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Role of noncoding RNAs in liver fibrosis

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Abstract

Liver fibrosis is a wound-healing response following chronic liver injury caused by hepatitis virus infection, obesity, or excessive alcohol. It is a dynamic and reversible process characterized by the activation of hepatic stellate cells and excess accumulation of extracellular matrix. Advanced fibrosis could lead to cirrhosis and even liver cancer, which has become a significant health burden worldwide. Many studies have revealed that noncoding RNAs (ncRNAs), including microRNAs, long noncoding RNAs and circular RNAs, are involved in the pathogenesis and development of liver fibrosis by regulating signaling pathways including transforming growth factor- β pathway, phosphatidylinositol 3-kinase/protein kinase B pathway, and Wnt/ β -catenin pathway. NcRNAs in serum or exosomes have been reported to tentatively applied in the diagnosis and staging of liver fibrosis and combined with elastography to improve the accuracy of diagnosis. NcRNAs mimics, ncRNAs in mesenchymal stem cell-derived exosomes, and lipid nanoparticles-encapsulated ncRNAs have become promising therapeutic approaches for the treatment of liver fibrosis. In this review, we update the latest knowledge on ncRNAs in the pathogenesis and progression of liver fibrosis, and discuss the potentials and challenges to use these ncRNAs for diagnosis, staging and treatment of liver fibrosis. All these will help us to develop a comprehensive understanding of the role of ncRNAs in liver fibrosis.

Key Words: MicroRNAs; Long noncoding RNAs; Circular RNAs; Liver fibrosis;

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Core Tip: Liver fibrosis is an inevitable stage in the development of various chronic liver diseases, and manifests as an imbalance between the formation and degradation of extracellular matrix. The key mechanism of liver fibrosis is the activation of hepatic stellate cells, which is coordinately regulated by a variety of cytokines, inflammatory factors and chemokines involved in multiple cells signaling pathways. In this review, we discuss the role of noncoding RNAs (ncRNAs) in regulating the signaling pathways in the formation and regression of liver fibrosis, and the limitations, challenges, and prospects of ncRNAs in the diagnosis and treatment of liver fibrosis.

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INTRODUCTION

Liver fibrosis is the result of excessive accumulation of extracellular matrix (ECM) caused by continuous liver injuries that promote wound healing[1]. Liver injuries can be caused by many factors including persistent hepatitis B virus (HBV)/hepatitis C virus (HCV) infections, excessive alcohol consumption, metabolic diseases, drugs, genetic diseases, cholestasis, and autoimmune diseases. Due to an increase in the prevalence of obesity and type 2 diabetes, liver fibrosis caused by nonalcoholic steatohepatitis (NASH) has been increasing annually in recent years[2]. Liver fibrosis can resolve at an early stage if the injuries subside. Progressive fibrosis is associated with architectural changes to hepatic lobules and may lead to cirrhosis, liver failure, portal hypertension, and even hepatocellular carcinoma (HCC).

Hepatic stellate cells (HSCs) play a central role in liver fibrosis. HSCs, also known as perisinusoidal cells, are located in the Disse space under healthy conditions. When injury occurs, HSCs are activated and transdifferentiate into myofibroblast-like cells which are the main source of ECM[3]. Hepatic fibrosis is a dynamic process coordinated by multiple cells in the liver. Acute injury, such as viral infection, induces an inflammatory response, necrosis, and apoptosis in hepatocytes which leads to liver regeneration and limited ECM deposition. However, if the damage persists, the injured hepatocytes attract an infiltration of inflammatory cells such as T lymphocytes and neutrophils, which will in turn activate HSCs by releasing cytokines, chemokines, and reactive oxygen species (ROS). Activated HSCs can maintain the active state by the mediators produced by the autocrine and paracrine system. In addition, platelet-derived growth factor (PDGF) secreted by liver macrophages (Kupffer cells) stimulates the continuous proliferation of HSCs. Therefore, inhibiting the activation and proliferation of HSCs, promoting the apoptosis of activated HSCs, and reducing the expression of fibrogenic factors are considered to be the key measures for the successful treatment of liver fibrosis.

Noncoding RNAs (ncRNAs) refer to RNAs that are transcribed from the genome but do not normally encode proteins, although some of them have recently been reported to encode small proteins[4]. According to their length, ncRNAs can be divided into short ncRNAs and long ncRNAs (lncRNAs). MicroRNAs (miRNAs) are a class of short ncRNAs of approximately 22 nucleotides in length that act as gene repressors by complementary binding to the 3' untranslated region of target mRNA to degrade or prevent it from being translated to protein[5,6]. LncRNAs are defined as ncRNAs longer than 200 bp with 5'-end m7G caps and 3'-end poly(A) tails. LncRNAs can regulate gene expression in *cis* or *trans*, change the structure and function of chromatin *via* interaction with proteins, or act as competitive endogenous RNAs (ce-RNAs) for post-transcriptional regulation[7]. Circular RNAs (circRNAs) are a novel form of ncRNAs with a covalently closed single-stranded structure, which is formed by back-splicing of the 3' and 5' ends of mRNAs[8]. Depending on their subcellular localization, circRNAs have different biological functions: interfering with signal transduction pathways and regulating the transcription and translation of target genes, sponge proteins and miRNAs[9].

