### 3.3 *Immune Defense and KSHV Encoded miRNAs*

Latent infection of KSHV were observed in 40–50 % of the population in south part of Africa, 10 % of the north American population and 4 % of the Japanese population; however, most of these people were kept healthy (Fujii et al. 1999). MiR-K12s are expressed in latently infected cells. To escape from host immune mechanism, miR-K12s may regulate this mechanism. MiR-K12-7 inhibits the expression of MHC class I polypeptide-related sequence B, which is recognized by NK cells (Nachmani et al. 2009). miR-K12-10a represses the tumor necrosis factor receptor superfamily member 12A, which regulates apoptosis and inflammatory response (Abend et al. 2010). MiR-K12s also alter human cytokine expression via targeting of the cytokine repressor C/EBPβ p20 (Qin et al. 2010b). C/EBPβ p20 is a repressor of IL-6 and IL-10. MiR-K12s induce the expression of these cytokines in murine macrophages (Qin et al. 2010b). A bioinformatics sequence analysis revealed that this could be attributed to viral miRNA-mediated expression of a known repressor of these cytokines.

To identify target genes of miR-K12s, a bioinformatics approach was used. Identifying target genes of viral miRNAs is much more difficult than identifying those of mammalian miRNAs, because species conservation of 3′-UTR miRNA targeting site is not useful for viral miRNAs. Recently, high-throughput sequencing of RNA isolated by cross-linking immunoprecipitation (HITS-CLIP) was developed to identify miRNA target gene by immunoprecipitation of Ago2-miRNAs and associated mRNAs. This method recovered approximately 1,000 cellular targeting genes of miR-K12s, including THBS1, BACH1, and C/EBPβin PEL cell lines (Haecker et al. 2012). Interestingly, HITS-CLIP revealed that the miR-K12s predominate Ago2-associated miRNAs and miR-K12smay contribute to global alteration of the human miRNAs pathway in KSHV-infected cells (Haecker et al. 2012). KSHV-positive KS is derived from endothelial cells and the mRNA expression profile of endothelial cells is not to the same as that of PEL. In the near future, the pathophysiological role of miR-K12s in endothelial cells will be identified using the HITS-CLIP method.

## 4 MicroRNAs in High-Risk Human Papillomavirus; Expression, Regulation and Function

### 4.1 *Basic Knowledge of HPV Infection*

Human papillomaviruses (HPVs) have small double-stranded circular genomic DNA that encode early genes (E1, E2, E4, E5, E6, and E7) and late genes (L1 and L2) (Zheng and Baker 2006). HPVs infect squamous epithelium, and then integrate into the epithelial stem cells on the basal membrane. HPV early genes

are expressed in the epithelial stem cells; however, expression of viral late genes and viral DNA replication are observed in differentiated epithelial layers. The E6 and E7 genes of high-risk HPVs (HPV16 and HPV18) have oncogenic activity and inactivate p53 and pRb, respectively (Scheffner et al. 1990; Dyson et al. 1989; Gonzalez et al. 2001).

## *4.2 MiRNAs Expression Profile of HPV Infected Cells and Pathophysiological Role of miRNAs in HPV Infection*

DNA viruses encode viral miRNAs and therefore are able to regulate viral life cycle or human immune defense. However, HPVs do not have viral miRNAs because they have small genome (size, 8 kb). Infection with high-risk HPVs leads to tumorigenesis in the epithelial stem cells by the inactivation of tumor suppressive factors. The component p53 interacts with the Drosha-DGCR8 complex component p68 and regulates part of miRNA processing (Suzuki et al. 2009). The effect of high-risk HPVs infection in miRNA expression is largely unknown.

