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REVIEW

The interactive role of microRNA and other non-coding RNA in hepatitis B (HBV) associated fibrogenesis

Kurt Sartorius[1,3] · Yanglong Wang[7] · Benn Sartorius[4] · Samuel O. Antwi[3,5] · Xiaodong Li[3] · Anil Chuturgoon[2] · Chongyuan Yu[6] · Yunjie Lu[3,6] · Yu Wang[8]

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Abstract

One of the outstanding features of chronic hepatitis B infection (CHB) is its strong association with liver fibrosis. CHB induced inflammation and injury trigger multiple biochemical and physical changes that include the promotion of a wide range of cytokines, chemokines and growth factors that activate hepatic stellate cells (HSCs) CHB induced activation of hepatic stellate cells (HSCs) is regarded as a central event in fibrogenesis to directly promote the synthesis of myofibroblasts and the expression of a range of materials to repair injured liver tissue. Fibrogenesis is modulated by the mainstream epigenetic machinery, as well as by non-coding RNA (ncRNA) that are often referred to as an ancillary epigenetic response to fine tune gene expression. Although extensive research has explained the regulatory role of ncRNA in liver fibrogenesis, most of this research relates to non-CHB etiologies. This review paper outlines the complex interactive regulatory role of microRNA (miRNA) and their interaction with long non-coding RNA (lncRNA), circular RNA (circRNA) and the mainstream epigenetic machinery in CHB induced liver fibrosis. The paper also illustrates some of the difficulties involved in translating candidate ncRNA into approved drugs or diagnostic tools. In conclusion, the important regulatory role of ncRNA in CHB induced liver fibrosis warrants further investigation to exploit their undoubted potential as diagnostic and therapeutic agents.

Keywords Liver fibrogenesis · Hepatic stellate cells · RNA-inhibition · Epigenetics · MiRNA · LncRNA · CircRNA

Introduction

Chronic hepatitis B infection (CHB) remains a global threat (Seto et al. 2018) that can induce liver fibrosis and increase the risk of hepatocellular carcinoma (HCC). Illustrating the close links between fibrosis/cirrhosis and HCC, it has been observed that ~80% of hepatitis B/C HCC patients have advanced fibrosis/cirrhosis(Idilman et al. 1998). Various estimates also indicate that 80–90% of all HCCs are incubated in fibrotic or cirrhotic livers (Seki et al. 2007; Seki and Schwabe 2015; Abdulrahman and Rahman 2012) differentiating this cancer from carcinogenesis in many other organs (Seki and Schwabe 2015; Affo et al. 2017). Understanding the upstream role of fibrogenesis in the pre-malignant

Kurt Sartorius and Yanglong Wang are joint first author.

✉ Kurt Sartorius
Sartorius@wits.ac.za

✉ Yunjie Lu
lyj0001@suda.edu.cn

✉ Yu Wang
wangyu@jtrmyy.com

[1] Faculty of Commerce, Law and Management, University of the Witwatersrand, Johannesburg, South Africa

[2] School of Laboratory Medicine and Molecular Sciences, UKZN, Durban, South Africa

[3] Africa Hepatobiliarypancreato Cancer Consortium (AHPBCC), Mayo Clinic, Jacksonville, AL, USA

[4] School of Public Health, University of Queensland, Brisbane, Australia

[5] Division of Epidemiology Department of Quantitative Health Sciences, Mayo Clinic, Jacksonville, AL, USA

[6] Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China

[7] Department of General Surgery, Xinyi People's Hospital, Xinyi, Jiangsu, China

[8] Department of Hepatobiliary Surgery, Jintan Affiliated Hospital of Jiangsu University, 213200 Changzhou, Jiangsu, China

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microenvironment (PME) is especially important given that HCC incidence is projected to increase 55% by 2040, as well as because it is a leading cause of cancer related mortality in 46 countries (Rumgay et al. 2022). The risk factors for developing liver fibrosis/cirrhosis are largely the same as those for HCC including alcohol, aflatoxin exposure, iron overload and hepatitis B/C virus (HBV/HCV) infection(Shabangu et al. 2021; Dhiman et al. 2018; Huang et al. 2021a, b) and (possibly) emerging risk factors like metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH) and autoimmune disease (Lim and Kim 2008; Bataller and Brenner 2005; Rinella et al. 2023). The molecular mechanisms of HBV induced fibrogenesis are uniquely regulated in an interactome that includes HBV viral expression, like the hepatitis B x protein (HBx) protein, and its interaction with non-coding RNAs (ncRNAs) (Zhang et al. 2023). The ncRNA interactome in HBV induced fibrogenesis includes microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) (Fig. 1). These interactive ncRNA act as 'fine-tuning' post-transcriptional gene silencers that collectively repress target mRNA expression(Yang et al. 2020a, b, c; Bushati and Cohen 2007). Given the persistent high incidence of CHB infection and HBV-HCC (Liu et al. 2023), it is important to understand how ncRNA regulate liver fibrogenesis in the presence of CHB infection and how this might differ from other etiologies (Heo et al. 2019). The deployment of ncRNA as diagnostic and therapeutic agents in HCC related fibrogenesis remains a work-in-progress that has yet to translate into successful clinical trials and authorized new drugs (Sartorius et al. 2022, Afra et al. 2023). The undoubted potential of RNA based drugs and vaccines offers some promise to deploy ncRNA based technology to offer alternative therapeutic and diagnostic options for CHB and

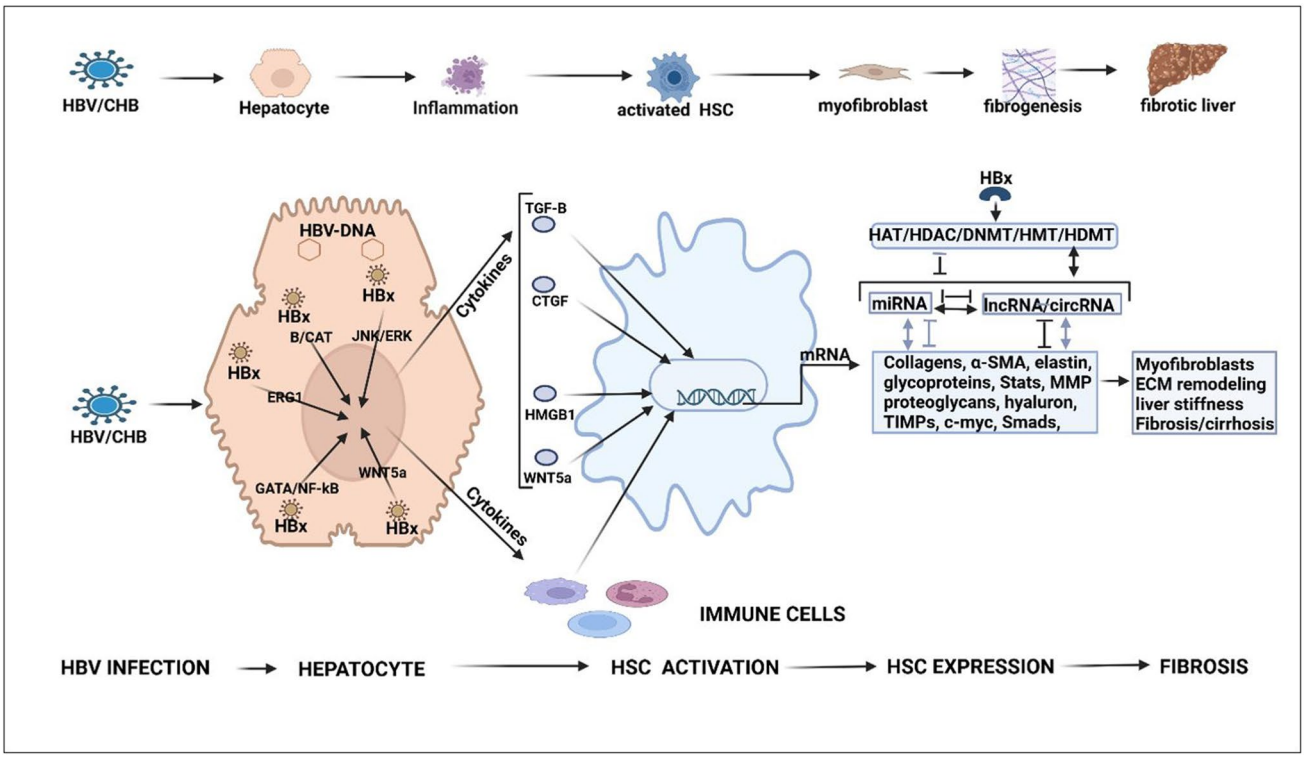


Fig. 1 Hepatitis B infection (HBV) can proceed to Chronic Hepatitis B infection (CHB) in infected hepatocytes causes inflammation and injury, as well as regulates its own replication and survival by synthesizing HBV-DNA and viral proteins like HBx that modulate multiple pathways including JNK/ERK, WNT/B-cat, NF-KB and ERG-1 to promote inflammatory cytokines and growth factors like TGF-B, CTGF, HMGB1 and WNT5a that activate HSCs. Pro-inflammatory cytokines and chemokines also triggers immune response that further promotes the activation of HSCs. Activated HSCs promote the transcription of a wide range of fibrogenic mRNA including collagens, α-SMA, glycoproteins, metalloproteinases (MMPs), proteoglycans, tissue inhibitors of metalloproteinases (TIMPs) and onco-proteins like B-Catenin and C-MYC. These mRNA, in turn, are modulated by ncRNA like miRNA that can suppress or be suppressed by other ncRNA like lncRNA/circ-RNA (see bi-direction arrows or blockers). Upstream of ncRNA expression, the HBx protein can influence the mainstream epigenetic machinery to both repress and promote ncRNA expression that can also repress and promote epigenetic expression (see two way blockers and arrows). The epigenetic machinery includes DNA methyl transferases (DNMTs) histone de-acetyltransferases (HDACs), histone acetyltransferases (HATs), histone methyl transferases (HMTs) and histone de-methylation transferases (HDMTs). Finally, HSC mRNA are transcribed into myofibroblasts and other collagenous materials resulting in ECM remodeling, liver stiffness and fibrosis

HBV-HCC. This review paper outlines the complex interactive regulatory role of ncRNA in HBV associated fibrogenesis. More specifically, this review outlines the role of key HBV dysregulated miRNAs that modulate CHB induced liver fibrogenesis and their interaction with lncRNAs, circRNAs and the mainstream epigenetic machinery. Finally, this paper comments on clinical trials and developments involving the use of ncRNA based technologies to illustrate some of the current challenges. This review focuses on the role of ncRNA in CHB induced liver fibrogenesis in order to differentiate it from recent publications (Li et al. 2023, Li H et al. 2023). A possible limitation is that a many ncRNA liver fibrogenesis papers investigating CHB influenced fibrosis have used non-HBV models. These non HBV models include carbon tetrachloride (CCL4) induced fibrosis which can dysregulate signaling in 36 pathways and > 3500 genes (Dong et al. 2016). Although both CCL4 and CHB pathways induce the expression of multiple inflammatory cytokines (Fareed et al. 2024) in liver fibrogenesis, the possibility remains that CCL4 pathways could differ from CHB induced fibrosis. These studies might have equated ncRNA expression in HBV infected serum or tissue with ncRNA expression in their non-HBV fibrogenesis models.

The HBV fibrogenesis continuum

HBV infected hepatocytes facilitate the synthesis of HBV-DNA and viral proteins (HBx) against a background of inflammation, apoptosis and injury to initiate a cascade of pro-inflammatory cytokines, chemokines and growth factors that activate hepatic stellate cells (HSCs), as well as, trigger immune responses that also promote the activation of HSCs (Su et al. 2014; Kisseleva and Brenner 2021) (Fig. 1). Immune responses that activate HSCs include monocytes, macrophages, T cells and NK cells (Li et al. 2015). In these conditions, characterized by ongoing hepatocyte regeneration, chronic inflammation, the stimulation of cytokines, angiogenic responses and the presence of reactive oxygen species (ROS), the ongoing need to repair damaged tissue promotes the risk of fibrosis/cirrhosis (Baglieri et al. 2019; Dhar et al. 2020). A central event initiating liver fibrogenesis is the activation of hepatic stellate cells (HSCs) that promote the production of myofibroblasts that are the most prominent effector cells involved in restoring the hepatic architecture (Seki and Schwabe 2015; Hernandez-Gea and Friedman 2011). Viral particles like the hepatis B surface antigen (HBsAg) and HBx can be directly transfected to HSCs from infected hepatocytes to influence their expression of fibrotic materials like collagen and alpha smooth muscle actin (α-SMA) (You et al. 2023). The HBx protein, for example, is able to regulate host gene, epigenetic and viral expression to manipulate HBV replication and survival (Martín-Vílchez et al. 2008). The HBx protein can also regulate the expression of Transforming growth factor beta (TGF-β), often cited as the master regulator of inflammation and fibrosis (Stewart et al. 2018), as well as growth factors like Platelet derived growth factor and Connective tissue growth factor (PDGF/CTGF) (Gong et al. 2016), Signal transducer and activator of transcription 3 (STAT3) induced High mobility group box 1 (HMGB1) (Li et al. 2018a, b) and Wingless related integration site 5a (WNT5a) (Li et al. 2019a, b) that are all capable of activating HSC expression (You et al. 2023).

Activated HSCs influence the expression of a multiplicity of extracellular matrix (ECM) materials that provide the structural and biochemical support to the hepatic architecture (Karsdal et al. 2015). ECM materials include 20 distinct types of collagen, as well as elastin, laminin, fibronectin, proteoglycans, matricellular proteins and CTGF to promote the synthesis of myofibroblasts, ECM depositions and ECM remodeling that essentially promotes features like liver stiffness and fibrosis/cirrhosis (Hay 1981; Bitto et al. 2018). Simultaneously, the expression of ECM depositions are regulated by ncRNAs like miRNA that, in turn, are regulated by other ncRNAs like lncRNAs and circRNAs (Li et al. 2023a, b) (Fig. 1). In this regulatory interactome, viral proteins like HBx, can influence both the mainstream epigenetic and ncRNA expression (You et al. 2023).

The non-coding RNA interactome

This section evaluates the regulatory role of miRNA in HBV induced liver fibrogenesis before examining their interactive roles with other ncRNA like lncRNA and circRNAs, as well as with the mainstream epigenetic machinery. To illustrate ncRNA interaction in HBV promoted liver fibrogenesis, a key set of HBV dysregulated miRNAs that modulate fibrogenesis have been selected. The interaction selected HBV dysregulated miRNA with specific lncRNA, circRNA and the mainstream epigenetic machinery particularly attempts to explain the ncRNA regulatory molecular mechanisms of HBV induced fibrogenesis.

miRNA modulation in the fibrogenesis continuum

MiRNAs act as an ancillary epigenetic system that fine tune mRNA translation in all cellular processes (Vidigal and Ventura 2015; Turchinovich and Cho 2014; Turchinovich et al. 2016) by forming argonaut based (AG) RNA-silencing complexes (RISCs) that bind to matching mRNA target mRNA in the 3'UTR region to inhibit mRNA translation (Frédérick and Simard 2022). In the HBV pathogenesis continuum, an increasing number of miRNAs become dysregulated with one study illustrating this by demonstrating that 37 miRNA were deregulated in otherwise healthy

controls (HC), 77 in asymptomatic HBV carriers (ASC), 101 in chronic hepatitis B infection (CHB) and 135 in acute liver failure (ALF) (Ji et al. 2011). Multiple miRNAs are dysregulated in HBV promoted fibrosis with one study that showed > 75 dysregulated miRNA could potentially regulate liver fibrogenesis in the PME (Sartorius et al. 2019) and another indicating 105 dysregulated miRNAs (Chen et al. 2017a, b) (Table 1). For example, miRNAs that directly target the TGF-β pathway in fibrogenesis include miR-17-5p/−122-5p/−181b/−21/−23a-5p/−26b/−27a-b/−30/−34a/−148a/−150/−151b/−152/−214-3p/−221-5p/−222/−29a-b/−33a/−942/−192/−200 (Sartorius et al. 2019).

