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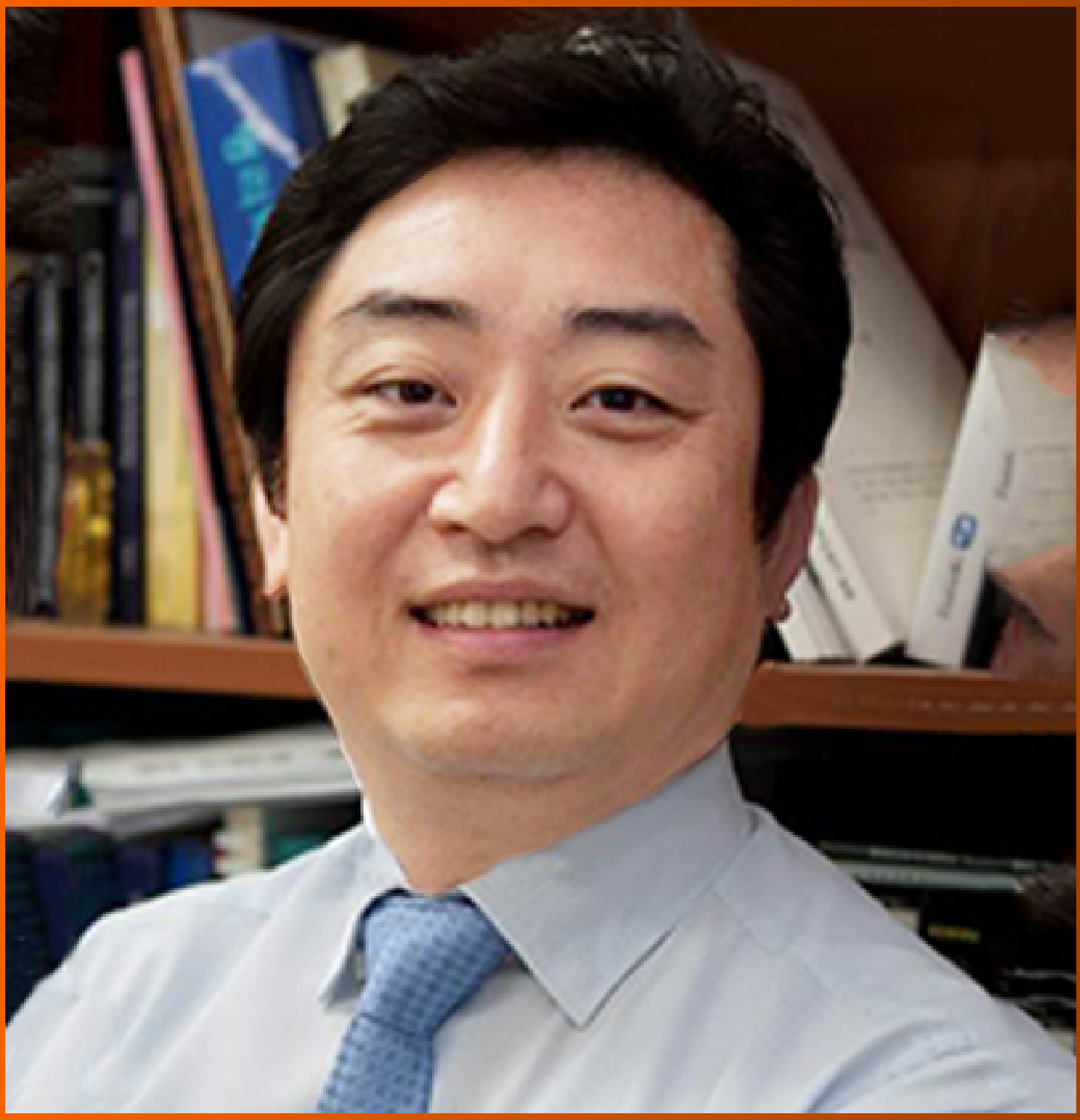

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REVIEW

Circulating microRNAs as non-invasive biomarkers for hepatitis B virus liver fibrosis

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Abstract

Viruses can alter the expression of host microRNAs (miRNA s) and modulate the immune response during a persistent infection. The dysregulation of host miRNA s by hepatitis B virus (HBV) contributes to the proinflammatory and profibrotic changes within the liver. Multiple studies have documented the differential regulation of intracellular and circulating miRNA s during different stages of HBV infection. Circulating miRNA s found in plasma and/or extracellular vesicles can integrate data on viral-host interactions and on the associated liver injury. Hence, the detection of circulating miRNA s in chronic HBV hepatitis could offer a promising alternative to liver biopsy, as their expression is associated with HBV replication, the progression of liver fibrosis, and the outcome of antiviral treatment. The current review explores the available data on miRNA involvement in HBV pathogenesis with an emphasis on their potential use as biomarkers for liver fibrosis.

