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MINIREVIEWS

Hepatitis C virus infection, microRNA and liver disease progression

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Abstract

Hepatitis C virus (HCV) is a global health problem with an estimated 170-200 million peoples (approximately 3% of world population) are chronically infected worldwide and new infections are predicted to be on rise in coming years. HCV infection remains categorized as a major risk factor for chronic hepatitis, liver cirrhosis and hepatocellular carcinoma worldwide. There has been considerable improvement in our understanding of virus life cycle since, the discovery of HCV two-decades ago. MicroRNAs (miRNAs) are important players in establishment of HCV infection and their propagation in infected hepatocytes. They target crucial host cellular factors needed for productive HCV replication and augmented cell growth. Very first anti-miRNA oligonucleotides, miravirsen has been tested in clinical trial and shown promising results as therapeutic agent in treatment against chronic HCV infection. Deregulated expression of miRNAs has been linked to the pathogenesis associated with HCV infection by controlling signaling pathways such as, proliferation, apoptosis and migration. Circulating miRNAs emerging as growing field in identification of biomarkers in disease progression and their potential as a means of communication between cells inside the liver is an exciting area of research in future. This review focuses on recent studies enforcing the contribution of miRNAs in HCV life cycle and coordinated regulation in HCV mediated liver disease progression.

Key words: Hepatitis C virus; MicroRNA; Liver disease; Interferon signaling; Circulatory microRNA

Core tip: Hepatitis C virus (HCV) is the major cause of chronic liver disease that gradually progresses from chronic hepatitis to cirrhosis and hepatocellular carcinoma (HCC) during the course of infection. MicroRNAs (miRNAs) are small RNA molecules and have the ability to regulate gene expression by targeting mRNA degradation or translational repression. miRNAs regulate HCV life cycle either by supporting viral replication or by inhibiting interferon signaling pathway. Several miRNAs play important roles in HCV related inflammation, fibrosis and HCC development. This review focuses on the involvement of miRNA in HCV life cycle and virus mediated liver disease progression, emerging role of circulating miRNAs and exploitation of miRNA as alternative therapeutic approach for HCV infection.

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INTRODUCTION

Hepatitis C virus (HCV) was first identified as a non-A, non-B hepatitis more than two decades ago[1]. It is a single stranded, positive sense RNA virus belongs to family *flaviviridae* and genus *hepacivirus*. The viral genome encodes

for a single precursor polyprotein of approximately 3010 amino acids, which is cleaved by viral and cellular proteases into three structural (core, E1 and E2) and seven non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) viral proteins. Core protein forms the capsid, which is surrounded by a lipid bilayer containing the glycoproteins, E1 and E2. These viral proteins are responsible for viral replication and various cellular functions[2]. HCV is a major cause of chronic liver disease, mostly asymptomatic in nature. Majority of the infected patients approximately, 80% develop persistent chronic infection and are at high risk for liver cirrhosis and hepatocellular carcinoma (HCC). An estimated 170-200 million peoples worldwide are infected with hepatitis C[3] and about 2.7-3.9 million peoples are living with HCV infection in the United States[4]. In addition, HCC and cirrhosis have been increasing among persons infected with HCV[5]. Recent approval of HCV NS3/4A protease inhibitors in standard treatment, consisting of pegylated interferon (IFN) alpha, and nucleoside analog, ribavirin (RBV) have shown improved rates of sustained virologic response in HCV infected patients[6]. Drugs targeted against HCV polymerase, NS5B has also been successfully validated in phase 2 clinical trials for the treatment of HCV infection[7].

MicroRNAs (miRNAs) were discovered in 1993 during a developmental timing experiment in the nematode *Caenorhabditis elegans*. Till date, human miRNA family has expanded to over 2000 mature miRNAs (miRBase v19.0; http://www.mirbase.org) and *in silico* prediction estimates that approximately 60% of human mRNA could be targets of miRNA[8]. miRNAs constitute a class of non-coding RNAs, about 18-22 nucleotides long and play crucial role in the regulation of gene expression. The production of miRNAs requires several processing steps, first primary miRNAs (pri-miRNAs) are cleaved by the ribonuclease Drosha to produce precursor miRNAs (pre-miRNAs) which in turn, cleaved by the ribonuclease Dicer to produce mature, single stranded miRNAs[9,10]. Once synthesized, mature miRNA associate with RNA induced silencing complex (RISC) together with Argonaute/EIF2C (AGO) proteins and mediates the target mRNA recognition. miRNA identify target mRNA through specific base-pairing interactions between the 5' end ("seed" region) of miRNA and sites within coding and untranslated regions (UTRs) especially 3' UTR of mRNAs that lead to mRNA destabilization. miRNA inhibits the target gene expression either by mRNA degradation or translational repression. miRNA promotes mRNA cleavage by inducing deadenylation or suppresses protein synthesis by repressing the translation initiation at the cap recognition or inducing ribosomes to drop off prematurely[11,12]. miRNA biogenesis is beyond the scope of this review and elegant reviews addressing miRNA synthesis and their mechanism of gene regulation is discussed in more detail elsewhere. A combinatorial nature of miRNA regulation, *i.e.*, each miRNA regulates hundreds of different mRNAs and further, a single mRNAs are targeted by multiple miRNAs, will allow us to focus on regulatory networks that determine the cell fate decisions. Viral infection can elicit changes in cellular miRNA expression profile, and several RNA viruses have been reported to interact directly with cellular miRNAs to facilitate their replication potential[13].