Various studies label miRNAs influencing fibrogenesis as being pro-fibrotic or anti-fibrotic. Downregulated miRNAs promoting fibrogenesis typically fail to regulate the overexpression of profibrotic mRNA expression that activates HSCs and their expression of fibrotic materials. Conversely, upregulated miRNAs can promote fibrogenesis by silencing inhibitors of fibrogenesis, as well as regulatory and cell-repair expression (Ji et al. 2011; Wang et al. 2021a, b, c). The molecular mechanisms of key HBV dysregulated miRNAs are illustrated in the next section.

Key HBV upregulated fibrogenesis miRNA influencing HSC expression

Key upregulated miRNA in HBV induced fibrogenesis (Table 2; Fig. 2) typically promote HSC activation by repressing HSC regulatory controls like Peroxisome proliferator activated receptor gamma (PPARy) which inhibits transcription of fibrotic materials like Alpha smooth muscle actin (α-SMA) and Collagen type 1 alpha 1 (COL1A1) (Hazra et al. 2004), tumor suppressors like Phosphatase and tensin homolog (PTEN), Tumor protein 53 (p53) and Tumor protein 27 (p27) (Takashima et al. 2009) and TGF-B/Small mothers against Decapentaplegic (SMAD) inhibitors like /Small mothers against Decapentaplegic 7 (SMAD7) (Dooley et al. 2003) and BMP and activin membrane inhibitor (BAMBI) (Weber et al. 2023). Conversely, upregulated miRNAs that repress fibrogenesis typically targets growth factors like TGF-B and CTGF. Examples of HBV induced upregulated miRNA in liver fibrogenesis include miR-17-5p/−21/−27a/−33a/−132/−181b/−214-5p/−222/−942 (Table 2). All of these miRNAs are upregulated by the HBX protein or are recorded as upregulated in serum or tissue of CHB patients.

MiR-17-5p The HBx protein has been observed to upregulate miR-17-5p (Connolly et al. 2008) and it has been proposed as a promising biomarker to differentiate HBV-HCC versus non HBV-HCC cases(Chen et al. 2016; Zheng et al. 2013). CCL4 liver fibrogenesis models show upregulated miR-17-5p can promote fibrogenesis by repressing WIF1 in the WNT/B-catenin pathway to activate HSCs (Yu et al. 2016a, 2016b, 2016c) or alternatively by repressing SMAD 7 to promote the activation of HSCs and their expression of fibrotic materials (Yu et al. 2015, 2015b,2015c). Further illustrating the role of this miRNA, another study using radiation induced fibrosis, demonstrated that the repression of miR-17-5p in the WNT/B-catenin pathway prompted PPAR-y expression to attenuate fibrogenesis (Hasan et al. 2017). The question remains, does miR-17-5p play the same roles in HBV induced fibrogenesis? The increased expression in the WNT-B-catenin pathway due to HBV induced fibrosis (D'souza et al. 2020) occurs in ~ 80% of HBV/HCV associated HCC cases (Idilman et al. 1998). Additional research is needed, however, to confirm the role of HBx upregulated miR-17-5p in liver fibrogenesis.

MiR-21 HBV infection directly induces TGF-B1 upregulation of miR-21-5p which is increasingly expressed as liver fibrogenesis progresses to cirrhosis (Fig. 2). The TGF-B1/miR-21-5p axis promotes the expression of fibrotic materials like α-SMA, COL1A1 by repressing SMAD 7 which is a key inhibitor of HSC activation (Li et al. 2021). The HBx protein can also directly promote miR-21 expression via AP-1 nuclear transcription to operate in a complex profibrogenic feedback loop that simultaneously includes TGF-β activated HSCs that promote SMAD2/3 driven fibrogenesis and the downregulation of its inhibitor SMAD 7 (Zhang et al. 2013; Qiu et al. 2013;Khosravi et al. 2024;Liu et al. 2011).

Furthermore, upregulated miR-21 can also downregulate PTEN expression thus promoting Mitogen activated kinase kinase enzyme/Extra signal regulated kinase (MEK/ERK) amplification of signaling in the SMAD2/3 pathway. Interestingly, upregulated miR-21 is sustained in a feedback loop that is maintained by activated HSC stimulation of Activating protein 1 (AP-1) while upregulated miR-21 can also repress expression of the AP-1 modulator, namely, Programmed death cell 4 (PDCD4) (Zhang et al. 2013). Illustrating its importance in the transition to the tumor microenvironment (TME), the interplay between miR-21/Smad7 has a crucial influence on TGF-B1 activation of cancer associated fibroblast (CAF) synthesis and the transition of the TME (Li et al. 2013a, b).

MiR-27a In HBV cirrhotic livers miR-27a is upregulated but other models of cirrhotic livers in HCC indicate that it can be downregulated(Zhang et al. 2018; Salvi et al. 2013). In a Dimethyl nitrosamine (DMN) model of liver fibrosis, upregulated miR-27a exercised a pro-fibrotic effect by repressing PPARγ/Forkhead box protein o 1 (FOXO1)/Adenomatous polyposis coli (APC)/p53 to induce the expression of α-SMA and COL1A1 in activated HSCs (Zhang

Table 1 Dysregulated miRNA in HBV-associated liver fibrosis/cirrhosis

miRNA	Deregulation	Comment	Author
miR-1	Up	Upregulated in late-stage fibrosis (f3-4)/targets *ATF2/E2F3/CREB3L2*/up in tissue and sera	(Singh et al. 2018)
miR-10b-5p	Up	Upregulated advanced fibrosis vs. early fibrosis/targets *ATF2/E2F3/CREB3L2*/up in tissue and sera	(Singh et al. 2018)
miR-101*	Down	Downregulated in HBV fibrosis/HBx downregulated via *EZH2*-induced methylation/suppresses *TGF-B* signaling to block collagen	(Hayes and Hayes 2016; Tu et al. 2014)
	Up	Suppresses *TGF-β* signaling to block collagen/upregulated in cirrhosis versus CHB	(Xie et al. 2014)
miR-122*	Up	Upregulated in early fibrosis/significant decrease as f0-2 progresses to f3-4	(Hayes and Chayama 2016; Lambrecht et al. 2017;Appourchaux et al. 2016; Nakamura et al. 2017)
	Down	Downregulated in advanced f4 vs. f0-1/suppresses *TGF-β* pathway to block collagen	(Nakamura et al. 2017)
miR-122-5p	Up	Correlates with degree of fibrogenic damage	(Wang et al. 2016; Cheng et al. 2018; Tan et al.2015)
miR-1224-3p	Up	Upregulated in early fibrosis (f1-2)/target *ELK1/AKT2*/upregulated in sera/tissue	(Singh et al. 2018)
miR-1227-3p	Up	Upregulated early fibrosis (f1-2)/target *HSPG2/PTEN*/downregulated in sera	(Singh et al. 2018)
miR-125b-5p	Up	Upregulated in cirrhosis	(Giray et al. 2014)
miR-125a-5p	Up	Targets *F1H1* in HBV-related fibrosis vs. H. Controls	(Li et al 2016; Zheng et al. 2015)
miR-126	Up	Upregulated in cirrhosis vs. CHB stage	(Zhang et al. 2018)
miR-1275	Down	Downregulated in cirrhosis vs. CHB stage	(Zhang et al. 2018)
miR-128	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-130a	Up	Upregulated in fibrosis/f3 > f0/upregulated in cirrhosis vs. CHB/IFNs trigger *JAK/STAT*	(Zhang et al. 2018)
miR-132*	Up	Promotes expression of COL1A1/TIMP by repressing SIRT1`	(Momen-Heravi et al. 2021)
miR-133a	Down	Downregulated in cirrhosis	(Sarkar and Chakravarty 2015)
miR-133b	Up	Upregulated in advanced vs. early fibrosis/targets *ATF2/E2F3/CREB3L2*/upregulated in sera and tissue	(Singh et al. 2018)
miR-140-5p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-141-3p	Down	Downregulated in cirrhosis vs. HCC	(Tan et al. 2015)
miR-142-3p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-143	Down	Downregulated in advanced fibrosis vs. early fibrosis	(Bao et al. 2017)
miR-146a	Up	Upregulated in CHB fibrosis/upregulated in cirrhosis vs. HC/HBx upregulated > CFH fiber proteins	(Appourchaux et al 2016; Zhang et al. 2018; Gui et al. 2011, Xin et al. 2014)
miR-148a/b*	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-149-5p	Down	Downregulated in HBV-induced cirrhosis	(Liu et al. 2017)
miR-150	Down	Inhibits collagen-1 expression and HSC activation/targets c-myb	(Venugopal et al. 2009)
miR-151a-3p	Down	Downregulated as injury increases	(Cheng et al. 2018)
miR-151-5p*	Up	Upregulated in cirrhosis vs. CHB/predictor of activated HSCs	(Zhang et al. 2018)
miR-17	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-17-3p	Down	Downregulated as injury increases/downregulated in cirrhosis vs. fibrosis	(Liu et al. 2017)
miR-17–92	Down	MiR-17–92 family (miR-19a/b/92) downregulated in activated HSCs	(Lakner et al. 2012)
miR-181b*	Up	Promote fibrosis via *TGF-β or NF-κB* pathways/correlates with HBV DNA/downregulated in f4 vs. f1/upregulated in cirrhosis	(Hayes and Chayama 2016; Sarkar and Chakravarty 2015)
miR-185	Down	TGF-1 > miR-185 > *RICTOR/RHEB* > HSCs > ECM > fibrosis/downregulated in HBV-induced fibrosis	(Zhou et al 208)

Table 1 (continued)

miRNA	Deregulation	Comment	Author
miR-1915	Down	Downregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-19b	Down	Downregulated in activated HSCs/CHB led fibrosis/ f3 > f0	(Lakner et al. 2012)
miR-192	Down	Downregulated in sera of CHB patients re ECVs	(Lambrecht et al. 2017)
miR-193-5p	Down	Downregulated in cirrhosis vs. HBV-HCC	(Tan et al. 2015)
miR-194	Down	Inhibits collagen-1 expression and HSC/targets *rac1*	(Venugopal et al. 2009)
	Up	Upregulated as injury increases/targets *ACVR28*	(Gao et al. 2018)
miR-199	Down	Downregulated as injury/cirrhosis develops	(Sarkar and Chakravarty 2015)
miR-199-5p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-199a-3p	Down	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-199a	Up	Upregulated in HBV-led fibrosis	(Li et al. 2014, 2014b)
miR-200a/b	Up	Upregulated in early HBV-fibrosis	(Lambrecht et al. 2017; Li et al. 2014)
miR-20a	Up	Upregulated in CHB fibrosis/f3-4 < f0-2	(Appourchaux et al. 2016)
miR-20b-5p	Down	Downregulated in advanced fibrosis versus early fibrosis/Targets *p21*/upregulated in sera	(Singh et al. 2018)
miR-206	Down	Downregulated in cirrhosis vs. HBV-HCC	(Tan et al. 2015)
miR-21*	Down	Downregulated in advanced fibrosis vs. early fibrosis/ acts via *TGF-B/NF-kB* pathways/downregulated f0-2 > f3-4 in CHB fibrosis	(Hayes and Chayama 2016; Zhang et al. 2018;, Bao et al. 2017)
	Down	Downregulated in cirrhosis progression	(Zhang et al. 2018; Jiang et al. 2018)
miR-214-3p	Down	AUC 0.87 predictor of fibrosis/suppresses TGF-B pathway blocks collagen	(Chen et al. 2017; Hayes and Chayama 2016)
miR-214-5p*	Up	Upregulated in cirrhosis	(Sarkar and Chakravarty 2015)
miR-215	Up	Upregulated in cirrhosis vs. HC	(Gui et al. 2011; Xin et al. 2014)
miR-221-3p	Up	Promotes fibrosis via *TGF-B/NF-kB* paths/f4 down vs. F1	(Singh et al. 2018; Zhang et al. 2018)
miR-221	Down	Downregulated in CHB fibrosis but/f3-4 < f0-2	(Hayes and Chayama 2016; Appourchaux et al. 2016)
	Up	Upregulated in cirrhosis	(Zhang et al. 2018; Sarkar and Chakravarty 2015)
miR-222*	Up	CHB fibrosis via *TGF-β/NF-κB* pathways/increasing significant upregulation from f0-4 Upregulation in cirrhosis	(Hayes and Chayama 2016; Appourchaux et al. 2016; Sarkar and Chakravarty 2015)
miR-222-3p	Up	Upregulated 13.88-fold in cirrhosis	(Giray et al 2014; Zhang et al. 2018)
miR-223	Down	Downregulated in advanced fibrosis vs. early fibrosis/ see article for path	(Bao et al. 2017)
miR-224	Down	Downregulated in CHB led fibrosis/f3-4 significantly less downregulated than f0-2	(Appourchaux et al. 2016)
	Up	Upregulated in cirrhosis vs. HC	(Gui et al. 2011, Xin et al. 2014)
miR-23a/b*	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-26a	Down	Increasingly downregulated in cirrhosis continuum	(Jiang et al. 2018)
miR-26b*	Down	Targets CTGF to (Fail to) modulate fibrogenesis	(Bao et al. 2018)
miR-26a-5p	Up	Upregulated in cirrhosis vs. HBV-HCC	(Tan et al. 2015)
miR-27-3p	Up/Down	Biomarker for cirrhosis	(Liu et al. 2017)
miR-27a*	Up	TGF-1 > miR-27a > *PPARγ*, *FOXO1*, *APC*, *P53* and *RXRα α-SMA* and *COL1A2* (activated HSCs)	(Zhang et al. 2018)
miR-27b*	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-2861	Up	Upregulated stage f4 vs. f0 fibrosis	(Zhang et al. 2018)
miR-29a*	Up	Upregulated in CHB fibrosis/f3-4 < f0-2	(Appourchaux et al. 2016)
	Down	Increasingly downregulated as cirrhosis develops via *TGF-B*, *NFκB*	(Li et al. 2014, 2014b)
miR-29b*	Down	Blocks collagen/TGF-B/targets *COL1A1*, *COL4A5*, *COL5A3*	(Hayes and Chayama 2016; Roderburg et al. 2011)
miR-30b/c*	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)