Key words: Hepatitis B virus; MicroRNA; Noncoding RNA; Liver fibrosis; Viral hepatitis; Non-invasive biomarkers; Extracellular vesicles; Hepatitis management

Core tip: The current review analyses the available data on the role of microRNAs (miRNA s) in the development and progression of liver fibrosis by focusing on their potential use as diagnostic and prognostic biomarkers for hepatitis B virus-infected patients. Cellular and circulating miRNA s (in plasma or extracellular vesicles) offer a unique glimpse into the virus-host relationship and the pathogenesis of chronic hepatitis

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B virus infection. The differential regulation of intracellular and circulating miRNA s during the natural and on treatment evolution of chronic hepatitis B is discussed.

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INTRODUCTION

MicroRNAs (miRNA s) are short noncoding RNAs involved in the epigenetic regulation of multiple intracellular and extracellular signalling pathways and in the posttranscriptional regulation of genes across numerous eukaryotic organisms[1-3]. Cellular miRNA s can modulate viral replication and the immune antiviral response[4,5]. Viruses can encode their own miRNA s[6] and can alter the cellular miRNome to create a favourable environment for viral replication or latency. Due to these complex roles, miRNA s have been increasingly evaluated as biomarkers for the diagnosis, prognosis and treatment of viral infections[7,8] as well as for distinct pathologies, including liver fibrosis.

Chronic hepatitis B virus (HBV) infection affects over 257 million people[9] and it is one of the most common causes of liver fibrosis. Liver fibrogenesis is a dynamic process, characterized by an excessive accumulation of extracellular matrix proteins in response to an ongoing liver inflammatory response, with gradual distortion of hepatic architecture and progression to liver cirrhosis[10]. Extracellular matrix is mainly synthesized by hepatic stellate cells (HSCs), which are activated following liver injury, together with proinflammatory cytokines and chemokines. Once activated, HSCs maintain this phenotype through autocrine or paracrine signalling loops[11]. Still, liver fibrosis is a reversible wound-healing process. Experimental studies have shown that an early detection and timely removal of the inciting factor can lead to a complete remission of the fibrotic changes, while interventions performed in later stages are less effective against the already formed architectural changes[12]. Furthermore, given the potential progression of liver fibrosis to hepatocellular carcinoma (HCC), an antifibrotic treatment would ideally need to be started early and would be precisely targeted against the molecular processes occurring at that stage.

Regarding HBV-associated fibrosis, between 8%-20% of untreated patients can progress to liver cirrhosis within 5 years depending on viral characteristics (HBV genotype, viral load, HBV mutations) and host-related factors (age, gender, other comorbidities or coinfections)[13]. Antiviral treatment, with either pegylated interferon-α or nucleoside analogues, halts or attenuates the development of fibrosis[14-18] and the initiation of treatment in the early stages of liver fibrosis is associated with a significant improvement of the histologic scores[17]. However, current treatment options do not ensure a complete cure of the HBV infection (with the elimination of viral reservoirs from hepatocytes) and a persistent activation of fibrotic signalling pathways is possible even in patients with undetectable HBV serum viral loads after treatment[19-21]. Hence, biomarkers which offer additional information on the viral-host interaction could potentially foreshadow new therapeutic agents.

Liver biopsy is currently the gold standard for a complete assessment of liver fibrosis, inflammation, and intrahepatic HBV replication. This technique is nevertheless limited by multiple risks and potential misclassifications, due to examiner variability and sampling[22]. Hence, a series of alternative non-invasive biomarkers have been proposed, including imaging data (elastographic techniques such as transient elastography, acoustic radiation force impulse imaging, two-dimensional shear wave elastography and magnetic resonance elastography), biochemical scores (APRI, Fib-4, Fibrotest), HBV RNA, and HBV core antigen[23-25] or even direct markers (molecules released in the serum following liver fibrogenesis of fibrolysis such as hyalyuronic acid, type IV collagen, matrix metalloproteases or tissue inhibitory metalloprotease-1)[26]. Non-invasive scores are more accessible, which explains why the World Health Organization recommends the use of Fib-4 and APRI for the assessment of liver fibrosis in HBV patients living in low-income countries[27]. Nevertheless, the diagnostic performance of these biomarkers in chronic HBV infection is moderate. Non-invasive methods are less reliable for the prediction of a specific stage of liver fibrosis, yet these can differentiate between an early and an

advanced stage of liver fibrosis or even cirrhosis (*e.g.*, F0-F1, ≥ F2 or ≥ F4)[26]. Therefore, combined scores with circulating and cellular miRNA s could represent an appealing alternative for the diagnosis and monitoring of viral-induced liver fibrosis[28] offering supplementary data on the viral-host interactions and the fibrotic signalling cascades in both the liver and blood.

