Cellular Signalling 24 (2012) 2268–2272

Contents lists available at SciVerse ScienceDirect

Cellular Signalling

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

Review

The potential of microRNAs in liver fibrosis

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ARTICLE INFO

Article history:
Received 4 July 2012
Accepted 28 July 2012
Available online 3 August 2012

Keywords:
miRNA
Liver fibrosis
Hepatic stellate cells
Signal transduction pathways

ABSTRACT

MicroRNAs (miRNAs) are a class of ~22-nucleotides noncoding RNAs that regulate gene expression by specifically binding with 3'-untranslated region (3'-UTR) of target gene mRNAs to posttranscriptionally effect mRNA stability and translation,and play essential roles in a variety of biological processes, including cell development, proliferation, differentiation, and apoptosis. Liver fibrosis is the occurrence of liver cell necrosis and inflammatory stimulation, and is characterized by excessive accumulation of extracellular matrices(ECMs). In the fibrotic liver, hepatic stellate cells (HSCs), which are regulated by multiple signal transduction pathways, undergo myofibroblastic transdifferentiation and are generally regarded as the major ECM producer responsible for liver fibrosis. A growing body of evidence suggests that divergent miRNAs participate in liver fibrotic process and activation of HSC. Moreover, members of many signal transduction pathways are important targets for miRNAs. In this review, we make a summary on current understanding of the roles of miRNAs in the development of liver fibrosis, HSC functions and their potential as novel drug targets.

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1. Introduction

MicroRNAs (miRNAs) were recently discovered molecules that regulated entire intracellular pathways at a posttranscriptional level through targeting the 3'-untranslated region(3'-UTR) of target gene mRNAs [1]. MiRNAs were approximately 22-nucleotide-long RNAs that were encoded in the genome and the majority of them resided in introns of protein-coding genes [2]. Recently it has shown that miRNAs regulated more than one–third of all human genes [3]. Similar to messenger RNAs (mRNAs), the primary miRNA(pri-miRNA) molecules were transcribed by RNA-Polymerase II. The cleavage of pri-miRNAs released small, approximately 65-nucleotide-long precursor miRNAs (pre-miRNAs). These pre-miRNAs were exported into the cytoplasm by exportin-5 and further processed into approximately 22-nucleotide-long mature miRNA by RNase III and Dicer [4,5]. Mature miRNAs integrated into the RNA-induced silencing complex(RISC), and this miRNA/RISC complex mediated gene repression activity by causing translational repression or transcript degradation [1,6,7]. One miRNA might bind to a number of mRNAs transcripts and in turn one mRNA could be targeted by a widespread panel of miRNA species. There is now overwhelming evidence that miRNAs can regulate a variety of biological processes, including cell development, proliferation, differentiation, and apoptosis, and that aberrant miRNA expression is related with the development of multiple diseases.

Liver fibrosis is the excessive accumulation of extracellular matrix that occurs in most types of chronic liver diseases. Hepatic stellate cells (HSCs) were believed to be the main matrix-producing cells in the liver and its activation had been identified as the major driver

Abbreviations: miRNA, microRNA; ECM, extracellular matrix; HSC, hepatic stellate cell; α-SMA, α-smooth muscle actin; TGF-β, transforming growth factor-β; 3'UTR, 3'untranslated region; PDGF, platelet-derived growth factor; HCC, hepatocellular carcinoma; ACSL1, acyl-CoA synthetase long-chain family member 1; RXRα, retinoid X receptor- α; TNC, tenascin-C; IFNs, Interferons; TGFβRII, TGFβ receptor II; SMAD3, Signaling effectors (mothers against decapentaplegic protein)3; FXR, nuclear receptor farnesoid X receptor; IGF, insulin-like growth factor; HGF, hepatocyte growth factor; TRAF6, TNF receptor associated factor 6; IRAK1, interleukin-1 receptor-associated kinase 1.

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0898-6568/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cellsig.2012.07.023

of liver fibrosis [8–10]. Following multiple injurious agents and/or exposure to inflammatory cytokines, activated HSCs lost their lipid droplets, migrated to injured sites and were transformed into myofibroblast-like cells that secreted large amounts of ECM leading finally to liver fibrosis [9,11]. A number of inflammatory cytokines have been identified, and transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) were proposed to play a central role in liver fibrosis [12–15]. Although current treatments typically target the inflammatory response, there are few effective therapies and the mechanism of liver fibrosis is poorly understood. However, accumulating studies have demonstrated that miRNAs played an important role in the progression of liver fibrosis and regulated proliferation/apoptosis of HSC. The unique expression profile and function of miRNAs in liver fibrosis and HSC suggested that miRNAs could be exploited as novel biomarkers for liver fibrosis diagnostics and might present a new strategy for miRNA gene therapy. In this regard, we have reviewed the growing body of evidence which suggests miRNAs are involved in the development of liver fibrosis and proliferation/apoptosis of HSC (Fig. 1).