ROLE OF MIRNAS IN HCV REPLICATION

Recent studies have identified several miRNAs as key players in virus-host interactions, regulating virus replication and pathogenesis during HCV infection. The most abundant miRNA in the liver, miR-122 is regulated by specific, liver-enriched transcription factor, hepatocyte nuclear factor 4α[14] and is responsible for liver homeostasis[15]. Several studies demonstrated that miR-122 is required for HCV replication in infected cells[16-18]. miR-122 positively modulates HCV infection through direct interactions with viral RNA and stimulates HCV translation[19]. It forms an oligomeric complex in which one miR-122 molecule binds to the 5' UTR of HCV RNA with 3' overhanging nucleotides, masking the 5' terminal sequences of HCV genome. Furthermore, specific internal nucleotides as well as 3' terminal nucleotides in miR-122 were absolutely required for maintaining HCV RNA abundance[20]. miR-122 recruits Argonaute 2 to the 5' end of the viral genome, stabilizing the viral RNA and avoid the degradation in infected cells[21]. Recent study also demonstrated that miR-122 protects HCV RNA from 5' decay by targeting 5' exonuclease Xrn1[22]. Exogenous expression of miR-122 allows efficient HCV RNA replication and/or infectious virion production in non-permissive cell line[23-25]. Apart from regulating viral replication, miR-122 is also involved in cell cycle progression in hepatoma cell line[26]. miR-122 is known to target cyclin G1 and use of miR-122 inhibitor has been reported to prevent the alcohol-induced increase in HCV RNA and protein levels[27].

Besides miR-122, other miRNAs have been involved in HCV replication. Overexpression of miR-448 and miR-196 were able to substantially attenuate viral replication by directly targeting CORE and NS5A coding region of the *HCV* genome, respectively[28]. Let-7b was also identified as novel cellular miRNAs that directly target HCV genome and elicits anti-HCV activity[29]. Mutational analysis identified let-7b binding sites at the coding sequences of NS5B and 5'-UTR of *HCV* genome that were conserved among various HCV genotypes. Overexpression of miR-199a inhibited HCV replication in cells bearing *HCV-1b* or *-2a* genome length replicon[30]. miR-196a inhibits HCV RNA and NS5A protein expression in replicon by regulating HMOX1/Bach1 expression[31]. In HCV infected patients, lower expression levels of miR-29 was observed in liver and overexpression of miR-29 inhibits viral RNA in HCV infected hepatocytes[32]. We have demonstrated that miR-130a expression is upregulated in liver biopsy from HCV infected patients as well as in HCV infected hepatocytes

in vitro[33]. We also observed that knockdown of miR-130a inhibits HCV replication in hepatocytes. Similar observation has been reported on miR-130a mediated regulation of viral replication in HCV infected cells[34]. Differential upregulation of hsa-miR-130a, hsa-miR-130b, hsa-miR-298, hsa-miR-193a-5p and hsa-miR-371-5p were also observed in HCV Con1 replicon in comparison to control cells. These miRNAs have been associated with cell growth by targeting genes PPARG, IRF1 and STAT3 in HCV infected cells[35]. Differential expression of miRNAs such as, miR-24, miR-149, miR-638 and miR-1181 were also identified following HCV infection and are involved in HCV entry, replication and propagation[36]. Delivery of miR-17-92 cluster has been reported to inhibit HCV replication by up to 95% *in vitro* cell culture system[37]. Recently, negative effect of miR-27a has been demonstrated in HCV replication. miR-27a repression increased the cellular lipid content, decreased the buoyant density of HCV particles and increased viral replication and infectivity[38]. miR-192/miR-215 and miR-491 are capable of enhancing HCV replication in replicon cells[39]. miR-141 mediated suppression of DLC-1 (a Rho GTPase-activating protein) enhances viral replication in HCV-infected primary human hepatocytes[40].

ROLE OF MIRNAS IN REGULATION OF INTERFERON RESPONSE IN HCV INFECTION

HCV infection also modulates several miRNAs, which in turn inhibits type 1 IFN signaling pathway. We have demonstrated that HCV inhibits IFITM1, an interferon stimulated gene, by upregulating miR-130a expression in HCV-infected hepatocytes. Introduction of anti-miR-130a in hepatocytes increased IFITM1 expression with concomitantly reduction in HCV replication[33]. Overexpression of miR-122 has also been associated with inhibition of IFN signaling pathway. Silencing of miR-122 enhances IFN-induced interferon stimulated response element activity, by decreasing expression of SOCS3. This decrease in SOCS3 level was also regulated by enhanced methylation at *SOCS3* gene promoter, implicating additional mechanism of inhibition of HCV replication using antisense oligonucleotides of miR-122[41]. miRNAs also regulate the expression of target genes involving immune response to viral infections mediated by type I IFN pathway. Upregulated miR-21 suppressed MyD88 and IRAK1 expression in hepatocytes, which subsequently repressed type I IFN effector gene expression and the type I IFN-mediated antiviral response, thereby promoting viral replication[42]. IFN-α treatment also modulates HCV-specific miRNAs expression in hepatocytes. miR-324-5p and miR-489 shown to be upregulated in the presence of IFN-α while differential expression of miR-30c and miR-130a were observed between HCV-infected Huh7.5 cells treated with or without IFN-α[34]. miR-30 cluster targets *SOCS1* and *SOCS3* genes that act as negative regulators of cytokine signaling. Specifically, SOCS1 and SOCS3 inhibit JAK tyrosine kinase activity and STATs in the JAK-STAT signaling pathway suggesting that IFN-α induced miRNAs modulates gene expression in HCV infected hepatocytes[34]. IFN-β treatment of Huh-7 cells showed an upregulation of miR-142-3p and miR-128a, and these miRNAs were downregulated in HCV replicon-expressing cells[43]. IFN-β induced miRNAs, in conjunction with the downregulation of miR-122, was also studied to prevent HCV replication. Introduction of anti-miRs against miR-196, miR-296, miR-351, miR-431 and miR-448, with and without the inclusion of miR-122 mimic, attenuated the IFN-β mediated reduction of viral RNA by approximately 75%[28]. Treatment with a toll-like receptor-7 (TLR-7) agonist, imiquimod, downregulates miR-146a and miR-155 in PBMCs from HCV infected patients as compared to their expression in PBMCs of healthy individuals[44].

