Regulatory roles of microRNA-21 in fibrosis through interaction with diverse pathways (Review)

RONG-HAN LIU*, BIN NING*, XIAO-EN MA, WEI-MING GONG and TANG-HONG JIA

Department of Spinal Surgery, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong 250013, P.R. China

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Abstract. MicroRNA-21 (miR-21) is a small, non-coding RNA which can regulate gene expression at the post-transcriptional level. While the fibrogenic process is vital in tissue repair, proliferation and transition of fibrogenic cells combined with an imbalance of secretion and degradation of the extracellular matrix results in excessive tissue remodeling and fibrosis. Recent studies have indicated that miR-21 is overexpressed during fibrosis and can regulate the fibrogenic process in a variety of organs and tissues via diverse pathways. The present review summarized the significant roles of miR-21 in fibrosis and discussed the underlying key pathways.

Contents

1. Introduction

MicroRNAs (miRs) are a class of small (18-22 nucleotides long), non-coding, evolutionarily conserved RNA molecules, which are significant regulators of gene expression at the post-transcriptional level though inhibiting the translation of messenger RNA (mRNA) and/or destroying the complete structure of mRNA (1,2). Since the first discovery of miR in 1993 (3), miRs have been identified as a distinct type of epigenetic regulators in the early 2000s (4-6), and 28,645 miRs have been identified to date. Studies have confirmed that miRs exert a variety of biological functions in various organs or tissues, which are associated with development, cell proliferation, cell growth and differentiation (1,2). The expression of several of these miRs has been identified to be dysregulated in various diseases (7-9).

Fibrosis is a reparative or reactive process, which occurs following wounds, burns, trauma, surgery or disease. In order to repair the damage and prevent infection, fibrogenic cells, including fibroblasts, increase their secretion capacity and form fibrous connective tissue. This process forms a scar to aid recovery. However, the formation of excess fibrous connective tissue has a negative effect on healing (10). Fibrous connective tissue is characterized by excessive and persistent accumulation of extracellular matrix (ECM) proteins. The imbalance between secretion and degradation of ECM results in tissue remodeling and fibrosis, which eventually impairs the function of the affected organ. The ECM is composed of a variety of proteins, including composition-like collagens (Cols), fibronectin (FN) and laminin. Fibrosis occurs in a variety of organs and tissues and the recovery of dysfunction requires long-term recovery. Studies have shown that the activation, proliferation and differentiation of fibrogenic cells participates in the development of fibrosis. Epithelial-to-mesenchymal transition (EMT) is a process required for the development of fibrosis (11), during which epithelial cells lose their epithelial cell-specific markers and start to express fibroblast-specific markers (12), including N-cadherin and vimentin (13). Furthermore, the process of endothelial-to-mesenchymal transition (EndMT) also contributes to fibroblast formation in fibrotic diseases in various types of tissues and organs, including the heart (14,15), kidney (16), lung (17) and liver (18). Fibroblasts are the major cell type in fibrosis and their differentiation into myofibroblasts enhances their fibrogenicity (19). In addition, epithelial cells undergoing EMT have been reported to be potential sources of myofibroblasts in lung (20), renal (21,22) and hepatic (18,23) fibrosis. These activated fibroblasts promote the secretion of ECM of fibrotic cells as well as their proliferation and survival.

In recent years, studies have focused on the effects of miRs on fibrosis, and the number of miRs with proven regulatory roles in fibrosis is increasing. For instance, miR-133 has been discovered to be linked with cardiac fibrosis and regulates fibroblast signatures though various signaling pathways (24,25). In pulmonary fibrosis, miR-92a regulates the expression of the matricellular protein WNT1-inducible

Correspondence to: Professor Tang-Hong Jia, Department of Spinal Surgery, Jinan Central Hospital Affiliated to Shandong University, 105 Jiefang Road, Jinan, Shandong 250013, P.R. China
E-mail: jiatanghong@hotmail.com

*Contributed equally

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signaling pathway protein 1 via the transforming growth factor beta (TGF-β) signaling pathway (26). The application of miRs to prevent fibrosis in a clinical setting has also been indicated, as miR-29b effectively inhibited fibrosis in mice subjected to peritoneal dialysis (27). Numerous further miRs, including miR-200, miR-29, miR-155 and miR-133, have been reported to be associated with cardiovascular diseases and fibrosis (28,29). Among these, miR-21 has become the focus of research on the pathophysiology of disease, particularly fibrosis in various organs and tissues.