2. The expression of miRNAs in the progression of liver fibrosis

Liver fibrosis and hepatocellular carcinoma(HCC) development are strongly related, but recently there is no effective treatment against liver fibrosis because the main mechanism of progression of liver fibrosis is not fully understood. In order to clarify how miRNAs contribute to the progression of liver fibrosis, Murakami et al. [16] analyzed the expression of miRNAs in mouse liver fibrosis model and human clinical samples by miRNA microarray analysis and then revealed that in the mice study, 11 miRNAs were correlated to the progression of liver fibrosis (mmu-let-7e, miR-125-5p, -199a-5p, -199b, -199b*, -200a, -200b, -31, -34a, -497, and −802). It's important that in both the mouse and human studies, 4 highly expression miRNAs (miR-199a, –199a*, –200a, and -200b) had similar expression pattern in both the human and the mice specimens and shared sequence between human and mouse, were positively and significantly associated with the progression of liver fibrosis [16]. The treatment of mice with carbon tetrachloride (CCl_4) was the well established model of liver fibrosis. Roderburg et al. [17] have reported that after 6 and 8 weeks of CCl_4 treatment, all miR-29 members (miR-29a, -29b, -29c) were significantly downregulated in liver fibrotic tissues compared with the control liver tissues. Interestingly, the progression of hepatic fibrosis was associated with progressive upregulation of 16 miRNAs (the 10 most upregulated miRNAs were miR-34b, -34c, -34a, -221, -146b, -214, -199a-5p, -199a-3p, -223, -324-5p) and downregulation of 7 miRNAs (the 3 most downregulated miRNAs were miR-378, -193, -878) in liver fibrotic tissues as compared with the control group in dimethylnitrosamine (DMN)-induced hepatic fibrosis in rats [18]. Among them, miR-34 family (miR-34a, miR-34b and miR-34c) were found to be the most upregulated and may be involved in lipid/fatty acid metabolism by targeting acyl-CoA synthetase long-chain family member 1 (ACSL1) [18]. These findings were expected to uncover the critical mechanism of liver fibrosis and strongly implied that these dysregulated miRNAs played a role in the development of liver fibrosis and could also be explored as novel disease markers for the diagnosis or monitoring of the progression of liver fibrosis.