Increasing evidence also suggests that miRNAs have a profound impact on host defense to HCV infection and clinical outcome of standard HCV therapy. miRNA expression profiles were examined to identify the miRNAs associated with the standard treatment (IFN-α with ribavirin) to CHC patients. Expression levels of 9 miRNAs were significantly different in the sustained virological response (SVR) and non-responder (NR) groups, suggesting that expression pattern of these hepatic miRNA are associated with therapeutic outcome in CHC patients[45]. The expression level of miR-122 was reportedly associated with early response to IFN treatment. HCV infected patients who did not respond to therapy had significantly lower miR-122 levels as compared to responder[46].

ROLE OF MIRNAS IN HCV RELATED INFLAMMATION AND FIBROSIS

Many miRNAs have been implicated in various cancers either as oncogenes or tumor suppressor genes. HCV infection induces chronic inflammation and regulation of inflammation related miRNA favors the initiation and progression of HCC. Gene expression analyses identified dysregulation of miR-449a in HCV patients but not in alcoholic and non-alcoholic liver diseases. YKL40 is an inflammatory marker known to be upregulated in patients with chronic liver diseases with fibrosis and miR-449a regulates the expression of YKL40 by targeting NOTCH signaling pathway following HCV infection[47].

In patients infected with HCV, miR-155 expression levels were markedly increased, and promote hepatocyte proliferation and tumorigenesis by modulating Wnt signaling[48]. Chronic HCV infection induced liver fibrosis is mediated by upregulation of transforming growth factor (TGF)-β[49]. In HCV-infected patient samples and in a mouse carbon tetrachloride fibrosis model, expression levels of miR-21 were positively correlated with fibrotic stage[50]. miR-21 was shown to target SMAD7, a negative regulator of TGF-β signaling, leading to increased fibrogenesis[50]. Inhibition of miR-29 was also linked with activation of hepatic stellate cells and collagen

Table 1 Altered expression of microRNAs in association with Hepatitis C virus infection and liver disease progression

miRNA	Expression[1]	Target genes	Function
MiRNAs that facilitates HCV infection			
miR-122	Up	5′ UTR in *HCV* genome	Promote HCV replication[16-18] and IRES mediated HCV translation[21]
		Xrn1	Inhibit 5′decay of HCV RNA[22]
		Cyclin G1	Promote Alcohol induced viral replication[27]
		SOCS3	Enhance methylation at SOCS3 gene promoter, inhibits IFN-induced ISRE activity[41]
miR-130a	Up	*IFITM1*	Inhibits type 1 IFN signaling pathway and promotes HCV replication[33]
miR-141	Up	*DLC-1*	Promote viral replication[40]
miR-21	Up	*MyD88* and *IRAK1*	Negatively regulate IFN signaling[42]
MiRNAs that suppresses HCV infection			
miR-448	Unknown	Core region in *HCV* genome	Inhibits viral replication[28]
miR-196/196a	Unknown	*NS5A* region in *HCV* genome	Inhibits viral replication[28]
		Bach1	Inhibits HCV RNA and NS5A protein expression, relieve oxidative stress by upregulating *HMOX1* gene expression[31]
let-7b	Unknown	*NS5B* and 5′UTR regions in *HCV* genome	Reduces HCV infectivity[29]
miR-199a	Unknown	5′ UTR in *HCV* genome	Inhibits viral replication[30]
miR-27a	Up	*RXRα* and *ABCA1*	Regulates lipid metabolism, decrease viral infectivity[38]
MiRNAs that promote inflammation and fibrosis upon HCV infection			
miR-449a	Down	*NOTCH1*	Regulates YKL40 promoter activity and promotes inflammation[47]
miR-21	Up	*SMAD7*	Increase TGF-β signaling and promote fibrosis[50]
miR-29	Down	*COL1A1*, *COL3A1*	Potentiate fibrosis by activating hepatic stellate cells[32]
miR-155	Up	*APC*	Promote cell proliferation by activating Wnt/β-Catenin signaling pathway[48]

[1]Denotes endogenous expression in Hepatitis C virus (HCV) infected liver biopsy patients or HCV infected hepatocytes. UTR: Untranslated region; IFN: Interferon; TGF: Transforming growth factor; miR/miRNA: MicroRNA.

synthesis[32].

ROLE OF MIRNAS IN HCV RELATED HCC

HCC is often considered as a complication of chronic liver disease, comprises of a single group, regardless of the etiology of liver disease. There are several risk factors associated with development of HCC, including chronic hepatitis C infection[51]. Progression towards HCC involves multiple steps that ultimately lead to deregulation of various signaling pathways and help host cells to acquire metastatic potential in presence of surrounding microenvironment[52]. Chronic hepatitis C is a major risk factor associated with HCC[53]. HCV encoded viral proteins both singly or in coordinated manner, interact with host cellular factors and regulate signaling pathways such as, cell proliferation and apoptosis for augmentation of hepatocyte growth that may contribute towards HCC progression[54]. miRNA dysregulation has been linked with initiation and progression of HCC[55-57], however, the role of miRNAs in HCV-related HCC is poorly understood. The identification of HCC related miRNA signatures is of great value for the early diagnosis of HCC, before the onset of disease in HCV-positive patients. Limited studies are available addressing the role of miRNA expression in HCV associated HCC. Differential miRNA expression from formalin fixed paraffin embedded HCV infected HCC specimens indicated 10 upregulated and 19 downregulated miRNAs[58]. Another study in HCV infected patients, 13 miRNAs were shown to be downregulated and were predicted to target genes related to immune response, antigen presentation, cell cycle, proteasome, and lipid metabolism signaling pathways[59]. However, validation of these miRNAs and their predicted targets are necessary for conclusive role of particular miRNA in HCV related HCC. A list of altered miRNAs associated with HCV infection and their proposed role in liver disease progression has been summarized in Table 1.