In this review, we summarize the latest findings about miRNAs, lncRNAs, and circRNAs in the pathogenesis and progression of liver fibrosis and discuss the potential of ncRNAs as biomarkers for diagnosis and as therapeutic targets for liver fibrosis.

NCRNAS IN THE PATHOGENESIS AND PROGRESSION OF LIVER FIBROSIS

The activation and proliferation of HSCs are essential steps in the development of liver fibrosis. Numerous studies have shown that ncRNAs exert profibrotic effects by regulating genes in the activation and proliferation signaling pathways of HSCs. Signaling pathways closely related to liver fibrosis mainly include transforming growth factor- β (TGF- β)/Smad, phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase 1 (AKT), Wnt/ β -catenin, and nuclear factor κ light chain enhancer of activated B cells (NF- κ B) pathways. Although some miRNAs[10] and lncRNAs[11] involved in liver fibrosis have been reviewed elsewhere, we focus on the most recent data published in the past 3 years as summarized in Figure 1.

ncRNAs regulating TGF- β /Smad signaling pathway in liver fibrosis

Transforming growth factor- β 1 (TGF- β 1) is a well-recognized fibrogenic cytokine that is widely expressed in damaged hepatocytes, Kupffer cells, HSCs, sinusoidal endothelial cells, and platelets. TGF- β 1 promotes HSC activation through a canonical (Smad) or noncanonical pathway[12]. In the TGF- β 1/Smad signaling pathway, TGF- β 1 binds to the TGF- β type II receptor (TGF- β RII) on the cell membrane and then recruits the TGF- β type I receptor (TGF- β RI) to form a heterotetrameric complex. This complex induces the phosphorylation of intracellular Smad2 and Smad3, which then bind with Smad4 and translocate to the nucleus to regulate expression of target genes[13-15]. In addition, TGF- β 1 induces the expression of Smad7, which maintains the balance between profibrotic and antifibrosis by negatively regulating TGF- β RI and Smad2[13].

Many miRNAs are involved in the regulation of the TGF- β /Smad signaling pathway and liver fibrosis. These miRNAs include miR-21, miR-497, miR-16, miR-98-5p, miR-199a-3p, miR-29a, and miR-130a-3p. MiR-21 is expressed abundantly in liver, is present in serum, and is positively associated with liver inflammation, fibrosis, and cancer[16]. TGF- β 1 induces transcription, processing and maturation of pri-miR-21 through a Smad3-dependent pathway, while mature miR-21 promotes the development of fibrosis by targeting the inhibitory Smad gene-small mothers against decapentaplegic7[15]. *Clonorchis sinensis* promotes hepatic fibrosis by inducing miR-497 and activating the TGF- β /Smad pathway[17]. Pan *et al*[18] revealed that miR-16 plays an essential role in the phenotypic remodeling of myofibroblasts. Overexpression of miR-16 restored the phenotype of HSCs and led to fibrotic regression by targeting Smad2 and Wnt3a to interfere with TGF- β and Wnt signaling pathways, respectively[18]. In patients with chronic HBV-induced liver fibrosis, expression of miR-98-5p was significantly downregulated. Further studies indicated that overexpression of miR-98-5p significantly inhibited HSC activation through targeting the TGF- β 1/Smad3 signaling pathway[19]. Yang *et al*[20] demonstrated that expression of miR-199a-3p was upregulated in carbon tetrachloride (CCl₄)-induced liver fibrotic rats, and miR-199a-3p activated HSCs by targeting caveolin-2 (CAV2) to increase expression of TGF- β RI. Stimulation with TGF- β resulted in the downregulation of miR-29a, which increased follistatin-like 1 expression and accelerated the progression of fibrosis by enhanced phosphorylation of Smad2[21]. MiR-130a-3p was significantly decreased in liver fibrosis caused by *Schistosoma japonicum*[22]. It has been shown that miR-130a-3p attenuates fibrosis by inhibiting the activation and proliferation of HSCs and promoting their apoptosis through regulation of mitogen-activated protein kinase 1 and TGF- β RI/II both *in vitro* and *in vivo*[22].

