British Medical Bulletin, 2019, **00**:1–11
doi: 10.1093/bmb/ldz015

Invited Review

MicroRNA in osteoarthritis: physiopathology, diagnosis and therapeutic challenge

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Editorial Decision 19 March 2019; Accepted 2 April 2019

Abstract

Background: Osteoarthritis (OA) is the most orthopedic condition. The pattern of gene expression and the transcription factors that exert control of chondrogenesis have been extensively studied.

Sources of data: A systematic search (up to July 2018) of articles assessing the role of microRNA (miRNA) in physiopathology, diagnosis and therapy of OA was performed, with the purpose of giving a critical perspective of the possibilities for diagnostic and therapeutic use of miRNA in the management of OA.

Areas of agreement: miRNAs are small noncoding RNAs that can regulate gene expression in human cells. miRNAs can be expressed in a different fashion in osteoarthritic compared to nonosteoarthritic cartilage.

Areas of controversy: The mechanisms that produce alteration of gene expression in OA are still not completely understood. miRNAs may be involved in the diagnosis of OA as well as in its treatment.

Growing points: There are complex interactions between miRNAs and their multiple target genes. These interactions may be important in gene regulation and the control of homeostatic pathways in OA.

Areas timely for developing research: miRNA could be useful for diagnostic or management purposes, but the issue of delivery of miRNA targeting agents needs to be overcome before miRNA can be applied in clinical practice.

Key words: osteoarthritis, *miRNA*, cartilage degeneration, gene regulation, miRNA-controlled delivery

Introduction

Osteoarthritis (OA) is a multifactorial condition, and genetic and nongenetic factors such as obesity, joint instability and ageing have been associated with its onset and progression.[1] Ageing is associated with impaired homeostatic balance between catabolic (degradation) and anabolic (repair) mechanisms in the articular cartilage. This contributes to the development of OA, with synovial inflammation, subchondral sclerosis and, in more advanced stages, formation of osteophytes.[2]

The dysregulation in the homeostatic balance of articular cartilage induces senescence and necrosis in joint cells.[2] These mechanisms of alteration in gene expression are not yet clarified, but the net result is an imbalance between degradation and synthesis of extracellular matrix (ECM) components, especially interfering with the synthesis of type II collagen and the proteoglycan aggrecan.[2]

The management of OA remains unsatisfactory. The most commonly used drugs only partially alleviate the symptoms of OA and do not reverse the progressive loss of ECM and the degeneration and progressive loss of articular cartilage.[3]

The effect of several genes in OA pathogenesis and progression has been widely studied,[4] and the mounting possibility of regulating gene expression may lead to develop new therapies that could reduce the progressive joint destruction or, even, stimulate its repair.[4]

OA dysregulation is mediated by gene and/or protein expression networks.[5] A schematic representation of the possible role of miRNA in the pathogenesis of OA is also illustrated in Figure 1. Chondrocytes, the cells present in cartilage, produce and maintain the ECM, thus determining the load-bearing properties of the tissue.[6] Chondrocytes arise from chondrogenic differentiation of mesenchymal stem cells (MSCs);[2] the investigation of the mechanisms mediating the differentiation of MSCs toward a chondrocytic phenotype and their regulation may help to develop new strategies to manage OA. Several transcription and growth factors, including, for example, the SOX family members SOX9, L-SOX5 and SOX6 regulate chondrogenesis and chondrocyte function.[7] Many members of the family of bone morphogenetic protein (BMP) and transforming growth factor β (TGFβ) signaling pathways have been studied to understand the control of chondrogenesis.[5] Epigenetic mechanisms, including DNA methylation, histone modifications and miRNAs, add an additional level of regulation in the evolution of OA.[8] Understanding the role of miRNA in influencing gene expression in chondrogenesis may offer novel interesting therapeutic approaches to OA. This review summarizes the current knowledge to give a critical perspective of the possible physiopathology mechanism, diagnostic and possible therapeutic use of miRNA in the management of OA.