Dreher et al. (2011) reported that the expression level of miR-145 was increased in high-risk- HPV infected cells compared to low-risk HPV-infected cells. High-risk HPV component E6 is one of the key factors for tumorigenesis, it suppresses the expression of miR-145 (Shi et al. 2012; Gunasekharan and Laimins 2013), miR-218 (Martinez et al. 2008), miR-34a (Wang et al. 2009b; Xie et al. 2013) and miR-23b (Au Yeung et al. 2011). Previously, miR-145 was identified as a tumor suppressive miRNA (called "anti-oncomir") (Cho et al. 2009) as it suppresses the expression of c-Myc (Sachdeva et al. 2009), MUC1 (Sachdeva and Mo 2010) and stem cell-related transcription factors (Xu et al. 2009). Tumor-related target genes of miR-218 are Robo1 (Tie et al. 2010), survivin (Alajez et al. 2011), Runx2 (Zhang et al. 2011b), and the mTOR component Rictor (Uesugi et al. 2011). Moreover, miR-34a and miR-23b repress c-Myc (Christoffersen et al. 2010; Gao et al. 2009) and these miRNAs are induced by p53. These reports suggest that the high-risk HPV E6 gene represses tumor suppressive miRNAs via p53 inactivation.

High-risk HPV E7 can inactivate pRb and induce the activation of the transcription factor E2F (Scheffner et al. 1990; Dyson et al. 1989; Gonzalez et al. 2001). Interestingly, E7 suppresses miR-203 expression and induces p63 expression; p63 is an enhancer of cancer stem cells (Melar-New and Laimins 2010; Keyes et al. 2011). MiR-203 is a repressor of dermal stem cells, but the molecular mechanism underlying the transcriptional regulation of miR-203 is unknown (Yi et al. 2008). Moreover, high-risk HPV E5 regulates miR-146a, miR-203, and miR-324-5p (Greco et al. 2011). High-risk HPV infection itself may regulate cell differentiation by repressing the expression of human miRNAs.

# 5 MicroRNAs in Hepatitis C Virus; Expression, Regulation and Function

## *5.1 Basic Knowledge of HCV*

Hepatitis C virus (HCV) has a 9.6 kb genome that encodes a single positive-strand polyprotein, which is organized in structural and the non-structural (NS-) replication proteins. The open reading frame is flanked by the 5′- and 3′ -UTRs that contain the cis-signals for the translation and replication of the viral RNA. The structural proteins, which form the viral particle, include the core protein and the envelope glycoproteins E1 and E2. The non-structural proteins include p7 ion channel, NS2-3 protease, NS3 serine protease and RNA helicase, NS4A polypeptide, NS4B and NS5A proteins, and NS5B RNA-dependent RNA polymerase (RdRp) (Appel et al. 2006; Moradpour et al. 2007) (Fig. 7.3). HCV infection is a cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (Wasley and Alter 2000).

## *5.2 The Expression and Role of miRNAs in Liver*

The miRNA expression pattern differs dramatically among internal organs. miR-122 constitutes ~70 % of the hepatic miRNAs (Landgraf et al. 2007), and its function in the liver is varied. MiR-122 maintains the hepatic function by down-regulating genes involved in cholesterol synthesis like HMG-CoA reductase, amongst others (Esau et al. 2006). The serum lipid profiles of both liver-specific and germline knockouts of miR-122 induced a 30 % reduction in the total cholesterol, LDL, HDL, and serum triglyceride level. Against expectations, the knockout miR-122 mice had progressive steatohepatitis (Hsu et al. 2012; Tsai et al. 2012). MiR-122 can also regulate lipid synthesis in the liver by controlling expression of *Agpat1* and *Cidec* (Hsu et al. 2012; Tsai et al. 2012). These genes are a part of the triglyceride biosynthesis pathway (Kim et al. 2008). Gatfield et al. (2009) showed that miR-122 is associated with circadian rhythm as the circadian metabolic regulators of the PPAR family are regulated by the miR-122-mediated metabolic control.

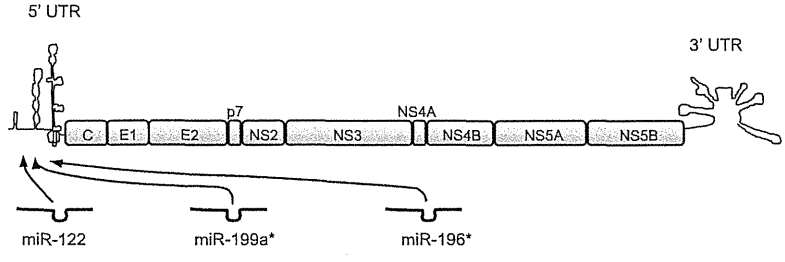


**Fig. 7.3** Structure of the HCV genome. The recognition sites of miR-122, miR-199a*, and miR-196* on the HCV genome and in miRNAs are shown. This confirms the *in vitro* replication of HCV