In addition to miRNAs, lncRNAs and circRNAs are associated with the TGF- β pathway and liver fibrogenesis. LncRNA small Cajal body-specific RNA 10 (lncRNA SCARNA10) was found to inhibit the expression of polycomb repressive complex 2 to induce hepatocytes apoptosis and HSC activation, thereby stimulating the TGF- β pathway and liver fibrogenesis[23]. CircRNA mitochondrial tRNA translation optimization 1 (circMTO1) was reported to inhibit liver fibrosis through interaction with miR-17-5p and Smad7[24].

ncRNAs regulating PI3K/AKT signaling pathway in liver fibrosis

The PI3K/AKT pathway is an essential intracellular signaling pathway in the regulation of the cell cycle. The AKT cascade can be activated by cytokine receptors such as receptors of TGF- β and PDGF. PI3K is activated to induce phosphorylation of Phosphatidylinositol-4,5-bisphosphate (PIP2) on the cell surface, leading to production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). AKT (also known as protein kinase B, PKB) binds to PIP3 and they are co-translocated to the nucleus, where they regulate target gene expression to stimulate cell proliferation and inhibit apoptosis. Phosphatase and tensin homology deleted on chromosome ten (PTEN) increases the number of activated HSCs by catalyzing dephosphorylation of PIP3 and downregulating the PI3K/AKT signaling pathway. A variety of miRNAs regulate the PI3K/AKT signaling pathway. MiR-21 is significantly upregulated in liver fibrosis induced by cadmium exposure, which leads to the progression of fibrosis by activating the PI3K/AKT pathway[25]. Lipotoxic hepatocyte-derived exosomal miR-1297 promotes HSC proliferation and activation by inhibiting expression of PTEN[26]. MiR-23a-5p activates the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway by inhibiting PTEN and can be targeted by lncRNA LOC102551149 to reduce liver fibrosis[27]. All these results indicate that ncRNAs, especially miRNAs and lncRNAs, play important roles in liver fibrosis through targeting the PI3K/AKT pathway.



ncRNAs regulating Wnt/ β -catenin signaling pathway in liver fibrosis

ncRNAs regulating NF- κ B signaling pathway in liver fibrosis

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special transcript 5 (lncRNA GAS5) decreased expression of miR-433-3p, which then intercepted the NF- κ B signaling pathway through targeting of toll-like receptor 10[36]. In addition, lncRNA maternally expressed gene 3 (lncRNA MEG3) targeted NLR Family CARD Domain Containing 5 (NLRC5) to reverse liver fibrosis[37]. All of these results indicate that ncRNAs regulating liver fibrosis through targeting the NF- κ B pathway are mainly lncRNAs, including lncRNAs NEAT1, Lfar1, GAS5, and MEG3.

ncRNAs regulating autophagy pathway in liver fibrosis

Autophagy is a process that regulates self-metabolism and maintains cellular homeostasis by removing cell debris, misfolded proteins and lipid droplets[38]. Activation of autophagy promotes liver fibrosis by increasing the digestion of lipid droplets and activating multiple signaling pathways, which implies that promoting regeneration of lipid droplets and restraining expression of proinflammatory factors inhibits liver fibrosis[38]. In hypoxic conditions, lncRNA plasmacytoma variant translocation 1 (lncRNA PVT1) regulates expression levels of autophagy-related gene (ATG)14 by decreasing miR-152, thereby activating HSCs through the autophagy pathway[39]. lncRNA small nucleolar RNA host gene 7 (lncRNA SNHG7) increased DNA methyltransferase 3 alpha (DNMT3A) expression through binding to miR-29b, which is involved in liver fibrosis and autophagy. Inhibition of lncRNA SNHG7 significantly decreases expression of collagen and autophagy factors, leading to inhibition of liver fibrosis[40]. In addition to lncRNAs, circRNAs are also associated with autophagy and mitophagy. Xu *et al*[41] illustrated that circRNA608/miR-222 regulates PTEN-induced putative kinase 1-mediated mitophagy and liver fibrosis in NASH-induced fibrotic mice.

