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Review

The potential of microRNAs in liver fibrosis

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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.

Contents

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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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.

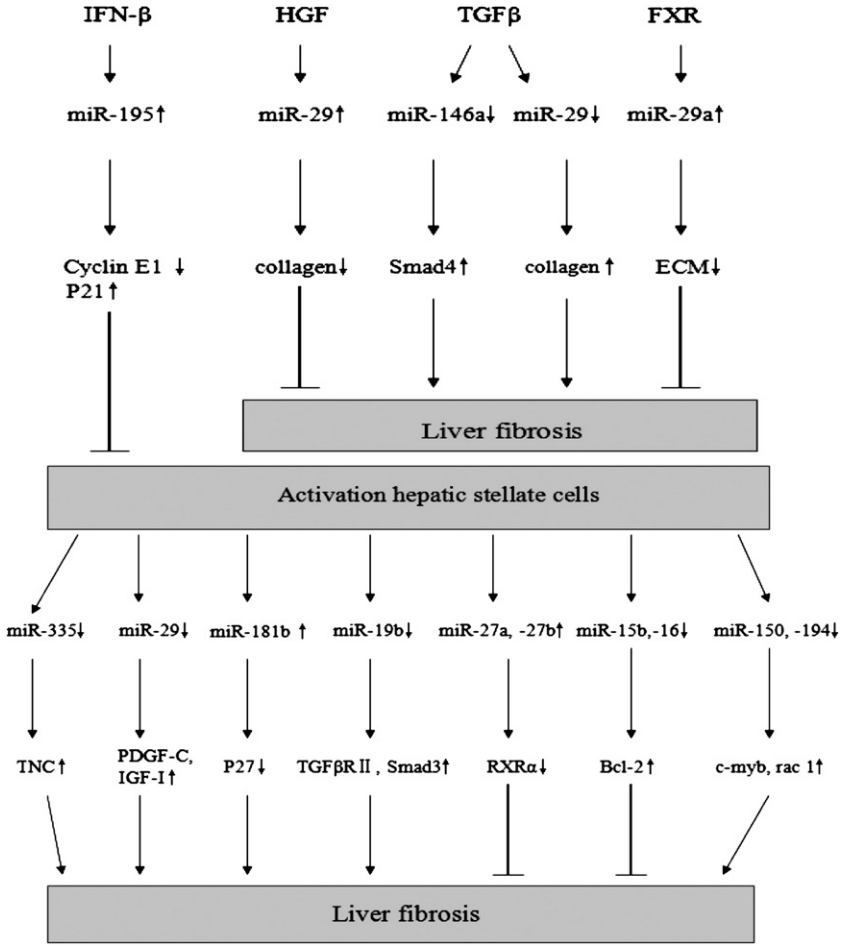

Fig. 1. Overview of the role of miRNAs in liver fibrosis.