Belloni L, Pollicino T, De Nicola F, Guerrieri F, Raffa G, Fanciulli M et al (2009) Nuclear HBx binds the HBV minichromosome and modifies the epigenetic regulation of cccDNA function. Proc Natl Acad Sci U S A 106(47):19975–19979

Belloni L, Allweiss L, Guerrieri F, Pediconi N, Volz T, Pollicino T et al (2012) IFN-alpha inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome. J Clin Invest 122(2):529–537

Berasain C, Castillo J, Perugorria MJ, Latasa MU, Prieto J, Avila MA (2009) Inflammation and liver cancer: new molecular links. Ann N Y Acad Sci 1155:206–221

Bhanja Chowdhury J, Shrivastava S, Steele R, Di Bisceglie AM, Ray R, Ray RB (2012) Hepatitis C virus infection modulates expression of interferon stimulatory gene IFITM1 by upregulating miR-130A. J Virol 86(18):10221–10225

Bihrer V, Friedrich-Rust M, Kronenberger B, Forestier N, Haupenthal J, Shi Y et al (2011) Serum miR-122 as a biomarker of necroinflammation in patients with chronic hepatitis C virus infection. Am J Gastroenterol 106(9):1663–1669

Boshoff C, Weiss R (2002) AIDS-related malignancies. Nat Rev Cancer 2(5):373–382

Brechot C, Pourcel C, Louise A, Rain B, Tiollais P (1980) Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. Nature 286(5772): 533–535

Budhu A, Jia HL, Forgues M, Liu CG, Goldstein D, Lam A et al (2008) Identification of metastasis-related microRNAs in hepatocellular carcinoma. Hepatology 47(3):897–907

Cai X, Lu S, Zhang Z, Gonzalez CM, Damania B, Cullen BR (2005) Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. Proc Natl Acad Sci U S A 102(15):5570–5575

Cai X, Schafer A, Lu S, Bilello JP, Desrosiers RC, Edwards R (2006) Epstein-Barr virus microRNAs are evolutionarily conserved and differentially expressed. PLoS Pathog 2(3):e23

Cermelli S, Ruggieri A, Marrero JA, Ioannou GN, Beretta L (2011) Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. PLoS One 6(8):e23937

Chen C, Ridzon DA, Broomer AJ, Zhou Z, Lee DH, Nguyen JT et al (2005) Real-time quantification of microRNAs by stem-loop RT-PCR. Nucleic Acids Res 33(20):e179

Chen SJ, Chen GH, Chen YH, Liu CY, Chang KP, Chang YS et al (2010) Characterization of Epstein-Barr virus miRNAome in nasopharyngeal carcinoma by deep sequencing. PLoS One 5(9) pii: e12745

Chen Y, Shen A, Rider PJ, Yu Y, Wu K, Mu Y et al (2011) A liver-specific microRNA binds to a highly conserved RNA sequence of hepatitis B virus and negatively regulates viral gene expression and replication. FASEB J 25(12):4511–4521

Cheung O, Puri P, Eicken C, Contos MJ, Mirshahi F, Maher JW et al (2008) Nonalcoholic steatohepatitis is associated with altered hepatic microRNA expression. Hepatology 48(6):1810–1820

Chirillo P, Pagano S, Natoli G, Puri PL, Burgio VL, Balsano C et al (1997) The hepatitis B virus X gene induces p53-mediated programmed cell death. Proc Natl Acad Sci U S A 94(15): 8162–8167

Cho WC, Chow AS, Au JS (2009) Restoration of tumour suppressor hsa-miR-145 inhibits cancer cell growth in lung adenocarcinoma patients with epidermal growth factor receptor mutation. Eur J Cancer 45(12):2197–2206

Choy EY, Siu KL, Kok KH, Lung RW, Tsang CM, To KF et al (2008) An Epstein-Barr virus-encoded microRNA targets PUMA to promote host cell survival. J Exp Med 205(11):2551–2560

Christoffersen NR, Shalgi R, Frankel LB, Leucci E, Lees M, Klausen M et al (2010) p53-independent upregulation of miR-34a during oncogene-induced senescence represses MYC. Cell Death Differ 17(2):236–245

Connolly E, Melegari M, Landgraf P, Tchaikovskaya T, Tennant BC, Slagle BL et al (2008) Elevated expression of the miR-17-92 polycistron and miR-21 in hepadnavirus-associated hepatocellular carcinoma contributes to the malignant phenotype. Am J Pathol 173(3):856–864

Cosmopoulos K, Pegtel M, Hawkins J, Moffett H, Novina C, Middeldorp J et al (2009) Comprehensive profiling of Epstein-Barr virus microRNAs in nasopharyngeal carcinoma. J Virol 83(5):2357–2367

Coulouarn C, Factor VM, Andersen JB, Durkin ME, Thorgeirsson SS (2009) Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. Oncogene 28(40):3526–3536

Datta J, Kutay H, Nasser MW, Nuovo GJ, Wang B, Majumder S et al (2008) Methylation mediated silencing of MicroRNA-1 gene and its role in hepatocellular carcinogenesis. Cancer Res 68(13):5049–5058

de Vries W, Berkhout B (2008) RNAi suppressors encoded by pathogenic human viruses. Int J Biochem Cell Biol 40(10):2007–2012

Dolken L, Malterer G, Erhard F, Kothe S, Friedel CC, Suffert G et al (2010) Systematic analysis of viral and cellular microRNA targets in cells latently infected with human gamma-herpesviruses by RISC immunoprecipitation assay. Cell Host Microbe 7(4):324–334

Dreher A, Rossing M, Kaczkowski B, Andersen DK, Larsen TJ, Christophersen MK et al (2011) Differential expression of cellular microRNAs in HPV 11, -16, and -45 transfected cells. Biochem Biophys Res Commun 412(1):20–25

Dyson N, Howley PM, Munger K, Harlow E (1989) The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science 243(4893):934–937

Edwards RH, Marquitz AR, Raab-Traub N (2008) Epstein-Barr virus BART microRNAs are produced from a large intron prior to splicing. J Virol 82(18):9094–9106

Esau C, Davis S, Murray SF, Yu XX, Pandey SK, Pear M et al (2006) miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. Cell Metab 3(2):87–98

Fan CG, Wang CM, Tian C, Wang Y, Li L, Sun WS et al (2011) miR-122 inhibits viral replication and cell proliferation in hepatitis B virus-related hepatocellular carcinoma and targets NDRG3. Oncol Rep 26(5):1281–1286

Feederle R, Haar J, Bernhardt K, Linnstaedt SD, Bannert H, Lips H et al (2011) The members of an Epstein-Barr virus microRNA cluster cooperate to transform B lymphocytes. J Virol 85(19):9801–9810

Fujii T, Taguchi H, Katano H, Mori S, Nakamura T, Nojiri N et al (1999) Seroprevalence of human herpesvirus 8 in human immunodeficiency virus 1-positive and human immunodeficiency virus 1-negative populations in Japan. J Med Virol 57(2):159–162

Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS et al (2008) MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. Mol Cell Biol 28(17):5369–5380

Ganem D, Prince AM (2004) Hepatitis B virus infection–natural history and clinical consequences. N Engl J Med 350(11):1118–1129

Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T et al (2009) c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature 458(7239):762–765

Gatfield D, Le Martelot G, Vejnar CE, Gerlach D, Schaad O, Fleury-Olela F et al (2009) Integration of microRNA miR-122 in hepatic circadian gene expression. Genes Dev 23(11):1313–1326. 9

Girard M, Jacquemin E, Munnich A, Lyonnet S, Henrion-Caude A (2008) miR-122, a paradigm for the role of microRNAs in the liver. J Hepatol 48(4):648–656

Godshalk SE, Bhaduri-McIntosh S, Slack FJ (2008) Epstein-Barr virus-mediated dysregulation of human microRNA expression. Cell Cycle 7(22):3595–3600

Gonzalez SL, Stremlau M, He X, Basile JR, Munger K (2001) Degradation of the retinoblastoma tumor suppressor by the human papillomavirus type 16 E7 oncoprotein is important for functional inactivation and is separable from proteasomal degradation of E7. J Virol 75(16):7583–7591

Gottwein E, Cullen BR (2010) A human herpesvirus microRNA inhibits p21 expression and attenuates p21-mediated cell cycle arrest. J Virol 84(10):5229–5237

Gottwein E, Mukherjee N, Sachse C, Frenzel C, Majoros WH, Chi JT et al (2007) A viral microRNA functions as an orthologue of cellular miR-155. Nature 450(7172):1096–1099

Gottwein E, Corcoran DL, Mukherjee N, Skalsky RL, Hafner M, Nusbaum JD et al (2011) Viral microRNA targetome of KSHV-infected primary effusion lymphoma cell lines. Cell Host Microbe 10(5):515–526

