

Role of miRNA and lncRNAs in organ fibrosis and aging

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ABSTRACT

Fibrosis is the endpoint of pathological remodeling. This process contributes to the pathogenesis of several chronic disorders and aging-associated organ damage. Different molecular cascades contribute to this process. TGF- β , WNT, and YAP/TAZ signaling pathways have prominent roles in this process. A number of long non-coding RNAs and microRNAs have been found to regulate organ fibrosis through modulation of the activity of related signaling pathways. miR-144-3p, miR-451, miR-200b, and miR-328 are among microRNAs that participate in the pathology of cardiac fibrosis. Meanwhile, miR-34a, miR-17-5p, miR-122, miR-146a, and miR-350 contribute to liver fibrosis in different situations. PVT1, MALAT1, GAS5, NRON, PFL, MIAT, HULC, ANRL, and H19 are among long non-coding RNAs that participate in organ fibrosis. We review the impact of long non-coding RNAs and microRNAs in organ fibrosis and aging-related pathologies.

Abbreviation: HCFs, human cardiac fibroblasts; Col1 α 1, collagens alpha type I; α -SMA, α -smooth muscle actin; PTEN, phosphatase and tensin homolog; MHECs, Mouse heart endothelial cells; AMPK, adenosine 5'-monophosphate protein kinase; CFs, Cardiac fibroblasts; DNMT3A, DNA methyltransferases 3A; P62, protein 62; CMs, cardiomyocytes; CD, Chagas disease; hiPSC, human induced pluripotent stem cells; TGF- β 1, Transforming growth factor- β 1; NLRC5, NOD-like receptor family CARD domain containing 5; CKD, chronic kidney disease; PI3K, phosphoinositide 3-kinase; IGF-1, insulin-like growth factor-1; CTGF, connective tissue growth factor; FN1, fibronectin; AS-IV, Astragaloside IV; SMAD, small mothers against decapentaplegic; HCMECs, Human cardiac microvascular endothelial cells; IRAK1, Interleukin-1 associated Kinase 1; AngII, angiotensin II; circRNAs, Circular RNAs; MMP16, matrix metalloproteinase 16; p38 MAPK, p38 mitogen-activated protein kinase; GSK-3 β , glycogen synthase kinase-3 β ; MTA3: metastasis-associated gene 3; FBXW4, F box and WD 40 domain-containing protein 4; FBXW7, F box and WD 40 domain-containing protein 7; LncRNAs: long non-coding RNAs; MiRNAs, microRNAs; Ago2, Argonaute-2; TGF β R2, transforming growth factor- β receptor 2; BMP-7, bone morphogenetic protein 7; IL-6, interleukin-6; Sirt1, sirtuin 1; NF- κ B, nuclear factor kappa B; ASICs, acid-sensing ion channels; MAPK/ERK, mitogen-activated protein kinase/Extracellular-signal-regulated kinases; SPRY2, Sprouty homolog 2; METTL3, methyltransferase like protein 3; rAAV: Recombinant adeno-associated virus; HK-2, human kidney cell line; Zeb2, zinc finger E-box binding homeobox 2; FGF11, fibroblast growth factor 11; FOXO, Forkhead transcription factor class O; NLRP3, NACHT, LRR, and PYD domain-containing protein3; ASC, apoptosis-associated speck-like protein containing CARD; PGC-1a, proliferator-activated receptor gamma coactivator 1 α ; PPAR α , peroxisome proliferator-activated receptor; PVT1, Plasmacytoma variant translocation 1; NRON, non-coding repressor of NFAT; GAS5, Growth arrest-specific 5; MMP-2, Matrix metalloprotease-2; PFL, pro-fibrotic lncRNA; CF, Cardiac fibrosis; lnc RNF7, lncRNA Homo sapiens ring finger protein 7; PCFL, Pro-cardiac fibrotic lncRNA; GRB2, Growth factor receptor-bound protein 2; MIAT, myocardial infarction-associated transcript; NLRP3, Nucleotide-binding domain and leucine-rich repeat-containing PYD-3; ACC, acetyl-CoA carboxylase; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; FAK, focal adhesion kinase.

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1. Introduction

Fibrosis is a process that is considered as the endpoint of pathological remodeling and contributes to the pathogenesis of several chronic disorders and aging-associated organ damage [1]. Pathological conditions in the heart, liver, lung, and kidney are associated with this process. Fibrosis is described by the exaggerated synthesis and deposition of extracellular matrix (ECM) proteins, including collagen fibers. Activated profibrotic fibroblasts have prominent roles in this process [2]. Disturbance in hemostasis between synthesis and degradation of ECM can be resulted from complex cascades of cell responses that are induced by organ injury. Although triggers of organ damage might exert their effects in an organ-specific manner, the fibrotic process and involved cascades are greatly conserved between various organs [2]. Different cascades and signaling pathways including WNT [1] and TGF- β [3] regulate organ fibrosis. In addition to induction of ECM synthesis, TGF- β enhances proliferation and migration of mesenchymal cells and their accumulation in the tissue. Therefore, TGF- β mainly induces fibrosis following chronic stages of inflammatory disorders. Yet, TGF- β has both aggravating and amending effects, depending on the stage of the disorder and the location of its actions [3]. YAP/TAZ signaling is another cascade that regulates fibrosis [4]. Although these three signaling pathways have a low level of molecular similarity, similar factors regulate their activity within the cytosol or nucleus [4]. In fact, TGF- β , WNT, and YAP/TAZ cascades are interrelated with each other in the context of fibrosis [4]. These pathways control the differentiation of myofibroblasts in concert. For example, during the pathogenic course of lung fibrosis, expressions and nuclear localization of YAP and TAZ have been found to be enhanced [5]. These events are associated with the accumulation of β -catenin and phosphorylated R-Smads in the nucleus. Fibrotic changes in the course of wound healing are also associated with enhancement of YAP and TAZ translocation to the nucleus and high levels of TGF- β 1 in the dermis, implying a functional link between induction of YAP and TAZ and TGF- β 1 synthesis [6].

In addition to these signaling pathways, a number of non-coding RNAs (ncRNAs) have been found to affect fibrotic processes. Although ncRNAs include a vast number of transcripts with different characteristics, two classes of these transcripts, namely long ncRNAs (lncRNAs) and microRNAs (miRNAs) have been more attractive as candidates for research in this field as they exert diverse regulatory effects on mRNA coding genes.

miRNAs are single-stranded transcripts with sizes of about 22 nucleotides. These small transcripts suppress the synthesis of proteins through base pairing to certain parts of mRNAs, particularly the 3' untranslated region (3'UTR). Based pairing to 5'UTR and coding regions have also been reported [7]. In mammals, miRNAs are produced from precursor miRNAs which have an approximate length of 60–100 nucleotides. They create a hairpin stem-loop configuration and are further modified by an RNase III endonuclease, namely Dicer [8]. This step results in the creation of a miRNA: miRNA duplex with a size of 21 nucleotides. Then, one or both strands of this duplex can be assimilated into the RNA-induced silencing complex and accomplish its role as a mature miRNA [9].

On the other hand, lncRNAs have sizes greater than 200 nucleotides. With a total quantity higher than protein-coding genes [10], their diversity and size are closely correlated with organismal complexity, even in a more precise manner than those of protein-coding genes [11]. Famous members of this class of transcripts have been found to affect important biological processes such as imprinting, chromosome configuration, and regulation of enzyme activity [12]. Moreover, lncRNAs have been distinctively dignified to regulate their genomic vicinities *in cis* [12].

Due to their versatile roles in the regulation of gene expression, both miRNAs and lncRNAs can control cellular and molecular phenomena and influence important biological processes such as organ fibrosis. In the present article, we review the impact of these transcripts in organ

fibrosis as well as aging. Fig. 1 illustrates the role of several non-coding RNAs in regulating the mechanisms of fibrosis associated with a varied range of diseases.

2. Impact of miRNAs on organ fibrosis and aging

2.1. Cardiac fibrosis

The role of miRNAs in the modulation of cardiac fibrosis following myocardial infarction (MI) has been assessed by independent groups. For instance, Yuan et al. have measured miRNA profile in a pig model of MI. Using this approach, 84 miRNAs have been found to be differentially expressed between MI and control animals among them has been miR-144-3p with significant over-expression in the infarct area. Experiments in cardiac fibroblasts have shown enhancement of cell proliferation, migration potential, and induction of expression of ECM-associated genes following miR-144-3p over-expression. Besides, miR-144-3p has been demonstrated to suppress the expression of PTEN, and inhibit PTEN-induced over-expression of α -SMA, Col1A1, and Col3A1. Taken together, miR-144-3p enhances proliferation, migration aptitude, and collagen synthesis of cardiac fibroblasts by interfering with the expression of PTEN, implying that miR-144-3p/PTEN axis can be a candidate for therapeutic strategies for cardiac fibrosis following MI [17].

miR-200b is another miRNA that affects cardiac fibrosis following abdominal aortic coarctation. While DNMT3A levels have been found to be increased in fibrotic tissues and cardiac fibroblast, the expression of this miRNA has been decreased in these cells. Moreover, miR-200b silencing has activated autophagy in cardiac fibroblasts of the rat. DNMT3A silencing has considerably enhanced miR-200b levels. Therefore, DNMT3A-mediated control of miR-200b expression affects autophagy of cardiac fibroblasts during cardiac fibrosis [18]. Another experiment has been performed in an animal model of MI produced by occlusion of the left coronary artery. Cardiomyocyte-specific over-expression of miR-328 has promoted the deposition of collagen and induced cardiac fibrosis through induction of the TGF- β 1 pathway. Consistently, expression of miR-328 has been found to be increased in cardiac fibroblasts co-cultured with cardiomyocytes transfected with miR-328 mimics, possibly via a paracrine route. The cardiomyocyte-mediated enhancement of miR-328 levels participates in fibrogenesis in cardiac fibroblasts, and this pro-fibrotic impact has been overturned following inhibition of miR-328 in cardiac fibroblasts. Thus, cardiomyocyte-derived miR-328 can mediate cardiac fibrogenesis through a paracrine manner [19].

Another experiment in mice model of streptozotocin (STZ)-induced diabetes has shown cardiac fibrosis 16 weeks after injection of STZ. However, at this time point, no sign of cardiac hypertrophy has been detected in mice. Subsequent suppression of miR-451 expression has decreased cardiac fibrosis and enhanced the function of the heart. Functionally, miR-451 silencing has been found to block endothelial to mesenchymal transition (EndMT) in cardiac tissues of diabetic mice. This study has also shown the effect of miR-451 silencing in attenuation of hyperglycemia-induced EndMT in mouse heart endothelial cells [20]. Mechanistically, AMPKa1/mTOR axis mediates the effects of miR-451 in cardiac tissue and hyperglycemia-induced endothelial cells. Therefore, miR-451 contributes to the pathology of diabetic cardiomyopathy through the regulation of AMPKa1 and subsequent affecting EndMT in endothelial cells [20]. Table 1 and Fig. 2 show the impact of miRNAs in cardiac fibrosis in different settings.