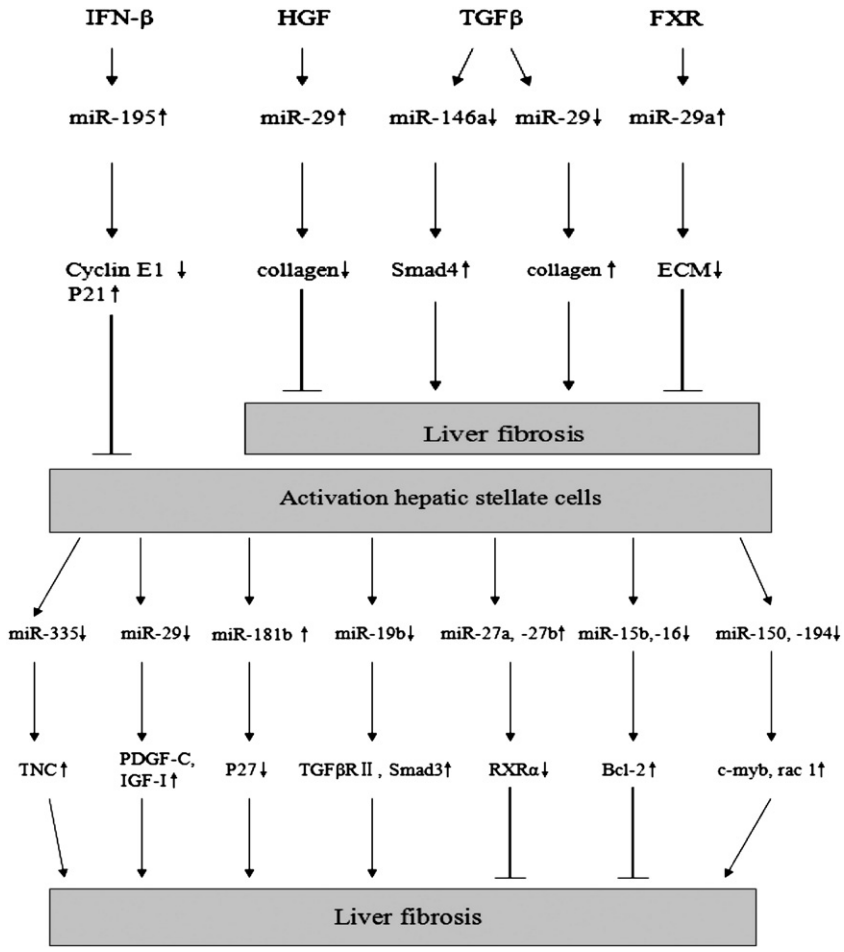

Fig. 1. Overview of the role of miRNAs in liver fibrosis.

3. MiRNAs regulate HSC proliferation and apoptosis

Hepatic stellate cells (HSCs) were widely recognized as playing a critically important role in liver fibrosis [9,19]. Currently, miRNAs have been found to play essential roles in HSC differentiation, proliferation, apoptosis and migration. The activated form of HSC secreted profibrogenic mediators, including TGF-β, and generated ECM components including α-smooth muscle actin(α-SMA), fibrillar collagens, fibronectin and laminin [9,20]. Recent studies have shown that measurement of the changes in miRNA expression in activated rat HSCs identified 12 up-regulated miRNAs (miR-874, -29c*, -501, -349, -325-5p, -328, -138, -143, -207, -872, -140, 193) and 9 down-regulated miRNAs (miR-341, -20b-3p, -15b, -16, -375, -122, -146a, -92b, -126) [21]. To our great surprise, 17 miRNAs(miR-345-5p, -152, -199a-5p, -218 -125b-5p, -214, -34c, -34b, -199a-3p, -425, -221, -301a, -222, -193, -31, -143, and −145) were upregulated and 14 miRNAs(miR-101a, -335, -877, -139-5p, -150, -126*, -192, -450a, -497, -338, -10a-5p, -378*, -195, and −126) were downregulated in both partially and fully activated HSCs when compared with quiescent HSCs respectively by using the mercury Array platform [22]. The anthors went on to demonstrate that restoring miR-335 expression significantly inhibited cell migration and reduced α-SMA and collagen type I level, at least in part, via decreasing the expression of TNC. In another *in vitro* study, overexpression of miR-150 and 194 resulted in cell proliferation inhibition in human HSCs(LX-2) as well as decreases in type I collagen and α-SMA, which were myofibroblast markers of HSC activation, at least in part, via inhibition of c-myb and rac1 expression [23]. HSCs, which resided in the Disse's space outside the liver sinusoids and contained bunches of vitamin A-riching lipid droplets, while activated HSCs lost cytoplasmic lipid droplets and transdifferentiated to proliferive, fibrogenic myofibroblasts [9,11,24]. Recently, a study carried out by Ji et al. [25] showed that downregulation of overexpressed miR-27a and 27b allowed activated HSCs to restore their ability to accumulate cytoplasmic lipid droplets and decreased HSCs proliferation. Moreover, the fatty acid metabolism and cell proliferation regulating properties of miR-27a and 27b maybe, at least partly mediated by affecting RXRa expression. But Silencing of miR-27a and 27b didn't affect cell apoptosis and other characteristics of activated HSCs such as enhanced matrix protein collagen type I expression and expression of α-SMA was almost not affected.

Cell apoptosis was also the main mechanism promoting the resolution of fibrosis, and spontaneous or targeted apoptosis of HSC was associated with regression of liver fibrosis in animal models and activation of HSC [26,27]. Specifically, administration of miR-15b and miR-16 was shown to inhibit HSC proliferation and induce apoptosis by inducing the mitochondrial-associated anti-apoptosis protein, Bcl-2, leading to activation of caspase 3, 8, and 9 [28]. Additional study by Guo et al. [29] have further demonstrated that overexpression of miR-16 greatly reduced cyclin D1 levels in addition to inhibiting cell proliferation and increasing cell apoptosis in activated HSCs. More recent studies by Wang et al. [30] have also shown that transient overexpression of miR-181b could promote HSC cell proliferation and cell cycle progression by increasing the number of S phase cells, and increase the growth of HSCs by directly targeting CDNK1B (encoding p27). Furthermore, the increased levels of miR-181b in serum of cirrhosis patients suggested that it may be potential diagnostic biomarkers for cirrhosis. Both *in vivo* and *in vitro* TGF-β1 could induce HSC activation and trigger the fibroblast phenotype to myofibroblasts including increased expression of α-SMA. Recently, the expression of miR-146a was downregulated in HSC in response to TGF-β1 stimulation in dose-dependent manner and overexpression of miR-146a suppressed TGF-β-induced HSC proliferation, and increased HSC apoptosis [31]. Interferons (IFNs) have a direct antifibrotic potential in the liver independently of their antivirus effect [32,33]. However, recently it has been reported that IFN-β induced miR-195 expression, then overexpression of miR-195 lowered cyclin E1 mRNA and protein expression levels, increased p21 mRNA and protein expression levels, and inhibited cell proliferation by delaying their G1 to S phase cell cycle progression in human HSC line LX-2 [34]. These observations revealed a new mechanistic aspect of the antifibrotic effect of IFNs in the liver fibrosis and the possibility of influencing miR-195 as a therapeutic strategy for liver fibrosis.

