**Regulatory Mechanisms of the Molecular Pathways in Fibrosis Induced by MicroRNAs**

Cui Yang\(^1\), Si-Dao Zheng\(^2\), Hong-Jin Wu\(^3\), Shao-Jun Chen\(^1\)

\(^1\)Department of Cardiology, Huairou Hospital of Traditional Chinese Medicine, Beijing 101400, China

\(^2\)Department of Cardiology, Beijing Hospital of Integrated Traditional Chinese and Western Medicine, Beijing 100039, China

\(^3\)Department of Cardiology, Beijing Haidian Hospital, Haidian Section of Peking University Third Hospital, Beijing 100191, China

**Objective:** MicroRNAs (miRNAs or miRs) play critical roles in the fibrotic process in different organs. We summarized the latest research progress on the roles and mechanisms of miRNAs in the regulation of the molecular signaling pathways involved in fibrosis.

**Abstract**

**Data Sources:** Papers published in English from January 2010 to August 2015 were selected from the PubMed and Web of Science databases using the search terms “microRNA”, “miR”, “transforming growth factor β”, “tgf β”, “mitogen-activated protein kinase”, “mapk”, “integrin”, “p38”, “c-Jun NH-terminal kinase”, “jnk”, “extracellular signal-regulated kinase”, “erk”, and “fibrosis”.

**Study Selection:** Articles were obtained and reviewed to analyze the regulatory effects of miRNAs on molecular signaling pathways involved in the fibrosis.

**Results:** Recent evidence has shown that miRNAs are involved in regulating fibrosis by targeting different substrates in the molecular processes that drive fibrosis, such as immune cell sensitization, effector cell activation, and extracellular matrix remodeling. Moreover, several important molecular signaling pathways involve in fibrosis, such as the transforming growth factor-beta (TGF-β) pathway, mitogen-activated protein kinase (MAPK) pathways, and the integrin pathway are regulated by miRNAs. Third, regulation of the fibrotic pathways induced by miRNAs is found in many other tissues in addition to the heart, lung, liver, and kidney. Interestingly, the actions of many drugs on the human body are also induced by miRNAs. It is encouraging that the fibrotic process can be blocked or reversed by targeting specific miRNAs and their signaling pathways, thereby protecting the structures and functions of different organs.

**Conclusions:** miRNAs not only regulate molecular signaling pathways in fibrosis but also serve as potential targets of novel therapeutic interventions for fibrosing diseases.

**Key words:** Fibrosis; Integrins; MicroRNAs; Mitogen-activated Protein Kinases; Signal Transduction Pathway; Transforming Growth Factor-beta

**INTRODUCTION**

MicroRNAs (miRNAs or miRs) are a class of noncoding endogenous RNA molecules that are ~22 nucleotides in length and are produced by two RNase III proteins (Drosha and Dicer). miRNAs are discovered in 1993 in *Caenorhabditis elegans* and are pivotal regulatory agents for messenger RNA (mRNA) expression at the posttranscriptional level.\(^1\) Different miRNA biogenesis pathways might exist, but the ultimate effect remains the same: The silencing of target mRNAs.\(^2\) By base pairing with the 3’ untranslated region (UTR) of the target mRNA, the miRNA induces translational repression and mRNA decay through the RNA-induced silencing complex, in which the Argonaute proteins function as RNA silencing effectors.

Tissue fibrosis driven by primary injury to organs might switch from its adaptive features in the short term to parenchymal scarring when the irritation remains for an excessively long period, eventually promoting cellular dysfunction and organ failure.\(^3\) miRNAs have been suggested to play important roles in regulating fibrosis. For example, the regulatory effects on heart fibrosis of the...
miRNAs miR-21, miR-29, miR-30, and miR-133, among others, have been studied.[54] Similarly, miR-29, miR-21, miR-433, miR-150, miR-let7, miR-324, and miR-200 affect kidney fibrosis,[55] and let-7d, miR-15b, miR-19b, miR-21, miR-24, miR-29c, miR-145, and miR-155 affect radiation-induced fibrosis.[56] In this review, we have summarized the current knowledge of miRNA-induced regulatory effects on the molecular fibrosis pathways and uncovered their characteristics in different organs.

