REVIEW

The role of microRNAs in hepatocyte metabolism and hepatitis B virus replication

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Though efficient vaccines against hepatitis B virus (HBV) and antiviral therapies are available, chronic HBV infection is still a global health problem. The process of HBV infection and HBV life cycle are extensively studied in last decades, however, the mechanisms of HBV-induced alterations of host cell metabolisms and host factors involved in modulating of viral replication are not fully understood. Thus, it is an important issue to examine these specific HBV-host interactions for development of novel strategies for antiviral therapies. Recently, microRNAs (miRNAs), a class of post-transcriptional regulatory small RNA, seem to be the relevant fine tuning factors of various cellular activities and pathways, including cell growth, metabolism, and viral replication. In this review, we summarize the up to date knowledge concerning the virus-host interactions and emphasizing on the role of miRNAs in regulation of HBV replication and host cell metabolism.

INTRODUCTION

MicroRNAs (miRNAs) are a class of endogenous short-stranded RNA that control target gene expression by binding to partially complementary sequences within the 3′ untranslated region (UTR) of specific mRNAs (Bartel, 2004). Although the exact functions for each miRNA is not fully exploited, it is suggested that a single miRNA may simultaneously target more than 100 mRNAs according to target databases based primarily on Watson-Crick base-pairing (Rottiers and Naar, 2012). Currently, more than 2000 miRNAs have been identified in humans and it is believed that they collectively regulate one third of the genes in the genome (Hammond, 2015). The liver is a primary organ of metabolism. Viral infection and abnormal metabolism may cause chronic liver disease and could lead to hepatocellular carcinoma (HCC).

A great number of studies indicate a pivotal role of miRNAs in tumor progress, including HCC. They can act both as tumor suppressors and oncogenes by targeting various relevant genes, thereby contributing to cell proliferation and metastasis pathways. A certain stability of miRNAs in peripheral blood makes them to be ideal candidates for diagnosis of cancers (Chu et al., 2014; Sidhu et al., 2015).

Hepatitis B virus (HBV) causes acute or chronic infection and also systematic metabolic alterations in hepatocytes. The majority of acutely HBV-infected patients recover. However, some cases may progress to chronicity and the risk for developing chronic HBV infection (CHB) is significantly higher for infants than adults (Schweitzer et al., 2015). CHB is considered to be a global public health issue since it is associated with chronic hepatitis, cirrhosis, and HCC. According to the data published from 1965 to 2013, the prevalence of HBsAg is 3.61% worldwide and about 5.49% in China (Schweitzer et al., 2015). The clinical intervention using interferon and/or nucleotide analogs to treat chronically HBV-infected patients could efficiently suppress viral replication, however, the currently available therapies do not lead to the termination of HBV infection in the ma-

jority of patients (Grimm et al., 2011; Zhang et al., 2013). Therefore, Understanding the HBV-host interaction will uncover the pathogenic mechanisms of HBV infection and identify potential new effective therapeutic strategies. In this review, we summarize the results of recent studies on cell metabolism and its changes in HBV infection and host factors participating in viral life cycle, with the focus on the central role of miRNAs.

miRNAs ARE INVOLVED IN GLUCOSE METABOLISM

miRNAs have recently been implicated in controlling glucose metabolism at multiple levels. In HCC tissues, miR-122 may mediate glycolytic activities through targeting pyruvate kinase M2 (PKM2), an isoform of pyruvate kinase that catalyzes the transfer of a phosphoryl group from phosphoenolpyruvate to ADP, generating ATP and pyruvate (Liu et al., 2014). The development of HCC is also accompanied by a significant reduction of serum insulin-like growth factor (IGF-1) levels. IGF-1 is produced mainly by the liver and represents a target of miR-190b. An increased expression of miR-190b may cause decreased IGF-1 and poor overall survival in HCC patients (Hung et al., 2014). Both miR-125b and -199a-5p target hexokinase II (HK2), an enzyme that catalyzes the irreversible first step of glycolysis in the liver, thereby suppressing glucose consumption (Jiang et al., 2014; Guo et al., 2015). Obesity-induced overexpression of miR-143 and −802 also impairs glucose metabolism through silencing of hepatocyte nuclear factor 1 beta (HNF1B) and inhibiting insulin-stimulated serine-threonine protein kinase (AKT) activation (Jordan et al., 2011; Kornfeld et al., 2013). Moreover, the overexpression of miR-214 in primary hepatocytes suppresses glucose production by targeting activating transcriptional factor 4 (ATF4) (Li et al., 2015b). Finally, miR-491-3p targets one of UDP-glucuronosyltransferases (UGT) 1A isoforms, which are highly expressed in the liver involved in the glucose metabolism and glucuronidation activity (Dluzen et al., 2014).