The current review analyses the available data on the role of miRNA s in chronic hepatitis B, with an emphasis on their role in liver fibrogenesis and on their potential use as non-invasive biomarkers in the diagnosis, evolution, and treatment of HBV induced-liver fibrosis.

miRNA BIOGENSIS AND INTERFERENCE WITH HBV

Genes encoding for miRNA s are transcribed by the RNA polymerase II/III into primary RNA transcripts (pri-miRNA), further processed in the nucleus by the Drosha ribonuclease to a hairpin loop structure of ~ 60 nucleotides (the pre-miRNA transcript). Pre-miRNA s are further exported to the cytoplasm, where the Dicer enzyme cleaves the hairpin loop and leads to the mature double-stranded miRNA .

One strand of the mature miRNA is degraded, while the other one (less stable at the 5′ end) becomes the guide strand and is recruited into an RNA-induced silencing complex together with Argonaute proteins, TAR RNA-binding proteins, and other proteins and binds to the 3′ untranslated region of the target mRNAs[29]. Noncanonical interactions can also occur through "seed-like" motifs at the 5′ untranslated region or coding regions[30,31]. This intricate binding mechanism does not imply a perfect complementarity one miRNA can regulate one or more mRNAs, and multiple miRNA s can bind to the same mRNA. The concentrations of intracellular miRNA s are extremely variable, depending on the cellular context (cell cycle, metabolism, or differentiation) and concurrent pathologies. This variability could be exploited during viral-host interactions to influence viral tropism and hijack the host transcriptional machinery or to enable the host control on viral infections[32].

HBV modulates miRNA biogenesis by decreasing the expression of Drosha ribonuclease[33]. Novellino *et al*[34] showed that serum hepatitis B surface antigen (HBsAg) particles transport both Ago2 proteins and a series of miRNA s (miR-27a, miR-30b, miR-122, miR-126, miR-145, miR-106b, and miR-223) and identified a different miRNA profile in HBsAg particles and plasma[34]. Ago2 interacts with hepatitis B core antigen and HBsAg in various subcellular compartments of infected cells, indicating a potential role of HBV on miRNA packaging into extracellular vesicles (EVs)[35]. The function of extracellular miRNA s is not well elucidated, yet data on miRNA s found in EVs (like apoptotic bodies, microvesicles, or exosomes[36,37]) suggest multiple roles in paracrine signalling[38], epigenetic regulation of the recipient cell and regulation of the cellular inflammatory response, through the activation of toll-like receptor signalling pathways[39,40]. Incidentally, the first discovered HBV-encoded miRNA , HBV-miR-3[41] modulates the release of HBV virions and is also incorporated into exosomes and HBV core particles but not into HBsAg subviral particles. It would be interesting to explore if this differential packaging is the result of a viral-host competition and sequestration of host/viral miRNA s into a certain particle and further exploit these findings for diagnostic or therapeutic purposes.

miRNA S AS KEY REGULATORS OF LIVER FIBROSIS

Host-encoded miRNA s

Intracellular miRNA : There is a significant amount of data documenting the role of cellular miRNA s in liver fibrosis but no consensus on their exact regulatory functions. Various miRNA s are being proposed as either profibrotic or antifibrotic (Figure 1). This classification is theoretical, based on predicted signalling pathways and reports from various studies[42-44]. Overall, miRNA s modulate numerous steps during the development of liver fibrosis, including: HSC activation, proliferation, migration, and apoptosis[45-49]; transcription of profibrogenic factors and signalling pathways (such as Col1a1, transforming growth factor beta (TGFβ)-RII[46,47], SPRY2, HNF4a[48], matrix metalloproteinases[49,50], MeCP2[51], retinoid X receptor alpha[52]); modulation of the immune response and intrahepatic recruitment of inflammatory cells, indirectly contributing to the release of profibrotic cytokines such as tumor necrosis factor alpha, Interleukin-6, and Interleukin-1β, regulation of interferon gamma signalling and of the inflammasome pathway[57-60], regulatory activity on the metabolism of lipids, drugs, and alcohol[50,57,58,61]; and the regulation of angiogenesis[63].