In miR-122-knock out animals, steatohepatitis and liver fibrosis were observed (Hsu et al. 2012; Tsai et al. 2012; Gatfield et al. 2009). MiR-122 is also related to liver inflammation (Lanford et al. 2010). Several researchers showed that the expression level of miR-122 is reduced in experimental models and clinical samples of HCC, and loss of miR-122 is associated with tumor invasiveness and cancer progression (Hsu et al. 2012; Tsai et al. 2012; Wu et al. 2009; Coulouarn et al. 2009; Bai et al. 2009; Cheung et al. 2008; Wang et al. 2012).

## *5.3 MiRNA and HCV Associated Liver Disease*

It was demonstrated that HCV replication is controlled by miR-122 (Jopling et al. 2005), and since then, the function of miR-122 in the hepatic tissue is mostly analyzed in relation to HCV replication. The reasons why HCV replication is controlled by suppressing the function of miR-122 are (1) The binding site of miR-122 is downstream to the internal ribosomal entry site, which controls duplication in the early stages of HCV infection (Henke et al. 2008), (2) It is possible that the isoprenoid biosynthetic pathway, controlled by miR-122, regulates HCV replication.miR-122 can directly regulate HCV replication when used as a target gene (Henke et al. 2008), (3) The recognition site of miR-122 in HCV is located in both the 5′-UTR and 3′-UTR domains. miR-122 forms an oligomeric complex in which one miR-122 molecule binds to the 5′-terminus of the HCV RNA, masking the 5′-terminal sequences of the HCV genome while the 3′ nucleotides are overhanging (Machlin et al. 2011). We highlight the most recent findings regarding the role of miRNAs in viral hepatitis, liver fibrosis, and HCC by analyzing the possible mechanisms by which they contribute to the progression of chronic liver disease. MiR-122, which is liver-tropic, can control HCV by stimulating and accelerating translation during replication of HCV (Jopling et al. 2005) and inhibition of miR-122 can block HCV replication.

Lohmann et al. (1999) have developed the HCV subgenomic replicon system, in which an HCV subgenomic replicon autonomously replicates in Huh-7 cells (HCV replicon cells). This technology has contributed greatly to the development of anti viral agents, and helped us to monitor the effect of miRNA on the replication of HCV. The algorithms that search miRNAs responsible for HCV-targets were demonstrated. MiRNAs, except miR-122, can also control the replication of HCV (Hsu et al. 2007) (Fig. 7.4). MiR-199a* can recognize the 5′-UTR region so over-expressing or inhibiting miR-199a* can respectively suppress or enhance HCV replication (Murakami et al. 2009). MiR-196, a HCV protein repressor, can recognize HCV genome as target gene (Hou et al. 2010) (Fig. 7.3).

MiR-130a expression was significantly higher in HCV-infected hepatocytes and liver biopsy specimens than in controls. MiR-130a can regulate interferon-induced trans-membrane 1 (IFITM1). Up-regulation of miR-130a in HCV infections reduces the expression level of IFITM1. This can inhibit HCV replication (Bhanja Chowdhury et al. 2012). The hepatic miRNA expression pattern that exists in