2. miR-21

miR-21 is a small, but crucial regulatory RNA in a large variety of physiological and pathological processes. Human miR-21 is a polycistronic miRNA whose gene is located in chromosome 17q23.2, where it overlaps with the protein-coding gene VMP1, also known as TMEM49. As for all miRs, the expression of miR-21 is regulated at the post-transcriptional level by a variety of regulatory proteins, including TGF-β receptor (TGF-βR), phosphatase and tensin homologue (PTEN) and Smad7 (30,31).

The expression of miR-21 has been assessed in numerous human diseases, particularly in tumors (32). In addition, aberrantly expressed miR-21 has been found to promote fibrogenic activation of fibroblasts (33,34). miR-21 is able to regulate protein expression in multiple organs and tissues and has an impact on tumor development, cancer, inflammation and the immune system (30,35-38).

3. Expressional changes of miR-21 in fibrosis

miR-21 is widely expressed, and has been detected to be increased in organs and tissues which have suffered fibrogenesis, including the heart, kidneys, lungs, skin and tumors (32,33,39-44). In mice, miR-21 was found to be overexpressed in cardiac fibroblasts after myocardial ischaemia/reperfusion (44). It was also indicated that miR-21 may contribute to pathological cardiac remodeling and the development of fibrosis (33,45). The increased expression of miR-21 in lung fibrosis has been indicated to promote EMT of lung epithelial cells (46). miR-21 was also found to be overexpressed in tubular epithelial cells after renal ischemia/reperfusion injury to protect them from death, which may promote the occurrence of renal fibrosis (47,48). In kidney fibrosis, miR-21 was overexpressed not only in primary fibroblasts, but also elevated in the blood (49). Traumatic injury of the central nervous system was shown to increase the levels of miR-21 in the lesion area (7,50). miR-21 may protect neurons by exerting anti-apoptotic effects (51). Studies have revealed that miR-21 may regulate the astrocytic response to nervous system injuries and protects fibroblasts to inhibit glial scar formation (52,53). Furthermore, elevated miR-21 expression has been detected in the liver following experimental hepatic fibrosis, while its inhibition with 3,3'-diindolylmethane ameliorated fibrosis (54,55). Skin wound healing is another fibrotic process, and enhanced fibroblast proliferation occurs in the hyperplastic scar. The expression of miR-21 in hyperplastic scars has been shown to be elevated compared to that in normal skin (56). In addition, miR-21 was found to be implicated in the proliferation of human keloid fibroblasts by directly targeting PTEN (57). Furthermore, miR-21 was shown to have a role in scleroderma fibrosis and was overexpressed in the skin of mice with radiation-induced fibrosis (39,58). In summary, miR-21 overexpressed in fibrotic tissues and has a significant function in the development of fibrosis; however, the underlying molecular mechanisms vary in different organs or tissues.

4. Signaling pathways associated with miR-21 in fibrosis

miR-21 affects the expression of a variety of proteins via binding to the 3'-untranslated region (3'-UTR) of their respective mRNAs, resulting in a complex interaction network due to various downstream effects on signaling pathways (59). To date, several signaling pathways has been identified to be involved in the pathophysiological processes of fibrosis, among which the TGF-β/Smads, phosphoinositide 3-kinase (PI3K)/AKT and extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathways have key roles.