The complete characterization of intracellular miRNA s is nevertheless difficult

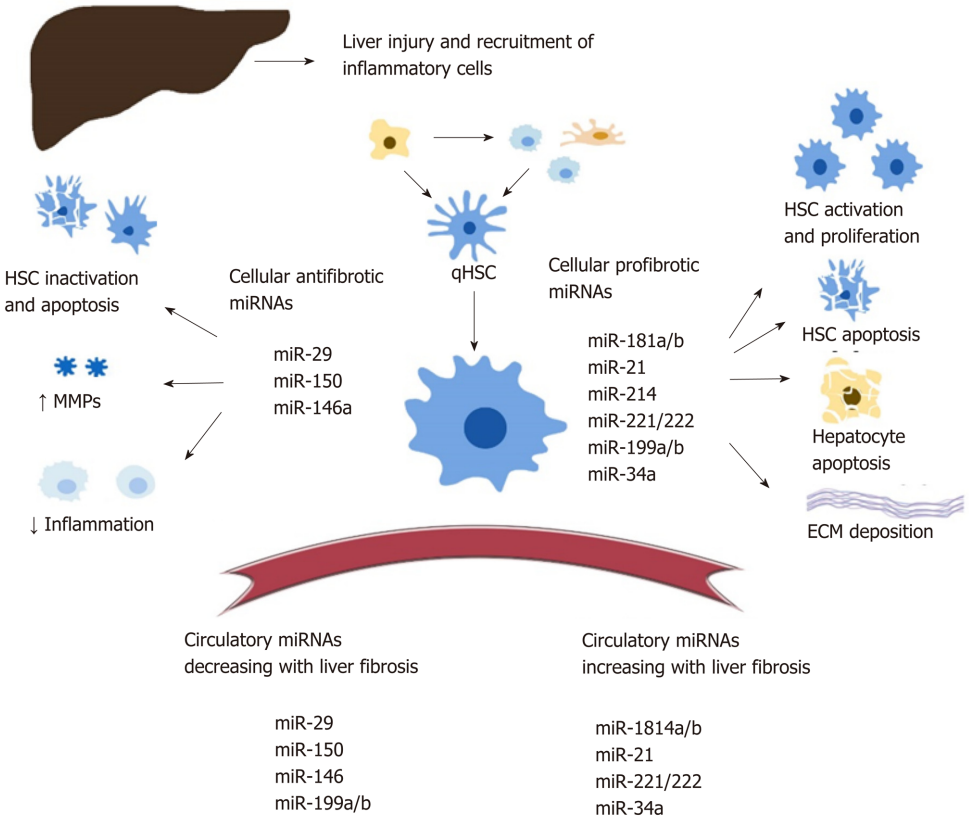

Figure 1 Profibrotic and antifibrotic intrahepatic and circulating microRNAs. MMP: Matrix metalloproteases, qHSC: Quiescent hepatic stellate cell, aHSC: Activated hepatic stellate cell; MiR: MicroRNA.

given that one miRNA can modulate multiple signalling pathways in various tissues. For example, miR-34 mediates both HSC activation through peroxisome proliferator-activated receptor gamma signalling[64] and hepatocyte apoptosis through the miR-34/sirtuin-1/p53 cascade[65]. On the other hand, miR-34a-5p can also display an antifibrotic role within HSC, as its overexpression was correlated with the downregulation of the TGFβ/Smad3 pathway[66].

Both miR-181b and miR-21 favour HSC activation through the inhibition of phosphatase and tensin homolog and activation of the phosphatidylinositol 3-kinase/Akt pathway[67,68]. MiR-29b, a significant antifibrotic cellular miRNA , induces HCS apoptosis, regulates the HSC phenotype, and decreases extracellular matrix synthesis through multiple signalling pathways (TGF-β / Smad, lipopolysaccharide / NF-kB, and oestradiol)[69-72]. HSC activation is also downregulated by multiple antifibrotic miRNA s, including miR-146 through the suppression of TGF-β / Smad[73], and miR-150 through c-myB and Sp1 signalling pathways[74,75].

Circulating miRNA s

Circulating miRNA s found in the plasma or serum have been extensively studied in the pathogenesis of liver disease due to various aetiologies, including viral hepatitis, nonalcoholic steatohepatitis and alcoholic liver disease, drug-associated liver injury, and HCC[62,76-79].

Circulating miRNA s correlate with the presence and progression of liver fibrosis and necroinflammation and can be used to predict the survival of patients with cirrhosis or HCC[80-82]. The link between circulating and cellular miRNA s is still under investigation. In this respect, Table 1 provides a correlation between the regulation of various miRNA s found in the serum and liver of patients with HBV infection.

miRNA S IN EVS

EVs are secreted in multiple body fluids and ensure the transport of various proteins, lipids or RNAs including miRNA s. Intrahepatic miRNA s are packaged into EVs and released from injured hepatocytes to further mediate the survival/proliferation or

Table 1 Circulating and intrahepatic microRNA regulation and target processes involved in liver fibrogenesis in hepatitis B virus infection