miRNAs ARE INVOLVED IN LIPID METABOLISM

Several miRNAs have been described to regulate lipid metabolism, including miR-122 which is highly expressed in liver, estimated to account for approximately 70% of all liver miRNA (Lagos-Quintana et al., 2002; Krutzfeldt et al., 2005). MiR-122 inhibition resulted in increased hepatic fatty-acid oxidation and a reduced cholesterol synthesis by 25 to 35% in the mouse model (Esau et al., 2006). Knockdown of miR-24 in high-fat diet-treated mice caused impaired hepatic lipid accumulation and reduced plasma triglycerides through regulat-

ing the target gene insulin-induced gene 1 (INSIG1). INSIG1 is a lipogenesis inhibitor that participates in the processing of lipid synthesis transcription factors sterol regulatory element binding proteins (SREBPs) (Ng et al., 2014). Mattis *et al.* (2015) identified miR-29a as the miRNA responsible for repressing lipoprotein lipase (LPL) in hepatocytes, which encodes an enzyme that facilitates cellular uptake of lipids from the circulation. A decreased hepatic miR-29a level causes lipids to accumulate in the mouse liver tissue. Besides, miR-33, which is located within the coding region of SREBPs and co-transcribed with them, also regulates cholesterol and fatty acid metabolism (Najafi-Shoushtari et al., 2010; Davalos et al., 2011; Rayner et al., 2011). miR-1, -206, and -613 target the nuclear receptor subfamily 1 group H member 3 (NR1H3, also known as LXRA), which plays a critical role in the transcriptional control of lipid metabolism through inducing the expression of lipogenic genes. These miRNAs repress LXRA-induced accumulation of lipid droplets in hepatocytes, accompanied with the inhibition of the expression of LXRA-regulated genes, such as SREBP1, fatty acid synthase (FAS), carbohydrate responsive element-binding protein (ChREBP), and acetyl-CoA carboxylase (ACC) (Zhong et al., 2013a; 2013b). Other miRNAs like miR-27a (Shirasaki et al., 2013), -106b (Kim et al., 2012), -302a (Hoekstra et al., 2012), -335 (Nakanishi et al., 2009), -370 (Iliopoulos et al., 2010), -378/378* (Gerin et al., 2010), and -758 (Ramirez et al., 2011) have also been shown to regulate lipid homeostasis through targeting transcription factors related to lipid metabolism.

HBV INFECTION CAUSES METABOLIC ALTERATION IN HOST CELLS

HCC development is often associated with HBV infection. It is reported that 69% of liver cancer cases in Asia are related to chronic HBV infection (Iavarone and Colombo, 2013). Metabolic alterations may be induced by HBV infection and are associated with carcinogenesis. The cancer cells often reveal higher glycolysis rate in comparison to normal liver tissue, accompanied with increased glucose consumption, decreased oxidative phosphorylation, and increased lactate production to support the increased demand of macromolecules for cell growth and proliferation (Hsu and Sabatini, 2008). *In vitro* and *in vivo* experiments showed that the host cellular glycogen level could be decreased through the interaction between HBV large surface protein and acid alpha-glucosidase (GAA), which is essential for the degradation of glycogen and plays an important role in glycogen balance (Hung et al., 2010; Teng et al., 2015). The biosynthesis of hexosamine and phosphatidylcholine could be up-regulated by activating glutamine-fructose-6-phosphate

amidotransferase 1 (GFAT1) and choline kinase alpha (CHKA) in hepatoma cells with HBV replication, respectively (Li et al., 2015a). Besides, HBV infection also induces lipid metabolic alteration. Abnormal lipid metabolism is considered as a hallmarker of tumorigenesis (Shi et al., 2016). The lipid metabolism-related genes, LXR, SREBP1, peroxisome proliferator-activated receptor alpha (PPARA), PPARG, HNF3B, and CCAAT/enhancer binding protein alpha (CEBPA) were identified to be significantly activated in hepatoma cells transfected with HBx or in HBx transgenic mice (Kim et al., 2007; Na et al., 2009; Wu et al., 2015; Xu et al., 2016). The cholesterol 7 alpha-hydroxylase (CYP7A), which catalyzes the first reaction in the cholesterol catabolic pathway in the liver, acts as the rate limiting step and the major site of regulation of bile acid synthesis. CYP7A and other cholesterol synthesis associated genes, including SREBF2, 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR), and low-density lipoprotein receptor (LDLR) were also found to be enhanced in HBV-infected human liver tissue in the chimeric mouse model (Oehler et al., 2014).

HOST METABOLIC FACTORS PARTICIPATE IN HBV REPLICATION

HBV is a small enveloped DNA virus, which contains a partially double stranded, relaxed circular DNA (rcDNA) in viral particles. The HBV rcDNA could be completed to form covalently closed circular DNA (cccDNA) in the cell nucleus likely by viral polymerase, assisted by certain host enzymes. The cccDNA serves as the template for transcription of pregenomic RNA (pgRNA) and three subgenomic RNA (sgRNA), including precore RNA, S RNA, and X RNA. The transcripts are then exported to cytoplasm and translated into viral proteins. After being encapsidated into the nucleocapsid, HBV pgRNA is reverse transcribed to viral DNA by the viral polymerase. The newly formed rcDNA is either recycled to the nucleus to amplify the cccDNA pool or enveloped by viral surface proteins and secreted as virions (Grimm et al., 2011; Hao et al., 2015). HBV gene expression is controlled mainly at the transcriptional level by recruitment of a whole set of cellular transcription factors (TFs) and coactivators to support viral transcription. Some liver-enriched transcription factors are required for the expression of several liver-specific genes and involve in the cell metabolism and known to be involved in the HBV transcriptional control: hepatic nuclear factors (HNFs) like HNF6 (Wang and Holterman, 2012; Hao et al., 2015); PGC-1α, a major metabolic regulator of gluconeogenesis and lipogenesis (Jhuang et al., 2015); PPAR, which forms a heterodimer with the retinoid X receptor