Methods

The data reported in the present review have been organized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

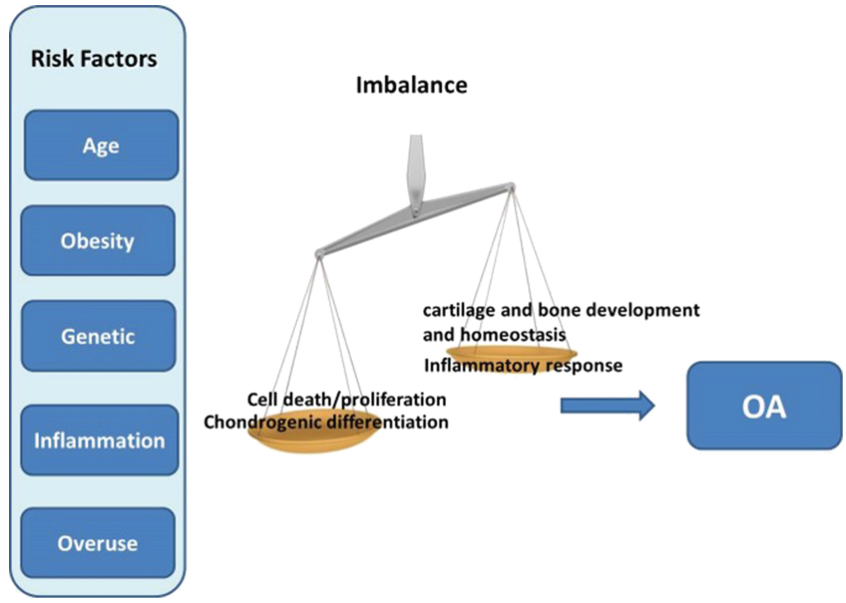

Fig. 1 Pathogenesis of OA and the suggested role of miRNA. miRNAs are essential for the maintenance of cellular function through fine-tuning the expression of multiple target genes. Systemic risk factors for OA (such as obesity and genetic alterations) combine with epigenetic changes and altered transcriptional regulation to disrupt signaling pathways in OA. Both upregulation and downregulation of miRNAs have been associated with OA; targeting these changes might be of future clinical benefit.

(PRISMA) guidelines[9] (Fig. 2). A systematic search (up to July 2018) in PubMed and Google Scholar electronic databases of articles assessing the role of miRNA in physiopathology, diagnosis and therapy of OA with no restrictions of language was performed. In the search, we used combinations of the following key terms: osteoarthritis; miRNA; cartilage degeneration; joint degeneration; gene regulation; miRNA control, with no limit of year nor language. Case reports, editorials, technical notes, abstracts, conference presentations, editorials, expert opinions, narrative and systematic review articles were excluded.

The initial literature search identified 377 potentially relevant citations.

After the removal of duplicate records and nonfocused articles on OA, the remaining 134 candidate studies were selected for comprehensive evaluation. Then, with the first inspection of the title and the abstract, 68 articles were excluded. A further full-text screening excluded other 29 articles because they did not comply with the inclusion criteria. Eventually, 37 articles were included in the present review.

Roles of miRNA in physiopathology of the OA

Many studies compared OA tissue with normal articular tissue, evidencing the role of the miRNA-altered expression.[10–12] The list of the recognized miRNA and their effect on OA is summarized in Table 1.

Iliopoulos *et al*.[13] described that miRNA-22 directly regulates the expression of peroxisome proliferator-activated receptor alpha and the BMP-7, stimulating peroxisome proliferation and the activation of receptor and BMP-7 signaling in both healthy and OA chondrocytes. Because of miRNA-22 upregulation, inflammatory and catabolic changes are induced in joint cells.[13] miRNA-9 and miRNA-98 inhibit the secretion of matrixmetalloproteinase-13 (MMP-13) and tumor necrosis factor (TNF) and