4. Signaling pathways regulated in HSCs by miRNAs

Activation of HSC was the key event in liver fibrosis and was regulated by multiple signal transduction pathways, including transforming growth factor-β(TGF-β)/Smad, platelet-derived growth factor, phosphatidylinositol 3-kinase (PI3K)—Akt pathway, mitochondrial pathway of apoptosis, mitogen-activated protein kinase(MAPK), Focal adhesion kinase [35,36]. Recently, Guo et al. [21] have revealed that 13 pathways were upregulated and 22 pathways were downregulated by miRNAs by performing comprehensive comparative bioinformatics analysis of microarrays of quiescent and activated HSCs. Furthermore, the mitochondrial pathway of apoptosis was likely to play a significant role in HSC activation by miRNA-targetd Bcl-2 and casepase-9.

Key cytokines were involved in liver fibrosis regulating the inflammatory response to injury and modulated hepatic fibrogenesis *in vivo* and *in vitro*. Among growth factors, TGF-β1 appeared to be a key mediator in fibrogenesis [37–40]. In particular, TGF-β1 mainly activated HSC through TGF-β1/Smad signal pathway, thus causing hepatic fibrosis [40,41]. In TGF-β1/Smad signaling pathway, smad2 and smad3 function as R-smads, smad4 functions as Co-smad, and smad7 functions as an anti-smad. Interestingly, it was observed that Inhibition of TGFβ signaling by miR-19b was confirmed by decreased expression of type I collagen and by blocking TGFβ-induced expression of α1(I) and α2(I) procollagen through targeting TGFβ receptor II (TGFβRII) and smad3 expression [42]. However, it was well established that inhibition of TGFβRII decreased the activation of HSCs and inhibited the production of fibrogenic ECM components in HSC [43]. So, miR-19b was a novel regulator of TGFβ signaling in HSCs suggesting a potential therapeutic approach for liver fibrosis. In addition, Overexpression of miR-146a suppressed TGF-β-induced HSC proliferation, increased HSC apoptosis, and the expression of α-SMA, at least in part, via decreasing the expression of smad4 [31]. Ogawa et al. [44] also found that miR-29b may be a novel regulator of type I collagen expression in addition to its involvement in the well-known Smad cascade by its interaction with SP1 expression in LX-2. Additionally, Overexpression of miR-29b suppressed primary-cultured mouse HSCs viability and the expression of a-SMA. These effects seemed to be independent of the activation of focal adhesion kinase (FAK), extracellular signal-regulated kinase (ERK), and phosphatidylinositol-3 kinase (PI3K)–Akt, but were partially dependent on the reduction of c-fos mRNA [45]. MiR-146a was a negative regulator of immune and inflammatory responses and was involved in the NF-κB pathway through the two known targets TRAF6 and IRAK1 [46–48]. Maubach et al. [49] have shown that IRAK1 and TRAF6 were downregulated by overexpression of miR-146a in a HSC cell line HSC-2 and miR-146a overexpression upregulated TIMP-3 mRNA, which suggested an association between miR-146a, TNF α activity and inflammation and particularly, the involvement of miR-26a, 29a and 214 in the regulation of Col I mRNA. However, the transcriptome changes caused by miR-146a overexpression were very complex and numerous pathways were affected. Therefore, it's necessary to study the mechanism behind miR-146a regulation in liver fibrosis and HSC. We are now at the beginning of understanding of the diverse roles of miRNAs in liver fibrosis, and in future we will have a better picture of this complex regulatory mechanism.