(RXR) to transcriptionally activate its target genes involved in fatty acid catabolism, gluconeogenesis, and lipoprotein assembly; farnesoid X receptor (FXR), which also forms a heterodimer with RXR and controls many aspects of lipid and cholesterol metabolism; and forkhead Box O1 (FOXO1, formerly FKHR), which is important for regulating glucose homeostasis. The nuclear receptor LXRA and cyclic-AMP response element-binding protein (CREB), involved in glucose and lipid metabolism by supporting the transcription of genes regulating those processes, also participate in the control of HBV transcription (Bar-Yishay et al., 2011; Kim et al., 2011). These transcription factors regulate HBV transcription by interacting with their respective binding sites within the HBV promoters and enhancers.

miRNAs ARE INVOLVED IN CONTROL OF HBV REPLICATION

Virus-host interactions may be mediated by cellular miRNAs to control gene expression. By transfecting antagomirs targeting 328 human miRNAs into HepG2 cells, Zhang et al. (2010) identified miR-199a-3p and miR-210 with the ability to suppress HBsAg expression. The direct effect of these two miRNAs on HBV RNA transcripts could be validated by GFP reporter assay. The seed sequence of miR-125a-5p was also found to be complementary paired with the coding sequence of HBV surface antigen, thus reducing the amount of secreted HBsAg (Potenza et al., 2011). Moreover, many cancer-related miRNAs, including miR-15a/-16-1 (Wang et al., 2013), -17-92 cluster (Khee et al., 2014), and -1236 (Huang et al., 2016), were recently shown to target HBV mRNAs directly by luciferase reporter assay and inhibit HBV replication. Besides the directly targeting to HBV genome, some cellular miRNAs, including epi-miRNAs, were found to be capable of inhibiting or stimulating HBV replication indirectly by regulating cellular transcription factors (Table 1). MiR-15b and −18a promoted HBV replication by augmenting HBV Enhancer I activity via direct targeting HNF1A and estrogen receptor alpha ESR1 respectively (Liu et al., 2009; Dai et al., 2014). Our group found that over-expression of epigenetically regulated miR-1 and -449a resulted in a marked increasement in HBV replication, accompanied with upregulated HBV transcription, antigen expression, and progeny secretion, primary through enhancement of transcriptional activity of the HBV core promoter by the nuclear receptor FXRA (Zhang et al., 2011; 2016). The miR-99 family including miR-99a, -99b, and -100 was also able to enhance HBV replication. However, this family had no influence on HBV promoter activities, different to miR-1 and -449a, but targeted autophagy

Table 1. MicroRNAs targeting TFs involved in HBV replication

Host miRNA	Regulating TFs	Effects on HBV replication	References
miR-1	FXRA	upregulate	Zhang et al., 2011
miR-15b	HNF1A	upregulate	Dai et al., 2014
miR-18a	ESR1	upregulate	Liu et al., 2009
miR-372/373	NFIB	upregulate	Guo et al., 2011
miR-449a	CREBFXRA	upregulate	Zhang et al., 2016
miR-34c	TGIF2	downregulate	Wang et al., 2015
miR-122	NDRG3	downregulate	Fan et al., 2011
miR-130a	PPARG	downregulate	Huang et al., 2015
miR-141	PPARA	downregulate	Hu et al., 2012
miR-155	CEBPB	downregulate	Sarkar et al., 2015
miR-370	NFIA	downregulate	Fan et al., 2016
miR-939	CEBPA	downregulate	Chen et al., 2016

through the Akt-mTOR pathway (Lin et al., 2016). Guo *et al.* (2011) found that miR-372 and -373 were positively related with HBV infection. They were upregulated in HBV-infected liver tissues and promote HBV gene expression through the pathway involving the transcription factor nuclear factor I/B (Gu et al., 2011). In contrast, there are several miRNAs reported negatively correlated with HBV replication. For example, miR-141 significantly suppressed HBV replication and gene expression through targeting PPARA in HepG2 cells (Hu et al., 2012). Restoration of miR-34c in hepatoma cells suppressed the transcription factor transforming growth factor-beta-induced factor homeobox 2 (TGIF2) expression, HBV replication, and viral antigen synthesis (Wang et al., 2015). Transfection of the miR-122 expression vector into the hepatoma cells could disturb HBV life cycle via repressing the transcription and expression of NDRG3 (Fan et al., 2011). miR-130a, -155, -370, and -939 may inhibit HBV replication via targeting transcription factors nuclear factor IA (NFIA), PPARG, CEBPA, and CEBPB, respectively (Huang et al., 2015; Sarkar et al., 2015; Chen et al., 2016; Fan et al., 2016).

On the other hand, viral infection may also cause miRNA expression alteration. Winther *et al.* (2013) have charaterized the plasma miRNA profiles of children chronically infected with HBV and found there were differential plasma miRNA profiles in HBeAg positive and negative children with CHB. In hepatoma cell lines, HBV may change miRNA expression levels through HBx protein. An inverse correlation was noted between the expression of HBx and that of the let-7 family, including let-7a, -7b -7c, miR-122, -145, and -16 in HCC patients or in hepatoma cell lines (Wang et al., 2010; Wu et al., 2011; Peng et al., 2014; Gao et al., 2015). In contrast, a positive correlation between the expression of HBx and some miRNAs were also found. Over-expressing HBx enhanced miR-21 expression (Damania et al., 2014). The expression of miR-331-3p was enhanced by HBx through enhancement of its promoter activity (Cao et al., 2015).