CIRCULATORY MIRNAS IN HCV INFECTION

One of the major challenges in HCV research is early detection of liver disease which allow us for rapid intervention and improved outcome of antiviral treatment. Liver biopsy is often recommended in patients with unexplained elevated serum aminotransferases in order to determine the cause, grade of hepatic inflammation and stage of hepatic fibrosis. Non-invasive or minimally invasive methods need to be developed which can evaluate disease severity and the likelihood of disease progression. Circulating miRNAs have been demonstrated to be very specific and stable in human serum and plasma. In addition, circulating miRNAs display consistent profiles between healthy individuals and significantly altered levels in disease conditions[60,61]. These characteristics of circulating miRNAs established their potential value as biomarkers for detection and as predictive marker for liver disease progression in HCV infection. We have performed serum/plasma specific miRNA array and observed that several circulating miRNAs are significantly upregulated in sera of HCV infected patients as compared to healthy controls[62]. We have shown that increased expression of

miR-20a and miR-92a is specific to HCV associated liver disease because we did not observe an upregulation of these miRNA in sera of patients with non-HCV related liver disease. Subsequently, we observed that elevated levels of miR-20a were positively correlated with disease severity in HCV infected patients, however, miR-92a expression is reduced with higher grade of fibrosis in HCV infected patients[62]. miRNA profiling was also performed to identify the expression of 940 human miRNAs in the serum of HCV infected individuals. Serum levels of miR-134, miR-320c and miR-483-5p were significantly upregulated in HCV infected patients[63]. Serum levels of miR-122 were correlated with disease parameters in patients with CHC by several groups. The higher levels of miR-122 and miR-192 was observed in sera from patients with CHC and in other etiologies associated with liver injury as compared to sera from healthy controls[64-68]. The serum level of miR-122 and miR-21 strongly correlates with serum alanine leucine transaminase levels (ALT) and higher necroinflammatory activity in the liver in patients with CHC infection suggesting their potential as a serum biomarker over ALT in predicting the presence of chronic HCV infection[64,65,68,69], although the specificity of miR-122 for HCV mediated liver disease is questionable. Levels of miR-125b and miR-146a were also increased in the serum of CHC patients compared to healthy controls[70]. Treatment-naïve patients with chronic HCV infection have been shown to have higher expression of miR-155 in their circulating monocytes as compared to individuals who cleared HCV infection after therapy, suggesting a possible correlation between increased miR-155 and HCV viral presence and/or replication[70].

Circulating miRNAs in urine were also examined for developing screening methods. Expression of 3 upregulated miRNAs, miR-625, miR-532 and miR-618, were evaluated as non-invasive biomarkers for the early diagnosis of HCC among high-risk HCV positive patients. Elevated expression of miR-625, miR-532 and miR-618 were observed in 56%, 62.5% and 72% of HCC-post HCV positive patients, respectively. In addition, miR-516-5p and miR-650 were found to be down-regulated in 50% and 72% of HCC-post HCV positive patients, respectively. Differential expressions of these miRNAs were predicted to possibly target genes related to HCC development and progression in high risk HCV patients[71]. The function of these extracellular circulating miRNAs is not well understood. The liver is a complex organ where various cell types reside and interact in close vicinity. During HCV infection, there could be multiple factors that contribute to release of miRNAs in the circulation. Secretion of miRNA from different cell types in a cell-specific manner in response to HCV infection cannot be ruled out. Further studies are warranted to investigate the cellular source of circulating miRNAs.

MIRNA AS THERAPEUTICS IN HCV INFECTION

Therapies that target essential host factors required for HCV replication could present an effective approach for the development of new HCV antiviral drugs. Therapeutic potential of miR-122 employing antisense oligonucleotide (SPC3649) complementary to the 5'-end of miR-122, has been evaluated in HCV infected chimpanzees[72]. SPC3649 therapy resulted in a reduction of HCV viral load in the liver and blood of chronically infected chimpanzees. In addition, reduction in viral load was accompanied by normalization of the endogenous interferon pathway, which is maximally induced in chronically infected chimpanzees, suggesting the restoration of host immune response following treatment with SPC3649[72]. Recently, miravirsen (a locked nucleic acid-modified antisense oligonucleotide for miR-122) showed prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance in chronic HCV genotype 1 infected patients in a phase Ⅱ a clinical trial[73]. No adverse side effects of miR-122 inhibition have been documented in either chimpanzees or chronic HCV infected patients. Additional host cell factors that help HCV for productive replication such as, cyclophilin A and phosphatidylinositol-4-kinase Ⅲ alpha have emerged as a promising alternative[74]. The efficacy of anti-miR-122 along with current anti-HCV drugs needs to be evaluated in future trials that could provide better therapy outcome in terms of lesser rate of relapse, interferon free regimens and reduced possibility of drug resistance. miRNAs function either as oncomiRs or tumor suppressors are involved in cell growth regulatory pathways, have rapidly emerged as targets for therapeutics in the pathogenesis of HCV infection. Successful delivery of either miRNA mimics to restore the activity of tumor suppressor miRNAs or anti-miR oligonucleotides for pharmacological inhibition of oncogenic miRNAs, understanding of potential off-target effects and physiologic consequences of long-term miRNA modulation *in vivo* are some of the important factors to keep into consideration in future development of miRNA therapeutics.