TGF-β/Smads signaling pathway. TGF-β is well known as a pivotal mediator in the pathogenesis of fibrosis (60,61). TGF-β upregulates numerous genes associated with fibrogenesis and promotes the development of fibrosis via its downstream mediators, including Smad2 and Smad3, while fibrosis is inhibited by Smad7 (62-64). Deletion of Smad3 protects from fibrosis in mice (65). However, deletion of Smad2 significantly enhanced Smad3 expression, thereby leading to ECM expansion and fibrosis development, which indicated that Smad2 functions as a negative regulator of TGF-β signaling (66). Activation of TGF-β receptor by TGF-β may induce the regulatory Smad3 proteins, which then initiate Smad4-dependent transcription (63). Of note, TGF-β1 is known to upregulate miR-21 expression (64). TGF-β signaling and Smad3 have important roles in miR-21 transcription, and Smad proteins control the maturation of miR-21 from pre-miR-21 (64,67). Smad2 and Smad3 have opposite roles in regulating the biogenesis of miR-21 - Smad3 promotes, while Smad2 prevents the expression of pre-miR-21 after stimulation with TGF-β (66,68). Smad7 is a direct target of miR-21 and is therefore depressed following upregulation of mature miR-21 (38,69).

TGF-β1 can induce the differentiation of fibroblasts into the more fibrogenic myofibroblasts (19). Its downstream mediator Smad3 was also shown to regulate the expression of Cols, fibronectin (FN), and α-smooth muscle actin (α-SMA) directly, by binding to their promoters (62). α-SMA has been proved to be critical for the trans-differentiation of hepatic stellate cells (HSCs) into myofibroblasts (70).

The crosstalk between miR-21 and the TGF-β/Smads signaling pathway can regulate the fibrotic procedure though downstream proteins in a variety of signaling pathways.

PI3K/AKT signaling pathway. TGF-β can activate PI3K/AKT signaling though inhibiting phosphatase and tensin homolog (PTEN) (71,72), and it is well known that PTEN is a negative factor of the PI3K/AKT signaling pathway (73,74). The expression of fibrotic proteins mediated TGF-β, including FN and Cols, is regulated by PI3K/AKT signal transduction (72,75).

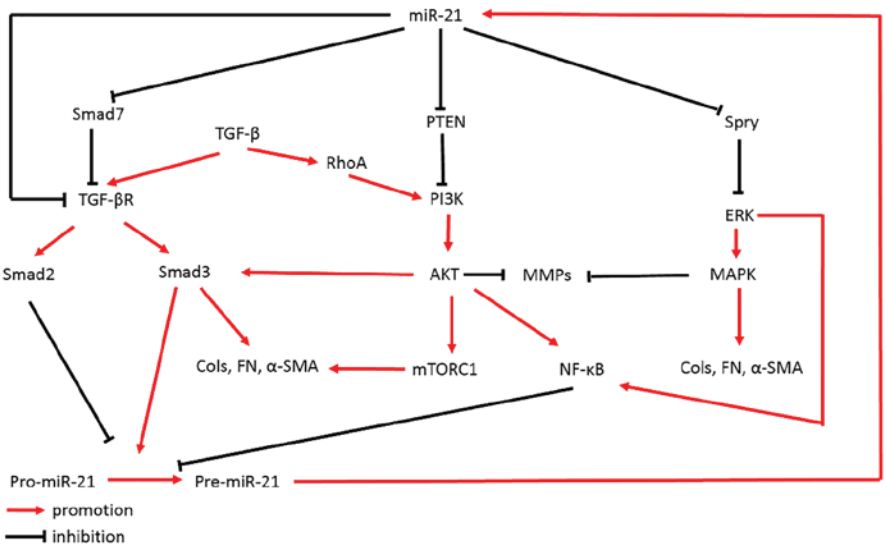

Figure 1. Interaction between miR-21 and diverse signaling pathways in the regulation of fibrosis. Schematic illustrating the feedback loop between miR-21 and diverse signaling pathways (TGF-β, PI3K/AKT or ERK/MAPK signaling pathway). miR, microRNA; TGF, transforming growth factor; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide-3 kinase.

TGF-β has been demonstrated to regulate PI3K-dependent mammalian target of rapamycin (mTOR) to increase cellular hypertrophy (76-78). mTOR is a downstream protein of the PI3K/AKT signaling pathway. It has been shown that TGF-β can activate PI3K/AKT signaling with targeting of PTEN, and RhoA may be an upstream mediator of Akt activation and involved in TGF-β-induced activation of PI3K/AKT signaling in response to TGF-β1 (71). Akt activation has an important role in the EMT (79) as well as the EndMT (80), likely though the nuclear factor-κB (NF-κB) pathway (79), as AKT signaling can activate NF-κB signaling (81). PTEN has been demonstrated to be a direct target of miR-21 (34,74). In conclusion, miR-21 can regulate the process of fibrosis though PI3K/AKT signaling by targeting PTEN.