MicroRNA	Plasma level	Liver tissue	Mediated processes involved in liver fibrosis	Ref.
miR-34a	↑	↑	Cell-cycle regulator (cell differentiation, proliferation, metabolism, apoptosis); HSC activation	Guo *et al*[45]; Singh *et al*[42]
miR-221 miR-222	↑	↑	Collagen synthesis; HSC proliferation; Liver fibrosis; Oncogenesis	Singh *et al*[42]
miR 27a/b	↑	↑	HSC activation, differentiation and proliferation	Zhang *et al*[131]
miR 181a/b	↑	↑	Cell cycle regulator; HSC activation and proliferation	Yu *et al*[132]
miR 199a/b	↓	↑	HSC activation	Murakami *et al*[91]
miR-223	↓; ↓ EVs	↑	Inflammatory response	Akamatsu *et al*[133]; Bao *et al*[43]; Ye *et al*[59]; Wang *et al*[106]
miR-125 (-125a-5p/ -125b)	↑	↑	HSC activation, proliferation	Zheng *et al*[134]; You *et al*[49]
miR 21-5p	↑in total plasma; ↓ in EVs	↑	Collagen synthesis; Oncogenesis	Bao *et al*[43]; Wei *et al*[68]; Wang *et al*[135]

↑ means upregulation. ↓ means downregulation. EVs: Extracellular vesicles; HSC: Hepatic stellate cell; miR: MicroRNA.

infection in neighbouring cells[83-85]. Additionally, miRNA s associated to EVs have been shown to play various roles in cell-to-cell communication between parenchymatous and non-parenchymatous cells (such as HSCs, liver sinusoidal endothelial cells, Kupffer cells, or cholangiocytes). Extracellular miRNA s have been shown to mediate both profibrotic and antifibrotic signalling cascades. For example, hepatitis C virus-infected hepatocytes release EVs containing miR-192 or miR-19a that induce profibrotic TGFβ signalling pathways and activate HSCs[86,87]. Quiescent HSCs release EVs containing miR-214 and miR-199a-5p in order to downregulate fibrogenic pathways in neighbouring activated HSCs and hepatocytes[88,89]. The antifibrotic potential of these EVs is particularly intriguing given that both miR-214 and miR-199a-5p/3p have been known for their profibrotic action[48,90,91].

Compared to the miRNA s found in the total plasma, EVs can display different miRNA concentrations and even discordant miRNA subsets[92]. Lambrecht *et al*[93] showed that the same miRNA species can be upregulated in the serum and downregulated in the EVs and suggested that the miRNA signature from circulating EVs reflects the profile found in the vesicles released by activated HSCs *in vitro*. These discrepancies can also indicate either a higher stability of miRNA s packaged into EVs against plasma ribonucleases, different intercellular signalling mechanisms[94,95] or could be attributed to the distinct methodology used for miRNA detection and quantification.

HBV-encoded miRNA s

Current data on circulating miRNA s in HBV cirrhosis are limited to host-miRNA s. The only confirmed HBV-encoded miRNA , HBV-miR-3 is released in the circulation packed in HBV virions and EVs[41]. Given that HBV-miR-3 downregulates the synthesis of HBV virions, it is probable that this miRNA plays a role in the establishment of chronic HBV infection. Hence, the incorporation of HBV-miR-3 into a miRNA diagnostic score could help indicate the contribution of intrahepatic HBV replication to the development of liver inflammation and fibrosis. However, no data are currently available on the role of HBV-miR-3 in HBV-associated liver fibrosis/cirrhosis.

miRNA S DETECTION AND QUANTIFICATION

The assessment of miRNA profiles involves the extraction of total RNA and quality control analysis of this purified fraction, followed by their quantification using either reverse-transcription PCR, microarrays, or even next-generation RNA sequencing.

Compared to other non-invasive biomarkers, circulating miRNA s are better able to withstand a low pH, extreme temperatures, ribonucleases, and multiple freeze-thaw cycles[96]. Still, the interpretation of miRNA concentration requires a careful consideration of the methodology, as it depends on the timing of the sample collection, the isolation protocol[97] (*e.g.*, plasma *vs* serum; miRNA s in exosomes *vs* free miRNA s in plasma or serum) and on the normalization method[98]. Currently, there are various approaches for normalization, including the use of exogenous spike-ins (such as cel-miR-39 from *Caenorhabditis elegans*), geometrical mean of the quantification cycle for the analysed miRNA s, and the use of one or more endogenous miRNA s, small RNAs, or even miRNA /small RNA constructs as reference points[99,100].

CIRCULATING miRNA S AS POTENTIAL BIOMARKERS OF LIVER FIBROSIS

One of the most important challenges for the use of circulating miRNA s in the clinical setting resides in their lack of specificity for a distinct tissue[101]. With few exceptions, such as miR-122, which accounts for an estimated 70% of all miRNA s in the liver[102], other miRNA s are less specific for the liver. Moreover, the significance of circulating miRNA s in chronic liver diseases is complicated by the simultaneous development of the necroinflammatory process and scarring as well as by the potential viral-host interactions. For example serum/plasma miR-122 appears to increase with the progression of the liver necro-inflammatory activity in patients with chronic hepatitis, including those with established liver fibrosis[103], yet it also varies with HBV replication within the liver. Hence, when looking at miRNA expression, a critical interpretation in the clinical context is required.

