Biomedicine & Pharmacotherapy 136 (2021) 111240

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Non-coding RNAs modulate function of extracellular matrix proteins

Nader Akbari Dilmaghnai [a], Hamed Shoorei [b], Guive Sharifi [a], Mahdi Mohaqiq [c], Jamal Majidpoor [d], Marcel E. Dinger [e], Mohammad Taheri [f,*], Soudeh Ghafouri-Fard [g,*]

[a] Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[c] Wake Forest Institute for Regenerative Medicine, School of Medicine, Wake Forest University, Winston-Salem, NC, USA
[d] Department of Anatomy, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[e] School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW 2052, Australia
[f] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
miRNA
lncRNA
Extracellular matrix
Expression

ABSTRACT

The extracellular matrix (ECM) creates a multifaceted system for the interaction of diverse structural proteins, matricellular molecules, proteoglycans, hyaluronan, and various glycoproteins that collaborate and bind with each other to produce a bioactive polymer. Alterations in the composition and configuration of ECM elements influence the cellular phenotype, thus participating in the pathogenesis of several human disorders. Recent studies indicate the crucial roles of non-coding RNAs in the modulation of ECM. Several miRNAs such as miR-21, miR-26, miR-19, miR-140, miR-29, miR-30, miR-133 have been dysregulated in disorders that are associated with disruption or breakdown of the ECM. Moreover, expression of MALAT1, PVT1, SRA1, n379519, RMRP, PFL, TUG1, TM1P3, FAS-AS1, PART1, XIST, and expression of other lncRNAs is altered in disorders associated with the modification of ECM components. In the current review, we discuss the role of lncRNAs and miRNAs in the modification of ECM and their relevance with the pathophysiology of human disorders such as cardiac/ lung fibrosis, cardiomyopathy, heart failure, asthma, osteoarthritis, and cancers.

1. Introduction

The extracellular matrix (ECM) constitutes a multifaceted network of diverse structural proteins, matricellular molecules, proteoglycans, hyaluronan, and various glycoproteins that cooperate and link with each other to produce a bioactive polymer. This polymer regulates the mechanical features of tissues and the behavior of the existing cells. The final configuration of the ECM is defined by several parameters that regulate the production and turnover of each ECM element. Alterations in the composition and configuration of ECM constituents influence the cellular phenotype [1]. Non-coding RNAs (ncRNAs) are regarded as a novel regulatory system for modulation of the conformation of the ECM and therefore the phenotype of the cells that are located in this environment [1]. These transcripts comprise the vast majority of transcriptome of the mammalian genome, since although 80 % of mammalian genome is actively transcribed, only 2 % produce coding RNAs [2]. The association between the complexity of an organism and the plethora of ncRNAs [3], further support the importance of these transcripts in the developmental processes. They are principally classified into two classes according to their length. Those with sizes larger than 200 nucleotides are named as long non-coding RNAs (lncRNAs), while others constitute the small non-coding RNAs. The latter include microRNAs (miRNAs) and several other transcripts such as small interfering RNAs and piwi-interacting RNAs [4]. LncRNAs have crucial roles in epigenetic regulation of chromatin arrangement through recruitment of epigenetic factors, promoter-specific control of gene expression, modulation of stability of transcripts, X-chromosome inactivation, and imprinting [4]. In addition, lncRNAs can function as structural coordinators to partake in the establishment of subcellular organelles [5]. Other ncRNAs such as miRNAs participate in other layers of gene expression regulation. miRNAs exert their regulatory role through pairing with the transcripts of protein-coding genes to repress their expression at the post-transcriptional level [6]. In the current review, we discuss the role of lncRNAs and miRNAs in the modification of ECM and their relevance with the pathophysiology of human disorders such as cardiac/ lung fibrosis, cardiomyopathy, heart failure, asthma,

* Corresponding authors.
E-mail addresses: mohammad_823@yahoo.com (M. Taheri), S.ghafourifard@sbmu.ac.ir (S. Ghafouri-Fard).

https://doi.org/10.1016/j.biopha.2021.111240
Received 9 November 2020; Received in revised form 19 December 2020; Accepted 31 December 2020
Available online 19 January 2021
0753-3322/© 2021 The Author(s). Published by Elsevier Masson SAS. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

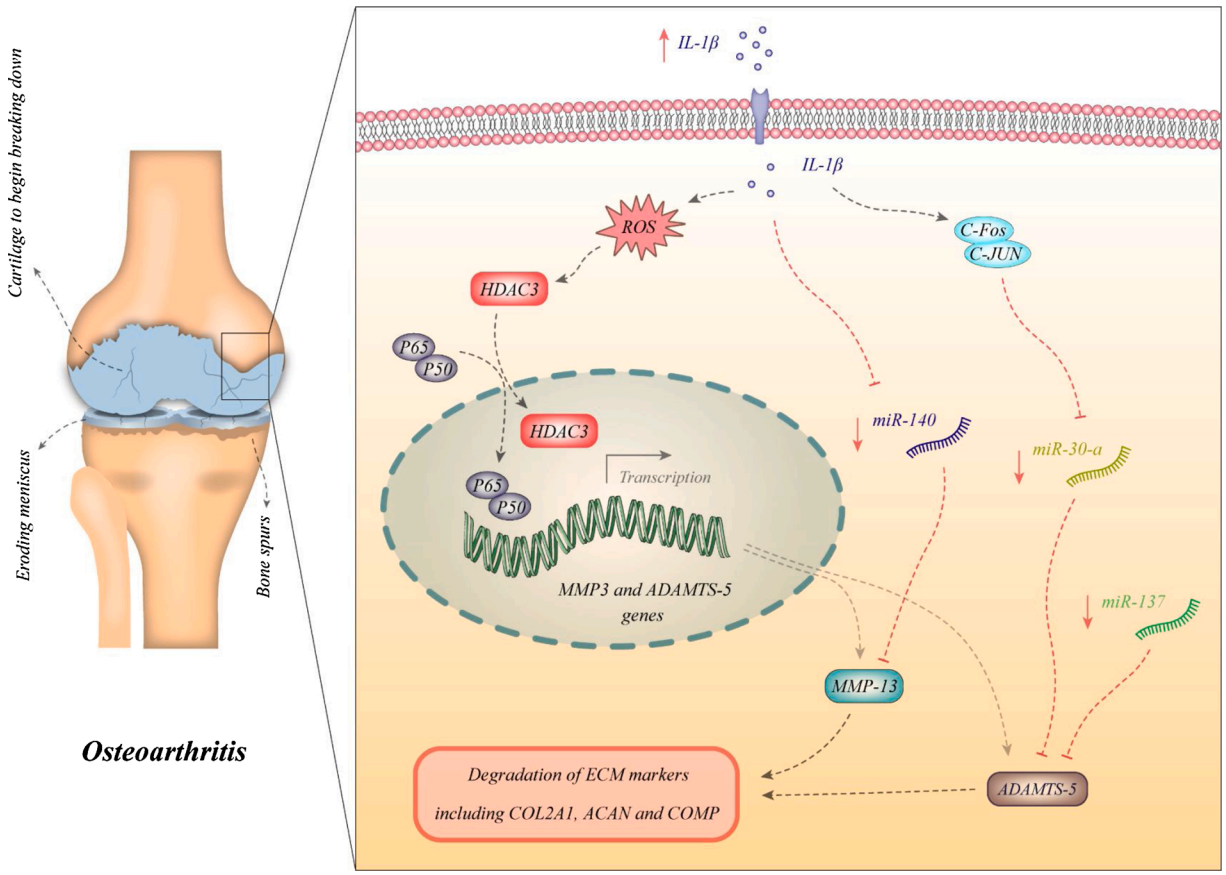

Fig. 1. IL-1β is increased in patients with osteoarthritis (OA). This cytokine increases reactive oxygen species (ROS) levels, activates HDAC3, and promotes nuclear transport of P65/P50 to enhance expression of MMP13 and ADAMTS-5 [17]. Moreover, IL-1β activates C-FOS and C-JUN and suppresses miR-30-a. This miRNA has a role in the suppression of ADAMTS-5 [18]. Another down-regulated miRNA in OA is miR-137. This miRNA has been shown to inhibit ADAMTS-5 expression [16]. Collectively, over-expression of MMP13 and ADAMTS-5 degrades ECM and participates in the pathogenesis of OA.

osteoarthritis and cancers.

1.1. miRNAs and ECM

These small non-coding RNAs are around 22 nucleotides in length and are produced through a multi-stage process. With the aid of RNA polymerase II, primary miRNAs are produced. RNA polymerase III is also involved in the transcription of some miRNAs, particularly miRNAs having upstream Alu sequences [7]. Subsequently, two cleavage events generate mature miRNAs from primary miRNAs. The first cleavage step is accomplished in the nucleus with the cooperation of Drosha and its cofactor DGCR8, while the second step is completed in the cytoplasm with the aid of another RNAse III enzyme termed Dicer. The resultant mature miRNAs amass into the RNA-induced silencing complex (RISC) [8].

1.2. miRNAs in the cardiac tissue

Cardiac fibrosis has been associated with dysregulation of several miRNAs, including miR-34a and miR-93. These two miRNAs inhibit the expression of c-Ski, a protein that is significantly reduced in cardiac fibrosis, and the TGF-β1-induced animal model of cardiac fibroblasts. Functional studies showed the role of the miR-34a/miR-93-c-Ski axis in the regulation of TGF-β1- and isoproterenol-stimulated cardiac fibrosis. The underlying mechanism of this process has been the enhancement of fibroblasts proliferation and ECM alterations [9]. Other studies have demonstrated the role of miR-21, miR-26, miR-29, miR-30, and miR-133a in the induction of ECM fibrosis [10]. However, circulating levels of these miRNAs are not significantly different between patients with new-onset and chronic dilated cardiomyopathy, or between patients with and without fibrosis. Expression of miR-26 is correlated with ECM fibrosis. Moreover, peripheral expression of these miRNAs is correlated with several serum indicators of collagen metabolism, and expression miR-133a correlates with all aspects of ECM metabolism, namely collagen production, fibrosis regulating parameters, and matrix metalloproteinases (MMPs) and the related tissue inhibitors (TIMPs) [11].

1.3. miRNAs in the pathogenesis of intervertebral disc degeneration (IDD)

ECM-associated miRNAs have also been implicated in the pathogenesis of intervertebral disc degeneration (IDD). Wang et al. have shown differential expression of 29 miRNAs between nucleus pulposus (NP) samples obtained from IDD patients versus healthy subjects. Notably, expression of miR-21 was higher in degenerated NP samples in correlation with the amplitude of disc degeneration. This miRNA suppresses autophagy and enhances the expression of MMP-3 and MMP-9, resulting in the induction of Col II and aggrecan degradation. These effects were mediated through the PTEN/Akt/mTOR signaling pathway [12]. Liu et al. have assessed the expression of miR-7 in degenerative NP tissues and in IL-1β-induced NP cells. They have reported the up-regulation of miR-7 in human degenerative NP tissues and in IL-1β induced NP cells versus normal control samples. They have also reported GDF5 as a target of this miRNA. Up-regulation of miR-7 has increased the IL-1β-induced ECM degeneration, while its suppression has blocked NP cell harmful catabolic alterations in reaction to IL-1β. miR-7 participates in the impairment of ECM in intervertebral discs via modulating GDF5 [13].

Table 1
List and function of ECM-related miRNAs in human/ animal disorders (NP: nucleus pulposus).

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
Cardiac Fibrosis (CF)	miR-34a, miR-93	SD rat	–	c-Ski, TGF-β1	–	miR-34a/miR-93 could affect TGF-β1-induced fibroblasts proliferation and ECM deposition through c-Ski.	[9]
CF	miR-154	12 pairs of cardiomyopathy and normal samples	HCF, CFs	GSK-3β, α-SMA	Wnt/β-catenin	miR-154 could inhibit GSK-3β expression by activating the Wnt/β-catenin pathway, which promotes myocardial fibrosis.	[24]
CF	miR-433	male C57BL/6 mice /Human; 4 pairs of cardiac fibrosis and normal heart tissues		AZIN1, JNK1	TGF-β/Smad3, ERK, p38	Downregulation of miR-433 could reduce cardiac fibroblast proliferation and myofibroblast differentiation in vivo and in vitro by targeting AZIN1 and JNK1.	[25]
CF	miR-26a-5p	SD rat	293 T	ULK1	–	miR-26a-5p could regulate the autophagic pathway in cardiac fibroblasts.	[26]
CF	miR-125b	C57BL/6 J mice/Human; 6 pairs of failing human hearts and normal hearts	HCFs	TGF-β, apelin	p53	miR-125b could affect the induction of cardiac fibrosis and act as a potent repressor of multiple anti-fibrotic mechanisms.	[27]
CF	miR-495	–	CFs	NOD1	NF-kB, TGF-β1/Smad	miR-495 could reduce ECM accumulation of cardiac fibroblasts through the downregulation of NOD1.	[26]
Dilated Cardiomyopathy (DCM)	miR-21, miR-26, miR-29, miR-30, miR-133a	70 consecutive DCM patients	–	PICP, PINP, PIIICP, PIIINP, OPN, CTGF, TGF-β1, MMP-2	MMPs/TIMPs	miR-26 could weakly correlate with ECM fibrosis. miR-26 and miR-133a could independently associate with ECM fibrosis. miR-26 and miR-133a could independently associate with fibrosis as well as correlated with the quantity of fibrosis.	[11]
Heart Failure (HF)	miR-19a-3p/ 19b-3p	20 pairs of HF and normal patients	HCF	TGF-βR II, TGF-β1	TGF-β /Smad2, Smad/Akt	Overexpression of miR-19a-3p/19b-3p could inhibit epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) production and invasion of HCF by targeting TGF-βR II.	[28]
Lung Fibrosis	miR-140	C57BL/6 mice	L-929, HEK-293 T	Fn	TGF-β 1/ Smad3	Downregulation of miR-140 could increase the risk of radiation-induced lung fibrosis through reprogramming fibroblasts and macrophages.	[29]
Lung Fibrosis	miR-1224-5p	C57BL/6 mice	NIH/3T3, MRC-5	BECN1, TGF-	PDGFR	miR-1224-5p could mediate mitochondrial damage to affect silica-induced pulmonary fibrosis by targeting BECN1.	[30]
Lung Fibrosis	miR-21	C57BL/6 mice	IMR-90	TGFβ1	pRK5/ SMAD2/3/4	miR-21 could increase effects on BLM-induced lung fibrosis and TGFβ1-induced ECM in IMR-90 cells.	[31]
Lung Fibrosis	miR-497	SD rat	RLE-6TN, HEK293	TGFβ1	EIF3A	miR-497 could inhibit TGFβ1-induced EMT, primary pulmonary fibroblast proliferation, and ECM protein expression.	[32]
Lung Fibrosis	miR-29	–	IMR-90	TGFβ1, COL1A1	Wnt/β-catenin	miR-29 could mediate TGFβ1-induced ECM synthesis through activation of the Wnt/β-catenin pathway inhuman pulmonary fibroblasts.	[33]
Lung Fibrosis	miR-29b	–	NIH-3T3, MRC-5, Raw264.7	TIMP-1	–	Overexpression of miR-29b could reduce the expression of ECM components in pulmonary fibrosis.	[34]
Asthma	miR-143-3p	9 pairs of asthma and healthy patients	ASMCs	TGF-β1, CDK4, Cyclin D1	NFATc1	Overexpression of miR-143-3p could decrease asthma airway remodeling by suppressing proliferation and ECM protein deposition in TGF-β1-mediated ASMCs via the negative regulation of NFATc1 signaling.	[35]
Asthma	miR-204-5p	9 pairs of primary asthmatic subjects and non-asthmatic subjects	HASMCs	TGF-β1	TGF/Smad3	miR-204-5p could reduce ECM production of airway smooth muscle cells by regulating Six1 in asthma.	[36]
Asthma	miR-223	SD rat	ASMCs	IGF-1R, TGF-β1	IGF-1R/PI3K-Akt	Overexpression of miR-223 could decrease the expression of proteins involved in the extracellular matrix, such as α-SMA (ACTA2), and type I and III collagens.	[14]
Keloid	miR-203	10 pairs of Keloid tissue specimens and normal skin tissues	–	EGR1, FGF2	–	miR-203 overexpression in vitro led to a significant decrease in ECM production in keloid fibroblasts.	[37]