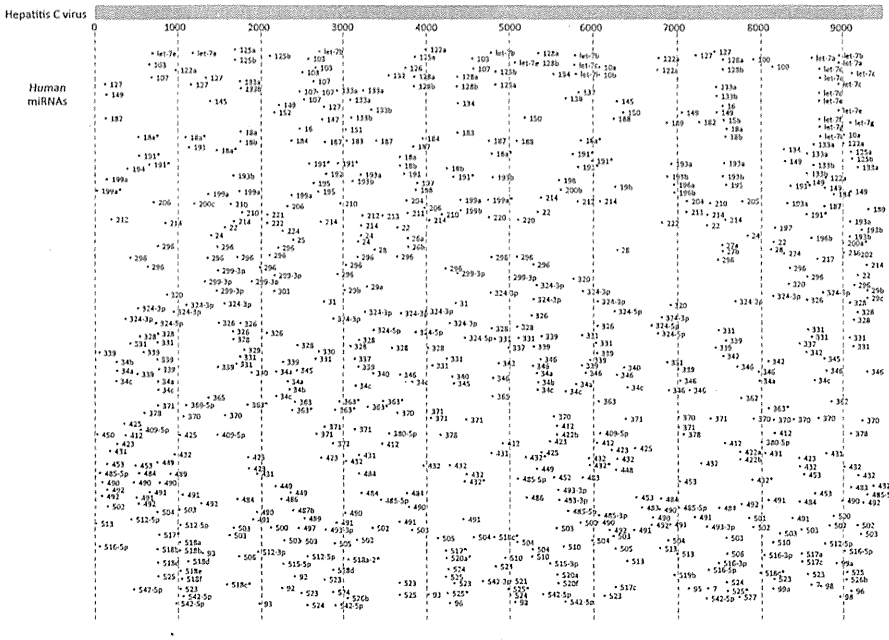


**Fig. 7.4** Hypothetical miRNAs target sites on HCV genome

chronic hepatitis c (CHC) patients before pegylated interferon and ribavirin combination therapy is associated with their therapeutic outcome. The expression level of nine miRNAs was significantly different in the sustained virological response (SVR) and non-responder (NR) groups. The accuracy of this diagnosis is 70.5 % (Murakami et al. 2010). Viral species may have different expression patterns for miRNA; for example, expression patterns of miRNAs are unique in HBV and HCV infections and are closely related to liver disease progression. When seventeen miRNAs are down-regulated in HCC, cancer –associated pathways such as cell cycle, adhesion, proteolysis, transcription, and translation are enhanced. However, when miRNAs are up-regulated in HCC, the anti-tumor immune response is suppressed (Murakami et al. 2010).

The miRNAs can recognize HCV genome by using the *in silico* target search algorithm (ViTa: http://vita.mbc.nctu.edu.tw). The number above the bar indicates the nucleotide number.

The paragraphs written above summarize the close relationship between miRNA and HCV infection and chronic liver disease. The accumulated information between expression pattern of miRNAs and HCV infection can pave the way for clinical application. This knowledge has opened the path to clinical applications of miRNA analysis. Many researchers have attempted to diagnose cancer using the miRNA expression in serum or plasma (Kosaka et al. 2010). Expression pattern in circulating miRNAs were used to diagnose chronic liver disease (Bihrer et al. 2011; Cermelli et al. 2011; van der Meer et al. 2013; Shrivastava et al. 2013; Murakami et al. 2012). The second phase of the clinical trial for chronic hepatitis C involves a complementary

based sequence of miR-122 and the uses of locked nucleic acid-miR-122 to control the function of liver miR-122 (Janssen et al. 2013). Biomarkers and nucleic acid drugs will be applied clinically in the near future.

## 6 MicroRNAs in Hepatitis B Virus; Expression, Regulation and Function

### *6.1 Basic Knowledge of HBV Infection*

The hepatitis B virus (HBV) is a small enveloped partially double-stranded DNA virus that belongs to the *Hepadnaviridae* family. This virus 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 (Ganem and Prince 2004). Epidemiological studies have revealed that chronic HBV infection is the major etiological factor in the development of HCC. Indeed, more than a half of the HCC patients are HBV carriers (Parkin 2006). Despite the availability of an efficacious vaccine, persistent HBV infection remains a challenging global health issue that requires a better understanding of the virus biology and pathogenesis for improved control and treatment.

The life cycle of HBV is complex (Fig. 7.5a). The initial stages of the acute HBV infection, including virion attachment, uncoating and nucleocapsid transport to the cell nucleus, are still poorly understood (Seeger and Mason 2000; Yan et al. 2012). Once delivered into the nucleus, the 3.2 kb relaxed circular DNA genome is converted into a covalently closed circular DNA (cccDNA) from which all the viral RNAs are transcribed. These transcripts include the pregenomic RNA (pgRNA) that will serve as template for reverse transcription and the subgenomic mRNAs that derive from the four overlapping gene sequences composing the viral genome. These sequences comprise the pre-S and surface genes, the precore and core 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 virion that will be secreted, or return to the nucleus to maintain the cccDNA amplification. When the immune system fails to clear the virus, the HBV infection becomes chronic (Fig. 7.5b). 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 (Brechot et al. 1980; Paterlini-Brechot et al. 2003).