The circulating miRNA s associated with liver fibrosis differ between studies, and there is still no consensus on their uses as biomarkers of choice for the diagnosis, staging, or prognosis of liver fibrosis.

miRNA s for detection of liver fibrosis

The individual expression of miRNA s in plasma/serum can reach a moderate accuracy for the detection of liver fibrosis. Such an example is miR-29, an antifibrotic miRNA that exhibits an area under the curve between 0.619 to 0.838 in various studies[43,47,69]. The use of multiple miRNA s or the combination of noncoding RNAs and of other laboratory markers have significantly increased their diagnostic and prognostic accuracy[79,104-106]. Individual miRNA s and composite scores for liver fibrosis in HBV-infected patients are shown in Table 2 and Table 3. In a meta-analysis by Guo *et al*[79], the authors identified a panel of eight circulating miRNA s that could serve as diagnostic markers for liver cirrhosis, irrespective of the viral or nonviral aetiology, displaying an area under the curve of 0.93 (95% confidence interval: 0.91–0.95). Similarly, Murakami *et al*[91] identified a miRNA score which differentiated between chronic hepatitis B and chronic hepatitis C, non-alcoholic steatohepatitis, and healthy controls with accuracy of 98.35%, 87.5%, or 89.29%, respectively.

Studies on HBV-infected patients have shown that serum/plasma miRNA signatures can assist in the differentiation from other viral or nonviral liver pathologies[93,105,107]. Recently, Shang *et al*[108] identified a profile of urinary miRNA s that could serve as diagnostic biomarkers for HBV infection and non-alcoholic steatohepatitis. Nevertheless, there is still insufficient data to recommend a miRNA panel for the specific diagnosis of HBV *vs* other pathologies. On the other hand, miRNA s have been associated with a specific HBV immune profile, with the evolution of ne-croinflammatory activity and with the development of chronic liver disease[42,109,110].

miRNA s for staging of liver fibrosis

miRNA s can distinguish between early and late fibrosis with a comparable or even higher sensibility and specificity than APRI or Fib-4[43,106,107]. Panels exclusively composed of miRNA s[106] or panels including both circulating miRNA s and biological markers (*e.g.*, platelet count and alkaline phosphates) have been evaluated[39,103]. Wang *et al*[106] showed that a miRNA signature displays a significantly higher accuracy than individual miRNA s for the detection of moderate and advanced liver fibrosis (area under the curve of 0.90 for stages beyond F2, 0.88 for F3-F4, and 0.83 for F4).

Serum/plasma miRNA s precede the increase of liver transaminases in studies on acute liver injury[111,112]. Translating this result in patients with chronic hepatitis is nevertheless challenging, due to the persistent elevation of laboratory markers in chronic liver diseases. In HBV-associated liver fibrosis diagnosis, it is important to

Table 2 Circulating microRNAs in hepatitis B virus infection and their significance for the staging of liver fibrosis

Circulating microRNAs, plasma or serum	Significance for liver disease	Ref.
Upregulated microRNAs		
miR-185	↑ in advanced (F3-F4) *vs* early liver fibrosis (F1-F2); and ↑ in early liver fibrosis *vs* healthy volunteers; No increase with HBV plasma DNA	Li *et al*[136]
miR-2861, miR-345-3p, miR-3620, miR-3656, miR-371a-5p, miR-4646-5p, miR-4651, miR-4695, miR-4800-5p, miR-638	Individually ↑ in F1-F4 *vs* F0; Plasma expression differs between each stage of liver fibrosis	Zhang *et al*[137]
miR-1, mR-10b-5p, miR-20b-5p, miR-96b-5p, miR-133b, miR-455-ep, miR-671-5p	Increase in the serum in F3-F4 liver fibrosis	Singh *et al*[42]
miR-499-5p	Increases in the serum in F1-F2 stages	Singh *et al*[42]
miR-106b, miR-181b	Panel for the diagnosis of liver cirrhosis due both HBV and non-HBV associated infection	Chen *et al*[44]
Downregulated microRNAs		
miR-29	↓ in liver cirrhosis *vs* healthy controls	Xing *et al*[138]; Wang *et al*[106]
miR-223	↓ with the progression of liver fibrosis from F0-F2 to F3-F4	Bao *et al*[43]; Wang *et al*[106]
miR-21		
miR-143		
miR-374		
miR-486-3p, miR-497-5p	Individually ↓ in F1-F4 *vs* F0; Plasma expression differs between each stage of liver fibrosis	Zhang *et al*[137]
miR-1227-3p	↓ in the serum in F1-F2 stages	Singh *et al*[42]