Table 1 (continued)

miRNA	Deregulation	Comment	Author
miR-30e	Down	HBx-led downregulation of miR-30e > > *P4HA2* fibrosis/cirrhosis	(Tan et al.2015; Zhang et al. 2018; Feng et al. 2017)
	Down	Targets *IL-6R* in fibrogenic pathway	(Chen et al. 2017)
miR-301a	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-324-5p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-33a	Up	Stimulates *TGF-B*, HSCs and promotes fibrosis/targets *SMAD7* to stimulate *TGF-B* HSCs/upregulated in cirrhosis vs. CHB	(Zhang et al. 2018, Huang et al. 2015)
miR-331-3p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-338-3p	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-34a/b/c*	Up	Upregulated in HBV-led fibrosis	(Li et al. 2014 , 2014b)
miR-34b-3p	Up	Upregulated in early fibrosis/targets *GRB10/PIK3CA*/ up in sera/tissue	(Singh et al. 2018)
miR-340	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-345-3p	Up	Upregulated in stage f4 vs. f0 fibrosis	(Zhang et al. 2015)
miR-346-3p	up	Upregulated in early CHB induced fibrosis stages f1-2	(Singh et al. 2018)
miR-3620-3p	Up	Upregulated in stage f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-3656	Up	upregulated stage f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-371a-5p	Up	Upregulated in stage f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-374	Down	Downregulated in advanced fibrosis vs. early fibrosis	(Bao et al. 2017)
miR-374b	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-377-3p	Up	Biomarker for cirrhosis	(Liu et al. 2017)
miR-410-3p	Up	Biomarker for cirrhosis	(Liu et al. 2017)
miR-424	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-455-3p	Down	Downregulated in advanced fibrosis vs. early fibrosis/ Targets *p21*/upregulated in sera	(Singh et al. 2018)
miR-4646-5p	Up	Upregulated f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-4651	Up	Upregulated f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-4695-5p	Up	Upregulated f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-4800-5p	Up	Upregulation f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-483-5p	Down	Downregulated in f3 vs. f0 fibrosis/cirrhosis	(Murakami et al. 2012)
miR-486-3p	Down	Downregulation f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-486-5p	Down	Downregulated in cirrhosis vs. HBV-HCC	(Tan et al. 2015)
miR-497-5p	Down	Downregulation f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-499a-5p	Down	Downregulated in early HBV-induced fibrosis/target *CDKNIA/IKBKB*/upregulated in sera	(Singh et al. 2018)
miR-513-3p	Up	Upregulated in early cirrhosis	(Hayes and Chayama 2016; Zhang et al. 2018)
miR-571	Up	Upregulated in early cirrhosis	(Hayes and Chayama 2016; Zhang et al. 2018)
miR-574-3p	Up	Upregulated in cirrhosis vs. HC	(Gui et al. 2011, Xin et al. 2014)
		Upregulated early cirrhosis/differentiates between cirrhosis and HBV-HCC	(Zhang et al. 2018)
miR-602	Up	Upregulated in cirrhosis vs. HC/increasing in HBV-HCC	(Xin et al. 2014, Yang et al. 2010)
miR-615-3p	Up	Promotes hypersplenism/cirrhosis	(Li et al. 2008)
miR-638	Up	Upregulated f4 vs. f0 fibrosis/cirrhosis	(Zhang et al. 2015)
miR-652	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-671-5p	Down	Downregulated in advanced versus early fibrosis/targets *ATF2/E2F3/CREB3L2*/up in sera and tissue	(Singh et al. 2018)
miR-744	Up	Upregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-885-5p	Up	Upregulated in cirrhosis versus HC	(Gui et al. 2011; Xin et al. 2014)
miR-92	Down	Downregulated in CHB fibrosis/f3-f4 > f0-f2	(Appourchaux et al. 2016)

Table 1 (continued)

miRNA	Deregulation	Comment	Author
miR-939	Down	Downregulated in cirrhosis vs. CHB	(Zhang et al. 2018)
miR-940	Down	Downregulated in cirrhosis vs. CHB	(Liu et al. 2017)
miR-942	Up	Upregulated in activated HSCs/TGF and LPS induced miR-942	(Tao et al. 2018)
miR-9-5p	Down	Fibrosis/activates HSCs via *TGFBR1/TGFBR2*	(Yu et al. 2017)
miR-96-5p	Up	Upregulated in advanced fibrosis vs. early fibrosis/targets *ATF2/E2F3/CREB3L2*/up in sera and tissue	(Singh et al. 2018)

f0-4 (fibrosis stage levels). The miRNA* in table selected for Table 2

et al. 2018). Conversely, other studies reveal that the HBx protein can also downregulate miR-27a-3p (Liu et al. 2021) that could then potentially promote an anti-fibrotic role by repressing this miRNA to attenuate HSC activation, however, this specifically needs to be tested in an HBV induced fibrogenesis model as miR-27a can be both upregulated and downregulated in HBV induced pathogenesis. Interestingly, miR-27a has also been identified as a potential biomarker for HBV-HCC (Zuo et al. 2016) and in metabolic associated liver disease (MAFLD) it appears that hepatocytes can express exosomal miR-27a to activate HSCs by PINK1 knockdown (Luo et al. 2021) that could also be tested in an HBV etiology.

MiR-33a In CHB patients miR-33a is significantly elevated in both serum and hepatic tissue and HSC activation via TGF-B1 stimulation also upregulated miR-33a in human and murine tissue to repress the SMAD 7 inhibitor thus directly promoting SMAD2/4 induced fibrotic materials (You et al. 2023; Huang et al. 2015). In addition, the TGF-B1 upregulation of miR-33a correlated with the expression of fibrotic materials like COL1A1 and α-SMA in activated HSCs as a result of the inhibition of PPAR α in the Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway (Li et al. 2014, 2014b). Interestingly, in a recent CCL4 induced model of liver fibrosis, elevated miR-33a activated WNT/Beta Catenin (Beta-cat) induced signaling induced fibrogenesis by targeting DKKI (Liu et al. 2023, 2023b, 2023c) and this miRNA has been identified as a biomarker for HBV induced fibrosis (Huang et al. 2014). Further testing of this important miRNA in HBV induced liver fibrogenesis models is suggested.

MiR-132 Other important upregulated miRNA tested in a CCL4 non HBV liver fibrogenesis model includes TGF-β upregulated miR-132 that can repress SIRT1 to promote the expression of fibrotic materials like COL1A1 in activated HSCs (Momen-Heravi et al. 2021). Interestingly, HBx can repress miR-132 by inducing DNMT methylation (Wei et al. 2013;, Khosravi et al. 2024) and could, therefore influence an anti-fibrotic effect that remains to be specifically tested. In another CCL4 model, it was also demonstrated that this miR-132 can repress CTGF expression in hepatocytes to attenuate HSC activation and fibrogenesis (Cai et al. 2018). This miRNA has also been proposed as a biomarker for distinguishing between different categories of HBV induced disease including cirrhosis (Liu et al. 2018, 2018b) suggesting the need for testing this miRNA to identify its specific role in HBV (HBx) induced fibrogenesis models.

MiR:181b Another important miRNA that regulates liver fibrogenesis is mIR-181b which is significantly upregulated in the serum of cirrhosis patients, as well as by the HBx protein by targeting ING5 (Wang et al. 2012;Xie et al. 2018). In a TGF- β induced model using an HSC cell line, upregulated miR-181b promoted HSC proliferation by repressing p27 modulation of cell cycle activation (Wang et al. 2012). Similarly, in another CCL4 induced fibrosis model TGF-B upregulation of miR-181b repressed PTEN regulation of HSC activation to promote COL1A1 and α-SMA (Zheng et al. 2015). Further research is suggested to confirm whether miR-181b can promote HSC activation by repressing p27/PTEN expression.

MiR-214-5p In other important examples involving non HBV induced etiologies, TGF-B upregulated miR-214-5p has displayed an anti-fibrotic effect by repressing CTGF (CCN2) to (Tao et al. 2018) reduce HSC synthesis of collagen and α-SMA (101), as well as by repressing TGF- β activation of HSCs and promoting Caspase 3 (CASP3)/HSC apoptosis (Izawa et al. 2015). This miRNA has also been reported as upregulated by HBV infection (Sarkar and Chakravarty 2015). Interestingly, HSCs can also attenuate the expression of miR-214 by repressing Twist family transcription factor 1 (TWIST1), a promoter of miR-214 expression, in order to reduce its modulation of CTGF thus promoting fibrogenesis (Chen et al. 2014). It needs to be tested, therefore, if HBV infection potentially dysregulates

Table 2 Key miRNA regulating HBV induced fibrogenesis

MiRNA	Upstream	Target	Regulation of fibrogenesis	Reference
Upregulated				
miR-17-5p	HBV/HBx/CCL4	WIF1/SMAD7	Activates HSCs represses WIF1/SMAD7	(Connolly et al. 2008; Yu et al. 2015a, b, c, d, 2016a , b, c)
miR-21-5p	HBx/TGF-β/AP-1	SMAD7/PTEN	Promotes SMAD2/3/4/TGF-B expression	(Noetel et al. 2012; Zhang et al. 2013; Meng et al. 2007; Wu et al. 2019)
miR-27a*	HBV/HBx/TGF-B	PPARy/FOXO1/APC/p53	Promotes upregulation of COL1A1,	(Zhang et al. 2018)
miR-33a	HBx/HBsAG/TGF-B	SMAD7/PPAR α	Promotes SMAD 2/4 and aHSC	(You et al. 2023; Huang et al. 2015a, b; Li et al. 2014a, b)
miR-132*	HBx/CCL4/TGF-B	SIRT1/CTGF	Represses COL1A1/TIMP3/CTGF	(Momen-Heravi et al. 2021; Cai et al. 2018; Wei et al. 2013)
miR-181b	HBx/CCL4/TGF-β	p27/PTEN	Promotes HSC/MMP/α-SMA expression	(Wang et al. 2010, 2012; Zheng et al. 2015a, b)
miR-214-5p	HBV/Ethanol/TGF-B	CTGF/TGF-B	Represses aHSC by HSC apoptosis	(Chen et al. 2014; Izawa et al. 2015)
miR-222	HBV/HCV/Other	TFRC	Reduces ferroptosis regulation of HSCs	(Ogawa et al. 2012; Shen et al. 2014; Zhang et al. 2022)
miR-942	HBV/TGF-B	BAMBI	Represses BAMB1 to activate HSCs	(You et al. 2023; Tao et al. 2018a, b)
Downregulated				
miR-18a	HBx	CTGF	Fails to regulate HSC activation	(You et al. 2023; Liu et al. 2016)
miR-19b	HBV	TGF-B/GRB2	Reduced inhibition TGF-B/aHSC/COL1A1	(Lakner et al. 2012)
mIR-185	HBx/HBsAg/TGF-B	RICTOR/RHEB/SREBF1	Activates HSCs by failing to regulate	(You et al. 2023; Zhou et al. 2018a, b, c; Li et al. 2016a, b)
miR-23a-5p	HBV/CCL4/PGE2	ERK/BMP2/CAV-1/CDH1	Induces apoptosis to repress HSCs	(Brea et al. 2018)
miR-23b/-27b	CHB/TGF-B	LOX/CTGF/TIMP1/Grem1	Fails to repress ECM, TIMP1 and aHSC	(Wan et al. 2022; Zeng et al. 2016)
miR-29b	CHB/CCL4/TGF-β	TGF-B/P13K/ AKT	Fails to regulate COL1A1/TIMP-1/α-SMA,	(Roderburg et al. 2011; Wang et al. 2015; Huang et al. 2014a, b)
miR-29a	CHB/HBx/TGF-β	IGF-1/PDGF	Fails to repress collagen 1, 3, 4/ECM	(Noetel et al. 2012; Huang et al. 2014a, b; Kwiecinski et al. 2012)
miR-30	HBV/TGF-B1	SNAIL1	Fails to regulate SNAIL1 led EMT/ECM	(Zhang et al. 2012)
miR-30e	HBX/EZH2	P4HA2	Enhances collagen depositions	(Feng et al. 2017)
miR-34a	HBx/STAT3	NF-kB/HMGB1/SMAD4	HMGB1 activation>JNK/ERK autophagy	(You et al. 2023; Feili et al. 2018)
miR-101b	HBV/CCL4/TGF-B	TGF-B/P13K/AKT/mTOR	Fails to repress α-SMA, collagen 1	(Xie et al. 2014; Lei et al. 2019)
miR-122	HBx/CCL4/TGF-β	TGFB1/KLF6/P4HA1	Fails to repress HSC collagen, α-SMA	(Tsai et al. 2012; Li et al. 2013a, b)
miR-146a	CHB/TGF-B1	Il-6/SMAD4	Fails to repress IL-6 induced aHSC	(Yang et al. 2019a, b; Liao et al. 2022a, b)
miR-148a	HBx/TME	IkB-α/ NUMB/ NOTCH	Fails to repress NOTCH signaling	(Jung et al. 2016)
miR-150	TGF-B	c-myb/Rac-1	Fails to regulate α-SMA/COL1A1	(Venugopal et al. 2009)
miR-152/-378a	HBV/CCL4	Gli3	Fails to repress collagen, α-SMA	(Li et al. 2019a, b; Hyun et al. 2016)
miR-200a	HBx/TGF-B	B-CAT	Fails to repress HSC activation	(Sun et al. 2014)

miR-214-5 in order to initiate an anti-fibrotic effect that could promote reduced immune surveillance.

MiR-222 HBx can also upregulate miR-222 (Sartorius et al. 2020;Bandopadhyay et al. 2014;Sokhanvar et al. 2021) and HBV infected hepatocytes also use exosomes to deliver miR-222 to repress TFRC associated ferroptosis thus enhancing HSC activation (You et al. 2023;2022). Interestingly, in a non HBV MASH setting, TNF-α/TGF-α upregulated miR-222 promotes fibrogenesis by repressing cell cycle

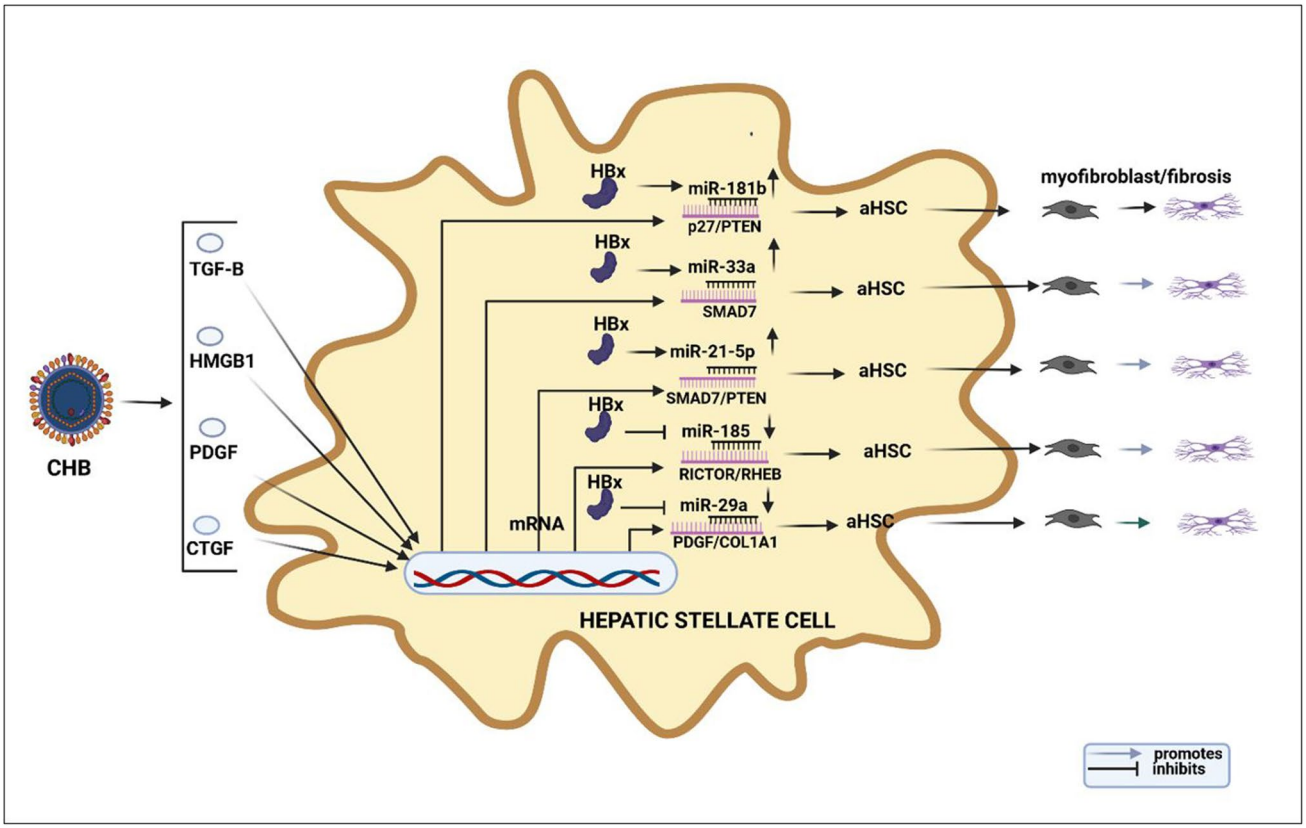


Fig. 2 HBx dysregulated miRNA modulation of liver fibrogenesis Chronic hepatitis B infection (CHB) activates hepatic stellate cells (HSC) via stimulating TGF-B, HMGB1, PDGF and CTGF expression. HSC mRNA expression of p27/PTEN is reduced by HBx upregulated miR-181b to promote HSC activation (aHSC) and its expression of fibrogenic depositions like myofibroblasts eventually contributing to fibrogenesis. Similarly, HSC expression of the SMAD7 inhibitor is reduced by HBx upregulated miR-33a to promote aHSC and its synthesis of myofibroblasts and HBx upregulation of miR-21-5p also suppresses SMAD7/PTEN to promote aHSC and synthesis of myofibroblasts. Conversely, HBx downregulates miR-185 which fails to regulate RICTOR/RHEB induced aHSC and the synthesis of myofibroblasts. Similarly, HBx downregulated miR-29a fails to regulate HSC mRNA expression of depositions like COL1A1 and growth factors like PDGF thus promoting fibrogenesis.

control Cyclin dependent kinase inhibitor 1B (CDKN1B) in HSCs to promote HSC proliferation and the expression of COL1A1, MMP-2 and α-SMA (Ogawa et al. 2012). Upregulated miR-222 in Biliary atresia can also inhibit expression of Protein phosphatase 2 regulatory subunit A (PPP2R2A) that is a regulatory sub-unit influencing HSC proliferation and their expression of fibrotic materials (Shen et al. 2014). This miRNA is associated with HSC activation in other non HBV fibrosis models (Ogawa et al. 2012;Abdel-Al et al. 2018) but this needs to be confirmed in CHB nfluenced HSC activation.

