase with Thrombospondin Type 1 Motif 5), MMP13 (Matrix Metalloproteinase 13), IGFBP5 (Insulin Like Growth Factor Binding Protein 5) and RALA (RAS like proto-oncogene A). ADAMTS5 and MMP13 are proteinases that mediate the degradation of several components of cartilage matrix and might play an important role in OA pathogenesis. IGFBP-5 (Insulin-like Growth Factor Binding Protein 5) is also involved in OA pathology by modulating the availability of IGF-1 in the joint. RALA (RAS like proto-oncogene A) is a small
GTPase that downregulates the transcription factor SOX9 (SRY-box 9). SOX9 is a master regulator of cartilage development and it enhances the production of cartilage matrix components. Downregulation of RALA by miR-140 results in upregulation of SOX9. Concerning the expression of miR-140, the cytokine Interleukin-1β (IL-1β), a key player in OA pathogenesis, inhibits the expression of miR-140 by chondrocytes, while the

Table 1: MicroRNAs dysregulated in OA and their target genes.

| MicroRNA | Target gene | Reference                          |
|----------|-------------|------------------------------------|
| miR-9    | MCPIP1      | Makki, Haseeb et al. 2015          |
|          | PTG         | Song, Kim, Chun et al. 2013        |
| miR-15a-5p| VEGFA       | Chen et al. 2017                   |
| miR-16-5p| SMAD3       | Li L et al. 2015                   |
| miR-21   | GDF5        | Zhang et al. 2014                  |
| miR-23a-3p| SMAD3       | Song et al. 2014                   |
| miR-24   | INK4A       | Philipot et al. 2014               |
| miR-26a  | INOS        | Rasheed et al. 2016                |
| miR-26b  | KPNA3       | Yin et al. 2017                    |
| miR-27b  | MPMP13      | Akhtar et al. 2010                 |
| miR-29   | -           | Saad, NFκB, and canonical Wnt signaling |
| miR-30a  | ADAMTS5     | Ji, Xu, Zhang et al. 2016          |
| miR-30b  | ERG         | Li, Yang et al. 2015               |
| miR-33   | CCL2        | Wei et al. 2016                    |
| miR-33a  | SMAD7       | Kostopoulos et al. 2015            |
| miR-34a  | SIRT1       | Yan et al. 2016                    |
| miR-98   | -           | Wang GL et al. 2016                |
| miR-105  | Runx2       | Ji, Xu, Xu et al. 2014             |
| miR-122  | IL1A        | Yang et al. 2015                   |
| miR-125b | ADAMTS4     | Matsukawa et al. 2013              |
| miR-127  | OPN         | Tu et al. 2016                     |
| miR-130  | TNFA        | Li ZC et al. 2015                  |
| miR-139  | MCPIP1      | Makki and Haqqi, 2015              |
|          | EIF4G2, IGF1R| Hu et al. 2016                     |
| miR-140  | ADAMTS5     | Miyaki et al. 2009, Miyaki et al. 2010 |
|          | IGFBP5      | Tardif et al. 2009                 |
| miR-142-3p| MPMP13      | Liang et al. 2012, Liang et al. 2016 |
| miR-146  | HMGB1       | Wang X et al. 2016                 |
| miR-148  | MMP13       | Yamasaki et al. 2009              |
| miR-149  | COL10A1, MMP13, ADAMTS5 | Li et al. 2011                     |
| miR-155  | TNFA, IL1B, IL6 | Santini et al. 2014             |
| miR-181  | PTEN        | Wu et al. 2017                     |
| miR-210  | DN6         | Zhang et al. 2015                  |
| miR-222  | HDAC-4      | Song, Jin et al. 2015             |
| miR-335  | -           | Tornero-Esteban et al. 2014        |
| miR-370  | SHMT-2      | Song, Kim et al. 2015             |
| miR-373  | MECP-2      | Song, Kim et al. 2015             |
| miR-381a-3p| IkBo       | Xia et al. 2016                    |
| miR-483-5p| Matn3, Timp2| Wang et al. 2017                   |
| miR-488  | ZIP8        | Song, Kim, Lee et al. 2013         |
| miR-558  | COX2        | Park et al. 2013                   |
| miR-634  | PIK3R1      | Cui et al. 2016                    |

Each microRNA is reported with its respective target genes and the bibliographical reference where the information was obtained.
transcription factor SOX9 enhances its expression (27). Moreover, the transcription factor SMAD3 (SMAD family member 3), a mediator of Transforming Growth Factor-β (TGF-β), downregulates miR-140 expression by articular chondrocytes. Therefore, Interleukin-1β (IL-1β) and Transforming Growth Factor-β (TGF-β) inhibit the expression of miR-140 in chondrocytes of osteoarthritic cartilage, resulting in increased expression of ADAMTS5, MMP13, IGFBP5 and RALA and degradation of articular cartilage matrix. In addition, targeted deletion of miR-140 in mice resulted in OA-like changes of articular cartilage, while overexpression of miR-140 protected it from antigen-induced arthritis, enhancing the hypothesis of miR-140 participating in OA pathogenesis. The basic interactions of miR-140 and its target genes is presented in Figure 2.

miR-146 in OA
Another miRNA that has been studied in OA is miR-146. Its expression is increased in osteoarthritic cartilage during the early stages of the disease and it gradually decreases as OA progresses. The target gene of miR-146 is MMP13 and the expression of this miRNA is upregulated by IL-1β. Thus, it seems that miR-146 is a negative feedback regulator of MMP13 and it possibly plays a protective role in OA cartilage. Indeed, miR-146 inhibits IL-1β-induced MMP13 and ADAMTS5 production by chondrocytes and IL-1β-induced suppression of collagen type II and aggregan, which are components of the cartilage matrix. miR-146 also inhibits IL-1β-induced TNF-α upregulation in OA cartilage. Moreover, miR-146 downregulates the expression of SMAD4, a transcription factor that is a mediator of TGF-β. Thus, upregulation of miR-146 in OA chondrocytes downregulates SMAD4, reduces cellular responsiveness to TGF-β and induces chondrocyte apoptosis. Downregulation of SMAD4 also leads to an increase in the expression of Vascular Endothelial Growth Factor (VEGF), which contributes to inflammation and pathological angiogenesis in OA. Furthermore, altered expression of miR-146 appears to play a role in pain-related pathways in OA. miR-146 is downregulated in dorsal root ganglia and in the dorsal horn of the spinal cords of rats with osteoarthritic pain. miR-146 decreases the expression of pain modulators that enhance pain perception, such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), Interleukin-8 (IL-8), COX-2 and iNOS, in astrocytes. Thus, it seems that downregulation of miR-146 in the central and peripheral nervous system of the rat OA model mediates osteoarthritic pain.