ERK/MAPK signaling pathway. ERK signaling is known to have a significant impact in fibrogenesis (82). Suppression of ERK expression can block EMT of hepatic fibrosis in rats (82). Sprouty (Spry) is a target of miR-21 (32,83,84) as well as a potent inhibitor of the ERK/MAPK signaling pathway (74). Spry1 expression and MAPK signaling activation in the myocardium were completely reversed by treatment with an antagonist of miR-21 (32). In addition, miR-21 inhibitors have been shown to increase the mRNA transcript levels of Spry2 and significantly reduce the expression of profibrotic genes in activated HSCs, including TGF-β1, α-SMA and collagen (85). In addition, ERK signaling can activate the NF-κB signaling pathway (86). NF-κB signaling was shown to inhibit miR-21 expression by binding directly to its promoter and regulate the process of arsenite-induced cell transformation (87).

Interaction network of miR-21. The signaling pathways of fibrosis are interconnected; for instance, the PI3K pathway positively regulates Smad3 transcription and increases Col production, suggesting that activation and interaction of diverse signaling pathways contributes to the pathogenesis of fibrosis (75) (Fig. 1). On the other hand, ERK signaling also interacts with AKT signaling through the NF-κB pathway, however, these pathways affect miR-21 production. In turn, miR-21 regulates these pathway through different target proteins. In conclusion, miR-21 may be a key factor in the interaction network.

It is worth mentioning that other targets of miR-21, including programmed cell death-4, tissue inhibitor of metalloproteinases-3 and reversion-inducing cysteine-rich protein with kazal motifs have functions in the migration and invasion of cancer cells or traumatic brain injury (88-90), and that these miR-21-mediated targets are negative regulators of matrix metalloproteinases (MMPs) (37,91-93). While the exact roles of miR-21 in these complex interactions remain to be fully elucidated, it has a key role in fibrosis through interlinking several fibrosis-associated pathways and is therefore a promising target for the treatment of fibrosis.

5. Functions of miR-21 in various organs and tissues

miR-21 has a key role in fibrosis though regulating fibrogenic cell activation, survival, secretion, hypertrophy and transition. It can promote the process of ECM formation and the EMT, leading to fibrosis development in a variety of tissues and organs (Table I) (32,39-44, 54,57,68,69,78,85,94-97).

Heart. The majority of cardiovascular diseases, including heart failure, myocardial infarction and atrial fibrillation, are associated with myocardial remodeling. Cardiac fibrosis is an important process in myocardial structural remodeling (98-100). miR-21 can control myocardial structural remodeling via several pathways. A study using a cardiovascular disease model demonstrated that cardiac stress can upregulate the expression of miR-21, which mediates the activation of ERK/MAPK signaling though targeting Spry1 to positively regulate cardiac fibroblast survival and growth factor secretion, resulting in fibrosis, remodeling and cardiac

Table I. Function of miR-21 in various organs and tissues though diverse pathways.

Organ	Target gene	Signaling pathway	Target cell type	Function	Ref
Liver	Smad7	TGF-β signaling pathway	Hepatic stellate cells	EMT, ECM formation	(43)
	Smad7	TGF-β signaling pathway	Hepatic stellate cells	Cell survival and proliferation	(54)
	PTEN	PI3K/AKT signaling pathway	Hepatic stellate cells	EMT	(42)
	PTEN	PI3K/AKT signaling pathway	Hepatic stellate cells	EMT, ECM formation	(94)
	Spry2	ERK/MAPK signaling pathway	Hepatic stellate cells	EMT, ECM formation	(85)
Heart	Spry1	ERK/MAPK signaling pathway	Fibroblasts	Cell survival and ECM formation	(32)
	Spry1	ERK/MAPK signaling pathway	Fibroblasts	Cell survival and ECM formation	(95)
	PTEN	PI3K/AKT signaling pathway	Fibroblasts	Cell hypertrophy and ECM formation	(44)
	TGF-βR	TGF-β signaling pathway	Fibroblasts	EMT, ECM formation	(96)
Kidney	PTEN	PI3K/AKT signaling pathway	Mesangial Cells	Cell hypertrophy and ECM formation	(78)
	PTEN	PI3K/AKT signaling pathway	Tubular epithelial cells	ECM formation	(41)
	Smad7	TGF-β signaling pathway	Tubular epithelial cells	EMT, ECM formation	(68,69)
Lung	Smad7	TGF-β signaling pathway	Fibroblasts	EMT, ECM formation	(40)
Skin	Smad7	TGF-β signaling pathway	Fibroblasts	EMT, ECM formation	(39)
	PTEN	PI3K/AKT signaling pathway	Fibroblasts	Cell hypertrophy and survival	(97)
	PTEN	PI3K/AKT signaling pathway	Fibroblasts	Cell survival and proliferation	(57)