MiR-942 Another important potential miRNA in HBV induced fibrosis is miR-942 that can be upregulated by HBx induced TGF-B1/SMAD2/3 signaling. Upregulated miR-942 represses BAMBI to activate HSCs in HBV induced liver fibrosis (You et al. 2023; Tao et al. 2018). Conversely, upregulated miR-942 in HBV infected patients can also attenuate HSC activation by repressing PPARy and it has been observed that PPARy can decrease in patients with CHB (Tao et al. 2020).

Key downregulated miRNA influencing liver fibrosis (Table 2):

TGF-β downregulated miRNA in liver fibrogenesis typically fail to modulate the expression of pro-fibrotic HSC pathways that are activated by a range of growth factors (GFs), cytokines, chemokines, reactive oxygen species (ROS) and Toll like receptor (TLR) signaling (Bao et al. 2018; Tahmasebi Birgani and Carloni 2017; Yavuz et al. 2020). Downregulated miRNA also fail to regulate oncogenic mRNA expression like B-CAT/C-MYB/Ras related C3 botulinum

toxin substrate 1 (RAC-1) that promote fibrogenesis (Venugopal et al. 2009; Sun et al. 2014). Many downregulated miRNAs, however, can play both pro and anti-fibrotic roles.

MiR-18a HBx expression in HBV infected hepatocytes can downregulate miR-18a which then fails to regulate CTGF expression promoting HSC activation (You et al. 2023). This miRNA has, however, been reported as upregulated in other models of liver fibrosis and can play a protective role by targeting TGF-B signaling. A feedback loop exists though because TGF-B signaling can also downregulate miR-18a (Ramachandran 2013). Interestingly, miR-18a has been reported as upregulated in HCV induced cirrhosis (Elghoroury et al. 2022) and has also been proposed as a potential biomarker for HBV-HCC (Li et al. 2012).suggesting the need to further test this miRNA in an HBV etiology to test the role it plays in regulating liver fibrogenesis.

MiR-19b MiR-19b has been reported as downregulated in both human and rat fibrotic livers (Lakner et al. 2012) and in a transfected HSC model this indicated a reduced ability to regulate paracrine TGF-B signaling and the downstream expression of COL1A1/2 (Lakner et al. 2012). Conversely, miR-19b has been reported as upregulated in HBV-HCC tissue (Connolly et al. 2008; Fan et al. 2014) and HCV serum (Murakami et al. 2010). In another non HBV model, miR-19b was able to attenuate HSC activation by repressing GRB2 resulting in the reduced expression of fibrotic materials like COL1A1 (Ge et al. 2015). The molecular mechanism of miR-19b, therefore, should be further tested in HBV induced fibrosis models.

MiR-23/−27 The miR-23/−27 families appear to play an important role in liver fibrogenesis in a range of non-HBV etiologies. PGE_2/TGF-β downregulated miR-23a-5p, for instance, can repress HSC activation to act as an anti-fibrotic agent because it fails to modulate ERK/BMP2/CAV-1/CDH1 induced apoptosis (Brea et al.2018). This miRNA has also been reported as downregulated in HBV resulting in it promoting an immune-suppressive effect as a result of the reduced regulation of Treg expression (Li et al. 2020, 2020b,2020c). Conversely, TGF-β downregulated miR-23b/−27b fails to regulate pro-fibrotic LOX/CTGF/TIMP1/Gremlin expression thus contributing to promoting fibrogenesis by HSC activation, as well as ECM remodeling (Wan et al. 2022, Zeng et al. 2016). The miR-23/−27 plays an interesting role in liver fibrosis. Individually, miR-23 can promote liver fibrosis by repressing PTEN and PPARy/p53/APC while miR-27/−23 combined repress Grem1 to attenuate liver fibrosis (Ru et al.2022). The important role of this family in HBV pathogenesis is illustrated by the fact that HBV infected hepatocytes in CHB patients can use exosomes to deliver miR-27b-3p that inhibits IFN-y production thus blocking the elimination of HBV associated proteins like HBsAG (You et al. 2022) and exosomes with declined miR-27b-3p triggered activation of RIG-I/TBK1 signaling in macrophages against HBV. Interestingly, miR-27b-3p is also proposed as a biomarker for CHB (You et al. 2022) thus warranting further investigation in its dual roles of modulating liver both HBV pathogenesis and liver fibrogenesis.

MiR-185 Elevated serum levels of miR-185 in HBV induced fibrosis have been observed and this miRNA has been proposed as a promising biomarker (You et al. 2023). It also plays an important role in a non HBV related DMN fibrosis model because it can target SREBF1 to activate HSCs and their expression of fibrotic materials (Li et al. 2016, 2016b). Conversely, in a HBV fibrogenesis model, HBx induced upregulation of ERG1 to promote TGF-B downregulation of miR-185 resulting in its reduced ability to regulate RICTOR/RHEB activation of HSC thus contributing to a unique HBv induced pathway to activate HSCs and promote fibrogenesis (Zhou et al. 2018, 2018b, 2018c).

MiR-29 The key anti-fibrotic miR-29 family is frequently reported as becoming increasingly downregulated in advanced stage fibrosis versus early stage (Li et al. 2014, 2014b; Roderburg et al. 2011). In various fibrogenesis models, TGF-B downregulated miR-29 fails to regulate P13K/AKT signaling and IGF/PDGF expression thus promoting collagen depositions and ECM remodeling (Noetel et al.2012; Kwiecinski et al.2012;, Roderburg et al. 1999). Similarly, miR-29b is often reported as increasingly downregulated in CCL4 induced advanced fibrotic liver tissues (Roderburg et al. 1999) this reducing its ability to repress PIK3R1 and AKT3 activation of α-SMA and collagen expression (Wang et al. 2012). The anti-fibrotic properties of miR-29a/b have been illustrated in an a CCL4 model that induced HGF/MET upregulation of miR-29a/b to repress collagen 1/4 (Kwiecinski et al. 2011). However, the HBx protein is reported as being able to upregulate miR-29a (Kong et al.2011), that can result in promoting HBV replication by its repression of SMARCE1 (Wu et al.2017). The question that remains to be tested then is whether HBx induced upregulation of miR-29a can also play an anti-fibrotic role with a view that this might be an HBV mechanism promoting survival.

MiR-30 In an HBV fibrogenesis model, it was demonstrated that the HBx protein can directly induce the mainstream epigenetic machinery (EZH2) to repress the expression of miR-30e to influence the progression of liver fibrogenesis by its reduced regulation of P4HA2 resulting in the increased expression of collagen (Feng et al. 2017). In other examples of miR-30 family members modulating liver fibrogenesis

in non HBV etiologies, TGF-β downregulated miR-30 fails to repress the expression of the SNAIL-1 transcription factor that triggers growth factor expression, inflammatory responses and ECM biosynthesis in fibrogenesis (Zhang et al. 2012, Rowe et al. 2011). The hepatis B p protein (HBp) can also promote the upregulation of miR-30b-5p through its interaction with FOXO3 to contribute to the development of HBV-positive HCC cells through the glycolytic bypass (Chen et al. 2021). Meanwhile, in another study miR-30c was found to be downregulated in liver fibrosis thus failing to regulate TGF-B2 and SNAIL1 (Roy et al. 2015). The role of miR-30 family members needs to be further tested in HBV induced fibrogenesis models.

MiR-34a HBV infection can elevate TGF-β activity to suppress the expression of microRNA-34a (Yang et al. 2012) and the HBx protein can also directly repress miR-34a expression (Ou et al. 2017). In an HBV induced fibrogenesis model, infected hepatocytes promoted TGF-β downregulation of miR-34a that promoted liver fibrosis by failing to modulate SMAD4 expression and the activation of HSCs (Feili et al. 2018). SMAD4 regulation by miR-34a expression in HSCs can also directly influence ERK1/2 induced activation of HSCs (You et al. 2023).The HBx protein can also promote STAT3 induced repression of miR-34a to reduce its modulation of NF-kB signaling that induces HMGB1 activation to promote EMT and activate HSCs via JNK/ERK induced autophagy (You et al. 2023;Zhang et al. 2021). This could be an additional way in which HBV infection negates the antifibrotic properties of this miRNA.

MiR-101 Another key miRNA, namely, miR-101-3p also plays an important role in liver fibrosis. This miRNA can directly inhibit HBV replication, as well as be downregulated by HBV (Xie et al. 2014; Sheng et al. 2014, Ding et al. 2019). It has also been recorded as downregulated in a non HBV (CCL4) induced fibrosis models (Teng and Ghoshal 2015) and miR-101 is regarded as an important tumor suppressor miRNA in HBV-HCC pathogenesis (Su et al. 2009). In a range of non HBV induced liver fibrogenesis models, miR-101-5p can repress TGF = B1 to attenuate HSC activation (Cuiqiong et al. 2020) and mIR-101 represses signaling in the PI3K/AKT/mTOR pathway to attenuate HSC activation and its expression of fibrotic materials like COL1A1 and α-SMA (Lei et al, 2019). Further investigation in HBV induced fibrosis models of this anti-fibrotic miRNA is warranted to test whether HBV infection induces a pro or antifibrotic effect by dysregulating miR-101 expression.

MiR-122 In HBV infection, the HBx protein can downregulate expression of miR-122 (Khosrav et al. 2024;Liu et al.2011; Yu et al. 2016a, 2016b,2016c) which is regarded as the most prolific liver miRNA (Bandiera et al. 2015). This miRNA is also reported as downregulated in a wide range of liver fibrosis models including biliary cirrhosis and HCV induced fibrosis (Trebicka et al. 2013). In a CCL4 induced fibrosis model, mIR-122 indicated its reduced expression can fail to repress P4HA1 promotion of collagens (Li et al. 2013, 2013b) while in another CCL4 induced model, exosomal miR-122, secreted by mesenchymal stem cells, attenuated TGF-B1 promotion of HSC activation and expression (Lou et al. 2017). Another CCL4 fibrosis model showed that TGF-B downregulated miR-122 would fail to regulate FN1/SRF induced expression of COL1A1 and α-SMA (Zeng et al. 2015). Interestingly, in NAFLD induced fibrosis, TGF-β downregulated miR-122, also fails to repress KLF6 resulting in the upregulation of TGFB1/HSC activation (Tsai et al. 2012; Miele et al. 2008). The question remains, if this miRNA regulates HBV induces fibrogenesis in the same pathways.

MiR-146a A pivotally important miRNA regulating liver fibrogenesis is miR-146a. In an HBV induced fibrogenesis setting, miR-146a was downregulated in HBV cirrhotic livers thus preventing it from regulating IL-6 expression that promotes the activation of HSCs (Yang et al. 2019, 2019b). Various studies, however, show varying levels of miR-146a dysregulation in HBV induced fibrosis with multiple studies indicating it can also be upregulated by the HBxprotein (Appourchaux et al. 2016;Zhang et al. 2018;Gui et al. 2011;Xin et al. 2014). Interestingly, in a CCL4 model inducing HSC activation, hepatocytes can use exosomal export of miR-146a-5p to HSCs where they repress EIF5A2 resulting in the inhibition of HSC activation and EMT (Lang et al.2023). This miRNA also plays a pivotal role in immune mediated response to inflammation and its linkages with liver fibrosis (Yang et al. 2019, 2019b;Fu et al. 2019;Wang et al. 2013). In a number of non HBV etiologies, upregulated mIR-146a in CCL4 induced models and TGF-B treated HSCs, repressed HSC expression of α-SMA and COL1A1 by repressing SMAD4 expression in the TGF-B pathway (Liao et al. 2022,2022b;Zou et al. 2017) warranting further testing of the anti-fibrotic properties of this important miRNA.

MiR-148a: In other examples of key fibrosis miRNA, it was demonstrated that the HBx protein can repress miR-148a expression (Xu et al. 2013) as a result of suppressing p53-mediated activation of this miRNA (Wang et al. 2017). In a HBV model, downregulation of miR-148a-5p resulted in the reduced regulation of NOTCH2 induced fibrosis that was reversed when its expression was upregulated (Zhou et al. 2022). In other studies, downregulated mIR-148a failed to regulate the I_KB kinase-α/NUMB/NOTCH signaling pathway in HSC activation and its synthesis of fibrotic materials (Jung et al. 2016;Ni et al. 2018) while a CCL4 liver fibrosis

model showed that miR-148a could attenuate fibrogenesis by regulating TGF-B induced signaling (Zhu et al. 2019).

MiR-200 The HBx protein can also downregulate other miRNA regulating liver fibrogenesis like miR-200a-3p (Shi et al. 2017). In non HBV etiologies, it has been demonstrated that downregulated miR-150/−200a fails to repress oncogenic mRNA expression of C-MYB/RAC-1 and B-catenin to promote the synthesis of collagens/α-SMA and HSC activation respectively (Venugopal et al. 2009;Sun et al. 2014). In this regard, C-MYB is a sequence-specific DNA binding protein that can regulate the expression of genes involved in cell proliferation and differentiation and is linked to HSC activation in liver injury, whereas the crosstalk between B-catenin and TGF-β signaling can stimulate liver fibrogenesis (Kitada et al. 1997;Lam and Gottardi 2011).

MiR-152/−378 Finally, downregulated miR-152 and miR-378a fail to modulate GLI3, an important transcriptional regulator in the Hedgehog pathway, thus resulting in the promotion of HSC expression and liver fibrosis (Li et al. 2019,2019b;Hyun et al. 2016). Interestingly, downregulated miR-152 in HBV infection has been shown to limit the repression of DNMT1 resulting in increased HBV replication of cccDNA (Huang et al. 2010) again making this a case to be tested that might influence fibrogenesis.