(*continued on next page*)

Table 1 (*continued*)

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
Hypertrophic Scar (HS)	miR-205-5p	15 pairs of HS and normal skin	CCC-ESF-1, HSFs	Smad2	AKT, TGF-β	miR-205-5p could regulate ECM production in HS by targeting Smad2.	[38]
Hypertrophic Scar (HS)	miR-21	BALB/c nude mice /Human; 9 pairs of HS tissue and matched normal skin tissues	–	Col1A1, Col3A1, FN, α-SMA	TGF-β1, miR-21, Smad7	miR-21 could affect hypertrophic scar formation in TGF- β1 /miR-21/Smad7 signaling.	[39]
Skin Fibrosis	miR-9-5p	C57BL/6 mice	HDFs	TGFBR2	TGF-β	miR-9-5p overexpression could decrease fibrogenesis in skin fibrosis.	[40]
Selective Intrauterine Growth Restriction (sIUGR)	miR-338-5p	5 pairs of cases complicated with sIUGR and normal patients	293 T, HTR-8/SVneo	EFEMP1	AKT	miR-338-5p could affect growth and invasion of trophoblast cells in selective intrauterine growth restriction by targeting epidermal growth factor-containing fibulin-like extracellular matrix protein 1.	[41]
–	miR-29	TSP2 KO mice	Primary dermal fibroblast	TSP2	–	Regulating of miR-29 by TSP2 could contribute to ECM production.	[42]
Uterine Leiomyoma	miR-21a-5p	–	A006-X, A005-X	TGF-β3, MMP2, MMP9, MMP11, Serpine1	TGF-β	Overexpression of miR-21a-5p could affect the expression of ECM mediators in uterine leiomyoma.	[43]
–	miR-126-3p	–	MC3T3, b. End5, HUVEC	Spred1, Plk2, Irs1	ERK1/2	miR-126-3p could promote matrix-dependent perivascular cell attachment, migration, and intercellular interaction.	[44]
Obesity	miR-181d	C57BL/6 J mice, BMP4 transgenic mice /Human; 30 Pairs of subcutaneous and visceral adipose tissues samples	SVF, C3H10T1/2	Adamts1	FAK–ERK1/2	miR-181d could promote adipocyte lineage commitment by regulating Adamts1-ECM-FAK–ERK axis.	[25]
–	miR-29c	SD rat	RAOSMCs	Col3A1, Col4A5, ELN, MMP2	–	miR-29c could mediate the inhibitory effect of glucocorticoids on ECM gene expression.	[45]
Glaucoma	miR-483-3p	–	HTMCs, 293 T	Smad4	TGF/Smad	miR-483-3p could reduce ECM production by targeting Smad4 in human trabecular meshwork cells.	[46]
–	miR-29b	C57 mice	–	TGF-β	TGF-β1/ Smad/CTGF	Overexpression of miR-29b could promote wound healing, alleviates pathomorphology change in scar tissues, and reduces ECM production by inhibiting TGF-β/Smad/CTGF signaling pathway in the scalded model of mice.	[47]
Osteoarthritis (OA)	miR-137	25 OA cartilage tissues and 15 normal control cartilage tissues	–	ADAMTS-5, IL-1β	–	Overexpression of miR-137 suppressed cell growth, ECM degradation through regulating ADAMTS-5 in chondrocytes.	[16]
OA	miR-449a	20 OA cartilage samples and 10 normal cartilage samples	SW1353	GDF5	–	miR-449a upregulation could promote chondrocyte ECM degradation in OA.	[48]
OA	miR 221/483-5p	8 OA cartilage samples and 5 normal cartilage samples	–	RAF1, MAPK3, MAPK1, ELK1	MAPK, p27	miR-221/483-5p could modulate proliferation and matrix synthesis in chondrocytes.	[49]
OA	miR-30a	Sd rat/Human; 11 OA patients and 7 healthy donors	–	Sox9	–	miR-30a could promote ECM degradation in articular cartilage via the downregulation of Sox9.	[50]
OA	miR-19b-3p	12 OA articular cartilage samples and 6 Normal none-OA cartilages	ATDC5	IL-1β, GRK6	GRK6-NF-kB	Overexpression of miR-19b-3p could decrease IL-1β induced ECM degradation and inflammatory injury in chondrocytes by targeting GRK6.	[51]
OA	miR-140	SD rat/Human; 10 OA cartilage samples and 7 normal cartilage samples	–	MMP-13, ADAMTS-5	–	miR-140 could reduce the OA progression by modulating ECM homeostasis in rats.	[52]
OA	miR-634	15 OA cartilage samples and 6 normal cartilage samples	–	PIK3R1	PI3K/Akt/S6, PI3K/Akt/ mTOR/S6	Overexpression of miR-634 could suppress survival and matrix synthesis of human OA chondrocytes by targeting PIK3R1.	[53]
OA	miR-29a, miR-140	sucking mice	–	IL-1β, MMP13, TIMP1	–	miR-29a and miR-140 synergistically could suppress cell-matrix signaling by regulating the TIMP1and MMP13 protein level and the release of type II collagen.	[54]
OA	miR-107	45 pairs of OA cartilage tissues and non-OA patient tissues	C28/I2	PTEN	–	miR-107 could induce chondrocyte growth and ameliorated cartilage degradation by targeting PTEN in OA.	[55]
OA	miR-497-5p	12 OA patients and 10 normal human cartilages	–	IL-1β	Wnt/β-catenin	miR-497-5p could reduce IL-1β-induced cartilage matrix degradation in chondrocytes via the Wnt/β-catenin pathway.	[56]

(*continued on next page*)

Table 1 (*continued*)

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
OA	miR-140	9 OA cartilage samples	–	MMP-13, IL-1β, ADAMTS-5	ER/miR-140	miR-140 could affect IL-1β-induced ECM degradation in human chondrocytes.	[57]
OA	miR-30a	76 pairs of OA tissues and adjusted normal tissues	–	ADAMTS-5	IL-1β/AP-1/ ADAMTS-5	miR-30a could act as a pivotal regulator of cartilage homeostasis in OA.	[58]
OA	miR-26a	C57BL/6 mice	PECs	Cd200, Col10a1	–	Downregulation of miR-26a expression could contribute to ECM changes in cartilage diseases.	[59]
OA	miR-101	SD rat	–	Sox9, MMPs, TIMPs, TGFs, VEGF	–	Downregulation of miR-101 could prevent cartilage degradation by regulating ECM related genes in a rat model of osteoarthritis.	[60]
OA	miR-221-3p	86 OA cartilage samples and 59 normal cartilage samples	SW1353, C28I2	IL-1β, SDF1	SDF1/CXCR4	Downregulation of miR-221-3p could contribute to IL-1β-induced cartilage degradation by directly targeting the SDF1/CXCR4 signaling pathway.	[61]
Diffuse Cutaneous Systemic Sclerosis (dSSc)	miR-21, miR-29a	14 dSSc tissues and 12 normal healthy tissues	–	a-SMA	TGF-b	miR-21 and miR-29a could modulate the expression of collagen in dermal fibroblasts of patients with systemic sclerosis.	[62]
Diabetic Nephropathy (DN)	miR-206	–	MCs	–	ERK	Overexpression of miR-206 could decrease the proliferation of ECM cells and secretion and expression of ECM protein in DN.	[63]
DN	miR-214	SD rat, OVE26 mice	MCs, PTEC	PTEN, GSK-3	Akt/ mTORC1, PRAS40/ tuberin	Overexpression of miR-214 could decrease cell hypertrophy and expression of the matrix protein fibronectin in DN.	[64]
DN	miR-146a	C57BL/6 crossed with CBA/J mice	HRECs	IL-6, TNFα, IL1β	NF/κB	miR-146 upregulation could prevent structural and functional changes in the kidneys and retina of diabetic animals.	[20]
DN	miR-206	–	293 T, HK-2	HIF-1α	–	miR-206 could reduce cell proliferation and ECM accumulation in DN by targeting HIF-1α.	[19]
DN	miR-370	SD rat	–	CNPY1	–	overexpression of miR-370 could promote mesangial cell proliferation and ECM accumulation by suppressing CNPY1 in a rat model of DN.	[21]
DN	miR-26a	Male C57BL/6 J mice/ Human; 11 DN patients	–	TGF-β, CTGF	TGF-β/SMAD	miR-26a could inhibit TGF-β/CTGF-induced ECM accumulation in diabetic nephropathy both in humans and in mice.	[65]
DN	miR-382	male C57BL/6 mice	–	FoxO1	FoxO	Downregulation of miR- 382 could inhibit ECM accumulation via FoxO1 in mice with diabetic nephropathy.	[26]
Diabetes	miR-146a	B6 mice	HCMECs	IL6, TNF-α, IL-1β, MCP-1, Col1α1, Col4α1	TRAF6/ IRAK1/NF-kB	miR-146a overexpression could mediate fibrosis in the heart in diabetic condition.	[66]
–	miR-590	–	HUMSCs	Smad7	TGF-β	Overexpression of miR-590 could promote the proliferation of HUMSCs and induces ECM synthesis by targeting Smad7.	[52]
Liver Fibrosis	miR-185	C57BL/6 mice/Human; 10 liver fibrosis patients, 8 healthy	LX-2	CCl4, TGF-b1, RHEB, RICTOR	DNMT1/ PTEN/Akt	miR-185 could prevent liver fibrogenesis by inhibiting HSC activation via inhibition of RHEB and RICTOR.	[22]
Liver Fibrosis	miR-19b-3p	C57BL/6 mice	HSCs, KCs	SphK1	SphK1/CCL2/ CCR2	miR-19b-3p could reduce CCR2-mediated liver fibrosis.	[67]
Liver Fibrosis	miR-203	–	HSC-T6	SMAD3, COL1A1, COL3A1, α-SMA	TGF-β/Smad	miR-203 could prevent the synthesis and deposition of ECM components, including COL1A1, COL3A1, and α-SMA in liver fibrosis.	[23]
Liver Fibrosis	miR-30c, miR-193	Mouse/Human; 72 liver fibrosis patients and 19 matched healthy controls	GRX	TGF-β2, SNAIL1	TGF-β	miR-30c and miR-193 could affect ECM genes in liver fibrosis by TGF-β-dependent regulatory network.	[68]
Liver Fibrosis	miR-200a	SD rat	HSC-T6	TGF-β1	SIRT1/Notch1	miR-200a could control hepatic stellate cell activation and fibrosis via SIRT1/ Notch1 signal pathway.	[69]
Liver Fibrosis	miR-34a	SD rat	L-02, LX-2	SIRT1, α-SMA, TGF-β1	SIRT1/p53	Activation of the miR-34a/sirt1/p53 signaling pathway contributes to the progress of liver fibrosis via inducing apoptosis in hepatocytes but not in HSCs.	[70]
Liver Fibrosis	miR-29a	C57BL/6 J 6 mice	LX-2	COL1A1	PDGFC		[71]

(*continued on next page*)

Table 1 (*continued*)

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
						miR-29a could prevent the activation of human stellate cells and promote recovery from liver fibrosis in mice.	
–	miR-34	–	VSMCs, UVECs, HEK293 T	AAT	–	miR-34 could affect vascular diseases by regulating cell apoptosis and ECM degradation.	[72]
Fuchs Endothelial Corneal Dystrophy (FECD)	miR-29b	6 human corneas	iFECD	COL1A1, COL4A1, LAMC1	–	Overexpression of miR-29b could decrease ECM protein production in human corneal endothelial cells.	[73]
Intervertebral Disc Degeneration (IDD)	miR-486-5p	–	NP, HEK293	FOXO1, MMP-3/13, ADAMTS-4, ADAMTS-5	–	miR-486-5p could inhibit ECM degradation in NP cells by directly targeting FOXO1.	[74]
IDD	miR-21	65 IDD NP lumbar samples and 45 control lumbar NP tissue samples	NPCs	PTEN	PTEN/Akt/ mTOR	miR-21 could promote ECM degradation through inhibiting autophagy via the PTEN/Akt/mTOR signaling pathway in human degenerated NP cells.	[12]
IDD	miR-145	24 IDD NP lumbar samples and 5 control lumbar NP tissue samples	NPCs	ADAM17	–	miR-145 overexpression could decrease apoptosis and increases matrix synthesis in nucleus pulposus cells.	[75]
IDD	miR-140-5p	16 NP lumbar samples	HNPCs	CREB1	NF-kB	Overexpression of miR-140 could affect ECM degradation.	[76]
IDD	miR-483-3p	SD rat/Human; 24 cases of IDD tissues and 16 cases of spinal cord injury tissues as control.	NP	MMP, ADAMTS, COL2A1, CTNNB1, GSK3B	Wnt	miR-483-3p could affect ECM remodeling in IDD by targeting GSK3B.	[76]
IDD	miR-132	SD rat/Human; 27 IDD NP lumbar samples and 14 control lumbar NP tissue samples	NPCs	GDF5, MMP13, ADAMTS4	MAPK/ERK	miR-132 upregulation could promote matrix degradation in intervertebral disc degeneration	[77]
IDD	miR-34a	10 lumbar NP tissues from IDD patient and 4 lumbar NP from normal control patient	HEK293, NPCs	IL-1b, GDF5	–	Downregulation of miR-34a could reduce IL-1b-induced ECM degradation in nucleus pulposus by increasing GDF5 expression	[50]
IDD	miR-7	12 lumbar NP tissues from IDD patient and 8 lumbar NP from normal control patient	HEK293, NPCs	IL-1b, GDF5	MAPK	Overexpression of miR-7 could increase the IL-1b-induced ECM degeneration.	[13]
IDD	miR-494	20 IDD NP samples	NPCs	SOX9	NF/κB	miR-494 could promote apoptosis and ECM degradation in degenerative human nucleus pulposus cells.	[78]
IDD	miR-98	116 lumbar NP specimens and 102 normal healthy samples	NPCs	IL-6	IL-6/STAT3	Dysregulation of miR-98 could Contribute to ECM degradation by targeting the IL-6/STAT3 pathway in human IDD.	[79]
IDD	miR-499a-5p	19 IDD NP lumbar samples and 5 control lumbar NP tissue samples	NPCs	SOX4, TNF-α	–	miR-499a-5p could decrease the apoptosis of human nucleus pulposus cells and degradation of their extracellular matrix by targeting SOX4.	[80]
IDD	miR-30d	20 IDD NP lumbar samples and 10 control lumbar NP tissue samples	NPCs	SOX9	–	Downregulation of miR-30d could reduce ECM degradation of degenerative human nucleus pulposus cells by upregulating SOX9.	[81]
IDD	miR-155	C57 mice/Human; 10 IDD NP lumbar samples and 5 control lumbar NP samples	HEK 293, NPCs	MMP-16	–	Downregulation of miR-155 could lead to the dehydration and degeneration of discs.	[82]
–	miR-29	C57BL/6 mice, SD rat	HS895-SK	MP2, FSTL1, TGFB3	–	miR-29 could decrease ECM expression and Fibroplasia in the Skin.	[83]
Psoriasis	miR-4516	15 psoriasis cases	HaCaT, NHEK	FN1, ITGA9	FN1/ITGA9	Downregulation of miR-4516 in psoriatic skin could accelerate migration, resistance to apoptosis, and differentiation as seen in psoriasis lesional keratinocytes.	[84]
Aortic Aneurysm	miR-29b	–	ASMCs	PGE_2	–	miR-29b could affect the fibrotic ECM expression in the abdominal aortic aneurysm by targeting PGE_2.	[85]
Glioma	miR-150-5p, miR-133a	20 pairs of glioma brain samples and adjusted normal tissue samples	U87, U251, 293 T	MT1-MMP	–	miR-150-5p and miR-133a could suppress glioma cell proliferation and migration by targeting membrane-type-1 matrix metalloproteinase.	[86]
Rheumatoid Arthritis (RA)	miR-124	80 RA patients and 32 control subjects	–	MMP-3	–	Downregulation of miR-124 in RA patients could affect MMP-3 levels and extracellular matrix remodeling, which is associated with the age of RA onset.	[87]
	miR-144	male miR-144 KO mice	–	Zeb1, LOX1	Zeb1/LOX1		[88]