2.2. Liver fibrosis

Treatment of liver cells with high glucose has induced epithelial-mesenchymal transition (EMT). In addition, the expression of miR-32 has been found to be enhanced in the liver tissue of STZ-induced diabetic animals and in high glucose-treated liver cells. The effect of EMT in liver fibrosis through influencing the expression of MTA3 under

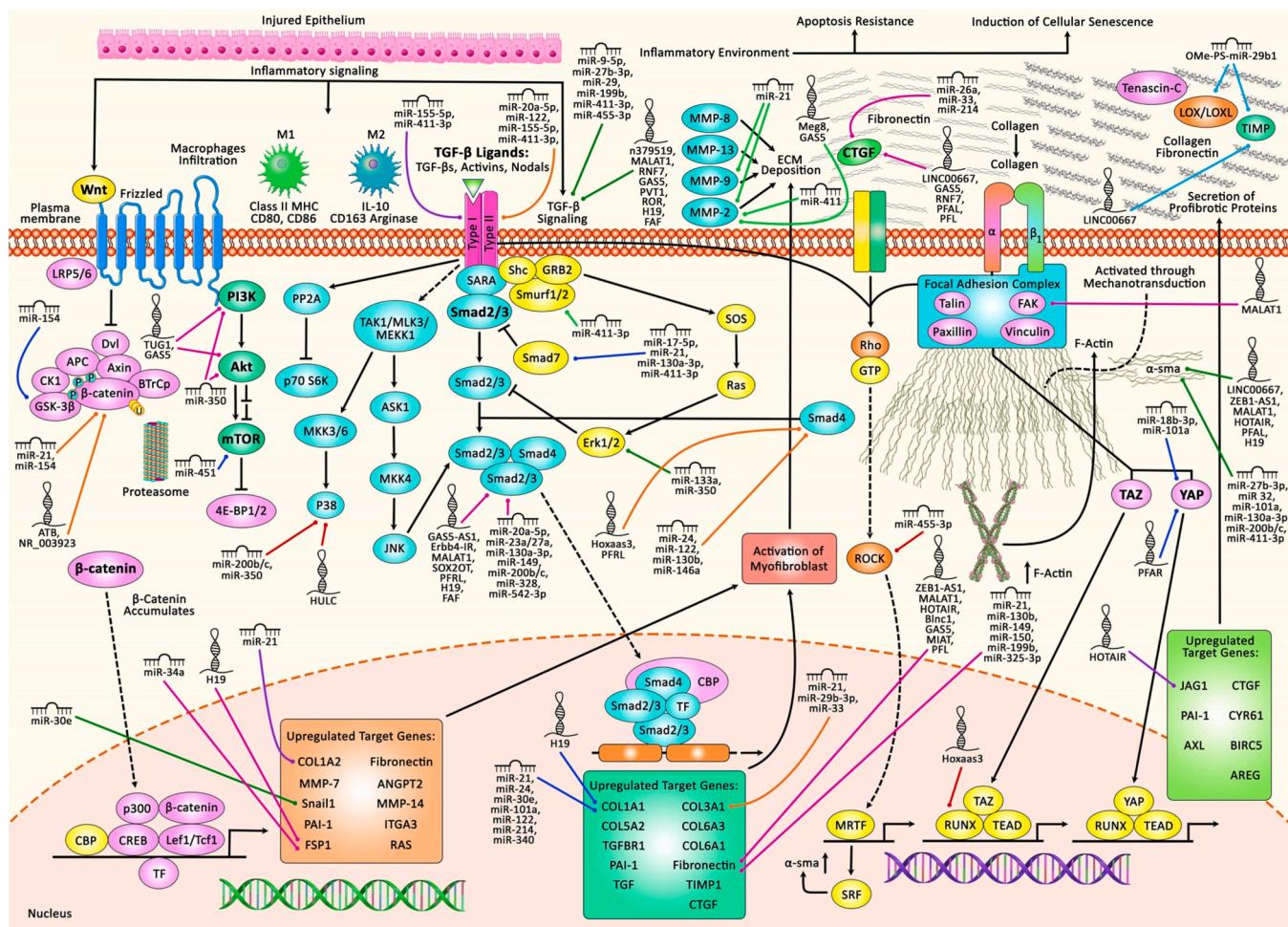


Fig. 1. A schematic representation of the role of various non-coding RNAs in modulating the mechanisms of fibrosis in a range of diseases. Thereby, pathologically excessive deposition of ECM proteins along with overexpressed myofibroblast function could lead to creating a chronic inflammatory environment with macrophage and immune cell infiltration. In this cellular milieu, cytokines and growth factors are plentifully released, containing TGF- β , Wnt1 which play a crucial role as potential effectors of the fibrotic process. Following that TGF- β and Wnt1 could bind to their cognate cell surface receptors and trigger downstream signaling cascades that eventually resulting in the nuclear translocation of Smad2/3 and CBP/ β -Catenin transcriptional modulators, respectively. This could in turn lead to promoting the expression level of target genes that function to further promote myofibroblast differentiation and the generation and secretion of ECM proteins containing collagen, fibronectin, and laminin. As excessive ECM deposition improves, the organization of the matrix could change and become rigid. ECM tension could be recognized by cells via mechanotransduction through cell surface integrin receptors that have an important part in triggering the activation of the Hippo signaling cascade and its primary downstream effectors YAP and TAZ. Subsequently, activated YAP and TAZ could be transferred to the nucleus and therefore contributing to upregulating the expression of profibrotic genes like CTGF and PDGF and enhancing myofibroblast proliferation and activation through the PI3K/AKT/mTOR cascade [13–16]. Mounting evidence has demonstrated that miRNAs as well as lncRNAs could play a remarkable role in regulating the mechanisms of fibrosis in a variety of diseases including cystic fibrosis, endometrial fibrosis, cardiac fibrosis, and skeletal muscle fibrosis to name a few. All information regarding the type of diseases as well as target genes of these non-coding RNAs can be seen in detail in Tables 1–12. Colored lines indicate the regulatory interactions between non-coding RNAs and their targets. In response to tissue destruction, myofibroblasts derived from a variety of sources containing mesenchymal cells, resident fibroblasts, circulating fibrocytes, as well as the trans differentiation of other cell types, could trigger a wound-healing response via remodeling the extracellular environment to reform tissue integrity and enhance the substitution of parenchymal cells.

hyperglycemic conditions has been inhibited by anti-miR-32. Taken together, miR-32 and MTA3 have been suggested as possible targets for the treatment of liver fibrosis under hyperglycemic conditions [33].

Expression of miR-378 has been shown to be enhanced in liver tissues of mice model of diet-induced obesity and patients with non-alcoholic steatohepatitis (NASH). miR-378 directly targets Prkag2 that encodes AMPK γ 2. AMPK signaling inhibits the activity of the NF- κ B-TNF α molecular axis by enhancing the deacetylase function of sirtuin 1. miR-378 decreases the activity of sirtuin 1 through targeting Prkag2, thus facilitating the NF- κ B-TNF α inflammatory axis. miR-378 silencing

induces Prkag2 expression, enhances the activity of sirtuin 1, and inhibits the activity of the NF- κ B-TNF α axis. Further studies have shown the role of AMPK signaling in the mediation of the effects of miR-378 on the NF- κ B-TNF α axis. Over-expression of miR-378 in liver tissues induces liver fibrosis and the development of NASH through enhancing the activity of the TNF α axis. Taken together, miR-378 partake in the development of liver inflammation and fibrosis through enhancing the activity of the NF- κ B-TNF α axis [34]. miR-18-3p is another miRNA that participates in liver fibrosis. This miRNA has interaction with circFBXW4. Expression of this circular RNA has been found to be

Table 1
Impact of miRNAs in cardiac fibrosis.

miRNA	Sample	Cell lines	Organ-specificity	List of known regulators/binding partners	Targets	Function	Brief Role in fibrosis	Refs.
miR-144-3p	Juema minipigs	HCFs	Just heart	PTEN	PTEN, α -SMA, Col1A1, Col3A1	miR-144-3p via targeting PTEN could enhance cardiac fibrosis after myocardial infarction.	Enhancing	[17]
miR-451	C57/B6 mice	MHECs	Just mouse heart	AMPK α 1	CD31, cadherin, α -SMA, vimentin, collagen I/III, AMPK α 1/2, mTOR, Cab39, LKB1	miR-451 antagonist could protect against cardiac fibrosis in diabetic mice.	Protective	[20]
miR-200b	SD rats	CFs	Just heart	DNMT3A	P62, LC3B I/II	DNMT3A regulation of miR-200b could be involved in cardiac fibroblast autophagy during cardiac fibrosis.	Protective	[18]
miR-328	C57BL/6 WT mice, KD mice	CMs, CFs	Just heart		TGF- β 1, smad2/3, TGF- β RIII, Col1 α 1, Col3 α 1	Cardiomyocyte-derived miR-328 by paracrine regulation of adjacent fibroblasts could promote cardiac fibrosis.	Protective	[19]
miR-19a-3p, miR-21-5p, miR-29b-3p, miR-30a-5p, miR-199b-5p, miR-208a-3p	Chagas patients (n = 28), healthy control (n = 10)	Cardiac fibroblasts, hiPSC	Just heart	DDR2	DDR2, α -SMA, vimentin	Mentioned miRNAs as potential biomarkers could be associated with cardiac fibrosis in Chagas disease cardiomyopathy.	Enhancing	[21]
miR-214-3p	C57/BL6 mice	Neonatal mouse cardiac fibroblasts	Just heart	NLRCS5	Col1 α 1, α -SMA, NLRCS5	The deficiency of miR-214-3p via targeting the miR-214-3p/NLRCS5 axis could exacerbate cardiac fibrosis.	Enhancing	[22]
miR-26a	CKD mouse	skeletal muscle satellite cells, cardiac H9C2 cells	Just kidney	FoxO1	TGF- β 1, Akt, PTEN, FoxO1, MuRF1, Atrogin1, TSG101, CTGF, collagen1A1	miR-26a could limit muscle wasting and cardiac fibrosis in chronic kidney disease.	Protective	[23]
miR-135a	SD rats	neonatal CFs	Just heart	TRPM7	TRPM7, TGF- β 1, Smad3/7, α -SMA, Collagen I	Astragaloside IV by targeting the miR-135a/TRPM7/TGF- β /Smads axis could inhibit cardiac fibrosis.	Protective	[24]
miR-133a	Mice, cardiac tissues	endothelial cells	Just heart	FN1	FN1, COL4A1, ERK1/2, SMAD	Overexpression of cardiac miR-133a could prevent early cardiac fibrosis in diabetes.	Protective	[25]
miR-146a	Cardiac tissues of TG mice	HCMECs	Just heart	IL6	IL6, TNF α , IL-1 β , MCP-1, NF- κ B, Col1 α 1, Col4 α 1	miR-146a could mediate fibrosis in the heart in diabetes.	Enhancing	[26]
miR-433	Heart samples of C57BL/6N mice	NIH/3T3, cardiac fibroblasts	Just heart	CircNFIB	CircNFIB, TGF- β	Upregulation of circNFIB via sponging miR-433 could attenuate cardiac fibrosis.	protective	[27]
miR-125b	human heart tissues, C57BL/6J mice	HCFs	Just heart	Ang II	α -SMA, Col1, p53, Ang-II	Inhibition of miR-125b could be a therapeutic method for cardiac fibrosis and other fibrotic diseases.	Enhancing	[28]
miR-29b-3p	Mice heart tissues	CFs	Just heart	circHIPK3	circHIPK3, Ang-II, α -SMA, COL1A1, COL3A1	Inhibition of circHIPK3 via sponging miR-29b-3p could prevent Ang-II-induced cardiac fibrosis.	Enhancing	[29]
miR-141	Diabetic db/db mice, C57BL/6 mice	CFs, 293T	Just heart	TGF- β 1	TGF- β 1, Col I, Col III, α -SMA	circRNA 010567 through suppressing miR-141 via targeting TGF- β 1 could promote myocardial fibrosis.	Enhancing	[30]
miR-33	SD rats	CFs	Just heart	MMP16	MMP16, p38 MAPK, CTGF, Col1A1, Col3A1	miR-33 by inhibiting MMP16 and stimulating p38 MAPK could promote myocardial fibrosis signaling.	Enhancing	[31]
miR-154	Blood samples from patients with cardiomyopathy (n = 51)	HCF	Just heart	GSK-3 β	a-SMA, β -catenin, GSK-3 β , Collagen I/III	miR-154 by targeting β -catenin could promote myocardial fibrosis.	Enhancing	[32]

reduced in liver fibrogenesis. Enforced expression of circFBXW4 has suppressed activity and proliferation of hepatic stellate cells, and induced apoptosis in these cells reduced hepatic fibrogenesis damage, and exhibited anti-inflammatory impact. The circFBXW4/miR-18b-3p/FBXW7 axis has been identified as the

functional axis in this regard [35]. FBXW7 is a tumor suppressor protein that regulates proteasome-associated degradation of oncoproteins, including cyclin E, c-Myc, Mcl-1, mTOR, Jun, Notch and AURKA [36]. Table 2 and Fig. 3 show the impact of miRNAs in liver fibrosis.