miR-26a and miR-26b in OA
The role of miR-26a and miR-26b in the pathogenesis of OA has been recently studied. The expression of miR-26a and miR-26b is significantly downregulated in cartilage from osteoarthritic joints, while the target gene of these miRNAs has been found to be the one encoding Karyopherin Subunit Alpha 3 (KPNA3). KPNA3 is a mediator of Nuclear Factor-κB (NF-κB) pathway which binds to NF-κB and facilitates its translocation from cytoplasm to nucleus. It is suggested that the NF-κB pathway might play a significant role in OA pathogenesis, since it induces production of proinflammatory cytokines, Cyclooxygenase-2 (COX-2) and metalloproteinases (MMPs), which result in joint inflammation and degradation of joint cartilage. Therefore, downregulation of miR-26a and miR-26b in OA cartilage results in upregulation of KPNA3 and NF-κB and production of MMPs and COX-2. In addition, activation of NF-κB pathway negatively regulates the expression of miR-26a, implying a reciprocal inhibition between miR-26a and NF-κB.
MicroRNAs involved in cartilage matrix degradation and joint inflammation in OA

Dysregulation of the expression of several miRNAs in OA results in increased production of cartilage matrix degrading enzymes (MMPs, ADAMTS proteases). Downregulation of miR-24, miR-27b, miR-148a, miR-210, miR-222, miR-370, miR-373 and miR-488 in OA cartilage leads directly or indirectly to an increase in the production of MMPs while downregulation of miR-30a, miR-105, miR-125b and miR-148a results in overproduction of NO and cartilage damage.\(^{35}\)

Besides, other microRNAs are involved in the production of proinflammatory cytokines like TNF-\(\alpha\), IL-1, IL-6 and IL-8 in OA. Downregulation of miR-142-3p and miR-210 in chondrocytes of OA cartilage leads to overexpression of High Mobility Group Box 1 (HMGB1) and Death Receptor 6 (DR6) respectively. As a result, the NF-\(\kappa\)B signaling pathway is activated and the production of TNF-\(\alpha\), IL-1, IL-6 and IL-8 is increased.\(^{49,50}\) Downregulation of miR-130a is another miRNA whose dysregulated expression leads to increased activation of the NF-\(\kappa\)B signaling pathway and facilitates the apoptosis of the chondrocytes.\(^{55}\)

MicroRNAs and autophagy in OA

Autophagy is a cell response to stress, in which cytoplasmic organelles and macromolecules are degraded by lysosomes and then recycled in order to support cellular metabolism and survival. Aging and age-related diseases, including OA, are related to reduced autophagy. Lately, several studies have been published about the involvement of microRNAs in reduced autophagy in OA.\(^{59,60}\)

miR-155 is upregulated in human osteoarthritic cartilage and takes part in reduced autophagy in OA chondrocytes. Bioinformatics predict that miR-155 targets the autophagy-related genes ATG3 (autophagy related 3), GABARAPL1 (GABA type A receptor associated protein-like 1), ATG5 (autophagy related 5), ATG2B (autophagy related 2B), LAMP2 (lysosomal associated membrane protein 2) and FOXO3 (forkhead box protein O3). Recent \textit{in vitro} study confirmed that miR-155 downregulates the expression of ATG3, GABARAPL1, ATG5 and FOXO3 in human articular chondrocytes, as well as the expression of other autophagy-related genes (ULK1 [unc-51-like autophagy activating kinase 1], MAP1LC3 [microtubule-associated protein 1 light chain 3 beta] and ATG14 [autophagy-related 14]), resulting in inhibition of autophagy.\(^{56}\) Adamo et al. conclude that miR-155 inhibits autophagy in chondrocytes and is partially responsible for defective autophagy in OA.\(^ {59}\)

miR-21-2 is another miRNA whose dysregulated expression leads to decreased autophagy in OA. Its target gene is GAS5 (Growth arrest-specific 5), which stimulates cell apoptosis and suppresses autophagy. The expression of
miR-21 is decreased in osteoarthritic chondrocytes, resulting in upregulation of GAS5, increased apoptosis and suppressed autophagy. Besides, GAS5 downregulates miR-21, implying a reciprocal interplay between miR-21 and GAS5. Furthermore, when miR-21 was injected in osteoarthritic joints of a mouse OA model, it reduced cartilage destruction, whereas intra-articular injection of an inhibitor of miR-21 worsened cartilage destruction.60

On the other hand, increased expression of miR-146 seems to have a protective effect in osteoarthritic cartilage by promoting chondrocytes autophagy. Zhang et al. studied the effect of hypoxia, a pathogenic mechanism contributing to OA development, on the expression of miR-146 and autophagy in chondrocytes. They demonstrated that hypoxia induces HIF-1α (Hypoxia-inducible factor-1α) in chondrocytes, which upregulates the expression of miR-146a. Uregulated miR-146a suppresses Bcl-2, an autophagy inhibitor, resulting in promotion of autophagy. Zhang et al. conclude that miR-146a plays probably a protective role in OA by enhancing chondrocyte autophagy.61

### Profiling multiple microRNAs expressed in osteoarthritic tissues

The aforementioned studies have examined the expression of one or a few miRNAs, which target a gene or a pathway that is already known to participate in the pathogenesis of OA. On the other hand, during recent years, other studies have used high-throughput methods, such as hybridization microarrays and next generation RNA-sequencing, in order to examine the profile of multiple miRNAs expressed in the cartilage and subchondral bone of osteoarthritic joints and compare it to healthy controls.32,62-68 A summary of the respective studies is presented in Table 2. Although these studies have some results in common, such as the downregulation of miR-140, most of their results do not overlap. There are plenty of reasons for this variety of results. Some studies measured miRNA expression in fresh samples of cartilage, subchondral bone or synovial fluid from osteoarthritic joints, while other studies used cultured chondrocytes from OA cartilage. Moreover, different studies used different sets of microarrays in order to examine the miRNA expression, while one study used next generation RNA-sequencing. In addition, sample size was small