(*continued on next page*)

Table 1 (*continued*)

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
Myocardial Infarction (MI)						Downregulation of miR-144 could interrupt ECM remodeling after MI by targeting the Zeb/LOX pathway.	
Bone Fracture	miR-214-5p	28 patients with a fracture and 6 healthy controls	Mc3T3-e1	coL4A1, coL-II, coL-X	–	Downregulation of miR-214-5p could promote cell survival and ECM formation by targeting coL4A1 in osteoblastic Mc3T3-e1 cells	[89]
Recessive Dystrophic Epidermolysis Bullosa (RDEB)	miR-29	C57Bl/6-TgH(*COL7A1*flNeo) 288LBT mice	HEK-293 T	COL7A1	TGF-β/Smad3/4	Downregulation of miR-29 in RDEB skin leads to an increase of pro-fibrotic extracellular matrix collagens.	[90]

1.4. miRNAs in the pathogenesis of airway disorders

Asthma has been associated with the remodeling of the airways by airway smooth muscle cells (ASMCs). miR-223 is among miRNAs whose up-regulation has resulted in the induction of a phenotypic shift in these cells leading to the down-regulation of proteins contributing in the ECM including α-SMA (ACTA2), and type I and III collagens. Insulin-like growth factor-1 receptor (IGF-1R) has been identified as the target of miR-223 which results in the phenotypic shift of ASMCs. Suppression of IGF-1R by miR-223 deceases AKT1 levels in ASMCs. Therefore, miR-223 inhibits the fibrotic phenotypes of ASMCs through the PI3K/Akt axis and IGF-1R [14]. Expression of miR-181a is enhanced in TGF-β1-induced airway smooth muscle cells. This miRNA has been shown to suppress cell proliferation, migration, and over-production of ECM. Mechanistically, miR-181a participates in this process through targeting PTEN. Thus, the effects of TGF-β1 in the induction of airway smooth muscle cell proliferation and airway remodeling are exerted through the miR-181a/PTEN axis and the subsequent activation of the Akt/mTOR pathway [15].

1.5. miRNAs in the pathogenesis of osteoarthritis (OA)

OA, as the most frequent degenerative disorder in the joints, is associated with the dysregulation of a number of miRNAs, including miR-137 whose expression in the chondrocytes is inhibited by IL-1β. The expression of miR-137 is decreased in OA patients compared with controls [16]. Functional studies have verified the binding of miR-137 with the 3' UTR of ADAMTS-5. Consistently, expression of ADAMTS-5 is higher in OA cases compared with controls. Up-regulation of miR-137 inhibits cell growth, ECM destruction, and inflammatory reactions in chondrocytes [16].

Fig. 1 shows the contribution of some miRNAs in the degradation of ECM in the context of OA.

1.6. miRNAs in the pathogenesis of diabetic nephropathy

Several miRNAs are involved in the pathogenic events in ECM in the context of diabetic nephropathy. In vitro studies have shown the role of miR-206 in the suppression of cell proliferation and ECM buildup through targeting HIF-1α in glomerular mesangial cells exposed to high concentrations of glucose. Yet, they demonstrated down-regulation of this miRNA in these cells following such exposure [19]. Moreover, in vivo animal studies have verified the role of miR-146a in the regulation of the glucose-induced upsurge in inflammatory cytokines and ECM proteins and are implicated in both diabetic retinopathy and nephropathy [20]. Experiments in model of diabetic nephropathy have shown over-expression of miR-370, fibronectin, type I and IV collagen, and plasminogen activator inhibitor-1 (PAI-1) while decrease in CNPY1 levels. Further functional experiments have validated the role of miR-370 in the enhancement of mesangial cell proliferation and ECM accretion through the suppression of CNPY1 [21].

Table 2
Role of ECM-associated miRNAs in cancer.

Disease	microRNA	Animal/human; numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
Breast Cancer (BC)	miR-200s	75 pairs of BC tissues and adjacent normal mammary tissues	CAFs, NFs, GES	Fli-1, TCF12	–	miR-200 s could affect BC cell invasion through ECM remodeling.	[92]
BC	miR-203	Robo1 mice/Human; 142 BC tissue sample	MDA–MB-231, HME50, NMuMG, MECs	ROBO1	ROBO1/Rac/ FAK, SLIT2/ ROBO1	Downregulation of miR-203 could regulate cell shape and matrix adhesion through ROBO1/Rac/FAK in BC.	[93]
BC	miR-106a/ b	–	MCF-7, MDA-231, SKBR3, SUM102, ZR75B, BT474, MCF10A, 1068SK	EMMPRIN, STAT3, HIF-1α	EMMPRIN/ STAT3	Downregulation of miR-106a/b could affect BC stem-like cell properties via interaction with fibroblasts through stat3 and hif-1α	[94]
Gastric Cancer (GC)	miR-92a	male BALB/C nude mice/ Human; 74 pairs of GC and adjacent normal specimens	BGC-823, MKN-45, MGC-803, SGC-7901	ECM1	–	Downregulation of miR-92a could facilitate the effect of ECM1 which promotes gastric cancer cell metastasis in cell migration assays by facilitating the expression of proteins involved in epithelial-mesenchymal transition (EMT).	[95]
Non-Small Cell Lung Carcinoma (NSCLC)	miR-17, miR-20a	47 pairs of NSCLC tumor lung tissue samples and normal-looking neighboring tissue (NLNT)	–	MMP2, TIMP3	–	miR-17 and miR-20a could influence ECM remodeling at a distance from the center of the lesion.	[96]
Colorectal Cancer (CRC)	miR-200b-3p	50 pairs of CRC samples and adjacent tissues	HCT116, NCM460, HEK293, SW-60	MAGP2	Notch	miR-200b-3p by targeting MAGP2 could be involved in CRC progression.	[97]

Table 3
Association between ECM-associated miRNAs and survival of affected individuals/ animals (OS: overall survival).

Sample number	Kaplan-Meier analysis	Ref
10 liver fibrosis patients, 8 healthy persons	Low expression of miR-185 was associated with poor OS rates.	[22]
50 pairs of colorectal cancer samples and adjacent tissues	Low expression of miR-200b-3p was associated with better OS rates.	[97]
75 pairs of breast tumor tissues and adjacent normal mammary tissues	Overexpression of miR-200 s was associated with poor OS rates.	[92]
Mouse/Human; 142 breast cancer tissue samples	Low expression of miR-203 was associated with better OS rates.	[93]
Mouse/Human; 74 pairs of gastric cancer and adjacent normal specimens	Low expression of miR-92a was associated with better OS rates.	[95]

1.7. miRNAs in the pathogenesis of liver fibrosis

Liver fibrosis is another example of an ECM-associated disorder that is associated with the activity of a number of miRNAs. Assessment of the role of miR-185 liver fibrosis identified decreased plasma levels of miR-185 in hepatitis B virus-related liver fibrosis patients compared with healthy subjects [22]. Animal studies showed down-regulation of this miRNA in CCl4-induced fibrotic liver tissues and TGF-β1-activated hepatic stellate cells, which was accompanied by up-regulation of RHEB and RICTOR. Mechanistically, miR-185 was shown to directly suppress the expression of these genes, thus preventing liver fibrosis [22]. miR-203 silencing has been shown to enhance proliferation of hepatic stellate cells, while its up-regulation has been shown to inhibit the proliferative aptitude of these cells. Besides, SMAD3 has been identified as a direct target of miR-203. miR-203 might inhibit the production and deposition of ECM constituents such as COL1A1, COL3A1 and α-SMA, and suppress proliferation of hepatic stellate cells via a SMAD3-dependent route [23]. Table 1 shows the list of ECM-related miRNAs and their function in human/ animal disorders.

1.8. ECM-associated miRNAs and cancer

Anomalous ECM dynamic has been regarded as a prominent feature of cancer. Desmoplasia in the tumor tissues has been associated with high levels of deposition of ECM proteins, dysregulation of their structures and altered pattern of post-translational modifications [91]. Numerous studies have reported aberrant expression of miRNAs in association with these abnormalities in ECM proteins (Table 2).

Expression of ECM-associated miRNAs is associated with the survival of affected individuals. Most of these studies have been conducted on cancer patients. For example, up-regulation of microfibril-associated glycoprotein 2 in colorectal cancer clinical samples and cells has been shown to be associated with numerous clinicopathologic characteristics of patients, and its over-expression predicted poor survival of patients [97]. The expression of this glycoprotein has been shown to regulate at the post-transcriptional level by miR-200b-3p. Therefore, the low expression of this miRNA has been suggested as an indicator of poor survival of patients with colorectal cancer [97]. As another example, downregulation of miR-200 s in normal fibroblasts led to the induction of features of activated cancer-associated fibroblasts (CAFs) in breast cancer tissues, such as enhanced migration and invasion. Forced expression of this miRNA in CAFs restored the phenotype of normal fibroblasts in these cells. miR-200 s has been shown to control CAF activation through modulation of expression of Fli-1 and TCF12. This miRNA has an additional effect on the enhancement of expression of fibronectin and lysyl oxidase. Finally, over-expression of miRNA-200 s targets Fli-1 and TCF12 in activated normal fibroblasts, and in breast cancer, the stromal milieu is associated with poor survival of breast cancer patients [92]. Table 3 shows the results of studies that assessed the association between ECM-associated miRNAs and survival of affected individuals/ animals.

1.9. LncRNAs and ECM

LncRNAs have been shown to regulate the expression of several ECM-associated molecules, thus being implicated in the pathogenesis of ECM-related disorders.

1.10. LncRNAs and glaucoma

Induction of apoptosis in human trabecular meshwork cells (HTMCs) and extreme accumulation of ECM constituents contribute to the pathogenesis of open-angle glaucoma. Assessment of the role of lncRNAs in HTMCs under oxidative stress conditions revealed altered expression of several TGF-β-associated lncRNAs and mRNAs [98,99]. Further investigation found that the lncRNA lnc-TGFβ2-AS1 led to increased ECM construction through modulation of TGF-β2 in HTMCs [98]. In addition, lncRNA-RP11-820 has regulatory functions in ECM synthesis in HTMCs. Expression of this lncRNA has been increased under oxidative stress in these cells. Functionally, lncRNA-RP11-820 binds with miR-3178, thus regulating MYOD1 levels. MYOD1 can induce ECM genes in HTMCs in coordination with STAT3 [100].

1.11. LncRNAs in cardiac tissue remodeling

In a mechanistic study, the lncRNA SRA1 was found to play a role in the stimulation of cardiac myofibroblasts [101]. The investigators showed up-regulation of SRA1 in an animal model of cardiac fibrosis and that SRA1 silenced suppressed cell proliferation, myofibroblast transformation, and collagen synthesis of cardiac myofibroblasts. Mechanistically, SRA1 was shown to target miR-148b in cardiac myofibroblasts [101]. MIAT has been shown to be involved in the induction of fibrosis in hypertrophic cardiomyopathy through suppression of expression of miR-29a. Both MIAT and miR-29a could predict the prognosis of patients with hypertrophic cardiomyopathy [102].

1.12. LncRNAs in diabetic nephropathy

Expression of MALAT1 has been increased while miR-145 has been decreased in kidney tissues of db/db mice. Moreover, hyperglycemia has been shown to increase the level of MALAT1 yet reduced miR-145 levels in a normal proximal tubular cell line. MALAT1 and miR-145 control high glucose-induced EMT and fibrosis. Functionally, MALAT1 acts as a sponge for miR-145 to up-regulate expression of ZEB2, thus activating inducing EMT and fibrosis [103]. Besides, LINC00968 knock down has suppressed secretion of ECM proteins and mesangial cells proliferation through the EZH2/p21 axis [104].

1.13. LncRNAs and OA and osteochondropathy

Wang et al. showed up-regulation of XIST in OA samples and articular chondrocytes extracted from OA tissues and IL-1β-exposed cells. XIST silencing was found to inhibit the destruction of the ECM via sponging miR-1277-5p. Experiments in an animal model of OA confirmed the protective role of XIST silencing against ECM degradation [102]. In addition, overexpression of FOXD2-AS1 by targeting miR-27a-3p could induce ECM degradation in chondrocytes [105]. LncRNAs are also implicated in the pathogenesis of Kashin-Beck disease, which is a deformative, endemic osteochondropathy. Using a microarray-based approach, differential expression of approximately 1000 lncRNAs was detected in KBD chondrocytes versus normal chondrocytes [106]. Co-expression and pathway analyses revealed that 34 mRNAs and 55 co-expressed lncRNAs organize a network that regulates the ECM [106].

Table 4
List and function of ECM-related lncRNAs in human/ animal disorders.