Gourzones C, Ferrand FR, Amiel C, Verillaud B, Barat A, Guerin M et al (2013) Consistent high concentration of the viral microRNA BART17 in plasma samples from nasopharyngeal carcinoma patients – evidence of non-exosomal transport. Virol J 10:119

Greco D, Kivi N, Qian K, Leivonen SK, Auvinen P, Auvinen E (2011) Human papillomavirus 16 E5 modulates the expression of host microRNAs. PLoS One 6(7):e21646

Grundhoff A, Sullivan CS, Ganem D (2006) A combined computational and microarray-based approach identifies novel microRNAs encoded by human gamma-herpesviruses. RNA 12(5):733–750

Gunasekharan V, Laimins LA (2013) Human papillomaviruses modulate microRNA 145 expression to directly control genome amplification. J Virol 87(10):6037–6043

Guo Y, Chen Y, Ito H, Watanabe A, Ge X, Kodama T et al (2006) Identification and characterization of lin-28 homolog B (LIN28B) in human hepatocellular carcinoma. Gene 384:51–61

Guo H, Liu H, Mitchelson K, Rao H, Luo M, Xie L et al (2011) MicroRNAs-372/373 promote the expression of hepatitis B virus through the targeting of nuclear factor I/B. Hepatology 54(3):808–819

Haecker I, Gay LA, Yang Y, Hu J, Morse AM, McIntyre LM et al (2012) Ago HITS-CLIP expands understanding of Kaposi's sarcoma-associated herpesvirus miRNA function in primary effusion lymphomas. PLoS Pathog 8(8):e1002884

Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S et al (2005) A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res 65(21):9628–9632

He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S et al (2005) A microRNA polycistron as a potential human oncogene. Nature 435(7043):828–833

Henke JI, Goergen D, Zheng J, Song Y, Schuttler CG, Fehr C et al (2008) microRNA-122 stimulates translation of hepatitis C virus RNA. EMBO J 27(24):3300–3310

Hitt MM, Allday MJ, Hara T, Karran L, Jones MD, Busson P et al (1989) EBV gene expression in an NPC-related tumour. EMBO J 8(9):2639–2651

Hou W, Tian Q, Zheng J, Bonkovsky HL (2010) MicroRNA-196 represses Bach1 protein and hepatitis C virus gene expression in human hepatoma cells expressing hepatitis C viral proteins. Hepatology 51(5):1494–1504

Hsu PW, Lin LZ, Hsu SD, Hsu JB, Huang HD (2007) ViTa: prediction of host microRNAs targets on viruses. Nucleic Acids Res 35(Database issue):D381–D385

Hsu SH, Wang B, Kota J, Yu J, Costinean S, Kutay H et al (2012) Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. J Clin Invest 122(8):2871–2883

Huang J, Wang Y, Guo Y, Sun S (2010) Down-regulated microRNA-152 induces aberrant DNA methylation in hepatitis B virus-related hepatocellular carcinoma by targeting DNA methyltransferase 1. Hepatology 52(1):60–70

Iizasa H, Wulff BE, Alla NR, Maragkakis M, Megraw M, Hatzigeorgiou A et al (2010) Editing of Epstein-Barr virus-encoded BART6 microRNAs controls their dicer targeting and consequently affects viral latency. J Biol Chem 285(43):33358–33370

Ishimoto T, Nagano O, Yae T, Tamada M, Motohara T, Oshima H et al (2011) CD44 variant regulates redox status in cancer cells by stabilizing the xCT subunit of system xc(−) and thereby promotes tumor growth. Cancer Cell 19(3):387–400

Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K et al (2013) Treatment of HCV infection by targeting microRNA. N Engl J Med 368(18):1685–1694

Jin WB, Wu FL, Kong D, Guo AG (2007) HBV-encoded microRNA candidate and its target. Comput Biol Chem 31(2):124–126

Jin J, Tang S, Xia L, Du R, Xie H, Song J et al (2013) MicroRNA-501 promotes HBV replication by targeting HBXIP. Biochem Biophys Res Commun 430(4):1228–1233

Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A et al (2005) RAS is regulated by the let-7 microRNA family. Cell 120(5):635–647

Jopling CL, Yi M, Lancaster AM, Lemon SM, Sarnow P (2005) Modulation of hepatitis C virus RNA abundance by a liver-specific microRNA. Science 309(5740):1577–1581

Jung YJ, Kim JW, Park SJ, Min BY, Jang ES, Kim NY et al (2013) c-Myc-mediated overexpression of miR-17-92 suppresses replication of hepatitis B virus in human hepatoma cells. J Med Virol 85(6):969–978

Keyes WM, Pecoraro M, Aranda V, Vernersson-Lindahl E, Li W, Vogel H et al (2011) DeltaNp63alpha is an oncogene that targets chromatin remodeler Lsh to drive skin stem cell proliferation and tumorigenesis. Cell Stem Cell 8(2):164–176

Kieff EaR AB (2007) Epstein-Barr virus and its replication. In: Fields virology, 5th edn. Lippincott Williams & Wilkins, Philadelphia

Kim do N, Chae HS, Oh ST, Kang JH, Park CH, Park WS et al (2007) Expression of viral microRNAs in Epstein-Barr virus-associated gastric carcinoma. J Virol 81(2):1033–1036

Kim YJ, Cho SY, Yun CH, Moon YS, Lee TR, Kim SH (2008) Transcriptional activation of Cidec by PPARgamma2 in adipocyte. Biochem Biophys Res Commun 377(1):297–302

Kogure T, Lin WL, Yan IK, Braconi C, Patel T (2011) Intercellular nanovesicle-mediated microRNA transfer: a mechanism of environmental modulation of hepatocellular cancer cell growth. Hepatology 54(4):1237–1248

Kosaka N, Iguchi H, Ochiya T (2010) Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. Cancer Sci 101(10):2087–2092

Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW et al (2009) Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. Cell 137(6):1005–1017

Kutay H, Bai S, Datta J, Motiwala T, Pogribny I, Frankel W et al (2006) Downregulation of miR-122 in the rodent and human hepatocellular carcinomas. J Cell Biochem 99(3):671–678

Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T (2002) Identification of tissue-specific microRNAs from mouse. Curr Biol 12(9):735–739

Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A et al (2007) A mammalian microRNA expression atlas based on small RNA library sequencing. Cell 129(7):1401–1414

Lanford RE, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME et al (2010) Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. Science 327(5962):198–201

Lee AT, Ren J, Wong ET, Ban KH, Lee LA, Lee CG (2005) The hepatitis B virus X protein sensitizes HepG2 cells to UV light-induced DNA damage. J Biol Chem 280(39):33525–33535

Lei X, Bai Z, Ye F, Xie J, Kim CG, Huang Y et al (2010) Regulation of NF-kappaB inhibitor IkappaBalpha and viral replication by a KSHV microRNA. Nat Cell Biol 12(2):193–199

Li W, Xie L, He X, Li J, Tu K, Wei L et al (2008) Diagnostic and prognostic implications of microRNAs in human hepatocellular carcinoma. Int J Cancer 123(7):1616–1622

Li LM, Hu ZB, Zhou ZX, Chen X, Liu FY, Zhang JF et al (2010) Serum microRNA profiles serve as novel biomarkers for HBV infection and diagnosis of HBV-positive hepatocarcinoma. Cancer Res 70(23):9798–9807

Li L, Guo Z, Wang J, Mao Y, Gao Q (2012) Serum miR-18a: a potential marker for hepatitis B virus-related hepatocellular carcinoma screening. Dig Dis Sci 57(11):2910–2916

Lin YT, Kincaid RP, Arasappan D, Dowd SE, Hunicke-Smith SP, Sullivan CS (2010) Small RNA profiling reveals antisense transcription throughout the KSHV genome and novel small RNAs. RNA 16(8):1540–1558

Lin X, Liang D, He Z, Deng Q, Robertson ES, Lan K (2011) miR-K12-7-5p encoded by Kaposi's sarcoma-associated herpesvirus stabilizes the latent state by targeting viral ORF50/RTA. PLoS One 6(1):e16224

Liu Y, Zhao JJ, Wang CM, Li MY, Han P, Wang L et al (2009) Altered expression profiles of microRNAs in a stable hepatitis B virus-expressing cell line. Chin Med J 122(1):10–14

Lo AK, To KF, Lo KW, Lung RW, Hui JW, Liao G et al (2007) Modulation of LMP1 protein expression by EBV-encoded microRNAs. Proc Natl Acad Sci U S A 104(41):16164–16169

Lo AK, Dawson CW, Jin DY, Lo KW (2012) The pathological roles of BART miRNAs in nasopharyngeal carcinoma. J Pathol 227(4):392–403

Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R (1999) Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 285(5424):110–113

