Role of MicroRNA in Osteoarthritis

Mingcai Zhang[1], Kate Lygrisse[1] and Jinxi Wang[1,2*]

[1]Harrington Laboratory for Molecular Orthopedics, Department of Orthopedic Surgery, University of Kansas Medical Center, Kansas City, Kansas, USA

[2]Department of Biochemistry & Molecular Biology, University of Kansas Medical Center, Kansas City, Kansas, USA

*Corresponding author: Jinxi Wang, Department of Orthopedic Surgery, University of Kansas Medical Center, 3901 Rainbow Boulevard, MS #3017, Kansas City, KS 66160, USA, Tel: 913-588-0870; Fax: 913-945-7773; Email: jwang@kumc.edu

Abstract

Although the potential effect of aberrant expression of catabolic and anabolic genes on the development of osteoarthritis (OA) is well-documented, the regulatory mechanism for the expression of these genes in articular chondrocytes remains to be elucidated. The recent advances in epigenetic studies have identified microRNA (miRNA) as one of the epigenetic mechanisms for the regulation of gene expression. This mini review highlights the role of miRNA in the regulation of gene expression in articular chondrocytes and its significance in the pathogenesis of OA, with a discussion on the potential of miRNA as a new biomarker and therapeutic target for OA. Further investigations are required to determine the specificity, sensitivity, and efficacy of miRNA for clinical applications

Keywords: MicroRNA; Osteoarthritis; Epigenetics; Gene expression; Biomarker

Abbreviations OA: Osteoarthritis; MiRNA: MicroRNA; NcRNA: Non-coding RNA; MRNA: Messenger; RNA; SiRNA: Short Interfering RNA; piRNA: Piwi-interacting RNA; ECM: Extracellular matrix; ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin Motifs; MMP13: Matrix Metalloproteinase 13; COL2: Type II Collagen; IL-1β: Interlukin 1-β; COL9: Type IX Collagen; TNF-α: Tumor Necrosis Factor-α; Runx2: Runt-Related Transcription Factor 2; NFAT: Nuclear Factor of Activated T-cells.

Introduction

In contrast to genetics which is the study of hereditable variation in DNA sequences, epigenetics refers to the study of the changes in gene transcriptional activity caused by mechanisms other than changes in DNA sequences. Traditional epigenetic covalent modifications include DNA methylation and histone protein modifications (e.g. acetylation, methylation, phosphorylation, ubiquitination and sumoylation). Recently, non-coding RNAs (ncRNAs) that possess epigenetic-like properties in the regulation of gene expression have also been considered as one of the epigenetic mechanisms [1,2]. With the use of high-throughput technologies, comprehensive assessment of the quantity of transcriptional molecules, including protein-coding messenger RNAs (mRNA) and ncRNAs, is now an area of rapid expansion in biomedical research of common diseases, such as Osteoarthritis (OA).

OA is the most common form of arthritis and is the leading cause of chronic disability in middle-aged and older populations [3]. Aberrant gene expression in articular chondrocytes of OA joints has been well documented in both animal and humans studies. However, the underlying regulatory mechanism that causes aberrant gene expression in OA cartilage has not yet been elucidated.

This review will first highlight the role of microRNA (miRNA), one of the most studied ncRNAs, in the regulation of aberrant gene expression in articular chondrocytes as it relates to the pathogenesis of OA, and then discuss the potential use of miRNA as a biomarker and potential therapeutic target for OA.

miRNA and OA

Biogenesis of miRNA

Classically, a gene is assumed to be transcribed into an mRNA and then translated into a protein; however, the discovery of genes encoding ncRNAs has extended the definition of a gene. The ncRNA genes produce transcripts functioning as structural, catalytic, or regulatory RNAs rather than being translated into proteins. Based on their length, ncRNAs can be divided into short ncRNAs (<30 nucleotides) and long ncRNAs (lncRNAs, >200 nucleotides). Short ncRNAs include miRNAs, short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) [4]. MiRNAs are transcribed from miRNA genes as long primary transcripts (pri-miRNAs) characterized by a hairpin structure and are processed as pre-miRNAs (around 70-nucleotides long) in the nucleus. After being transported into the cytoplasm, pre-miRNAs are cleaved by Dicer and then matured into miRNA of 22-24 nucleotides [5].