**MicroRNA-related Cell Signaling Pathways in Fibrosis**

Beyond the multiple cell types (inflammatory cells, epithelial cells, fibrogenic effector cells, endothelial cells, and others) involved in the fibrogenic response, three cellular signal transduction pathways play leading roles in the process of fibrosis: transforming growth factor-beta (TGF-β), mitogen-activated protein kinases (MAPKs) and integrins.[57]

**MicroRNA-related transforming growth factor-beta pathway in fibrosis**

Different ligands can bind to TGF-β receptors on the cell surface, allowing regulatory messages to be transferred into the cell by activating the signaling effectors and the Smad-Mad-related proteins (Smads) and ultimately interacting with deoxyribonucleic acid.[57] Both Smad2 and Smad3 are activated by TGF-β, myostatin, or activin whereas Smad1, Smad5, and Smad8 are activated by bone morphogenetic proteins; the activation of these proteins results in the interaction with Smad4, leading to the modulation of target gene expression. Interestingly, activation of the TGF-β pathway also upregulates Smad6 and Smad7 expression, which can deactivate the pathway.[57] Evidence has also shown that Smad2 and Smad7 alleviate fibrosis whereas Smad3 promotes fibrosis.[57] Many miRNAs and their substrates are involved in regulating the TGF-β signal transduction pathway [Table 1].

**MicroRNA-related mitogen-activated protein kinase pathways in fibrosis**

The MAPKs, including p38 MAPK, c-Jun NH2-terminal kinase (JNK), and extracellular signal-regulated kinase in mammals, mediate signaling that is either triggered by extracellular stimuli, such as growth factors and cytokines, or intracellular stimuli.[49] The effector molecules of MAPKs play important roles in regulating cellular activities, including proliferation, differentiation, apoptosis, and survival. It is not surprising that the regulatory processes of MAPKs are induced by miRNAs, among which the roles of miR-29, miR-133, miR-146, miR-155, miR-350, miR-378, and miR-451 have been investigated [Table 2].

**MicroRNA-related integrin pathway in fibrosis**

Integrins are composed of α and β subunits and act as surface receptors in all cell types except red blood cells.[58] In conjunction with extracellular receptors, integrins initiate the signal transduction pathways involved in the fibrotic process by coordinating with the intracellular integrin-linked kinase.[59-61] Regulatory effects of miRNAs on integrin expression have been confirmed by studies on miR-29, miR-31, miR-17-92 cluster, miR-124, miR-126, miR-148b, and miR-184.[62] Here, we summarize the miRNAs involved in fibrosis, among which miR-21, miR-29, miR-133, miR-140, miR-146, miR-155, miR-199, miR-350, miR-378, and miR-451 play important roles [Table 3].

**MicroRNA-related Signaling Pathways in Different Tissues**

**Heart**

Cardiac fibrosis is characterized by the aberrant proliferation of fibroblasts and excessive extracellular matrix (ECM) production in the myocardial interstitium, ultimately leading to heart failure. This process is regulated by many miRNAs and their targets.[70,68]

**MicroRNA-related transforming growth factor-beta pathway in cardiac fibrosis**

By targeting the common ECM protein connective tissue growth factor (CTGF), miR-18a and miR-19b downregulated collagen (COL) 1A1 and COL3A1 expression, resulting in the alleviation of cardiac fibrosis in age-related heart failure induced by TGF-β activation.[69] A reciprocal loop has been identified between miR-21 and its target TGF receptor III, leading to ECM remodeling and fibrosis. Cardiac miR-21 was upregulated in infarcted hearts due to TGF-β activation whereas its target gene (TGF receptor III) was downregulated. However, low TGF receptor III expression could reinforce TGF-β activation.[10] miR-24 was protective against cardiac fibrosis in response to myocardial infarction depending on the suppressive effect on its target gene FURIN, through which the TGF-β signaling pathway was inhibited.[13] Upregulation of miR-29b due to TGF/Smad3 inactivation resulted in the downregulation of COL1A1, COL3A1, and alpha smooth muscle actin (α-SMA) and contributed to the cardioprotective effect of cardexil against acute myocardial infarction-induced myocardial fibrosis.[116] Another study confirmed that the targets of miR-29b (insulin-like growth factor 1 and leukemia inhibitory factor) were involved in regulating cardiac fibroblast activation and ECM proliferation.[23] miR-101 was downregulated in infarcted heart in rats and in angiotensin-cultured cardiac fibroblasts. Interestingly, overexpression of mir-101 suppressed proliferation and COL production by suppressing its target c-Fos and the downstream protein TGF-β.[31] The same protective effect of miR-122 for myocardial fibrosis in human aortic stenosis was revealed and was dependent on the targeting and inhibition of TGF-β.[133] Studies showed that overexpression of mir-133a inhibited cardiac fibrosis in both diabetes and angiotensin II-dependent hypertension although the effector proteins differed for diabetes (fibronectin and COL4A1) and angiotensin II-dependent hypertension (COL1A1).[34,52]
Table 1: miRNA-related TGF-β pathway involved in fibrosis