### Table 2. High-throughput methods used in OA literature.

| Study                  | Experimental material                                                                 | Number of samples | Methodology            | Results                                      |
|------------------------|----------------------------------------------------------------------------------------|-------------------|------------------------|----------------------------------------------|
| Jones et al. 200932    | Cartilage and subchondral bone from OA vs normal joints                                | 4/4               | Microarrays (157 miRNAs) | 47 differentially expressed miRNAs           |
| Iliopoulos et al. 200834 | Cultured chondrocytes from OA vs normal cartilage                                      | 33/10             | Microarrays (365 miRNAs) | 11 differentially expressed miRNAs           |
| Swingler et al. 201237 | Discovery: Cultured chondrocytes Validation: Cartilage from OA vs normal joints       | 10/10             | Discovery: Microarrays Validation: RT-PCR | 39 miRNAs differentially expressed during chondrogenesis 2 miRNAs differentially expressed in OA vs normal cartilage |
| Diaz-Prado et al. 201263 | Cultured chondrocytes from OA vs normal cartilage                                      | 6/4               | Microarrays (723 miRNAs) | 7 differentially expressed miRNAs           |
| Tornero-Estaban et al. 201568 | Cultures of bone marrow mesenchymal stem cells from OA patients vs controls          | 10/10             | Microarrays (754 miRNAs) | 246 differentially expressed miRNAs         |
| Crowe et al. 201662   | Discovery: Cartilage from OA joints Validation: Cartilage from OA vs normal joints   | 11/6              | Discovery: Next generation RNA-sequencing Validation: RT-PCR | 60 new miRNAs expressed in OA cartilage 3 differentially expressed miRNAs |
| Li YH et al. 201665    | Synovial fluid from late-stage vs early-stage OA joints                                | 4/4               | Microarrays (752 miRNAs) | 7 differentially expressed miRNAs           |
| Rasheed et al. 201666  | Cultured chondrocytes from OA cartilage, stimulated or not with IL-1β                 | Unknown           | Microarrays (1347 miRNAs) | 36 differentially expressed miRNAs         |

Studies that used high-throughput methods in order to examine the profile of multiple miRNAs expressed in cartilage, subchondral bone and synovial fluid of osteoarthritic joints.
and there were no adjustments for confounding factors, such as age, gender or obesity. However, these studies have identified a lot of new miRNAs and genes that potentially participate in OA pathogenesis. Further studies will investigate the role of these miRNAs in OA and reveal novel pathogenetic mechanisms related with them.

**Extracellular Vesicles and microRNAs IN OA**

miRNAs may be packaged in extracellular vesicles such as exosomes, secreted from the cell that produces them and transferred to another cell, regulating thus the gene expression of the latter. In OA, miRNAs in exosomes are altered and these alterations seem to get involved in OA pathogenesis. Recent study demonstrated that the expression of several miRNAs was altered in exosomes contained in synovial fluid derived from osteoarthritic joints compared to normal joints. In another study, Kato et al. used IL-1β to stimulate synovial fibroblasts and examined the effect of exosomes derived from the stimulated synovial fibroblasts on articular chondrocytes. IL-1β is a key player of OA pathogenesis mediating synovial inflammation and cartilage degradation. Kato et al. demonstrated that exosomes from IL-1β-stimulated synovial fibroblasts upregulated the expression of degrading enzymes MMP13 and ADAMTS5 in articular chondrocytes and downregulated the expression of cartilage matrix components (type II collagen and aggrecan). They also showed that the expression of 50 miRNAs was dysregulated in exosomes derived from IL-1β-stimulated synovial fibroblasts compared with non-stimulated synovial fibroblasts. In addition, Nakasa et al. showed that exosomes derived from IL-1β-stimulated OA cartilage upregulated the expression of MMP13, IL-1β, TNF-α and COX-2 in OA synovium. Thus, miRNAs packaged in exosomes participate in OA pathogenesis by mediating cell to cell communication in osteoarthritic joints.

**MicroRNAs as Biomarkers in OA**

miRNAs may be detected in peripheral blood and synovial fluid incorporated in extracellular vesicles or bound to lipoproteins and RNA-binding proteins. The stability of miRNAs in circulation and their different levels between patients with OA and healthy population offer the opportunity of using these molecules as biomarkers for this disease. Murata et al. showed that plasma levels of miR-16 and miR-132 differentiated OA patients from healthy controls, since they were significantly lower in the former. Moreover, synovial fluid concentrations of miR-16, miR-146a, miR-155 and miR-223 were significantly lower in patients with OA compared to patients with rheumatoid arthritis and could differentiate those two groups of patients. In the same study, Murata et al. discovered that there was no correlation between plasma and synovial fluid miRNA levels, implying different origins for them, and then demonstrated that synovial membrane is the main source of synovial fluid miRNAs. In another study, Borgonio Cuadra et al. compared plasma levels of 380 miRNAs between OA patients and healthy subjects and found 12 miRNAs that were overexpressed in the plasma of OA patients (miR-16, miR-20b, miR-29c, miR-30b, miR-93, miR-126, miR-146a, miR-184, miR-186, miR-195, miR-345, miR-885-5p). Recently, Withrow et al. demonstrated that the concentration of miR-7-5p and miR-200c-3p in exosomes derived from synovial fluid was significantly higher in OA patients in comparison to healthy subjects. Moreover, Okuhara et al. have shown that peripheral blood mononuclear cells express significantly higher levels of miR-146a, -155, -181a, and -223 in OA patients compared to healthy population. Furthermore, in an interesting study, Beyer et al. investigated the possibility of using plasma miRNA levels in order to predict the development of severe knee and hip OA. They discovered that lower plasma levels of let-7e were associated with severe knee and hip OA requiring total joint arthroplasty. Therefore, although results are limited and sometimes contradicting, miRNAs have the potential of being used as biomarkers for OA. Their stability, ease of measurement and different expression in the blood and synovial fluid of OA patients offer the opportunity of using them to predict the prognosis or even measure disease activity or predict response to treatment. However, more studies are needed for this to become possible.

**Therapeutic Potential of microRNAs in OA**

Current treatment of OA includes drugs such as Non-steroidal Anti-Inflammatory Drugs (NSAIDs) for alleviating symptoms and total joint arthroplasty in cases of severe OA. There are no drugs that halt the progress of the disease, like disease-modifying drugs do in rheumatoid arthritis. miRNAs represent a promising target for the treatment of OA. A remarkable number of miRNAs participate in the pathogenesis of OA. Inhibition of these miRNAs with antisense oligonucleotides (anti-miRs) or administration of miRNAs that silence genes participating in OA pathogenesis could be a novel approach for arresting the progress of OA. An advantage of this approach is that synovial joints are an isolated environment and intra-articular administration of miRNAs would not have systemic effects. However, an important issue is the delivery method of the miRNAs or the anti-miRs. Several solutions have been proposed, including extracellular vesicles (exosomes), nanoparticles and antibodies. An example of targeting miRNAs for the treatment of OA is the inhibition of miR-34a. The upregulation of miR-34a in osteoarthritic chondrocytes results in inhibition of SIRT1, leading to increased cell apoptosis. Abouheif et al. demonstrated that silencing of miR-34a with oligonucleotides of antisense miR-34a inhibited chondrocytes apoptosis in rat chondrocyte cultures treated with...
and transferred from one cell to another. Thus, they par