miRNAs LINK HBV LIFE CYCLE AND HOST CELL METABOLISM

Up to now, the majority of studies focused on the role of miRNA in HBV life cycle and host cell metabolism independently. Yet, the direct link of miRNA-metabolism-HBV replication needs to be examined in future study. miR-125b-5p is apparently associated with HBV infection (Winther et al., 2013; Li et al., 2015) and is able to regulate HBV replication via LIN28B/*let-7* axis, which is a major pathway in the regulation of cell growth and metabolism (Zhu et al., 2011; Shyh-Chang and Daley, 2013; Ma et al., 2014). Transient transfection of miR-125b-5p into hepatoma cell lines resulted in upregulation of HBV replication and also in modulation of genes related to liver-specific metabolic functions, including UGT1A6, UGT1A9, UGT2A3, UGT2B10 and UGT2B15 (our own unpublished data). Besides, Huang *et al.* (2015) found miR-130a could inhibit HBV RNA transcription and DNA replication by targeting at two major metabolic regulators PGC1α and PPARγ, respectively. Both transcription factors are able to potently stimulate HBV replication (Huang et al., 2015). On the other hand, HBV infection may also induce abnormal host cell metabolism through affecting miRNA expression. Cui *et al.* (2014) found that HBx could suppress miR-205, which might contribute to the abnormal lipid metabolism through
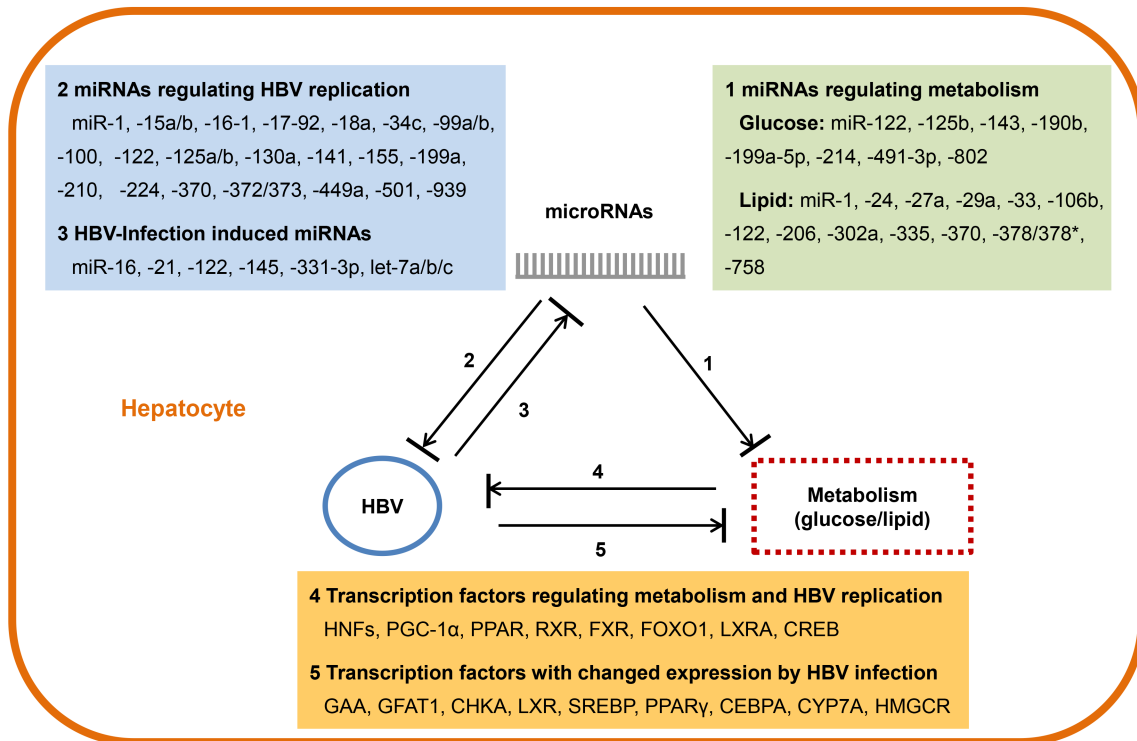
Figure 1. The role of miRNAs in HBV-host interaction. MicroRNAs regulate cell glucose and lipid metabolism (arrow 1), and modulate HBV replication directly by binding to its genome or indirectly through the host transcriptional factors (arrow 2). Meanwhile, HBV infection causes aberrant miRNA expression and host cell metabolic abnormality (arrow 3 and 5), in turn, cellular metabolic factors participate in regulation of HBV replication (arrow 4). The arrows with bars represent they may promote/suppress the functions of other factors.

acyl-CoA synthetase long-chain family member 4 (ACSL4) in hepatoma cells.

CONCLUSION

miRNAs are thought to exert a profound effect on almost every aspect of liver biology and pathology. The interactions among miRNAs, HBV infection, and hepatocyte metabolism are complex but closely linked as indicated in Figure 1. Viral infection often changes host cell metabolic activities through affecting various cellular factors and pathways (line 5). The action of miRNAs represents one of the major central-regulatory principles (line 3 and 1). On the other hand, miRNAs regulate hepatocyte lipid and glucose metabolisms which are closely related to HBV replication (line 1 and 4). Moreover, miRNAs may also regulate HBV replication via binding to HBV genome directly or modulation of HBV-related transcriptional factors to indirectly regulate HBV enhancer or promotor activities (line 2). Despite of the progress in drug discovery and development, the clinical use of direct-acting antivirals against HBV is still very limited. Therefore, the development of effective, well tolerated, and affordable antiviral treatment is crucial to control

chronic HBV infection, cirrhosis, and HCC (Mizuguchi et al., 2015). The viral-induced abnormal miRNA expression and host metabolic alteration suggests that miRNAs may serve as potential targets for treatment of HBV infection and HBV-associated HCC. Finally, miRNAs are able to regulate virus replication and therefore, could be explored for novel strategies for therapeutic approaches.