Cancer type	lncRNA	Animal/human; Numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
Glaucoma	TGFβ2-AS1	–	HTMCs	TGF-β2, SMAD2, SMAD3	TGF-β	The expression of ENST00000414452 (TGFβ2-AS1) was increased in HTMCs when treated with H_2O_2. TGFβ2-AS1 via targeting TGF-β2 could promote ECM production in human trabecular meshwork cells.	[98]
Glaucoma	RP11-820	–	HTMCs	miR-3178, MYOD1, STAT3, Coll-I, Fibronectin	–	RP11-820 via regulating miR-3178/MYOD1 axis could promote ECM production in human trabecular meshwork cells.	[100]
Cardiac Fibrosis (CF)	SRA1	SD rats	Cardiac myofibroblasts	miR-148b	–	ββ by competitively binding miR-148b could promote the activation of cardiac myofibroblasts	[101]
CF	n379519	SD rat	Cardiac myofibroblasts	miR-30, Coll-I/III	–	n379519 by targeting miR-30 could promote cardiac fibrosis in post-infarct myocardium.	[109]
CF	GAS5	Male C57BL/6 mice	–	PTEN, MMP-2, Coll-I, α-SMA	–	Overexpression of GAS5 via regulating the PTEN/MMP-2 signal pathway could attenuate cardiac fibrosis in mice.	[110]
CF	RMRP	SD rat	Cardiac myofibroblasts	miR-613, α-SMA, Coll-I	–	Upregulation of RMRP by regulating miR-613 could promote the activation of cardiac fibroblasts.	[111]
CF	PFL	C57BL/6 mice	Cardiac myofibroblasts	let-7d, CTGF, Fibronectin-1, COL1A1, COL3A1	–	PFL by targeting let-7d could contribute to cardiac fibrosis.	[112]
CF	GAS5	C57BL/6 mice	–	PTEN, MMP-2, Coll-I, α-SMA	–	Overexpression of GAS5 via regulating the PTEN/MMP-2 signal pathway could attenuate cardiac fibrosis in mice.	[110]
CF	GAS5	SD rat	Cardiac myofibroblasts	COL1A1, α-SMA, miR-21	PTEN/ MMP-2	GAS5 by targeting miR-21 via the PTEN/MMP-2 signaling pathway could control cardiac fibroblast activation and fibrosis.	[113]
Osteoarthritis (OA)	TUG1	Cartilage tissues from patients with OA (n = 15) and patients without OA (n = 15)	Chondrocyte	miR-195, MMP-13, Coll-II, Aggrecan	–	TUG1 via the miR-195/MMP-13 axis could promote OA-induced degradation of chondrocyte ECM.	[114]
OA	TM1P3	45 pairs of RF and adjacent normal control tissues	Chondrocyte	miR-22, ALK1, MMP13,SMAD1/ 5	TGF-β	TM1P3 via the miR-22/MMP13/ TGF-β axis is involved in the degradation of chondrocyte ECM.	[115]
OA	FAS-AS1	Cartilage tissues from patients with OA (n = 20) and patients without OA (n = 20)	Chondrocyte	MMP1/13, COL2A1	–	FAS-AS1 could promote the degradation of ECM of cartilage in OA.	[116]
OA	PART1	Cartilage tissues from patients with OA (n = 35) and patients without OA (n = 15)	Chondrocyte	miR-373-3p, SOX4, MMP13, Coll-II, Aggrecan	–	PART1 via regulating the miR-373-3p/SOX4 axis could modulate chondrocyte proliferation and ECM degradation in OA.	[117]
OA	XIST	Samples of cartilage collected from non-OA (n = 20) and OA (n = 40)	Chondrocyte	miR-1277-5p, MMP-13, ADAMTS5	–	XIST by targeting miR-1277-5p could promote ECM degradation in OA.	[102]
OA	CIR	Samples of cartilage collected from non-OA (n = 8) and OA (n = 30)	Chondrocyte	MMP-13, miR-27	–	CIR by targeting miR-27b could promote chondrocyte ECM degradation in OA.	[47]
OA	FOXD2-AS1	Samples of cartilage collected from non-OA (n = 35) and OA (n = 35)	C28/I2	miR-27a-3p, TLR4, Coll-II, Aggrecan, MMP-13	–	Overexpression of FOXD2-AS1 by targeting miR-27a-3p could induce ECM degradation in chondrocytes.	[105]
OA	MALAT1	Samples of cartilage collected from non-OA (n = 11) and OA (n = 26)	Chondrocyte	miR-145, COL2A1, ADAMTS5, Aggrecan	–	MALAT1 by miR-145/ADAMTS5 could adjust IL-1β-Induced chondrocytes viability and cartilage ECM degradation in Human OA.	[118]
OA	MEG3	Mal SD rat	Chondrocyte	MMP-13, ADAMTS-5,		MEG3 by targeting miR-93/ TGFBR2 Axis could inhibit the	[117]

(*continued on next page*)

Table 4 (*continued*)

Cancer type	lncRNA	Animal/human; Numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
				COL2A1, miR-93, TGFBR2		degradation of the ECM of chondrocytes in OA.	
Diabetic Nephropathy (DN)	CDKN2B-AS1	24 patients with DN and 20 diabetes patients without DN	HGMC	miR-424-5p, HMGA2	PI3/Akt	Silencing of CDKN2B-AS1 via the miR-424-5p/HMGA2 axis could repress proliferation and ECM accumulation.	[119]
DN	NEAT1	Male SD rat	Mesangial	miR-27b-3p, ZEB1, ASK1, Fibronectin, TGF-β1	–	Overexpression of NEAT1 by targeting miR-27b-3p and ZEB1 could promote ECM accumulation and EMT in diabetic nephropathy.	[120]
DN	NR_033515	Normal patient serum (n = 111) and DN patient serum (n = 111)	Mesangial, 293 T	E-cadherin, p38, Vimentin, ASK1, α-SMA, miR-743b-5p, Fibronectin	–	NR_033515 by targeting miR-743b-5p could promote proliferation and fibrogenesis in DN.	[121]
DN	MALAT1	db/db mice	HK-2, 293 T	E-cadherin, α-SMA, ZEB2, miR-145	–	MALAT1 via targeting the miR-145/ZEB2 axis could facilitate high glucose (HG) induced fibrosis.	[103]
DN	PVT1	db/db mice	Mesangial	miR-93-5p, N-Cadherin, Vimentin, Coll-IV, E-cadherin, Fibronectin, CyclinD1, CDK4	PI3K/Akt/ mTOR	Silencing of PVT1 by targeting miR-93-5p via PI3K/Akt/mTOR pathway could inhibit fibrosis of HG-induced mouse mesangial cells.	[122]
DN	Dlx6os1	–	MMCs	Fibronectin, Coll-I	–	Inhibition of Dlx6os1 could decrease cell proliferation and fibrosis in DN.	[123]
DN	LINC00968	C57BL/KsJ-db/db mice	Mesangial	EZH2	p21	Silencing of LINC00968 via EZH2/p21 axis could inhibit the ECM proteins secretion and proliferation in mesangial cells.	[104]
DN	Blnc1	SD rat/ human; 30 pairs of serum samples from DN patients, and normal patients	HK-2	NRF2/HO-1, PTEN, Fibronectin, Coll-I/IV	NF-kB	Blnc1 via NRF2/HO-1 and NF-kB pathways could attenuate renal fibrosis.	[124]
DN	H19	–	SV40-MES-13, mesangial	miR-143-3p, TGF-β1	–	Metformin by regulating the H19/miR-143-3p/TGF-b1 axis could inhibit ECM accumulation of mesangial cells in DN.	[122]
DN	Arid2-IR	Male C57BL/6 J mice	Mesangial	Col1A1, α-SMA,	–	Early growth response protein 1 (Egr1) by upregulating Arid2-IR could promote ECM production in diabetic kidney disease.	[125]
DN	CYP4B1-PS1-001	C57BL/KsJ-db/db mice	Mesangial, 293 T, HK-2	Fibronectin, Coll-I	–	CYP4B1-PS1-001 could regulate proliferation and fibrosis in DN.	[126]
DN	TGU1	C57BL/KsJ-db/db mice	Mesangial	PPARγ, PAI-1, TGF-β1, miR-377, fibronectin, Coll-IV	–	TGU1 via mediating miR-377/ PPARγ axis could alleviate ECM accumulation in DN.	[127]
DN	ZEB1-AS1	db/db mice/human; The DN renal tissues from 26 DN patients and normal tissues from 10 patients with kidney carcinoma without diabetes	HK-2	miR-217, MAFB, Coll-I/IV, α-SMA	–	ZEB1-AS1 by regulating the miR-217/MAFB axis could inhibit renal fibrosis in DN.	[128]
DN	CASC2	Serum samples from 2 DN patients and 50 healthy volunteers	HMC	miR-133b, FOXP1, Coll-IV, Fibronectin	–	CASC2 via miR-133b/FOXP1 axis could regulate high glucose-induced proliferation and ECM accumulation of human mesangial cells	[129]
Intervertebral Disc Degeneration (IDD)	FAM83H-AS1	Nondegenerated intervertebral disc (IVD, n = 5) tissues and degenerative IVD (n = 30) samples	NP	Col-II, MMP-3/13, Coll-IV, Fibronectin	Notch1	Overexpression of FAM83H-AS1 by targeting Notch1 could induce nucleus pulposus cell growth and modulate ECM expression.	[130]
IDD	TUG1	10 degenerative tissues and 10 control NP tissues	NP	Coll-II, miR-26a, HMGB1	NF-kB, p65	TUG1 via modulating miR-26a/ HMGB1 axis and regulating NF-kB activation could promote ECM degradation in IDD patients.	[131]
IDD	HOTAIR	Male SD rat/human; IVD tissue samples from patients with lumbar disc herniation (n = 30) and	NP	ULK1, MMP3/13, ADAMT4/5	AMPK/ mTOR	HOTAIR via regulating the AMPK/mTOR/ULK1 pathway could stimulate ECM catabolism.	[132]

(*continued on next page*)

Table 4 (*continued*)

Cancer type	lncRNA	Animal/human; Numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
		idiopathic scoliosis (n = 10)					
IDD	RP11-296A18.3	36 degenerative tissues and 30 control NP tissues	NP	MMP-13, Coll-I, miR-138, HIF1A	–	RP11-296A18.3 via the miR-138/HIF1A axis could regulate the proliferation ECM synthesis of NP cells.	[133]
IDD	NEAT1	10 degenerative tissues and 6 control NP tissues	NP	ADAMTS-4, Aggrecan, MMP-13, Coll-II,	ERK/ MAPK, p21, p53,	NEAT1 could contribute to ECM degradation in degenerative human NP cells.	[134]
Keloid	H19	keloid tissues (n = 80), normal skin tissues (n = 91), normal fibrous tissues (n = 63)	Fibroblast	miR-29a, COL1A1, E-cadherin, Fibronectin, Vimentin	–	H19/miR-29a axis through acting upon COL1A1 could affect the viability and apoptosis of keloid fibroblasts.	[135]
Keloid	ATB	Keloid tissues and paired normal skin tissue samples from 57 patients	Fibroblast	TGF-β2, miR-200c, ZNF217	–	Knockdown of ATB by targeting ZNF217 via miR-200c could suppress the autocrine secretion of TGF-β2 in keloid fibroblasts	[136]
Skin Fibrosis	GAS5	C57BL/6 J mice	NIH-3T3, fibroblast	Col1A, α-SMA	SMAD-3	GAS5 via inhibiting the SMAD-3 pathway could attenuate fibroblast activation.	[137]
Renal Fibrosis (RF)	HOTAIR	Male SD rat	HK-2	miR-124, Fibronectin, E-cadherin	Notch1/ JAG1	Silencing of HOTAIR by upregulating miR-124 and blocking Notch1 could alleviate renal interstitial fibrosis.	[138]
RF	ENST00000453774.1	C57BL/6 J mice/ human; 28 pairs of RF and adjacent normal control tissues	HK-2	NQO-1 HO-1	Nrf2-keap1	LncRNA 74.1 downregulated in the TGF-β1 (5 ng/mL)-induced HK-2 cells. Overexpression of lncRNA 74.1 via the Nrf2 axis could ameliorate renal fibrosis and relieve ECM.	[139]
RF	ZEB1-AS1	db/db and WT mice/ human; kidney biopsy samples from patients with DN (n = 8) and minimal change disease (n = 8)	HK-2	Coll-I/IV, Fibronectin, α-SMA	p53	ZEB1-AS1 via p53 could associate with renal fibrosis in human DN.	[140]
Thermal Injury	XIST	Patients with deep partial-thickness burn (n = 25) and normal skin tissues (n = 25)	HSF	miR-29b-3p, COL1A1, α-SMA	–	XIST by targeting miR-29b-3p/ COL1A1 could promote ECM synthesis and proliferation in human skin fibroblasts after thermal injury.	[141]
Chronic Kidney Disease (CKD)	MALAT1	Male C57BL/6 J mice /human; renal fibrotic tissues from patients with obstructive nephropathy (ON, n = 20) and patients without NO (n = 20)	HK-2	miR-145, FAK, E-cadherin, α-SMA, ZO1, N-cadherin	–	m^6A-induced MALAT1 via the miR-145/FAK pathway could aggravate renal fibrogenesis in ON.	[142]
Alcoholic Liver Disease (ALD)	Gm5091	Male C57BL/6 J mice	HSC	α-SMA, Coll-I, miR-27b/23b/24	–	Gm5091 by sponging miR-27b/ 23b/24 could alleviate ALD in mice.	[143]
Hepatic Fibrosis	GAS5	SD rat	HSCs	PTEN, miR-23a, E-cadherin, α-SMA, Coll-I	PI3K/Akt	GAS5 by targeting miR-23a via the PTEN/PI3K/Akt pathway could restrain CCl_4-induced hepatic fibrosis.	[144]
Hepatic Fibrosis	ANRIL	SD rat	HSC-T6	Col1A1, α-SMA, DNMT3A	–	Silencing of ANRIL via activating the AMPK pathway could enhance liver fibrosis.	[145]
Hepatic Fibrosis	ATB	18 HCV-infected patients with liver fibrosis and 6 matched healthy subjects	HSCs, LX-2	Col1A1, miR-200a, α-SMA,	β-catenin	ATB via the miR-200a/β-catenin could contribute to the development of liver fibrosis in HCV patients.	[146]
Idiopathic Pulmonary Fibrosis (IPF)	PFAL	C57BL/6 mice	Fibroblast	CTGF, miR-18a, Col1A1, Col3A1	–	PFAL by regulating the miR-18a could be involved in pulmonary fibrosis.	[147]
IPF	PFAR	Male C57BL/6 mice	Fibroblast	miR-15a, α-SMA, Coll-I/III	–	Silencing of PFAR by targeting miR-15a could attenuate TGF-β1 induced fibrogenesis in primary lung fibroblasts.	[148]
IPF	H19	Male C57BL/6 mice	MRC-5, 293 T	miR-196a, COL1A1, α-SMA	–	H19 by regulating the miR-196a/ COL1A1 axis could mediate pulmonary fibrosis.	[149]
IPF	PFAR	C57BL/6 mice	Fibroblast	miR-138, Fibronectin, Col1A1, Col3A1	YAP1-Twist	PFAR by targeting miR-138 to regulate the YAP1-Twist axis could promote lung fibroblast activation and fibrosis.	[150]

(*continued on next page*)

Table 4 (*continued*)