LncRNA-HBV/HBx/miRNA modulation in liver fibrosis

Long non-coding RNAs (lncRNA) are a type of RNA generally defined as transcripts more than 200 nt. that can interact with proteins, DNA, and other RNA like miRNA. LncRNA mostly regulate gene and protein expression in the process of hepatic fibrosis by modulating transcriptional and posttranscriptional processes (He et al. 2020). LncRNA can act as miRNA sponges, as histone or DNMT modifiers, and can directly stimulate or inhibit transcription (He et al. 2020). Various studies have indicated 5550 dysregulated lncRNA in CHB (Chen et al. 2019) and 15328 in HBV-HCC (Susluer et al. 2018) and more than 400 lncRNAs are uniquely enriched in hepatic stellate cells (He et al. 2020). LncRNAs can act as pro or anti-fibrotic agents. lncRNA acts as an anti-fibrotic agent by sponging pro-fibrotic miRNA that can repress HSC activation and the production of myofibroblasts. For example, fibrogenesis is attenuated by lncRNA that sponge miRNA inhibition of HSC inhibitor mRNA like SMAD 7, PTEN, WNT inhibitor-1 (WIF1), LDL receptor protein 6 (LRP6) and Tumor suppressor protein 14/16 (P14/16) (Table 3). Conversely, lncRNA acts as a pro-fibrotic agent by sponging miRNA that target mRNA that promote HSC activation and the expression of fibrotic materials including COL1A1, TGF-1, SMAD4, B-CAT, Rac family small GTPase 1 (RAC1), Kruppel-like factor 6 (KLF6) and Serum response factor (SRF) (Table 3). Specific examples of liver fibrogenesis involving lncRNA-miRNA interaction modulating HSC induced fibrosis are illustrated in ascending miRNA numbers (Table 3; Fig. 3. The interaction of lncRNAs and HBV/HBx dysregulated miRNAs are illustrated by miRNAs in Table 2.

MiR-17-5p In a non HBV etiology, lncRNA-p21 can act as an anti-fibrotic agent because it sponges miR-17-5p to reduce its repression of WIF1 which inhibits WNT/B-CAT expression thus attenuating HSC expression (Yu et al. 2017a, b, c, d). In the absence of lncRNA-p21 sponging this miRNA, miR-17-5p, would exert a pro-fibrotic effect to repress WIF1 thus promoting WNT/B-CAT led fibrogenesis (Yu et al. 2016a, b, c). However, in the presence of HBV infection, the HBx protein can upregulate miR-17-5p (Connolly et al. 2008) thus potentially negating the sponging effect of lncRNA-p21. Other studies also confirm that miR-17-5p can target SMAD7 to act as a pro-fibrotic agent by reducing its inhibition of SMAD2/3 induced fibrogenesis (Yu et al. 2015a, b, c, d) so HBx upregulated miR-17-5p would act as a pro-fibrotic agent in the absence of lncRNa sponging.

MiR-18a In the case of miR-18a, TGF-B1/SMAD3 upregulated lncRNA UCA1 can sponge miR-18a to reduce its regulation of COL1A1/2/3 thus exerting a pro-fibrotic effect (Yang et al. 2022, 2022b). Interestingly, the HBx protein can also downregulate miR-18a which would reduce its regulation of CTGF (Liu et al. 2016) that would further reduce its regulation of HSC activation thus promoting a pro-fibrotic effect that needs to be further tested in an HBV fibrogenesis model that incorporates lncRNA UCAI.**MiR-21**: In another significant interaction, lncRNA MEGA3 sponges TGF-B upregulated miR-21 in liver fibrosis to reduce its modulation of LRP6 thus promoting an anti-fibrotic influence because LRP6 inhibits mTOR signaling(Huang et al. 2019). LRP6 is a co-receptor of critical inhibitors of myofibroblast expression in multiple pathways including the WNT/B-CAT signaling pathway (Yu et al. 2020). The anti-fibrotic response of MEGA3, however, could be limited because this lncRNA is frequently downregulated in liver fibrogenesis while miR-21 is often reported as upregulated (Huang et al. 2019,2019b; Yu et al. 2020). TGF-B upregulated miR-21 is generally regarded as a key pro-fibrotic miRNA that can repress SMAD7 induced inhibition of SMAD2/3 induced HSC activation and their expression of fibrotic materials (Noetel et al. 2012;Zhang et al. 2013;Meng et al. 2007). It should be noted, however, that the HBx protein can upregulate miR-21 which is also reported as upregulated in HBV-HCC (Qiu et al. 2013;Khosravi et al. 2024;Liu et al. 2011)

Table 3 LncRNA modulation of table 2 miRNA

lncRNA	miRNA target	Impact on HSC induced fibrogenesis	REF
ANXA6	miR-9-5p	Promotes fibrosis by sponging miRNA repression of TGF-B1	(Liao et al. 2022a, b)
LncRNA-p21	miR-17-5p	Sponges miRNA to promote WIF1 attenuation of B-CAT induced fibrosis	(Yu et al. 2016a, b, c, 2017a, b, c, d)
UCA1	miR-18a	HBx promoted UCA1 sponges miR-18a to promote SMAD3 led fibrosis	(Yang et al. 2022a, b; Hu et al. 2016)
MEGA3	miR-21	Sponges miRNA modulation of LRP6 to promote HSC activation	(Huang et al. 2019a, b; Yu et al. 2020)
GAS5	miR-21	Attenuates fibrosis by sponging miRNA	(Peng et al. 2018)
NEAT1	miR-22-3p	Promotes fibrosis by sponging miRNA modulation of CYTH3	(Huang et al. 2021a, b)
GAS5	miR-23a	HSC activation attenuated by sponging miRNA attenuation of PTEN	(Dong et al. 2019)
LOC102551149	miR-23a-5p	HSC attenuation by sponging miRNA repression of PTEN	(Dong et al. 2020)
Gm5091	miR-23b	Sponges miRNA repression of COLO1A1 to promote HSC activation	(Zhou et al. 2018a, b, c)
MALAT1	miR-26b	Sponges miRNA modulation of COL1A1/2 to promote fibrosis	(Dai et al. 2019)
Gm5091	miR-27b	Fibrosis/HSC activation attenuated by sponging miRNA that target IL-1β	(Zhou et al. 2018a, b, c)
NEAT1	miR-29b	miRNA targeting ATG9A/ IGFBPrP1 is sponged to promote fibrosis	(Kong et al. 2019a, b)
HOTAIR	miR-29b	DNMT1 of PTEN/p53 induced by sponging miRNA to increase fibrosis	(Yu et al. 2017a, b, c, d)
SNHG7	miR-29b	Attenuates HSC activation by sponging miRNA modulation of DNMT3A	(Xie et al. 2021)
TUG1	miR-29b	Promotes HSC activation by sponging miRNA repress of COL1A1	(Han et al. 2018)
LncRNA-p21	miR-30	Sponges miRNA to reduce repression of KLF11/TGF-B1/TIMP1/COL1A1	(Tu et al. 2017)
CCAT2	miR-34a	Sponges miR-34a that fails to repress CCAT2 induced Smad4	(Gao et al. 2022)
MALAT1	miR-101b	Sponges miRNA modulation of RAC1 to promote fibrosis	(Yu et al. 2015a, b, c, d)
NEAT1	miR-122	miRNA repression of KLF6 sponged thus promoting fibrosis and HSCs	(Yu et al. 2017a, b, c, d)
NEAT1	miR-139-5p	Promotes fibrosis by sponging miRNA regulation of B-CAT/SOX9	(Wang et al. 2021a, b, c)
HOTTIP*	miR-148a	Sponges miRNA modulating TGFBR1/2 promoting HSC activation	(Li et al. 2018a, b)
HOTTIP	miR-150	Sponges miRNA modulating SRF Induced HSC activation	(Zheng et al. 2019)
NEAT1	miR-148a-3p	Promotes fibrosis by sponging miRNA modulation of CYTH3	(Huang et al. 2021a, b)
PVT1	miR-152	Sponges miRNA repression of PTCH1 induced Fibrogenesis	(Zheng et al. 2016)
lncRNA-p21	miR-181b	Sponges miRNA repression of PTEN to attenuate HSC led fibrosis	(Yu et al. 2016a, b, c)
SIRT1	miR-199-5p	ceRNA with miRNA to reduce its repression of COL1A1 depositions	(Lu et al. 2023)
MEGA3	miR-212	Attenuates HSC activation by sponging miRNA repression of SMO	(Yu et al. 2018)
HOTAIR	miR-218	Attenuates fibrogenesis by sponging miRNA modulation of P14/P16	(Fu et al. 2015)
LncRNA-ATB	miR-200a	Sponges miRNA that regulate B-CAT promoting HSC activation	(Fu et al. 2017)
Gpr137b	miR-200a-3p	Sponges miRNA repression of CXCL14 to promote fibrosis	(Liao et al. 2021)
GAS5	miR-222	Sponges miRNA modulation of p27 to attenuate HSC activation	(Yu et al. 2015a, b, c, d)
SNHG7	miR-378a-3p	Sponges miRNA to reduce modulation of DVL2/B-CAT led fibrosis	(Yu et al. 2019)

and that this could potentially counter its sponging lncRNA MEGA3 and induce a pro-fibrotic that remains to be tested.

MIR-23a/b In other important lncRNA/miRNA interaction examples, TGF-B downregulated mIR-23a is further sponged by the lncRNA GAS3 to reduce its repression of PTEN expression thus promoting a dual lncRNA/miRNA anti-fibrotic attenuation of HSC activation (Dong et al. 2019). This miRNA is also reported as downregulated in HBV infection (Li et al. 2020, 2020b,2020c) Similarly, the lncRNA LOC10255114 sponges miR-23a-5p to reduce its modulation of PTEN thus also promoting the attenuation of HSC activation and fibrosis (Dong et al. 2020). Interestingly, the downregulation of miR-23a-5p can also have an anti-fibrotic effect because of its reduced modulation ERK/BMP2/CAV1/CDH1 induced apoptosis (Brea et al. 2018). Conversely, the downregulation of this miRNA can promote a pro-fibrotic effect by failing to modulate fibrotic materials like COL1A1 and α-SMA(Brea et al. 2018). The importance of the miR-23 family in liver fibrogenesis is further emphasized in another lncRNA/miRNA interaction in which lncRNA Gm5091 exerts a pro-fibrotic effect by sponging miR-23b to reduce its repression of COLO1A1 and HSC activation (Zhou et al. 2018, 2018b,2018c). Attenuating miR-23b expression could also induce a pro-fibrotic by reducing its regulation of TGF-β2/GREMLIN1/LOX/and ITGA22/ITGα5 induced HSC activation (Wan et al. 2022) but these pro/anti fibrotic effects need to be further tested.

MiR-26b Other examples of lncRNA/miRNA interaction inducing a pro-fibrotic effect (not illustrated in Table 2) in liver fibrogenesis can occur when upregulated lncRNA MALAT1 sponges miR-26b to reduce its modulation of COL1A1/2 thus promoting fibrogenesis (Dai et al. 2019). This miRNA is also reported as downregulated by HBV also potentially exerting a profibrotic effect (Zhang et al. 2023) illustrating the complexity of this interactome. Interestingly, downregulated miR-26b can also fail to repress targets like CTGF/PDGFR-B that also result in an increase in fibrogenesis (73,228) that needs to be confirmed in an HBV etiology.

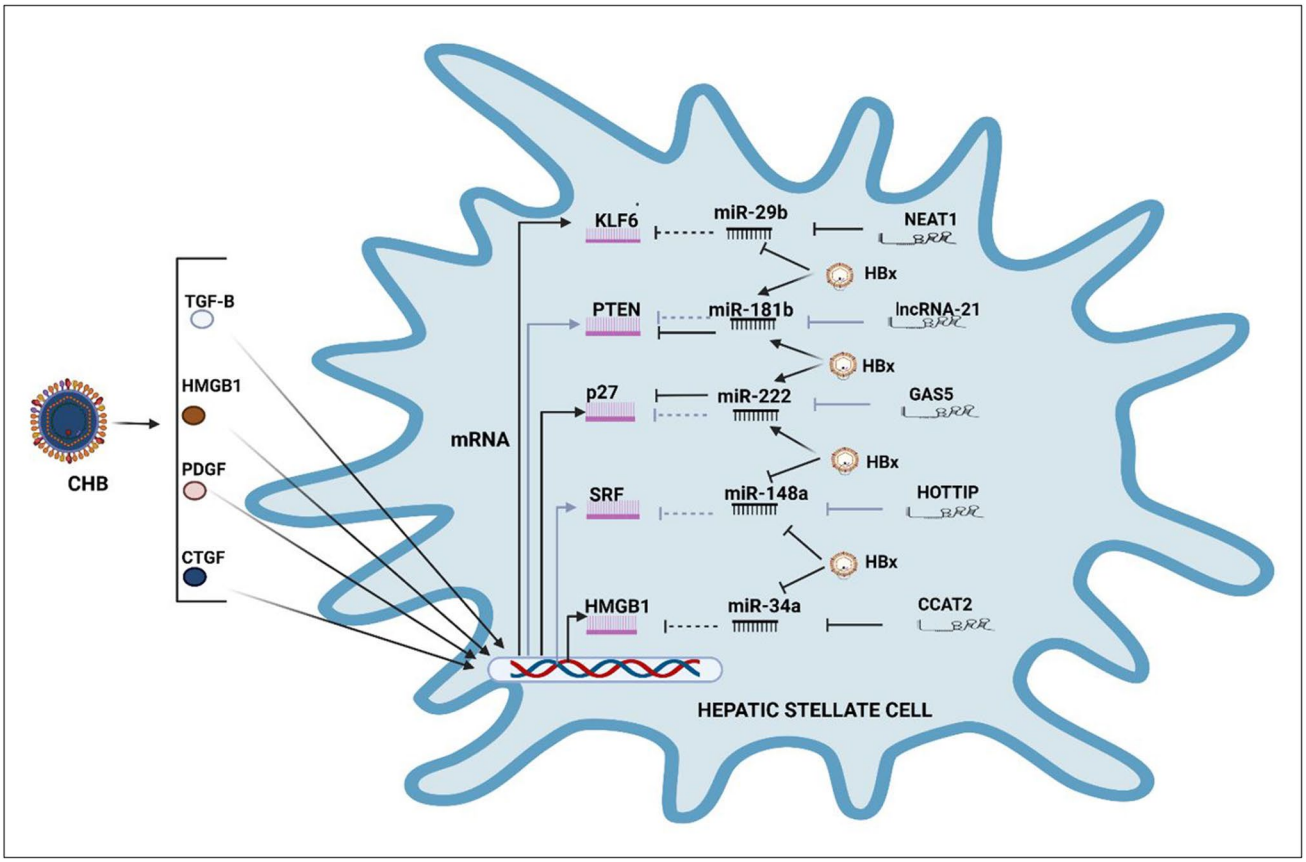


Fig. 3 HBx/miRNA-lncRNA modulation of HSC transcription: CHB activated TGF-B, HMGB1, PDGF and CTGF promote HSC activation and expression of pro and anti-fibrotic mRNA that are regulated by both miRNA and lncRNA expression. The lncRNA NEAT1 sponges miR-29b that can also be repressed by the HBx protein resulting in the reduced regulation of KLF6 thus promoting autophagy induced fibrogenesis. Conversely, lncRNA-p21 plays an anti-fibrotic role by sponging miR-181b to reduce its repression PTEN expression. The HBx protein, however, can upregulate miR-181b expression thus countering the effect of lncRNA-p21 and promoting a pro-fibrotic influence. Similarly, the lncRNA GAS5 sponges miR-222 to reduce its repression of p27 thus acting in an anti-fibrotic role. The HBx protein, however, can upregulate miR-222 thus influencing a pro-fibrotic influence. The lncRNA HOTTIP sponges miR-148a to reduce its repression of the transcription factor SRF thus promoting expression of COL1A1. This repression of SRF is further reduced by HBx downregulation of miR-148a to promote fibrogenesis. HMGB1 induced fibrogenesis in activated HSCs is promoted by both HBx and lncRNA CCAT2 downregulation of miR-34a which directly targets HMGB1

MiR-27b In another lncRNA-miRNA interaction, the lncRNA Gm5091 sponges miR-27b to promote HSC activation by reducing its ability to repress the potent pro-inflammatory cytokine Il-1β (206) which is also reported as being dysregulated in CHB (146) illustrating the potential synergies in the miRNA interactome influencing fibrogenesis. however, Gm5091 is often itself downregulated in liver fibrosis and this could reduce its anti-inflammatory effect by its diminished ability to sponge its target miRNA (206). In summary, miR-27b is often downregulated in fibrosis failing to modulate targets like LOX/TIMP1 thus contributing to HSC activation (110) illustrating that many anti-fibrotic ncRNA in fibrogenesis are often downregulated thus negating this ability. These models need to be tested in HBV fibrogenesis specific etiologies.