COMPLIANCE WITH ETHICS GUIDELINES

The author declares that they have no competing interests. This article does not contain any study with human or animal subjects performed by any of the authors.

REFERENCES

Bar-Yishay I, Shaul Y, Shlomai A. 2011. Hepatocyte metabolic signalling pathways and regulation of hepatitis B virus expression. Liver Int, 31: 282–290.

Bartel DP. 2004. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell, 116: 281–297.

Cao Y, Chen J, Wang D, Peng H, Tan X, Xiong D, Huang A, Tang H. 2015. Upregulated in Hepatitis B virus-associated hep-

atocellular carcinoma cells, miR-331–3p promotes proliferation of hepatocellular carcinoma cells by targeting ING5. Oncotarget, 6: 38093–38106.

Chen C, Wu M, Zhang W, Lu W, Zhang M, Zhang Z, Zhang X, Yuan Z. 2016. MicroRNA-939 restricts Hepatitis B virus by targeting Jmjd3-mediated and C/EBPalpha-coordinated chromatin remodeling. Sci Rep, 6: 35974.

Chu R, Mo G, Duan Z, Huang M, Chang J, Li X, Liu P. 2014. miRNAs affect the development of hepatocellular carcinoma via dysregulation of their biogenesis and expression. Cell Commun Signal, 12: 45

Cui M, Wang Y, Sun BD, Xiao ZL, Ye LH, Zhang XD. 2014. MiR-205 modulates abnormal lipid metabolism of hepatoma cells via targeting acyl-CoA synthetase long-chain family member 1 (ACSL1) mRNA. Biochem Bioph Res Co, 444: 270–275.

Dai X, Zhang W, Zhang H, Sun S, Yu H, Guo Y, Kou Z, Zhao G, Du L, Jiang S, Zhang J, Li J, Zhou Y. 2014. Modulation of HBV replication by microRNA-15b through targeting hepatocyte nuclear factor 1alpha. Nucleic Acids Res, 42: 6578–6590.

Damania P, Sen B, Dar SB, Kumar S, Kumari A, Gupta E, Sarin SK, Venugopal SK. 2014. Hepatitis B virus induces cell proliferation via HBx-induced microRNA-21 in hepatocellular carcinoma by targeting programmed cell death protein4 (PDCD4) and phosphatase and tensin homologue (PTEN). PLoS One, 9: e91745.

Davalos A, Goedeke L, Smibert P, Ramirez CM, Warrier NP, Andreo U, Cirera-Salinas D, Rayner K, Suresh U, Pastor-Pareja JC, Esplugues E, Fisher EA, Penalva LO, Moore KJ, Suarez Y, Lai EC, Fernandez-Hernando C. 2011. miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A, 108: 9232–9237.

Dluzen DF, Sun D, Salzberg AC, Jones N, Bushey RT, Robertson GP, Lazarus P. 2014. Regulation of UDP-glucuronosyltransferase 1A1 expression and activity by microRNA 491–3p. J Pharmacol Exp Ther, 348: 465–477.

Esau C, Davis S, Murray SF, Yu XX, Pandey SK, Pear M, Watts L, Booten SL, Graham M, McKay R, Subramaniam A, Propp S, Lollo BA, Freier S, Bennett CF, Bhanot S, Monia BP. 2006. miR-122 regulation of lipid metabolism revealed by *in vivo* antisense targeting. Cell Metab, 3: 87–98.

Fan CG, Wang CM, Tian C, Wang Y, Li L, Sun WS, Li RF, Liu YG. 2011. miR-122 inhibits viral replication and cell proliferation in hepatitis B virus-related hepatocellular carcinoma and targets NDRG3. Oncol Rep, 26: 1281–1286.

Fan H, Lv P, Lv J, Zhao X, Liu M, Zhang G, Tang H. 2016. miR-370 suppresses HBV gene expression and replication by targeting nuclear factor IA. J Med Virol. doi: 10.1002/jmv.24695.

Gao F, Sun X, Wang L, Tang S, Yan C. 2015. Downregulation of MicroRNA-145 Caused by Hepatitis B Virus X Protein Promotes Expression of CUL5 and Contributes to Pathogenesis of Hepatitis B Virus-Associated Hepatocellular Carcinoma. Cell Physiol Biochem, 37: 1547–1559.

Gerin I, Bommer GT, McCoin CS, Sousa KM, Krishnan V, MacDougald OA. 2010. Roles for miRNA-378/378* in adipocyte gene expression and lipogenesis. Am J Physiol Endocrinol Metab, 299: E198–E206.

Grimm D, Thimme R, Blum HE. 2011. HBV life cycle and novel drug targets. Hepatol Int, 5: 644–653.

Guo H, Liu H, Mitchelson K, Rao H, Luo M, Xie L, Sun Y, Zhang L, Lu Y, Liu R, Ren A, Liu S, Zhou S, Zhu J, Zhou Y, Huang A, Wei L, Guo Y, Cheng J. 2011. MicroRNAs-372/373 promote the expression of hepatitis B virus through the targeting of nuclear factor I/B. Hepatology, 54: 808–819.

Guo W, Qiu Z, Wang Z, Wang Q, Tan N, Chen T, Chen Z, Huang S, Gu J, Li J, Yao M, Zhao Y, He X. 2015. MiR-199a-5p is negatively associated with malignancies and regulates glycolysis and lactate production by targeting hexokinase 2 in liver cancer. Hepatology, 62: 1132–1144.