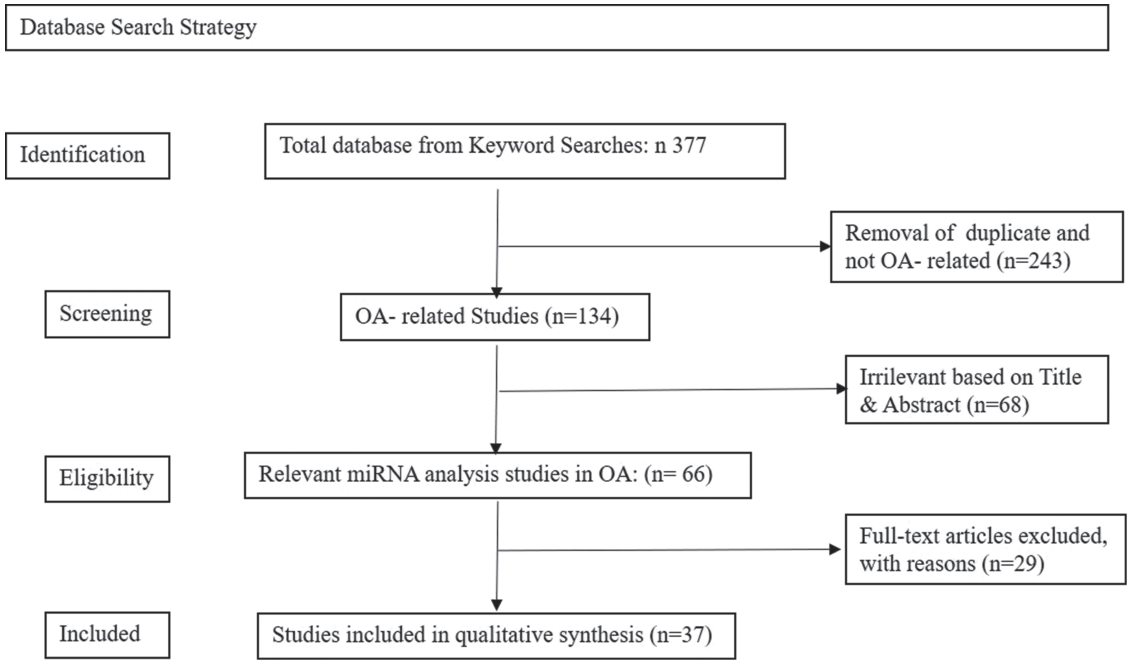

Fig. 2 PRISMA flow diagram.

interleukin 1 beta (IL1β; also known a lymphocyte-activating factor), stimulating human chondrocytes in patients with OA.[14] Furthermore, miRNA-27b may regulate the expression of MMP-13 in human chondrocytes.

Following *in vitro* stimulation of chondrocytes with IL1β, Akhtar *et al.*[15] identified through *in silico* analysis a sequence in the 3′-untranslated region (3′-UTR) of MMP-13 mRNA that was complementary to the seed sequence of miRNA-27b. The increased expression of MMP-13 was associated with the downregulation of miR-27b. On the other hand, miR-27b was overexpressed; this seemed to suppress the activity of a reporter construct containing the 3′-UTR of human MMP-13 mRNA and inhibit the IL1β-induced expression of MMP-13 protein in chondrocytes. IL1β-induced activation of signal transduction pathways associated with the expression of MMP-13 resulted in downregulation of the expression of miR-27b.[15]

The relationship between miRNA, inflammation and OA was demonstrated[16] in the cartilage of 15 osteoarthritic patients by evidencing that miRNA-146a was expressed more robustly in grade I (mild) OA cartilage (particularly in the chondrocytes in the superficial layer of the articular cartilage) compared to the levels expressed in stage II (moderate) and III (severe) OA samples. Cultured normal articular chondrocytes stimulated with IL1β markedly increased the expression of miRNA-146a.[16]

More recently, Chen *et al.*[17] investigated whether miRNA-485-5p can play a role in OA by promoting inflammatory factor secretion and acting on bone marrow MSCs (BMSCs), more specifically by inhibiting their differentiation to the chondrogenic phenotype. Their study showed that the degree of differentiation of the BMSCs is inversely proportional to the miRNA-485-5p level, while the expression of cartilage surface inflammation factors, including IL and TNF, was significantly enhanced. The opposite was observed when miRNA-485-5p was inhibited.

The profiling of 723 miRNAs identified 7 miRNAs that were differentially expressed in OA