| miRNA | Target | Action |
|-------|--------|--------|
| miR-21 | Smad7[11], TGF-β receptor III[10], PDLC4[11,12] | Promoting bleomyacin-induced skin fibrosis,[9] increasing COL production in cardiac fibroblasts,[10] contributing to hepatic fibrosis,[9] and promoting myofibroblast differentiation.[12] |
| miR-24 | FURIN[13] | Attenuating heart fibrosis after myocardial infarction[11] |
| miR-29 | ADAM12[12], ADAM19[12], COL1A1[13], COL1A2[14], COL3A1[15], TPI1[16], IGF[17], LIF[18], TPML[19], LAM-C1[20] | Blocking pulmonary fibrosis[3] and TGF-β-mediated renal fibrosis,[15] promoting myogenic differentiation. Suppressing the transdifferentiation of myoblasts into myofibroblasts,[21] repressing COL 1 and 4 synthesis in HSCs,[22] downregulating ECM genes in periodontal ligament cells,[22] ECM deposition in cardiac hypertrophy[23] and acute infarct hearts,[24] preventing COL in skin fibroblasts,[20] mesangial cells in diabetic kidney disease,[25] ochratoxin A-induced human embryonic kidney cells,[19] and bleomycin-induced pulmonary fibrosis.[27] Inhibiting peritoneal fibrosis associated with peritoneal dialysis,[25] regulating ECM component production in TECs,[26] suppressing renal interstitial fibrosis induced by HIFs,[28] inhibiting cancer cell migration and invasion.[27] |
| miR-30 | KLF11[29], UCP2[29] | Protecting against CCl₄-induced liver fibrosis,[29] inhibiting TGF-β₁-induced kidney fibrosis[29] |
| miR-34 | Notch1[10], Jagged1[10] | Preventing hypoxia-induced EMT in TECs[30] |
| miR-101 | e-Fl[31] | Mitigating interstitial fibrosis in postinfarct hearts[31] |
| miR-122 | P4HA1[32], TGF-β1[33] | Decreasing COL maturation and ECM production in HSCs,[33] Inhibiting myocardial fibrosis in aortic stenosis patients.[33] |
| miR-133 | TGF-β1[33] | Preventing diabetes-induced cardiac fibrosis[34] |
| miR-144 | TGF1[35] | Increasing α-SMA and fibronectin in lung fibroblasts[35] |
| miR-145 | Smad3[36] | Suppressing airway inflammation in cystic fibrosis[36] |
| miR-146 | Smad4[37,38] | Attenuating α-SMA expression in dermal fibroblasts[33] and HSCs[37] |
| miR-188 | KIAA1199[39] | Suppressing ECM formation in synovial fibroblasts[39] |
| miR-199 | HGF[40] | Promoting TGF-β₁-induced fibrotic remodeling[40] |
| miR-200 | ZEB1[41], ZEB2[42], TGF-β2[43], VEGF[44], FBLN5[45], TIMP2[46] | Suppressing matrix remodeling in leiomyomas,[43] suppressing TGF-β₁-induced tubular EMT,[44] preventing TGF-β₁-dependent EMT in renal fibrogenesis[45] |
| miR-302 | TGF-β receptor II[41] | Attenuating TGF-β₁-induced mesangial production[41] |
| miR-346 | Smad3[41], Smad4[41] | Ameliorating fibrogenesis in DN mice[41] |
| miR-744 | TGF-β1[41] | Inhibiting endogenous TGF-β₁ synthesis[41] |