Hammond SM. 2015. An overview of microRNAs. Adv Drug Deliv Rev, 87: 3–14.

Hao R, He J, Liu X, Gao G, Liu D, Cui L, Yu G, Yu W, Chen Y, Guo D. 2015. Inhibition of hepatitis B virus gene expression and replication by hepatocyte nuclear factor 6. J Virol, 89: 4345–4355.

Hoekstra M, van der Sluis RJ, Kuiper J, Van Berkel TJ. 2012. Nonalcoholic fatty liver disease is associated with an altered hepatocyte microRNA profile in LDL receptor knockout mice. J Nutr Biochem, 23: 622–628.

Hsu PP, Sabatini DM. 2008. Cancer cell metabolism: Warburg and beyond. Cell, 134: 703–707.

Hu W, Wang X, Ding X, Li Y, Zhang X, Xie P, Yang J, Wang S. MicroRNA-141 represses HBV replication by targeting PPARA. PLoS One. 2012; 7: e34165.

Huang JY, Chen HL, Shih C. 2016. MicroRNA miR-204 and miR-1236 inhibit hepatitis B virus replication via two different mechanisms. Sci Rep, 6: 34740.

Huang JY, Chou SF, Lee JW, Chen HL, Chen CM, Tao MH, Shih C. 2015. MicroRNA-130a can inhibit hepatitis B virus replication via targeting PGC1alpha and PPARgamma. RNA, 21: 385–400.

Hung JH, Yan CW, Su IJ, Wang HC, Lei HY, Lin WC, Chang WT, Huang W, Lu TJ, Lai MD. 2010. Hepatitis B virus surface antigen interacts with acid alpha-glucosidase and alters glycogen metabolism. Hepatol Res, 40: 633–640.

Hung TM, Ho CM, Liu YC, Lee JL, Liao YR, Wu YM, Ho MC, Chen CH, Lai HS, Lee PH. 2014. Up-regulation of microRNA-190b plays a role for decreased IGF-1 that induces insulin resistance in human hepatocellular carcinoma. PLoS One, 9: e89446.

Iavarone M, Colombo M. 2013. HBV infection and hepatocellular carcinoma. Clin Liver Dis, 17: 375–397.

Iliopoulos D, Drosatos K, Hiyama Y, Goldberg IJ, Zannis VI. 2010. MicroRNA-370 controls the expression of microRNA-122 and Cpt1alpha and affects lipid metabolism. J Lipid Res, 51: 1513–1523.

Jhuang HJ, Hsu WH, Lin KT, Hsu SL, Wang FS, Chou CK, Lee KH, Tsou AP, Lai JM, Yeh SF, Huang CYF. 2015. Gluconeogenesis, lipogenesis, and HBV replication are commonly regulated by PGC-1 alpha-dependent pathway. Oncotarget, 6: 7788–7803.

Jiang JX, Gao S, Pan YZ, Yu C, Sun CY. 2014. Overexpression of microRNA-125b sensitizes human hepatocellular carcinoma cells to 5-fluorouracil through inhibition of glycolysis by targeting hexokinase II. Mol Med Rep, 10: 995–1002.

Jordan SD, Kruger M, Willmes DM, Redemann N, Wunderlich FT, Bronneke HS, Merkwirth C, Kashkar H, Olkkonen VM, Bottger T, Braun T, Seibler J, Bruning JC. 2011. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. Nat Cell Biol, 13: 434–446.

Khee SG, Yusof YA, Makpol S. 2014. Expression of senescence-associated microRNAs and target genes in cellular aging and modulation by tocotrienol-rich fraction. Oxid Med Cell Longev, 2014: 725929.

Kim HY, Cho HK, Kim HH, Cheong J. 2011. Oxygenated derivatives of cholesterol promote hepatitis B virus gene expression through nuclear receptor LXR alpha activation. Virus Research, 158: 55–61.

Kim J, Yoon H, Ramirez CM, Lee SM, Hoe HS, Fernandez-Hernando C. 2012. MiR-106b impairs cholesterol efflux and in-

creases Abeta levels by repressing ABCA1 expression. Exp Neurol, 235: 476–483.

Kim KH, Shin HJ, Kim K, Choi HM, Rhee SH, Moon HB, Kim HH, Yang US, Yu DY, Cheong J. 2007. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology, 132: 1955–1967.

Kornfeld JW, Baitzel C, Konner AC, Nicholls HT, Vogt MC, Herrmanns K, Scheja L, Haumaitre C, Wolf AM, Knippschild U, Seibler J, Cereghini S, Heeren J, Stoffel M, Bruning JC. 2013. Obesity-induced overexpression of miR-802 impairs glucose metabolism through silencing of Hnf1b. Nature, 494: 111–115.

Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M. 2005. Silencing of microRNAs in vivo with 'antagomirs'. Nature, 438: 685–689.

Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. 2002. Identification of tissue-specific microRNAs from mouse. Curr Biol, 12: 735–739.

Li F, Zhou P, Deng W, Wang J, Mao R, Zhang Y, Li J, Yu J, Yang F, Huang Y, Lu M, Zhang J. Serum microRNA-125b correlates with hepatitis B viral replication and liver necroinflammation. Clin Microbiol Infect. 2016 Apr; 22: 384.

Li H, Zhu W, Zhang L, Lei H, Wu X, Guo L, Chen X, Wang Y, Tang H. 2015a. The metabolic responses to hepatitis B virus infection shed new light on pathogenesis and targets for treatment. Sci Rep, 5: 8421.