MiRNAs play key roles in the regulation of almost every cellular process in all multicellular eukaryotes (Bartel 2009). As intracellular pathogens, viruses are affected by these post-transcriptional modulators and have found a way to subvert their effects. Several viruses, especially the herpesviruses, encode for miRNAs that increase their replication potential and/or allow the evasion from the innate immune system (Skalsky and Cullen 2010). This chapter will outline the implication of miRNAs in the HBV biology and the associated pathogenesis, including HCC development. We will also outline the present and future miRNA-based strategies for the diagnosis, prognosis and treatment of the HBV-related HCC.

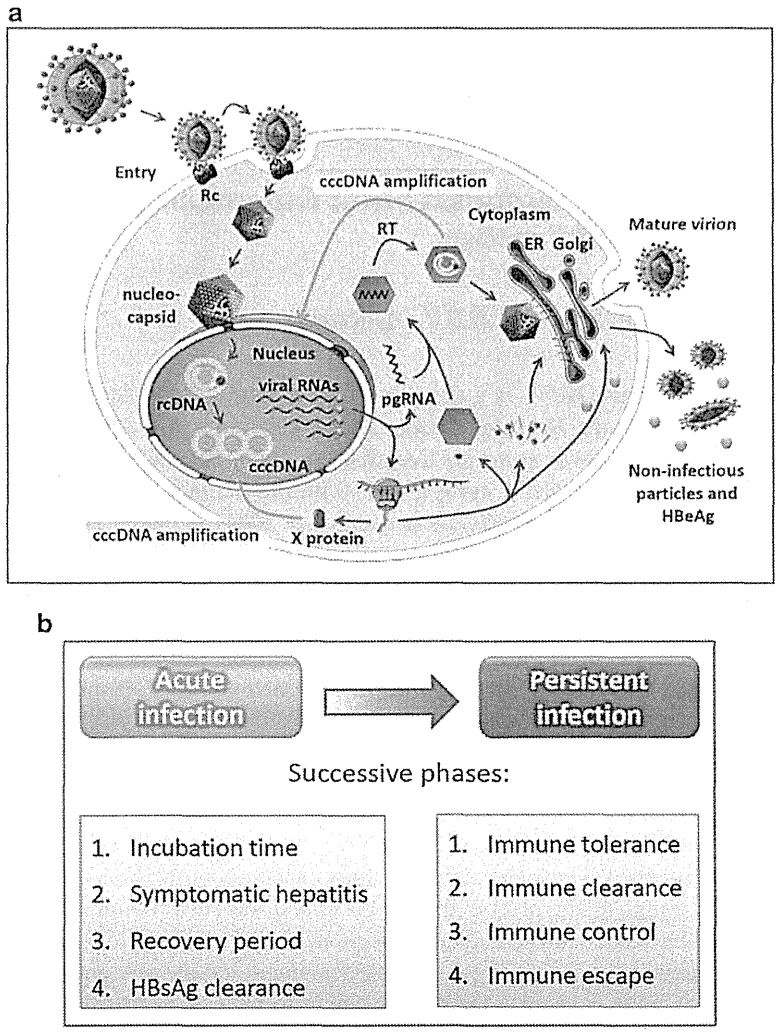


**Fig. 7.5** The HBV infection (**a**) Schematic representation of the HBV life cycle. (**b**) HBV natural history of infection. Abbreviations: *cccDNA* covalently closed circular DNA, *ER* endoplasmic reticulum, *HBeAg* hepatitis B extracellular "e" antigen, *HBsAg* HBV surface antigen, *pgRNA* pregenomic RNA, *Rc* receptor, *rcDNA* relaxed circular DNA, *RT* reverse transcription