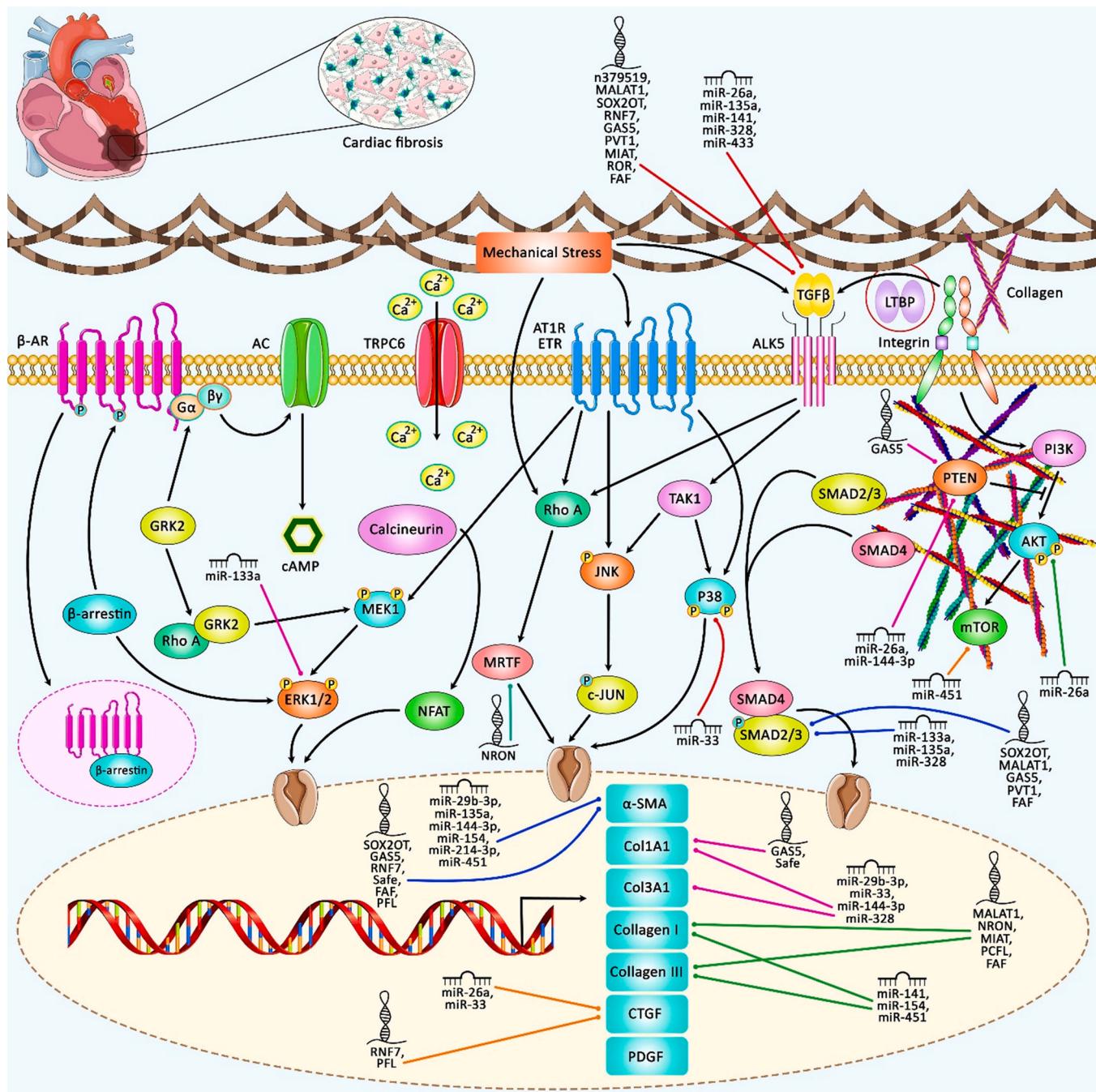


Fig. 2. A schematic diagram of the role of several non-coding RNAs in regulating signaling cascades involved in myofibroblast activation. Several signaling cascades have an important role in triggering the activation of cardiac fibroblasts and the induction of pathological remodeling. The cardiac injury could enhance the activation of multiple receptors including the type 1 angiotensin II receptor (AT1R), β -adrenergic receptor (β -AR), endothelin receptor (ETR), transient receptor potential channel C6 (TRPC6), activin receptor-like kinase 5 (ALK5), and integrins, which could induce pathological signaling via numerous mediators, resulting in the transcription of factors that could modulate myofibroblast activation and fibrotic remodeling [112]. Growing pieces of evidence authenticate the modulatory role of various miRNAs as well as lncRNAs in causing cardiac fibrosis. The comprehensive information regarding the role of these non-coding RNAs involved in the modulation of cardiac fibrosis could be seen in Tables 1 and 7.

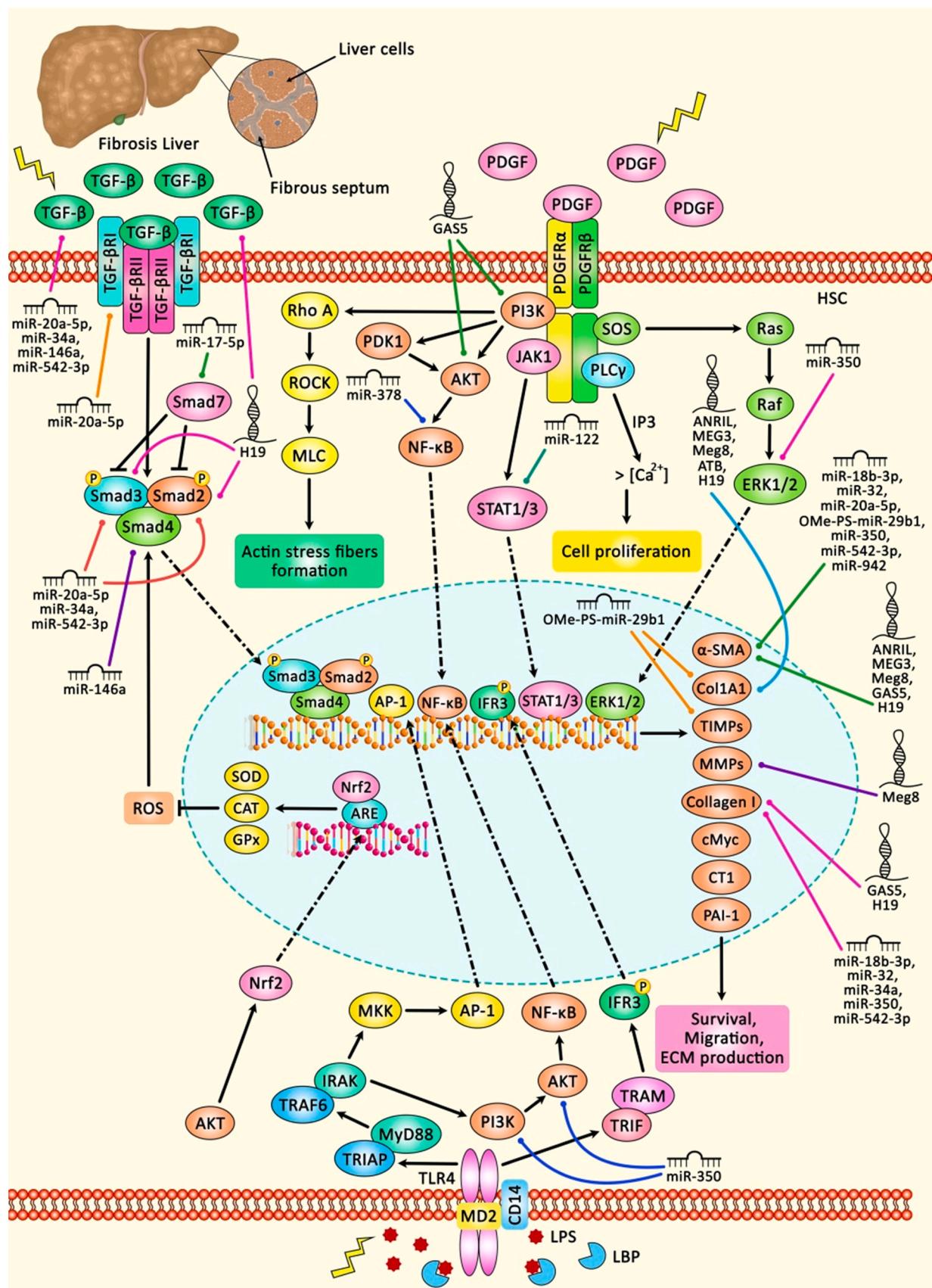
2.3. Renal fibrosis

The expression of several miRNAs has been changed in the fibrotic kidney. TGF- β has been shown to induce the expressions of miR-21, miR-192, miR-214, and the let7 family while inhibiting expressions of miR-29 and miR-200 [46], all of them being associated with organ fibrosis. Expression of miR-29 has also been found to be decreased in animal models of chronic kidney disease resulting in up-regulation of YY1, a transcription factor that suppresses proliferation of muscle satellite cells

and facilitates muscle wasting [47]. In addition, miR-29 has been found to reverse unilateral ureteral obstruction (UUO)-associated with muscle wasting and kidney fibrosis. Exosome-mediated transfer of miR29 has enhanced muscle cross-sectional area and reduced UUO-associated over-expression of TRIM63/MuRF1 and FBXO32/atrogin-1. Moreover, kidney fibrosis has been partly decreased in treated animals as confirmed by reduction TGF- β , alpha-SMA, fibronectin, and COL1A1 in the renal tissues of UUO animals. miR-29 exerts these effects through inhibition of YY1 and TGF- β 3 [48]. miR-9-5p is another miRNA that

Table 2
Impact of miRNAs in liver fibrosis.