MiR-29b One of the most widely cited miRNA in liver fibrogenesis is miR-29b (Wang et al. 2023) which interacts with five lncRNA including NEAT1, HOTAIR, SNHG7, TUG1 and MEGA3 (Table 3). lncRNA NEAT1 sponges miR-29b to promote ATG9a/IGFBPrP1 induced HSC activation thus promoting liver fibrosis (Kong et al. 2019) while HOTAIR sponges miR-29b to promote DNMT silencing of PTEN/p53 expression thus also acting as a pro-fibrotic agent (Yu et al 2017, 2017b,2017c,2017d). This miRNA is also reported as downregulated in CHB (Huang et al. 2014) potentially enhancing the effect of lncRNA sponging. Conversely, the lncRNA SNHG7 attenuates HSC activation by sponging miR-29b to reduce its modulation of DNMT3 silencing of COL1A1, α-SMA (Xie et al. 2021) while TUG1 promotes HSC activation by sponging miR-29b to reduce its modulation

of COL1A1. In a reverse interaction, miR-29b can act as a ceRNA to MEGA3 illustrating the complex lncRNA-miR-29b interactome (Braconi et al. 2011) in which multiple lncRNA/miR-29b interactions can exert both pro or anti-fibrotic effects.

MiR-30 In other examples of lncRNA/miRNA interaction, lncRNA-p21 can modulate both miR-30 family members to influence liver fibrogenesis. In the first instance, TGF-β upregulated lncRNA-p21 exerts a pro-fibrotic effect as a ceRNA to the miR-30 family by preventing it from modulating KLF11 which is an early response transcription factor that promotes TGF-β/SMAD induced fibrosis (Tu et al. 2017;2015). However, the hepatitis B p protein (HBp) has been demonstrated to have the potential to upregulate some members of the miR-30 family (Chen et al. 2021) potentially offsetting the sponging effect of lncRNA-p21 further illustrating the complexity of these ncRNA interactions that need to be further tested in an HBV etiology.

MiR-181b lncRNA-p21 can also sponge miR-181b to reduce its repression of the PTEN tumor suppressor thus exerting an anti-fibrotic influence. However, this lncRNA-p21 is often downregulated in liver fibrosis and this would reduce its anti-fibrotic properties since miR-181b can simultaneously be upregulated by TGF-B1 signaling (Yu et al. 2016a, 2016b,2016c). Similarly, miR-181b can be upregulated by the HBx protein (Xie et al. 2018) which would potentially further reduce the anti-fibrotic effect of lncRNA-p21 but this will need to be specifically further tested.

MiR-34a/−101 In other examples, lncRNA CCAT2 sponges miR-34a to reduce its repression of TGF-B/Smad4 expression thus promoting a pro-fibrotic effect (Gao et al. 2022). The HBx protein can also directly downregulate miR-34a (Ou et al. 2017) which potentially would enhance the pro-fibrotic influence of lncRNA CCAT2. Similarly, upregulated MALAT1 can sponge miR-101b to inhibit its modulation of RAC1 induced HSC activation (Yu et al. 2015, 2015b,2015c,2015d). This miRNA is also reported to be downregulated in HBV infection and a feedback loop indicates it can also regulate HBV replication (Sheng et al. 2014;Ding et al. 2019). RAC1 acts as a GTP binding protein in the RHO family that promotes oxidative stress, which in turn, promotes pro-fibrotic signaling (Choi et al. 2006).

The broader implications of MALAT1 regulation of miR-101b is highlighted because this miRNA also represses the important P13K/AKT/mTOR fibrosis pathway (Lei et al. 2019). These interactions need to be further tested in HBV fibrogenesis models.

MiR-122 Another important pro-fibrotic lncRNA/miRNA interaction occurs when CCL4 upregulated NEAT1 represses miR-122 expression to promote KLF6 induced HSC autophagy promoted fibrogenesis (Yu et al. 2017,2017b,2017c,2017d). MiR-122 is also frequently reported as downregulated by the HBx protein(Khosravi et al. 2024; Liu et al. 2011) illustrating how this miRNA can be dyregulated to influences fibrogenesis. Interestingly, miR-122, which is regarded as the most prolific ncRNA in the liver, can also be downregulated by lncRNA HOTAIR induced DNMT suppression of this miRNA (Cheng et al. 2018).

MiR-148a Illustrating further examples of lncRNA/miRNA interactions based on Table 2, the lncRNA HOTTIP can act as a pro-fibrotic ceRNA to downregulate miR-148a repression of TGFBR1/2 promoted fibrogenesis (Li et al. 2018,2018b). The potential pro-fibrotic effect could be enhanced because the HBx protein can also downregulate miR-148a (Wang et al.2017). Furthermore, it has been demonstrated that miR-148a can modulate NOTCH signaling (Jung et al. 2016) indicating a potentially wider role for HOTTIP in liver fibrosis that needs to be further examined.

MiR-150/−152 In another example, upregulated HOTTIP in activated HSCs can also sponge miR-150 to reduce their modulation of SRF induced fibrogenesis (Zheng et al.2019). SRF is a transcription factor in the nucleus of HSCs that promotes the expression of fibrotic materials and the ablation of SRF leads to reduced expression of COL1A1/2 (Kong et al. 2019,2019b). This miRNA has also been related specifically to HBV induced fibrosis (Venugopal et al. 2009) but its role in this etiology needs further testing. In another example, miR-152 can be sponged by the lncRNA PVT1 resulting in the reduced repression of the PTCH1 inhibitor in the Hedgehog SMO pathway thus reducing HSC activation (Zheng et al. 2016). The PTCH1 inhibitor inactivates Hedgehog (Hh) induced signaling and therefore repressing PTCH1 promotes Hedgehog SMO induced promotion of fibrogenesis (Yang et al. 2022,2022b). This miRNA is also reported to be downregulated in HBV which reduces its ability to modulate HBV replication (Huang et al. 2010).

MiR-200a TGF-β upregulated lncRNA-ATB can sponge miR-200a to reduce its repression of B-CATENIN which can directly promote fibrogenesis by promoting the expression of ECM materials (Fu et al. 2017;Nishikawa et al. 2018). In addition lncRNA Gpr137b can also sponge miR-200a-3p to reduce its repression of CXCL14 to promote fibrosis (Liao et al. 2021). This miRNA is also reported to be downregulated by the HBx protein (Shi et al. 2017) which could indicate joint repression of miR-200a-3p by both lncRNAs and the HBx protein, however these interactions should be further tested.

MiR-222 The lncRNA GAS5 can attenuate HSC activation by acting as a ceRNA with miR-222 to reduce its repression

of p27 which is a critical transcriptional regulator of cell growth (Razavipour et al. 2020). However, the HBx protein could potentially counter this sponging effect because it can upregulate miR–222 (Sartorius et al. 2020;Bandopadhyay et al. 2014;Sokhanvar et al. 2021) but this remains to be tested in an HBV fibrogenesis model. The anti-fibrotic potential of GAS5 in liver fibrosis is further illustrated by the fact that upregulated miR-222 can potentially promote the expression of multiple HSC materials by targeting important HSC cell cycle regulators like CDKN1B (Ogawa et al. 2012;Brea et al. 2018;Wan et al.2022;Yang et al. 2020a, 2020b, 2020c).

MiR-378 Finally, the upregulated lncRNA SNHG7 can downregulate miR-378-5p thus reducing its modulation of DVL2/B-CATENIN induced fibrosis in which DVL2 plays an important role in facilitating signal transduction in the WNT/B-CATENIN pathway (Yu et al. 2019). This miRNA has also been found to be downregulated in HBV-HCC cases (Zou et al. 2020) but its role in HBV induced fibrosis is unclear.

CircRNA-miRNA modulation in liver fibrosis

The study of circular RNAs (circRNAs) has become one of the more recent areas of focus in the field of RNA inhibition that illustrates its complex interactome with other ncRNA in liver fibrogenesis. One study identified a total of 10,389 circRNA that were detected by microarray screening in fibrotic liver tissue. Compared with the normal group, there were 69 circRNAs that were differentially expressed in fibrotic liver tissue of which 14 were upregulated and 55 were downregulated (Zhou et al. 2019). CircRNAs, described as highly stable molecules in the cytosol, modulate liver fibrosis by regulating the activity of other ncRNA targets like miRNA or interacting with RNA-binding proteins (Kristensen et al. 2022). In liver fibrosis models, circRNA can modulate miRNA expression by acting as a miRNA sponge (Zhu et al. 2021), they can sponge and recruit proteins, and are also able to influence transcription in the nucleus (Nokkeaw et al. 2023). The widespread function of circRNA/miRNA interaction in liver fibrosis modulates signaling in multiple pathways including the TGF-β, JAK/STAT, P13K/AKT, WNT/B-CAT, Notch and Hedgehog signaling pathways (Nokkeaw et al. 2023). In these pathways, 19 circRNA/miRNA interactions are illustrated (Table 4; Fig. 4) that demonstrate that circRNA can act as miRNA sponges to influence both a pro or anti-fibrotic effect. Pro-fibrotic circRNA typically sponge miRNAs that modulates TLR4 signaling, SMAD2/3, collagen, and a range of transcription factors. Conversely, anti-fibrotic circRNA sponge miRNA that target fibrosis inhibitors and tumor suppressors like SMAD7 or PTEN (Nokkeaw et al. 2023; Chien et al. 2020). Selected miRNA from Table 2 are used to illustrate ciRC/miRNA regulation of fibrogenesis.

MiR-17-5p The first example of circRNA/miRNA interaction in the TGF-β pathway, illustrates that circMTO1 can attenuate fibrogenesis by sponging miR-17-5p to reduce its repression of SMAD7 inhibition of SMAD2/3 pathway

Table 4 circ-RNA modulation of miRNA in liver fibrosis

circRNA	miRNA	Impact on HSC induced fibrogenesis	REF
circ_0071410	miR-9-5p	Promotes HSC activation by sponging miRNA	(Chen et al. 2017a, b)
circ_MTO1	miR-17-5p	Attenuates fibrosis by sponging miRNA that repress SMAD7	(Wang et al. 2019)
circ-CDK13	miR-17-5p	Attenuates fibrosis by regulating miRNA repression of KAT2	(Ma et al. 2023)
circ_FBXW4	miR-18b-3p	HSC activation reduced when circRNA sponges miRNA modulation of FBXW7	(Chen et al. 2020a, b)
circ_34116	miR-22-3p	Might attenuate activation of HSCs by sponging miRNA repression of BMP7	(Zhou et al. 2018a, b, c)
circ_PSD3	miR-92-3p	Attenuates fibrosis by sponging miRNA modulation of SMAD7	(Bu et al. 2021)
circ_MTM1	miR-122	Promotes fibrosis by sponging miRNA attenuation of IL7R	(Li et al. 2022a, b)
circ_P14KB	miR-122	Promotes fibrosis by sponging miRNA to reduce repression of lipid depositions	(Liu et al. 2023a, b, c)
ciec_DIDO1	mIR-141-3p	Attenuates HSC activation by sponging miRNA repression of PTEN	(Ma et al. 2022)
circ_TUBD1	miR-146a-5p	Promotes fibrosis by sponging miRNA repression of TLR4 signaling	(Niu et al. 2020)
circ_RSF1	miR-146a-5p	Promotes fibrosis by sponging miRNA repression of RAC1	(Chen et al. 2020a, b)
circ_Ube2k	miR-149-5p	Promotes fibrogenesis by sponging miRNA modulation of TGF-B2	(Zhu et al. 2021)
circ_0067835	miR-155	Attenuates fibrosis by sponging miRNA repression of FOX03	(Zhu et al. 2018)
circ_MTO1	miR-181b	Attenuates fibrosis by reduces miRNA repression of PTEN	(Jin et al. 2020a, b)
circ_0004018	miR-183-5p	Promotes HSC activation by regulating miRNA repression of COL1A1	(Li et al. 2022a, b)
circ_CHD2	miR-200b-3p	Promotes fibrosis by sponging miRNA repression of Il-6/STAT3	(Hu et al. 2022; Xiang et al. 2018).
curc_TUBD1	miR-203a-3p	Promotes fibrosis by sponging miRNA modulation of SMAD3	(Niu et al. 2022)
circ_608	miR-222	Attenuates fibrosis by sponging miR-222 repression of PINK1	(Xu et al. 2022)
circ_0070963	miR-223-3p	Attenuates fibrosis by sponging miRNA repression of LEMD3	(Ji et al. 2020)
circ- PWWP2A	mIR-203/–223	Promotes fibrosis by sponging miRNA repression of Fstl1 and TLR4	(Liu et al. 2019)
circ_0004018	miR-660-3p	Suppresses fibrogenesis by modulating miRNA repression of TEP1	(Li et al. 2020a, b, c)
circ_CREBB	miR-1291	Attenuates fibrosis by sponging miRNA modulation of LEFTY2/TGF-B/smad3	(Yang et al. 2020a, b, c, 2021)

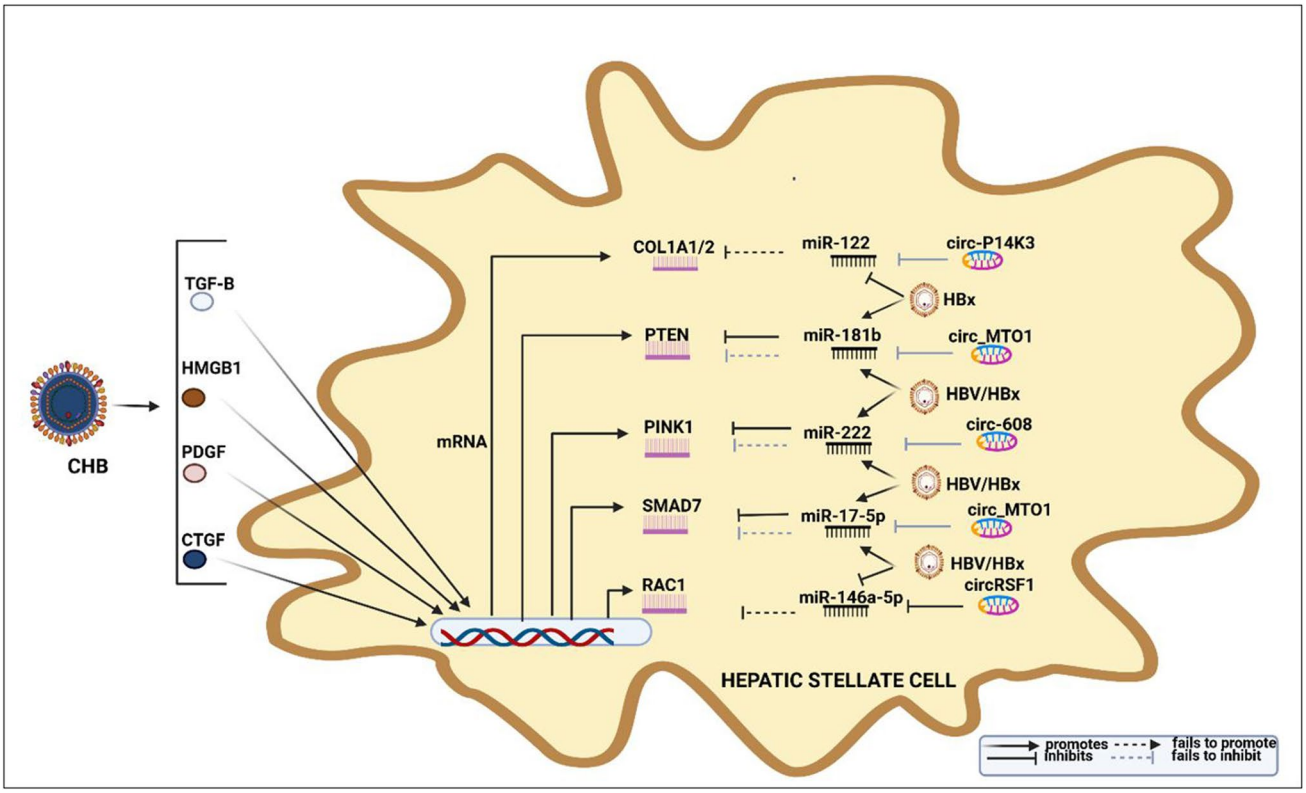


Fig. 4 HBx circRNA-miRNA modulation of fibrogenesis: CHB activated TGF-B, HMGB1, PDGF and CTGF promote HSC activation and expression of pro and anti-fibrotic mRNA that are regulated by both miRNA and lncRNA expression. HBx and circ-P14K3 both repress miR-122 expression thus reducing miR-122 modulation of COL1A1 expression to promote a pro-fibrotic influence. Conversely, circMTO1 acts as an anti-fibrotic agent by repressing miR-181b to reduce its attenuation of tumor suppressor PTEN mRNA. Similarly, circ608 acts as an anti-fibrotic agent by sponging miR-222 to reduce its repression of PINK1 resulting in mitophagy based restoration of homeostasis. The circMTO1 also plays an anti-fibrotic role by sponging miR-17-5p that reduces its modulation of the SMAD7 inhibitor. Conversely, the circRSF1 can repress miR-146a-5p that can also be downregulated by HBV/HBx thus reducing its repression of RAC1 to further promote liver fibrogenesis