Other ncRNAs targeting host genes involved in liver fibrosis

Chen *et al*[42] demonstrated that miR-451 and miR-185 were downregulated in activated HSCs, and they exerted antifibrotic effects synergistically by targeting erythropoietin-producing hepatocellular receptor B2. MiR-451 upregulated expression of miR-185. This occurs at the post-transcriptional level by targeting nuclear export receptor exportin 1 (XPO-1). Zhao *et al*[43] demonstrated that lncRNA molecule interacting with CasL2 (lncRNA Mical2) upregulated p66 Src homologous-collagen homologue (p66Shc) through sponging miR-203a-3p, which promoted reactive oxygen species (ROS)-mediated epithelial-mesenchymal transition and liver fibrosis. It has been reported that lncRNA X-inactive-specific transcript (lncRNA XIST) damages mitochondrial function and increases ROS production to promote HSC activation by regulating miR-539-3p and ADAM metalloproteinase with thrombospondin type 1 motif 5 (ADAMTS5)[44]. Studies from cholestatic liver injury caused by biliary atresia have indicated that expression of lncRNA H19 is significantly upregulated in exosomes derived from liver and serum. lncRNA H19 deficiency protects mice from liver fibrosis by inhibiting sphingosine-1-phosphate receptor 2/sphingosine kinase 2 activation and by sponging let-7 to upregulate high-mobility group AT-hook 2 expression[45]. It has also been reported that depletion of macrophages significantly reduced lncRNA H19 and inhibited cholestatic liver injury in bile duct ligation mice[46]. lncRNA actin alpha 2-antisense RNA 1 (lncRNA ACTA2-AS1) accelerated liver fibrosis and epigenetic activation by targeting the p300/ETS transcription factor (ELK1) complex in biliary diseases[47]. CircRNA F-box and WD repeat domain containing 4 (circFBXW4) was downregulated significantly in HSCs of mice with liver fibrosis. Overexpression of circFBXW4 inhibited HSC activation by targeting miR-18b-3p to increase FBXW7 expression[48]. Similarly, CircRNA CREB binding protein (circCREBBP) inhibited liver fibrosis by targeting miR-1291 to regulate the expression of left-right determinant cluster 2 (LEFTY2)[49]. Hsa_circ_0071410 inhibited activation of HSCs by binding to miR-9-5p in irradiation-induce liver fibrosis[50]. All these ncRNAs in the pathogenesis and progression of liver fibrosis are summarized in Table 1[51-60].

POTENTIAL APPLICATION OF NCRNAS IN THE DIAGNOSIS OF LIVER FIBROSIS

Liver-related mortality increases with the progression of fibrosis. Therefore, it is essential for the early diagnosis of liver fibrosis. At present, the gold standard for the diagnosis of liver fibrosis is still liver biopsy, although it has some limitations such as sampling error, inter- and intra-observer variability [61], invasiveness to patients, and many other complications. Several noninvasive examinations have been introduced in clinical settings, including serum markers, combined indices or scores, and imaging techniques. Hepascore and enhanced liver fibrosis score are based on serum liver fibrosis markers such as tissue metalloproteinases and hyaluronic acid [62]. Elastography, including ultrasound elastography and magnetic resonance elastography, is a method to access liver stiffness quantitatively and it is more accurate than serological markers for diagnosis of advanced liver fibrosis. However, elastography has disadvantages such as unreliable results due to high body mass index (BMI) and high cost, making it unsuitable for population screening[62]. As ncRNAs in the blood are easily accessible for detection, they have potential as novel noninvasive biomarkers for diagnosis of liver fibrosis.

Recent research has shown that stimulation of HSCs with TGF- β and PDGF-BB decreased the intracellular miR-29 expression level but significantly increased miR-29 level in the supernatant vesicles [63]. They verified the results in serum from patients with HCV-related liver fibrosis and mice with CCl₄

Table 1 Noncoding RNAs in the pathogenesis and progression of liver fibrosis

ncRNAs	Target genes	Signaling pathways	Ref.
miR-199a-3p	CAV2	TGF- β /Smad	[20]
miR-497	Smad7	TGF- β /Smad	[17]
miR-21	Smad2/3/7	TGF- β /Smad	[15]
	TGF- β	PI3K/ AKT	[25]
	-	PPAR α	[51]
	-	PDCD4/ AP-1	[51,52]
	-	Smad7/Smad2/3/NOX4, Spry1/ERK/NF- κ B	[51,53]
	-	HIF-1 α /VEGF	[54]
miR-16	Smad2, Wnt3a	TGF- β /Smad, Wnt	[18]
miR-130a-3p	TGF- β RI, TGF- β RII; MAPK1	TGF- β ; MAPK	[22]
miR-98-5p	TGF- β RI	TGF- β 1/Smad3	[19]
miR-6133-5p	TGF- β RII, FGFR1	TGF- β /Smad2/3, AKT/ERK/JNK	[55]
miR-708	ZEB1	Wnt/ β -catenin	[29]
exo-miR-1297	PTEN	PI3K/ AKT	[26]
miR-350	SPRY2	PI3K/ AKT and ERK	[56]
miR-34c	ACSL1	-	[57]
miR-200c	HAS2	-	[58]
miR-451, miR-185	EphB2	-	[42]
miR-20b-5p	STAT3	STAT3	[97]
lncRNA SNHG7	miR-29b, DNMT3A	Autophagy pathway	[40]
lncRNA PVT1	miR-152, ATG14	Autophagy pathway	[39]
lncRNA SCARNA10	PRC2	TGF- β	[23]
lncRNA LOC102551149	miR-23a-5p, PTEN	PI3K/ AKT/ mTOR/ Snail	[27]
lncRNA MALAT1	-	Wnt/ β -catenin	[31]
lncRNA NEAT1	miR-139-5p, β -catenin	β -catenin/SOX9/ TGF- β 1	[30]
	miR-129-5p, PEG3	NF- κ B	[32]
	miR-129-5p, SOCS2	-	[33]
	miR-148a-3p, miR-22-3p, Cytth3	-	[34]
lncRNA Lfar1	-	NF- κ B	[35]
lncRNA GAS5	miR-433-3p, TLR10	NF- κ B	[36]
lncRNA-ROR	miR-6499-3p	NF- κ B	[99]
lncRNA Airn	EZH2	KLF2-eNOS-sGC	[98]
lncRNA MEG3	NLR5	-	[37]
lncRNA NORAD	miR-495-3p, S1PR3	-	[60]
lncRNA XIST	miR-539-3p, ADAMTS5	-	[44]
lncRNA Mical2	miR-203a-3p, p66Shc	-	[43]
circRNA608	miR222, PINK1	Autophagy pathway	[41]
circMTO1	miR-17-5p, Smad7	-	[24]
circFBXW4	miR-18b-3p, FBXW7	-	[48]
circCREBBP	miR-1291, LEFTY2	-	[49]
circ_0071410	miR-9-5p	-	[50]