miRNA	Sample	Cell lines	Organ-specificity	List of known regulators/binding partners	Targets	Brief Role in fibrosis	Function	Ref
miR-32	Control and T2DM Wistar rats	AML12	Just Liver	MTA3	Col-1, E-cad, α -SMA, vimentin, MTA3	Enhancing	High glucose could promote hepatic fibrosis by targeting the miR-32/MTA3 axis.	[33]
miR-378	Human liver tissues of Non-Alcoholic Steatohepatitis (NASH) patients (n = 38), normal tissues (n = 24), C57BL/6 mice	HepG2	Just Liver	Prkag2	Prkag2, NF- κ B, TNF- α	Enhancing	miR-378 by modulating the NF- κ B/TNF- α pathway could promote hepatic fibrosis.	[34]
miR-18b-3p	C57BL/6J mice	HSCs, LX-2	Just Liver	FBXW7	circFBXW4, α -SMA, col I, Yap1, FBXW7	Protective	circFBXW4 by targeting the miR-18b-3p/FBXW7 axis could suppress hepatic fibrosis.	[35]
OMe-PS-miR-29b1	C57BL/6J male mice	HSC-T6 hPBMC	Just Liver	Ago2	Ago2, Col1A1, TIMP-1, α -SMA, E-cadherin, LOXL2,	Protective	Micellar delivery of OMe-PS-miR-29b1 could be involved in the treatment of liver fibrosis.	[37]
miR-20a-5p	Liver fibrosis patients (n = 26), liver diseases patients except for liver fibrosis (n = 19), C57BL/6 mice	Hepa1-6, macrophage Raw264.7	Just Liver	TGF- β R2	TGF- β , TGF- β R2, α -SMA, Desmin, Smad-2/3	Enhancing	Targeting miR-20a-5p/TGF- β R2 axis, could affect pro-inflammatory macrophages and aggravate liver fibrosis.	[38]
miR-942	70 pairs of CHB liver fibrosis and adjacent normal tissues	Human HSCs, LX2	Just Liver	PPAR γ	PPAR γ , α -SMA	Enhancing	PPAR γ /mir-942 axis could inhibit hepatic stellate cell activation in chronic hepatitis B liver fibrosis.	[39]
miR-542-3p	C57/BL6 male mice	HSC-T6, LX-2	Just Liver	BMP-7	TGF β , α -SMA, Col 1, Smad-2/3, BMP-7,	Enhancing	miR-542-3p by targeting BMP-7 could control HSCs activation and fibrosis.	[40]
miR-34a	SD rats	BRL-3A	Just Liver	Sirt1	Sirt1, p53, TGF- β 1, Smads, E-cadherin, FSP1, collagen 1	Enhancing	Pterostilbene via suppressing miR-34a/Sirt1/p53 and TGF- β 1/Smads pathways could prevent hepatocyte EMT in fructose-induced liver fibrosis.	[41]
miR-17-5p	Serum samples from CHB patients (n = 360), healthy control (n = 360)	LX-2	Just Liver	CircMTO1	Smad-7, CircMTO1	Enhancing	CircMTO1 by regulation of miR-17-5p/Smad7 axis could inhibit liver fibrosis.	[42]
miR-122	–	Huh-7.5	Just Liver	HNF4A	STAT3, HNF4A, NRF2, NS3, BIP, EIF2A, Core	Enhancing	Hepatic Stress induced by HCV could Promote STAT3-associated suppression of HNF4A/miR-122 axis in LiF.	[43]
miR-146a	SD rats	L02	Multiple organs	TGF- β 1	TGF- β 1, vimentin, E-cadherin, SMAD4	Protective	miR-146a by inhibiting TGF- β 1 mediated EMT could attenuate liver fibrosis in hepatocytes.	[44]
miR-350	C57BL/6J mice	HSC-T6	Multiple organs	ASIC1a	α -SMA, collagen I, ASIC1a, SPRY2, METTL3, PI3K/AKT, ERK	Enhancing	acid-sensitive ion channel 1a (ASIC1a) via N6-methyladenosine could regulate miR-350/SPRY2 to promote LiF.	[45]



(caption on next page)

Fig. 3. A schematic illustration of the role of multiple non-coding RNAs involved in modulating the main molecular cascades underlying liver fibrosis. Oxidative stress in the liver has a remarkable role in triggering the activation of TGF- β 1 that could involve in the hepatic stellate cells (HSCs) activation via regulating the expression and secretion of various proteases and their regulators [123]. TGF- β 1 can also self-induce its generation thus reinforcing its functions [124]. The TGF- β cascade could be activated upon the interaction of TGF- β RII with the ligand. This interaction could lead to the phosphorylation of TGF- β RI, thereby triggering a signal pathway of phosphorylation events on SMAD resulting in the creation of a complex that could transfer into the nucleus and function as a transcription factor of various fibrogenic genes. ROS could also have a significant part in modulating concomitant events like inflammation and lipid metabolism dysregulation. These events could be activated via stressful insults containing radiations and result in the enhancing of the fibrogenic process, mostly via the interplay between the TGF- β cascade and Wnt signaling that positively could modulate each other, whilst the expression of PPAR γ decreases and fails to alleviate TGF- β for the adverse interplay of the canonical Wnt/ β -catenin cascade [125,126]. The proliferation, differentiation, and migration of HSCs could also be modulated via PDGF cascade which could, in turn, play an effective role in the activation of numerous downstream pathways, containing PI3K/Akt, RhoA/ROCK, JAK/STAT, Ras/Raf resulting in triggering the activation of crucial transcription factors like NFkB, STAT1/3 as well as Erk1/2, which could promote the expression of genes relevant to survival, migration and ECM production [127]. TLR4 cascade could also modulate the inflammatory response, fibrogenesis, and survival processes [128]. The activated downstream pathways, MyD88/MKK/PI3K and TRIF/IFR3 could also contribute to the onset of numerous chronic liver diseases [129]. Several studies manifested that various non-coding RNAs could have a considerable role in regulating liver fibrosis which could be seen in detail in Tables 2 and 8.

protects from kidney fibrosis. Another study in the mice model of UUO has shown its role in down-regulation of pro-fibrotic markers, reduction in the quantities of infiltrating monocytes/macrophages, and amendment of tubular epithelial cell damage. In addition, it has a role in the reduction of TGF- β 1-related de-differentiation of human kidney proximal tubular cells. Moreover, miR-9-5p has inhibited the under-expression of genes contributing to important metabolic pathways. Therefore, miR-9-5p induces a protective effect against chronic kidney damage and kidney fibrosis through stimulating reprogramming of the metabolic imbalance and mitochondrial dysfunction [49]. Table 3 shows the impact of miRNAs in renal fibrosis.

2.4. Pulmonary fibrosis

miRNAs have essential roles in pulmonary fibrosis in patients with pneumoconiosis. Certain miRNAs have also been suggested as circulating markers for this condition. A high throughput miRNA profiling in dust-exposed patients with pulmonary fibrosis and healthy controls have shown differential expression of more than 1000 miRNAs between two groups. These miRNAs have been functionally related to anatomical structure development, hemophilic cell adhesion, and cell-cell adhesion via plasma membrane proteins. Among these miRNAs has been has-miR-4516 whose levels can predict the progression of pulmonary fibrosis in patients with pneumoconiosis [67]. Another study has shown the effect of TGF- β 1 in the reduction of miR-411-3p levels in silicosis rats and lung fibroblasts. Up-regulation of miR-411-3p has led to inhibition of TGF- β 1-induced proliferation and migration of pulmonary fibroblasts and attenuation of pulmonary fibrosis in silicotic mice. Functionally, miR-411-3p inhibits Smurf2 expression and decreases ubiquitination-mediated degradation of Smad7, resulting in suppression of TGF- β /Smad cascade [68]. Table 4 shows the impact of miRNAs in pulmonary fibrosis in different conditions.

2.5. Other organs

Assessment of miRNA profile in macrophages of patients with cystic fibrosis and healthy controls has revealed differential expression of 22 miRNAs between two groups. Among these miRNAs, miR-146a targets have been associated with pathways such as responses to microorganisms and inflammation. Suppression of miR-146a in lipopolysaccharide-stimulated macrophages from patients with cystic fibrosis has resulted in enhancement of production of IL-6, suggesting that up-regulation of miR-146a in cystic fibrosis may have a function in restriction of the inflammatory response [74]. Based on the role of macrophages in fibrogenic processes [75], this miRNA might affect the fibrosis of target tissues in patients with cystic fibrosis.

Expression of miR-411 has been found to be downregulated in vein wall tissue and vascular smooth muscle cells of an animal model of deep vein thrombosis while expression levels of Collagen I, HIF-1 α , and MMP-2 have been increased in these cells. HIF-1 α has been identified as a target of miR-411. Injection of miR-411 mimic has suppressed vein wall

fibrosis in a rat model of deep vein thrombosis through decreasing MMP-2 levels [76].

Bone marrow stem cells (BMSCs)-derived exosomes or miR-340 + BMSCs have been shown to increase levels of miR-340 in primary cultured endometrial stromal cells. Treatment of rats with BMSCs has enhanced functional recovery and decreased levels of COL1 α 1, α -SMA, and TGF- β 1 at day 14 following mechanical damage. miR-340 conveyed by BMSCs exosomes has suppressed TGF- β 1-induced upregulation of fibrotic genes in endometrial stromal cells. Taken together, miR-340 transfer by BMSCs induces an antifibrotic function. This route of miR-340 transfer is an alternative method for the prevention of intrauterine adhesion [77].

Table 5 shows the impact of miRNAs in fibrotic processes in different organs.

2.6. Aging

Aging is a multifactorial process in which several molecular mechanisms may contribute. Assessment of miRNA profile in Zmpste24-deficient mice, as a model of Hutchinson-Gilford progeria syndrome, has demonstrated up-regulation of miR-29 family in the progeroid mice. Notably, this miRNA family has also been found to be up-regulated during normal aging in the mouse. Expression of miR-29 has been shown to be induced in response to DNA damage and occurs in a p53-dependent manner [84].

Another study has shown an association between older age of humans and higher median of expression levels of miR-34a and miR-9. Functionally, miR-9 interacts with the 3'UTR of SIRT1 mRNA. In addition, the expression of SIRT1 has been negatively correlated with miR-34a levels. Therefore, age-related reduction in SIRT1 levels in peripheral blood mononuclear cells might be resulted from the up-regulation of miR-34a and miR-9 [85]. Two other miRNAs, namely miR-181a [86] and miR-181ab1 [87] have been found to affect T cell aging. An increase in miR-34a and subsequent decrease in its target, SIRT1, in blood specimens can be suggested as accessible biomarkers for age-dependent changes in the brain; and could predict an impending decline in brain function [88]. Meanwhile, miR-1468-3p can promote aging-related cardiac fibrosis [89] and miR-217 can aggravate atherosclerosis and age-related cardiac dysfunction [90]. Table 6 shows the impact of miRNAs in aging.

3. Impact of lncRNAs on organ fibrosis

3.1. Cardiac fibrosis

Expression of PVT1 has been found to be elevated in atrial muscle tissues from atrial fibrillation in correlation with levels of collagen I and collagen III. Up-regulation of PVT1 has increased Ang-II-associated proliferation of atrial fibroblasts, collagen synthesis, and increased activity of TGF- β 1/Smad cascade, while PVT1 silencing has the opposite effects. PVT1 knockdown has also ameliorated the Ang-II-induced atrial

Table 3
Impact of miRNAs in renal fibrosis.

miRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
miR-29	C57BL/6J mice	Primary Muscle Satellite Cells	–		TRIM63/MuRF1, FBXO32/atrogin-1, Tsg101, myoD, myogenin, eMyHC, YY1, PTEN, MuRF1, atrogin1, TGF-β3, TGF-β1	–	Exo/miR29 amends skeletal muscle atrophy and decreases renal fibrosis through decreasing YY1 and TGF-β pathway proteins.	[48]
miR-33	C57BL/6 (WT) mice	HKC-8	Just kidney	α-SMA	α-SMA, FN1, COLIII, ABCA1, CPT1A, CROT	Enhancing	Inhibition of miR-33 could protect from kidney fibrosis.	[50]
miR-9-5p	C57BL/6 mice	HKC-8	Kidney, Liver, lung, peritoneum, skin	TGF-β1	α-SMA, TGF-β1, PPARα, PGC-1α	Protective	miR-9-5p through metabolic reprogramming could protect from kidney fibrosis.	[49]
miR-150	C57BL/6 mice	NRK-52E, NRK-49F	Multiple organs including liver and kidney	α-SMA	CD63, TSG101, α-SMA, collagen I, fibronectin	Enhancing	Injured tubular epithelial cells via miR-150-containing exosomes could activate fibroblasts to promote kidney fibrosis.	[51]
miR-325-3p	C57BL/6J mice	HMCs, HK2	Heart, kidney, liver, lung	CCL19	CCL19, collagen I, collagen III, collagen IV, fibronectin, TNF-α, IL-6, IL-1β,	Protective	miR-325-3p via targeting CCL19 could inhibit renal inflammation and fibrosis in diabetic nephropathy.	[52]
miR-133b, miR-199b	OLETF rats	HK-2, 293T	Just kidney	SIRT1	SIRT1, TGF-β1, COL I, fibronectin, α-SMA, E-cadherin	Enhancing	miR-133b and miR-199b knockdown by targeting SIRT1 could attenuate TGF-β1-induced EMT and renal fibrosis in diabetic nephropathy.	[53]
miR-214	C57BL/6 mice	HK-2	Just kidney	Twist	Twist, ZO-1, E-cadherin, α-SMA, vimentin	Enhancing	The activation of the Twist/miR-214/E-cadherin axis through Hypoxia could promote renal tubular EMT and renal fibrosis.	[53]
miR-27b-3p	C57BL/6 mice	HK-2	Just kidney	STAT1	α-SMA, collagen III, Fibronectin, Vimentin, TGF-β1, STAT1, Caspase-3/8, Fas	Protective	miR-27b-3p by suppressing STAT1 could inhibit the progression of renal fibrosis.	[54]
miR-98-5p	C57BL/Ks mice	293T	Just kidney	Hmga2	Hmga2, E-cadherin, N-cadherin, HMGAA2, TGF-β1, COL4A1,	Protective	miR-98-5p via Targeting Hmga2 could alleviate EMT and kidney fibrosis in diabetic nephropathy.	[55]
miR-130a-3p	–	HRPTEpiCs, HK-2	Multiple organs including the kidney	SnoN	TGF-β1, Smad-2/3, Smad7, SnoN, α-SMA, Vimentin, Fibronectin, and Collagen IV, E-cadherin	Enhancing	Inhibition of miR-130a-3p via targeting TGF-β1/Smad/ SnoN could protect against renal fibrosis in vitro.	[56]
miR-21	male C57BL/6J mice	Primary podocytes	Just kidney	β-catenin	AS-IV, α-SMA, nephrin, Smad-3/7, TGF-β1, β-catenin	Enhancing	AS-IV via suppression of miR-21 overexpression-induced podocyte dedifferentiation and MC activation in diabetic renal disease could ameliorate kidney function and renal fibrosis.	[57]
miR-200b	CKD patients with different degrees of renal fibrosis (n = 38), healthy control (n = 12)	–	Just kidney	CD63	CD63, CD13	Protective	Non-proximal renal tubule-originated urinary exosomal miR-200b could be a marker of kidney fibrosis.	[58]
miR-455-3p	SD rats	primary HMC, HK-2	Just kidney	ROCK2	TGF-β1, ROCK2	Protective	miR-455-3p via repression of ROCK2 could suppress renal fibrosis in diabetic nephropathy.	[58]
miR-101a	C57BL/6 mice	HK-2	Just kidney	KDM3A	KDM3A, YAP-TGF-β, Smad, TGF-β2, Col1a1, fibronectin, α-SMA	Protective	Upregulation of miR-101a by Regulating KDM3A via blockade of the YAP-TGF-β-Smad Pathway could suppress chronic RF.	[59]
miR-23a/27a	C57BL/6J mice			Akt	GFP, myostatin, SMAD2/3, Akt, PTEN,	Protective	Up-regulation of miR-23a/27a in muscle could attenuate renal	[60]

(continued on next page)

Table 3 (continued)

miRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
		Primary muscle satellite GnECs	Multiple organs including the kidney Just kidney		FoxO1, MuRF1, Atrogin1		fibrosis lesions via muscle–kidney crosstalk.	
miR-103a-3p	C57BL/6J mice, urine and Serum samples from hypertensive patients (n = 60), healthy control (n = 18)			SNRK	SNRK, NF-κB, p65, Mcp-1, Tnf-α, collagen I/IV	Enhancing	miR-103a-3p through targeting SNRK/NF-κB/p65 axis could contribute to angiotensinII-induced renal fibrosis.	[61]
miR-29b	C57BL/6 mice	NRK-49F, NRK-52E, TECs	Just kidney	TGF-β1	TGF-β1	Protective	rAAV6-mediated miR-29b delivery could inhibit kidney fibrosis.	[62]
miR-21	Mice	HK-2,	kidneys, lungs, heart	TGFβ-1, TNF-α	Col1A1, TGFβ-1, TNF-α	Protective	Targeting miR-21 could be a novel therapeutic method for the treatment of renal fibrosis.	[63]
miR-30e	nephropathy tissues (n = 15), normal samples (n = 10), SPF-grade KM mice	HK-2, NRK-52e, 293 T	Just kidney	Snail, Slug, Zeb2	TGF-β1, Snail, Slug, Zeb2, α-SMA, vimentin, E-cadherin, Col1a1, Col4a1 fibronectin, Col-4, TGF-β1, FGF11	Protective	Schisandrin B through miR-30e-mediated inhibition of EMT could attenuate renal fibrosis.	[64]
miR-24-3p	DN mice	MCs	Just kidney	FGF11		Enhancing	Circ_0080425 by sponging miR-24-3p and targeting FGF11 could inhibit fibrosis in diabetic nephropathy.	[65]
miR-130b	50 pairs of DN and adjacent normal tissues	HMCs	Just kidney	TGF-β1	TGF-β1, Smad2/3, SMAD4, coll, collIV, fibronectin	Enhancing	miR-130b via targeting the TGF-β1 could increase fibrosis of HMC cells in diabetic nephropathy.	[66]

fibrosis in mice. Functionally, PVT1 sponges miR-128-3p to enhance Sp1 expression, thus increasing the activity of the TGF-β1/Smad cascade [97]. NRON up-regulation has been shown to suppress Ang II-associated inflammatory responses in primary cultured atrial myocytes. This lncRNA suppresses Ang II-associated transport of NFATc3 to the nucleus and the expression of IL-12 in atrial myocytes. Taken together, NRON ameliorates atrial fibrosis via inhibition of M1 macrophages activated by atrial myocytes [98]. GAS5 by targeting the miR-21/PTEN/MMP-2 axis can modulate the activity of cardiac fibroblasts and fibrosis [99]. In addition, MIAT/miR-133a-3p axis could be involved in atrial fibrillation and atrial fibrillation-induced myocardial fibrosis [82]. Table 7 shows the impact of lncRNAs in cardiac fibrosis. Fig. 2 depicts involving of several lncRNAs and miRNAs in regulating cardiac fibrosis.

3.2. Liver fibrosis

Liver fibrosis is a communal pathological result of persistent wound healing responses to sustained hepatic damage, described by the high amount of extracellular matrix biosynthesis and buildup. If unsettled, fibrotic processes can lead to organ dysfunction, and ultimately death as a result of cirrhosis. Macrophages have essential effects in the progression of liver fibrosis. This effect is associated with inflammatory responses and pyroptosis which is an inflammatory kind of programmed cell death. Lfar1 is a lncRNA with high expression in liver tissues. This lncRNA has been found to induce liver fibrosis via increasing activation of hepatic stellate cells and stimulating hepatocytes apoptosis. Expression of Lfar1 has also been found to be altered in the course of activation of proinflammatory M1 macrophages and pyroptosis of macrophages. Inhibition of expression of lnc-Lfar1 has amended CCl₄- and BDL-associated activation of proinflammatory M1 macrophages and NLRP3 inflammasome-mediated pyroptosis. Moreover, cell line studies have

shown that lnc-Lfar1 silencing suppresses LPS- and IFN-γ-associated inflammatory activation of macrophage, and blocks NLRP3 inflammasome-associated pyroptosis. These effects are mediated via the NF-κB pathway [113].

Expression of lncRNA-ATB has been found to be increased in fibrotic hepatic tissues and activated LX-2 cells treated with conditioned media from HepG2 cells being transfected with HCV core protein. This lncRNA has binding sites for miR-200a and β-catenin. Consistently, hepatic tissues from patients with HCV-related liver fibrosis and activated hepatic stellate cells (HSCs) exhibit down-regulation of miR-200a and up-regulation of β-catenin. Suppression of lncRNA-ATB has resulted in down-regulation of β-catenin through enhancing the expression of miR-200a and inhibiting the activity of LX-2 cells. Taken together, the lncRNA-ATB/miR-200a/β-catenin axis might participate in the pathology of hepatic fibrosis in HCV patients. Therefore, lncRNA-ATB silencing has been suggested as a possible therapeutic modality for HCV-associated hepatic fibrosis [114].

Several other lncRNAs can affect liver fibrosis. For instance, GAS5 via targeting miR-23a through the PTEN/PI3K/Akt pathway could restrain hepatic fibrosis [115]. In addition, Meg8 by targeting the Notch could suppress activation of HSCs and EMT of hepatocytes [116]. Fig. 3 represents the role of various non-coding RNAs in modulating liver fibrosis. Table 8 shows the impact of lncRNAs in liver fibrosis.

3.3. Renal fibrosis

Expressions of LINC00667 and CTGF have been found to be elevated in renal tissues of patients with chronic renal failure (CRF), parallel with down-regulation of miR-19b-3p levels. Suppression of LINC00667 expression has led to enhancement of proliferation and migration of renal tubular epithelial cells, and inhibition of apoptosis. Moreover, the

Table 4
Impact of miRNAs in pulmonary fibrosis.

miRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
has-miR-4516	dust-exposed patients with PF (n = 4), healthy individuals (n = 4)	–	Just lungs	basonuclin2	basonuclin2, sha-1-related subfamily member 1	Enhancing	The level of serum miR-4516 could be a marker for early detection of PF in patients with pneumoconiosis.	[67]
miR-411-3p	Wistar rats, C57BL/6 mice	Primary fibroblasts	Multiple organs including lungs	Smurf2	α-SMA, Smurf2, Col I, Smad7, TGF-βR1, TGF-βR2, TGF-β1, Smad2/3	Protective	miR-411-3p via regulating Smurf2/TGF-β axis could alleviate Silica-induced pulmonary fibrosis.	[68]
miR-21	SD rats	MRC-5	Just lungs	MAPK/AP-1	Smad7, fibronectin, COL1 A1, COL1 A2, α-SMA, TGF-β/Smad, MAPK/AP-1	Enhancing	Resveratrol by regulating miR-21 through MAPK/AP-1 pathways could inhibit pulmonary fibrosis.	[69]
miR-96	SD rats	16HBE, rat lung cells	Just lungs	NLRP3	α-SMA, NLRP3, ASC, pro-caspase1, caspase-1, IL-1b, FOXO3a	Protective	Carbon black nanoparticles via NLRP3/miR-96/FOXO3a axis could induce pulmonary fibrosis.	[70]
miR-200	Mice, normal human lung tissue samples	Primary AECs, MRC-5, RLE-6TN	Just lungs	TGF-β1	TGF-β1, Vimentin, SMA-α, E-cadherin, GATA3, ZEB1/2, fibronectin	Protective	Restoring miR-200 expression in the lung tissues could be a therapeutic method for pulmonary fibrotic diseases.	[71]
miR-200b/c	C57BL/6 mice	RLE-6TN	Just lungs	ZEB1/2	ZEB1/2, E-cadherin, Vimentin, α-SMA, p38 MAPK, TGF-β/smad3	Protective	miR-200b/c by targeting the ZEB1/2 axis via p38 MAPK and TGF-β/smad3 pathway could attenuate lipopolysaccharide-induced early pulmonary fibrosis.	[72]
miR-21	C57BL/6J mice	pulmonary fibroblast	Just lungs	Smad7	TGF-β1, Smad7, COL1A1, COL3A1, MMP-2/9,	Enhancing	Knocking out miR-21 could ameliorate Nano-Ni-induced pulmonary fibrosis.	[73]

expression of miR-19b-3p has been up-regulated following LINC00667 silencing. Renal fibrosis and EMT have been also inhibited. Therefore, LINC00667 silencing can enhance the proliferation of renal tubular epithelial cells and amend renal fibrosis in CRF through the miR-19b-3p/LINC00667/CTGF axis [130].