Cancer type	lncRNA	Animal/human; Numbers of clinical samples	Assessed cell line	Targets/ Regulators	Signaling Pathways	Function	Ref
IPF	ZEB1-AS1	SD rat	RLE-6TN	miR-141-3p, ZEB1, Coll-I, Fibronectin-1,	–	ZEB1-AS1 via the ZEB1/miR-141-3p axis could promote pulmonary fibrosis.	[151]
Pulmonary Fibrosis (PF)	H19	Lung samples from PF patients (n = 15) and normal lung (n = 15)	A549, HBE	miR-140, Coll-I/ III	TGF-β/Smad3	Knockdown of H19 by regulating miR-140 via the TGF-β/Smad3 pathway could suppress the progress of pulmonary fibrosis.	[152]
PF	CHRF	Male C57BL/6 mice	RAW 264.7, NIH/3T3, THP-1, MRC-5	miR-489, MyD88, α-SMA, E-cadherin, Vimentin	Smad3	CHRF via miR-489/MyD88/ Smad3 axis could inhibit silica-induced pulmonary fibrosis.	[153]
PF	XIST	C57BL/6 mice	IMR-90, NIH-3T3	miR-139, α-SMA, Coll-I	β-catenin	XIST via miR-139/β-catenin axis could regulate bleomycin-induced ECM and pulmonary fibrosis.	[154]
Hypertrophic Scar (HS)	AC067945.2	15 HS tissues and their adjacent normal skin (NS)	NSF	COL1A1, COL1A2, COL3A1, α-SMA,	VEGF, Wnt	Overexpression of AC067945.2 via VEGF and Wnt pathways could downregulate collagen expression in skin fibroblasts.	[155]
Hypertrophic Cardiomyopathy (HCM)	MIAT	69 patients with HCM including a fibrosis (+) group (N = 30) and a fibrosis (−) group (N = 39)	A-204, H9C2	miR-29a-3p	–	MIAT by mediating the expression of miR-29a-3p could regulate fibrosis in HCM.	[102]
Ischemic Cardiomyopathy (ICM)	n379599, n342359	15 pairs of cardiac samples from patients with ICM and controls	–	PAI-1, Snai1, Snai2	TGF-β	lncRNAs could be associated with fibrosis in the hearts of ICM patients.	[156]
Kashin-Beck Disease (KBD)	ENST00000531202.1	Articular cartilage samples from KBD patients (n = 5) and normal donors (n = 5)	Chondrocyte	ADAMTS9, COL4A5, COL8A2, ADAMTS9	–	LncRNAs could be associated with ECM degradation in kashin-beck disease.	[106]
Kashin-Beck Disease (KBD)	TCONS_00015374	Articular cartilage samples from KBD patients (n = 5) and normal donors (n = 5)	Chondrocyte	ADAMTS9, COL4A5, COL8A2, ADAMTS9	–	LncRNAs could be associated with ECM degradation in Kashin-beck disease.	[106]
Abdominal Aortic Aneurysm (AAA)	PVT1	C57BL/6 J mice/ human: AAA patients (n = 20) and control subjects (n = 20)	VSMC	MMP-2, MMP-9, TIMP-1	–	Knockdown of PVT1 could inhibit ECM disruption in a murine abdominal aortic aneurysm model.	[157]
Atrial Fibrillation (AF)	PVT1	C57BL/6 J mice/ human; sinus rhythm (SR) group (n = 20) and AF group (n = 30)	Atrial fibroblast	miR-128-3p, Sp1, Coll-I/III	TGF-β1/ Smad	PVT1 via miR-128-3p/SP1/TGF-β1/Smad axis could regulate atrial fibrosis in AF.	[158]

1.14. ECM-associated lncRNAs and cancer

ECM constructs a physical hurdle whose incapacitation is an important event during cancer progression. A number of lncRNAs contribute in this process through destruction of the basal lamina and facilitating release of metastatic cells into blood or lymphatic vessels [107]. In addition, certain splice variants of lncRNAs may be involved in the pathogenesis of specific types of human malignancies. Expression of a novel isoform of HOTAIR is activated in Claudin-low breast cancer cells that are linked with ECM. This is mediated by the binding of BRD4 with a novel HOTAIR-N promoter. Activation of HOTAIR expression is necessary for the invasive growth of Claudin-low breast cancer cells in laminin-rich ECM-based three-dimensional cultures [106,108].

Table 4 shows the list of ECM-related lncRNAs and their function in human/ animal disorders.

1.15. ECM-associated lncRNAs and cancer

ECM constructs a physical hurdle whose incapacitation is an important event during cancer progression. A number of lncRNAs contribute in this process through destruction of the basal lamina and facilitating release of metastatic cells into blood or lymphatic vessels [107]. In addition, certain splice variants of lncRNAs may be involved in the pathogenesis of specific types of human malignancies. Expression of a novel isoform of HOTAIR is activated in Claudin-low breast cancer cells that are linked with ECM. This is mediated by the binding of BRD4 with a novel HOTAIR-N promoter. Activation of HOTAIR expression is necessary for the invasive growth of Claudin-low breast cancer cells in laminin-rich ECM-based three-dimensional cultures [106,108]. Table 5 shows the role of ECM-associated lncRNAs in cancer.

Table 5
The role of ECM-associated lncRNAs in cancer.

Cancer type	lncRNA	Assessed cell line	Targets/ Regulators	Function	Ref
Breast Cancer	HOTAIR-N	MDA-MB-231, Hs578T	BRD4	Induction of a novel isoform of HOTAIR by attaching to ECM could be involved in invasive growth of breast cancer cells.	[106]
Prostate Cancer	H19	P69	miR-675, TGFBI	H19/miR-675 axis suppresses metastatic ability of prostate carcinoma cells.	[159]

2. Discussion

ECM has a heterogeneous arrangement. Several proteins, glycosaminoglycans, proteoglycans and ECM remodeling enzymes contribute

in the construction of ECM. Notably, the composition of ECM and the related chemical modifications depend on the natute of tissue of origin [160]. Meanwhile, ncRNAs have specific signature in each tissue or physiopathological condition. Therefore, these transcripts might be involved in the tissue-/condition-specific modifications of ECM. NcRNAs contribute to several processes leading to the deposition of ECM components and the regulation of cell apoptosis/ survival in tissue microenvironments. Thus, ncRNAs are considered to contribute to the pathogenesis of diverse disorders ranging from cancer to degenerative disorders such as OA and IDD and fibrotic pathologies. In malignant conditions, ncRNAs regulate the activation of CAFs, which is an important process leading to tumor progression. Moreover, alternative ECM proteins that are originated from CAFs prompt ECM transformation and cancer cell invasion [92]. NF-kB, MAPK, STAT, AKT, TGF-β, and Notch pathways are among signaling cascades that are involved in the modulation of ECM by ncRNAs. Several growth factors and their receptors are also implicated in the modulation of ECM proteins by ncRNAs.

The role of lncRNAs in the modulation of ECM is exerted via the regulation of several targets, including miRNAs. Some examples of these lncRNA/ miRNA axes are RP11-820/ miR-3178, PFAR/ miR-15a, Gas5/ miR-23a, Gm5091/ miR-27b/23b/24, CASC2/ miR-133b, TUG1/ miR-377 and MIAT/ miR-29a-3p. Thus, the interaction between lncRNAs and miRNAs has a pivotal role in the modulation of ECM. Based on the extensive functions of ncRNAs in the pathogenesis of ECM-related disorders, these transcripts are regarded as promising therapeutic targets in a vast spectrum of human disorders. Although the extent to which lncRNAs can affect miRNAs is unclear, identification of lncRNA-miRNA competing endogenous networks is an important consideration for the selection of best therapeutic targets and implementation of targeted therapies. Some lncRNA/ miRNA axes have been successfully targetted for the treatment of ECM-related conditions. For instance, H19/miR-29a axis has been targeted for the treatment of keloids. Expression assays displayed over-expression of H19 while down-regulation of miR-29a in keloid tissues and fibroblasts compared with normal skin tissues and fibroblasts. H19 knockdown and miR-29a overexpression could inhibit metastasis and proliferation of fibroblasts [135]. Several animal studies have shown the efficacy of lncRNA or miRNA-targeted therapies in ECM-related pathological conditions. For instance, siRNA-mediated silencing of XIST has been shown to be effective in the prevention of OA in rat models [102]. Moreover, miR-101 silencing can inhibit cartilage destruction in a rat model of OA through modulation of ECM related genes [60]. However, the translation of these basic data into clinical application is a complicated process due to the presence of several safety and bioavailability concerns.

NcRNAs are effectively involved in the dynamics of ECM which in turn controls initiation, expansion and metastaisis of tumors. It is worth mentioning that idenification of the role of ncRNAs in the modification of ECM needs precise isolation of different cell populations and assessment of expression of these transcripts in each cell population in different pathological conditions. The role of ncRNAs in the modulation of tumor-stroma interaction is also exerted through relaese of cell-free particles such as exosomes. Therefore, assessment of expression of these transcripts in the exosomes is another approach that facilitates identification of the role of ncRNAs in this regard.

NcRNAs are also involved in the molecular mechanisms leading to the efficacy of prescribed medications for ECM-associated pathologies. For instance, metformin is an effective drug prescribed for diabetic nephropathy and has been shown to suppress ECM deposition, inflammatory responses, and proliferation of mesangial cells through modulation of the H19/miR-143-3p/TGF-β1 pathway [122].

Finally, ncRNAs can serve as diagnostic and prognostic markers in ECM-related pathologies. Notably, a number of lncRNAs and miRNAs that work together can be exploited to enhance diagnostic or prognostic accuracy. For instance, both MIAT and miR-29a have been shown to predict the prognosis of patients with hypertrophic cardiomyopathy [102]; thus, the combination of these markers might enhance the prognostic value. The prognostic role of a number of ECM-associated miRNAs has been evaluated in cancer patients. However, the diagnostic/ prognostic values of other ECM-associated ncRNAs have not been evaluated in other conditions. Thus, a potentially important future direction for research would be in the identification of ncRNA markers, particularly in peripheral blood or serum samples of patients to allow a non-invasive diagnosis of ECM-related pathologies.

Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgment

This study was financially supported by Shahid Beheshti University of Medical Sciences.

References

[1] Z.J. Rutnam, T.N. Wight, B.B. Yang, miRNAs regulate expression and function of extracellular matrix molecules, Matrix Biol. 32 (2) (2013) 74–85. PubMed PMID: 23159731. Epub 11/15. eng.
[2] E.P. Consortium, An integrated encyclopedia of DNA elements in the human genome, Nature 489 (7414) (2012) 57–74.
[3] G.M. Rubin, M.D. Yandell, J.R. Wortman, G.L. Gabor, C.R. Nelson, I.K. Hariharan, et al., Comparative genomics of the eukaryotes, Science 287 (5461) (2000) 2204–2215.
[4] S. Hombach, M. Kretz, Non-coding RNAs: classification, biology and functioning. Non-coding RNAs in Colorectal Cancer, Springer, 2016, pp. 3–17.
[5] T. Naganuma, T. Hirose, Paraspeckle formation during the biogenesis of long non-coding RNAs, RNA Biol. 10 (3) (2013) 456–461.
[6] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2) (2009) 215–233.
[7] G.M. Borchert, W. Lanier, B.L. Davidson, RNA polymerase III transcribes human microRNAs, Nat. Struct. Mol. Biol. 13 (12) (2006) 1097–1101.
[8] L.-A. MacFarlane, P. R Murphy, MicroRNA: biogenesis, function and role in cancer, Curr. Genomics 11 (7) (2010) 537–561.
[9] C. Zhang, Y. Zhang, H. Zhu, J. Hu, Z. Xie, MiR-34a/miR-93 target c-Ski to modulate the proliferaton of rat cardiac fibroblasts and extracellular matrix deposition in vivo and in vitro, Cell. Signal. 46 (June) (2018) 145–153. PubMed PMID: 29551367.
[10] E.L. Vegter, P. van der Meer, L.J. de Windt, Y.M. Pinto, A.A. Voors, MicroRNAs in heart failure: from biomarker to target for therapy, Eur. J. Heart Fail. 18 (5) (2016) 457–468.
[11] P. Rubis, J. Toton-Zuranska, S. Wisniowska-Smialek, K. Holcman, M. Kolton-Wroz, P. Wolkow, et al., Relations between circulating microRNAs (miR-21, miR-26, miR-29, miR-30 and miR-133a), extracellular matrix fibrosis and serum markers of fibrosis in dilated cardiomyopathy, Int. J. Cardiol. 231 (March 15) (2017) 201–206. PubMed PMID: 27889210.
[12] W.J. Wang, W. Yang, Z.H. Ouyang, J.B. Xue, X.L. Li, J. Zhang, et al., MiR-21 promotes ECM degradation through inhibiting autophagy via the PTEN/akt/mTOR signaling pathway in human degenerated NP cells, Biomed. Pharmacother. 99 (March) (2018) 725–734. PubMed PMID: 29710470.
[13] W. Liu, Y. Zhang, P. Xia, S. Li, X. Feng, Y. Gao, et al., MicroRNA-7 regulates IL-1beta-induced extracellular matrix degeneration by targeting GDF5 in human nucleus pulposus cells, Biomed. Pharmacother. 83 (October) (2016) 1414–1421. PubMed PMID: 27583982.
[14] D. Liu, J. Pan, D. Zhao, F. Liu, MicroRNA-223 inhibits deposition of the extracellular matrix by airway smooth muscle cells through targeting IGF-1R in the PI3K/Akt pathway, Am. J. Transl. Res. 10 (3) (2018) 744–752. PubMed PMID: 29636864. Pubmed Central PMCID: PMC5883115.
[15] X. Lv, Y. Li, Q. Gong, Z. Jiang, TGF-β1 induces airway smooth muscle cell proliferation and remodeling in asthmatic mice by up-regulating miR-181a and suppressing PTEN, Int. J. Clin. Exp. Pathol. 12 (1) (2019) 173–181. PubMed PMID: 31933731. eng.
[16] H. Zhang, L. Ji, Y. Yang, Y. Wei, X. Zhang, Y. Gang, et al., The therapeutic effects of treadmill exercise on osteoarthritis in rats by inhibiting the HDAC3/NF-KappaB pathway in vivo and in vitro, Front. Physiol. 10 (2019) 1060.
[17] Y. Zhang, G. Wang, L. Ma, C. Wang, L. Wang, Y. Guo, et al., miR-137 suppresses cell growth and extracellular matrixdegradation through regulating ADAMTS-5 in chondrocytes, Am. J. Transl. Res. 11 (11) (2019) 7027–7034. PubMed PMID: 31814906. Pubmed Central PMCID: PMC6895521.
[18] Q. Ji, X. Xu, Q. Zhang, L. Kang, Y. Xu, K. Zhang, et al., The IL-1β/AP-1/miR-30a/ADAMTS-5 axis regulates cartilage matrix degradation in human osteoarthritis, J. Mol. Med. 94 (7) (2016) 771–785.
[19] Y. Cao, X. Cao, L. Sun, Y. Li, miR-206 inhibits cell proliferation and extracellular matrix accumulation by targeting hypoxia-inducible factor 1-alpha (HIF-1alpha) in mesangial cells treated with high glucose, Med. Sci. Monit. 25 (December 27)