miRNA: MicroRNA; TGF-β: Transforming growth factor-beta; Smad: Sma- and Mad-related proteins; PDCD: Programmed cell death protein; COL: Collagen; ADAM: A-disintegrin and metalloprotease; SP: Specificity protein; IGF: Insulin-like growth factor; TPM: Tropomyosin; LAM: Laminin; HSCs: Hepatic stellate cells; ECM: Extracellular matrix; TECs: Tubular epithelial cells; HIF: Hypoxia-inducible factor; KLF: Krüppel-like factor; UCP: Uncoupling protein; CCl₄: Carbon tetrachloride; EMT: Epithelial-mesenchymal transition; TGIF: Transforming growth factor-beta-induced E-box binding factor; PDGF: Platelet-derived growth factor; PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1; COL: Collagen; IRAK: Interleukin receptor-associated kinase; SHIP: Phosphatidylinositol-3,4,5-Trisphosphate 5-phosphatase; Grb: Growth factor receptor-bound protein; DN: Diabetic nephropathy; ↓: Downregulated.

Table 2: miRNA-related MAPK pathway in fibrosis

| miRNA | Target | Action |
|-------|--------|--------|
| miR-21 | PTEN[49] | Activating HSCs[49] |
| miR-29 | IGF1[49], PDGF-C[49], PIK3RI[49], AKT3[49] | Targeting COL biosynthesis and interfering with profibrogenic cell communication in HSCs,[49] inhibiting HSC activation and inducing HSC apoptosis[49] |
| miR-133 | COL1A1[50] | Inhibiting angiotensin II-induced myocardial fibrosis[50] |
| miR-146 | IRAK1[51] | Inhibiting pro-inflammatory cytokine secretion in gingival fibroblasts[51] |
| miR-155 | SHIP1[52] | Promoting inflammation in cystic fibrosis[52] |
| miR-350 | MAPK 8/9/11/14[53] | Inducing pathological heart hypertrophy[53] |
| miR-378 | Grb2[54], IGF1 receptor[55] | Blocking cardiac hypertrophy[56,57] |
| miR-451 | Yb1[58] | Suppressing mesangial hypertrophy in early DN[58] |

miRNA: MicroRNA; MAPK: Mitogen-activated protein kinases; PTEN: Phosphatase and tensin homologue deleted on chromosome ten; HSCs: Hepatic stellate cells; IGF: Insulin-like growth factor; PDGF: Platelet-derived growth factor; PIK3RI: Phosphoinositide-3-kinase regulatory subunit 1; COL: Collagen; IRAK: Interleukin receptor-associated kinase; SHIP: Phosphatidylinositol-3,4,5-Trisphosphate 5-phosphatase; Grb: Growth factor receptor-bound protein; DN: Diabetic nephropathy; ↓: Downregulated.

MicroRNA-related mitogen-activated protein kinase pathway in cardiac fibrosis

miR-378 blocked activation of Ras signaling in cardiac hypertrophy by targeting of the cardiac hypertrophy modulator growth factor receptor-bound protein 2, leading to the alleviation of cardiac remodeling.[56] However, miR-250 was sufficient to induce cardiac hypertrophy through the suppression of p38 and JNK protein synthesis by targeting MAPK11/14 and MAPK8/9 in rats with transverse aortic constriction.[55] These miRNAs (miR-378 and miR-250)
played important roles countering one another in the regulation of the cardiac MAPK signal, and both were predicted to be targets for the prevention of cardiac fibrosis.

**Lung**

**MicroRNA-related transforming growth factor-beta and integrin pathways in pulmonary fibrosis**

miR-29 played an important role in fibroproliferation, leading to bronchiolitis obliterans syndrome after human lung transplantation.\[35\] Overexpression of miR-144 led to a reduction in TGF-β-induced factor homeobox 1 and an increase in profibrotic factors whereas knockdown of miR-144 diminished fibrogenesis.\[35\] miR-199a-5p overexpression in TGF-β-induced lung fibroblasts could promote pulmonary fibrosis by targeting caveolin-1, through which pulmonary fibroblasts proliferate, migrate, and differentiate into myofibroblasts.\[70\]

An interesting study revealed that the miR-29 expression level was inversely related to the expression of the profibrotic target genes laminin and integrin α as well as the severity of pulmonary fibrosis.\[14\] Moreover, miR-29 could be suppressed by TGF-β activation, supporting the hypothesis that both the TGF-β and integrin pathways were involved in pulmonary fibrosis mediated by miR-29, which could be an important potential target for medical practice. Finally, the study proved that miR-29 prevented bleomycin-induced fibrosis in the lungs; this finding was also supported by other research.\[17\] miR-29c, which targeted both matrix metalloproteinase 2 and integrin β3, could inhibit ECM proliferation and lung cancer cell adhesion to the ECM.\[63\]