in extracellular membranous vesicles such as exosomes

pathways in OA. In addition, miRNAs are incorporated

induction of joint inflammation, as well as in pain-related

in the production of proinflammatory cytokines and the

contributing to cartilage damage. They are also involved

cartilage matrix components, facilitate chondrocyte

apoptosis and inhibit autophagy in chondrocytes, thus

miR-483-5p is upregulated in articular cartilage from

OA patients and it targets and downregulates matri

3 (Matn3) and tissue inhibitor of metalloproteinase 2

(Timp2). Matn3 is a protein of the cartilage matrix and

Timp2 is an inhibitor of cartilage degrading metallopro
teinases. Wang et al. recently studied the results of si

lencing miR-483-5p in an experimental OA mouse mod

el. Lentiviruses encoding oligonucleotides of antisense

miR-483-5p (anti-miR-483-5p) were injected in the OA

joints and it was demonstrated that anti-miR-384-5p

attenuated cartilage damage and loss and inhibited the

formation of fibrous cartilage.77

miR-140 is one of the most studied miRNAs in OA. Karlsen et al. studied the protective effect of miR-140 in

an in vitro model of OA. They transfected miR-140 into IL-

1β-treated articular chondrocyte and mesenchymal stem

cell cultures and they demonstrated that miR-140 upreg

ulated the synthesis of cartilage matrix components and

downregulated the production of cartilage degradation

enzymes.78 In a recent study, Tao et al. used exosomes

in order to transfer miR-140 into osteoarthritic joints in a

rat OA model. They acquired exosomes rich in miR-140

by transfecting mesenchymal stem cells (MSCs) with len
tivirus encoding miR-140 and by isolating the exosomes
derived from the miR-140-overexpressing-MSCs. They

first transfected articular chondrocytes with miR-140-

exosomes and showed that miR-140 downregulated RA

LA and upregulated SOX9, aggrecan and collagen
type II. Then they injected miR-140-exosomes into os

teoarthritic joints of rats and demonstrated that miR-140

reduced the damage of the articular cartilage in compar

tion to the control group.79

CONCLUSIONS

Multiple studies demonstrate that miRNAs potentially

play an important role in the pathogenesis of OA. The
dysregulation of their expression affects several path

ways involved in OA pathogenesis. Dysregulated miRNAs

increase the expression of cartilage degrading enzymes

by articular chondrocytes, decrease the production of

cartilage matrix components, facilitate chondrocyte

apoptosis and inhibit autophagy in chondrocytes, thus

contributing to cartilage damage. They are also involved

in the production of proinflammatory cytokines and the

induction of joint inflammation, as well as in pain-related

pathways in OA. In addition, miRNAs are incorporated

in extracellular membranous vesicles such as exosomes

and transferred from one cell to another. Thus, they par

ticipate in the communication between synoviocytes and

articular chondrocytes in osteoarthritic joints, enhancing

the production of degrading enzymes and cytokines by

these cells.

The role of miRNAs in OA still remains to be elucidated.

Yet, based on the available data and the overall role of

miRNA molecular machinery, it is possible to gain some

insight on their participation in OA. Hence, there are some

general concepts governing miRNA physiology. Their role

depends mainly on the target gene. This means that if a

gene has an enhancing or suppressive effect on a certain

physiological procedure, the down- or up-regulation of

the respective miRNA signifies the opposite effect. For

example, in the case of miR-146 we have mentioned that it
decreases the expression of pain modulators that en

hance pain perception, such as TNF-α, IL-6, IL-8, COX-2

and iNOS, in astrocytes. Thus, it seems that downregu

lation of miR-146 in the central and peripheral nervous

system signals the upregulation of the target genes. In

other words, the genes that mediate pain are inhibited by

miR-146. Further on, although it is known that miRNA

expression and binding to target-genes is linked to gene

negative regulation, the only way to determine miRNA

role is through experimental validation; this varies from

one pathophysiological condition to another.

Besides, it seems that dysregulation of miRNA expression

in OA is both a consequence of upstream events (such as

increased production of proinflammatory cytokines) and

a consequence of negative feedback from downstream

events. For example, as mentioned above, increased

production of the proinflammatory cytokine IL-1β in OA

results in the downregulation of miR-26a and miR-140.

On the other hand, downregulation of miR-26a in OA

leads to upregulation of KPN3 and activation of NF-κβ

pathway. In turn, the activated NF-κβ pathway negatively

regulates miR-26a (negative feedback).

Moreover, the protective or harmful role of miRNA in OA

is a subject of intensive discussion. As aforementioned,

several miRNAs have been reported to have a protective

role in OA, such as miR-140 or miR-146, yet at the same

time several other miRNAs are reported to play a nega

tive role in OA, such as miR-155 and miR-195.

On the other hand, different expression of miRNAs in

peripheral blood and synovial fluid between OA patients

and healthy population, their stability in body fluids and

the ease of their measurement creates the potential of

utilizing them as biomarkers of the disease. Besides,

next generation RNA-sequencing will facilitate the identi

fication of new miRNAs in order to be used as biomark

ers. In the future, miRNAs may be used as biomarkers of
disease activity or as predictors of prognosis or of

response to treatment. However, further studies are still

needed in this direction.

Furthermore, targeting of miRNAs is a potential novel

therapeutic strategy in OA. Inhibition of miRNAs contrib-
REFERENCES

The authors declare no conflict of interest.

CONFLICT OF INTEREST

1. Bijlsma J W, Berenbaum F, Lafeber F P. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115-26. Epub 2011/06/21. https://doi.org/10.1016/s0140-6736(11)60243-2. PubMed PMID: 21684382.

2. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton J L, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res 2017;5:6004. Epub 2017/02/06. https://doi.org/10.1038/bones.2016.44. PubMed PMID: 28149655; PubMed Central PMCID: PMC4520031.

3. Reynard L N. Analysis of genetics and DNA methylation in osteoarthritis: What have we learnt about the disease? Semin Cell Dev Biol 2016;62:57-66. Epub 2016/05/01. https://doi.org/10.1016/j.semcdb.2016.04.017. PubMed PMID: 27130636.

4. Castano Betancourt M C, Cailotto F, Kerkhof H J, Cornelis F PKP. The present work was supported in part from the FUNDING from the National and Kapodistrian University of Athens, Medical School.

AUTHORS’ CONTRIBUTIONS

PKP: collected literature, drafted the manuscript. GIL: drafted the manuscript, proof-read the manuscript, gave final permission for submission.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Bőkönyi K, Golomb A, Török G, et al. Identification of new susceptibility variants in the 5′UTR of GDF5 associated with osteoarthritis and tendon rupture. Eur J Hum Genet 2010;18:292-7. Epub 2010/03/03. https://doi.org/10.1038/ejhg.2009.175. PubMed PMID: 20117354; PubMed Central PMCID: PMC2841168.