(2019) 10036–10044. PubMed PMID: 31880296. Pubmed Central PMCID: PMC6946049.
[20] S. Chen, B. Feng, A.A. Thomas, S. Chakrabarti, miR-146a regulates glucose induced upregulation of inflammatory cytokines extracellular matrix proteins in the retina and kidney in diabetes, PLoS One 12 (3) (2017) e0173918. PubMed PMID: 28301595. Pubmed Central PMCID: PMC5354466.
[21] Hu M.L. Yu FN, X.F. Wang, X.P. Li, B.H. Zhang, X.Q. Lu, et al., Effects of microRNA-370 on mesangial cell proliferation and extracellular matrix accumulation by binding to canopy 1 in a rat model of diabetic nephropathy, J. Cell. Physiol. 234 (May (5)) (2019) 6898–6907. PubMed PMID: 30317577.
[22] L. Zhou, S. Liu, M. Han, Y. Ma, S. Feng, J. Zhao, et al., miR-185 inhibits fibrogenic activation of hepatic stellate cells and prevents liver fibrosis, Mol. Ther. Nucleic Acids 10 (March 2) (2018) 91–102. PubMed PMID: 29499960. Pubmed Central PMCID: PMC5735261.
[23] D. Hu, Y. Hu, W. Xu, H. Yu, N. Yang, S. Ni, et al., miR203 inhibits the expression of collagenrelated genes and the proliferation of hepatic stellate cells through a SMAD3dependent mechanism, Mol. Med. Rep. 16 (August (2)) (2017) 1248–1254. PubMed PMID: 28586069. Pubmed Central PMCID: PMC5561992.
[24] P. Dong, W.J. Liu, Z.H. Wang, MiR-154 promotes myocardial fibrosis through beta-catenin signaling pathway, Eur. Rev. Med. Pharmacol. Sci. 22 (April (7)) (2018) 2052–2060. PubMed PMID: 29687862.
[25] L. Tao, Y. Bei, P. Chen, Z. Lei, S. Fu, H. Zhang, et al., Crucial role of miR-433 in regulating cardiac fibrosis, Theranostics 6 (12) (2016) 2068–2083. PubMed PMID: 27698941. Pubmed Central PMCID: PMC5039681.
[26] S. Wang, X. Wen, X.R. Han, Y.J. Wang, M. Shen, S.H. Fan, et al., Repression of microRNA-382 inhibits glomerular mesangial cell proliferation and extracellular matrix accumulation via FoxO1 in mice with diabetic nephropathy, Cell Prolif. 51 (October (5)) (2018) e12462. PubMed PMID: 29701296. Pubmed Central PMCID: PMC6528942.
[27] V. Nagpal, R. Rai, A.T. Place, S.B. Murphy, S.K. Verma, A.K. Ghosh, et al., MiR-125b is critical for fibroblast-to-myofibroblast transition and cardiac fibrosis, Circulation 133 (January 19 (3)) (2016) 291–301. PubMed PMID: 26585673. Pubmed Central PMCID: PMC5446084.
[28] M. Zou, F. Wang, R. Gao, J. Wu, Y. Ou, X. Chen, et al., Autophagy inhibition of hsa-miR-19a-3p/19b-3p by targeting TGF-beta R II during TGF-beta1-induced fibrogenesis in human cardiac fibroblasts, Sci. Rep. 6 (April 21) (2016) 24747. PubMed PMID: 27098600. Pubmed Central PMCID: PMC4838850.
[29] N. Duru, Y. Zhang, R. Gernapudi, B. Wolfson, P.K. Lo, Y. Yao, et al., Loss of miR-140 is a key risk factor for radiation-induced lung fibrosis through reprogramming fibroblasts and macrophages, Sci. Rep. 6 (December 20) (2016) 39572. PubMed PMID: 27996039. Pubmed Central PMCID: PMC5172237.
[30] Q. Wu, T. Xu, Y. Liu, Y. Li, J. Yuan, W. Yao, et al., miR-1224-5p mediates mitochondrial damage to affect silica-induced pulmonary fibrosis by targeting BECN1, Int. J. Mol. Sci. 18 (November (11)) (2017). PubMed PMID: 29112159. Pubmed Central PMCID: PMC5713326.
[31] J. Zhou, Q. Xu, Q. Zhang, Z. Wang, S. Guan, A novel molecular mechanism of microRNA-21 inducing pulmonary fibrosis and human pulmonary fibroblast extracellular matrix through transforming growth factor beta1-mediated SMADs activation, J. Cell. Biochem. 119 (September (9)) (2018) 7834–7843. PubMed PMID: 29943845.
[32] R. Guo, Y. Lv, Y. Ouyang, S. Liu, D. Li, The role of miR-497/EIF3A Axis in TGFbeta1-Induced epithelial-mesenchymal transition and extracellular matrix in rat alveolar epithelial cells and pulmonary fibroblasts, J. Cell. Biochem. 118 (October (10)) (2017) 3401–3408. PubMed PMID: 28322466.
[33] Y. Wang, J. Liu, J. Chen, T. Feng, Q. Guo, MiR-29 mediates TGFbeta 1-induced extracellular matrix synthesis through activation of Wnt/beta -catenin pathway in human pulmonary fibroblasts, Technol. Health Care 23 (Suppl 1) (2015) S119–25. PubMed PMID: 26410313.
[34] X. Lian, X. Chen, J. Sun, G. An, X. Li, Y. Wang, et al., MicroRNA-29b inhibits supernatants from silica-treated macrophages from inducing extracellular matrix synthesis in lung fibroblasts, Toxicol. Res. (Camb) 6 (November (6)) (2017) 878–888. PubMed PMID: 30090550. Pubmed Central PMCID: PMC6062342.
[35] W. Cheng, K. Yan, L.Y. Xie, F. Chen, H.C. Yu, Y.X. Huang, et al., MiR-143-3p controls TGF-beta1-induced cell proliferation and extracellular matrix production in airway smooth muscle via negative regulation of the nuclear factor of activated T cells 1, Mol. Immunol. 78 (October) (2016) 133–139. PubMed PMID: 27639060.
[36] Z. Yang, Z. Qu, M. Yi, Z. Lv, Y. Wang, Y. Shan, et al., MiR-204-5p inhibits transforming growth Factor-beta1-Induced proliferation and extracellular matrix production of airway smooth muscle cells by regulating Six1 in Asthma, Int. Arch. Allergy Immunol. 181 (4) (2020) 239–248. PubMed PMID: 31955160.
[37] K. Shi, X. Qiu, W. Zheng, D. Yan, W. Peng, MiR-203 regulates keloid fibroblast proliferation, invasion, and extracellular matrix expression by targeting EGR1 and FGF2, Biomed. Pharmacother. 108 (December) (2018) 1282–1288. PubMed PMID: 30372829.
[38] K. Xu, Z. Zhang, J. Qian, S. Wang, S. Yin, H. Xie, et al., LncRNA FOXD2-AS1 plays an oncogenic role in hepatocellular carcinoma through epigenetically silencing CDKN1B (p27) via EZH2, Exp. Cell Res. 380 (2) (2019) 198–204.
[39] G. Li, R. Zhou, Q. Zhang, B. Jiang, Q. Wu, C. Wang, Fibroproliferative effect of microRNA-21 in hypertrophic scar derived fibroblasts, Exp. Cell Res. 345 (July (1)) (2016) 93–99. PubMed PMID: 27207585.
[40] V. Miguel, O. Busnadiego, M. Fierro-Fernandez, S. Lamas, Protective role for miR-9-5p in the fibrogenic transformation of human dermal fibroblasts, Fibrogenesis Tissue Repair 9 (7) (2016). PubMed PMID: 27274768. Pubmed Central PMCID: PMC4891847.
[41] H. Wen, Y. Hu, L. Chen, L. Zhao, X. Yang, miR-338-5p targets epidermal growth factor-containing fibulin-like extracellular matrix protein 1 to inhibit the growth and invasion of trophoblast cells in selective intrauterine growth restriction, Reprod. Sci. 27 (June (6)) (2020) 1357–1364. PubMed PMID: 32056133. Pubmed Central PMCID: PMC7190678.
[42] N.E. Calabro, A. Barrett, A. Chamorro-Jorganes, S. Tam, N.J. Kristofik, H. Xing, et al., Thrombospondin-2 regulates extracellular matrix production, LOX levels, and cross-linking via downregulation of miR-29, Matrix Biol. 82 (September) (2019) 71–85. PubMed PMID: 30876926. Pubmed Central PMCID: PMC6710120.
[43] E.R. Cardozo, R. Foster, A.E. Karmon, A.E. Lee, L.W. Gatune, B.R. Rueda, et al., MicroRNA 21a-5p overexpression impacts mediators of extracellular matrix formation in uterine leiomyoma, Reprod. Biol. Endocrinol. 16 (May (1)) (2018) 46. PubMed PMID: 29747655. Pubmed Central PMCID: PMC5946472.
[44] L. Pitzler, M. Auler, K. Probst, C. Frie, V. Bergmeier, T. Holzer, et al., miR-126-3p promotes matrix-dependent perivascular cell attachment, migration and intercellular interaction, Stem Cells 34 (May (5)) (2016) 1297–1309. PubMed PMID: 26934179.
[45] T.D. Chuang, W.J. Pearce, O. Khorram, miR-29c induction contributes to downregulation of vascular extracellular matrix proteins by glucocorticoids, Am. J. Physiol. Cell Physiol. 309 (July (2)) (2015) C117–25. PubMed PMID: 26017148. Pubmed Central PMCID: PMC4504943.
[46] W. Shen, Y. Han, B. Huang, Y. Qi, L. Xu, R. Guo, et al., MicroRNA-483-3p inhibits extracellular matrix production by targeting Smad4 in human trabecular meshwork cells, Invest. Ophthalmol. Vis. Sci. 56 (December (13)) (2015) 8419–8427. PubMed PMID: 26747772.
[47] J. Guo, Q. Lin, Y. Shao, L. Rong, D. Zhang, miR-29b promotes skin wound healing and reduces excessive scar formation by inhibition of the TGF-beta1/Smad/CTGF signaling pathway, Can. J. Physiol. Pharmacol. 95 (April (4)) (2017) 437–442. PubMed PMID: 28092445.
[48] J. Wu, M. Zou, A. Ping, Z. Deng, L. Cai, MicroRNA-449a upregulation promotes chondrocyte extracellular matrix degradation in osteoarthritis, Biomed. Pharmacother. 105 (September) (2018) 940–946. PubMed PMID: 30021388.
[49] M. Yang, L. Zhang, G.J. Gibson, Chondrocyte miRNAs 221 and 483-5p respond to loss of matrix interaction by modulating proliferation and matrix synthesis, Connect. Tissue Res. 56 (June (3)) (2015) 236–243. PubMed PMID: 25738598.
[50] T. Chang, J. Xie, H. Li, D. Li, P. Liu, Y. Hu, MicroRNA-30a promotes extracellular matrix degradation in articular cartilage via downregulation of Sox9, Cell Prolif. 49 (April (2)) (2016) 207–218. PubMed PMID: 26969024. Pubmed Central PMCID: PMC6496402.
[51] L. Duan, D. Duan, W. Wei, Z. Sun, H. Xu, L. Guo, et al., MiR-19b-3p attenuates IL-1beta induced extracellular matrix degradation and inflammatory injury in chondrocytes by targeting GRK6, Mol. Cell. Biochem. 459 (September (1–2)) (2019) 205–214. PubMed PMID: 31227976.
[52] H.B. Si, Y. Zeng, S.Y. Liu, Z.K. Zhou, Y.N. Chen, J.Q. Cheng, et al., Intra-articular injection of microRNA-140 (miRNA-140) alleviates osteoarthritis (OA) progression by modulating extracellular matrix (ECM) homeostasis in rats, Osteoarthr. Cartil. 25 (October (10)) (2017) 1698–1707. PubMed PMID: 28647469.
[53] X. Cui, S. Wang, H. Cai, Y. Lin, X. Zheng, B. Zhang, et al., Overexpression of microRNA-634 suppresses survival and matrix synthesis of human osteoarthritis chondrocytes by targeting PIK3R1, Sci. Rep. 6 (March 14) (2016) 23117. PubMed PMID: 26972586. Pubmed Central PMCID: PMC4789801.
[54] X. Li, Z. Zhen, G. Tang, C. Zheng, G. Yang, MiR-29a and MiR-140 protect chondrocytes against the anti-proliferation and cell matrix signaling changes by IL-1beta, Mol. Cells 39 (February (2)) (2016) 103–110. PubMed PMID: 26608362. Pubmed Central PMCID: PMC4757797.
[55] F. Tian, J. Wang, Z. Zhang, J. Yang, miR-107 modulates chondrocyte proliferation, apoptosis, and extracellular matrix synthesis by targeting PTEN, Int. J. Clin. Exp. Pathol. 12 (2) (2019) 488–497. PubMed PMID: 31933853. Pubmed Central PMCID: PMC6945102.
[56] L. Hou, H. Shi, M. Wang, J. Liu, G. Liu, MicroRNA-497-5p attenuates IL-1beta-induced cartilage matrix degradation in chondrocytes via Wnt/beta-catenin signal pathway, Int. J. Clin. Exp. Pathol. 12 (8) (2019) 3108–3118. PubMed PMID: 31934153. Pubmed Central PMCID: PMC6949713.
[57] Y. Liang, L. Duan, J. Xiong, W. Zhu, Q. Liu, D. Wang, et al., E2 regulates MMP-13 via targeting miR-140 in IL-1beta-induced extracellular matrix degradation in human chondrocytes, Arthritis Res. Ther. 18 (May (1)) (2016) 105. PubMed PMID: 27165343. Pubmed Central PMCID: PMC4863330.
[58] Q. Ji, X. Xu, Q. Zhang, L. Kang, Y. Xu, K. Zhang, et al., The IL-1beta/AP-1/miR-30a/ADAMTS-5 axis regulates cartilage matrix degradation in human osteoarthritis, J. Mol. Med. 94 (July (7)) (2016) 771–785. PubMed PMID: 27067395.
[59] J. Etich, T. Holzer, L. Pitzler, B. Bluhm, B. Brachvogel, MiR-26a modulates extracellular matrix homeostasis in cartilage, Matrix Biol. 43 (April) (2015) 27–34. PubMed PMID: 25766405.
[60] L. Dai, X. Zhang, X. Hu, Q. Liu, Z. Man, H. Huang, et al., Silencing of miR-101 prevents cartilage degradation by regulating extracellular matrix-related genes in a rat model of osteoarthritis, Mol. Ther. 23 (August (8)) (2015) 1331–1340. PubMed PMID: 25921548. Pubmed Central PMCID: PMC4817865.
[61] X. Zheng, F.C. Zhao, Y. Pang, D.Y. Li, S.C. Yao, S.S. Sun, et al., Downregulation of miR-221-3p contributes to IL-1beta-induced cartilage degradation by directly targeting the SDF1/CXCR4 signaling pathway, J. Mol. Med. 95 (June (6)) (2017) 615–627. PubMed PMID: 28236026.
[62] S. Jafarinejad-Farsangi, F. Gharibdoost, A. Farazmand, H. Kavosi, A. Jamshidi, E. Karimizadeh, et al., MicroRNA-21 and microRNA-29a modulate the expression

