Review Article

The roles of miRNAs in liver diseases

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Abstract: Liver, the largest internal organ in vertebrates, plays an essential role in metabolic processes in the body. Many factors, such as viruses and alcohol, can lead to function disorders or even liver failure. Every year more than a million patients suffer from various liver diseases. miRNAs have evolved as important regulators in in liver development, homeostasis, dysfunction, and regeneration. Increasing evidences have shown that miRNAs play an important role in various liver diseases, including acute liver failure (ALF), chronic liver failure as well as liver carcinoma. In this review, we update the roles of miRNAs in liver regeneration, fibrosis and cancer.

Keywords: microRNA; acute liver failure (ALF); liver fibrosis; liver carcinoma

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Introduction

Liver disease and its subsequent consequences have always been a tremendous clinical challenge. Many etiologies cause liver diseases and consequently, a variety of physiological symptoms. Based on cause and pathology of liver diseases, we can group liver diseases into three categories: acute liver failure (ALF) associated with direct liver injury (rapid loss of hepatocytes); chronic liver failure with widespread liver damage or cirrhosis; and hereditary liver disease (1,2).

miRNAs comprise a family of 21–25-nucleotide small, non-coding RNAs, which mainly mediate post transcriptional regulation of targeted gene (3,4). The first miRNAs were discovered in 1993 by Lee *et al.* in nematodes (5). Accordingly, extensive research leads to discovery of new miRNAs, their biogenesis and functions in various organs (6,7). The biogenesis of miRNAs was initiated by cleavage of Drosha-DGCR8 complex, which process primary miRNA hairpins into pre-miRNA (8). Pre-miRNAs are exported to the cytosol by exportin 5 and processed into double-strand miRNAs by Dicer complex. Then the two miRNA strands are separated and loaded to RISC, which contains Argonaute 2 (9,10). MiRNAs bind the 3'UTR of target mRNAs at the seed sequence, leading to translational inhibition. In some cases, several miRNAs can target the same mRNA, which leads to complexity of miRNAs-mediated regulation of gene expression.

miRNAs are known play important roles in liver development, homeostasis, dysfunction, and regeneration (11). Especially, in ALF, liver fibrosis and liver cancer, numerous reports have showed that miRNAs are deeply involved the development of these diseases. In this review, we update the roles of miRNAs in ALF, fibrosis and cancer.

miRNAs in ALF

ALF, also called fulminant hepatic failure, is defined as rapid loss of liver function (takes only days or weeks) in patients with no pre-existing liver disease. Although, it is less common than chronic liver disease, with an incidence of fewer than 10 cases per million persons per year in the developed world, it causes greater than 80% mortality (12).

The acute injury causes necrosis of hepatocytes, leading to release of alanine transaminase or aspartate transaminase—biomarkers of liver injury—into blood, followed by excessive bleeding or brain swelling (13).

Song *et al.* generated mice with hepatocyte-specific inactivation of DGCR8, an essential component for miRNA processing, and demonstrated miRNA regulate liver regeneration, suggesting miRNAs play an important role in ALF (14). They performed two thirds partial hepatectomy (PH) on mice to induce acute liver injury, which leads to rapid liver regeneration. They also discovered induction of miR-21 and repression of miR-378 upon PH in wildtype mice, which regulate DNA synthesis and hepatocytes proliferation (14). Subsequently, some other miRNAs have been identified as biomarkers of ALF in mice and human, including miR-122, miR-192, miR-101a (15-17). miR-122, the most abundant miRNA in the liver, also affects hepatic cholesterol and lipid metabolism (18,19). MiR-378 has been reported to regulate ALF by targeting Cyp2e1 (20,21). Recently, Russo *et al.* described profiles of miRNAs in serum of drug induced liver injury patients and reported a number of elevated miRNAs, including miR-122, miR-1246, -4270, -4484, -4532 and decreased levels of miR-455-3p, -1281. They demonstrated that serum miRNA-122 combined with albumin were associated with 6 months mortality, suggesting prognostic significance of miRNAs (22).

In addition to be potential biomarkers in ALF, miRNAs have also been reported to be anti-ALF agents. Sharma *et al.* identified miR-221 as an up-regulated miRNA in response to FAS-induced fulminant liver failure and reported overexpression of miR-221 delays FAS-induced fulminant liver failure by regulating PUMA (23). Similarly, miR-221 overexpression also improve hepatocyte proliferation during liver regeneration in two-thirds PH mouse model (24). In addition, Yang *et al.* and her colleagues identified miR-125b-5p as a critical regulator of hepatocyte death using miRNA screens and showed that administration of miR-125b-5p mimic in mouse liver miR-125b-5p regulates expression of nuclear factor-E2-related factor 2 by targeting kelch-like ECH-associated protein 1, which improves survival in acetaminophen or N-acetyl-p-aminophenol (APAP) induced ALF models, suggesting miRNAs may also serve as therapeutic agent to treat ALF (25).

miRNAs in liver fibrosis

Currently, worldwide estimates show that 844 million people suffer from chronic liver diseases, with a mortality rate of 2 million deaths per year (26). There are two general types of chronic liver failure, hepatocellular (injury to hepatocytes, such as chronic viral hepatitis and NASH) and cholestasis (obstruction of bile flow, such as primary biliary cirrhosis and primary sclerosing cholangitis) (13). Following liver injury, apoptotic or necrotic hepatocytes recruit tissue macrophages and trigger the activation of HSCs through the chemokine ligand 2 and its receptors pathways (27). Thus, vitamin A storing quiescent HSCs are activated, leading to loss of vitamin A droplets, increased proliferation, release of profibrogenic cytokines and deposition of ECM components (28). Compared to quiescent HSCs, myofibroblasts also up-regulate expression of fibrosis related genes, i.e., alpha-smooth muscle actin, collagen type I alpha 1 chain and desmin. Upon sustained liver injury, progressive fibrosis results in further abnormal liver vascular architecture and nodules, called cirrhosis, and finally leads to an increased risk of liver cancer and mortality (29). Conversely, removal of underlying etiologies results in partial resolution of liver fibrosis by mediating apoptosis and senescence of myofibroblasts (30), suggesting amelioration of liver fibrosis as a feasible approach to treat chronic liver disease.