expression (Wang et al. 2019). SMAD7 is an important inhibitor that attenuates myofibroblast activation and the synthesis of ECM materials like collagens and α-SMA and SMAD7 also represses TGF-β activation of the SMAD2/3 fibrogenesis pathway (Humeres et al. 2022). Interestingly, miR-17-5p can be upregulated by the HBx protein (Connolly et al. 2008) and is also often upregulated in liver fibrosis thereby initiating a pro-fibrotic effect by targeting SMAD7 (Yu et al. 2015a, b, c, d). Furthermore, circMTO1 can be downregulated in liver fibrosis, suggesting its modulation of miR-17-5p would be reduced thus limiting its anti-fibrotic properties (Humeres et al. 2022). From the previous section, it was demonstrated that lncRNA-p21 can also sponge miR-17-5p thus illustrating the complexity of the ncRNA interactome that modulates fibrogenesis in an HBV driven etiology (Yu et al. 2016a, b, c).

MiR-181b In another example, circMTO1 can sponge miR-181b to attenuate fibrogenesis by reducing its repression of the PTEN tumor suppressor (Jin et al. 2020a, b) but mIR-181b can be upregulated by the HBx protein (Xie et al. 2018) to potentially counter circMTO1 repression. Upregulated miR-181b is regarded as a pro-fibrotic miRNA in liver fibrosis that also targets TIMP3/p27 to reduce cell cycle controls and promote ECM remodeling (Wang et al. 2010, 2012). Again illustrating the ncRNA interactome, lncRNA-p21 also targets miR-181b to promote an anti-fibrotic effect by reducing miR-181b repression of the PTEN tumor suppressor (Yu et al. 2016a, b, c).

MiR-122 The tumor suppressor miR-122, is often prevented from playing this role by being downregulated in fibrotic livers (Tsai et al. 2012; Li et al. 2013a, b), as well as by the HBx protein (Khosravi et al. 2024; Liu et al. 2011). Upregulated circMTM1 in fibrosis, can further sponge mIR-122 to reduce its modulation of IL7R induced signaling, thus promoting the transcription of fibrotic materials (Li et al. 2022a, b). In this interactome, miR-122 can also be sponged by the lncRNA NEAT1 to reduce its modulation of KLF6 to promote fibrogenesis (Yu et al. 2017a, b, c, d). Interestingly,

a meta study contradicts these observations by showing that miR-122 is upregulated in every form of liver fibrosis and, in particular, NASH/NAFLD induced liver disease (Liu et al. 2018a, b). Other studies in different fibrosis etiology settings, like HBV/HCV (Trebicka et al. 2013) induced disease, contradict this finding by demonstrating that miR-122 is often downregulated, however, differential expression of this miRNA has been observed in circulating vs. tissue based miRNA (Sartorius et al. 2019). Interestingly, miR-122 is also targeted by circRNA-P14KB in NAFLD to downregulate its expression and promote lipid depositions (Liu et al. 2023a, b, c) that are a feature of fibrotic livers (Jia et al. 2023). Further illustrating the complexity of the miR-122 interactome, circ1639 modulates miR-122 expression in AFLD (Lu et al. 2019) and circRNA-002581 modulates this miRNA in NASH (Jin et al. 2020a, b). The central role of miR-122 demands further investigation in a range of HBV induced fibrogenesis models.

MiR-200b In liver cirrhosis, upregulated circCHD2 can act as a pro-fibrotic agent by sponging miR-200b-3p to repress its modulation of HLF/IL-6/STAT3 signaling thus inducing activation of HSC expression of COL1A1 and α-SMA (Hu et al. 2022; Xiang et al. 2018). Interestingly, miR-200-3p can also be sponged by lncRNA-ATB to induce a pro-fibrotic effect further illustrating ncRNA interaction in fibrogenesis (Fu et al. 2017) and miR-200a-3p can be downregulated by the HBx protein (Shi et al. 2017). In general, the miR-200 family plays a major modulating role in the B-CATENIN fibrogenesis pathway (Sun et al. 2014), as well as in the miR-200-dependent SIRT1/MAPK signaling pathway in liver fibrosis (Wang et al. 2020). Further testing in an HBV etiology is suggested.

MiR-222: Another important circRNA/miRNA interaction in NASH related liver fibrosis occurs when downregulated circ608 fails to sponge miR-222 thus repressing PINK1 induced mitophagy based attenuation of fibrosis (Xu et al. 2022). This miRNA can also be upregulated by the HBx protein (Sartorius et al. 2020; Bandopadhyay et al. 2014; Sokhanvar et al. 2021) possibly further augmenting a pro-fibrotic effect that should be further tested. Mitophagy is an anti-fibrotic process that involves the clearance of dysfunctional materials and there is growing evidence that mitochondrial dysfunction contributes to the development and progression of fibrosis (Li et al. 2020, 2020b,2020c). Interestingly, PINK1 participates in the regulation of multiple biological functions, including hepatic cell growth and apoptosis in ACLF via the mTORC2/AKT signaling pathway (Yin et al. 2022). Furthermore, upregulated miR-222 in fibrotic livers is purported to promote HSC cell proliferation by silencing cell cycle controls like CDKN1B to promote transcription of COL1A1, α-SMA and MMP-2 (Ogawa et al. 2012). Illustrating the ncRNA interactome, miR-222 is also sponged by lncRNA like GAS5 in activated HSCs which influences its ability to repress p27 and its role in HSC activation (Yu et al. 2015,2015b,2015c,2015d). The complexity of miR-222 interaction with other ncRNA is also illustrated in the PDGF induced RAS/RAF pathway, in which the lncRNA GAS5 can promote fibrogenesis by sponging miR-222 to reduce its repression of ERK1/2 expression (Ying et al. 2017).

ncRNA modulation and the mainstream epigenetic machinery

The mainstream epigenetic machinery, including DNA methylation (DNMT), histone acetylases (HATs), histone de-acetylases (HDACs), histone methyl transferases (HMTs) and histone de-methylation transferases (HDMTs) modulate gene expression without changes to DNA sequence (Nakamura et al. 2017;Wang et al. 2016). This section illustrates the interaction between ncRNA and the epigenetic machinery in liver fibrosis largely illustrating this by using miRNA/lncRNA/circRNA previously discussed but specifically includes the role of HBV infection in each illustration (Fig. 5).

DNMT and ncRNA interaction DNMTs incorporate the addition of a methyl group by the enzymes DNMT1/2/3A/3B to silence target gene promoters or enhance target gene expression by silencing transcription regulators (Sartorius et al. 2021). The expression of multiple ncRNAs can be altered in fibrogenesis because of DNA methylation of the CpG island promoters and, in turn, the DNMT machinery can be modulated by ncRNA to promote a pro- or anti-fibrotic outcome depending on which transcription factor is silenced (Yang et al. 2015). The extent of ncRNA interaction with the epigenetic machinery is illustrated by a study that demonstrates that the expression of MECP2, a methyl binding CpG protein in HSCs, can result in the altered expression of 284 miRNAs and 244 lncRNAs (Moran-Salvador et al. 2019).

The key miR-29 fibrotic miRNA family interacts directly with the epigenetic machinery to influence downstream expression in activated HSCs but as previously stated, miR-29b is often downregulated in HSCs by NF-kB signaling which dilutes its modulatory effect (Li et al. 2014a, b; Roderburg et al. 2011; Zheng et al. 2014). Moreover, miR-29b is recorded as downregulated in CCL4 induced fibrosis, as well as increasingly downregulated as HBV infection progresses to CHB (Roderburg et al. 2011; Wang et al. 2015; Huang et al. 2014a, b). This downregulation, in turn could promote a pro-fibrotic effect because it would reduce miR-29b repression of DNMT3a resulting in the silencing

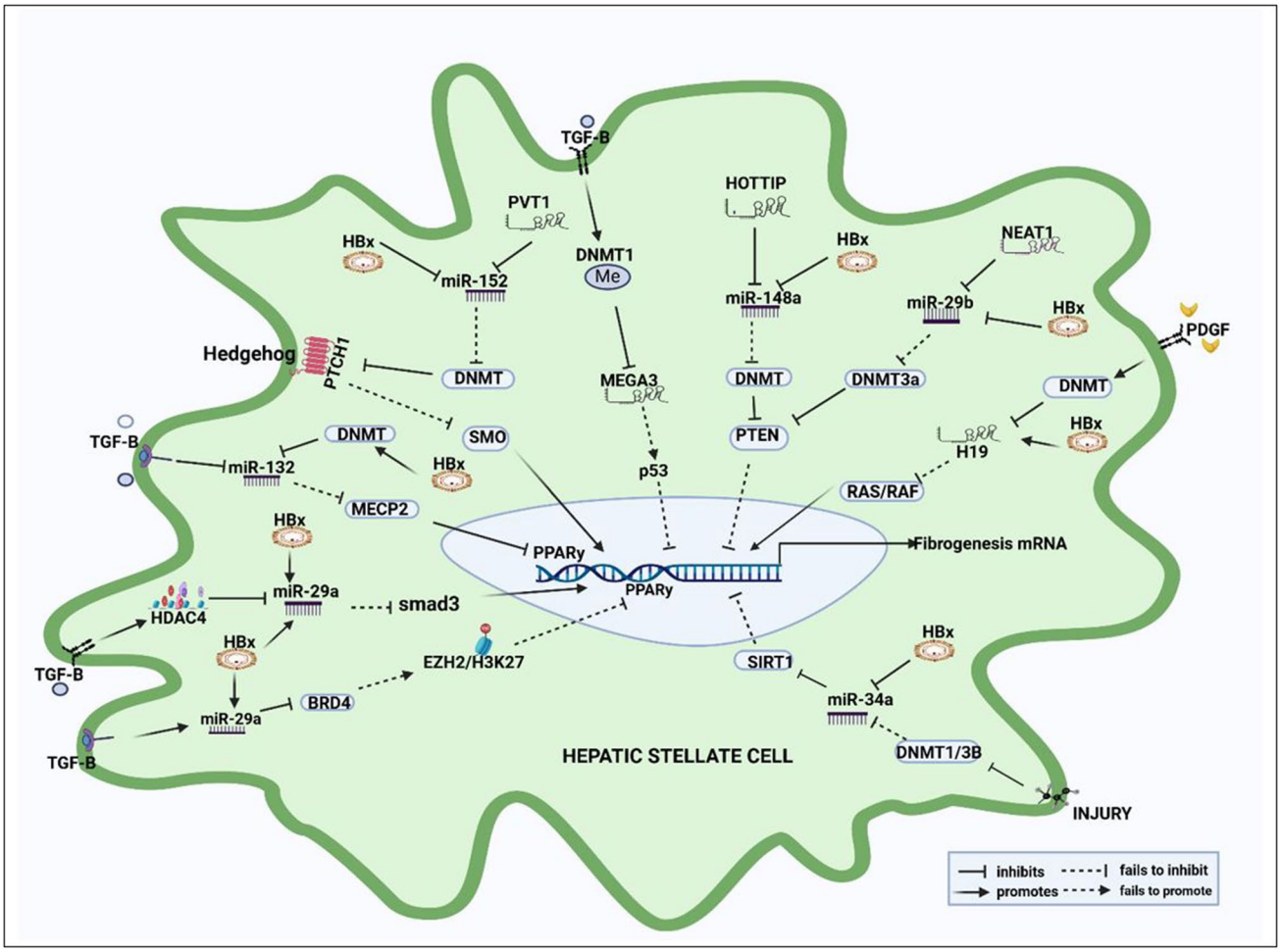


Fig. 5 ncRNA interaction mainstream epigenetic machinery in liver fibrosis: In clockwise sequence from the top RHS, lncRNA NEAT1 and HBx can sponge miR-29b to reduce its modulation of DNMT3a that then silences PTEN inhibition of fibrogenesis. PDGF expression can promote the DNMT of the lncRNA H19 that fails to regulate RAS/RAF signaling to promote fibrotic expression. Injury can promote miR-34a expression while HBx represses it. Injury can promote the downregulation of DNMT1/B resulting in upregulated miR-34a that represses SIRT1 which fails to inhibit fibrogenesis (e.g. COL1A1 expression). TGF-β signaling and HBx can promote miR-29a expression to repress BRD4 induction of H3K27 induced silencing of PPARγ thus inducing an anti-fibrotic effect. TGF-β signaling can also activate HDAC4 silencing of miR-29a which reduces its repression of SMAD3 induced HSC activation and expression to promote fibrogenesis. HBx can upregulate miR-29a to reduce this effect. TGF-B signaling and HBx (via inducing DNMT) can downregulate miR-132 which promotes MECP2 silencing of PPARy thus promoting fibrogenesis. TGF-B, HBx and PVT1 can all repress miR-152 which prevents it from modulating the DNMT of PTCH1 which fails to regulate pro-fibrogenic SMO induced fibrogenesis expression in the Hedgehog (Hh) pathway. TGF-B induced DNMT represses the lncRNA MEGA3 inhibition of p53/caspase thus an anti-fibrotic effect and LncRNA HOTTIP and HBx can sponge miR-148a that fails to repress DNMT of PTEN thus exerting a pro-fibrotic effect by reducing its inhibition in pathways like MEK/ERK

of PTEN inhibited liver fibrogenesis (Yu et al. 2017a, b, c, d). In addition, miR-29b can be sponged by the lncRNA NEAT1 and HOTAIR (Kong et al. 2019a, b; Yu et al. 2017a, b, c, d) and SNHG7 (Xie et al. 2021) thus potentially further reducing its ability to regulate DNMT3a silencing of PTEN augmenting a pro-fibrotic influence that remains to be tested. In another example of ncRNA involving the miR-29 family with the DNMT machinery in liver fibrogenesis, downregulated miR-29a fails to modulate DNMT1/2 which results in the silencing of lncRNA MEGA3 (Braconi et al. 2011), however, miR-29a can be upregulated by the HBx protein (Kong et al, 2011) to potentially reverse this effect. In another ncRNA anti-fibrotic interaction with MEGA3, TGF-B promoted DNMT1 silences MEGA3 to negate its promotion of p53 induced apoptosis thus exerting a pro-fibrotic influence in activated HSCs (He et al. 2014). This ncRNA interactome with the mainstream epigenetic machinery needs to be further tested in an HBV etiology. In potential examples involving the lncRNA MEGA3 which need to be tested, TGF-β upregulation of DNMT1 to repress