**Liver**

**MicroRNA-related transforming growth factor-beta pathway in liver fibrosis**

miR-21 upregulated activation protein 1 by targeting programmed cell death protein 4 (PDCD4) in hepatic stellate cells (HSCs), thereby enhancing ECM production; however, the elevated activation protein 1 activity upregulated miR-21 expression to form an autofeedback loop and promoted the progression of liver fibrosis.\[13\] Unlike miR-21, miR-29 appeared to be a suppressor of hepatic fibrosis by downregulating COL1 and COL4 induced by TGF-β activation in HSCs.\[16\] The same antifibrotic effect was found with miR-30, whose target was Krüppel-like factor 11 (KLF11), which was an inhibitor of Smad7 in the TGF-β pathway.\[28\] miR-30 was able to deactivate HSCs by inhibiting TGF-β activation through the target and substrate mentioned previously. Interestingly, miR-122 was found to be an antifibrotic miRNA by downregulating prolyl 4-hydroxylase subunit alpha 1, thereby decreasing COL maturation and ECM production.\[52\] Another miRNA (miR-146a) also suppressed TGF-β-induced HSC activation and hepatic fibrosis development by targeting Smad4.\[37\]

**Kidney**

**MicroRNA-related transforming growth factor-beta pathway in kidney fibrosis**

Fibrosis, which was one of the features of diabetic nephropathy (DN), could be reversed by miR-29b and the downregulation of its target genes specificity protein 1 (an effector for the TGF-β-Smad3-induced fibrotic response) and tbx21 (a transcription factor that enhances the Th1 immune response).\[24\] Moreover, miR-29 downregulation and the consequent upregulation of the target gene COL1A1 contributed to Ochratoxin A-induced COL formation and the development of kidney fibrosis.\[19\] In addition to miR-29b, miR-29c was shown to target specificity protein 1, thereby abolishing TGF-β-induced COL1 production in kidney tubular epithelial cells (TECs).\[47\] miR-29c was upregulated by hypoxia-inducible factor α activation to inhibit the direct targets COL2A1 and tropomyosin 1 and attenuate renal tubulointerstitial fibrosis.\[26\] Two other targets of miR-29 (A disintegrin and metalloprotease (ADAM) 12 and ADAM19) were reported to be effectors that antagonized TGF-β signaling-induced renal fibrosis.\[15\] miR-302, whose target was TGF-β receptor II, was reportedly upregulated in both unilateral ureteral obstruction-induced kidney fibrosis and mesangial cells treated with CTGF.\[44\] The study further showed that miR-302 was a mediator of the regulation of TGF-β by CTGF, thereby supporting an important role for miRNAs in preventing TGF-β-induced renal fibrosis.\[44\] Recent evidence showed that miR-346 could bind the 3’-UTR of Smad3/4, downregulate Smad3/4 expression, and block TGF-β signal activation, resulting in the amelioration of kidney fibrosis in DN.\[45\]
Other miRNAs were also thought to be involved in the regulation of TGF-β-related renal fibrosis. For example, miR-30e inhibited TGF-β1-induced ECM production in TECs by targeting mitochondrial uncoupling protein 2, whereas miR-34a promoted kidney fibrosis by targeting Notch 1 and Jagged 1 in hypoxia-induced renal TECs.

**MicroRNA-related mitogen-activated protein kinases pathway in kidney fibrosis**

miR-451 negatively regulated the expression of its target gene Ywhaz, which was required for the activation of p38 MAPK signaling, and inhibited glomerular mesangial cell proliferation in early DN, thus preventing mesangial hypertrophy. The roles and mechanisms of other miRNAs that regulate renal fibrosis could be found elsewhere.

**Skin**

**MicroRNA-related transforming growth factor-beta pathway in skin fibrosis**

Smad7, which was one of the substrates that negatively regulate TGF-β signal-induced excessive fibrosis in systemic sclerosis (SSc), has been shown to be the target of miR-21, which was upregulated by bleomycin and downregulated by bortezomib. The study suggested that miR-21 could be a new target for combating the fibrotic process of SSc. However, miR-29b acted as a protective regulator by targeting COL1A1 and COL1A2, leading to the deactivation of ECM production. Unlike miR-21, miR-146a targeted Smad4 in TGF-β-stimulated HSCs, deactivating both HSCs and human dermal fibroblasts. In addition to Smad7 and Smad4, Smad3 was also a fibrotic miRNA target. A study showed that miR-145 inhibited the inflammatory response in cystic fibrosis by downregulating the Smad3 expression levels.