of collagen in dermal fibroblasts of patients with systemic sclerosis, Autoimmunity 52 (May (3)) (2019) 108–116. PubMed PMID: 31155965.
[63] L. Juan, L. Changyan, G. Fang, miR-206 inhibits high glucose-induced cell proliferation and extracellular matrix accumulation in mice glomerular mesangial cells, Adv. Boil. Med. 3 (3) (2018) 41–55.
[64] A. Bera, F. Das, N. Ghosh-Choudhury, M.M. Mariappan, B.S. Kasinath, G. Ghosh Choudhury, Reciprocal regulation of miR-214 and PTEN by high glucose regulates renal glomerular mesangial and proximal tubular epithelial cell hypertrophy and matrix expansion, Am. J. Physiol. Cell Physiol. 313 (October (4)) (2017). C430–C47. PubMed PMID: 28701356. Pubmed Central PMCID: PMC5668576.
[65] K. Koga, H. Yokoi, K. Mori, M. Kasahara, T. Kuwabara, H. Imamaki, et al., MicroRNA-26a inhibits TGF-beta-induced extracellular matrix protein expression in podocytes by targeting CTGF and is downregulated in diabetic nephropathy, Diabetologia 58 (September (9)) (2015) 2169–2180. PubMed PMID: 26063197.
[66] B. Feng, S. Chen, A.D. Gordon, S. Chakrabarti, miR-146a mediates inflammatory changes and fibrosis in the heart in diabetes, J. Mol. Cell. Cardiol. 105 (April) (2017) 70–76. PubMed PMID: 28279663.
[67] T. Lan, C. Li, G. Yang, Y. Sun, L. Zhuang, Y. Ou, et al., Sphingosine kinase 1 promotes liver fibrosis by preventing miR-19b-3p-mediated inhibition of CCR2, Hepatology 68 (September (3)) (2018) 1070–1086. PubMed PMID: 29572892. Pubmed Central PMCID: PMC6174945.
[68] S. Roy, F. Benz, D. Vargas Cardenas, M. Vucur, J. Gautheron, A. Schneider, et al., miR-30c and miR-193 are a part of the TGF-beta-dependent regulatory network controlling extracellular matrix genes in liver fibrosis, J. Dig. Dis. 16 (September (9)) (2015) 513–524. PubMed PMID: 26120970.
[69] Y. Zhang, H.-H. Li, R. Yang, B.-J. Yang, Z.-Y. Gao, Association between circulating microRNA-208a and severity of coronary heart disease, Scand. J. Clin. Lab. Invest. 77 (5) (2017) 379–384.
[70] X.F. Tian, F.J. Ji, H.L. Zang, H. Cao, Activation of the miR-34a/SIRT1/p53 signaling pathway contributes to the progress of liver fibrosis via inducing apoptosis in hepatocytes but not in HSCs, PLoS One 11 (7) (2016), e0158657. PubMed PMID: 27387128. Pubmed Central PMCID: PMC4936740.
[71] Y. Matsumoto, S. Itami, M. Kuroda, K. Yoshizato, N. Kawada, Y. Murakami, MiR-29a assists in preventing the activation of human stellate cells and promotes recovery from liver fibrosis in mice, Mol. Ther. 24 (October (10)) (2016) 1848–1859. PubMed PMID: 27480597. Pubmed Central PMCID: PMC5112039.
[72] H. Wang, F. Wang, X. Wang, X. Wu, F. Xu, K. Wang, et al., Friend or foe: a cancer suppressor microRNA-34 potentially plays an adverse role in vascular diseases by regulating cell apoptosis and extracellular matrix degradation, Med. Sci. Monit. 25 (March 15) (2019) 1952–1959. PubMed PMID: 30873956. Pubmed Central PMCID: PMC6434609.
[73] T. Toyono, T. Usui, G. Villarreal Jr., L. Kallay, M. Matthaei, L.M. Vianna, et al., MicroRNA-29b overexpression decreases extracellular matrix mRNA and protein production in human Corneal Endothelial Cells, Cornea 35 (November (11)) (2016) 1466–1470. PubMed PMID: 27490049. Pubmed Central PMCID: PMC5067961.
[74] X. Chai, H. Si, J. Song, Y. Chong, J. Wang, G. Zhao, miR-486-5p inhibits inflammatory response, matrix degradation and apoptosis of nucleus pulposus cells through directly targeting FOXO1 in intervertebral disc degeneration, Cell. Physiol. Biochem. 52 (1) (2019) 109–118. PubMed PMID: 30790508.
[75] J. Zhou, J. Sun, D.Z. Markova, S. Li, C.K. Kepler, J. Hong, et al., MicroRNA-145 overexpression attenuates apoptosis and increases matrix synthesis in nucleus pulposus cells, Life Sci. 221 (March 15) (2019) 274–283. PubMed PMID: 30797016.
[76] S. Yang, L. Li, L. Zhu, C. Zhang, Z. Li, Y. Guo, et al., Bu-Shen-Huo-Xue-Fang modulates nucleus pulposus cell proliferation and extracellular matrix remodeling in intervertebral disk degeneration through miR-483 regulation of Wnt pathway, J. Cell. Biochem. 120 (December (12)) (2019) 19318–19329. PubMed PMID: 29393545.
[77] W. Liu, P. Xia, J. Feng, L. Kang, M. Huang, K. Wang, et al., MicroRNA-132 upregulation promotes matrix degradation in intervertebral disc degeneration, Exp. Cell Res. 359 (October (1)) (2017) 39–49. PubMed PMID: 28793234.
[78] L. Kang, C. Yang, Y. Song, K. Zhao, W. Liu, W. Hua, et al., MicroRNA-494 promotes apoptosis and extracellular matrix degradation in degenerative human nucleus pulposus cells, Oncotarget 8 (April (17)) (2017) 27868–27881. PubMed PMID: 28427186. Pubmed Central PMCID: PMC5438614.
[79] M.L. Ji, J. Lu, P.L. Shi, X.J. Zhang, S.Z. Wang, Q. Chang, et al., Dysregulated miR-98 contributes to extracellular matrix degradation by targeting IL-6/STAT3 signaling pathway in human intervertebral disc degeneration, J. Bone Miner. Res. 31 (April (4)) (2016) 900–909. PubMed PMID: 26587789.
[80] J.C. Sun, B. Zheng, R.X. Sun, Y.K. Meng, S.M. Wang, H.S. Yang, et al., MiR-499a-5p suppresses apoptosis of human nucleus pulposus cells and degradation of their extracellular matrix by targeting SOX4, Biomed. Pharmacother. 113 (May) (2019) 108652. PubMed PMID: 30856535.
[81] J. Lv, S. Li, T. Wan, Y. Yang, Y. Cheng, R. Xue, Inhibition of microRNA-30d attenuates the apoptosis and extracellular matrix degradation of degenerative human nucleus pulposus cells by up-regulating SOX9, Chem. Biol. Interact. 296 (December 25) (2018) 89–97. PubMed PMID: 30243741.
[82] W.L. Zhang, Y.F. Chen, H.Z. Meng, J.J. Du, G.N. Luan, H.Q. Wang, et al., Role of miR-155 in the regulation of MMP-16 expression in intervertebral disc degeneration, J. Orthop. Res. 35 (June (6)) (2017) 1323–1334. PubMed PMID: 27227700. Pubmed Central PMCID: PMC5485035.
[83] C.L. Gallant-Behm, J. Piper, J.M. Lynch, A.G. Seto, S.J. Hong, T.A. Mustoe, et al., A microRNA-29 mimic (Remlarsen) represses extracellular matrix expression and fibroplasia in the skin, J. Invest. Dermatol. 139 (May (5)) (2019) 1073–1081. PubMed PMID: 30472058.
[84] S. Chowdhari, K. Sardana, N. Saini, miR-4516, a microRNA downregulated in psoriasis inhibits keratinocyte motility by targeting fibronectin/integrin alpha9 signaling, Biochim Biophys Acta Mol Basis Dis. 1863 (December (12)) (2017) 3142–3152. PubMed PMID: 28844950.
[85] Z. Han, T. Zhang, Y. He, G. Li, G. Li, X. Jin, Inhibition of prostaglandin E2 protects abdominal aortic aneurysm from expansion through regulating miR-29b-mediated fibrotic ECM expression, Exp. Ther. Med. 16 (July (1)) (2018) 155–160. PubMed PMID: 29896234. Pubmed Central PMCID: PMC5995085.
[86] M. Sakr, T. Takino, H. Sabit, M. Nakada, Z. Li, H. Sato, miR-150-5p and miR-133a suppress glioma cell proliferation and migration through targeting membrane-type-1 matrix metalloproteinase, Gene 587 (August (2)) (2016) 155–162. PubMed PMID: 27154818.
[87] M. Pavkova Goldbergova, J. Lipkova, J. Fedorko, P. Nemec, J. Gatterova, L. Valkova, et al., Relationship of epigenetic variability of miR-124 to extracellular matrix remodelling and age-related MMP-3 expression in rheumatoid arthritis, Gen. Physiol. Biophys. 37 (September (6)) (2018) 703–710. PubMed PMID: 30431436.
[88] Q. He, F. Wang, T. Honda, J. James, J. Li, A. Redington, Loss of miR-144 signaling interrupts extracellular matrix remodeling after myocardial infarction leading to worsened cardiac function, Sci. Rep. 8 (November (1)) (2018) 16886. PubMed PMID: 30443020. Pubmed Central PMCID: PMC6237773.
[89] X. Qin, J. Chen, L. Wu, Z. Liu, MiR-30b-5p acts as a tumor suppressor, repressing cell proliferation and cell cycle in human hepatocellular carcinoma, Biomed. Pharmacother. 89 (2017) 742–750.
[90] M. Vanden Oever, D. Muldoon, W. Mathews, R. McElmurry, J. Tolar, miR-29 regulates type VII collagen in recessive dystrophic epidermolysis bullosa, J. Invest. Dermatol. 136 (October (10)) (2016) 2013–2021. PubMed PMID: 27328306. Pubmed Central PMCID: PMC5341382.
[91] M.W. Pickup, J.K. Mouw, V.M. Weaver, The extracellular matrix modulates the hallmarks of cancer, EMBO Rep. 15 (12) (2014) 1243–1253.
[92] X. Tang, Y. Hou, G. Yang, X. Wang, S. Tang, Du YE, et al., Stromal miR-200s contribute to breast cancer cell invasion through CAF activation and ECM remodeling, Cell Death Differ. 23 (January (1)) (2016) 132–145. PubMed PMID: 26068592. Pubmed Central PMCID: PMC4815985.
[93] L.T. Le, O. Cazares, J.K. Mouw, S. Chatterjee, H. Macias, A. Moran, et al., Loss of miR-203 regulates cell shape and matrix adhesion through ROBO1/Rac/FAK in response to stiffness, J. Cell Biol. 212 (March (6)) (2016) 707–719. PubMed PMID: 26975850. Pubmed Central PMCID: PMC4792073.
[94] Y. Liu, J. Zhang, X. Sun, M. Li, EMMPRIN down-regulating miR-106a/b modifies breast Cancer Stem-like cell properties via interaction with fibroblasts through STAT3 and HIF-1alpha, Sci. Rep. 6 (June 21) (2016) 28329. PubMed PMID: 27325313. Pubmed Central PMCID: PMC4914854.
[95] L.Q. Liu, L. Hu, X.B. Hu, J. Xu, A.M. Wu, H. Chen, et al., MiR-92a antagonized the facilitation effect of extracellular matrix protein 1 in GC metastasis through targeting its 3'UTR region, Food Chem. Toxicol. 133 (November) (2019) 110779. PubMed PMID: 31472228.
[96] K.H. Czarnecka, B. Szmyd, M. Baranska, M. Kaszkowiak, J. Kordiak, A. Antczak, et al., A strong decrease in TIMP3 expression mediated by the presence of miR-17 and 20a enables extracellular matrix remodeling in the NSCLC lesion surroundings, Front. Oncol. 9 (1372) (2019). PubMed PMID: 31921636. Pubmed Central PMCID: PMC6923190.
[97] W. Feifei, G. Hui, Z. Ruiqiang, J. Qunxiang, X. Yu'an, MAGP2, a component of extracellular matrix, is upregulated in colorectal cancer and negatively modulated by miR-200b-3p, Technol. Cancer Res. Treat. 18 (January 1) (2019), 1533033819870777. PubMed PMID: 31426719. Pubmed Central PMCID: PMC6702771.
[98] Y. Lv, Z. Zhang, X. Xing, A. Liu, lncRNA TGFβ2-AS1 promotes ECM production via TGF-β2 in human trabecular meshwork cells, Biochem. Biophys. Res. Commun. (2020).
[99] S. Ghafouri-Fard, H. Shoorei, M. Taheri, Non-coding RNAs are involved in the response to oxidative stress, Biomed. Pharmacother. 127 (2020), 110228.
[100] W. Shen, B. Huang, Y. He, L. Shi, J. Yang, Long non-coding RNA RP11-820 promotes extracellular matrix production via regulating miR-3178/MYOD1 in human trabecular meshwork cells, FEBS J. 287 (5) (2020) 978–990.
[101] S. Zhang, S. Gao, Y. Wang, P. Jin, F. Lu, lncRNA SRA1 promotes the activation of cardiac myofibroblasts through negative regulation of miR-148b, DNA Cell Biol. 38 (4) (2019) 385–394.
[102] J. Zhou, Y. Zhou, Cx Wang, LncRNA-MIAT regulates fibrosis in hypertrophic cardiomyopathy (HCM) by mediating the expression of miR-29a-3p, J. Cell. Biochem. 120 (5) (2019) 7265–7275.
[103] B. Liu, L. Qiang, G. Wang, Q. Duan, J. Liu, LncRNA MALAT1 facilities high glucose induced endothelial to mesenchymal transition and fibrosis via targeting miR-145/ZEB2 axis, Eur. Rev. Med. Pharmacol. Sci. 23 (8) (2019) 3478–3486.
[104] Z. Li, Z. Yu, X. Meng, P. Yu, LncRNA LINC00968 accelerates the proliferation and fibrosis of diabetic nephropathy by epigenetically repressing p21 via recruiting EZH2, Biochem. Biophys. Res. Commun. 504 (2) (2018) 499–504.
[105] Y. Qi, Z. Wang, F. Wu, B. Yin, T. Jiang, B. Qiang, et al., Long noncoding RNA HOXD-AS2 regulates cell cycle to promote glioma progression, J. Cell. Biochem. 120 (5) (2019) 8343–8351.
[106] C. Wu, H. Liu, W. Shao, L. Yang, Y. Ning, S. Wang, et al., Long noncoding RNA expression profile reveals lncRNAs signature associated with extracellular matrix degradation in kashin-beck disease, Sci. Rep. 7 (1) (2017) 1–10.