CONCLUSION

We are still in the infancy stage of understanding the potential of manipulating miRNAs for the treatment of HCV infection. HCV infection modulates a set of miRNAs that regulate host immune response and cell growth interconnected with multiple signaling pathways. miRNA mediated regulation of gene expression will help us to understand the signaling pathway and disease progression associated with HCV infection. Therapeutic silencing of miR-122 opens a door for novel drugs and therefore, identification of miRNAs with a prominent role in HCV viral life cycle and its implication in liver disease progression is emerging as a therapeutic option against chronic HCV infections. A major drawback of exploiting miRNA as therapy may have adverse side effects because of the biological properties of miRNA where, a single miRNA binds to multiple targets and regulate various signaling pathways simultaneously. On the contrary, recent studies

on circulating miRNAs generates an alternative approach for identification of minimally invasive biomarker for HCV mediated liver disease and as predictive biomarker to categorize patients those may develop end stage liver disease due to viral infection. Indeed, further in-depth studies are needed to identify mechanistic insights behind modulated miRNAs by HCV infection.

REFERENCES

1 **Choo QL**, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; **244**: 359-362 [PMID: 2523562 DOI: 10.1126/science.2523562]

2 **Moradpour D**, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol* 2007; **5**: 453-463 [PMID: 17487147 DOI: 10.1038/nrmicro1645]

3 **Gravitz L**. Introduction: a smouldering public-health crisis. *Nature* 2011; **474**: S2-S4 [PMID: 21666731 DOI: 10.1038/474S2a]

4 **Smith BD**, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N, Alter M, Yartel A, Ward JW. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; **61**: 1-32 [PMID: 22895429]

5 **Kanwal F**, Hoang T, Kramer JR, Asch SM, Goetz MB, Zeringue A, Richardson P, El-Serag HB. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology* 2011; **140**: 1182-1188.e1 [PMID: 21184757 DOI: 10.1053/j.gastro.2010.12.032]

6 **Jacobson IM**, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]

7 **Kanda T**, Imazeki F, Yokosuka O. New antiviral therapies for chronic hepatitis C. *Hepatol Int* 2010; **4**: 548-561 [PMID: 21063477 DOI: 10.1007/s12072-010-9193-3]

8 **Friedman RC**, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; **19**: 92-105 [PMID: 18955434 DOI: 10.1101/gr.082701.108]

9 **Meister G**, Tuschl T. Mechanisms of gene silencing by double-stranded RNA. *Nature* 2004; **431**: 343-349 [PMID: 15372041 DOI: 10.1038/nature02873]

10 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

11 **Filipowicz W**, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat Rev Genet* 2008; **9**: 102-114 [PMID: 18197166 DOI: 10.1038/nrg2290]

12 **Winter J**, Jung S, Keller S, Gregory RI, Diederichs S. Many roads to maturity: microRNA biogenesis pathways and their regulation. *Nat Cell Biol* 2009; **11**: 228-234 [PMID: 19255566 DOI: 10.1038/ncb0309-228]

13 **Roberts AP**, Lewis AP, Jopling CL. The role of microRNAs in viral infection. *Prog Mol Biol Transl Sci* 2011; **102**: 101-139 [PMID: 21846570 DOI: 10.1016/B978-0-12-415795-8]

14 **Li ZY**, Xi Y, Zhu WN, Zeng C, Zhang ZQ, Guo ZC, Hao DL, Liu G, Feng L, Chen HZ, Chen F, Lv X, Liu DP, Liang CC. Positive regulation of hepatic miR-122 expression by HNF4α. *J Hepatol* 2011; **55**: 602-611 [PMID: 21241755 DOI: 10.1016/j.jhep.2010.12.023]

15 **Tsai WC**, Hsu SD, Hsu CS, Lai TC, Chen SJ, Shen R, Huang Y, Chen HC, Lee CH, Tsai TF, Hsu MT, Wu JC, Huang HD, Shiao MS, Hsiao M, Tsou AP. MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis. *J Clin Invest* 2012; **122**: 2884-2897 [PMID: 22820290 DOI: 10.1172/JCI63455]

16 **Jopling CL**, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* 2005; **309**: 1577-1581 [PMID: 16141076 DOI: 10.1126/science.1113329]

17 **Randall G**, Panis M, Cooper JD, Tellinghuisen TL, Sukhodolets KE, Pfeffer S, Landthaler M, Landgraf P, Kan S, Lindenbach BD, Chien M, Weir DB, Russo JJ, Ju J, Brownstein MJ, Sheridan R, Sander C, Zavolan M, Tuschl T, Rice CM. Cellular cofactors affecting hepatitis C virus infection and replication. *Proc Natl Acad Sci USA* 2007; **104**: 12884-12889 [PMID: 17616579 DOI: 10.1073/pnas.0704894104]

18 **Jangra RK**, Yi M, Lemon SM. Regulation of hepatitis C virus translation and infectious virus production by the microRNA miR-122. *J Virol* 2010; **84**: 6615-6625 [PMID: 20427538 DOI: 10.1128/JVI.00417-10]

19 **Zhang C**, Huys A, Thibault PA, Wilson JA. Requirements for human Dicer and TRBP in microRNA-122 regulation of HCV translation and RNA abundance. *Virology* 2012; **433**: 479-488 [PMID: 22999255 DOI: 10.1016/j.virol.2012.08.039]

20 **Machlin ES**, Sarnow P, Sagan SM. Masking the 5′ terminal nucleotides of the hepatitis C virus genome by an unconventional microRNA-target RNA complex. *Proc Natl Acad Sci USA* 2011; **108**: 3193-3198 [PMID: 21220300 DOI: 10.1073/pnas.1012464108]

21 **Roberts AP**, Lewis AP, Jopling CL. miR-122 activates hepatitis C virus translation by a specialized mechanism requiring particular RNA components. *Nucleic Acids Res* 2011; **39**: 7716-7729 [PMID: 21653556 DOI: 10.1093/nar/gkr426]

22 **Li Y**, Masaki T, Yamane D, McGivern DR, Lemon SM. Competing and noncompeting activities of miR-122 and the 5′ exonuclease Xrn1 in regulation of hepatitis C virus replication. *Proc Natl Acad Sci USA* 2013; **110**: 1881-1886 [PMID: 23248316 DOI: 10.1073/pnas.1213515110]

