

**Review article:**

## **Role of microRNA in liver disease**

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**Abstract:**

MicroRNAs are 20-22 nucleotides long noncoding RNAs that were first described in 1993, in developmental timing experiment in the nematode *Caenorhabditis elegans*. MicroRNA play an important role in miscellaneous cellular process including development, immunity, cell-cycle control metabolism, viral or bacterial disease, stem cell differentiation and oncogenesis. In the human the first indication of microRNA contributing to disease came from the identification of person suffering from Digeorge syndrome which result in dysfunction microRNA biogenesis. MicroRNAs play an important role in liver disease. The physiological important of metabolic pathways, immunity, viral hepatitis, cancer, and liver fibrosis. Micro RNA biogenesis has been well characterized and basically consists of 6 steps: transcription, cleavage, export, further cleavage, strand selection, and interaction with target messenger RNAs. In the hepatitis C up regulation of miR-296, miR-351, and miR-155 and down regulation of miR-221, miR-222, and miR-181.[8,9] In the hepatitis B up regulation of miR-373, miR-370, and miR532 and down regulation miR-122, miR-223, miR-29, miR-199, and miR-198.[8] In the non-alcoholic fatty liver and non-alcoholic steatohepatitis up regulation of miR-155, miR-34, miR-146, and miR-200 and down regulation of miR-122, miR-617, and miR-451.[6,10-12] In the alcoholic liver disease up regulation of miR-155, miR-705, miR-224, and miR-212 and down regulation of miR-182, miR-183, and miR-199.[13] In the liver fibrosis up regulation of miR-199a, miR-200, miR-21, miR-223, and miR-34 and down regulation of miR-29 family, miR-122, miR-146a, miR-15b, miR-150, and miR-194.

**Keywords :** Hepatitis B , Micro RNA

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**Introduction:**

MicroRNAs are 20-22 nucleotides long noncoding RNAs that were first described in 1993, in developmental timing experiment in the nematode *Caenorhabditis elegans*. [1] MicroRNA play an important role in miscellaneous cellular process including development, immunity, cell-cycle control metabolism, viral or bacterial disease, stem cell differentiation and oncogenesis.[2-4] In the human the first indication of microRNA contributing to disease came from the identification of person suffering from Digeorge syndrome which result in dysfunction microRNA biogenesis.[5] MicroRNAs play an

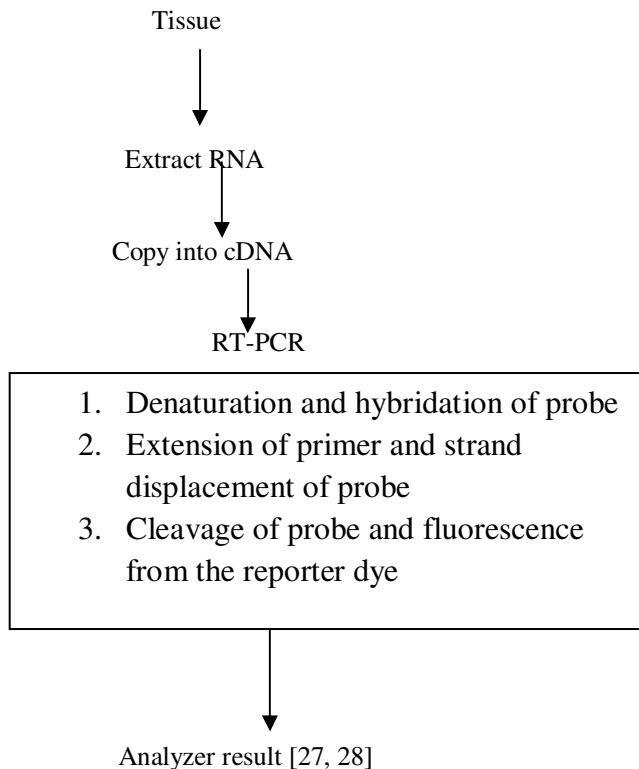
important role in liver disease. The physiological important of metabolic pathways, immunity, viral hepatitis, cancer, and liver fibrosis.[3,6-7] Micro RNA biogenesis has been well characterized and basically consists of 6 steps: transcription, cleavage, export, further cleavage, strand selection, and interaction with target messenger RNAs. In the hepatitis C up regulation of miR-296, miR-351, and miR-155 and down regulation of miR-221, miR-222, and miR-181.[8,9] In the hepatitis B up regulation of miR-373, miR-370, and miR532 and down regulation miR-122, miR-223, miR-29, miR-199, and miR-198.[8] In the non-alcoholic fatty liver and non-

alcoholic steatohepatitis up regulation of miR-155, miR-34, miR-146, and miR-200 and down regulation of miR-122, miR-617, and miR-451.[6,10-12] In the alcoholic liver disease up regulation of miR-155, miR-705, miR-224, and miR-212 and down regulation of miR-182, miR-183, and miR-199.[13] In the liver fibrosis up regulation of miR-199a, miR-200, miR-21, miR-223, and miR-34 and down regulation of miR-29 family, miR-122, miR-146a, miR-15b, miR-150, and miR-194.[14,15]