LncRNA 1700020I14Rik via targeting miR-34a-5p/Sirt1/HIF-1α axis could alleviate cell proliferation and fibrosis in diabetic nephropathy [131]. Similarly, GAS5 via targeting miR-221/SIRT1 axis could inhibit cell proliferation and fibrosis in diabetic nephropathy [132]. On the other hand, MALAT1 via targeting the miR-145/ZEB2 axis could facilitate high glucose-induced EMT and fibrosis [133]. In addition, MALAT1 could aggravate renal fibrogenesis in obstructive nephropathy via targeting the miR-145/FAK axis [134]. Table 9 shows the impact of lncRNAs in renal fibrosis.

3.4. Pulmonary fibrosis

Expression of ZEB1-AS1 has been found to be elevated in the lung tissue of BLM-induced rats and TGF-β1-induced rat lung epithelial cells. Its expression has been positively correlated with the expression of ZEB1, a key regulator of EMT. ZEB1-AS1 silencing has amended BLM-associated fibrogenesis in animal models by suppressing EMT. Functionally, ZEB1-AS1 enhances fibrogenesis via modulation of miR-141-3p expression [145]. PFAR is another lncRNA that contributes to pulmonary fibrosis via different mechanisms. It can serve as a sponge for miR-138 to regulate the YAP1-Twist axis and promote lung fibroblast activation and fibrosis [146]. Moreover, via binding with miR-15a, PFAR can regulate the expression of TGF-β1, collagen 1, α-SMA, YAP1, and Twist [147]. In addition, ATB can serve as a sponge for miR-200c to promote EMT during silica-induced pulmonary fibrosis [148]. Table 10 shows the impact of lncRNAs in pulmonary fibrosis.

3.5. Other organs

In addition to the mentioned common fibrotic processes, lncRNAs have been found to participate in a number of less common fibrotic conditions. For instance, GAS5-AS1 has been found to inhibit myofibroblast activities in oral submucous fibrosis [153]. NR_003923 via targeting the miR-760/miR-215-3p/IL22RA1 axis could promote cell proliferation, migration, fibrosis, and autophagy in human Tenon's capsule fibroblasts [154]. Finally, TUG1 by targeting the miR-590-5p/Fasl axis could promote endometrial fibrosis and inflammation in intrauterine adhesions [155]. Table 11 shows the outlines of these studies.

3.6. Aging

Aging-associated osteoporosis has been shown to be associated with the switch between osteogenic and adipogenic differentiation of BMSCs. Xist lncRNA has been found to be involved in this process through sponging miR-19a-3p. Expression of miR-19a-3p has been decreased in BMSCs of aged human subjects as well as mice. Up-regulation of miR-19a-3p has attenuated aging-associated bone loss in animal models and enhanced osteogenic differentiation of BMSCs. Hoxa5 has been found to be under-expressed in the BMSCs of aged animals. This gene has a role in the miR-19a-3p-induced osteoblast differentiation since it is the direct target of miR-19a-3p. Therefore, Xist/miR-19a-3p/Hoxa5 pathway has been suggested as a target for the treatment of osteoporosis [156]. ENSMUST00000134285 is another lncRNA that is involved in the process of aging-related myocardial apoptosis. ENSMUST00000134285 could increase MAPK11 activity and regulate aging-related myocardial apoptosis [157]. Finally, animal and cell line studies have indicated that H19 could regulate endothelial cell aging through the inhibition of Stat3 [158]. Table 12 shows the impact of lncRNA in aging.

Table 5

Impact of miRNAs in fibrosis in other organs.

Disease	miRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
Cystic Fibrosis (CF)	miR-146a	CF patients (n = 16), Blood samples from healthy donors as controls	non-CF macrophages	Multiple organs including lungs	IL-6	IL-6, TRAF6	Protective	In cystic fibrosis macrophages, miR-146a has been over-expressed and could control IL-6 production.	[74]
CF	miR-199a-3p	CF patients (n = 8)	CFBE41o-	Multiple organs including lungs	IKBKB	IKBKB, IL8, NF- κ B	Protective	miR-199a-3p could be involved in cystic fibrosis.	[78]
Deep Venous Thrombosis (DVT)	miR-411	SD rats	VSMCs	Multiple organs	HIF-1 α	Collagen I, HIF-1 α , MMP-2, SM α -actin, SM22 α	Protective	miR-411 by targeting HIF-1 α via downregulating MMP-2 could suppress vein wall fibrosis.	[76]
Endometriosis Fibrosis	miR-340	female SD rats	BMSC	uterine	CD63	CD63, TGF- β 1, α -SMA, col1a1	Protective	Exosomal transfer of BMSCs derived miR-340 is involved in the attenuation of fibrosis.	[77]
	miR-214	24 pairs of ovarian endometriosis and adjacent normal tissues/ 12 female nude mice (Balb/c)	ecto-ESCs, euto-ESCs	uterine	CTGF	CTGF, α -SMA, collagen α 1, TGF- β 1	Protective	An increase in CTGF and fibrotic markers in endometriosis could be involved in a reciprocal down-regulation of miR-214.	[79]
Ischemia-Induced Fibrosis	miR-149	BALB/c nude mice	Myoblasts	Multiple organs	PGC-1 α , TNF- α	Smad-2, collagen I, Fibronectin, IDO-1, TNF- α , PGC-1 α	Protective	Melatonin through regulating miR-149 could suppress ischemia-induced fibrosis.	[80]
Peritendinous Fibrosis	miR-21-5p	C57BL/6 mice	NIH 3T3	tendons	Smad7	COL I, COL III, α -SMA, TGF- β 1, CD9, TSG101, CD63, ALIX, CD68, Smad7	Protective	Macrophage-derived miR-containing exosomes via targeting the miR-21-5p/Smad7 axis could induce peritendinous fibrosis after tendon injury.	[81]
Silicosis	miR-155-5p	Male Wistar rats, male C57BL/6 mice	NR8383 macrophages, primary lung fibroblasts, mouse embryonic fibroblasts	Just lungs	meprin a	pro-COL I, meprin a, MCP-1, TGF- β 1, TGF- β R I, TGF- β R II, Smad2/3, α -SMA	Enhancing	Inhibition of miR-155-5p via targeting Meprin could exert anti-fibrotic effects in silicotic mice.	[82]
Skeletal Muscle Fibrosis	miR-24, miR-122	mice	C2C12, 293 T	skeletal muscle	Smad2, TGF- β	Smad2/3/4, TGF- β , Col1a1, α -SMA, VIM, Tgfr β 2, TGF- β /Smad	Protective	miR-24 and miR-122 could negatively regulate the TGF- β /Smad pathway in skeletal muscle fibrosis.	[83]

4. Discussion

Organ fibrosis is a final step in several pathologies, particularly in age-related pathologies. This process has been found to be regulated by several lncRNAs and miRNAs. Modulation of TGF- β signaling is an appreciated route of the contribution of these transcripts in organ fibrosis. Although WNT and YAP/TAZ are other signaling cascades with prominent roles in organ fibrosis, the regulatory roles of lncRNAs and miRNAs on these pathways have been less studied in the context of fibrogenesis.

EMT and EndMT are two cellular processes that have been shown to be affected by miRNAs during this process. LncRNAs mainly affect fibrogenesis through sponging miRNAs. PVT1/miR-128-3p, GAS5/miR-21, PFL/let-7d, MIAT/miR-214-3p, n379519/miR-30 and RNF/miR-543 are among molecular axes that regulate cardiac fibrosis. In the

course of renal fibrosis, LINC00667/miR-19-3p, 1700020I14Rik/miR-34a-5p, GAS5/miR-221, MALAT1/miR-145, MIAT/miR-147a, Erbb4-IR/miR-29b, HOTAIR/miR-124, GAS5/miR96-5p, TCONS_00088786/miR-132, NR_038323/miR-324-3p and H19/miR-29a have been found to exert functional effects.

Notably, some lncRNAs such as ZEB1-AS1, HOTAIR, Gas5, TUG1, NEAT1, MIAT, and ATB have been found to affect fibrogenesis in different organs, representing common routes for this phenomenon in different pathological situations. Therefore, these lncRNAs are potential common targets for interfering with organ fibrosis.

Several other lncRNA/miRNA axes have been also identified that affect pathogenesis of organ fibrosis or age-related changes in organs.

Serum levels of miRNAs have the potential to be used as markers for the evaluation of the progression of fibrosis in different tissues. This potential has been successfully appraised in pulmonary fibrosis [67].

Table 6
Impact of miRNAs in aging.

Disease	miRNA	Sample	Cell lines	List of known regulator/binding partners	Targets	Brief Role	Function	Refs.
Aging	miR-29	Zmpste24-null mice	Fibroblast, 293T	p53	p53, anti-Flag	Enhancing	Aging and chronic DNA damage response by targeting miR-29/p53 axis could activate.	[84]
Aging	miR-34a, miR-9	Healthy individuals (n = 165)	293 T	SIRT1	SIRT1/7	Enhancing	Overexpression of miR-34a/miR-9 axis and downregulation of SIRT genes could be involved in aging.	[85]
T cell Aging	miR-181a	Healthy individuals (n = 206)	PBMCs	YY1	YY1, TCR	Enhancing	YY1 via upregulating miR-181a could control the TCR pathway in T-cell aging.	[86]
T cell Aging	miR-181ab1	individuals previously recovered from WNV (West Nile virus) infection (n = 48), C57BL/6 J (B6) mice	BHK, Vero, Plat-E	–	–	Protective	The deficiency of miR-181a could be involved in a defect in antiviral T-cell responses inflicted by aging.	[87]
Brain Aging	miR-34a	Brain and blood specimens of C57/B6 mice	PBMC	SIRT1	SIRT1, Bcl2, p53	Enhancing	An increase in miR-34a and subsequent decrease in its target, SIRT1, in blood specimens could be the markers for age-dependent alterations in the brain; and could predict an impending decline in brain function.	[88]
Aging-Related Cardiac Fibrosis	miR-1468-3p	human samples from cardiovascular disease (CVD) victims (n = 5869), healthy cardiac tissues	hCFs	TGF-β1	TGF-β1, P16, P21, P53, collagen 1, periostin, CTGF	Enhancing	miR-1468-3p could promote aging-related cardiac fibrosis.	[89]
Cardiovascular Disease (CVD)	miR-217	Plasma samples from coronary atherosclerosis patients (n = 32), disease-free nonagenarian individuals (n = 41), C57BL/6J mice.	Primary human vein endothelial cells, Lung endothelial cells from mouse	Sirt1	Sirt1	Enhancing	Aging-associated miR-217 could aggravate atherosclerosis and could promote cardiovascular dysfunction.	[90]
Aging-Related Fibrosis of Kidney	miR-21	Rats, human kidney tissues of nephrectomy patients	primary human PTCs	PPARα	α-SMA, E-cadherin, vimentin, PPARα, HIF-1α, TGF-β1	Enhancing	Caloric restriction via downregulation of miR-21 could alleviate aging-related fibrosis of the kidney.	[91]
Human Mesenchymal Stem Cell Aging	miR-543, miR-590-3p	C57BL/6 mice	hMSCs	AIMP3/p18	AIMP3/p18, p16INK4A, p21CIP1/WAF1	Protective	miR-543 and miR-590-3p by targeting of AIMP3/p18 axis could regulate human mesenchymal stem cell aging.	[92]
Human Endothelial Cell Aging	miR-146a	–	Human umbilical vein endothelial cells	NOX4	NOX4	Protective	miR-146a could be modulated in the human endothelial cell with aging.	[93]
Hepatic Aging	miR-126a	C57BL/6J mice	293 A, 293 T, BMSC, HeLa, NIH 3T3, 3T3-L1	VCAN	TERT, CRISPR, Cas9, γ-H2A.X, NF-κB P65, STAT3, Lamin B, VCAN	Protective	Deletion of miR-126a could promote hepatic aging.	[94]
Human Liver Aging	miR-31-5p, miR-141-3p, miR-200c-3p	heart-beating and brain death liver donors (n = 71)	293 T	GLT1	GLT1	Enhancing	miR-31-5p, miR-141-3p, miR-200c-3p, and GLT1 are markers for liver aging.	[95]
Aging-Induced Osteoarthritis	miR-146a	Human cartilage tissue from Osteoarthritis (OA) patients (n = 13), C57BL/6 J (WT) mice, Col2a1-Cre mice	Human/Mouse articular chondrocytes	Notch1	Notch1, IL-1/6, IL-1β, Notch1	Protective	miR-146a via inhibiting Notch1/IL-6/IL-1 axis mediated catabolism could attenuate aging- and trauma-induced osteoarthritis.	[96]

Although dysregulation of miRNAs has been associated in different other fibrotic situations, their biomarkers roles have not been fully understood.