## *6.2 MiRNAs Involved in the Regulation of HBV Gene Expression, Replication and Effects on the Carcinogenesis*

Viruses, nuclear DNA viruses in particular, need some time to complete their life cycle. During this period, the host cell can develop defense mechanisms such as cell cycle arrest and viral clearance. By taking advantage of the cellular miRNA machinery,

**Table 7.2** Cellular miRNAs and their effects on HBV biology, pathogenesis or related-HCC HBV (↑): Promotes HBV replication, HBV (↓): Inhibits HBV replication, HCC (↑): Development and/or growth of HCC

| Target genes | miRNAs | miRNA expressions | HBV or HCC status | Reference |
|---|---|---|---|---|
| *Viral target genes* | | | | |
| HBsAg | miR-199-3p | Up | HBV(↓) | Zhang et al. (2010) |
| HBVpre-S1 | miR-210 | Up | HBV(↓) | Zhang et al. (2010) |
| *Cellular target genes* | | | | |
| HDAC4 | miR-1 | Up | HBV (↑) | Zhang et al. (2011a) |
| c-myb | miR-15a | Down | HCC (↑) | Liu et al. (2009) |
| E2F1 (c-myc repressor) | miR-17-92 cluster | Up | HCC (↑) | Connolly et al. (2008) |
| PTEN (?) | miR-21 | Up | HCC (↑) | Connolly et al. (2008) |
| cyclin G1 (p53 modulator) | miR-122 | Down | HBV (↑), HCC (↑) | Wang et al. (2012) |
| DNMT1 | miR-152 | Down | HBV (↓) | Huang et al. (2010) |
| SOCS1 (STAT inhibitor) | miR-155 | Up | HBV(↓) | Su et al. (2011) |
| HLA-A (miR-181) | miR-181a, -181b, 200b | Up | HBV (↑) | Liu et al. (2009) |
| NFIB | miR-372,-373 | Up | HBV (↑) | Guo et al. (2011) |
| STAT3 | let-7 family | Down | HBV (↑?), HCC (↑) | Wang et al. (2010) |

these viruses can more easily and efficiently help to promote a favorable cellular environment for viral replication and achievement of the life cycle (Skalsky and Cullen 2010). The modulation of the machinery could be made by direct action on the cellular miRNAs (Backes et al. 2012; Jopling et al. 2005) (inhibition or up-regulation) or by expression of their own miRNAs that will mimic their cellular counterparts (Gottwein et al. 2007; Lu and Cullen 2004). Despite the fact that HBV is a nuclear DNA virus, none viral-encoded miRNA has been identified so far. Only one putative HBV-miRNA, with hypothetical regulation role on its own genome, was deduced by computational approach (Jin et al. 2007). However, several cellular miRNAs are involved in the HBV viral replication. They are presented here above and summarized in Table 7.2.

### 6.2.1 Cellular miRNAs That Promote HBV Replication

MiR-1 can enhance the HBV core promoter transcription and thus increase the viral replication by modulating the expression of several host genes such as transcription factors (Zhang et al. 2011a). The report has confirmed that the histone deacetylase 4 (HDAC4) expression is down-regulated by miR-1. Knowing that the cccDNA amplification is controlled by epigenetic regulation (Pollicino

et al. 2006), miR-1 could act in complementarity with the nuclear HBV X protein (HBx) in order to induce these modifications (Belloni et al. 2009). However, miR-1 can also inhibit the cell proliferation and even induce a reverse cancer cell phenotype (Zhang et al. 2011a). The roles of miR-1 in the cell proliferation and hepatocellular carcinogenesis (Datta et al. 2008) seem to be contradictory with the viral replication and with the characteristics of oncogenic virus but must represent benefit for HBV survival.

Another miRNA, miR-501, has also been suggested to work together with HBx for the benefit of viral replication (Jin et al. 2013). HBx itself has also the ability to deregulate the cellular miRNAs expression. This small protein is a key regulator of HBV infection. It is usually over-expressed in HCC and accumulated evidence indicates that HBx can promote hepatocarcinogenesis by disrupting the normal physiologic mechanisms of the host cell (Chirillo et al. 1997; Lee et al. 2005; Tian et al. 2013). The let-7 family of miRNAs has been demonstrated to be negatively regulated by HBx (Wang et al. 2010). This miRNA family is often observed down-regulated in many cancers including HCC (Guo et al. 2006; Johnson et al. 2005; Yu et al. 2007). The consequence of this down-regulation is the increase activity of that signal transducer and activator of transcription 3 (STAT3) that supports the cell proliferation, and potentially the hepatocarcinogenesis.