Table 1 List of studied miRNA and their effect on OA

miRNA	Function in cartilage	Expression	Reference
22	Inflammatory response and ageing	Increased in OA	13
9 and 98	Reduce production on TNF	Increased in OA	14
27b	Regulating the expression of MMP-13 in chondrocytes	Decreased in OA	15
146a	Inflammatory response regulating the expression of VEGF, Smad4 and TGFβ	Increased or decreased dependent on stage of OA	12, 16, 27, 30 and 31
485-5p	Inhibit chondrogenic differentiation and inflammatory response	Increased in OA	17
149-3p, 582-3p, 1227, 634, 576-5p and 641	Cartilage and bone development and homeostasis	Increased in normal condrocytes	18
483	Promotes inflammation regulating the expression of BMP7, TGFβ, IL1β and MMP3	Increased in OA	18
140	Cartilage and bone development and homeostasis	Increased or decreased dependent on stage of OA	10, 11 and 36
210	Promoted osteoblast differentiation by inhibiting the activity of TGFβ type I receptor	Decreased in OA	25 and 26
2861	Promotes osteogenic differentiation through inhibition of Hdac5	Decreased in OA	23 and 26
223	Promotes chondrocyte apoptosis regulating the expression of NF1A and MCSFR	Increased in OA	27 and 29
21	Associated with CRP and TGFβ signaling	Increased in OA	28
155	Promotes inflammation	Increased in OA	29 and 31
138-5p	Modulates FOXC1, contributing to IL1β-induced ECM degradation in chondrocytes	Increased in OA	30
146a	Regulation of catabolic factors through negative feedback	Decreased in OA	30
335	Regulate chondrogenic differentiation	Increased in OA	30

VEGF means vascular endothelial growth factor; MCSFR, macrophage colony-stimulating factor receptor.

and normal human chondrocytes.[18] This study showed upregulation of miRNA-483-5p in OA chondrocytes; in normal chondrocytes, other miRNAs, including miRNA-149-3p, miRNA-582-3p, miRNA-1227, miRNA-634, miRNA-576-5p and miRNA-641, were upregulated.[18]

These data were upheld through the detection of some miRNAs with a quantitative chain reverse polymerase chain reaction (qPCR). *In silico* analyses predicted that the main molecular pathways, potentially altered by miRNAs, differentially expressed in OA compared to normal chondrocytes, include the TGFβ, gene Wingless/Integrated, Erb gene and mechanistic target of rapamycin signaling. All of them take a part in the regulation of the balance between the development, homeostasis and destruction of articular cartilage, through the synthesis of their functional gene product made of proteins that transmit signals into a cell through cell surface receptors.[18]

Sirtuin-1 (SIRT1) is a nicotinamide adenine dinucleotide-dependent histone deacetylase involved in the regulation of gene expression, differentiation, development and life span of an organism. SIRT1 expression is decreased in osteoarthritic cartilage and chondrocytes. SIRT1 expression regulates apoptosis and the expression of chondrogenic and OA related genes in mice cells and tissues.[19]

The pathways of the endoplasmic reticulum stress, which play a key role in the development of several diseases, and can be either activated or regulated by miRNAs,[14,20] are involved in the pathogenesis of OA.[21] SIRT1 attenuates the PERK–eIF2a apoptotic pathway of the unfolded protein response (UPR) that impairs chondrogenesis,[22] reinforcing the hypothesis that indicates the PERK–eIF2a axis of the UPR as a new possible therapeutic target in OA.[23]

Different factors may increase the risk of OA, including age, joint trauma, chronic mechanical stress and inflammation.[3,4] These factors may regulate the expression of several miRNAs associated with OA. The relationship between the expression of miRNA and ageing is not fully understood, but they take part in the regulation of cell cycle progression, proliferation, gene expression and stress-induced responses.[24] For example, miRNA-140 is the major miRNA implicated in OA to date. Its encoding gene, miRNA-140, is remarkably conserved among all vertebrates and is powerfully and almost exclusively expressed in chondrocytes, playing a role in chondrogenesis and cartilage development.[10]

Excessive mechanical stress is implicated in the development of OA, while an appropriate amount of mechanical stress is necessary for physiological cartilage homeostasis. The ability of miRNA-140 to regulate not only the cartilage development but also the joint homeostasis was demonstrated by Miyaki *et al.*[10] They developed a surgical OA model, in miRNA-140 deficient mice and in wild-type mice, by destabilizing the knee joint resecting the medial meniscotibial ligament.[10] Eight weeks after surgery, miRNA-140 deficient mice showed accelerated proteoglycan loss and fibrillation of the articular cartilage in the knee compared with wild-type mice.[10] A deeper understanding of mechanotransduction in chondrocytes might be a means to control cartilage homeostasis; miRNAs are also involved in this aspect of OA.