miR-21 can regulate the development of fibrosis in various organs and tissues though diverse pathways (TGF-β, PI3K/AKT or ERK/MAPK signaling pathways) via different target genes (Smad7, PTEN, Spry, TGF-βR) and cell types (hepatic stellate cells, tubular epithelial cells, fibroblasts, mesangial cells). miR-21 decreases the expression of target genes and activates target cells. Target cells are converted into activated myofibroblasts, which are more fibrogenic, or promoted to survive hypertrophy and hyperplasia, leading to increased secretion and ECM formation. miR, microRNA; TGF, transforming growth factor; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide-3 kinase; EMT, epithelial-to-mesenchymal transition; ECM, extracellular matrix.

dysfunction; however, this process was inhibited by silencing of miR-21 (32). Similarly, a study on patients with atrial fibrillation showed that miR-21 was upregulated and Spry1 was decreased (95). In mice, the increased expression of miR-21 and the decreased expression of Spry1 by angiotensin II contributed to fibroblast survival and structural remodeling in the atrial myocardium (95). Studies on other pathways have reported a variety of roles for miR-21. In the pathogenic process of myocardial fibrosis, miR-21 and TGF-β1 were shown to be upregulated, while TGF-βRIII was downregulated (96). Overexpression of TGF-βRIII inhibited the expression of miR-21 in fibroblasts, probably via phosphorylated Smad3. However, overexpression of miR-21 induced by TGF-β1 led to the differentiation of fibroblasts into pathological myofibroblasts and increased the Cols content. Fibrosis is therefore regulated by a reciprocal feedback loop between TGF-βRIII and miR-21 (96). MMP-2 degrades the ECM and knocks down PTEN in cardiac fibroblasts, resulting in marked phosphorylation of AKT signaling and induction of MMP-2. In a murine model of myocardial infarction, miR-21 was shown to regulate MMP-2 expression in fibroblasts via PTEN, leading to cell hypertrophy and matrix protein expression (44). These findings may provide a direction for further studies.

Liver. miRs have been extensively studied in liver fibrosis, particularly the miR-29 family, miR-122 and miR-21 (101,102). Among them, miR-21 was found to have significant effects in the process of fibrosis development, while numerous risk factors, including hepatitis C virus (HCV), fatty liver, alcohol consumption and schistosome infection can cause fibrosis (54). The target cells in liver fibrosis are HSCs (42,43,54,85,94,103), and activated HSCs are responsible for the imbalance of secretion and degradation of the ECM (104). Livers of mice and humans with hepatic fibrosis in non-alcoholic steatohepatitis have shown increased levels of miR-21 with co-localized overexpression of TGF-β, Cols, α-SMA and Smad2/3-Smad4, while the protein levels of Smad7 were decreased (43). However, treatment with leptin-nicotinamide adenine dinucleotide phosphate oxidase reversed these effects in mice. Similar observations were made in HCV patients: miR-21 overexpression enhanced TGF-β signaling, and Smad7 was a negative regulator of TGF-β signaling in a positive feedback cycle to promote HSC survival and proliferation (54,103). The fibrogenic role of miR-21 was also found in biliary atresia patients and in an *in vitro* experiment, which it exerted through the PTEN/AKT signaling pathway and targeting of PTEN. miR-21 was shown to activate AKT signaling via phosphorylation, alongside decreased expression of MMP-2 and increased expression of α-SMA (42,94), which indicated that miR-21 promotes the transdifferentiation of HSCs into myofibroblasts as well as ECM formation. HSCs are likely to be activated via various routes, including the ERK signaling pathway. miR-21

directly interacts with the 3'-UTR of Spry2, resulting in enhanced ERK signaling in HSCs (85). Enhanced expression of α-SMA and vimentin showed that miR-21 can regulate the EMT as well as ECM formation through ERK signaling (85).