Finally, the miRNAs can promote the viral replication by the indirect stimulation the HBV enhancer element I or II. It is the case for the CCAAT/enhancer binding protein that binds and activates the HBV enhancer II in a dose-dependent manner (Lopez-Cabrera et al. 1991). miR-372, together with miR-373, targets the nuclear factor I/B, an important regulator of several viruses (Nagata et al. 1983), and so supports the HBV expression (Guo et al. 2011).

### 6.2.2 Cellular miRNAs That Prevent HBV Replication

One of the best studied miRNAs in 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) (Lagos-Quintana et al. 2002) and is pivotal in numerous aspects of the liver function such as lipid metabolism, liver development, differentiation, growth and neoplastic transformation (Girard et al. 2008). The essential role of mir-122 in the HCV replication reflects furthermore the importance of this miRNA in the infection process (Jopling et al. 2005). While the loss of miR-122 expression is impeding HCV replication, it is enhancing the replication in the circumstance of HBV infection (Wang et al. 2012). In fact, miR-122 can negatively regulate the viral gene expression and replication by direct binding to a highly conserved sequence of HBV (Chen et al. 2011). This repression effect can apparently be impeded by a negative feedback loop involving the Heme oxygenase-1 (Qiu et al. 2010). A recent study has reported the indirect implication of HBx in miR-122 deregulation (Song et al. 2013) that could, at least partially, explain the difference observed between the two viruses. Knowing that miR-122 expression is low in HBV and HCC tissues (Wang et al. 2012; Kutay et al. 2006)

and that HBV replication is usually low or absent in HCC cells (Wong et al. 2006), miR-122 is a highly potential linker between HBV infection and liver carcinogenesis (Wang et al. 2012; Fan et al. 2011) and therefore a predilected target for future clinical applications.

The miR-17-92 cluster is also important in the HBV-associated HCC. This polycistron includes six miRNAs (miR-17-5p, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a-1) and its up-regulated expression is associated with malignancies (Hayashita et al. 2005). By using human HBV-positive human HCC tissues, hepatoma cell lines and woodchuck hepatitis virus -induced HCC animal model (Popper et al. 1987), Connolly and colleagues were able to demonstrate the elevated expression of miR-17-92 cluster and its implication in the malignant phenotype (Connolly et al. 2008). The expression could be amplified by c-myc activation (He et al. 2005), under HBx control (Terradillos et al. 1997), to contribute to HBV latency state (Jung et al. 2013). The consequence is the induction of liver oncogenesis. Since the RNA intermediates of HBV (pgRNA and transcripts) are good targets of miRNA action, it is not surprising to observe several cellular miRNAs with different binding sites. So, in addition to miR-122 that targets the polymerase region (Chen et al. 2011), the mir-199a-3p and mir-210 can repress the S and pre-S1 regions, respectively (Zhang et al. 2010).

All the examples illustrating cellular miRNAs as inhibitors of the viral replication are a bit difficult to comprehend initially because of their obvious negative effect on HBV infection. However, it can be understood by keeping in mind the survival of the virus into the host organism. The natural history of HBV infection shows often a transition from acute to chronic infection, especially in young children. This step corresponds to a failure of the immune system to eradicate the virus (Fig. 7.5b). One of the escape pathways is the successful adaptation to the immune-induced down-regulation of replication. The virus could evade the immune system by reaching a dormant state into the infected hepatocytes, under the cccDNA form, and survive until its eventual life cycle reactivation (Ganem and Prince 2004; Belloni et al. 2009, 2012; Huang et al. 2010). The study of Huang and colleagues reports the CpG islands methylation of the cccDNA by the DNA methyltransferase 1 (DNMT1) to prevent the viral gene expression and therefore the viral antigen presentation. DNMT1 over-expression is induced by a decrease of miR-152, under the effect of HBx (Huang et al. 2010).