Inflammation plays a major involvement in the development of OA. Indeed, the level of inflammatory cytokines such as TNF and IL1β is dramatically increased in osteoarthritic joints, and the cell signaling mechanisms triggered by these inflammatory cytokines interfere negatively with the homeostasis of articular cartilage.[11] For example, *in vivo* the expression of miRNA146a in rats is reduced in cells of the dorsal root ganglion and in the dorsal horn of spinal cords isolated from rats with pain from experimental OA.[12] Therefore, this miRNA could be implicated not only in joint homeostasis and OA but also in pain control through the regulation of inflammation in cartilage and pain-related factors in glial cells.[12]

In mouse osteogenesis, miRNA-210 targets the activin A receptor type 1B (AcvR1b) gene; furthermore, SB431542 inhibits TGFβ/activin signaling in ST2 cells and promotes osteoblastic differentiation. miRNA210 may positively regulate osteoblastic differentiation by inhibiting the TGFβ/activin signaling pathway by inhibiting AcvR1b.[25] miRNA-2861 has been recently identified; highly expressed in primary mouse osteoblasts, miRNA-2861 promotes osteogenic differentiation by inhibiting histone deacetylase 5 (Hdac5) through the increase in acetylation of the osteogenic master gene, runt-related transcription factor 2 (Runx2).[23]

miRNA-29, miRNA-141, miRNA-200a, miRNA-206, miRNA-210 and miRNA-2861 have also been identified as regulators of osteoblastogenesis.[26]

Diminished signaling through this pathway in ageing and in OA contributes to cartilage loss. Crosstalk at molecular level between cartilage and bone may influence OA-related tissue degradation. Potentially, chondrocyte expression of miRNAs at the osteochondral junction might be important to maintain cartilage–bone differentiation.

miRNA for OA diagnosis

In a not-too-distant future, miRNAs may be also used as markers of disease, given their intracellular and extracellular role in regulating gene expression.

Okuhara *et al*[27] investigate the expression patterns of miRNAs in OA progression using qPCR. The relative expression of miRNA-146a, -155, -181a and -223 in OA patients was significantly higher than in healthy controls. In early OA, the expression of miRNA-146a ($P < 0.01$) and miRNA-223 ($P < 0.01$) was significantly higher than at later stages.[27] miRNA-21 levels were associated with C-reactive protein (CRP), a marker of inflammation and TGFβ signaling.[28]

However, it should be clarified that, while there is an overexpression of a miRNA in OA, the opposite is not necessarily true, i.e. the overexpression of a miRNA is not necessarily linked to OA. Murata *et al.*[29] investigated whether the level of miRNAs in synovial fluid and plasma could be used as biomarkers of rheumatoid arthritis. The levels of miRNA-16 ($P < 0.01$), miRNA-146a ($P < 0.05$), miRNA-155 ($P < 0.05$) and miRNA-223 ($P < 0.05$) were significantly higher in the synovial fluid of rheumatoid arthritis (RA) than OA patients, and the levels of miRNA-16 and miRNA-146a in peripheral blood mononuclear cell (PBMC) and plasma correlated with the activity of RA.

Recently, *Kopańska et al.*[30] compared tissue samples from patients who underwent replacement of the OA joint with tissue from patients undergoing total hip arthroplasty unrelated to OA. Total RNA, including miRNAs, from cartilage was extracted using a mirVana miRNA isolation kit. The quantitative PCR was used to evaluate in real time the expression of 19 miRNA; 4 miRNAs, miR-138-5p, miR-146a-5p, miR-335-5p and miR-9-5p, were significantly upregulated in OA tissues.[30]

Another recent study[31] demonstrated that miRNA 146a influenced regulating and signal pathways in relation to OA pathogenesis and disease progression.[31] PBMC were extracted from healthy subjects and OA patients. The expression levels of miRNA-146a and miRNA-155 were quantified using the real-time PCR test. Patients with early OA exhibited an increase in miRNA-155 expression, while an increase in miRNA-146a was observed in the more advanced OA stages (grade 3 and grade 4).[31]

Thus, to detect and measure the concentration of some specific biomarkers allowing an earlier diagnosis could be another promising way to use miRNAs in the future, but it will always be very important to use them with criteria.

miRNA for OA therapy

If upregulation of a given miRNA contributes to disease pathology, it stands to reason that inhibition therapy of that miRNA can be used to block the repression exerted by miRNAs of protein expression. On the other hand, when the downregulation of a miRNA contributes to the development of a given condition, miRNA replacement therapy can modify the natural course of the disease. In humans and animals several potential molecular targets for the management of OA, including proteases, cell signaling molecules and transcription factors, have been identified,[31] but clinical success in regulating these molecules has thus far been inadequate.