2. Miao C G, Yang Y Y, He X, Xu T, Huang C, Huang Y, et al. New sequence variants in HLA class II/III region associated with susceptibility to knee osteoarthritis identified by genome-wide association study. PLOS One 2010;5:e9723. Epub 2010/03/23. https://doi.org/10.1371/journal.pone.0009723. PubMed PMID: 20305777; PubMed Central PMCID: PMC2841168.

3. Styrkarsdottir U, Thorleifsson G, Helgadottir H, Bomer N, Metrutsy S, Bierma-Zeinstra S, et al. Severe osteoarthritis of the hand associates with common variants within the ALDH1A2 gene and with rare variants at SNP3. PLoS Genet 2011;7:e200388. Epub 2011/03/09. https://doi.org/10.1371/journal.pgen.1002089. PubMed PMID: 21457464; PubMed Central PMCID: PMC3072069.

4. Zeggani E, Panoutoupoulou K, Southam L, Rayner N W, Day-Williams A G, Lopes MC, et al. Identification of new susceptibility locus on chromosome 7q22. Arthritis Rheum 2010;62:499-510. Epub 2010/01/30. https://doi.org/10.1002/art.27184. PubMed PMID: 20112360; PubMed Central PMCID: PMC3354739.

5. Miyamoto Y, Tabuchi A, Shi D, Kubo T, Takatori Y, Saito S, et al. A functional polymorphism in the 5′ UTR of GDF5 is associated with osteoarthritis. Nature Genet 2007;39:529-33. Epub 2007/03/27. https://doi.org/10.1038/ng.2007.12. PubMed PMID: 17384641.

6. Miyamoto Y, Shi D, Nakajima M, Ozaki K, Sudo A, Kotani A, et al. Common variants in DWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis. Nature Genet 2008;40:994-8. Epub 2008/07/16. https://doi.org/10.1038/ng.176. PubMed PMID: 18622395.

7. Nakajima M, Takahashi A, Kou I, Rodriguez-Fonterna C, Gomez-Reino J J, Furuchi T, et al. New sequence variants in HLA class II/L region associated with susceptibility to knee osteoarthritis identified by genome-wide association study. PLoS One 2010;5:e9723. Epub 2010/03/23. https://doi.org/10.1371/journal.pone.0009723. PubMed PMID: 20305777; PubMed Central PMCID: PMC2841168.

8. Valdes A M, Evangelou E, Kerkhof H J, Tamm A, Doherty S A, Kisdan K, et al. The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. Ann Rheum Dis 2011;70:873-5. Epub 2010/09/28. https://doi.org/10.1136/ard.2010.134155. PubMed PMID: 20870806; PubMed Central PMCID: PMC3448999.

9. Zeggani E, Panoutoupoulou K, Southam L, Rayner N W, Day-Williams A G, Lopes MC, et al. Identification of new susceptibility loci for osteoarthritis (arcQGEN): a genome-wide association study. Lancet 2012;380:815-23. Epub 2012/07/06. https://doi.org/10.1016/s0140-6736(12)60681-3. PubMed PMID: 22763110; PubMed Central PMCID: PMC3448999.

10. Berger S L, Kouzarides T, Shiekhattar R, Shilatifard A. An overview of microRNAs: molecular mechanisms and clinical applications. Adv Genet 2007;57:1-30. Epub 2007/03/28. https://doi.org/10.1007/978-0-387-78471-0_1. PubMed PMID: 17384641.

11. Toh T B, Lim J J, Chow E K. Epigenetics in cancer stem cells. Mol Cancer 2017;16:29. Epub 2017/02/06. https://doi.org/10.1186/s12943-017-0596-9. PubMed PMID: 28148257; PubMed Central PMCID: PMC5521963.

12. Bartel D P. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97. Epub 2004/01/28. PubMed PMID: 14744438.

13. Miao C G, Yang Y Y, He X, Xu T, Huang C, Huang Y, et al. New advances of microRNAs in the pathogenesis of rheumatoid arthritis, with a focus on the crosstalk between DNA methylation and the microRNA machinery. Cell Signal 2013;25:111-25. Epub 2013/02/07. https://doi.org/10.1016/j.cellsig.2013.01.024. PubMed PMID: 23385088.

14. Jing D, Hao J, Shen Y, Tang G, Li M L, Huang S H, et al. The role of microRNAs in bone remodelling. Int J Oral Sci 2015;7:131-43. Epub 2015/07/25. https://doi.org/10.1038/ijos.2015.22. PubMed PMID: 26208091; PubMed Central PMCID: PMC4582559.

15. Chen X, Liang H, Zhang J, Zhen K, Zhang C Y. Secreted microRNAs: a new form of intercellular communication. Trends Cell Biol 2012;22:125-32. Epub 2012/01/21. https://doi.org/10.1016/j.tcb.2011.12.001. PubMed PMID: 22260888.
22. Miyaki S, Nakasa T, Otsuki S, Grogan S P, Higashiyama R, Inoue A, et al. MicroRNA-140 is expressed in differentiated human articular chondrocytes and modulates interleukin-1 responses. Arthritis Rheum 2009;60:2723-30. Epub 2009/08/29. https://doi.org/10.1002/art.24745. PubMed PMID: 19714579; PubMed Central PMCID: PMC2806094.

23. Nitoumou E, Tzefis M, Braoudaki M, Lambrou G, Poulou M, Malizos K, et al. Serum microRNA K-array analysis identifies miR-30e-5p, miR-33b-3p and miR-217-3p as potential osteoarthritis biomarkers involved in metabolic processes. Clin Epigenetics 2017;9:127. Epub 2017/12/20. https://doi.org/10.1186/s13148-017-0428-1. PubMed PMID: 29255496; PubMed Central PMCID: PMC5728069.

24. Liang Z J, Zhuang H, Wang G X, Li Z, Zhang H T, Yu T Q, et al. Expression of MicroRNA-140 in osteoarthritis cartilage. Arthritis Res Ther 2012;14:R75. Epub 2012/04/18. https://doi.org/10.1186/ar3798. PubMed PMID: 22507670; PubMed Central PMCID: PMC3464469.

25. Tardif G, Hum D, Pelletier J P, Duval N, Martel-Pelletier J. Regulation of the IGFBP-5 and MMP-13 genes by the microRNAs miR-140 and miR-27a in human osteoarthritic chondrocytes. BMC Musculoskeletal Disord 2009;10:148. Epub 2009/12/02. https://doi.org/10.1186/1471-2474-10-148. PubMed PMID: 19948051; PubMed Central PMCID: PMC2792220.

26. Karlsen T A, Jakobsen R B, Mikkelsen T S, Brinchmann J E. miRNA-140 targets RALA and regulates chondrogenic differentiation of human mesenchymal stem cells by translational enhancement of SOX9 and ACAN. Stem Cells Dev 2014;23:290-304. Epub 2013/09/26. https://doi.org/10.1089/scd.2013.0209. PubMed PMID: 24063364.