Lopez-Cabrera M, Letovsky J, Hu KQ, Siddiqui A (1991) Transcriptional factor C/EBP binds to and transactivates the enhancer element II of the hepatitis B virus. Virology 183(2):825–829
Lu S, Cullen BR (2004) Adenovirus VA1 noncoding RNA can inhibit small interfering RNA and microRNA biogenesis. J Virol 78(23):12868–12876
Lu F, Stedman W, Yousef M, Renne R, Lieberman PM (2010) Epigenetic regulation of Kaposi's sarcoma-associated herpesvirus latency by virus-encoded microRNAs that target Rta and the cellular Rbl2-DNMT pathway. J Virol 84(6):2697–2706
Lung RW, Tong JH, Sung YM, Leung PS, Ng DC, Chau SL et al (2009) Modulation of LMP2A expression by a newly identified Epstein-Barr virus-encoded microRNA miR-BART22. Neoplasia 11(11):1174–1184
Machlin ES, Sarnow P, Sagan SM (2011) Masking the 5′ terminal nucleotides of the hepatitis C virus genome by an unconventional microRNA-target RNA complex. Proc Natl Acad Sci U S A 108(8):3193–3198
Marquitz AR, Raab-Traub N (2012) The role of miRNAs and EBV BARTs in NPC. Semin Cancer Biol 22(2):166–172
Marquitz AR, Mathur A, Nam CS, Raab-Traub N (2011) The Epstein-Barr virus BART microRNAs target the pro-apoptotic protein Bim. Virology 412(2):392–400
Martinez I, Gardiner AS, Board KF, Monzon FA, Edwards RP, Khan SA (2008) Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. Oncogene 27(18):2575–2582
Melar-New M, Laimins LA (2010) Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. J Virol 84(10):5212–5221
Moradpour D, Penin F, Rice CM (2007) Replication of hepatitis C virus. Nat Rev Microbiol 5(6):453–463
Mrazek J, Kreutmayer SB, Grasser FA, Polacek N, Huttenhofer A (2007) Subtractive hybridization identifies novel differentially expressed ncRNA species in EBV-infected human B cells. Nucleic Acids Res 35(10):e73
Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T et al (2006) Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. Oncogene 25(17):2537–2545
Murakami Y, Aly HH, Tajima A, Inoue I, Shimotohno K (2009) Regulation of the hepatitis C virus genome replication by miR-199a. J Hepatol 50(3):453–460
Murakami Y, Tanaka M, Toyoda H, Hayashi K, Kuroda M, Tajima A et al (2010) Hepatic microRNA expression is associated with the response to interferon treatment of chronic hepatitis C. BMC Med Genomics 3:48
Murakami Y, Toyoda H, Tanahashi T, Tanaka J, Kumada T, Yoshioka Y et al (2012) Comprehensive miRNA expression analysis in peripheral blood can diagnose liver disease. PLoS One 7(10):e48366
Nachmani D, Stern-Ginossar N, Sarid R, Mandelboim O (2009) Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. Cell Host Microbe 5(4):376–385
Nagata K, Guggenheimer RA, Hurwitz J (1983) Specific binding of a cellular DNA replication protein to the origin of replication of adenovirus DNA. Proc Natl Acad Sci U S A 80(20):6177–6181
O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D (2007) MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci U S A 104(5):1604–1609
Parkin DM (2006) The global health burden of infection-associated cancers in the year 2002. Int J Cancer 118(12):3030–3044
Paterlini-Brechot P, Saigo K, Murakami Y, Chami M, Gozuacik D, Mugnier C et al (2003) Hepatitis B virus-related insertional mutagenesis occurs frequently in human liver cancers and recurrently targets human telomerase gene. Oncogene 22(25):3911–3916
Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, van Eijndhoven MA, Hopmans ES, Lindenberg JL et al (2010) Functional delivery of viral miRNAs via exosomes. Proc Natl Acad Sci U S A 107(14):6328–6333

Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J et al (2004) Identification of virus-encoded microRNAs. Science 304(5671):734–736

Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser FA et al (2005) Identification of microRNAs of the herpesvirus family. Nat Methods 2(4):269–276

Pollicino T, Belloni L, Raffa G, Pediconi N, Squadrito G, Raimondo G et al (2006) Hepatitis B virus replication is regulated by the acetylation status of hepatitis B virus cccDNA-bound H3 and H4 histones. Gastroenterology 130(3):823–837

Popper H, Roth L, Purcell RH, Tennant BC, Gerin JL (1987) Hepatocarcinogenicity of the woodchuck hepatitis virus. Proc Natl Acad Sci U S A 84(3):866–870

Pratt ZL, Kuzembayeva M, Sengupta S, Sugden B (2009) The microRNAs of Epstein-Barr virus are expressed at dramatically differing levels among cell lines. Virology 386(2):387–397

Qin Z, Freitas E, Sullivan R, Mohan S, Bacelieri R, Branch D et al (2010a) Upregulation of xCT by KSHV-encoded microRNAs facilitates KSHV dissemination and persistence in an environment of oxidative stress. PLoS Pathog 6(1):e1000742

Qin Z, Kearney P, Plaisance K, Parsons CH (2010b) Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes. J Leukoc Biol 87(1):25–34

Qiu L, Fan H, Jin W, Zhao B, Wang Y, Ju Y et al (2010) miR-122-induced down-regulation of HO-1 negatively affects miR-122-mediated suppression of HBV. Biochem Biophys Res Commun 398(4):771–777

Raab-Traub N (2012) Novel mechanisms of EBV-induced oncogenesis. Curr Opin Virol 2(4): 453–458

Ramakrishnan R, Donahue H, Garcia D, Tan J, Shimizu N, Rice AP et al (2011) Epstein-Barr virus BART9 miRNA modulates LMP1 levels and affects growth rate of nasal NK T cell lymphomas. PLoS One 6(11):e27271

Riley KJ, Rabinowitz GS, Yario TA, Luna JM, Darnell RB, Steitz JA (2012) EBV and human microRNAs co-target oncogenic and apoptotic viral and human genes during latency. EMBO J 31(9):2207–2221

Sachdeva M, Mo YY (2010) MicroRNA-145 suppresses cell invasion and metastasis by directly targeting mucin 1. Cancer Res 70(1):378–387

Sachdeva M, Zhu S, Wu F, Wu H, Walia V, Kumar S et al (2009) p53 represses c-Myc through induction of the tumor suppressor miR-145. Proc Natl Acad Sci U S A 106(9):3207–3212

Samols MA, Hu J, Skalsky RL, Renne R (2005) Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. J Virol 79(14):9301–9305

Samols MA, Skalsky RL, Maldonado AM, Riva A, Lopez MC, Baker HV et al (2007) Identification of cellular genes targeted by KSHV-encoded microRNAs. PLoS Pathog 3(5):e65

Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM (1990) The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell 63(6):1129–1136

Seeger C, Mason WS (2000) Hepatitis B virus biology. Microbiol Mol Biol Rev MMBR 64(1):51–68

Seto E, Moosmann A, Gromminger S, Walz N, Grundhoff A, Hammerschmidt W (2010) Micro RNAs of Epstein-Barr virus promote cell cycle progression and prevent apoptosis of primary human B cells. PLoS Pathog 6(8):e1001063

Shi M, Du L, Liu D, Qian L, Hu M, Yu M et al (2012) Glucocorticoid regulation of a novel HPV-E6-p53-miR-145 pathway modulates invasion and therapy resistance of cervical cancer cells. J Pathol 228(2):148–157

Shrivastava S, Petrone J, Steele R, Lauer GM, Bisceglie AM, Ray RB (2013) Upregulation of circulating miR-20a is correlated with hepatitis C virus mediated liver disease progression. Hepatology 58(3):863–871

Skalsky RL, Cullen BR (2010) Viruses, microRNAs, and host interactions. Annu Rev Microbiol 64:123–141

Skalsky RL, Samols MA, Plaisance KB, Boss IW, Riva A, Lopez MC et al (2007) Kaposi's sarcoma-associated herpesvirus encodes an ortholog of miR-155. J Virol 81(23):12836–12845

Skalsky RL, Corcoran DL, Gottwein E, Frank CL, Kang D, Hafner M et al (2012) The viral and cellular microRNA targetome in lymphoblastoid cell lines. PLoS Pathog 8(1):e1002484

Song K, Han C, Zhang J, Lu D, Dash S, Feitelson M et al (2013) Epigenetic regulation of miR-122 by PPARgamma and hepatitis B virus X protein in hepatocellular carcinoma cells. Hepatology. doi:10.1002/hep.26514. [Epub ahead of print]

Su C, Hou Z, Zhang C, Tian Z, Zhang J (2011) Ectopic expression of microRNA-155 enhances innate antiviral immunity against HBV infection in human hepatoma cells. Virol J 8:354

Suzuki HI, Yamagata K, Sugimoto K, Iwamoto T, Kato S, Miyazono K (2009) Modulation of microRNA processing by p53. Nature 460(7254):529–533