**Discussion :**

MiRNAs are good biomarkers because they are well defined, chemically uniform, restricted to a manageable number of species, and stable in cells and in the circulation.[16-18] Analyzing patterns of miRNAs need polymerase chain reaction (PCR)-based techniques, and hybridization assays.[19,20] QRT-PCR method based on the reverse transcription of miRNA into cDNA and next amplification by QPCR are used to quantify the amplified product

sequences. QRT-PCR is the most sensitive method representing a useful validation of candidate miRNA identified by more sophisticated and extensive approaches.[21,22] quantitative reverse transcriptase QRT-PCR based method are generally difficult to reconcile with large sample numbers and probe sets. If sample from a homogeneous patient population are available, one viable approach for exploratory studies could be to perform multiplex PCR [23] with pooled samples, followed by analyses of individual samples. [24] Conventional qRT-PCR and micro fluidic qRT-PCR platforms each have better limits of detection and dynamic ranges than expression microarrays [25] but cannot compete with the ability of these assays to analyze thousands of targets. Direct hybridization with RNA in solution, using color-coded probes, offers a more highly multiplexed analysis without a need for amplification.[26]



Most of the Doctors had studied on the microRNA in liver disease. They have published their study related to liver diseases. I have taken 11 review articles on microRNA and re-analyzed their study.

**List of microRNAs in liver disease**

S.no	Author name	Liver disease	Up regulation of miRNA	Down regulation of miRNA	References
1	Sara Ceccarelli	NAFLD/NASH	10,16,29,33,34,146	99,122,132,150,511	7,21,29-37
		Fibrosis	34,125,199,200,221,223	29,30,96,132,193,341,183,	7,38-40
2	Robert F. Schwabe and John W. Wiley	ALD	125,155,146	122	41,42
		Fibrosis	199,200	29	43
		HCC	221,181,17,92	122,let-7,26,10	44
3	Shubham Shrivastava, Anupam Mukherjee, Ratna B Ray	HCV	448,196,29,130,155,	122,let-7	45,46
4	Ying-Feng Wei, Guang-Ying Cui, Ping Ye, Jia-Ning Chen, Hong-Yan Diao	HBV	244	145,199	47
5	Catherine L. Jopling	HCV		122	48,49
6	Shashi Bala and Gyongyi Szabo	ALD	132,155	27,214,199,182,183,200,222	50
7	Gyongyi Szabo, Peter Sarnow, Shashi Bala	HCV	miR-296, miR-351, miR-155, miR-146	miR-29, miR-221, mir-222, miR-181	8,9
		HBV	miR-373, miR-370, miR-523	miR-122, miR-223, miR-29, mir-199, miR-198	8
		NAFLD/NASH	miR-155, miR-34a, miR-146b, miR-200	miR-122, miR-617, miR-451	10-12
		ALD	miR-155, miR-705, miR-1224, miR-212	miR-182, miR-183, miR-199	13
		Fibrosis	miR-199, miR-200, miR-21, let-7, mir-223, miR-34	miR-29 family, miR-122, miR-146, miR-15, miR-150, miR-194	14,15
		HCC	miR-21, miR-221, miR-22, miR-15, miR-517	miR-122, miR-29 family, miR-26, miR-124, let-7, miR-199	51

In the hepatitis c virus miRNA-122 inhibit the circulation of HCV and form antagomirs, it is modified, anti-sense mirRNA-122 molecules. Antagomirs decrease the HCV RNA level so that miRNA gene expression more and increase the miRNA-122.miRNA have same effect on HBV and increase miRNA-122 level.[52]

In the alcohol liver disease abuse of alcohol cause increased intestine permeability and ROS generation. Kupffer cell and TNF alpha cell activation occur and signaling cascade to amplify the inflammation. Over expression of miRNA-155 and miRNA-132.[53] And in the fatty liver 23 miRNAs regulating cell proliferation, apoptosis, inflammation, oxidative stress and metabolism were either over expressed or under expressed. miR-155, miR-34 were over expressed and miR-122 was under expressed.[52]