Aberrant gene expression in OA cartilage

Adult articular cartilage is an avascular tissue in which chondrocytes are the only cellular component. Articular chondrocytes maintain the low-turnover of the extracellular matrix (ECM) by delicately regulating the expression of catabolic and anabolic genes. Progressive degradation of articular cartilage ECM is the major pathophysiological feature of OA. Increased expression of catabolic genes and decreased expression of anabolic genes are usually observed in OA chondrocytes, which disrupt the metabolic balance in articular cartilage.

A number of catabolic genes have been proposed to be involved in the development of OA, including the genes encode: 1) Aggrecanases, such as ADAMTS (a disintegrin and metalloproteinase with

thrombospondin motifs)-4 and -5, two major aggrecanases which have been shown to play important role in development of OA [6-9]; 2) Collagenases, particularly MMP (matrix metalloproteinase)-13, a major type II collagen (COL2A1)-degrading collagenase, which contributes to the initiation and progression of OA [10,11]; 3) Pro-inflammatory cytokines, such as IL (interleukin)-1β, IL-6, and TNF-α (tumor necrosis factor)[12,13]; 4) RunX2 (Runt- related transcription factor 2), which contributes to the pathogenesis of OA by promoting chondrocyte hypertrophy and matrix breakdown in articular cartilage. Runx2+/- mice exhibit decreased cartilage destruction and osteophyte formation, along with reduced expression of type X collagen and MMP-13, as compared with wild-type mice [14]. Upregulation of these catabolic genes contributes to the increased degradation of articular cartilage ECM.

A number of anabolic genes have been proposed to be involved in the structure and function of articular cartilage, including the genes encode: 1) Aggrecan, a major proteoglycan in articular cartilage [15,16]; decreased aggrecan expression is often evident in OA cartilage [17,18]. 2) Collagens, collagen type II is one of the major ECM components of the articular cartilage. Mice bearing a small deletion mutation in type II collagen gene developed OA-like lesions [19]. 3) SOX9 (SRY-Box 9), SOX9 is a master transcription factor for chondrogenesis during the development of the skeletal system, in cooperation with SOX5 and SOX6 [20,21]. Although mice with conditional postnatal deletion of Sox9 in chondroytes do not develop OA [22], later OA usually is associated with decreased SOX9 expression [23]. 4) NFAT1 (Nuclear Factor of Activated T-cells 1), which is a member of the NFAT transcription factor family originally identified as a regulator of the expression of cytokine genes during the immune response [24,25].

NFAT1 has recently been shown to play an important role in maintaining the permanent cartilage phenotype in adult mice. Nfat1 knockout (Nfat1-/-) mice exhibit normal skeletal development, but display over-expression of numerous matrix-degrading proteinases and pro-inflammatory cytokines, as well as loss of collagen-2 and aggrecan during the early stage of OA. These initial changes are followed by articular chondrocyte clustering, formation of chondro-osteophytes, progressive articular surface destruction, formation of subchondral bone cysts, and exposure of thickened subchondral bone, all of which resemble human OA [26]. Down regulation of these anabolic genes contributes to the decreased ECM synthesis, impairing the repair ability of articular cartilage.

Regulation of gene expression in OA by miRNAs

The importance of epigenetic regulation of gene expression to the development of OA has recently been reported [27-29]. A number of miRNAs have been identified to be involved in the pathogenesis of OA in recent epigenetic studies. miRNAs may directly bind to catabolic and anabolic mRNAs to regulate their expression at a post-transcriptional level in cytoplasm with a complimentary sequence to induce cleavage and degradation, or block translation [30-32]. New findings indicate that the regulatory effect of miRNAs on the expression of catabolic and anabolic genes in OA may take place at upstream levels prior to their transcription. First, miRNAs target upstream signaling pathways or transcription factors. The activity of several signaling pathways, such as NF-kappaB pathway [33,34], Wnt/beta-Catenin pathway [35], SIRT1/p53 pathway [36] and SDF1/CXCR4 pathway [37], were found to be modulated by miRNAs in chondrocytes during the development of OA. Moreover, miRNAs have

also been reported to regulate transcription factor SOX9 in the development of OA [38,39]. Second, miRNAs target upstream epigenetic factors. Histone deacetylase-2 [40], -4 [41-43], and NAD-dependent deacetylase sirtuin-1 [44] have been found to be regulated by miRNAs in OA cartilage, indicating that the interaction among different epigenetic mechanisms is involved in OA pathogenesis.

miRNA and treatment of OA

The development of disease-modifying pharmacologic therapy for OA currently faces major obstacles largely because the pathogenesis of OA remains unclear. The aberrant expression catabolic and anabolic genes are a well-characterized molecular finding in OA; however, clinical trials targeting a single inflammatory mediator or proteinase did not slow the progression of OA [45-47]. This is probably due to the involvement of multiple factors in the pathogenesis of OA. In this regard, upstream molecular regulators would be more favorable therapeutic targets.