Taraboletti G, Benelli R, Borsotti P, Rusnati M, Presta M, Giavazzi R et al (1999) Thrombospondin-1 inhibits Kaposi's sarcoma (KS) cell and HIV-1 Tat-induced angiogenesis and is poorly expressed in KS lesions. J Pathol 188(1):76–81

Terradillos O, Billet O, Renard CA, Levy R, Molina T, Briand P et al (1997) The hepatitis B virus X gene potentiates c-myc-induced liver oncogenesis in transgenic mice. Oncogene 14(4):395–404

Tian Y, Yang W, Song J, Wu Y, Ni B (2013) Hepatitis B virus x protein-induced aberrant epigenetic modifications contributing to human hepatocellular carcinoma pathogenesis. Mol Cell Biol 33(15):2810–2816

Tie J, Pan Y, Zhao L, Wu K, Liu J, Sun S et al (2010) MiR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. PLoS Genet 6(3):e1000879

Tili E, Michaille JJ, Cimino A, Costinean S, Dumitru CD, Adair B et al (2007) Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. J Immunol 179(8):5082–5089

Tsai WC, Hsu SD, Hsu CS, Lai TC, Chen SJ, Shen R et al (2012) MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis. J Clin Invest 122(8):2884–2897

Uesugi A, Kozaki K, Tsuruta T, Furuta M, Morita K, Imoto I et al (2011) The tumor suppressive microRNA miR-218 targets the mTOR component Rictor and inhibits AKT phosphorylation in oral cancer. Cancer Res 71(17):5765–5778

Umbach JL, Cullen BR (2010) In-depth analysis of Kaposi's sarcoma-associated herpesvirus microRNA expression provides insights into the mammalian microRNA-processing machinery. J Virol 84(2):695–703

Ura S, Honda M, Yamashita T, Ueda T, Takatori H, Nishino R et al (2009) Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma. Hepatology 49(4):1098–1112

van der Meer AJ, Farid WR, Sonneveld MJ, de Ruiter PE, Boonstra A, van Vuuren AJ et al (2013) Sensitive detection of hepatocellular injury in chronic hepatitis C patients with circulating hepatocyte-derived microRNA-122. J Viral Hepat 20(3):158–166

Vereide DT, Seto E, Chiu YF, Hayes M, Tagawa T, Grundhoff A et al (2013) Epstein-Barr virus maintains lymphomas via its miRNAs. Oncogene. doi:10.1038/onc.2013.71. [Epub ahead of print]

Waidmann O, Bihrer V, Pleli T, Farnik H, Berger A, Zeuzem S et al (2012) Serum microRNA-122 levels in different groups of patients with chronic hepatitis B virus infection. J Viral Hepat 19(2):e58–e65

Wang B, Majumder S, Nuovo G, Kutay H, Volinia S, Patel T et al (2009a) Role of microRNA-155 at early stages of hepatocarcinogenesis induced by choline-deficient and amino acid-defined diet in C57BL/6 mice. Hepatology 50(4):1152–1161

Wang X, Wang HK, McCoy JP, Banerjee NS, Rader JS, Broker TR et al (2009b) Oncogenic HPV infection interrupts the expression of tumor-suppressive miR-34a through viral oncoprotein E6. RNA 15(4):637–647. d

Wang Y, Lu Y, Toh ST, Sung WK, Tan P, Chow P et al (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(1):57–66

Wang S, Qiu L, Yan X, Jin W, Wang Y, Chen L et al (2012) Loss of microRNA 122 expression in patients with hepatitis B enhances hepatitis B virus replication through cyclin G(1)-modulated P53 activity. Hepatology 55(3):730–741

Wasley A, Alter MJ (2000) Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis 20(1):1–16

Wong DK, Yuen MF, Poon RT, Yuen JC, Fung J, Lai CL (2006) Quantification of hepatitis B virus covalently closed circular DNA in patients with hepatocellular carcinoma. J Hepatol 45(4):553–559

Wu X, Wu S, Tong L, Luan T, Lin L, Lu S et al (2009) miR-122 affects the viability and apoptosis of hepatocellular carcinoma cells. Scand. J Gastroenterol 44(11):1332–1339

Xia T, O'Hara A, Araujo I, Barreto J, Carvalho E, Sapucaia JB et al (2008) EBV microRNAs in primary lymphomas and targeting of CXCL-11 by ebv-mir-BHRF1-3. Cancer Res 68(5):1436–1442

Xie X, Piao L, Bullock BN, Smith A, Su T, Zhang M et al (2013) Targeting HPV16 E6-p300 interaction reactivates p53 and inhibits the tumorigenicity of HPV-positive head and neck squamous cell carcinoma. Oncogene. doi:10.1038/onc.2013.25. [Epub ahead of print]

Xu N, Papagiannakopoulos T, Pan G, Thomson JA, Kosik KS (2009) MicroRNA-145 regulates OCT4, SOX2, and KLF4 and represses pluripotency in human embryonic stem cells. Cell 137(4):647–658

Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z et al (2012) Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. eLife 1:e00049

Yi R, Poy MN, Stoffel M, Fuchs E (2008) A skin microRNA promotes differentiation by repressing 'stemness'. Nature 452(7184):225–229

Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C et al (2007) let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell 131(6):1109–1123

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. Antivir Res 88(2):169–175

Zhang X, Zhang E, Ma Z, Pei R, Jiang M, Schlaak JF et al (2011a) Modulation of hepatitis B virus replication and hepatocyte differentiation by MicroRNA-1. Hepatology 53(5):1476–1485

Zhang Y, Xie RL, Croce CM, Stein JL, Lian JB, van Wijnen AJ et al (2011b) A program of microRNAs controls osteogenic lineage progression by targeting transcription factor Runx2. Proc Natl Acad Sci U S A 108(24):9863–9868

Zheng ZM, Baker CC (2006) Papillomavirus genome structure, expression, and post-transcriptional regulation. Front Biosci 11:2286–2302

Zhou J, Yu L, Gao X, Hu J, Wang J, Dai Z et al (2011) Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. J Clin Oncol 29(36):4781–4788

Zhu JY, Pfuhl T, Motsch N, Barth S, Nicholls J, Grasser F et al (2009) Identification of novel Epstein-Barr virus microRNA genes from nasopharyngeal carcinomas. J Virol 83(7):3333–3341

Ziegelbauer JM, Sullivan CS, Ganem D (2009) Tandem array-based expression screens identify host mRNA targets of virus-encoded microRNAs. Nat Genet 41(1):130–134

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Review

Roles of microRNAs in the Hepatitis B Virus Infection and Related Diseases

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Abstract: The hepatitis B virus (HBV) is a small enveloped DNA virus that belongs to the *Hepadnaviridae* family. HBV can cause acute and persistent infection which can lead to hepatocellular carcinoma (HCC). MicroRNAs (miRNAs) play a crucial role in the main cellular events. The dysregulation of their expression has been linked to the development of the cancer as well as to viral interference. This chapter will describe the involvement of miRNAs in the case of HBV infection and their implication in the development of the HBV-related diseases.

Keywords: hepatitis B virus; microRNA; hepatocellular carcinoma

1. Introduction

The microRNAs (miRNAs or miRs) are small non-coding RNAs of 19–23 nucleotides that play key roles in the regulation of almost every cellular process in all multicellular eukaryotes [1]. As intracellular pathogens, viruses are affected by these post-transcriptional modulators and have evolved to subvert them. Several viruses, especially the herpesviruses, encode for their own miRNAs that increase their replication potential and/or allow the evasion from the innate immune system [2]. Other viruses, such as the hepatitis B virus (HBV), modulate the cellular miRNAs in order to achieve the same effects.

HBV is a small enveloped DNA virus that belongs to the *Hepadnaviridae* family. It primarily infects hepatocytes and causes acute and chronic liver disease. Among the 2,000 million people

worldwide infected with HBV, more than 350 million remain chronically infected and become carriers of the virus [3]. Epidemiological studies have uncovered chronic HBV infection as the major etiological factor in the development of hepatocellular carcinoma (HCC) [4]. Despite the availability of an efficient vaccine, persistent HBV infection remains a challenging global health issue. The recent discovery of miRNAs involvement in HBV infection provides new insights into the virus biology and pathogenesis [5,6].

This chapter will outline the roles of miRNAs in the HBV biology and associated pathogenesis. We will also outline present and future miRNA-based strategies for the diagnosis, prognosis and treatment of the HBV-related diseases.

2. Biogenesis and Functions of miRNAs

miRNAs are most commonly transcribed in the nucleus by the RNA polymerase II (Pol II), as monocistronic or polycistronic pri-miRNAs that are further processed in pre-miRNAs (Figure 1). These pre-miRNAs are exported to the cytoplasm where they undergo cleavage by the RNAse III enzyme called Dicer that produces a miRNA duplex. This duplex splits to generate the single-stranded mature miRNA that incorporates the RNA-induced silencing complex (RISC). Based on the complementarity with its target gene sequence, the mature miRNA induce either translational repression (partial complementarity) or mRNA degradation (perfect complementarity) [7]. Besides, the mature miRNA can increase the expression of the target gene under growth arrest condition [8]. Finally, it has been recently reported that miRNA can also act in a RISC-independent manner on the transcriptional level by interaction with ribonucleoprotein or direct binding to DNA [9–11].