Therapeutic modulation of lncRNAs or miRNAs expressions has been proposed as a strategy to combat organ fibrosis and related pathologies.

Targeted suppression of miRNA and lncRNAs by different strategies such as antisense oligonucleotides and forced over-expression of anti-fibrosis/anti-aging miRNAs and lncRNAs in tissues have been successfully implemented in animal models. Although the efficacy of these strategies has been well appraised in animal models [159,160], the

Table 7
Impact of lncRNAs in cardiac fibrosis.

IncRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
PVT1	C57BL/6J mice	Human atrial fibroblasts	Just heart	miR-128-3p	miR-128-3p, SP1, TGF- β 1, Smad	Enhancing	PVT1 by miR-128-3p/SP1/TGF- β 1/Smad axis can control atrial fibrosis in atrial fibrillation.	[97]
NRON	–	mouse primary atrial myocytes, RAW264.7 macrophages	Just heart	Ang II	Ang II, IL-12, Collagen I/III	Protective	NRON via suppression of M1 macrophages activated by atrial myocytes could alleviate atrial fibrosis.	[98]
NRON	AF patients (n = 34), SR patients (n = 20), C57BL/6J mice	atrial fibroblasts	Just heart	NFATc3	NFATc3, collagen I, collagen III	Protective	NRON by promoting NFATc3 phosphorylation could alleviates atrial fibrosis.	[100]
GAS5	SD rats	CFs	Multiple organs including heart	miR-21	miR-21, Col1A1, α -SMA, PTEN/MMP-2	Protective	GAS5 through modulation of miR-21/PTEN/MMP-2 axis could control cardiac fibroblast activation and fibrosis.	[99]
PFL	C57BL/6 mice	CFs, CMs	Just heart	let-7d	let-7d, α -SMA, collagen 1 α , fibronectin 1, CTGF, Ptafr	Enhancing	PFL via acting as a competing endogenous RNA of let-7d could contribute to cardiac fibrosis.	[101]
MIAT	Blood samples from diabetic patients (n = 12) and healthy control, C57BL/6 mice	Primary cardiomyocytes and fibroblasts	Just heart	miR-214-3p	IL-17, miR-214-3p, collagen I/III	Enhancing	In diabetic cardiomyopathy, MIAT-mediated miR-214-3p silencing had been involved in the production of IL-17 and cardiac fibrosis.	[102]
n379519	SD rats	CFs cells	Just heart	miR-30	miR-30, TGF- β 1	Enhancing	n379519 via targeting miR-30 enhances cardiac fibrosis in post-infarct myocardium.	[103]
RNF7	SD rats	Primary rat cardiac fibroblasts	Just heart	miR-543	miR-543, THBS1, Collagen I, TGF β 1, CTGF, Fibronectin, α -SMA	Enhancing	RNF7 via targeting miR-543/THBS1 axis and TGF β 1 activation could promote cardiac fibrosis in the rat.	[104]
Safe	CD1 mice	Cardiac fibroblasts	Multiple organs	SFRP2, HuR	COL1A1, α -SMA, SFRP2, HuR	Enhancing	Safe via Safe-Sfrp2-HuR complex could contribute to cardiac fibrosis.	[105]
GAS5	C57BL/6 mice	–	Just heart	PTEN, MMP-2	PTEN, MMP-2, α -SMA, and collagen I	Protective	Up-regulation of GAS5 through modulation of PTEN/MMP-2 axis could attenuate cardiac fibrosis in mice.	[106]
FAF	SD rats	CFs, CMs	Just heart	FGF9	TGF- β 1, α -SMA, Collagen I/III, Smad-2/3, FGF9	Protective	FAF by angiotensinogen II/TGF β 1-P-Smad2/3 axis via targeting FGF9 could inhibit fibrosis induced in cardiac fibroblasts.	[107]
GAS5	SD rats	Primary cardiac fibroblasts from the hearts of neonatal SD rat	Just heart	MeCP2	MeCP2, α -SMA, collagen I, TGF- β 1, Smad3	Protective	GAS5 by inactivating MeCP2 could trigger cardiac fibroblasts activation in cardiac fibrosis.	[108]
PCFL	C57BL/6 mice	Cardiac fibroblasts	Just heart	miR-378	miR-378, GRB2, Col I, Col III	Enhancing	PCFL via targeting the miR-378/GRB2 axis could promote cardiac fibrosis following myocardial infarction.	[109]
MALAT1	KM mice	Neonatal mouse cardiac fibroblasts	Just heart	miR-141	miR-141, TGF- β 1, Smad2/3, Col-I, Col-III, NLRP3, ASC, IL-1 β , IL-18	Enhancing	Melatonin via inhibiting MALAT1 by targeting the miR-141/NLRP3/TGF- β 1/Smads axis could alleviate cardiac fibrosis in diabetic cardiomyopathy.	[110]
SOX2OT	C57BL/6 mice	CFs	Just heart	miR-138-5p	collagen I, α -SMA, TGF- β 1, Smad3, miR-138-5p	Enhancing	SOX2OT/Smad3 feedback loop could promote myocardial fibrosis in heart failure.	[111]
MIAT	Blood samples from Atrial Fibrillation (AF) patients (n = 35), healthy people (n = 30), SD rats	–	Just heart	miR-133a-3p	miR-133a-3p, collagen I, collagen III, TGF- β 1	Enhancing	MIAT/miR-133a-3p axis could be involved in atrial fibrillation and atrial fibrillation-induced myocardial fibrosis.	[82]
ROR	rats	Myocardial Cells	Multiple organs including the heart	C-Myc	C-Myc, TGF- β , IL-6	Enhancing	ROR by targeting C-Myc could facilitate myocardial fibrosis in rats.	[94]

Table 8

Impact of lncRNAs in liver fibrosis (HSC: hepatic stellate cells).

lncRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Ref
ATB	Liver tissues from HCV patients (n = 18), healthy control (n = 6)	HepG2, LX-2	Just liver	miR-200a	miR-200a, β-catenin, Col1A1	Enhancing	ATB/microRNA-200a/β-catenin axis participates in the progression of HCV-related liver fibrosis.	[114]
Lfar1	C57BL/6 mice	RAW264.7	Just liver	NLRP3	F4/80, CD11, LY6C, NLRP3, GSDMD, MCP-1	Enhancing	Silencing Lfar1 could alleviate activation and pyroptosis of macrophage in liver fibrosis.	[113]
GAS5	SD rats	HSCs	Just liver	miR-23a	miR-23a, E-cadherin, α-SMA, collagen I, PTEN/PI3K/Akt	Enhancing	GAS5 via targeting miR-23a through the PTEN/PI3K/Akt pathway could limit liver fibrosis.	[115]
HULC	SD rats	–	Multiple organs including the liver	p38 MAPK	Caspase-3, Bax, Bcl-2, p38 MAPK, JNK	Enhancing	Inhibition of HULC via influencing the MAPK could improve hepatic fibrosis and hepatocyte apoptosis in rats with nonalcoholic fatty liver disease.	[117]
Meg8	–	HSCs, LX-2, AML12	Just liver	Mmp2	α-SMA, COL1a1, Mmp2, PCNA	Enhancing	Meg8 by targeting the Notch could suppress activation of HSCs and EMT of hepatocytes.	[116]
MEG3	CHB patients (n = 139), healthy control (n = 60)	Primary HSCs	Just liver	miR-212	miR-212, α-SMA, Col1A1, E-cadherin, BMP-7, Desmin, Vimentin, PTCH1, SMO, GLI3	Protective	MEG3 via targeting the SMO/miR-212 axis could inhibit the activation of hepatic stellate cells.	[118]
ANRIL	SD rats	HSC-T6	Just liver	DNMT3A	AMPK, DNMT3A, α-SMA, Col1A1	Protective	Epigenetic silencing of ANRIL via activating AMPK could enhance liver fibrosis and HSC activation.	[119]
H19	C57BL/6J mice	HSC, LX-2, 293 T/17, HSC, EMT	Just liver	miR-148a	miR-148a, USP4, TGF-β, α-SMA, Col1A1, SMAD2/3, E-cadherin, Vimentin	Enhancing	H19/miR-148a/USP4 axis via enhancing TGF-β pathway could facilitate liver fibrosis in both hepatic stellate cells and hepatocytes.	[120]
H19	C57 mice, human Liver cirrhosis samples, and normal Control tissues	Primary hepatocytes, AML12	Multiple organs including the liver	Sox9	Sox9, Col I	Enhancing	Sox9/H19 axis could contribute to hepatocyte death and liver fibrosis.	[121]
NEAT1	–	BRL3A	Just liver	miR-506	miR-506, GLI3, SMO, GLI2, FAS, ACC	Enhancing	NEAT1 via targeting the miR-506/GLI3 axis could regulate fibrosis and inflammatory responses associated with nonalcoholic fatty liver.	[122]

clinical utility of these methods needs to be tested in future studies.

5. Conclusions and future perspectives

Evidence for the role of ncRNAs modulation of gene expression in the progression of organ fibrosis has been expanded these days. In the future, the modulation of various ncRNAs could be targeted and influenced via pharmacological or genetic interventions. Moreover, subsequent studies will also play a key role in providing more accurate information at the molecular level regarding the recognition of the particular genes which are directly influenced by miRNAs as well as lncRNAs modifications. As an illustration, ncRNA suppressors could be efficient in ameliorating cardiac fibrosis. In cardiac fibrosis, these ncRNAs suppressors may have an important part in becoming the first used drug in future clinical life. Therefore, detecting the most effective cellular cascades that target these ncRNAs is an important question that must be answered. Whilst, suitable combination remedy could be essential with the aim of implementing the productive treatment. Hence, this points out that ncRNAs inhibitors will now be utilized in cardiac fibrosis as a monotherapy and in combination remedy with other chemotherapies [161]. Besides, accumulating finding has illustrated that

extracellular vesicles (EVs) could be active mediators of intercellular communication in a variety of pathological situations, like liver fibrosis. The defective hepatocytes could generate EVs which function in a paracrine way to modulate important processes of hepatic fibrosis, including Hepatic stellate cell (HSC) activation, angiogenesis, and coagulation, thereby enhancing the development of liver fibrosis. Analysis of the EVs cargo, especially ncRNAs, could play an effective role in providing further insight into the epigenetic modulation of genes and pathways linked to hepatic fibrogenesis. In the future, engineering native EVs carrying anti-fibrotic ncRNAs could be applied with the aim of delivering remedial molecules to promote liver regeneration. Interestingly, mesenchymal stromal cell (MSC)-derived EVs could be considered as beneficial candidates in the delivery of antifibrogenic miRNAs as well as lncRNAs to HSCs, therefore reducing hepatic fibrosis [162]. In addition, growing evidence confirms that lncRNAs could contribute to gene expression through versatile systems of action that could enable these lncRNAs to perform various functions including modulating biological processes of kidney cells, mesenchymal cell phenotype transition as well as vascular damage and rarefaction during renal fibrosis. Therefore, lncRNAs could play a remarkable role in applying them as diagnostic markers and remedial target during renal