23 **Narbus CM**, Israelow B, Sourisseau M, Michta ML, Hopcraft SE, Zeiner GM, Evans MJ. HepG2 cells expressing microRNA miR-122 support the entire hepatitis C virus life cycle. *J Virol* 2011; **85**: 12087-12092 [PMID: 21917968 DOI: 10.1128/JVI.05843-11]

24 **Kambara H**, Fukuhara T, Shiokawa M, Ono C, Ohara Y, Kamitani W, Matsuura Y. Establishment of a novel permissive cell line for the propagation of hepatitis C virus by expression of microRNA miR122. *J Virol* 2012; **86**: 1382-1393 [PMID: 22114337 DOI: 10.1128/JVI.06242-11]

25 **Fukuhara T**, Kambara H, Shiokawa M, Ono C, Katoh H, Morita E, Okuzaki D, Maehara Y, Koike K, Matsuura Y. Expression of microRNA miR-122 facilitates an efficient replication in nonhepatic cells upon infection with hepatitis C virus. *J Virol* 2012; **86**: 7918-7933 [PMID: 22593164 DOI: 10.1128/JVI.00567-12]

26 **Fehr C**, Conrad KD, Niepmann M. Differential stimulation of hepatitis C virus RNA translation by microRNA-122 in different cell cycle phases. *Cell Cycle* 2012; **11**: 277-285 [PMID: 22189820 DOI: 10.4161/cc.11.2.18699]

27 **Hou W**, Bukong TN, Kodys K, Szabo G. Alcohol facilitates HCV RNA replication via up-regulation of miR-122 expression and inhibition of cyclin G1 in human hepatoma cells. *Alcohol Clin Exp Res* 2013; **37**: 599-608 [PMID: 23126531 DOI: 10.1111/acer.12005]

28 **Pedersen IM**, Cheng G, Wieland S, Volinia S, Croce CM, Chisari FV, David M. Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature* 2007; **449**: 919-922 [PMID: 17943132 DOI: 10.1038/nature06205]