One single miRNA has the ability to regulate multiple targets and thereby to affect a broad network of genes (up to 100 genes) [12]. This specific characteristic makes the miRNAs key mediators of most of the cellular events. In animal, miRNAs mainly regulate mRNAs by interacting with their 5' end (5p) to the 3'-untranslated region (3'-UTR) of their target [13]. However, recent studies have revealed miRNAs target sites in the 5'-UTR, which interacts with the 3' end (3p) of miRNAs, and even simultaneous 5'-UTR and 3'-UTR interaction sites [14,15].

The abnormal expression levels of miRNAs have been revealed in various diseases such as cancer [16,17], inflammation [18,19], Alzheimer [20], cardiovascular disease [21] and viral infection including HBV [2,22].

3. Role of miRNAs in HBV Infection

Despite the fact that HBV is a nuclear DNA virus, none viral-encoded miRNA has been so far identified. Only one putative HBV miRNA, with hypothetical regulation role on its own genome, was deduced by computational approach [23]. However, HBV can modulate the expression of several cellular miRNAs in order to promote a favorable environment for its replication and survival. They are presented in this section and summarized in Table 1.

3.1. Brief Description of HBV Infection

The HBV infection is characterized by two phases; the acute and the chronic infection [24]. The initial stages of the acute infection include virion attachment [25], uncoating and nucleocapsid transport to the cell nucleus (Figure 2, steps 1 and 2). The 3.2 kb relaxed circular DNA genome is released into the nucleus and converted into a covalently closed circular DNA (cccDNA) from which all the viral RNAs are transcribed (Figure 2, steps 3 to 5). The pregenomic RNA (pgRNA) serves as template for reverse transcription (Figure 2, steps 8 and 9). The subgenomic mRNAs comprise the pre-surface (S) and S genes, the pre-core (C) and C genes, the polymerase gene, and the X gene. The newly formed nucleocapsids can either assemble with envelope proteins in the endoplasmic reticulum and form mature virions that will be secreted (Figure 2, steps 10 and 11), or return to the nucleus to maintain the cccDNA amplification. When the immune system fails to clear the virus, the HBV infection becomes chronic and it remains under a dormant state into the cell. Eventually, the viral genetic material or sequences can integrate into the host cellular DNA. The integration has been frequently observed and is associated with HCC [26,27].

Figure 1. Schematic representation of miRNA biogenesis. The mature miRNAs originate from successive different steps. An initial DNA transcription generates pri-miRNAs that are cleaved in pre-miRNAs before their exportation to the cytoplasm. There, an RNAse III enzyme, Dicer, cleaves it to generate a miRNA duplex that subsequently joins an RNA-induced silencing complex (RISC) to produce the mature miRNA. The sequence complementarity to the target will decide its fate. Some miRNAs can act on the transcriptional level independently from the RISC.

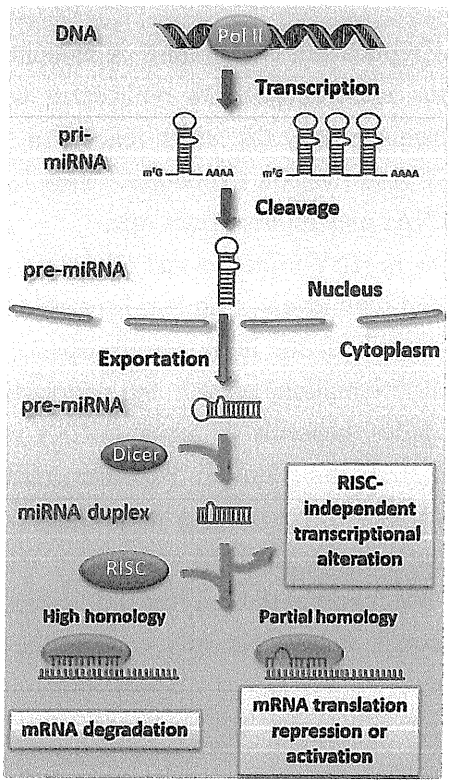


Table 1. Cellular miRNAs and their effects on HBV infection or HBV related-diseases. HBV (↑): Promotes HBV replication; HBV (↓): Inhibits HBV replication; HCC (↑): Development and/or growth of HCC; Fibrosis (↑): Promotes liver fibrosis.

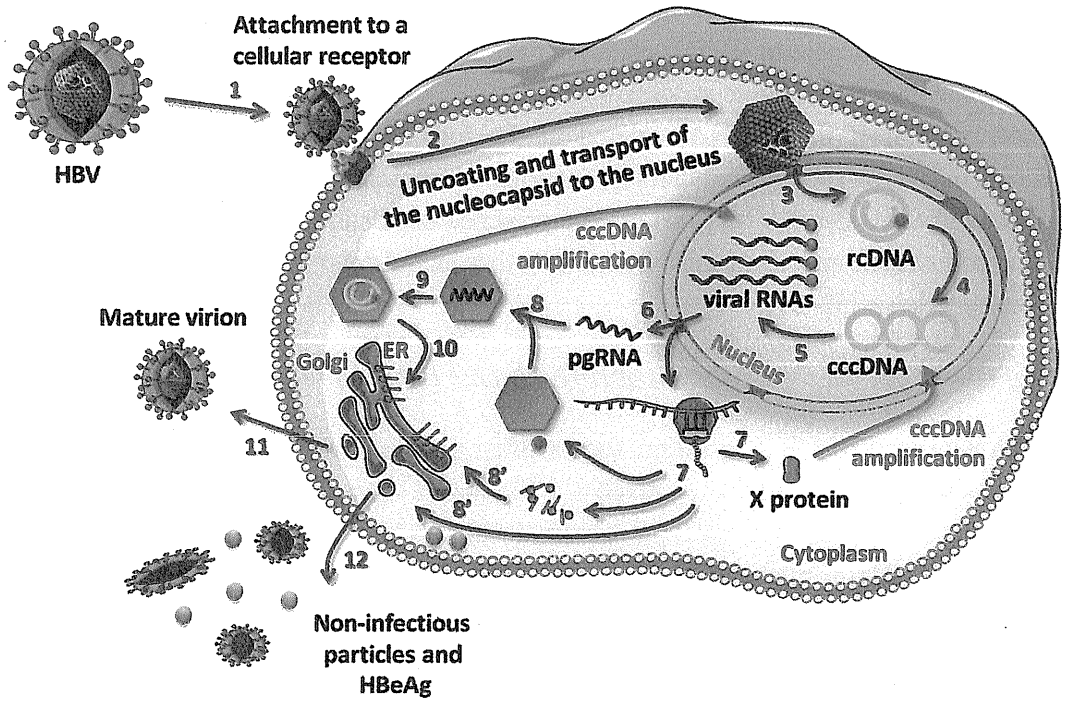
miRNAs	miRNA expression	Target genes	HBV or disease status	Ref.
		Cellular targets		
miR-1	up	HDAC4 (histone deacetylase 4)	HBV (↑)	[28]
miR-17-92 cluster	up	E2F1 (c-myc repressor)	HBV (↑?), HCC (↑)	[29]
miR-155	up	C/EBPβ (CCAAT/enhancer binding protein)	HCC (↑)	[30]
		SOCS1 (JAK/STAT signaling)	HBV (↓)	[31]
miR-181a	up	HLA-A? (MHC class I)	HBV (↑)	[5]
miR-372	up	NFIB (nuclear factor I/B)	HBV (↑)	[32]
miR-373	up	NFIB (nuclear factor I/B)	HBV (↑)	[32]
miR-501	up	HBIP (HBx inhibitor)	HBV (↑)	[33]
mir-29 family	down	collagen	Fibrosis (↑)	[22,34]
miR-122	down	cyclin G1 (p53 modulator)	HBV (↑), HCC (↑)	[6]
miR-152	down	DNMT1 (DNA methyltransferase 1)	HBV (↓)	[35]
let-7 family	down	STAT3 (transcription factor)	HBV (↑?), HCC (↑)	[36]
		Viral targets		
miR-122	up	HBV DNA polymerase	HBV (↓)	[37]
miR-125a-5p	up	HBsAg (HBV surface antigen)	HBV (↓)	[38]
miR-199-3p	up	HBsAg	HBV (↓)	[39]
miR-210	up	HBV pre-S1 (pre-surface 1)	HBV (↓)	[39]

3.2. Role of miRNAs in the HBV Replication

The role of miRNAs in HBV replication is therefore dependent on the phase of HBV infection. During the acute phase, the virus must activate its replication while avoiding destruction by the immune system. During the chronic phase, the virus reaches a "dormant" state where the viral replication must be restricted and viral evasion maintained. This leads to a time-dependent intricate interaction network in which miRNAs play an important role.