Hypoxia-inducible factor 2α could be a potential target in OA therapy, given its ability to stimulate chondrocyte expression of genes such as RUNX2, a major regulator of OA inducer in both mice and humans.[32] RUNX2, a major player in the pathogenesis of OA, regulates a disintegrin and metalloproteinase with thrombospondin motifs 5 expression and hedgehog signaling.[33] Endogenous miRNA-21 is upregulated in OA patients; its overexpression could interfere with chondrogenesis.[34,35]

Si *et al.*[36] evaluated *in vivo* whether intra-articular injection of miRNA-140 can affect the progression of OA. OA was induced surgically, and subsequently rats were allocated in a random fashion to one of three groups. Each group received via intra-articular injection equal amounts (100 µl) of normal saline, nonspecific negative oligonucleotide (5 nmol) and miRNA-140 agomir (5 nmol). At 4, 8 and 12 weeks after the procedure, the progression of OA was evaluated macroscopically, histologically and immunohistochemically. Cartilage thickness, chondrocyte

numbers and collagen II expression in articular cartilage were significantly higher. The pathological scores and the expression levels of MMP-13 and ADAMTS-5 were significantly lower in the miRNA-140 agomir than in the control group. This indicated that the intra-articular injection of miRNA-140 can slow down the progression of OA in rats.[36]

miRNA may be heavily involved in the maintenance of homeostasis in chondrocytes, and therefore they may be a target for cartilage tissue engineering and regenerative medicine. However, of all innovative therapies, inactivating transcription factors in cartilage presents some important limits. Probably, the most important is the delivery of miRNA through the avascular ECM that surrounds chondrocytes and prevents access to them.[4] Indeed, the major issue to develop the clinical potential of miRNA may be to obtain an adequate delivery to target cell, without cytotoxicity. Many problems remain to be overcome, including an appropriate and effective drug-delivery system and the identification of the off-target effects.

miRNA-controlled delivery and potential application in clinic

miRNA-based therapies may restore or repress miRNA expression and activity. However, major hurdles involve the delivery of miRNA-targeting agents before they can be applied in clinical practice. miRNAs have a very short half-life, are relatively unstable *in vivo* and exhibit inappropriate biodistribution, disruption and saturation of endogenous RNA machinery and several side effects.[37]

The development of highly technological and precise carriers will be the key strategy for miRNA therapeutic application. These carriers should (i) protect RNA from degradation; (ii) accurately deliver RNA to the desired cells, avoiding delivery to nontarget cells; (iii) encourage efficient cellular uptake; and (iv) release RNA within the target cell. RNAs are easily degraded *in vivo* by RNAses; therefore, chemical strategies must be developed to improve miRNA stability.[38] At the same time, these various modifications to the miRNAs cannot affect the complexation of RNA-induced silencing complex.[38]

Viral vectors are widely used *in vitro*. However, viral vectors exhibit several disadvantages, including toxicity, cellular immune response and oncogenicity from insertional mutagenesis, and quality control, which limit their application as gene delivery agents.[36,37,39]

Nonviral vectors are biocompatible and safe; mainly, biopolymer nanoparticles and lipid vesicles have been described for RNA-controlled delivery (Fig. 3).

Lipid-based carriers are described as the most promising candidates for miRNA delivery.[38]

These vesicles are composed by lipids that, though able to assemble into stable delivery systems, may be affected by the nucleic acid payload. Lipid-based miRNA delivery systems are usually internalized into cells trough endocytosis; correspondingly, materials that can facilitate endosomal escape are required to allow delivery.[38] Indeed, the introduction of cholesterol as a component of some DNA/RNA carriers can improve transfection *in vivo* compared to carriers not containing cholesterol.[38]

The design of miRNA-specific delivery systems for an *in vivo* disease target is the key to the development of miRNAs for therapeutic purposes. Indeed, the possibility of developing RNA inhibitor therapy in the future will depend precisely on the ability to develop technologies able to accurately reach the target cells and tissues.

Furthermore, it is unclear whether targeting the expression of extracellular regulators and intracellular signaling mechanisms (such as FGF-18 and BMP-7) can positively affect joint homeostasis.[4] The delivery of miRNAs in a functional fashion to the affected joint to antagonize the negative effects of genes implicated in the development of OA seems to be the key to understanding their function and their possible therapeutic use.