[107] E. D'Angelo, M. Agostini, Long non-coding RNA and extracellular matrix: the hidden players in cancer-stroma cross-talk, Noncoding RNA Res. 3 (4) (2018) 174–177. PubMed PMID: 30533566. eng.
[108] M. Taheri, H. Shoorei, M.E. Dinger, S. Ghafouri-Fard, Perspectives on the role of non-coding RNAs in the regulation of expression and function of the estrogen receptor, Cancers 12 (8) (2020) 2162.
[109] X. Wang, C. Yong, K. Yu, R. Yu, R. Zhang, L. Yu, et al., Long Noncoding RNA (lncRNA) n379519 promotes cardiac fibrosis in post-infarct myocardium by targeting miR-30, Med. Sci. Monit. 24 (2018) 3958.
[110] H. Liu, C. Chen, Y. Sun, Overexpression of lncRNA GAS5 attenuates cardiac fibrosis through regulating PTEN/MMP-2 signal pathway in mice, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 4414–4418.
[111] H. Luo, R. Xu, B. Chen, S. Dong, F. Zhou, T. Yu, et al., MicroRNA-940 inhibits glioma cells proliferation and cell cycle progression by targeting CKS1, Am. J. Transl. Res. 11 (8) (2019) 4851.
[112] H. Liang, Z. Pan, X. Zhao, L. Liu, J. Sun, X. Su, et al., LncRNA PFL contributes to cardiac fibrosis by acting as a competing endogenous RNA of let-7d, Theranostics 8 (4) (2018) 1180.
[113] H. Tao, J.-G. Zhang, R.-H. Qin, C. Dai, P. Shi, J.-J. Yang, et al., LncRNA GAS5 controls cardiac fibroblast activation and fibrosis by targeting miR-21 via PTEN/MMP-2 signaling pathway, Toxicology 386 (2017) 11–18.
[114] L. Tang, J. Ding, Z. Liu, G. Zhou, LncRNA TUG1 promotes osteoarthritis-induced degradation of chondrocyte extracellular matrix via miR-195/MMP-13 axis, Eur. Rev. Med. Pharmacol. Sci. 22 (24) (2018) 8574–8581.
[115] Y. Li, Z. Li, C. Li, Y. Zeng, Y. Liu, Long noncoding RNA TM1P3 is involved in osteoarthritis by mediating chondrocyte extracellular matrix degradation, J. Cell. Biochem. 120 (8) (2019) 12702–12712.
[116] J. Zhu, T. He, Z. Wei, Y. Wang, LncRNA FAS-AS1 promotes the degradation of extracellular matrix of cartilage in osteoarthritis, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 2966–2972.
[117] K. Chen, H. Zhu, M.-Q. Zheng, Q.-R. Dong, LncRNA MEG3 inhibits the degradation of the extracellular matrix of chondrocytes in osteoarthritis via targeting miR-93/TGFBR2 axis, Cartilage (2019), 1947603519855759.
[118] H. Wu, H.Y. Liu, W.J. Liu, Y.L. Shi, D. Bao, miR-377-5p inhibits lung cancer cell proliferation, invasion, and cell cycle progression by targeting AKT1 signaling, J. Cell. Biochem. 120 (5) (2019) 8120–8128.
[119] Y. Li, L.-l Zheng, D.-g Huang, H. Cao, Y.-h Gao, Z.-c. Fan, LNCRNA CDKN2B-AS1 regulates mesangial cell proliferation and extracellular matrix accumulation via miR-424-5p/HMGA2 axis, Biomed. Pharmacother. 121 (2020), 109622.
[120] X. Wang, Y. Xu, Y.C. Zhu, Y.K. Wang, J. Li, X.Y. Li, et al., LncRNA NEAT1 promotes extracellular matrix accumulation and epithelial-to-mesenchymal transition by targeting miR-27b-3p and ZEB1 in diabetic nephropathy, J. Cell. Physiol. 234 (8) (2019) 12926–12933.
[121] J. Gao, W. Wang, F. Wang, C. Guo, LncRNA-NR_033515 promotes proliferation, fibrogenesis and epithelial-to-mesenchymal transition by targeting miR-743b-5p in diabetic nephropathy, Biomed. Pharmacother. 106 (2018) 543–552.
[122] J. Xu, P. Xiang, L. Liu, J. Sun, S. Ye, Metformin inhibits extracellular matrix accumulation, inflammation and proliferation of mesangial cells in diabetic nephropathy by regulating H19/miR-143-3p/TGF-β1 axis, J. Pharm. Pharmacol. (2020).
[123] J. Cheng, L. Cheng, Y. Tang, H. Li, W. Peng, S. Huang, Inhibition of lncRNA Dlx6os1 decreases cell proliferation and fibrosis and increases cell apoptosis in diabetic nephropathy, Int. J. Clin. Exp. Pathol. 11 (7) (2018) 3302.
[124] X. Feng, J. Zhao, J. Ding, X. Shen, J. Zhou, Z. Xu, LncRNA Blnc1 expression and its effect on renal fibrosis in diabetic nephropathy, Am. J. Transl. Res. 11 (9) (2019) 5664.
[125] Z. Tang, Y. Fang, R. Du, MicroRNA-107 induces cell cycle arrests by directly targeting cyclin E1 in ovarian cancer, Biochem. Biophys. Res. Commun. 512 (2) (2019) 331–337.
[126] M. Wang, S. Wang, D. Yao, Q. Yan, W. Lu, A novel long non-coding RNA CYP4B1-PS1-001 regulates proliferation and fibrosis in diabetic nephropathy, Mol. Cell. Endocrinol. 426 (2016) 136–145.
[127] L.-J. Duan, M. Ding, L.-J. Hou, Y.-T. Cui, C.-J. Li, D.-M. Yu, Long noncoding RNA TUG1 alleviates extracellular matrix accumulation via mediating microRNA-377 targeting of PPARγ in diabetic nephropathy, Biochem. Biophys. Res. Commun. 484 (3) (2017) 598–604.
[128] Y. Song, C. Miao, J. Wang, LncRNA ZEB1-AS1 inhibits renal fibrosis in diabetic nephropathy by regulating the miR-217/MAFB axis, RSC Adv. 9 (52) (2019) 30389–30397.
[129] X. Zhang, H. Zhu, Y. Zhang, C. Zhang, J. Jiao, X. Xing, LncRNA CASC2 regulates high glucose-induced proliferation, extracellular matrix accumulation and oxidative stress of human mesangial cells via miR-133b/FOXP1 axis, Eur. Rev. Med. Pharmacol. Sci. 24 (2) (2020) 802–812.
[130] R. Wei, Y. Chen, Z. Zhao, Q. Gu, J. Wu, LncRNA FAM83H-AS1 induces nucleus pulposus cell growth via targeting the Notch signaling pathway, J. Cell. Physiol. 234 (12) (2019) 22163–22171.
[131] N. Tang, Y. Dong, T. Xiao, B. Yu, H. Zhao, LncRNA TUG1 Promotes the Intervertebral Disc Degeneration and Nucleus Pulposus Cell Apoptosis Though Modulating miR-26a/HMGB1 Axis and Regulating NF-κB Activation, Available at SSRN 3493212, 2019.
[132] S. Zhan, K. Wang, Q. Xiang, Y. Song, S. Li, H. Liang, et al., lncRNA HOTAIR upregulates autophagy to promote apoptosis and senescence of nucleus pulposus cells, J. Cell. Physiol. 235 (3) (2020) 2195–2208.
[133] J. Jin, Y. Wang, Y. Xu, X. Zhou, Y. Liu, X. Li, et al., MicroRNA-144 regulates cancer cell proliferation and cell-cycle transition in acute lymphoblastic leukemia through the interaction of FMN2, J. Gene Med. 19 (6-7) (2017) e2898.
[134] Z. Ruan, H. Ma, J. Li, H. Liu, H. Jia, F. Li, The long non-coding RNA NEAT1 contributes to extracellular matrix degradation in degenerative human nucleus pulposus cells, Exp. Biol. Med. 243 (7) (2018) 595–600.
[135] Z. Wang, C. Feng, K. Song, Z. Qi, W. Huang, Y. Wang, lncRNA-H19/miR-29a axis affected the viability and apoptosis of keloid fibroblasts through acting upon COL1A1 signaling, J. Cell. Biochem. (2020).
[136] H.-Y. Zhu, W.-D. Bai, C. Li, Z. Zheng, H. Guan, J.-Q. Liu, et al., Knockdown of lncRNA-ATB suppresses autocrine secretion of TGF-β2 by targeting ZNF217 via miR-200c in keloid fibroblasts, Sci. Rep. 6 (1) (2016) 1–9.
[137] R. Tang, Y.-C. Wang, X. Mei, N. Shi, C. Sun, R. Ran, et al., LncRNA GAS5 attenuates fibroblast activation through inhibiting Smad3 signaling, Am. J. Physiol. Cell Physiol. (2020).
[138] H. Zhou, L. Gao, Zh Yu, Sj Hong, Zhang Zw, Qiu Zz, LncRNA HOTAIR promotes renal interstitial fibrosis by regulating Notch1 pathway via the modulation of miR-124, Nephrology 24 (4) (2019) 472–480.
[139] X. Xiao, Q. Yuan, Y. Chen, Z. Huang, X. Fang, H. Zhang, et al., LncRNA ENST00000453774. 1 contributes to oxidative stress defense dependent on autophagy mediation to reduce extracellular matrix and alleviate renal fibrosis, J. Cell. Physiol. 234 (6) (2019) 9130–9143.
[140] J. Wang, J. Pan, H. Li, J. Long, F. Fang, J. Chen, et al., lncRNA ZEB1-AS1 was suppressed by p53 for renal fibrosis in diabetic nephropathy, Mol. Ther. -Nucleic Acids. 12 (2018) 741–750.
[141] W. Cao, Y. Feng, LncRNA XIST promotes extracellular matrix synthesis, proliferation and migration by targeting miR-29b-3p/COL1A1 in human skin fibroblasts after thermal injury, Biol. Res. 52 (2019).
[142] P. Liu, B. Zhang, Z. Chen, Y. He, Y. Du, Y. Liu, et al., m6A-induced lncRNA MALAT1 aggravates renal fibrogenesis in obstructive nephropathy through the miR-145/FAK pathway, Aging (Albany NY) 12 (6) (2020) 5280.
[143] B. Zhou, W. Yuan, X. Li, LncRNA Gm5091 alleviates alcoholic hepatic fibrosis by sponging miR-27b/23b/24 in mice, Cell Biol. Int. 42 (10) (2018) 1330–1339.
[144] Z. Dong, S. Li, X. Wang, L. Si, R. Ma, L. Bao, et al., lncRNA GAS5 restrains CCl4-induced hepatic fibrosis by targeting miR-23a through the PTEN/PI3K/Akt signaling pathway, Am. J. Physiol. -Gastrointestinal Liver Physiol. 316 (4) (2019). G539–G50.
[145] J.J. Yang, Y. Yang, C. Zhang, J. Li, Y. Yang, Epigenetic silencing of LncRNA ANRIL enhances liver fibrosis and HSC activation through activating AMPK pathway, J. Cell. Mol. Med. 24 (4) (2020) 2677–2687.
[146] N. Fu, S.-X. Zhao, L.-B. Kong, J.-H. Du, W.-G. Ren, F. Han, et al., LncRNA-ATB/microRNA-200a/β-catenin regulatory axis involved in the progression of HCV-related hepatic fibrosis, Gene 618 (2017) 1–7.
[147] X. Li, T. Yu, H. Shan, H. Jiang, J. Sun, X. Zhao, et al., lncRNA PFAL promotes lung fibrosis through CTGF by competitively binding miR-18a, FASEB J. 32 (10) (2018) 5285–5297.
[148] J. Sun, W. Su, X. Zhao, T. Shan, T. Jin, Y. Guo, et al., LncRNA PFAR contributes to fibrogenesis in lung fibroblasts through competitively binding to miR-15a, Biosci. Rep. 39 (7) (2019).
[149] Q. Lu, Z. Guo, W. Xie, W. Jin, D. Zhu, S. Chen, et al., The lncRNA H19 mediates pulmonary fibrosis by regulating the miR-196a/COL1A1 axis, Inflammation 41 (3) (2018) 896–903.
[150] X. Zhao, J. Sun, Y. Chen, W. Su, H. Shan, Y. Li, et al., lncRNA PFAR promotes lung fibroblast activation and fibrosis by targeting miR-138 to regulate the YAP1-twist axis, Mol. Ther. 26 (9) (2018) 2206–2217.
[151] W. Qian, X. Cai, Q. Qian, W. Peng, J. Yu, X. Zhang, et al., lncRNA ZEB1-AS1 promotes pulmonary fibrosis through ZEB1-mediated epithelial–mesenchymal transition by competitively binding miR-141-3p, Cell Death Dis. 10 (2) (2019) 1–12.
[152] X. Wang, Z. Cheng, L. Dai, T. Jiang, L. Jia, X. Jing, et al., Knockdown of lncRNA H19 represses the progress of pulmonary fibrosis through the TGF-β/Smad3 pathway by regulating miR-140, Mol. Cell. Biol. (2019). MCB. 00143–19.
[153] Q. Wu, L. Han, W. Yan, X. Ji, R. Han, J. Yang, et al., miR-489 inhibits silica-induced pulmonary fibrosis by targeting MyD88 and Smad3 and is negatively regulated by lncRNA CHRF, Sci. Rep. 6 (2016) 30921.
[154] R. Jiang, J. Tang, Y. Chen, L. Deng, J. Ji, Y. Xie, et al., The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion, Nat. Commun. 8 (1) (2017) 1–15.
[155] L. Chen, J. Li, Q. Li, X. Li, Y. Gao, X. Hua, et al., Overexpression of LncRNA AC067945. 2 down-regulates collagen expression in skin fibroblasts and possibly correlates with the VEGF and Wnt signalling pathways, Cell. Physiol. Biochem. 45 (2) (2018) 761–771.
[156] Z.-P. Huang, Y. Ding, J. Chen, G. Wu, M. Kataoka, Y. Hu, et al., Long non-coding RNAs link extracellular matrix gene expression to ischemic cardiomyopathy, Cardiovasc. Res. 112 (2) (2016) 543–554.
[157] Z. Zhang, G. Zou, X. Chen, W. Lu, J. Liu, S. Zhai, et al., Knockdown of lncRNA PVT1 inhibits vascular smooth muscle cell apoptosis and extracellular matrix disruption in a murine abdominal aortic aneurysm model, Mol. Cells 42 (3) (2019) 218.
[158] F. Cao, Z. Li, W.-m Ding, L. Yan, Q.-y. Zhao, LncRNA PVT1 regulates atrial fibrosis via miR-128-3p-SP1-TGF-β1-Smad axis in atrial fibrillation, Mol. Med. 25 (1) (2019) 7.
[159] M. Zhu, Q. Chen, X. Liu, Q. Sun, X. Zhao, R. Deng, et al., lncRNA H19/miR-675 axis represses prostate cancer metastasis by targeting TGFBI, FEBS J. 281 (August (16)) (2014) 3766–3775. PubMed PMID: 24988946. Epub 2014/07/06. eng.
[160] A.D. Theocharis, S.S. Skandalis, C. Gialeli, N.K. Karamanos, Extracellular matrix structure, Adv. Drug Deliv. Rev. 97 (2016) 4–27.