**MicroRNA-related integrin pathway in skin fibrosis**

miR-378a inhibited fibroblast migration and differentiation by decreasing its targets integrin β1 and vimentin in vitro and suppressed wound healing of the skin in vivo, suggesting its pivotal role in regulating skin recovery. miR-150 also targeted integrin β1, leading to decreased ECM production in SSc fibroblasts.

Another report suggested that miR-152 reduced cellular adhesion and ECM remodeling in human dermal fibroblasts partially through integrin α4 downregulation.

**Other tissues**

**MicroRNA-related transforming growth factor-beta pathway**

miR-21 was involved in TGF-β1 signal activation in the cancer stroma by targeting PDCD4 and promoting myofibroblast differentiation when miR-21 was downregulated, thereby inhibiting differentiation when upregulated. miR-29 suppressed the transdifferentiation of myofibroblasts into myofibroblasts through the downregulation of the ECM genes. The study further demonstrated that miR-29 was under negative regulation by TGF-β-Smad3 signaling by the dual mechanisms of MyoD binding inhibition and Yin Yang 1-recruited Polycomb association enhancement. Moreover, the study confirmed the final effector molecules under negative regulation by miR-29 were COL1A1, COL1A2, and COL3A1. Using similar targets, miR-29 inhibited profibrotic gene expression in periodontal ligament cells. One additional study showed that miR-29b could alleviate peritoneal dialysis-associated fibrosis by targeting specificity protein 1 and consequently inhibiting TGF-β1-Smad2/3 signaling. It was obvious that the effects of miR-29 were induced by multiple targets. Another miRNA (miR-200c) showed the same multi-target characteristic. This miRNA inhibited ECM remodeling in leiomomyomas by targeting zinc finger e-box-binding homeobox, vascular endothelial growth factor a, tissue inhibitor of metalloproteinase 2, and FBLN 5. By targeting TGF-β1, miR-744 was involved in many different pathophysiological processes, including fibrosis. A recent study showed that miR-188-5p indirectly regulated COL1A1 and COL1A2 in the ECM of synovial fibroblasts in rheumatoid arthritis, suggesting a potential antifibrotic therapeutic effect.

**MicroRNA-related mitogen-activated protein kinase pathway**

miR-146 inhibited interleukin (IL)-1β, IL-6, and tumor necrosis factor-α secretion through IL-1 receptor-associated kinase 1 in human gingival fibroblasts, indicating that miR-146 was a negative regulator of periodontal inflammation. miR-155 (another MAPK-related miRNA) activated the PI3K/AKT signaling pathway through the promotion of the IL-8-dependent inflammatory response in cystic fibrosis lung epithelial cells by lowering SHIP1 expression.

**Conclusions**

Fibrosis is mediated by different signaling pathways composed of cellular constituents, including inflammatory cells, epithelial cells, and fibrogenic effector cells, and is a general condition leading to organ injury and failure. Although the cellular and molecular processes underlying fibrosis have been illustrated, the strategies and targets for the treatment of fibrosis are still unsatisfactory. Epigenetic modification, including miRNA posttranscriptional modification, is capable of controlling the fibrotic process by regulating fibroblast activity, thereby providing a novel therapeutic target for the treatment of fibrosis.

Based on the studies mentioned above and others, we conclude that special miRNAs are involved in fibroblast activation, ECM production, and other fibrotic processes and that moderating miRNA expression might be a novel therapy for fibrotic diseases. A single fibrotic miRNA and related signaling pathway might show similar activity in different organs. For example, miR-199a-5p shows an elevated expression level in three types of organ fibrosis (unilateral ureteral obstruction model of the kidney, carbon tetrachloride-damaged liver, and bleomycin-treated lungs); the underlying mechanisms share a common regulatory mechanism involving the TGF-β signaling pathway.
Moreover, the miRNA-induced therapeutic effects of drugs such as bortezomib and carvedilol have been confirmed. Thus, it is encouraging that blocking or reversing the fibrotic process can be achieved by targeting special miRNAs and their signaling pathways, thereby protecting the structures and functions of different organs.

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**Conflicts of interest**

There are no conflicts of interest.

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