Li K, Zhang J, Yu J, Liu B, Guo Y, Deng J, Chen S, Wang C, Guo F. 2015b. MicroRNA-214 suppresses gluconeogenesis by targeting activating transcriptional factor 4. J Biol Chem, 290: 8185–8195.

Lin Y, Deng W, Pang J, Kemper T, Hu J, Yin J, Zhang J, Lu M. 2016. The microRNA-99 family modulates hepatitis B virus replication by promoting IGF-1R/PI3K/Akt/mTOR/ULK1 signaling-induced autophagy. Cell Microbiol. doi: 10.1111/cmi.12709.

Liu AM, Xu Z, Shek FH, Wong KF, Lee NP, Poon RT, Chen J, Luk JM. 2014. miR-122 targets pyruvate kinase M2 and affects metabolism of hepatocellular carcinoma. PLoS One, 9: e86872.

Liu WH, Yeh SH, Lu CC, Yu SL, Chen HY, Lin CY, Chen DS, Chen PJ. 2009. MicroRNA-18a prevents estrogen receptor-alpha expression, promoting proliferation of hepatocellular carcinoma cells. Gastroenterology, 136: 683–693.

Ma XY, Li CC, Sun LC, Huang D, Li TT, He XP, Wu GW, Yang Z, Zhong XY, Song LB, Gao P, Zhang HF. 2014. Lin28/let-7 axis regulates aerobic glycolysis and cancer progression via PDK1. Nat Commun, 5: 5212.

Mattis AN, Song G, Hitchner K, Kim RY, Lee AY, Sharma AD, Malato Y, McManus MT, Esau CC, Koller E, Koliwad S, Lim LP, Maher JJ, Raffai RL, Willenbring H. 2015. A screen in mice uncovers repression of lipoprotein lipase by microRNA-29a as a mechanism for lipid distribution away from the liver. Hepatology, 61: 141–152.

Mizuguchi Y, Takizawa T, Uchida E. 2015. Host cellular microRNA involvement in the control of hepatitis B virus gene expression and replication. World J Hepatol, 7: 696–702.

Na TY, Shin YK, Roh KJ, Kang SA, Hong I, Oh SJ, Seong JK, Park CK, Choi YL, Lee M-O. 2009. Liver X Receptor Mediates Hepatitis B Virus X Protein-Induced Lipogenesis in Hepatitis B Virus-Associated Hepatocellular Carcinoma. Hepatology, 49: 1122–1131.

Najafi-Shoushtari SH, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, Naar AM. 2010. MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. Science, 328: 1566–1569.

Nakanishi N, Nakagawa Y, Tokushige N, Aoki N, Matsuzaka T, Ishii K, Yahagi N, Kobayashi K, Yatoh S, Takahashi A, Suzuki H, Urayama O, Yamada N, Shimano H. 2009. The up-regulation of microRNA-335 is associated with lipid metabolism in liver and white adipose tissue of genetically obese mice. Biochem Biophys Res Commun, 385: 492–496.

Ng R, Wu H, Xiao H, Chen X, Willenbring H, Steer CJ, Song G. 2014. Inhibition of microRNA-24 expression in liver prevents hepatic lipid accumulation and hyperlipidemia. Hepatology, 60: 554–564.

Oehler N, Volz T, Bhadra OD, Kah J, Allweiss L, Giersch K, Bierwolf J, Riecken K, Pollok JM, Lohse AW, Fehse B, Petersen J, Urban S, Luetgehetmann M, Heeren J, Dandri M. 2014. Binding of Hepatitis B Virus to Its Cellular Receptor Alters the Expression Profile of Genes of Bile Acid Metabolism. Hepatology, 60: 1483–1493.

Peng F, Xiao XQ, Jiang YF, Luo KZ, Tian Y, Peng ML, Zhang M, Xu Y, Gong GZ. 2014. HBx Down-Regulated Gld2 Plays a Critical Role in HBV-Related Dysregulation of miR-122. PLoS One, 9: e92998.

Potenza N, Papa U, Mosca N, Zerbini F, Nobile V, Russo A. 2011. Human microRNA hsa-miR-125a-5p interferes with expression of hepatitis B virus surface antigen. Nucleic Acids Res, 39: 5157–5163.

Ramirez CM, Davalos A, Goedeke L, Salerno AG, Warrier N, Cirera-Salinas D, Suarez Y, Fernandez-Hernando C. 2011. MicroRNA-758 regulates cholesterol efflux through posttranscriptional repression of ATP-binding cassette transporter A1. Arterioscler Thromb Vasc Biol, 31: 2707–2714.

Rayner KJ, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, Temel RE, Moore KJ. 2011. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Nature, 478: 404–407.

Rottiers V, Naar AM. 2012. MicroRNAs in metabolism and metabolic disorders. Nat Rev Mol Cell Biol, 13: 239–250.

Sarkar N, Panigrahi R, Pal A, Biswas A, Singh SP, Kar SK, Bandopadhyay M, Das D, Saha D, Kanda T, Sugiyama M, Chakrabarti S, Banerjee A, Chakravarty R. 2015. Expression of microRNA-155 correlates positively with the expression of Toll-like receptor 7 and modulates hepatitis B virus via C/EBP-beta in hepatocytes. J Viral Hepat, 22: 817–827.

Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. 2015. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet, 386: 1546–1555.

Shi YX, Huang CJ, Yang ZG. 2016. Impact of hepatitis B virus infection on hepatic metabolic signaling pathway. World J Gastroenterol, 22: 8161–8167.