ncRNAs: Noncoding RNAs; CAV2: Caveolin-2; TGF- β : Transforming growth factor- β ; PI3K: Phosphatidylinositol 3-kinase; AKT: Serine/threonine kinase 1; PPAR: Peroxisome proliferator-activated receptor; PDCD4: Programmed cell death protein 4; AP-1: Activation protein-1; NOX4: Nicotinamide adenine dinucleotide phosphate oxidase 4; Spry1: Sprouty 1; ERK: Extracellular regulated kinase; NF- κ B: Nuclear factor κ light chain enhancer of activated B cells; HIF-1 α : Hypoxia-inducible factor-1 α ; VEGF: Vascular endothelial growth factor; TGF- β RI: TGF- β type I receptor; MAPK: Mitogen-activated protein kinase; FGFR: Fibroblast growth factor receptor; JNK: c-Jun N-terminal kinase; ZEB1: Zinc finger E-box binding homeobox 1; PTEN: Phosphatase and tensin homology deleted on chromosome ten; ACSL1: Acyl-CoA synthetase long chain family member 1; HAS2: Hyaluronic acid synthase; EphB2: Erythropoietin-producing hepatocellular receptor B2; SNHG7: Small nucleolar RNA host gene 7; DNMT3A: DNA methyltransferase 3 alpha; PVT1: Plasmacytoma variant translocation 1; ATG: Autophagy-related gene; SCARNA10: Small Cajal body-specific RNA 10; PRC2: Polycomb repressive complex 2; mTOR: Mammalian target of rapamycin; MALAT1: Metastasis-associated lung adenocarcinoma transcript1; NEAT1: Nuclear enriched abundant transcript1; SOX9: SRY-related high mobility group-box gene9; PEG3: Paternally expressed gene 3; SOCS2: Suppressor of cytokine signaling 2; Cyth3: Cytohesin 3; Lfar1: Liver fibrosis associated lncRNA1; GAS5: Growth arrest-special transcript 5; TLR: Toll-like receptor; MEG3: Maternally expressed gene 3; NLR5: NLR Family CARD Domain Containing 5; NORAD: Non-coding RNA activated by DNA damage; S1PR3: Sphingosine 1-phosphate receptor 3; XIST: X-inactive-specific transcript; ADAMTS5: ADAM metalloproteinase with thrombospondin type 1 motif 5; Mical2: Molecule interacting with CasL2; Shc: Src homologous-collagen homologue; PINK1: PTEN-induced putative kinase 1; MTO1: Mitochondrial tRNA translation optimization 1; FBXW4: F-box and WD repeat domain containing 4; CREBBP: CREB binding protein; LEFTY2: Left-right determinant cluster 2; Ube2k: Ubiquitin conjugating enzyme E2 K; STAT3: Signal transducer and activator of transcription 3; Airn: Antisense Igf2r RNA; ROR: Regulator of reprogramming; EZH2: Enhancer of zeste homolog 2; KLF2: Krüppel-like transcription factor 2; eNOS: Endothelial nitric oxide synthase; sGC: Soluble guanylate cyclase.