↑ means upregulation. ↓ means downregulation. HBV: Hepatitis B virus; miR: MicroRNA.

distinguish between miRNA s that signal the presence of liver inflammation *vs* fibrosis, a challenge in practice because both can be present in the progression of chronic livery injury. Examples of circulating miRNA s that correlate with either liver necroinflammation and/or fibrosis are presented in Table 4. Still, circulating miRNA s could be used as prognostic markers for survival as well as for the developing risk of HCC in cirrhotic patients, including those with chronic hepatitis B[113,114].

miR-122 gradually decreases in the serum of patients with decompensated liver cirrhosis and its value is independently associated with the survival and MELD score[115], while miR-34 indicates the degree of portal hypertension in patients with liver cirrhosis[116]. miRNA scores also yield a satisfactory sensitivity and sensibility for the detection of HCC in patients with cirrhosis due to viral and non-viral aetiologies[117-120]. Various profibrotic miRNA s, such as miR-21 and miR-221/222, are also well-known oncogenic miRNA s and regulate tumoral signalling pathways. Circulating miR-21 is associated with the detection of HCC and with the presence of distant metastasis[49,77,121-123]. Similarly, serum miR-221 plays an important role in the growth and proliferation of tumoral cells[124] and appears to be regulated by HBx[125]. In this respect, Huang *et al*[117] devised a miRNA score that differentiated between HBV- or hepatitis C virus-associated HCC.

Circulating miRNA s as predictive biomarkers during HBV treatment

Plasma miRNA expression varies in response to antiviral treatment and could provide a promising tool for treatment selection. Van der Ree *et al*[126] found higher pretreatment levels of miR-301a-3p and miR-145-5p in patients with HBsAg loss, while Yang *et al*[127] devised a combination of miR-3960 and miR-126-3p that correlated with the clearance of HBsAg.

miRNA panels have also been studied in patients receiving either interferon or nucleoside analogues. Zhang *et al*[128] constructed a model of 11 miRNA s for the prediction of an early virological response to an interferon-based regimen, while Brunetto *et al*[129] defined a miR-B index (combining serum miR-122, miR-99, miR-192, miR-335, miR-126, miR-320) for the prediction of a sustained virological response. Li *et al*[130] used a miRNA panel composed of miR-22, miR-210, and alanine aminotransaminase to predict the early and sustained virological response but did not find any correlations with HBsAg or HBeAg clearance during a regimen with interferon-alpha.

Further studies on the serum miRNA dynamics during treatment could help establish the correlation between a specific pretreatment miRNA profile and the outcome of the treatment measured as both viral suppression and fibrosis regression.

Table 3 Overview of the major studies on the use of microRNAs in hepatitis B virus infected patients for the staging of liver fibrosis