Conclusion

miRNAs have been identified as a novel and efficient means to regulate gene expression. The complex interactions between miRNAs and their multiple target genes have important roles in gene

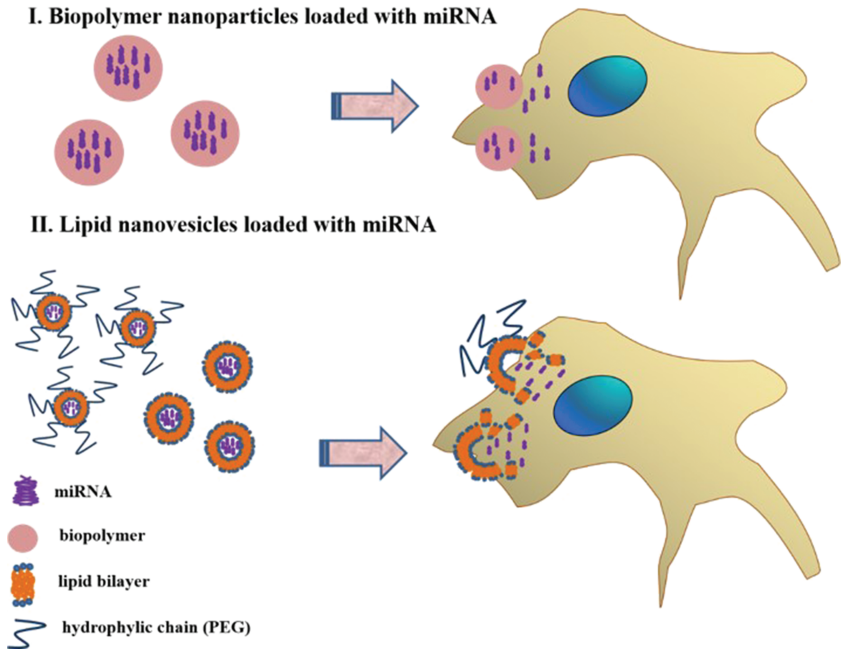

Fig. 3 Biopolymer nanoparticles with biodegradability and controlled release ability have been used in gene transfer; with a size <100 nm. They could overcome the absorption barrier of the cell membrane by penetrating in the cell via endocytosis. Poly-lactic-co-glycolic acid nanoparticle is a large biopolymer used to escape from the endolysosomal compartment to the cytoplasmic compartment and release their contents over extended periods of time (I). Lipid-based carriers with a size <100 nm have also been described as the most promising candidates for therapeutic miRNA delivery. The lipids must be able to assemble into stable delivery systems, which may be affected by the nucleic acid payload. Internalization of lipid-based siRNA delivery systems into cells typically occurs through endocytosis; accordingly, delivery requires materials that can facilitate endosomal escape (II).

regulation and the control of disease pathways. Also, a single miRNA, as shown for miRNA-140, can exert major effects on the development of OA *in vivo*.

Few miRNAs, such as miRNA-140 and miRNA 146a, have been studied in OA, and further investigations in this field are required. The use of miRNAs for therapeutic purposes in other conditions, coupled with improvement in delivery to joint tissues, should aid clinically relevant development of miRNA-based therapies in OA. Furthermore, circulating miRNAs may be useful for diagnostic purposes and provide novel methods for intracellular delivery of therapeutic molecules.

Understanding how miRNA expression and regulation may enhance chondrogenic differentiation or maintain phenotype would open new perspectives for cell and tissue engineering that could be employed to develop new therapeutics to treat and prevent tissue destruction in OA. The investigation of the role that miRNAs play in joint physiopathology may shed light on the diagnosis, prevention and treatment of OA.

Recent evidence suggests that miRNA-based therapies may be a great hope for the future, both to suppress and stimulate their expression and therefore the genetic pathways associated with them. The limitations to overcome with an appropriate delivery system include, but are not limited to, poor *in vivo* stability, inappropriate biodistribution and undesirable side effects.

However, despite the great potential, to date there remain several obstacles that must be overcome before translation into clinical applications, first of all the administration of miRNA as therapeutic agents in a targeted manner.

Conflict of interest statement

The authors have no potential conflicts of interest.

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