-induced fibrosis[63]. These findings indicate that elevated miR-29 Level in serum may be a promising biomarker for diagnosis of liver fibrosis[63]. Another set of biomarkers (NIS4) consisting of miR-34a-5p, α -2 macroglobulin, YKL-40 and glycated hemoglobin have been developed to successfully identify patients who have a higher risk of disease progression with non-alcoholic fatty liver disease and liver fibrosis. The diagnostic value of the NIS4 algorithm was not affected by age, gender, BMI and transaminase[64]. Similarly, Azar *et al*[65] constructed a miRNA regulatory network using bioinformatics tools and identified five upregulated miRNAs (miR-21-5p, miR-222-3p, miR-221-3p, miR-181b-5p, and miR-17-5p) that targeted tissue inhibitor of metalloproteinase 3 in activated HSCs, and these results have been verified in a mouse model of liver fibrosis. Zhang *et al*[66] performed a logistic regression analysis to show that miR-1225-3p, miR-1238, miR-3162-3p, miR-4721, and miR-H7 could distinguish, with high sensitivity and specificity, nonsignificant fibrosis from significant fibrosis in chronic hepatitis B (CHB) patients. Some researchers screened miRNAs in serum from HCV-related liver fibrosis patients and found that miR-484 was significantly downregulated in advanced liver fibrosis compared to early liver fibrosis and liver cancer[67], which indicates that miR-484 may be used as a biomarker for staging liver fibrosis in patients with HCV. Besheer *et al*[68] performed diffusion-weighted magnetic resonance imaging of livers in patients with liver fibrosis caused by chronic hepatitis C and compared the apparent diffusion coefficient (ADC) with miRNA expression pattern in liver biopsies. They found that ADC was closely associated with expression of miR-200b, miR-21, and miR-29, and the accuracy of ADC combined with miR-200b to distinguish early and late liver fibrosis was 80.2%[68]. In a discovery cohort of 183 patients with non-alcoholic fatty liver disease, scientists identified that plasma miR-193a-5p was consistently maintained at a high level and was closely associated with grade of fibrosis, which was verified in a cohort of 372 additional cases[69]. Results from another study confirmed that miR-103a-3p and miR-425-5p were stably expressed in exosomes of serum derived from mice and humans infected with schistosomiasis[70]. MiR-146a-5p could distinguish mild (grades 0 and I) and severe fibrosis (grades II and III) and could be used for staging liver fibrosis[70].

LncRNAs are useful in the diagnosis of liver fibrosis. A study compared lncRNAs profiles of serum exosomes from patients with liver fibrosis and healthy controls and found that the expression level of lncRNA MALAT1 was significantly increased in the serum of fibrotic patients[31]. Serum lncRNA GAS5 was significantly upregulated in patients with advanced liver fibrosis compared with nonfibrotic patients[71]. Serum lncRNA-p21 had 70% specificity and 100% sensitivity in diagnosing liver fibrosis in patients with CHB[72]. LncRNA SCARNA10 was higher in liver and serum samples in patients with advanced liver fibrosis compared with healthy controls[23].

In addition to miRNAs and lncRNAs, circRNAs have shown differential expression in patients with liver fibrosis. The expression level of circRNA death inducer-obliterators 1 (circDIDO1) was decreased in serum exosomes derived from patients with liver fibrosis[73], while serum circMTO1 was negatively correlated with the degree of liver fibrosis in patients with CHB[24]. All these findings suggest that ncRNAs have potential as novel noninvasive biomarkers for the diagnosis and staging of liver fibrosis with high sensitivity and specificity.

POTENTIAL APPLICATION OF NCRNAS FOR THE TREATMENT OF LIVER FIBROSIS

Early liver fibrosis is deemed to be reversible. When the injury is removed, activated HSCs (myofibroblasts) are reduced through deactivation or apoptosis to slow down the fibrotic process and even lead to

regression. Studies have shown that patients with chronic hepatitis B or chronic hepatitis C have reduced liver fibrosis after receiving antiviral therapy[74]. In addition, therapies such as antioxidants, renin-angiotensin system inhibitors, and traditional Chinese medicine[75] are also considered promising for treatment of liver fibrosis, although more clinical trials are needed to confirm their safety and efficacy. As extensive cytokines and signaling pathways are involved in the pathogenesis and progression of liver fibrosis, ncRNA-based therapies that target various signaling pathways are being developed based on the outstanding gene silencing effect of miRNAs and the sponging effect of lncRNAs and circRNAs.