MiRNAs could be potential upstream targets for treatment of OA as one miRNA may regulate several genes. Furthermore, miRNAs regulate gene expression in OA cartilage at multiple levels and in a sequence-specific manner [48,49]. However, a large number of miRNAs have recently been identified in OA joint tissues, and one gene may be regulated by several miRNAs (Table 1).

Further investigations are needed to identify the articular cartilage specific miRNA(s) and to validate their efficacy in animal models of OA and in patients with OA. Specific transcription factors that regulate multiple catabolic and anabolic genes, such as NFAT1 [26,27,29], could also be potential upstream targets for treatment of OA.

miRNA and OA biomarker

Currently, X-ray and MRI (magnetic resonance imaging) are the established methods for the diagnosis of OA in clinical practice [30-49]. However, specific blood testing that can be used to aid in the diagnosis and monitoring of OA progression is still under development. Clinicians and scientists are striving for a novel molecule(s) which can be used as a biomarker for early OA detection and for monitoring the progression of OA [50].

Given the high frequency of miRNAs expression in OA and the remarkably stable form of miRNAs present in clinical samples of plasma and serum [51,52], miRNAs could be ideal blood-based biomarkers for OA [53]. However, more studies are needed to identify the OA-specific miRNAs with high sensitivity to OA changes.

Conclusion

The recent advances in epigenetic studies have shed light on the importance of miRNAs in regulation of gene expression at multiple levels related to the pathogenesis of OA [54-65]. This warrants the potential of miRNAs as therapeutic targets for OA. The tissue-specificity and high frequency of miRNA expression in OA renders miRNAs novel molecules as potential biomarkers for diagnosing OA, monitoring OA progression, and evaluating treatment efficacy.

Further studies are required to identify which miRNAs out of the large number of miRNAs reported in the literature (Table 1) have high specificity, sensitivity and efficacy and could be used for clinical validation in OA patients [66-78].

miRNA	Species	Change in OA	Target gene	Reference
miR-125b	H		ADAMTS4	[54]
miR-140	M		ADAMTS5	[31,55,56]
Has-miR-15a	H			
miR-30a	H			
miR-98	R		Bcl2	[57]
miR-199a	H		COX2	[58]
miR-210	R		DR6	[34]
miR-221-3p	H		Est-1	[59]
miR-138-5p	H		FOXC1	[60]
miR-21	H		GDF5	[61]
miR-92a-3p	H		HADC2	[62]
miR-365	H		HDAC4	[43]
miR-142-3p	M		HMGB1	[63]
miR-140	H		IGFBP-5	[64]
miR-27a	H			
miR-381a-3p	H		IKBalpha	[65]
Has-miR26a-5p	H		iNOS	[66]
miR-26a	H		KPNA3	[60]
miR-26b	H			
miR-139	H		MCPIP	[67]
miR-373	H		MECP-2	[68]
miR-27a	H		MMP-13	[30,64,69,70]
miR-27b	H			
miR-127-5p	H			
miR-320	H			
miR-9	H		NF-kappaB1	[33]
miR-634	H		PIK3R1	[71]
miR-221-3p	H		SDF1	[37]
miR-370	H		SHMT-2	[68]
miR-34a	H		SIRT1	[36,44]
miR-449q	H			
miR-145	H		SMAD3	[72]
miR-146a	R		SMAD5	[73]
miR-101	R		SOX9	[39,74]
miR-30a	H			
miR-125b-5p	H		SYVN1	[75]

miR-130A	R		TNFα	[76]
miR-145	H		TNFRSF11B	[77]
miR-562-5p	H		TRAF2	[78]

Hsa: homo sapiens; H: human; M: mouse; R: rat; : upregulation; : downregulation

Table 1: Summary of differentially expressed miRNAs and their target(s) in OA cartilage.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest

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