27. Nakamura Y, He X, Kobayashi Y, Tan Y L, Postlethwait J H, Warman M L. Unique roles of microRNA140 and its host gene WW2P2 in cartilage biology. J Musculoskeletal Neuronal Interact 2006;6:321-2. Epub 2009/01/17. PubMed PMID: 19147957; PubMed Central PMCID: PMC2757261.

28. Tardif G, Pelletier J P, Fahmi H, Hum D, Zhang Y, Kapoor M, et al. NTA3 and TGF-beta/SMAD3 regulate the expression of miR-140 in OA. Arthritis Res Ther 2013;15:R197. Epub 2013/11/22. https://doi.org/10.1186/ar3798. PubMed PMID: 22237361.

29. Miyaki S, Sato T, Inoue A, Otsuki S, Ito Y, Yokoyama S, et al. MiR-140 antagonizes the IL-1beta responsive miRNA, induces vascular endothelial growth factor and chondrocyte apoptosis by targeting Smad4. Arthritis Res Ther 2012;14:R75. Epub 2012/04/18. https://doi.org/10.1186/ar3798. PubMed PMID: 22507670; PubMed Central PMCID: PMC3464469.

30. Yoo X, Wang J Q, Yan S Y. Reduced miR26a and miR20b expression contributes to the pathogenesis of osteoarthritis via the promotion of p65 translocation. Mol Med Rep 2017;15:551-8. Epub 2016/12/22. https://doi.org/10.3892/mmr.2016.6058. PubMed PMID: 28008846.

31. Li X, Wei M, Kang X, Liu D, Quan Y, Pan X, et al. Reciprocal inhibition between miR-26a and NF-kappab regulates obesity-related chronic inflammation in chondrocytes. Biosci Rep 2015;35:e02004. Epub 2015/07/17. https://doi.org/10.1042/ bsor20150021. PubMed PMID: 26182366; PubMed Central PMCID: PMC4613702.

32. Rasheed Z, Al-Shobaili H A, Rasheed N, Mahmood A, Khan M I. MicroRNA-26a-5p regulates the expression of inducible nitric oxide synthase via activation of NF-kappab pathway in human osteoarthritic chondrocytes. Arch Biochem Biophys 2016;594:61-7. Epub 2016/02/09. https://doi.org/10.1016/j.abb.2016.02.002. PubMed PMID: 26854724.

33. Akhtar N, Rasheed Z, Ramamurthy S, Anbazhagan A N, Voss F R, Haqqi T M. MicroRNA-27b regulates the expression of matrix metalloproteinase 13 in human osteoarthritic chondrocytes. Arthritis Rheum 2010;62:1361-71. Epub 2010/02/05. https://doi.org/10.1002/art.24739. PubMed PMID: 20131257; PubMed Central PMCID: PMC3139404.

34. Li Z, Meng D, Li G, Xu J, Tian K, Li Y. Overexpression of microRNA-210 promotes chondrocyte proliferation and extracellular matrix deposition by targeting HIF-3alpha in OA. Mol Med Rep 2013;16:2797-86. Epub 2016/02/11. https://doi.org/10.3892/mmr.2016.4678. PubMed PMID: 26861791.

35. Philipot D, Gueuet D, Patatano D, Chuchana P, Ollivoto E, Espinoza F, et al. p16INK4a and its regulator miR-24 link senescence and chondrocyte terminal differentiation-associated matrix remodeling in OA. Arthritis Res Ther 2014;16:1(5);R58. Epub 2014/02/28. https://doi.org/10.1186/ar4494. PubMed PMID: 24572376; PubMed Central PMCID: PMC4060445.

36. Song J, Jin E H, Kim D, Kim K Y, Chun C H, Jin E J. MicroRNA-222 regulates MMP-19 via targeting HDAC-4 during osteoarthritis pathogenesis. BBA Clin 2015;3:79-89. Epub 2015/12/18. https://doi.org/10.1016/j.bbakin.2015.11.009. PubMed PMID: 26673737; PubMed Central PMCID: PMC4661531.

37. Song J, Kim D, Chun C H, Jin E J. miR-370 and miR-373 regulate the pathogenesis of osteoarthritis by modulating one-carbon metabolism via SHMT1 and MECP-2, respectively. Aging Cell 2015;14:826-37. Epub 2015/06/25. https://doi.org/10.1111/agec.12363. PubMed PMID: 26103880; PubMed Central PMCID: PMC4568890.

38. Song J, Kim M, Lee C H, Lee M S, Chun C H, Jin E J. MicroRNA-488 regulates zinc transporter SLC39A8/ZIP8 during pathogenesis of OA. UBS NJM 2013;20:31. Epub 2013/05/22. https://doi.org/10.1016/j.ubsnjm.2013.04.005. PubMed PMID: 23988335; PubMed Central PMCID: PMC3970624.

39. Voron L A, Kräften A H, Dher W J, Sarsis D B, Creemers L B. Overexpression of has-miR-148a promotes cartilage production and inhibits cartilage degradation by osteoarthritic chondrocytes. Osteoarthritis Cartilage 2014;22:145-53. Epub 2013/11/26. https://doi.org/10.1016/j.joca.2013.11.006. PubMed PMID: 24269354.

40. Jin Q, Xu X, Xu Y, Fan Z, Kang J, Li L, et al. miR-195/Rum2 axis mediates FGFR2-induced ADAMTS expression in osteoarthritic cartilage. Int J Mol Med 2016;38:681-94. Epub 2016/01/28. https://doi.org/10.3892/ijmms.2015.2620. PubMed PMID: 26816250.

41. Jin Q, Xu X, Zhang Q, Kang L, Xu Y, Zhang K, et al. The IL-1beta/PA-1/miR-30A/ADAMTS-5 axis regulates cartilage matrix degradation in human OA. Int J Mol Med 2016;38:771-85. Epub 2016/04/14. https://doi.org/10.3892/ijmms.2015.2620. PubMed PMID: 27067395.

42. Matsukawa T, Sakai T, Yonezawa T, Hiraiwa H, Hamada T, Nakashima M, et al. MicroRNA-125b regulates the expression of aggrecanase-1 (ADAMTS-4) in human osteoarthritic chondrocytes. Arthritis Res Ther 2011;13:R29. Epub 2012/03/15. https://doi.org/10.1186/ar367. PubMed PMID: 23046992; PubMed Central PMCID: PMC3672767.
47. Kang L, Yang C, Song Y, Liu W, Wang K, Li S, et al. MicroRNA-23a-3p promotes the development of osteoarthritis by directly targeting SMAD3 in chondrocytes. Biochem Biophys Res Commun 2016;478:467-73. Epub 2016/06/19. https://doi.org/10.1016/j.bbrc.2016.06.071. PubMed PMID: 27318087.