29 **Cheng JC**, Yeh YJ, Tseng CP, Hsu SD, Chang YL, Sakamoto

N, Huang HD. Let-7b is a novel regulator of hepatitis C virus replication. *Cell Mol Life Sci* 2012; **69**: 2621-2633 [PMID: 22391672 DOI: 10.1007/s00018-012-0940-6]
30 **Murakami Y**, Aly HH, Tajima A, Inoue I, Shimotohno K. Regulation of the hepatitis C virus genome replication by miR-199a. *J Hepatol* 2009; **50**: 453-460 [PMID: 19144437 DOI: 10.1016/j.jhep.2008.06.010]
31 **Hou W**, Tian Q, Zheng J, Bonkovsky HL. MicroRNA-196 represses Bach1 protein and hepatitis C virus gene expression in human hepatoma cells expressing hepatitis C viral proteins. *Hepatology* 2010; **51**: 1494-1504 [PMID: 20127796 DOI: 10.1002/hep.23401]
32 **Bandyopadhyay S**, Friedman RC, Marquez RT, Keck K, Kong B, Icardi MS, Brown KE, Burge CB, Schmidt WN, Wang Y, McCaffrey AP. Hepatitis C virus infection and hepatic stellate cell activation downregulate miR-29: miR-29 overexpression reduces hepatitis C viral abundance in culture. *J Infect Dis* 2011; **203**: 1753-1762 [PMID: 21606534 DOI: 10.1093/infdis/jir186]
33 **Bhanja Chowdhury J**, Shrivastava S, Steele R, Di Bisceglie AM, Ray R, Ray RB. Hepatitis C virus infection modulates expression of interferon stimulatory gene IFITM1 by upregulating miR-130A. *J Virol* 2012; **86**: 10221-10225 [PMID: 22787204 DOI: 10.1128/JVI.00882-12]
34 **Zhang X,** Daucher M, Armistead D, Russell R, Kottilil S. MicroRNA expression profiling in HCV-infected human hepatoma cells identifies potential anti-viral targets induced by interferon-α. *PLoS One* 2013; **8**: e55733 [PMID: 23418453 DOI: 10.1371/journal.pone.0055733]
35 **Steuerwald NM**, Parsons JC, Bennett K, Bates TC, Bonkovsky HL. Parallel microRNA and mRNA expression profiling of (genotype 1b) human hepatoma cells expressing hepatitis C virus. *Liver Int* 2010; **30**: 1490-1504 [PMID: 20825557 DOI: 10.1111/j.1478-3231.2010.02321.x]
36 **Liu X**, Wang T, Wakita T, Yang W. Systematic identification of microRNA and messenger RNA profiles in hepatitis C virus-infected human hepatoma cells. *Virology* 2010; **398**: 57-67 [PMID: 20006370 DOI: 10.1016/j.virol.2009.11.036]
37 **Yang X**, Marcucci K, Anguela X, Couto LB. Preclinical evaluation of an anti-HCV miRNA cluster for treatment of HCV infection. *Mol Ther* 2013; **21**: 588-601 [PMID: 23295950 DOI: 10.1038/mt.2012.247]
38 **Shirasaki T**, Honda M, Shimakami T, Horii R, Yamashita T, Sakai Y, Sakai A, Okada H, Watanabe R, Murakami S, Yi M, Lemon SM, Kaneko S. MicroRNA-27a regulates lipid metabolism and inhibits hepatitis C virus replication in human hepatoma cells. *J Virol* 2013; **87**: 5270-5286 [PMID: 23449803 DOI: 10.1128/JVI.03022-12]
39 **Ishida H**, Tatsumi T, Hosui A, Nawa T, Kodama T, Shimizu S, Hikita H, Hiramatsu N, Kanto T, Hayashi N, Takehara T. Alterations in microRNA expression profile in HCV-infected hepatoma cells: involvement of miR-491 in regulation of HCV replication via the PI3 kinase/Akt pathway. *Biochem Biophys Res Commun* 2011; **412**: 92-97 [PMID: 21802413 DOI: 10.1016/j.bbrc.2011.07.049]
40 **Banaudha K**, Kaliszewski M, Korolnek T, Florea L, Yeung ML, Jeang KT, Kumar A. MicroRNA silencing of tumor suppressor DLC-1 promotes efficient hepatitis C virus replication in primary human hepatocytes. *Hepatology* 2011; **53**: 53-61 [PMID: 20967756 DOI: 10.1002/hep.24016]
41 **Yoshikawa T**, Takata A, Otsuka M, Kishikawa T, Kojima K, Yoshida H, Koike K. Silencing of microRNA-122 enhances interferon-α signaling in the liver through regulating SOCS3 promoter methylation. *Sci Rep* 2012; **2**: 637 [PMID: 22957141 DOI: 10.1038/srep00637]
42 **Chen Y**, Chen J, Wang H, Shi J, Wu K, Liu S, Liu Y, Wu J. HCV-induced miR-21 contributes to evasion of host immune system by targeting MyD88 and IRAK1. *PLoS Pathog* 2013; **9**: e1003248 [PMID: 23633945 DOI: 10.1371/journal.ppat.1003248]
43 **Bruni R**, Marcantonio C, Tritarelli E, Tataseo P, Stellacci E, Costantino A, Villano U, Battistini A, Ciccaglione AR. An integrated approach identifies IFN-regulated microRNAs and targeted mRNAs modulated by different HCV replicon clones. *BMC Genomics* 2011; **12**: 485 [PMID: 21970718 DOI: 10.1186/1471-2164-12-485]
44 **El-Ekiaby N**, Hamdi N, Negm M, Ahmed R, Zekri AR, Esmat G, Abdelaziz AI. Repressed induction of interferon-related microRNAs miR-146a and miR-155 in peripheral blood mononuclear cells infected with HCV genotype 4. *FEBS Open Bio* 2012; **2**: 179-186 [PMID: 23650597 DOI: 10.1016/j.fob.2012.07.005]
45 **Murakami Y**, Tanaka M, Toyoda H, Hayashi K, Kuroda M, Tajima A, Shimotohno K. Hepatic microRNA expression is associated with the response to interferon treatment of chronic hepatitis C. *BMC Med Genomics* 2010; **3**: 48 [PMID: 20969775 DOI: 10.1186/1755-8794-3-48]
46 **Sarasin-Filipowicz M**, Krol J, Markiewicz I, Heim MH, Filipowicz W. Decreased levels of microRNA miR-122 in individuals with hepatitis C responding poorly to interferon therapy. *Nat Med* 2009; **15**: 31-33 [PMID: 19122656 DOI: 10.1038/nm.1902]
47 **Sarma NJ**, Tiriveedhi V, Subramanian V, Shenoy S, Crippin JS, Chapman WC, Mohanakumar T. Hepatitis C virus mediated changes in miRNA-449a modulates inflammatory biomarker YKL40 through components of the NOTCH signaling pathway. *PLoS One* 2012; **7**: e50826 [PMID: 23226395 DOI: 10.1371/journal.pone.0050826]
48 **Zhang Y**, Wei W, Cheng N, Wang K, Li B, Jiang X, Sun S. Hepatitis C virus-induced up-regulation of microRNA-155 promotes hepatocarcinogenesis by activating Wnt signaling. *Hepatology* 2012; **56**: 1631-1640 [PMID: 22610915 DOI: 10.1002/hep.25849]
49 **Schuppan D**, Krebs A, Bauer M, Hahn EG. Hepatitis C and liver fibrosis. *Cell Death Differ* 2003; **10** Suppl 1: S59-S67 [PMID: 12655347 DOI: 10.1038/sj.cdd.4401163]
50 **Marquez RT**, Bandyopadhyay S, Wendlandt EB, Keck K, Hoffer BA, Icardi MS, Christensen RN, Schmidt WN, McCaffrey AP. Correlation between microRNA expression levels and clinical parameters associated with chronic hepatitis C viral infection in humans. *Lab Invest* 2010; **90**: 1727-1736 [PMID: 20625373 DOI: 10.1038/labinvest.2010.126]
51 **Severi T**, van Malenstein H, Verslype C, van Pelt JF. Tumor initiation and progression in hepatocellular carcinoma: risk factors, classification, and therapeutic targets. *Acta Pharmacol Sin* 2010; **31**: 1409-1420 [PMID: 20953207 DOI: 10.1038/aps.2010.142]
52 **Hernandez-Gea V**, Toffanin S, Friedman SL, Llovet JM. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. *Gastroenterology* 2013; **144**: 512-527 [PMID: 23313965 DOI: 10.1053/j.gastro.2013.01.002]
53 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]
54 **Banerjee A**, Ray RB, Ray R. Oncogenic potential of hepatitis C virus proteins. *Viruses* 2010; **2**: 2108-2133 [PMID: 21994721 DOI: 10.3390/v2092108]
55 **Law PT**, Wong N. Emerging roles of microRNA in the intracellular signaling networks of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2011; **26**: 437-449 [PMID: 21332540 DOI: 10.1111/j.1440-1746.2010.06512.x]
56 **Huang S**, He X. The role of microRNAs in liver cancer progression. *Br J Cancer* 2011; **104**: 235-240 [PMID: 21102580 DOI: 10.1038/sj.bjc.6606010]
57 **Giordano S**, Columbano A. MicroRNAs: new tools for diagnosis, prognosis, and therapy in hepatocellular carcinoma? *Hepatology* 2013; **57**: 840-847 [PMID: 23081718 DOI: 10.1002/hep.26095]
58 **Varnholt H**, Drebber U, Schulze F, Wedemeyer I, Schirmacher P, Dienes HP, Odenthal M. MicroRNA gene expres-

sion profile of hepatitis C virus-associated hepatocellular carcinoma. *Hepatology* 2008; **47**: 1223-1232 [PMID: 18307259 DOI: 10.1002/hep.22158]