One of the best studied miRNAs in HBV infection and other liver-related diseases is miR-122. This liver-specific miRNA is expressed at high levels in normal hepatocytes (about 70% of the total miRNA population in the adult liver) [40] and is pivotal in numerous aspects of the liver function such as lipid metabolism, liver development, differentiation, growth and neoplastic transformation [41]. While the loss of miR-122 expression impedes hepatitis C virus (HCV) replication [42], it enhances the replication in the circumstance of HBV infection [6]. However, miR-122 can negatively regulate the viral gene expression and replication by direct binding to a highly conserved sequence of HBV [37]. This repression effect can apparently be impeded by a negative feedback loop involving the Heme oxygenase-1 [43]. A recent study has reported the indirect implication of the HBV X protein (HBx) in miR-122 dysregulation [44] that could, at least partially, explain the difference observed between the two viruses.

Figure 2. Schematic representation of HBV life cycle. The virus infects a cell by an initial attachment to a cellular receptor that allows its internalization (step 1). In the cytoplasm, the virus is uncoated and the nucleocapsid is transported to the nuclear membrane (step 2). The viral genome is released into the nucleus under its relaxed circular form (rcDNA) and converted into a covalently closed circular DNA (cccDNA) from which all the viral RNAs are produced (steps 3 to 5). The viral RNAs transfer to the cytoplasm for traduction of the different viral proteins (steps 6 and 7) or for subsequent reverse transcription of the pregenomic RNA (pgRNA, steps 6, 8 and 9). All the viral components move to the proper place and assemble together to form new mature virions (steps 8, 10 and 11). The virus also produces non-infectious particles and extracellular antigen (HBeAg) as a decoy for the immune system of the host (step 12). The nucleocapsid containing the rcDNA and the HBV X protein (HBx) can go back to the nucleus in order to amplify the cccDNA and maintain the viral production.



On the other hand, miR-1 can enhance the HBV core promoter transcription by down-regulating the expression of the histone deacetylase 4 (HDAC4) [45]. This miRNA might act complementary to the nuclear HBx in order to induce epigenetic modifications on the cccDNA and amplify the viral genome [45,46].

miR-372, together with miR-373, also supports HBV gene expression by targeting the nuclear factor I/B [47]. This cellular protein is known to be an important regulator of several viruses [48].

The let-7 family of miRNAs has been demonstrated to be negatively regulated by HBx [36]. The consequence of this down-regulation is the increase activity of the signal transducer and activator of transcription 3 (STAT3) that supports cell proliferation, and potentially viral replication and hepatocarcinogenesis.

Finally, miR-501 has been suggested to work with HBx for the benefit of viral replication [33]. HBx itself has also the ability to dysregulate the cellular miRNAs expression. This small protein is a key regulator of HBV infection. It is usually overexpressed in HCC and is involved in hepatocarcinogenesis [48].

3.3. Role of miRNAs in the Immune Evasion of HBV

miRNAs are important in the development and function of immune system [49]. In particular, miR-155 has multi-roles during innate immune response such as regulation of the acute inflammatory response after recognition of pathogens by the toll-like receptors [50,51]. Su and collaborators demonstrated that ectopic expression of miR-155 in human hepatoma cells could enhance the innate immunity through promotion of the janus kinase (JAK)/STAT pathway and down-regulate HBx expression [31].

On the other hand, a study analyzing the modified expression profiles of miRNAs in a stable HBV-expressing cell line revealed the upregulation of miR-181a [5]. The dysregulation of this miRNA in liver cell might participate to HBV replication through inhibition of the human leukocyte antigen A (HLA-A)-dependent HBV antigen presentation.

It is now unclear if the miRNAs altered in the infected hepatocytes, such as miR-181a and miR-146 [5], that have specific regulatory functions in the immune cells as well [49], could affect directly these cells to support viral evasion. The presence of circulating miRNAs and the existence of intercellular nanovesicle-mediated miRNA transfer that modulates the environment, could potentially support that hypothesis [52–57].

3.4. Role of miRNAs in the Establishment of HBV Chronic Infection

The natural history of HBV infection shows often a transition from acute to chronic infection, especially in young children. The virus reaches a "dormant" state into the infected hepatocytes, under the cccDNA form, and survive until its eventual life cycle reactivation [3,35,45,58]. One study reported the CpG islands methylation of the cccDNA by DNA methyltransferase 1 (DNMT1) to prevent the viral gene expression and therefore the viral antigen presentation. The DNMT1 overexpression is induced by a decrease of miR-152, under the effect of HBx [35].

miR-1 illustrates the duality of actions that can be observed in the course of HBV infection. As said previously, this miRNA can promote viral replication but it can also inhibit the cell proliferation and even induce a reverse cancer cell phenotype [28]. The effect on HCC was confirmed in another study [59].

Also, miR-122 can bind directly to the polymerase region in order to repress its expression [37]. Similar observations were made for miR-125a-5p, miR-199a-3p that can affect the S region and miR-210 that can affect the pre-S1 region [38,39]. Since the RNA intermediates of HBV (pgRNA and transcripts) are good targets of miRNA action, it is not surprising to observe several cellular miRNAs targeting them. However, it remains to be determined whether the targeting of HBV transcripts represents an active anti-viral mechanism of the host or if the virus has evolved to hijack these cellular miRNAs in order to reach its "dormant" state.

4. Role of miRNAs in HBV-Related Diseases

The modifications induced as a result of HBV infection profoundly alter the cellular and overall organism homeostasis. They are usually associated with diseases, including liver cirrhosis with fibrosis and HCC. The liver cirrhosis turns most of the time into HCC.

4.1. Role of miRNAs in HBV-Related Cirrhosis

Numerous studies have tried to identify and characterize the miRNAs involved in liver cirrhosis and therefore differently expressed during this intermediate phase. Roderburg et al. investigated the role of miRNAs in liver fibrosis on a carbon tetrachloride-induced hepatic fibrogenesis and bile-duct ligation mouse models [34]. They observed a significant down-regulation of all the members of the miR-29 family in the two models. The decreased expression was induced by the transforming growth factor beta (TGF-β), inflammatory signals and the nuclear factor kappa B (NFκB) pathways. miR-29c was also identified in another report focusing on the miRNA expression profile in patients with HCC-positive or HCC-negative chronic hepatitis B and hepatitis C virus [22] (Table 1).

Nevertheless, the global miRNA expression profile analysis of human liver tissues from different inflammation, infection and cancer states are not always consistent. It sometimes revealed a particular profile due to the association of both viral hepatitis and cirrhosis [60] or regarding to the type of viral hepatitis [22] and sometimes showed no difference [61]. Further experiments are therefore required to identify the exact molecular mechanisms implicating miRNAs and viral components in the development of cirrhosis and in the transition from cirrhosis to HCC in the patients with chronic viral hepatitis.

4.2. Role of miRNAs in HBV-Related HCC

When the cellular modifications and inflammation are too high and maintained for too long, the liver cirrhosis usually evolves into HCC.

The miR-17-92 cluster is important in the HBV infection and associated HCC. This polycistron includes six miRNAs (mir-17-5p, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a-1) and its upregulated expression is associated with malignancies [62]. By using human HBV-positive human HCC tissues, hepatoma cell lines and woodchuck hepatitis virus-induced HCC animal model [63], Connolly and colleagues were able to demonstrate the elevated expression of miR-17-92 cluster and its implication in the malignant phenotype [29] (Table 1). The expression could be amplified by c-myc activation [64], under HBx control [65], to contribute to HBV latency state [66]. The consequence is the induction of liver oncogenesis.

Because of its role in immune response, miR-155 is also implicated in hepatocarcinogenesis. Indeed, its upregulation can lead to prolonged exposure to inflammation, a well-known causal agent to cancers like HCC [67]. Using HCC-induced mouse model, Wang and collaborators have demonstrated the oncogenic role of miR-155 at the early stages of the tumorigenesis [30] (Table 1).

To conclude, the liver-specific miR-122 has been extensively studied in the liver-associated diseases. Its expression is low in HCC tissues, including those with viral chronic hepatitis [6,68] (Table 1). As described in point 3.2, the regulation of miR-122 is very complex and helps either promotion or

inhibition of the HBV replication. In HCC cells, the "dormant" state of HBV implicates a replication rate very low or inexistent [69]. The recent data accumulate evidence of miR-122 as a highly potential linker between HBV infection and liver carcinogenesis [6,70]. Because of its characteristics, miR-122 is therefore a target of choice for future clinical applications.