48. Li J, Liu X, Yang S, Ye S, Yang W, et al. MicroRNA-16-5p Controls Development of Osteoarthritis by Targeting SMAD3 in Chondrocytes. Curr Pharm Des 2015;21:1560-7. Epub 2015/09/09. https://doi.org/10.2174/1381612815666150909104182. PubMed PMID: 26497636.

49. Wang X, Guo Y, Wang C, Yu H, Yu X, Yu H. MicroRNA-142-3p Inhibits Chondrocyte Apoptosis and Inflammation in osteoarthritis by Targeting HMGB1. Inflammation 2016;39:1718-28. https://doi.org/10.1007/s10753-016-0406-3.

50. Zhang D, Cao X, Li J, Liu X, Yang S, Ye S, et al. MicroRNA-210 inhibits NF-kappaB signaling pathway by targeting DR6 in osteoarthritis. Sci Rep 2015;5:12775. Epub 2015/08/08. https://doi.org/10.1038/srep12775. PubMed PMID: 26244598; PubMed Central PMCID: PMC4525484.

51. Li Z C, Han N, Li X, Li G, Liu Y, Sun G X, et al. Decreased expression of microRNA-130a correlates with TNF-alpha in the development of osteoarthritis. Int J Clin Exp Pathol 2015;8:2555-64. Epub 2015/06/06. PubMed PMID: 26047561; PubMed Central PMCID: PMC4400070.

52. Santini P, Politi L, Vedova P D, Scandurra R, Scotto d’Abusco A. MiR-210 inhibits NF-kappaB signaling pathway by targeting DR6 in osteoarthritis. Sci Rep 2015;5:12775. Epub 2015/08/08. https://doi.org/10.1038/srep12775. PubMed PMID: 26244598; PubMed Central PMCID: PMC4525484.

53. Li L, Jia J, Liu X, Yang S, Ye S, Yang W, et al. MicroRNA-16-5p Contributes to osteoarthritis by Targeting IkBa. Cell Physiol Biochem 2015;37:1442-53. Epub 2015/10/23. https://doi.org/10.1159/000438513. PubMed PMID: 26492575.

54. Crowe N, Swilinger T E, Le L T, Barter M J, Wheeler G, Pais H, et al. Detecting new microRNAs in human osteoarthritic chondrocytes identifies miR-30B5 as a human, chondrocyte-selective, microRNA. Osteoarthritis Cartilage 2016;24:534-43. Epub 2015/10/27. https://doi.org/10.1016/j.joca.2015.10.015. PubMed PMID: 26497636; PubMed Central PMCID: PMC4769044.

55. Diaz-Prado S, Cicioni C, Munos-Lopez E, Hermida-Gomez T, Oreiro N, Fernandez-Lopez C, et al. Characterization of microRNA expression profiles in normal and osteoarthritic human chondrocytes. BMC Musculoskeletal Disord 2012;13:144. Epub 2012/08/14. https://doi.org/10.1186/1471-2474-13-144. PubMed PMID: 22883423; PubMed Central PMCID: PMC3495209.

56. Yan S, Wang M, Zhao J, Zhang H, Zhou C, Jin L, et al. MicroRNA-210 targets the TNF-alpha pathway by targeting DR6 in osteoarthritis. Sci Rep 2015;5:12775. Epub 2015/08/08. https://doi.org/10.1038/srep12775. PubMed PMID: 26244598; PubMed Central PMCID: PMC4525484.

57. Li Y H, Tavalaee G, Tokar T, Nakamura A, Sundarrarajan K, Weston A, et al. Identification of synovial fluid microRNA signature in knee OA: differentiating early- and late-stage knee osteoarthritis. Osteoarthr Cartilage 2016;24:1577-86. Epub 2015/06/05. https://doi.org/10.1016/j.joca.2016.04.019. PubMed PMID: 27143385.

58. Rasheed Z, Al-Shobaili H A, Rasheed N, Al Saloom A A, Al-Shaya O, Mahmoud A, et al. Integrated Study of Globally Expressed microRNAs in IL-1beta-stimulated Human Chondrocytes and osteoarthritis Relevant Genes: A Microarray and Bioinformatics Analysis. Nucleic Acids Research 2016;35:335-55. Epub 2015/06/07. https://doi.org/10.1093/nar/gkw277. PubMed PMID: 1663980; PubMed Central PMCID: PMC27152662.

59. Swilinger T E, Wheeler G, Carment V, Elliott H R, Barter M J, Abu-Elmagd M, et al. The expression and function of microRNAs in chondrogenesis and OA. Arthritis Rheum 2012;64:1909-19. Epub 2012/11/07. https://doi.org/10.1002/art.33514. PubMed PMID: 22143896.

60. Tommero-Esteban P, Rodriguez-Rodriguez L, Abasolo L, Tome M, Lopez-Romero P, Herranz E, et al. MicroRNA-210 inhibits NF-kappaB signaling pathway by targeting DR6 in osteoarthritis. Sci Rep 2015;5:12775. Epub 2015/08/08. https://doi.org/10.1038/srep12775. PubMed PMID: 26244598; PubMed Central PMCID: PMC4525484.

61. Wilthor J, Murphy C, Dukes A, Fulzele S, Liu Y, Hunter M, et al., editors. Synovial Fluid Exosomal MicroRNA Profiling of osteoarthritis Patients and Identification of Synovocyte-Chondrocyte Communication Pathway. ORS 2016 Annual Meeting; 2016; Orlando.

62. Kato T, Miyaki S, Ishitobi H, Nakamura Y, Nakasa T, Lotz MK, et al. Exosomes from IL-1beta stimulated synovial fibroblasts induce osteoarthritic changes in articular chondrocytes. Arthritis Res Ther 2014;16:R163. Epub 2014/08/06. https://doi.org/10.1186/ar679. PubMed PMID: 25032378; PubMed Central PMCID: PMC4261911.

63. Nakasa T, Miyaki S, Kato T, Takada T, Nakamura Y, Ochi M, editors. Exosome derived from osteoarthritis cartilage induces catabolic factor gene expressions in synovium. ORS 2012 Annual Meeting; 2012; San Francisco.

64. Murata K, Yostomi H, Tanida S, Ishikawa M, Nishitani K, Ito H, et al. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and OA. Arthritis Res Ther 2014;16:R163. Epub 2014/08/06. https://doi.org/10.1186/ar679. PubMed PMID: 25032378; PubMed Central PMCID: PMC4261911.

65. Okuhara A, Nakasa T, Shibuya H, Nimoto T, Adachi N, Deie M, et al. Detecting new microRNAs in human osteoarthritic chondrocytes identifies miR-30B5 as a human, chondrocyte-selective, microRNA. Osteoarthritis Cartilage 2016;24:534-43. Epub 2015/10/27. https://doi.org/10.1016/j.joca.2015.10.015. PubMed PMID: 26497636; PubMed Central PMCID: PMC4769044.