With strong inhibitory effects on a variety of fibrotic diseases such as myocardial fibrosis[76], pulmonary fibrosis[77], and renal fibrosis[78], miR-29 families are regarded as a potential therapeutic target for fibrosis. Yang *et al*[79] reported that miR-29a reduced liver fibrosis and ECM by directly targeting PI3Kp85 α in cholestatic liver fibrosis, and this supports the potential of miR-29a for the treatment of liver fibrosis. However, recent studies showed that, even though upregulation of miR-29 inhibited fibrosis, it could also lead to type 2 diabetes and insulin resistance[80]. Researchers have assessed the therapeutic effect of a synthetic miR-223 analog in a murine NASH model and have found that miR-223 treatment inhibited HSC activation through the downregulation of transcription of proinflammatory cytokines and chemokines together with NOD-like receptor 3 (NLRP3) inflammasome [81]. In addition, miR-223 was reported to inhibit the activation and proliferation of HSCs by targeting Gliotactin family zinc finger 2 (GLI2) and PDGFR α/β in CCl₄-induced liver fibrotic mice[82]. These studies clearly demonstrate the potential of miR-223 as a therapeutic strategy for liver fibrosis, although the underlying mechanisms vary.

Exosomes are small vesicles that are stable in body fluids, low in immunogenicity, can be engulfed by cells, and have been used as delivery vectors for easily degradable molecules such as RNA to treat diseases like liver cancer[83]. Exosomes have also been explored in treating liver fibrosis. Gao *et al*[84] found that miR-690 produced by Kupffer cells could be delivered to HSCs by exosomes to inhibit fibrosis by targeting nicotinamide adenine dinucleotide kinase. In a murine NASH model, miR-690 mimics decreased liver fibrosis markers and alleviated NASH phenotypes significantly. Exosomal miR-223 derived from natural killer cells has also been shown to target ATG7 in HSCs by inhibiting autophagy, leading to reduced fibrosis[85]. In addition, mesenchymal stem cell (MSC)-derived exosomes have been well studied as a promising treatment option for liver fibrosis[86]. Human bone MSCs (hB-MSCs)-derived exosomal miR-618[87] and human tonsil-derived MSCs (hT-MSCs)-derived exosomal miR-486[88] have been shown to alleviate liver fibrosis by targeting *Smad4* and *smoothed (Smo)* genes, respectively. MiR-6766-3p derived from 3D-cultured human embryonic stem cells were enriched in exosomes and attenuated TGF β 1/SMADs by targeting TGF β RII to inhibit proliferation of HSCs[89]. In another study, adipose-derived stromal cells were transfected with miR-150, and the culture supernatants were collected to treat HSCs or infuse into mice with liver fibrosis. Expression of several fibrosis markers such as Collagen 1A1 and α -smooth muscle actin (α -SMA), as well as the levels of systemic inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α were significantly decreased in miR-150-treated mice compared with the control group[90]. This indicates that the exosomal miR-150 has antifibrotic activity through targeting of the TGF- β pathway. Zhou *et al*[91] co-cultured HSCs with human umbilical cord MSCs and found that expression of miR-148a-5p in HSCs was significantly upregulated, which decreased liver fibrosis by inhibiting Notch2 *in vivo* and *in vitro*.

Bone marrow MSCs have also been shown to reduce liver fibrosis by altering expression of lncRNAs. One such example comes from lncRNA BIHAA1 derived from bone marrow MSC-treated HSCs. Bone marrow MSCs inhibited liver fibrosis by lncRNA BIHAA1 targeting miR-667-5p[92]. Sun *et al*[93] found that silencing lncRNA SNHG promoted differentiation of bone marrow MSCs into hepatocyte-like cells and reduced cirrhosis through the miR-15a/Smad ubiquitin regulatory factor 1 (SMURF1)/UV radiation resistance associated gene (UVRAG)/ATG5/Wnt5a axis.

CircRNAs have also been investigated to treat liver fibrosis. Ma *et al*[73] reported that circDIDO1 in exosomes derived from MSCs regulated the PTEN/AKT pathway by sponging miR-141-3p, thereby inhibiting activation of HSCs and reducing expression of α -SMA and Collagen I to alleviate liver fibrosis. Similarly, MSC-derived exosomal circRNA cyclin dependent kinase 13 (circCDK13) inhibited activation of PI3K/AKT and NF- κ B signaling pathways to reduce liver fibrosis by regulating miR-17-5p and its target gene K (lysine) acetyltransferase 2B (KAT2B)[94].

Delivery systems are one of the key issues to be resolved in order to protect ncRNAs from being degraded. Lipid nanoparticles (NPs) for ncRNAs delivery have been developed. Hu *et al*[95] encapsulated miR-30a-5p and an antifibrotic peptide Relaxin into NPs and injected them into fibrotic mice. NPs increased the exosomal miR-30a-5p level, which in turn reversed the activated HSCs into a quiescent state by targeting liver macrophages[95]. Furthermore, NPs encapsulated with miR-29b and Germacrone, a major component of the traditional Chinese medicine *Rhizoma curcuma*, have been shown to have robust antifibrotic activity *in vitro* and *in vivo*[96]. The ncRNAs showed the potential for the treatment of liver fibrosis are collected in Table 2.