Shirasaki T, Honda M, Shimakami T, Horii R, Yamashita T, Sakai Y, Sakai A, Okada H, Watanabe R, Murakami S, Yi M, Lemon SM, Kaneko S. 2013. MicroRNA-27a Regulates Lipid Metabolism and Inhibits Hepatitis C Virus Replication in Human Hepatoma Cells. Journal of Virology, 87: 5270–5286.

Shyh-Chang N, Daley GQ. 2013. Lin28: primal regulator of growth and metabolism in stem cells. Cell Stem Cell, 12: 395–406.

Sidhu K, Kapoor NR, Pandey V, Kumar V. 2015. The "Macro" World of microRNAs in Hepatocellular Carcinoma. Front Oncol, 5: 68.

Teng CF, Hsieh WC, Wu HC, Lin YJ, Tsai HW, Huang W, Su IJ. 2015. Hepatitis B Virus Pre-S2 Mutant Induces Aerobic Glycolysis through Mammalian Target of Rapamycin Signal Cascade. PLoS One, 10: e0122373.

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Wang K, Holterman AX. 2012. Pathophysiologic role of hepatocyte nuclear factor 6. Cell Signal, 24: 9–16.

Wang Y, Jiang L, Ji X, Yang B, Zhang Y, Fu XD. 2013. Hepatitis B Viral RNA Directly Mediates Down-regulation of the Tumor Suppressor MicroRNA miR-15a/miR-16–1 in Hepatocytes. J Biol Chem, 288: 18484–18493.

Wang Y, Lu Y, Toh ST, Sung WK, Tan P, Chow P, Chung AY, Jooi LL, Lee CG. 2010. Lethal-7 is down-regulated by the hepatitis B virus x protein and targets signal transducer and activator of transcription 3. J Hepatol, 53: 57–66.

Wang Y, Wang CM, Jiang ZZ, Yu XJ, Fan CG, Xu FF, Zhang Q, Li LI, Li RF, Sun WS, Zhang ZH, Liu YG. 2015. MicroRNA-34c targets TGFB-induced factor homeobox 2, represses cell proliferation and induces apoptosis in hepatitis B virus-related hepatocellular carcinoma. Oncol Lett, 10: 3095–3102.

Wei B, Song Y, Zhang Y, Hu M. 2013. microRNA-449a functions as a tumor-suppressor in gastric adenocarcinoma by targeting Bcl-2. Oncol Lett, 6: 1713–1718.

Winther TN, Bang-Berthelsen CH, Heiberg IL, Pociot F, Hogh B. 2013. Differential Plasma MicroRNA Profiles in HBeAg Positive and HBeAg Negative Children with Chronic Hepatitis B. PLoS One, 8: e58236.

Wu G, Yu F, Xiao Z, Xu K, Xu J, Tang W, Wang J, Song E. 2011. Hepatitis B virus X protein downregulates expression of the miR-16 family in malignant hepatocytes in vitro. Br J Cancer, 105: 146–153.

Wu YL, Peng XE, Zhu YB, Yan XL, Chen WN, Lin X. 2015. Hepatitis B Virus X Protein Induces Hepatic Steatosis by Enhancing the Expression of Liver Fatty Acid Binding Protein. J Virol, 90: 1729–1740.

Xu Z, Zhai L, Yi T, Gao H, Fan F, Li Y, Wang Y, Li N, Xing X, Su N, Wu F, Chang L, Chen X, Dai E, Zhao C, Yang X, Cui C, Xu P. 2016. Hepatitis B virus X induces inflammation and cancer in mice liver through dysregulation of cytoskeletal remodeling and lipid metabolism. Oncotarget. doi: 10.18632/ oncotarget.12372.

Zhang GL, Li YX, Zheng SQ, Liu M, Li X, Tang H. 2010. Suppression of hepatitis B virus replication by microRNA-199a-3p and microRNA-210. Antiviral Res, 88: 169–175.

Zhang X, Hou J, Lu M. 2013. Regulation of hepatitis B virus replication by epigenetic mechanisms and microRNAs. Front Genet, 4: 202.

Zhang X, Liu H, Xie Z, Deng W, Wu C, Qin B, Hou J, Lu M. 2016. Epigenetically regulated miR-449a enhances hepatitis B virus replication by targeting cAMP-responsive element binding protein 5 and modulating hepatocytes phenotype. Sci Rep, 6: 25389.

Zhang X, Zhang E, Ma Z, Pei R, Jiang M, Schlaak JF, Roggendorf M, Lu M. 2011. Modulation of hepatitis B virus replication and hepatocyte differentiation by MicroRNA-1. Hepatology, 53: 1476–1485.

Zhong D, Huang G, Zhang Y, Zeng Y, Xu Z, Zhao Y, He X, He F. 2013a. MicroRNA-1 and microRNA-206 suppress LXRalpha-induced lipogenesis in hepatocytes. Cell Signal, 25: 1429–1437.

Zhong D, Zhang Y, Zeng YJ, Gao M, Wu GZ, Hu CJ, Huang G, He FT. 2013b. MicroRNA-613 represses lipogenesis in HepG2 cells by downregulating LXRalpha. Lipids Health Dis, 12: 32.

Zhu H, Shyh-Chang N, Segre AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, Urbach A, Thornton JE, Triboulet R, Gregory RI, Altshuler D, Daley GQ. 2011. The Lin28/let-7 axis regulates glucose metabolism. Cell, 147: 81–94.