Many altered miRNAs have been reported during chronic liver disease. Altered miR-571 and miR-652 serum levels reveals their putative roles in progression of liver fibrosis and cirrhosis, suggesting they may be potential diagnostic biomarkers for fibrosis and cirrhosis (31). miR-181b serum levels is also elevated in patient and regulate activation of HSCs by targeting p27 (32). In addition, miR-199a, miR-200a and miR-200b levels also correlate with progression of liver fibrosis in both human and mouse (33).

A study of miRNAs in the liver revealed that miR-122 controls liver homeostasis by targeting KLF6, a profibrogenic factor, since miR-122a deficient mice develop steatohepatitis, fibrosis, and finally hepatocellular carcinoma (HCC) (34). Similarly, downregulation of miR-122 was also observed in liver of chronic alcohol injured mice (35). miR-221/222 is also upregulated in activated stellate cells and fibrotic liver tissue, indicating it may be new markers for liver fibrosis progression (36). Matsuura *et al.* determined profiles of circulating miRNAs in serum of chronic hepatitis C patients and identified decreased let7-family levels in severer fibrosis patients and elevated miR-122-5p associated with an increased inflammatory activity (37). Recently, Tsay *et al.* investigated crosstalk between hepatocytes and hepatic

stellate cells and identified miRNA-221-3p as a regulator of liver fibrosis. In this study, they performed co-culture of hepatocytes and hepatic stellate cells *in vitro* and examined fibrogenic role of 302 miRNAs using a miRNA screening approach. Blocking miRNA-221-3p function in hepatocytes reduced secretion of C-C motif chemokine ligand 2 by targeting GNAI2, leading to amelioration of liver fibrosis, which suggests miRNAs mediated cross-talk between different cell types may serve as a new therapeutic approach for liver fibrosis (38).

miRNAs in liver cancer

Liver cancer is one of the most lethal cancers worldwide, which consists of HCC, cholangiocarcinoma (CCC), as well as liver sarcomas and carcinomas (39). However, HCC is the most common cancer, which always arises within underlying diseased liver. Many prominent factors, including hepatitis infection (either HBV or HCV), alcohol, as well as high fat diets, lead to chronic liver diseases and favors cancer development (40,41). Chronic liver disease, such as liver inflammation, fibrosis and cirrhosis are prominent risk factors, which predispose patients to HCC development. HCV infected patients are more susceptible to cirrhosis development and increase the risk of HCC development (42). Repeated alcohol consumption increases pro-inflammatory cytokines as well as oxidative stress, which promotes hepatocarcinogenesis (43). Chronic liver inflammation promotes oncogenes activation (e.g., RAS) and downregulates expression of tumor-suppressor genes (e.g., p53) in hepatocytes, which favors liver cancer development (44). Campbell *et al.* reported hepatocarcinogenic potential of cirrhotic microenvironment and the molecular mechanisms underlying cirrhosis-induced HCC (45).

Several studies have showed altered miRNAs expression in human HCC. Murakami *et al.* investigated miRNA signatures associated with HCC and identified a few aberrant miRNAs in HCC, including MiR-222, miR-106a, miR-92, miR-17-5p, miR-20, and miR-18 (46). Another study revealed that a majority of the metastasis-related miRNAs were associated with survival of HCC patients by investigating miRNA expression profiles of cancerous and noncancerous specimens (47). MiR-26 was identified as a tumour suppressor and shown to be associated with survival and response to adjuvant therapy with interferon alfa (48). Systemic administration of miR-26 using adeno-associated virus induces tumour-specific apoptosis and suppression of tumour (49). miR-122, the most abundant miRNA in liver, also inhibited tumorigenesis in a mouse model of HCC (50). In addition, specific miRNA signatures associated with HCC also showed deregulation of tumour suppressor miRNAs like oncogenes such as miR-494 (51) and miR-21 (52,53). Nevertheless, miRNAs play a crucial role in HCC development and progression. Future investigations on miRNA/anti-miRNA for HCC treatment represent a novel therapeutic strategy against HCC.

Conclusions

MiRNAs play an important role in liver, including liver development, liver homeostasis, as well as various liver diseases (54-56). Increasing studies have shown that miRNAs should be a potential biomarkers or therapeutic agent for different liver diseases. Many etiologies could lead to liver diseases, such as virus infection (HAV, HBV, HCV), immune system abnormality, alcohol, fat diet, certain chemicals or toxins, as well as many genetic mutations and so on (57,58). Although some features of miRNAs in various liver diseases, such as ALF, chronic liver fibrosis or cirrhosis and HCC, have been described, the etiologies-specific miRNAs alterations are still not well defined. Moreover, liver consists of several different cell types, mainly including hepatocytes, hepatic stellate cells, sinusoidal endothelial cells, Kupffer cells as well as cholangiocytes and liver progenitor cells. Alteration of miRNAs in different cell type awaits further investigation. Finally, further studies are still needed to determine miRNAs signatures and molecular mechanism during different liver disease progression. To sum up, miRNAs based diagnose and therapies offer a potential approach for liver diseases in the future.

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Footnote

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