Study group	Fibrosis staging/validation method	microRNA detection method/sample[1]	Data normalization	microRNA regulation depending on fibrosis staging			microRNA panel for liver fibrosis	Ref.
102 treatment naïve CHB	58 pts F0-F2; 44 pts F3-F4 / liver biopsy and laboratory data	RT-qPCR / serum samples	Spiked-in cel-miR-39	F3-F4 *vs* F0-F2	miR-122, -27b miR-222, -224	↑ ↓	miR-122, -222, PLT, ALP	Appourchaux *et al*[107], 2016
330 CHB, 165 HC	165 pts F0-F3; 165 pts F4 / clinical and laboratory data	RT-qPCR / serum samples	Exogenous control using cel-miR-67	CHB: F4 *vs* F0-F3 CHB F4 *vs* HC CHB *vs* HC	miR-18a-5p, -21-5p, -29c-3p, -122-5p, -106b-5p, 185-5p miR-1, -146a-5p miR-451a miR-21-5p, -27a-3p, -122-5p, -146a-5p	↓ ↑ ↓ ↑	Three panels: F4 *vs* other stages: miR-18a-5p, -21-5p -29c-3p, -122-5p, -106b-5p, 185-5p; F4 *vs* HC: miR-1, -146a-5p, -451a; CHB *vs* HC: miR-21-5p, -27a-3p -122-5p, -146a-5p	Jin *et al*[139], 2015
123 treatment naïve CHB	69 pts F0-F2 *vs* 54 staged F3-F4 / liver biopsy	RT-qPCR; Serum samples	Spiked-in cel-miR-39	F3-F4 *vs* F0-F2	miR-29a, -143, -223, -21, -374	↓	miR-29a, -143, -223, PLT	Bao *et al*[43], 2017
8 ASC, 8 AVH, 7 HC, 49 treatment naïve CHB	49 CHB patients: 16 pts F0, 19 pts F1-F2, 14 pts F3-F4 / liver biopsy, clinical and laboratory data	RT-qPCR and microarray analysis; Serum samples	U6 RNA control relative miRNA	F1-F2 F3-F4	miR-499-5p miR-1227-3p miR-34b-3p, -1224-3p, -1, -10b-5p, -20b-5p, -96b-5p, -133, -455-3p, -671-5p	↑ ↓ ↑	Analysis of miRNA networks and of individual miRNA s	Singh *et al*[42], 2018
19 CHB, 14 HC	19 CHB pts with F0-F2	RT-qPCR total plasma EVs/liver stiffness	Spiked-in cel-miR-39	Plasma (F0-F2) EVs (F0-F2)	miR-192, -200b miR-192, -200b, -92a, -150	↑ ↓	Expression pattern of each individual miRNA in EVs *vs* total plasma	Lambrecht *et al*[93], 2017
207 CHB, 47 non-HBV-LC, 7 non-CHB, 137 HC	207 CHB of which: 127 pts F4; 79 pts F0-F3 / liver biopsy	RT-qPCR / plasma samples	miR-1228 control with a log-2 scale transformation	CHB F4 and non-CHB F4; *vs* other groups; (panel for F4 diagnosis)	miR-106b miR-181b	↓ ↑	Panel composed of miR-106 and miR-181b	Chen *et al*[44], 2013
50 treatment naïve CHB	10 pts F0, 10 pts F1, 10 pts F2, 10 pts F3, 10 pts F4 / liver biopsy	Microarray analysis / plasma samples	Log standardization of miRNA s whose target gene expression levels > 2 folds and FDR < 0.05	F4 *vs* F0	miR-2861, -345-3p, -3620-3p, -3656, -371a-5p, -4646-5p, -4651, 4695-5p, -4800-5p, -638, miR-497-5p, -486-3p	↑ ↓	Detailed differential expression of individual miRNA s for each stage of liver fibrosis F0-F4	Zhang *et al*[137], 2015
92 CHB	11 pts F0, 16 pts F1, 12 pts F2, 13 pts F3, 40 pts F4 / liver biopsy and laboratory data	RT-qPCR; Plasma samples	Quanto, EC1, EC2 controls; relative miRNA expression was assessed using $2^{-\Delta\Delta Cq}$ calculation	≥ F2 ≥ F3 F4 *vs* F0	miR-122-5p miR-223, -29c-3p miR-122-5p miR-122-5p, -29c-3p, -146a-5p, -223	↑ ↓ ↑ -/↓	miR-122-5p, -21-5p, -146a-5p, -223, -29c-3p, -22-3p, -381-3p	Wang *et al*[106], 2018

[1]miRNA sample refers only to the samples collected from the serum/plasma in each of the mentioned studies. ↑ means upregulation. ↓ means downregulation. ALP: Alkaline phosphatase; ASC: Asymptomatic carriers; AVH: Acute viral hepatitis; CHB: Chronic hepatitis B; EVs: Extracellular vesicles; FDR: False discovery rate; HC: Healthy controls; LC: Liver cirrhosis; miR: MicroRNA; PLT: Platelet; Pts: Patients; RT-qPCR: Real time quantitative polymerase chain reaction.

Table 4 Circulating microRNAs in hepatitis B virus infection and their role in necroinflammation *vs* fibrosis

Circulating microRNA	microRNA regulation	Clinical significance in HBV infection	Ref.
miR-122	↑	Correlates with the necroinflammatory activity, HBsAg and HBV DNA; Also correlated with ≥ F2 stage of liver fibrosis	Waidmann *et al*[103], Ji *et al*[109], Wang *et al*[106]
miR-210	↑	Marker of necroinflammation; Varies with the severity of HBV hepatitis	Song *et al*[140]
miR-125 (-125a-5p/ -125b)	↑	Correlates with HBV intrahepatic replication and necroinflammatory activity	Li *et al*[141], Zheng *et al*[134]
miR-124	↑	Marker of HBV-associated necroinflammation	Wang *et al*[142]
miR-29	↓	Marker of liver fibrosis irrespective of aetiology	Xing *et al*[139]
miR-223	↓	Marker of liver fibrosis, decreases with the progression to cirrhosis	Bao *et al*[43]
miR-185	↑	Increases in advanced HBV fibrosis; Could play a therapeutic role in HBV gene suppression in tumoral cells	Li *et al*[136], Fan *et al*[143]

↑ means upregulation. ↓ means downregulation. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; miR: MicroRNA.

CONCLUSION

Cellular and circulating miRNA s offer a unique glimpse into the intrahepatic development of liver fibrosis and intrahepatic viral replication. Diagnostic and prognostic panels that combine different serum miRNA s alone or with other biological parameters display a moderately high sensibility and sensitivity compared to validated non-invasive scores. Although current data remain heterogenous, there is growing proof that serum miRNA s correlate with virologic, immunologic, and fibrotic changes in liver and could become powerful biomarkers during HBV infection.

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