59 **Ura S**, Honda M, Yamashita T, Ueda T, Takatori H, Nishino R, Sunakozaka H, Sakai Y, Horimoto K, Kaneko S. Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma. *Hepatology* 2009; **49**: 1098-1112 [PMID: 19173277 DOI: 10.1002/hep.22749]

60 **Brase JC**, Wuttig D, Kuner R, Sültmann H. Serum microRNAs as non-invasive biomarkers for cancer. *Mol Cancer* 2010; **9**: 306 [PMID: 21110877 DOI: 10.1186/1476-4598-9-306]

61 **Allegra A**, Alonci A, Campo S, Penna G, Petrungaro A, Gerace D, Musolino C. Circulating microRNAs: new biomarkers in diagnosis, prognosis and treatment of cancer (review). *Int J Oncol* 2012; **41**: 1897-1912 [PMID: 23026890 DOI: 10.3892/ijo.2012.1647]

62 **Shrivastava S,** Petrone J, Steele R, Lauer GM, Di Bisceglie AM, Ray RB. Up-regulation of circulating miR-20a is correlated with hepatitis C virus-mediated liver disease progression. *Hepatology* 2013 Feb 6; Epub ahead of print [PMID: 23390075 DOI: 10.1002/hep.26296]

63 **Shwetha S**, Gouthamchandra K, Chandra M, Ravishankar B, Khaja MN, Das S. Circulating miRNA profile in HCV infected serum: novel insight into pathogenesis. *Sci Rep* 2013; **3**: 1555 [PMID: 23549102 DOI: 10.1038/srep01555]

64 **Bihrer V**, Friedrich-Rust M, Kronenberger B, Forestier N, Haupenthal J, Shi Y, Peveling-Oberhag J, Radeke HH, Sarrazin C, Herrmann E, Zeuzem S, Waidmann O, Piiper A. Serum miR-122 as a biomarker of necroinflammation in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 2011; **106**: 1663-1669 [PMID: 21606975 DOI: 10.1038/ajg.2011.161]

65 **Cermelli S**, Ruggieri A, Marrero JA, Ioannou GN, Beretta L. Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. *PLoS One* 2011; **6**: e23937 [PMID: 21886843 DOI: 10.1371/journal.pone.0023937]

66 **Starkey Lewis PJ**, Dear J, Platt V, Simpson KJ, Craig DG, Antoine DJ, French NS, Dhaun N, Webb DJ, Costello EM, Neoptolemos JP, Moggs J, Goldring CE, Park BK. Circulating microRNAs as potential markers of human drug-induced liver injury. *Hepatology* 2011; **54**: 1767-1776 [PMID: 22045675 DOI: 10.1002/hep.24538]

67 **Bala S**, Petrasek J, Mundkur S, Catalano D, Levin I, Ward J, Alao H, Kodys K, Szabo G. Circulating microRNAs in exosomes indicate hepatocyte injury and inflammation in alcoholic, drug-induced, and inflammatory liver diseases. *Hepatology* 2012; **56**: 1946-1957 [PMID: 22684891 DOI: 10.1002/hep.25873]

68 **van der Meer AJ**, Farid WR, Sonneveld MJ, de Ruiter PE, Boonstra A, van Vuuren AJ, Verheij J, Hansen BE, de Knegt RJ, van der Laan LJ, Janssen HL. Sensitive detection of hepatocellular injury in chronic hepatitis C patients with circulating hepatocyte-derived microRNA-122. *J Viral Hepat* 2013; **20**: 158-166 [PMID: 23383654 DOI: 10.1111/jvh.12001]

69 **Bihrer V**, Waidmann O, Friedrich-Rust M, Forestier N, Susser S, Haupenthal J, Welker M, Shi Y, Peveling-Oberhag J, Polta A, von Wagner M, Radeke HH, Sarrazin C, Trojan J, Zeuzem S, Kronenberger B, Piiper A. Serum microRNA-21 as marker for necroinflammation in hepatitis C patients with and without hepatocellular carcinoma. *PLoS One* 2011; **6**: e26971 [PMID: 22066022 DOI: 10.1371/journal.pone.0026971]

70 **Bala S**, Tilahun Y, Taha O, Alao H, Kodys K, Catalano D, Szabo G. Increased microRNA-155 expression in the serum and peripheral monocytes in chronic HCV infection. *J Transl Med* 2012; **10**: 151 [PMID: 22846613 DOI: 10.1186/1479-5876-10-151]

71 **Abdalla MA**, Haj-Ahmad Y. Promising Candidate Urinary MicroRNA Biomarkers for the Early Detection of Hepatocellular Carcinoma among High-Risk Hepatitis C Virus Egyptian Patients. *J Cancer* 2012; **3**: 19-31 [PMID: 22211142 DOI: 10.7150/jca.3.19]

72 **Lanford RE**, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME, Kauppinen S, Ørum H. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. *Science* 2010; **327**: 198-201 [PMID: 19965718 DOI: 10.1126/science.1178178]

73 **Janssen HL**, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, Persson R, King BD, Kauppinen S, Levin AA, Hodges MR. Treatment of HCV infection by targeting microRNA. *N Engl J Med* 2013; **368**: 1685-1694 [PMID: 23534542 DOI: 10.1056/NEJMoa1209026]

74 **Bühler S**, Bartenschlager R. New targets for antiviral therapy of chronic hepatitis C. *Liver Int* 2012; **32** Suppl 1: 9-16 [PMID: 22212566 DOI: 10.1111/j.1478-3231.2011.02701.x]

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