5. miRNAs as Molecular Tools Against HBV Infection and HBV-Related Diseases

The significance of miRNAs in viral replication, antiviral immunity and liver carcinogenesis emphasizes their values as diagnostic, prognostic and therapeutic targets for HBV infection and HBV-induced diseases.

miR-122 and miR-18a are of particular interest for diagnostic and/or prognostic applications. They are both released in the blood and could be used as potential non-invasive biomarkers for HBV-related HCC screening [5,53,54]. Some other reports suggest the use of a miRNA panel in order to improve the specificity of the test [55,56]. In addition with the current routinely used markers such as HBV surface antigen (HBsAg), HBV extracellular antigen (HbeAg) and alanine aminotransferase (ALT), the circulating miRNAs represent a significant clinical value for better evaluation of the HBV-infection status, liver injury and early diagnosis of HCC.

In the therapeutic perspective, the liver cirrhosis is an event prior to HCC development and being able to interfere with this process would prevent carcinogenesis. For example, a strategy based on administration of miR-29 mimic might prevent liver fibrosis (Section 4.1) [34]. However, the disease is often discovered when hepatocarcinogenesis has already developed and HCC does not always show underlying cirrhosis [71]. Finding therapeutic targets involved in HCC is thus a major issue.

For this purpose, the work of Ura's group is valuable [22]. They analyzed the livers of HBV and HCV positive patients with HCC to identify the miRNAs that are differentially expressed. Nineteen miRNAs were clearly differentiated between HBV and HCV groups, six specific for HBV and thirteen specific for HCV. Based on the miRNAs profile, they made a pathway analysis of candidate targeted genes and were also able to distinguish the cellular mechanisms altered in HBV or HCV-infected livers. The HBV infection alters mostly the pathways related to signal transduction, inflammation and natural killer toxicity, DNA damage, recombination, and cell death, while HCV infection modifies those involved in immune response involving antigen presentation, cell cycle and cell adhesion. Although very interesting, their results are not consistent with those presented in other reports [60,61] and confirmation of the targets needs to be done before considering their clinical application.

Finally, technological advances in the delivery of miRNA and RNA interference enable safe and efficient *in vivo* miRNA gene therapy, as exemplify by the recent study from Kota and colleagues on the liver cancer [72]. They used an adeno-associated virus to deliver miR-26a in a mouse model of HCC. This resulted in the successful inhibition of the cancer cell proliferation, induction of the tumor-specific apoptosis, and protection from disease progression without toxicity.

6. Conclusions

miRNAs have emerged as new key players in the control of gene expression in cells. Investigations of their profiling have unveiled specific miRNA dysregulations in tumors and during viral infection.

The HBV is a widespread pathogen that is implicated in HCC development. Numerous cellular miRNAs interacting with HBV have been identified. They reflect the cellular pathways that are altered as a result of the viral infection, viral infection that triggers the liver cirrhosis and carcinogenesis as side effects. On the viral point of view, the dysregulated pathways mirror the strategies of the virus to allow its replication and evade the host defense mechanisms to survive. On the cellular point of view, they mirror the immune response that tries to get rid of the intruder and that becomes dysregulated. The present and future knowledge about the interaction between miRNA, HBV infection and HCC development and progress will probably allow developing strategies and tools to cope, efficiently and at various steps, with the liver carcinogenesis induced by HBV infection.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Bartel, D.P. MicroRNAs: Target recognition and regulatory functions. *Cell* **2009**, *136*, 215–233.
2. Skalsky, R.L.; Cullen, B.R. Viruses, microRNAs, and host interactions. *Annu. Rev. Microbiol.* **2010**, *64*, 123–141.
3. Ganem, D.; Prince, A.M. Hepatitis B virus infection—Natural history and clinical consequences. *N. Engl. J. Med.* **2004**, *350*, 1118–1129.
4. Parkin, D.M. The global health burden of infection-associated cancers in the year 2002. *Int. J. Cancer* **2006**, *118*, 3030–3044.
5. Liu, Y.; Zhao, J.J.; Wang, C.M.; Li, M.Y.; Han, P.; Wang, L.; Cheng, Y.Q.; Zoulim, F.; Ma, X.; Xu, D.P. Altered expression profiles of microRNAs in a stable hepatitis B virus-expressing cell line. *Chin. Med. J.* **2009**, *122*, 10–14.
6. Wang, S.; Qiu, L.; Yan, X.; Jin, W.; Wang, Y.; Chen, L.; Wu, E.; Ye, X.; Gao, G.F.; Wang, F.; *et al.* Loss of microRNA 122 expression in patients with hepatitis B enhances hepatitis B virus replication through cyclin G(1)-modulated P53 activity. *Hepatology* **2012**, *55*, 730–741.
7. He, L.; Hannon, G.J. MicroRNAs: Small RNAs with a big role in gene regulation. *Nat. Rev. Genet.* **2004**, *5*, 522–531.
8. Vasudevan, S.; Tong, Y.; Steitz, J.A. Switching from repression to activation: Micrornas can up-regulate translation. *Science* **2007**, *318*, 1931–1934.

9. Eiring, A.M.; Harb, J.G.; Neviani, P.; Garton, C.; Oaks, J.J.; Spizzo, R.; Liu, S.; Schwind, S.; Santhanam, R.; Hickey, C.J.; *et al.* miR-328 functions as an RNA decoy to modulate hnRNP E2 regulation of mRNA translation in leukemic blasts. *Cell* **2010**, *140*, 652–665.
10. Gonzalez, S.; Pisano, D.G.; Serrano, M. Mechanistic principles of chromatin remodeling guided by siRNAs and miRNAs. *Cell Cycle* **2008**, *7*, 2601–2608.
11. Kim, D.H.; Saetrom, P.; Snove, O., Jr.; Rossi, J.J. MicroRNA-directed transcriptional gene silencing in mammalian cells. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 16230–16235.
12. Lim, L.P.; Lau, N.C.; Garrett-Engele, P.; Grimson, A.; Schelter, J.M.; Castle, J.; Bartel, D.P.; Linsley, P.S.; Johnson, J.M. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* **2005**, *433*, 769–773.
13. Ambros, V. The functions of animal microRNAs. *Nature* **2004**, *431*, 350–355.
14. Baek, D.; Villen, J.; Shin, C.; Camargo, F.D.; Gygi, S.P.; Bartel, D.P. The impact of microRNAs on protein output. *Nature* **2008**, *455*, 64–71.
15. Lee, I.; Ajay, S.S.; Yook, J.I.; Kim, H.S.; Hong, S.H.; Kim, N.H.; Dhanasekaran, S.M.; Chinnaiyan, A.M.; Athey, B.D. New class of microRNA targets containing simultaneous 5'-UTR and 3'-UTR interaction sites. *Genome Res.* **2009**, *19*, 1175–1183.
16. Calin, G.A.; Sevignani, C.; Dumitru, C.D.; Hyslop, T.; Noch, E.; Yendamuri, S.; Shimizu, M.; Rattan, S.; Bullrich, F.; Negrini, M.; Croce, C.M. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2999–3004.
17. Calin, G.A.; Ferracin, M.; Cimmino, A.; di Leva, G.; Shimizu, M.; Wojcik, S.E.; Iorio, M.V.; Visone, R.; Sever, N.I.; Fabbri, M.; *et al.* A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N. Engl. J. Med.* **2005**, *353*, 1793–1801.
18. Bi, Y.; Liu, G.; Yang, R. MicroRNAs: Novel regulators during the immune response. *J. Cell Physiol.* **2009**, *218*, 467–472.
19. Fasseu, M.; Treton, X.; Guichard, C.; Pedruzzi, E.; Cazals-Hatem, D.; Richard, C.; Aparicio, T.; Daniel, F.; Soule, J. C.; Moreau, R.; *et al.* Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. *PLoS One* **2010**, *5*, doi:10.1371/journal.pone.0013160.
20. Sethi, P.; Lukiw, W.J. Micro-RNA abundance and stability in human brain: Specific alterations in Alzheimer's disease temporal lobe neocortex. *Neurosci. Lett.* **2009**, *459*, 100–104.
21. Latronico, M.V.; Catalucci, D.; Condorelli, G. Emerging role of microRNAs in cardiovascular biology. *Circ. Res.* **2007**, *101*, 1225–1236.
22. Ura, S.; Honda, M.; Yamashita, T.; Ueda, T.; Takatori, H.; Nishino, R.; Sunakozaka, H.; Sakai, Y.; Horimoto, K.; Kaneko, S. Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma. *Hepatology* **2009**, *49*, 1098–1112.
23. Jin, W.B.; Wu, F.L.; Kong, D.; Guo, A.G. HBV-encoded microRNA candidate and its target. *Comput. Biol. Chem.* **2007**, *31*, 124–126.
24. Seeger, C.; Mason, W.S. Hepatitis B virus biology. *Microbiol. Mol. Biol. Rev.* **2000**, *64*, 51–68.
25. Yan, H.; Zhong, G.; Xu, G.; He, W.; Jing, Z.; Gao, Z.; Huang, Y.; Qi, Y.; Peng, B.; Wang, H.; *et al.* Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *Elife* **2012**, *1*, e00049.