lncRNA MEG3 expression (He et al. 2014) could influence its failure to sponge miR-21 which could induce an anti-fibrotic effect by reducing the expression of LRP6(Huang et al. 2019a, b; Yu et al. 2020) and downregulated MEG3 could also fail to regulate miR-212 which would increase its repression of SMO induced fibrosis (Yu et al. 2018). In addition, both miR-21 and miR-212 can be upregulated in HBV infection(Qiu et al. 2013; Zhang et al. 2019) possibly further exercising an HBV induced anti-fibrotic effect that needs to be further examined in HBV fibrogenesis models. In other examples of lncRNA interaction with the DNMT machinery in liver fibrogenesis, PDGF signaling can promote DNMT silencing of lncRNA H19 that then fails to regulate RAS/RAF/MEK/ERK signaling promoting HSC activation and fibrosis (Yang et al. 2018). Interestingly, the HBx protein can upregulate lncRNA-H19 (Wang et al. 2021) which would then attenuate DNMT silencing possibly also fibrogenesis. In other studies involving ncRNA interaction with the epigenetic machinery, the lncRNA HOTTIP can sponge miR-148a which reduces its repression of DNMT silencing of PTEN to promote a pro-fibrotic effect (Li et al. 2018,2018b;Zheng et al. 2019). The HBx protein can also downregulate miR-148a expression (Xu et al. 2013) which could potentially further enhance the sponging effect of HOTTIP to reduce the regulation of DNMT silencing of tumor suppressors like PTEN (Zheng et al. 2014) and promote a pro-fibrotic effect. Sal B upregulated miR-152 can repress DNMT1 and its silencing of PTCH1, resulting in the inhibition of SMO induced fibrosis because PTCH1 binds to SMO (Huang et al. 2010), however, miR-152 has been reported as downregulated by HBV infection (Huang et al. 2010) and that would potentially reduce its ability to downregulate DNMT1 silencing of SMO. Upregulated lncRNA PVT1 can also sponge miR-152 to promote DNMT silencing of PTCH1 to promote SMO induced fibrosis in the Hedgehog pathway suggesting that both the HBx protein and lncRNA PVT1 can also promote a pro-fibrotic influence because they can both repress miR-152 (Zheng et al. 2016). The HBx protein can induce DNMT to repress miR-132 expression (Wei et al. 2013;Khosravi et al. 2024) and activated HSCs can also repress miR-132 which then fails to regulate the transcription repressor MECP2 which is attracted to the 5' end of the PPARy transcription factor to induce H3K9 methylation of PPARy and suspend its recruitment of the transcription repressor HP1α thus promoting a pro-fibrotic effect (Mann et al. 2010). Interestingly, the WNT pathway also activates HSCs by expressing MECP2 to repress PPARy expression (Mann et al. 2010;Kweon et al. 2016). Finally, DNMT-lncRNA interaction is illustrated by DNMT1 regulation of the lncRNA H19/ERK signaling to promote HSC activation and liver fibrogenesis which could also be influenced by HBx upregulation of lncRNA-H19 (Wang et al. 2021,2021b,2021c). In other ncRNA interactions with the DNMT machinery, the lncRNA ANRIL is regulated by DNMT3a during HSC activation to promote the expression of α-SMA, Col1A1 (Yang et al. 2018;Giovarelli et al. 2014).

Histone modifications and RNAi Histone modifications include histone acetyltransferases (HATs), histone deacetyltransferases (HDACs), histone methyl transferases (HMTs) and histone methyl de-transferases (HDMTs). HATs and HDACs generally refer to the promotion or repression of transcriptional activity respectively by the addition or removal of acetyl groups. Histone methyl transferases (HMTs) can both repress or stimulate transcription as a result of the addition of methyl groups to specific histone sites and histone methyl de-transferases (HDMTs) remove methyl groups from histone sites to regulate transcription (Moran-Salvador and Mann 2017; Ganguly and Chakrabarti 2021). For example, HSCs activated by injury can promote the H3K4 (MLL1) HMT to activate WNT/B-CAT promotion of liver fibrosis, and alcohol induced liver injury promotes H3K4 activation of elastin in activated HSCs (Qiang et al. 2016). Fibrogenesis can be induced by HSC transcription factors recruiting histone modifiers to enhance transcription of pro-fibrotic expression. For example, activated HSCs promote SMAD 3 expression that recruits pro-MRTF-A to HSCs in order to activate H3K4 promotion of pro-fibrotic promoters like ASH2/WDR5/SET1 and TGF-β induced activation of HSCs and fibrogenesis (Tian et al. 2016). Various studies indicate that HDACs play a bigger role in HSC activation and liver fibrogenesis than HATs and both of these histone modifications interact with ncRNA to both repress and activate liver fibrogenesis (Barcena-Varela et al. 2019). For example, in one ncRNA-epigenetic interaction, CCL4 and alcohol liver injury promotes the upregulation of miR-34a by downregulating DNMT1/3B. Upregulated miR-34a can then repress SIRT1 expression thus preventing it from inhibiting HSC activation. and inducing a pro-fibrotic effect (Yang et al. 2015;Meng et al. 2012). The HBx protein, however, can directly repress miR-34a (Ou et al. 2017) thus potentially countering this effect but this needs to be further investigated in HBV induced fibrosis. The miR-29 family again illustrates its multiple modulatory roles in fibrogenesis The inhibition of HDAC2 in the fibrotic microenvironment, for instance, promotes the expression of the anti-fibrotic miR-29 family that can repress HSC cell proliferation and their expression of collagens and α-SMA (Mannaerts et al. 2013). However, when miR-29a is repressed by TGF-β upregulated HDAC4 expression, this anti-fibrotic miRNA can lose its ability to modulate TGF-β/SMAD3 promoted fibrosis and, conversely, if HDAC4 inhibition is reversed, then the miR-29a role as an anti-fibrotic agent can be restored (Huang et al. 2015,2015b). Again, it should be noted that miR-29a can also be upregulated by the HBx protein (Kong et al. 2011) and this would potentially

increase its repression of SMAD3 thus attenuating fibrogenesis, however, this effect needs to be tested in a HBV fibrogenesis model. EZH2 is a histone methyltransferase (HMT) that inhibits transcription via the tri-methylation of histone 3 lysine 27 (H3K27). EZH2 can also recruit HDAC1/2 and DNMTs to further inhibit transcription (Lue et al. 2016) and TGF-β activated HSCs can express EZH2 induced H3K27 to repress PPARy to promote fibrogenesis (Martin-Mateos et al. 2019). However, TGF-B/HBx upregulated miR-29a can play an anti-fibrotic role by repressing BRD4 activation of C-MYC induced EZH2/H3K27 silencing of PPARy to attenuate HSC activation and fibrogenesis (Huang et al. 2019,2019b). These fibrogenesis models need to be further investigated in an HBV etiology.

Diagnostic and therapeutic management options

Despite extensive literature that explains the biology and roles of miRNA, lncRNA and circRNA in hepatitis B induced fibrosis/cirrhosis no clinical trials have progressed beyond phase 2 and all of these involve the deployment of siRNA to target HBV replication (NCT04225715, NCT04847440, NCT04820686 and NCT06154278) and only NCT04225715 is specifically designed to act as an anti-fibrotic agent. All of these clinical trials test these siRNA based drugs alongside other anti-viral and anti-inflammatory agents. No lncRNA or circRNA based clinical trials have been developed for either targeting HBV replication and/or attenuating HBV induced fibrosis cirrhosis. The use of siRNA instead of miRNA is because siRNA can only target specific mRNA nucleotide sequences thus negating a primary negative aspect of miRNA based therapeutics, namely, unintended consequences because miRNA can target multiple gene targets (Lam et al. 2015). This is illustrated by a clinical trial involving miR-34a (NCT01829971) that was abandoned after phase 1 because of unintended consequences (Kim and Croce 2023). The HBx protein can promote STAT3 signaling to repress miR-34a modulation of NF-KB thus inducing HMGB1 activation and HSC activation (Zhang et al. 2021). This miRNA has been proposed as a promising candidate to manage CHB induced fibrosis because it regulates the TGF-B/SMAD3 pathway in HSCs (Feili et al. 2018) suggesting that it can be refined and deployed as an anti-fibrotic siRNA based drug to treat HBV related fibrosis. Downregulated miRNAs typically fail to modulate drivers of fibrogenesis while upregulated miRNAs repress fibrogenesis inhibitors. Anti-fibrotic miRNAs that are downregulated in CHB induced fibrosis can potentially be replaced by siRNA-based drugs that target key drivers of HSC activation like TGF-B, CTGF, HMGB1 and PDGF. Typically, downregulated miRNAs in HBV infection like miR-19b/−23b/−29b/101b/−122 fail to modulate TGF-B induced HSC activation (Tadokoro et al. 2021) and these key anti-fibrotic miRNA can be developed as targeted siRNA based drugs to regulate HSC activation. Similarly, downregulated miR-18a/−23b (Liu et al. 2016; Wan et al. 2022) can be upregulated as siRNA to modulate CTGF expression while miR-29a can be upregulated to repress IGF/PDGF promotion of HSC activation and downstream fibrogenesis specifically induced by chronic HBV infection (Noetel et al. 2012; Huang et al. 2014a, b; Kwiecinski et al. 2012). Conversely, in HBV induced fibrogenesis, upregulated miRNA can typically repress inhibitors of fibrogenesis like SMAD7, PTEN, p27 and PPARy (see Table 1). The SMAD7 inhibitor is typically repressed by HBx upregulated miR-17-5p (Connolly et al. 2008; Yu et al. 2015a, b, c, d, 2016a, b, c), miR-21-5p (Noetel et al. 2012; Zhang et al. 2013; Meng et al. 2007; Wu et al. 2019) and miR-33a (You et al. 2023; Huang et al. 2015a, b; Li et al. 2014a, b) in HBV induced HSC activation. In terms of developing therapeutic options for these upregulated miRNAs, the use of competing RNA (ceRNA) or a novel class of chemically engineered oligonucleotides called antagomirs can act as miRNA inhibitors. For example, it has been demonstrated that HBV induced TGF-B induced expression of HSC activation and α-SMA and COL1A1 expression was attenuated by miR-21-5p inhibitors (Li et al. 2021). Similarly, antagomirs for HBx upregulated miR-181b can reduce its repression of the p27 inhibitor of HSC and MMP activation (Wang et al. 2010, 2012). MiRNAs as diagnostic agents for HBV induced liver fibrosis/cirrhosis have identified strong candidate miRNA that include miR-21-5p, miR-125a-5p, miR-27a and miR-181b. miR-21-5p expression is strongly positively correlated with hepatic fibrosis and causes HBV-induced hepatic fibrosis via TGF-β1 signaling (Wu et al. 2019) while miR-125a-5p levels are significantly increased in patients with cirrhosis and could be a novel biomarker for HBV related liver injury (Zheng et al. 2015a, b). miR-27a is elevated in HBV-associated cirrhosis and is a predictor of HSC activation, differentiation, and proliferation (Zhang et al. 2018). miR-181b activates HSCs through the PTEN/protein kinase B (Akt) pathway and has been identified as an independent predictor of disease progression in HBV (Yu et al. 2015a, b, c, d).

The role of lncRNAs and circRNAs as therapeutic agents for HBV induced liver fibrosis has yet to translate into any registered clinical trials. In this paper, we largely investigate their interaction with miRNAs to illustrate their regulatory role in liver fibrogenesis. In a majority of the examples offered in this paper, lncRNAs and circRNAs acted as miRNA sponges (Tables 2 and 3) that could possibly be more easily created by synthetic siRNAs or antagomirs. Much interest, however, has been invested in the regulatory role of lncRNA interaction with the mainstream epigenetic machinery to silence gene expression (Peng et al. 2021) with

lncRNAs like HOTAIR and HOTTIP listed as direct epigenetic regulators (Smekalova et al. 2016) and MEGA3 that can directly influence HSC activation and ECM accumulation (Teng and Ghoshal 2015). In line with this paper, a majority of cases of circRNA regulation of liver fibrogenesis include a co-miRNA sponging relationship but circRNAs like 0004018/0003570 have been identified as novel biomarkers for hepatitis B associated carcinoma (Kang et al. 2023). So, what are the reasons this promising field has not moved beyond the laboratory? This review attempts to illustrate that one of the reasons is the complexity of the ncRNA interactome. This is illustrated by multiple studies that are based on the role of a single ncRNA family member in liver fibrogenesis using cell line type models. These studies, therefore, do not capture the complexity of vivo intra ncRNA interaction or their interaction with the mainstream epigenetic machinery. In addition, gene expression in vivo is simultaneously modulated by an orchestra of ncRNA with matching nucleotide sequences that need to be considered when evaluating the therapeutic influence of a single ncRNA. In addition, individual ncRNA in vivo, that have very low levels of expression, will have little effect on modulating gene expression even if they are significantly dysregulated in terms of fold change. Furthermore, the practical delivery of these nano molecules (miRNA) using viral models, liposomes, exosomes, polymers and peptides has also often proved problematic. These delivery problems include loading capacity, stability, enhanced half-life in circulation, minimal toxicity and rapid degradation of the selected ncRNA(Sartorius et al. 2022; Dasgupta and Chatterjee 2021). These issues tend to suggest that multiple ncRNA based studies identifying the potential of an individual ncRNA might be classified as simplistic in terms of their in vivo application. It should also be borne in mind that ncRNA modulation of any specific mRNA by multiple ncRNA species is still only considered to exert an ancillary fine-tuning player influence on target gene expression. In terms of ncRNA based diagnostics, multiple studies have developed highly predicted biomarker panels but as yet these have also not been translated into diagnostic tests used by clinicians (Kim and Croce 2023). A number of reasons, apart from a cost benefit perspective, include the fact that dysregulated miRNA, identified as biomarkers, are not disease specific. In addition, there is a limited overlap observed between the findings of very similar studies in the same disease. Some of these problems are explained by flaws in study design, a small number of participants, or unstandardized (e.g. different age, sex, length of disease, etc.) participants, as well as a wide range of confounding factors, conditions and outcomes, and methodological issues (Pogribny 2018). Nevertheless, the high levels of specificity and predictability obtained in multiple studies underline the potential of deploying ncRNA as diagnostic biomarkers.

Conclusion

Fibrosis is a common feature in CHB infection and HBV-HCC pathogenesis is commonly associated with fibrosis/cirrhosis. This review investigated the molecular mechanisms of ncRNA regulation of HBV induced liver fibrogenesis. In summary, despite a significant understanding of how ncRNA regulate fibrogenesis little progress has been made deploying ncRNA as therapeutic or diagnostic agents. This review illustrates that potentially one of the reasons is the complex interaction of the ncRNA interactome. The review also demonstrates that the role of HBV infection needs to be further explored in the ncRNA interactome because of the multiple effects it can exert on a single ncRNA that potentially can exert both pro and anti-fibrotic outcomes. A limitation of our understanding of the regulatory role of ncRNA in CHB induced fibrosis is possibly that ncRNA expression was measured in non-HBV fibrogenesis model (CCL4), as well as in HBV serum or tissue possibly assuming the same outcome would occur in an HBV induced fibrogenesis model. CCL4 induced fibrosis models, for example, can dysregulate signaling in 36 pathways and > 3500 genes (Dong et al. 2016). Although both CCL4 and CHB pathways induce the expression of multiple inflammatory cytokines (Fareed et al. 2024) like TGF-B in liver fibrogenesis, the possibility remains that CCL4 pathways could differ from CHB induced fibrosis. Despite the problems facing the practical deployment of ncRNA as therapeutic and diagnostic agents, RNA based technology has undoubted potential that has been illustrated by the development of vaccine technology that have provided a groundbreaking insight as to what the future may hold. A better understanding of the role of ncRNA in CHB induced fibrogenesis is especially important considering the modest efficacy of current therapy for advanced stages of this disease.

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Declarations

Competing interests The authors declare no competing interests.

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