5. Conclusion and Prospective

As outlined in this review, there is now increasing evidence that miRNAs regulate the progression of liver fibrosis, HSC activation and

apoptosis, and signaling pathways in HSCs (Fig. 1). In particular, miR-29 families were emerging as an very important and common regulator of liver fibrosis. Bioinformatics approaches showed that miR-29 families as novel antifibrogenic mediators can repress collagen synthesis via direct binding to its 3' UTR (Table 1). Significantly, a number of studies showed that miR-29 was not only involved in collagen type I but also in type IV synthesis of myofibroblastic HSC and TGF-β stimulation led to decreased miR-29 levels, but to pronounced upregulation of collagen synthesis, hepatocyte growth factor(HGF) stimulation led to elevated miR-29 expression, but to repression of collagen synthesis [50], and furthermore miR-29 acted as an antifibrogenic mediator not only by targeting collagen biosynthesis, but also by interfering with profibrogenic cell communication via platelet-derived growth factor (PDGF)-C and insulin-like growth factor (IGF)-I [51]. In addition, it's interesting that the nuclear receptor farnesoid X receptor (FXR) negatively regulated the expression of ECM by targeting miR-29a in HSCs [52]. To our delight, an artificial intronic miRNA expression system has been established, and the miRNA expression system could successfully produced mature anti-TGF-β1 miRNAs in an activated-HSC-specific manner to realize antifibrosis *in vitro* [53]. So

Table 1
The region of Collagen mRNA 3'UTR predicted to be targeted by miR-29 families. Bioinformatics approaches (TargetScan Human Release 5.1) was used for the target prediction.

	Col1A1	Position 274-280 of Col11a1 3' UTR 5' ...CUAUUUGAAUUUCUU-UGGUGCUG... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 274-280 of Col11a1 3' UTR 5' ...CUAUUUGAAUUUCUU-UGGUGCUG... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 274-280 of Col11a1 3' UTR 5' ...CUAUUUGAAUUUCUU-UGGUGCUG... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU Position 322-328 of Col11a1 3' UTR 5' ...UAUUCAUAAAAAAUAUGGUGCUC... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU Position 322-328 of Col11a1 3' UTR 5' ...UAUUCAUAAAAAAUAUGGUGCUC... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 322-328 of Col11a1 3' UTR 5' ...UAUUCAUAAAAAAUAUGGUGCUC... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU
	Col2A1	Position 361-368 of Col2a1 3' UTR 5' ...GUGUGUCCUACACAAUGGUGCUA... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 361-368 of Col2a1 3'UTR 5' ...GUGUGUCCUACACAAUGGUGCUA... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 361-368 of Col2a1 3'UTR 5' ...GUGUGUCCUACACAAUGGUGCUA... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU
miR-29 families	Col3A1	Position 242-249 of Col3a1 3' UTR 5' ...UUCAAAAUGUCUCAAUGGUGCUA... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 242-249 of Col3a1 3' UTR 5' ...UUCAAAAUGUCUCAAUGGUGCUA... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU Position 242-249 of Col3a1 3' UTR 5' ...UUCAAAAUGUCUCAAUGGUGCUA... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 682-689 of Col3a1 3' UTR 5' ...UAAAGACGCAUGUUAUGGUGCUA... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU Position 682-689 of Col3a1 3' UTR 5' ...UAAAGACGCAUGUUAUGGUGCUA... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 682-689 of Col3a1 3' UTR 5' ...UAAAGACGCAUGUUAUGGUGCUA... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU
	Col4A1	Position 30-37 of Col4a1 3' UTR 5' ...GCUAAUGUCACAACAUGGUGCUA... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 30-37 of Col4a1 3' UTR 5' ...GCUAAUGUCACAACAUGGUGCUA... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 30-37 of Col4a1 3' UTR 5' ...GCUAAUGUCACAACAUGGUGCUA... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU Position 308-314 of Col4a1 3' UTR 5' ...AUCAGAAAACCAAAGGGUGCUAG... hsa-miR-29c 3' AUUGGCUAAAGUUUACCACGAU Position 308-314 of Col4a1 3' UTR 5' ...AUCAGAAAACCAAAGGGUGCUAG... hsa-miR-29b 3' UUGUGACUAAAGUUUACCACGAU Position 308-314 of Col4a1 3' UTR 5' ...AUCAGAAAACCAAAGGGUGCUAG... hsa-miR-29a 3' AUUGGCUAAAGUCUACCACGAU

future developments will be crucially dependent upon understanding the function and mechanism of action of these liver fibrosis-related miRNAs. In the future, it is anticipated that miRNAs will be used for novel therapeutic strategies against hepatic fibrogenesis and also might evolve as biomarkers in the diagnosis of liver fibrosis.

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