Table 9
Impact of lncRNAs in renal fibrosis.

lncRNA	Sample	Cell lines	Organ specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
LINC00667	CRF patients (n = 138)	renal tubular epithelial cells	Just kidney	miR-19b-3p	miR-19b-3p, CTGF, α -SMA, TIMP-1	Enhancing	LINC00667 via targeting miR-19b-3p/LINC00667/CTGF axis could affect renal tubular epithelial cell proliferation, apoptosis, and renal fibrosis in chronic renal failure.	[130]
1700020I14Rik	C57BL/KsJ mice	MCs	Just kidney	miR-34a-5p	miR-34a-5p, Sirt1, HIF-1 α , cyclin D1, p21, Col-4, fibronectin, TGF- β 1	Protective	LincRNA 1700020I14Rik via targeting miR-34a-5p/Sirt1/HIF-1 α axis could alleviate cell proliferation and fibrosis in DN.	[131]
GAS5	SD rats	Mesangial cells	Just kidney	miR-221	miR-221, SIRT1, fibronectin, Col-4, TGF- β , p53, p21, Ago2	Protective	GAS5 via targeting miR-221/SIRT1 axis could inhibit cell proliferation and fibrosis in diabetic nephropathy.	[132]
MALAT1	db/db mouse, C57BL/Ks mice	HK-2, 293T	Just kidney	miR-145	miR-145, ZEB2, Col I, E-cadherin, α -SMA, Vimentin, ZEB1, fibronectin	Enhancing	MALAT1 via targeting the miR-145/ZEB2 axis can increase high glucose-induced EMT and fibrosis.	[133]
NEAT1	mice	SV40 MES13, MMCs	Just kidney	Cyclin D	Cyclin D, PCNA	Enhancing	Downregulation of NEAT1 could inhibit mouse mesangial fibrosis but could promote apoptosis in diabetic nephropathy.	[135]
MIAT	renal samples from DN patient (N = 30), normal kidney tissues as healthy control (n = 30)	human mesangial cells	Just kidney	miR-147a	E2F3, miR-147a, collagen IV, fibronectin, TGF- β 1	Enhancing	Loss of MIAT via reducing E2F3 expression could ameliorate fibrosis of diabetic nephropathy.	[102]
TUG1	SD rats	Mouse-derived mesangial cells	Just kidney	TGF- β 1	TGF- β 1, fibronectin, COL-IV, PI3K, AKT	Protective	TUG1 by inhibiting the PI3K/AKT pathway could inhibit fibrosis of mesangial cells in diabetic nephropathy.	[136]
Erbb4-IR	db/db mice	MEF	Just kidney	miR-29b	miR-29b, AGE, Smad3, T2DN, TGF- β /Smad	Enhancing	Erbb4-IR via Targeting miR-29b could Promote Diabetic Kidney Injury in db/db mice.	[137]
HOTAIR	SD rats	HK-2	Just kidney	miR-124	miR-124, TGF- β 1, JAG1, Notch1, NICD, α -SMA, fibronectin, E-cadherin	Enhancing	HOTAIR via targeting Notch1/miR-124 axis could promote renal interstitial fibrosis.	[138]
ZEB1-AS1	C57BL6/KsJ-leprdb mice, WT control C57 mice, human kidney biopsy samples from DN patients (n = 8), and MCD patients (n = 8)	HK-2	Multiple organs including the kidney	p53	p53, collagen I, collagen IV, fibronectin, α -SMA,	protective	ZEB1-AS1 could be suppressed via p53 for renal fibrosis in diabetic nephropathy.	[139]
GAS5	C57BL/6 mice, human Kidney samples	HK-2	Just kidney	miR-96-5p	miR-96-5p, COL1, fibronectin1, CTGF	Enhancing	GAS5 via acting as a competing endogenous RNA of miR-96-5p could exacerbate renal tubular epithelial fibrosis.	[140]
TCONS_00088786	Kidney samples from mice	NRK52E	Just kidney	miR-132	miR-132, Collagen I, Collagen III, TGF- β	Enhancing	Silencing of TCONS_00088786 via targeting miR-132 could reduce renal fibrosis.	[141]
MALAT1	C57BL/6J mice	HK2	Just kidney	miR-145	miR-145, FAK, TGF- β 1, E-cad, ZO1, N-cadherin, α -SMA	Enhancing	m6A-induced MALAT1 via targeting miR-145/FAK axis could aggravate renal fibrogenesis in obstructive nephropathy.	[134]
Blncl	Blood serum from DN patients (n = 30), normal patients (n = 30), SD rats	HK-2	Just kidney	NRF2, HO-	PTEN, fibronectin, collagen I, collagen IV, NRF2, HO-1, I κ B, NF- κ B P65	Enhancing	Blncl expression via targeting the Nrf2/HO-1/NF- κ B axis could affect inflammation, oxidative stress, and kidney fibrosis in diabetic nephropathy.	[142]
NR_038323	Wistar rats, Human kidney samples from MCD patients (n = 10) and DN patients (n = 9)	HK-2	Just kidney	miR-324-3p	miR-324-3p, DUSP1, Collagen I, Collagen IV, Fibronectin	Enhancing	NR_038323 via targeting the miR-324-3p/DUSP1 axis could suppress renal fibrosis in diabetic nephropathy.	[143]
H19	CD1 mice	HMVECs	Just kidney	miR-29a	miR-29a, CD31, FSP-1, α -SMA, TGF β /SMAD3	Enhancing	Knockdown of H19 via suppressing miR-29a-mediated EMT could ameliorate kidney fibrosis in diabetic mice.	[144]

Table 10

Impact of lncRNAs on pulmonary fibrosis.

IncRNA	Sample	Cell lines	Organ specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Ref
ZEB1-AS1	SD rats	Alveolar type II epithelial	Just lungs	miR-141-3p	miR-141-3p, collagen 1, fibronectin 1, α -SMA, E-cadherin, TGF- β 1	Enhancing	ZEB1-AS1 through ZEB1-mediated EMT via binding miR-141-3p could promote pulmonary fibrosis.	[145]
PFAR	C57BL/6 mice	lung fibroblasts	Just lungs	miR-138	miR-138, collagen1, YAP1, α -SMA, Twist, FN1	Enhancing	PFAR via targeting miR-138 could regulate the YAP1-Twist axis and enhance the activity of lung fibroblasts and fibrosis.	[146]
PFAR	C57BL/6mice	Primary lung fibroblasts	Just lungs	miR-15a	miR-15a, TGF- β 1, collagen 1, α -SMA, YAP1, Twist	Enhancing	PFAR via binding to miR-15a could contribute to fibrogenesis in lung fibroblasts.	[147]
HOXAAS3	Lung tissues from IPF patients (n = 18), normal lung tissues (n = 18), C57BL/6 mice	CMLF	Multiple organs including lungs	miR-450b	miR-450b-5p, Runx1, Fibronectin, α -SMA, Vimentin, TGF- β 1/ Smad4	Enhancing	Hoxaas3 by targeting miR-450b-5p/Runx1 axis could promote lung fibroblast activation and fibrosis.	[149]
PFRL	C57BL/6 mice	NMPFs	Just lungs	miR-26a	miR-26a, smad-2, collagen 1, fibronectin 1, Smad4, CTGF	Enhancing	Inhibition of PFRL through disrupting the miR-26a/smad2 axis could prevent pulmonary fibrosis.	[150]
ATB	Male C57BL/6 mice	Beas-2B, A549	Just lungs	miR-200c	miR-200c, E-cadherin, Vimentin, ZEB1, U6, Fibronectin, α -SMA, TGF- β 1	Enhancing	ATB by competitively binding miR-200c could promote EMT during silica-induced pulmonary fibrosis.	[148]
H19	C57BL/6 mice	MRC-5, HEK-293T	Just lungs	miR-196a	miR-196a, COL1A1, α -SMA	Enhancing	H19 via targeting the miR-196a/COL1A1 axis mediates pulmonary fibrosis.	[151]
PFAL	C57BL/6 mice	Neonatal mouse lung fibroblasts	Multiple organs including lungs	miR-18a	CTGF, miR-18a, collagen 1, fibronectin1, α -SMA	Enhancing	PFAL via targeting CTGF/miR-18a axis could promote lung fibrosis.	[152]

Table 11

Impact of lncRNAs on fibrosis in other organs.

Disease	IncRNA	Sample	Cell lines	Organ-specificity	List of known regulator/binding partners	Targets	Brief Role in fibrosis	Function	Refs.
Oral Submucous Fibrosis (OSF)	GAS5-AS1	tissues from OSF specimen (n = 25)	BMFs, fBMFs	Multiple organs	α -SMA	α -SMA, Smads	Protective	GAS5-AS1 could inhibit myofibroblast activities in oral submucous fibrosis.	[153]
Fibrosis in Glaucoma	NR_003923	6 pairs of humans fascia tissue	HTFs	eye	miR-760, miR-215-3p	miR-760/miR-215-3p/IL22RA1, E-cadherin, α -SMA, β -catenin, p62, fibronectin, LC3BII	enhancing	NR_003923 via targeting the miR-760/miR-215-3p/IL22RA1 axis could promote cell proliferation, migration, fibrosis, and autophagy in human Tenon's capsule fibroblasts.	[154]
Endometrial Fibrosis	TUG1	rats	hESCs	uterine	miR-590-5p	miR-590-5p, Fasl, α -SMA, E-cadherin, collagen I, fibronectin 1, vimentin	enhancing	TUG1 by targeting the miR-590-5p/Fasl axis could promote endometrial fibrosis and inflammation in intrauterine adhesions.	[155]

fibrosis [163]. Therefore, insight into the biological mechanism of novel ncRNAs inhibitors could provide a key role in enhancing novel fibrosis therapeutic procedures. An in-depth comprehension of the association of lncRNAs with organ fibrosis procedures could be provided through cutting-edge discoveries containing sequence information and chromosomal location, to publicly achievable datasets. Important lncRNA databases are MFLDA, LNCipedia, InCeDB, lncRNA Ontology, NeuraNetL2GO, lnc2Meth, NONCODE, lncRNADisease, and lncAtlas. In addition, mounting studies have revealed that non-coding SNPs located

in the regulatory or functional elements play a crucial role in regulating gene expression in trans in terms of long-range genome interactions [164]. Subsequent detection is required to figure out the process by which these lncRNA-associated locus result in organ fibrosis pathogenesis which then broadens our knowledge of a variety of fibrotic diseases. Applying genome-editing technologies like CRISPR/Cas9 system and gapmer silencing could advance our understanding of a certain lncRNA-associated SNP during organ fibrosis.

Disease	LncRNA	Sample	Cell line	List of known regulator/binding partners	Target	Brief Role in aging	Function	Ref.s
Aging-Induced Osteoporosis	Xist	bone marrow tissues from osteoarthritis patients (n = 123), C57BL/6 mice	BMSCs	miR-19a-3p, Hoxa5	miR-19a-3p, Hoxa5	Enhancing	Xist via targeting miR-19a-3p could regulate osteoblast differentiation in aging-induced osteoporosis.	[156]
Aging-Related Myocardial Apoptosis	ENSMUST00000134285	C57 mouse, C57Bl/6J mice	primary cardiomyocytes	MAPK11	MAPK11	Protective	ENSMUST00000134285 could increase MAPK11 activity and regulate aging-related myocardial apoptosis.	[157]
Endothelial Cell Aging	H19	C57Bl/6J mice	HUVECs	Stat3	Stat3, p16/21, VCAM-1	Protective	H19 by inhibition of Stat3 could regulate endothelial cell aging.	[158]

CRediT authorship contribution statement

SGF wrote the draft and revised it. MT designed and supervised the study. AB designed and revised the figures. NAD, WB, HS and SFT collected the data and designed the tables. All the authors read and approved the submitted version.

Conflict of interest

The authors declare they have no conflict of interest.

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