In the liver fibrosis activation of stellate cells and expression of matrix metalloproteinases and tissue inhibitors of metalloproteinase. And over expression of miR-199, miR-200 and under expression of miR-29 family, miR-122.[52]

In the hepatitis cellular carcinoma can cause by the chronic infection of HCV, in case miRNA-122 not form antagomirs then under expression of miRNA-122 and over expression of miRNA-21 and miRNA-221.[54]

**Figure 1. Showing miRNA biogenesis and therapeutic delivery.** miRNA are transcribed as pri-miRNA in the nucleus and exported to the cytoplasm as pre miRNA and later processed as mature miRNAs. Sense or guide strand is loaded into the Ago complex, which is named RNA inducing silencing complex (RISC). Depending on complementary of sense strand to target gene, either the target mRNA is degraded (100% complementary) or translation is inhibited (partial complementary). miRNA function

can be inhibited by using antisense oligonucleotides (ASO) such as lock nucleic acid (LNA), antagomirs, miR Zip, 2'-O-methyl, etc. Nanoparticles or adeno-associated vectors (AAV) can be used for tissue-specific anti-miRNA delivery particularly in in vivo systems. For overexpression of a particular miR, miRNA mimics can be used directly or delivery can be mediated by AAV or nanoparticles.

Eric R Gamazon, Federico Innocenti, Rongrong Wei, Libo Wang, Min Zhang, Snezana Mirkov,

Jacqueline Ramirez, R Stephanie Huang, Nancy J Cox, Mark J Ratain and Wanqing Liu they have conducted the study on A genome-wide integrative study of microRNAs in human liver

(2013).

According to their study they have taken 206 sample for gene expression profiling in liver. The liver samples were mostly derived from donor livers not used for whole organ transplants. miRNA expression was measured in 79 of the liver samples using the Exiqon miRCURY LNA Array v10.0. These 79 samples were a subset of the 206 liver tissue samples used for the mRNA expression profiling. To confirm the expression of select miRNAs and mRNAs, the correlations between the miRNAs and mRNAs, and the miR-eQTLs, quantitative PCR (Q-PCR) studies of two miRNAs (miR-148a and miR-185a) and two mRNAs (PTGIS and ADRB2) were conducted. We performed correlation analyses between the Q-PCR and microarray data, between the miRNAs and mRNAs, and between the miR-eQTLs and the miRNAs. The Q-PCR confirmation was performed in the samples for which total RNA was still available. Q-PCR for miRNAs was performed with Taqman MicroRNA Assays using ViiA™ 7 Real-Time PCR System according to the manufacturer's instructions. The U6 gene (RNU6B) was used as an

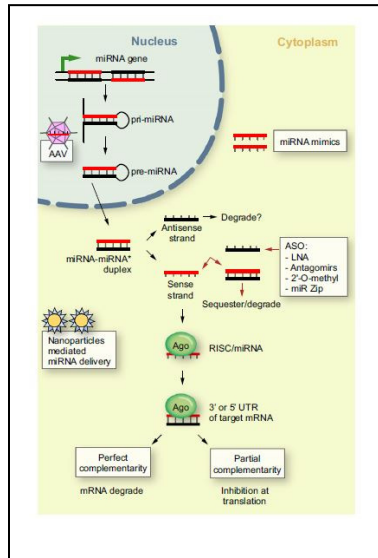
internal control. Q-PCR for the two mRNA genes was conducted using iQ™ SYBRW Green Supermix according to the protocol developed in our previously study .

Annealing temperature used for the Q-PCR reactions for both genes was 65°C. The relative expression levels between the quantified miRNA or mRNA genes and the respective internal control genes were used in the data analyses.

### Conclusion

MiRNAs are good biomarkers. Pattern of elevation varies in different diseases. They are specific for the HBV, HCV, NASH, ALD, HCC, and liver fibrosis.

In the hepatitis B microRNA 122 is decreased and in the HCV microRNA 122 is increased. In ALD micro RNA 155 and 132 are elevated and micro RNA 122 is decreased. In HCC micro RNA 21 Micro RNA221 and microRNA 222 are increased and 122 is decreased. In liver fibrosis micro RNA 199, micro RNA 200 and Let 7 is increased and micro RNA 29 and micro RNA 122 is decreased. The above article gives the information about micro RNA 122 as specific for liver disease it participate in many liver diseases like cirrhosis, fatty liver, necrosis, cholestasis.



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