26. Brechot, C.; Pourcel, C.; Louise, A.; Rain, B.; Tiollais, P. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* **1980**, *286*, 533–535.
27. Paterlini-Brechot, P.; Saigo, K.; Murakami, Y.; Chami, M.; Gozuacik, D.; Mugnier, C.; Lagorce, D.; Brechot, C. Hepatitis B virus-related insertional mutagenesis occurs frequently in human liver cancers and recurrently targets human telomerase gene. *Oncogene* **2003**, *22*, 3911–3916.
28. Zhang, X.; Zhang, E.; Ma, Z.; Pei, R.; Jiang, M.; Schlaak, J.F.; Roggendorf, M.; Lu, M. Modulation of hepatitis B virus replication and hepatocyte differentiation by MicroRNA-1. *Hepatology* **2011**, *53*, 1476–1485.
29. Connolly, E.; Melegari, M.; Landgraf, P.; Tchaikovskaya, T.; Tennant, B.C.; Slagle, B.L.; Rogler, L.E.; Zavolan, M.; Tuschl, T.; Rogler, C.E. Elevated expression of the miR-17-92 polycistron and miR-21 in hepadnavirus-associated hepatocellular carcinoma contributes to the malignant phenotype. *Am. J. Pathol.* **2008**, *173*, 856–864.
30. Wang, B.; Majumder, S.; Nuovo, G.; Kutay, H.; Volinia, S.; Patel, T.; Schmittgen, T.D.; Croce, C.; Ghoshal, K.; Jacob, S.T. Role of microRNA-155 at early stages of hepatocarcinogenesis induced by choline-deficient and amino acid-defined diet in C57BL/6 mice. *Hepatology* **2009**, *50*, 1152–1161.
31. Su, C.; Hou, Z.; Zhang, C.; Tian, Z.; Zhang, J. Ectopic expression of microRNA-155 enhances innate antiviral immunity against HBV infection in human hepatoma cells. *Virol. J.* **2011**, *8*, doi:10.1186/1743-422X-8-354.
32. Guo, H.; Liu, H.; Mitchelson, K.; Rao, H.; Luo, M.; Xie, L.; Sun, Y.; Zhang, L.; Lu, Y.; Liu, R.; *et al.* MicroRNAs-372/373 promote the expression of hepatitis B virus through the targeting of nuclear factor I/B. *Hepatology* **2011**, *54*, 808–819.
33. Jin, J.; Tang, S.; Xia, L.; Du, R.; Xie, H.; Song, J.; Fan, R.; Bi, Q.; Chen, Z.; Yang, G.; *et al.* MicroRNA-501 promotes HBV replication by targeting HBXIP. *Biochem. Biophys. Res. Commun.* **2013**, *430*, 1228–1233.
34. Roderburg, C.; Urban, G.W.; Bettermann, K.; Vucur, M.; Zimmermann, H.; Schmidt, S.; Janssen, J.; Koppe, C.; Knolle, P.; Castoldi, M.; *et al.* Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. *Hepatology* **2010**, *53*, 209–218.
35. Huang, J.; Wang, Y.; Guo, Y.; Sun, S. Down-regulated microRNA-152 induces aberrant DNA methylation in hepatitis B virus-related hepatocellular carcinoma by targeting DNA methyltransferase 1. *Hepatology* **2010**, *52*, 60–70.
36. Wang, Y.; Lu, Y.; Toh, S.T.; Sung, W.K.; Tan, P.; Chow, P.; Chung, A.Y.; Jooi, L.L.; Lee, C.G. Lethal-7 is down-regulated by the hepatitis B virus x protein and targets signal transducer and activator of transcription 3. *J. Hepatol.* **2010**, *53*, 57–66.
37. Chen, Y.; Shen, A.; Rider, P.J.; Yu, Y.; Wu, K.; Mu, Y.; Hao, Q.; Liu, Y.; Gong, H.; Zhu, Y.; *et al.* A liver-specific microRNA binds to a highly conserved RNA sequence of hepatitis B virus and negatively regulates viral gene expression and replication. *FASEB J.* **2011**, *25*, 4511–4521.
38. Potenza, N.; Papa, U.; Mosca, N.; Zerbini, F.; Nobile, V.; Russo, A. Human microRNA hsa-miR-125a-5p interferes with expression of hepatitis B virus surface antigen. *Nucleic Acids Res.* **2011**, *39*, 5157–5163.
39. Zhang, G.L.; Li, Y.X.; Zheng, S.Q.; Liu, M.; Li, X.; Tang, H. Suppression of hepatitis B virus replication by microRNA-199a-3p and microRNA-210. *Antiviral Res.* **2010**, *88*, 169–175.

40. Lagos-Quintana, M.; Rauhut, R.; Yalcin, A.; Meyer, J.; Lendeckel, W.; Tuschl, T. Identification of tissue-specific microRNAs from mouse. *Curr. Biol.* **2002**, *12*, 735–739.
41. Girard, M.; Jacquemin, E.; Munnich, A.; Lyonnet, S.; Henrion-Caude, A. miR-122, a paradigm for the role of microRNAs in the liver. *J. Hepatol.* **2008**, *48*, 648–656.
42. Jopling, C.L.; Yi, M.; Lancaster, A.M.; Lemon, S.M.; Sarnow, P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* **2005**, *309*, 1577–1581.
43. Qiu, L.; Fan, H.; Jin, W.; Zhao, B.; Wang, Y.; Ju, Y.; Chen, L.; Chen, Y.; Duan, Z.; Meng, S. miR-122-induced down-regulation of HO-1 negatively affects miR-122-mediated suppression of HBV. *Biochem. Biophys. Res. Commun.* **2010**, *398*, 771–777.
44. Song, K.; Han, C.; Zhang, J.; Lu, D.; Dash, S.; Feitelson, M.; Lim, K.; Wu, T. Epigenetic regulation of miR-122 by PPARgamma and hepatitis B virus X protein in hepatocellular carcinoma cells. *Hepatology* **2013**, doi: 10.1002/hep.26514.
45. Belloni, L.; Pollicino, T.; de Nicola, F.; Guerrieri, F.; Raffa, G.; Fanciulli, M.; Raimondo, G.; Levrero, M. Nuclear HBx binds the HBV minichromosome and modifies the epigenetic regulation of cccDNA function. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 19975–19979.
46. Pollicino, T.; Belloni, L.; Raffa, G.; Pediconi, N.; Squadrito, G.; Raimondo, G.; Levrero, M. Hepatitis B virus replication is regulated by the acetylation status of hepatitis B virus cccDNA-bound H3 and H4 histones. *Gastroenterology* **2006**, *130*, 823–837.
47. Nagata, K.; Guggenheimer, R.A.; Hurwitz, J. Specific binding of a cellular DNA replication protein to the origin of replication of adenovirus DNA. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 6177–6181.
48. Tian, Y.; Yang, W.; Song, J.; Wu, Y.; Ni, B. HBV X protein-induced aberrant epigenetic modifications contributing to human hepatocellular carcinoma pathogenesis. *Mol. Cell. Biol.* **2013**, *33*, 2810–2816.
49. Baltimore, D.; Boldin, M.P.; O'Connell, R.M.; Rao, D.S.; Taganov, K.D. MicroRNAs: New regulators of immune cell development and function. *Nat. Immunol.* **2008**, *9*, 839–845.
50. O'Connell, R.M.; Taganov, K.D.; Boldin, M.P.; Cheng, G.; Baltimore, D. MicroRNA-155 is induced during the macrophage inflammatory response. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1604–1609.
51. Tili, E.; Michaille, J.J.; Cimino, A.; Costinean, S.; Dumitru, C.D.; Adair, B.; Fabbri, M.; Alder, H.; Liu, C.G.; Calin, G.A.; Croce, C.M. Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. *J. Immunol.* **2007**, *179*, 5082–5089.
52. Arataki, K.; Hayes, C.N.; Akamatsu, S.; Akiyama, R.; Abe, H.; Tsuge, M.; Miki, D.; Ochi, H.; Hiraga, N.; Imamura, M.; *et al.* Circulating microRNA-22 correlates with microRNA-122 and represents viral replication and liver injury in patients with chronic hepatitis B. *J. Med. Virol.* **2013**, *85*, 789–798.
53. Waidmann, O.; Bihrer, V.; Pleli, T.; Farnik, H.; Berger, A.; Zeuzem, S.; Kronenberger, B.; Piiper, A. Serum microRNA-122 levels in different groups of patients with chronic hepatitis B virus infection. *J. Viral Hepat.* **2012**, *19*, e58–e65.
54. Li, L.; Guo, Z.; Wang, J.; Mao, Y.; Gao, Q. Serum miR-18a: A potential marker for hepatitis B virus-related hepatocellular carcinoma screening. *Dig. Dis. Sci.* **2012**, *57*, 2910–2916.