Table 2 Noncoding RNAs for the potential treatment of liver fibrosis

ncRNAs	Target genes	Signaling pathways	Ref.
miR-29a	<i>PI3KP85a</i>	PI3K/AKT	[79]
	<i>Fstl</i>	TGF- β /Smad2, JNK	[21]
miR-223	<i>NLRP3</i> inflammasome	NOD signaling pathway	[81]
	<i>GLI2</i> , <i>PDGFRα/β</i>	Hedgehog, PDGF	[82]
hB-MSCs-derived exo-miR-618	<i>Smad4</i>	TGF- β /Smad2	[87]
3DhESCs-derived exo-miR-6766-3p	<i>TGFβRII</i>	TGF- β /Smad	[89]
hT-MSCs-derived exo-miR-486	<i>Smo</i>	Hedgehog/GLI2	[88]
NK cells-derived exo-miR-223	<i>ATG7</i>	Autophagy pathway	[85]
KCs-derived exo-miR-690	<i>NADK</i>	-	[84]
lncRNA SNHG	<i>miR-15a</i> , <i>MURF1</i>	UVRAG/ATG5/Wnt5a	[93]
lncRNA BIHAA1	<i>miR-667-5p</i>	-	[92]
MSCs-derived exo-circDIDO1	<i>miR-141-3p</i>	PTEN/AKT	[73]
MSCs-derived exo-circCDK13	<i>miR-17-5p</i> , <i>KAT2B</i>	PI3K/AKT, NF- κ B	[94]

ncRNAs: Noncoding RNAs; PI3K: Phosphatidylinositol 3-kinase; AKT: Serine/threonine kinase 1; Fstl: Follistatin-like 1; TGF- β : Transforming growth factor- β ; JNK: c-Jun N-terminal kinase; NLRP3: NOD-like receptor family, pyrin domain containing 3; Smo: Smoothened; GLI2: Gliotactin family zinc finger 2; PDGFR: Platelet-derived growth factor receptor; MSC: Mesenchymal stem cell; hB-MSC: Human bone MSC; hT-MSC: Human tonsil-derived MSC; 3DhESC: 3D-cultured human embryonic stem cells; TGF- β RII: TGF- β type II receptor; ATG: Autophagy-related gene; KCs: Kupffer cells; NADK: NAD kinase; SNHG: Small nucleolar RNA host gene; SMURF1: Smad ubiquitin regulatory factor 1; UVRAG: UV radiation resistance associated gene; DIDO1: Death inducer-obscurator 1; PTEN: Phosphatase and tensin homology deleted on chromosome ten; CDK13: Cyclin dependent kinase 13; KAT2B: K (lysine) acetyltransferase 2B.

CONCLUSION

It is well known that persistent liver fibrosis leads to irreversible fibrosis, decompensated cirrhosis, and even HCC, which emphasizes the importance of treatment during early-stage fibrosis to prevent disease progression. Therefore, it is important to diagnose liver fibrosis before clinical symptoms appear. Although liver biopsy is considered the gold standard for the diagnosis of liver fibrosis, its invasive nature limits its clinical use, especially in early disease stages. Although some ncRNAs are closely associated with the pathogenesis and progression of liver fibrosis, there is still insufficient evidence for diagnosing and staging liver fibrosis using ncRNAs alone. Some studies have suggested combining ncRNAs with other indicators (biomarkers) in blood or with imaging techniques to increase the accuracy of liver fibrosis diagnosis. There is no specific anti-hepatic fibrosis drug in clinical use, although several candidates have already been enrolled in clinical trials. The main strategy for antifibrosis therapy is to treat the etiology and alleviate liver inflammation. NcRNAs are able to target various inflammation-related signaling pathways to reduce liver fibrosis. The latest studies have found that miR-20b-5p[97] and lncRNA Antisense Igf2r RNA (lncRNA Airn)[98] can inhibit HSCs activation to alleviate liver fibrosis process. Salvianolic acid B treatment relieved the activation of HSCs through decreasing the expression of lncRNA regulator of reprogramming (lncRNA-ROR)[99], which providing new targets for the treatment of liver fibrosis. Although most of these findings are based on *in vitro* studies, and therefore, need validation *in vivo*. With the rapid progress of techniques such as gene editing, NP-based delivery systems, and synthetic biology, MSC-derived exosomal ncRNAs may become promising treatment options for liver fibrosis in the near future.

FOOTNOTES

Author contributions: Gong T and Xie H collected the references; Li QY drafted the initial manuscript; Huang YK and Kang L drew the figure and tables; Chen LM and Duan XQ reviewed and revised the initial draft; Warner CA polished the language; all authors contributed to the manuscript and approved the submitted version; Chen LM and Duan XQ contributed equally to this manuscript.

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