66. Ou hazardous factor 1 alpha. Eur Rev Med Pharmacol Sci 2015;19:545-51. Epub 2015/03/11. PubMed PMID: 25753888.

67. D’Adamo S, Alvarez-Garcia O, Muramatsu Y, Flamigni F, Lotz M K. MicroRNA-155 suppresses autophagy in chondrocytes by modulating expression of autophagy proteins. Osteoarthritis Cartilage 2016;24:1082-91. Epub 2016/01/26. https://doi.org/10.1016/j.joca.2016.01.005. PubMed PMID: 26805018; PubMed Central PMCID: PMC4587587.

68. Song J, Ahn C, Chun CH, Jin E J. A long non-coding RNA, GAS5, plays a critical role in the regulation of miR-21 during osteoarthritis. J Orthop Res. 2014;32:1629-35. Epub 2014/09/10. https://doi.org/10.1002/jor.22718. PubMed PMID: 25196583.

69. Zhang F, Wang J, Chu J, Yang C, Xiao H, Zhao C, et al. MicroRNA-148a Induced by Hypoxia Promotes Chondrocyte Autophagy through Bcl-2. Cell Physiol Biochem 2015;37:1442-53. Epub 2015/10/23. https://doi.org/10.1159/000438513. PubMed PMID: 26492575.
The involvement of microRNAs in osteoarthritis and recent developments: A narrative review

74. Beyer C, Zampetakis A, Lin N Y, Kleyer A, Perricone C, Lagnozzi A, et al. Signature of circulating microRNAs in OA. Ann Rheum Dis 2015;74:e18. Epub 2014/02/12. https://doi.org/10.1136/annrheumdis-2013-204698. PubMed PMID: 24519554.
75. Li Z, Rana T M. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov 2014;13:622-38. Epub 2014/07/12. https://doi.org/10.1038/nrd4359. PubMed PMID: 25011539.
76. Abouheif M M, Nakasa T, Shibuya H, Niimoto T, Kongcharoencomb W, Ochi M. Silencing microRNA-34a inhibits chondrocyte apoptosis in a rat osteoarthritis model in vitro. Rheumatology (Oxford) 2010;49:2054-60. Epub 2010/08/03. https://doi.org/10.1093/rheumatology/ker247. PubMed PMID: 20675358.
77. Wang H, Zhang H, Sun Q, Wang Y, Yang J, Yang J, et al. Intra-articular Delivery of Antago-miR-483-5p Inhibits osteoarthritides by Modulating Matrilin 3 and Tissue Inhibitor of Metalloproteinase 2. Mol Ther 2017. Epub 2017/02/01. https://doi.org/10.1016/j.mther.2016.12.020. PubMed PMID: 28139355.
78. Karlsen T A, de Souza G A, Odegaard B, Engebretsen L, Brinchmann J E. microRNA-140 Inhibits Inflammation and Stimulates Chondrogenesis in a Model of Interleukin 1-beta-induced osteoarthritis, Mol Ther Nucleic Acids 2016;5:e373. Epub 2017/01/31. https://doi.org/10.1038/mtna.2016.64. PubMed PMID: 28131279.
79. Tao S C, Yuan T, Zhang Y L, Yin W J, Guo S C, Zhang C Q. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. Theranostics 2017;7:180-95. Epub 2017/01/04. https://doi.org/10.7150/thno.17133. PubMed PMID: 28042326; PubMed Central PMCID: PMC5196895.
80. Song J, Kim D, Chun C-H, Jin E-J. MicroRNA-9 regulates survival of chondroblasts and cartilage integrity by targeting proteoglycan. Cell Commun Signal 2013;11:66. https://doi.org/10.1186/1478-811X-11-66.
81. Chen H, Tian Y. MiR-15a-5p regulates viability and matrix degradation of human osteoarthritis chondrocytes via targeting VEGF. Biosci Trends 2017;11:92-7. Epub 2016/12/07. https://doi.org/10.5582/bst.2016.01187. PubMed PMID: 27916780.
82. Zhang Y, Jia J, Yang S, Liu X, Ye S, Tian H. MicroRNA-21 controls the development of osteoarthritis by targeting GDF-5 in chondrocytes. Exp Mol Med 2014;46:e79. Epub 2014/03/01. https://doi.org/10.1038/emmm.2013.152. PubMed PMID: 24577233; PubMed Central PMCID: PMC3944443.
83. Le L T, Swingler T E, Crowe N, Vincent T L, Barter M J, Donell S T, et al. The microRNA-29 family in cartilage homeostasis and osteoarthritis. J Mol Med 2016;94:583-96. Epub 2015/12/22. https://doi.org/10.1007/s00109-015-1374-z. PubMed PMID: 26687115; PubMed Central PMCID: PMCPmc4856728.
84. Li L, Yang C, Liu X, Yang S, Ye S, Jia J, et al. Elevated expression of microRNA-30b in osteoarthritis and its role in ERG regulation of chondrocyte. Biomed Pharmacother 2015;76:94-9. Epub 2015/12/15. https://doi.org/10.1016/j.biopha.2015.10.014. PubMed PMID: 26653555.
85. Wei M, Xie Q, Zhu J, Wang T, Zhang F, Cheng Y, et al. MicroRNA-33 suppresses CCL2 expression in chondrocytes. Biosci Rep 2016;36:e00332. Epub 2016/04/20. https://doi.org/10.1042/bsr20160032. PubMed PMID: 27123933; PubMed Central PMCID: PMC4859085.
86. Kostopoulou F, Malizos K N, Papathanasiou I, Tsezou A. MicroRNA-NA-33a regulates cholesterol synthesis and cholesterol efflux-related genes in osteoarthritic chondrocytes. Arthritis Res Ther 2015;17:42. Epub 2015/04/17. https://doi.org/10.1186/s13075-015-0556-y. PubMed PMID: 25880168; PubMed Central PMCID: PMCPmc4375845.
87. Wang J, Chen L, Jin S, Lin J, Zhang H, Zhang H, et al. MiR-98 promotes chondrocyte apoptosis by decreasing Bcl-2 expression in a rat model of osteoarthritis. Acta Biochim Biophys Sin (Shanghai) 2016;48:923-9. Epub 2016/09/04. https://doi.org/10.1038/abbs. grw084. PubMed PMID: 27590083.
88. Yang F, Hu A, Zhao D, Guo L, Yang L, Wang B, et al. An insertion/deletion polymorphism at the microRNA-122 binding site in the interleukin-1alpha 3’-untranslated region is associated with a risk for osteoarthritis. Mol Med Rep 2015;12:6199-206. Epub 2015/08/05. https://doi.org/10.3892/mmr.2015.412. PubMed PMID: 26239639.