Kidney. Renal fibrosis is characterized by an excess accumulation of ECM and myofibroblasts, as fibrosis in other organs, and features tubule atrophy. Gene therapy by Smad7 overexpression in obstructive nephropathy-induced fibrosis suppresses miR-21, Col, FN and α-SMA (69). Furthermore, TGF-β1 was shown to upregulate miR-21 expression via Smad3, but to downregulates it via Smad2 in tubular epithelial cells (TECs) (68). It is therefore indicated that miR-21 and its regulation via TGF-β/Smads signaling has a significant role in renal fibrosis though ECM formation and EMT. Interstitial fibrosis and tubular atrophy influence renal outcomes of immunoglobulin (Ig)A nephropathy (105). A recent study on both podocytes and TECs of patients with IgA nephropathy showed that miR-21 expression was upregulated (41). Inhibition of miR-21 prevented fibrogenic activation in podocytes and TECs by reversing the overexpression of FN and Col though inhibiting AKT pathway activation. Another study has revealed that miR-21 can suppress the AKT pathway via its target PTEN and activate the downstream protein mTORC1, leading to hypertrophy of mesangial cells and matrix protein expression (78), as mesangial cells also take a vital role in renal fibrosis (61).

Lung. Like in other tissues and organs, TGF-β1 is well known to be an important conditioner of lung fibrosis and can induce fibroblast-to-myofibroblast differentiation characterized by α-SMA expression and high expression of ECM (46,106). The EMT has a distinct role in lung fibrosis. In a study of idiopathic pulmonary fibrosis, miR-21 was shown to be highly expressed and primarily localized to myofibroblasts, alongside an increase in α-SMA expression (40). The increased miR-21 promotes fibrogenic activity of TGF-β1 in fibroblasts though regulating the expression of Smad7. Another study showed that miR-21 is upregulated in isolated lung epithelial cells induced by bleomycin. Furthermore, PTEN has been shown to have a negative regulatory role in experimental lung fibrosis (107).

Skin. Systemic sclerosis is known as a process of fibrosis with increased expression of miR-21 (39). TGF-β is also implicated in the pathogenesis and progression of skin fibrosis (108). Normal skin fibroblasts incubated with TGF-β1 showed overexpression of miR-21 (39). In bleomycin-treated mice, the pro-fibrogenic activity caused by α-SMA and Cols overexpression stimulated by miR-21 was identified to be mediated via the TGF-β signaling pathway by targeting Smad7 (39). Hypertrophic scarring, the most common type of skin disorder, occurs after abnormal wounding, and miR-21 has been reported to be of relevance in this process via the PI3K/AKT signaling pathway through regulating the expression of human telomerase reverse transcriptase (hTERT) (97). It was revealed that fibroblasts transfected with PTEN showed decreased hTERT mRNA and protein expression. An identical mechanism was found to promote cell survival and proliferation in keloid fibroblasts (57).

6. Conclusions and perspectives

An increasing number of studies have demonstrated that miR-21 has a key role in fibrosis though regulating fibrogenic cell activation, survival, secretion, hypertrophy and transition. Previous studies suggested that targeting miR-21 may be an attractive method to inhibit the process of fibrosis.

The present review highlighted three signaling pathways via which miR-21 is involved in fibrosis, namely the TGF-β/Smads, PI3K/AKT and ERK/MAPK signaling pathways, as well as their inhibitors Smad7, PTEN and Spry, which are also targets of miR-21. Of note, miR-21 has a key role in regulating the interaction of these pathways. The mechanisms presented in this review as well as their complex crosstalk are likely to be the key pathways underlying the role of miR-21 in fibrosis. Due to its key regulatory role in these processes, miR-21 is a potential target for the treatment of fibrosis.

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