## *6.3 MiRNAs in the Modulation of the Immune System and Effects on the Carcinogenesis*

HBV must adapt to a very complex network in order to survive. It has to cope with the modification of homeostasis, the cell cycle arrest, the apoptosis and the destruction of the host cell by the immune cells. MiRNAs are also important in the development and function of immune system (Baltimore et al. 2008). Some miRNAs in particular are crucial for modulating innate and adaptive immune responses. MiR-155 has multi-roles during an innate immune response such as the regulation of the acute inflammatory response after recognition of pathogens by the toll-like

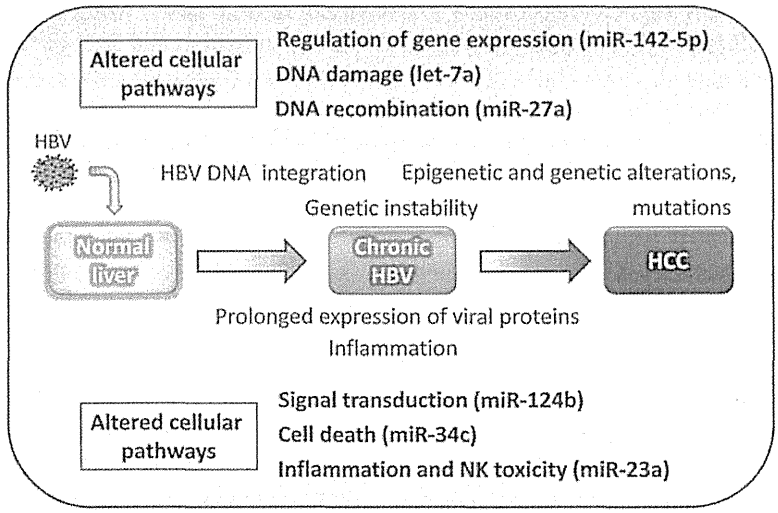


**Fig. 7.6** Chronology of events from the HBV infection until HCC development. The indicated altered miRNAs and related pathways are based on the results from Ura et al. (2009)

receptors (O'Connell et al. 2007; Tili et al. 2007). The up-regulation of miR-155 can lead to prolonged exposure to inflammation, a well-known causal agent to cancers like HCC (Berasain et al. 2009). Two recent studies suggest a role of miR-155 in hepatocarcinogenesis and HBV infection (Table 7.2). Using HCC-induced mouse model, Wang and collaborators have demonstrated an oncogenic role of miR-155 at the early stages of the tumorigenesis (Wang et al. 2009a). On the other hand, the ectopic expression of miR-155 in human hepatoma cells enhances the innate immunity through promotion of the JAK/STAT pathway and down-regulates HBx expression (Su et al. 2011).

A study analyzing the modified expression profiles of miRNAs in a stable HBV-expressing cell line revealed the up-regulation of miR-181a (Liu et al. 2009) (Table 7.2). The deregulation of this miRNA in liver cell might participate to the establishment of HBV persistence through inhibition of the human leukocyte antigen A (HLA-A) -dependent HBV antigen presentation. To date, it is unclear if miRNAs altered in the host cell, like miR-181a and miR-146a also present in Liu's study, miRNAs involved in ubiquitous and cell-specific regulatory functions, could affect directly the immune cells. The presence of circulating miRNAs, as well as the existence of intercellular nanovesicle-mediated miRNA transfer and its impact on the environmental modulation, could potentially support that hypothesis (Arataki et al. 2013; Waidmann et al. 2012; Li et al. 2010, 2012; Zhou et al. 2011; Kogure et al. 2011). The current knowledge shows an altered miRNA profile expression between normal and HCC liver at the different stages, and between the HBV and HCV-induced HCC (Murakami et al. 2006; Li et al. 2008; Budhu et al. 2008; Ura et al. 2009). For the latest one, this reflects the variation in the cellular pathways that are modulated as a consequence of the viral infection (Fig. 7.6).

### *6.4 MiRNAs as Biomarkers and Treatment-Based Strategies for HBV Infection and HBV-Induced HCC*

It is important to know the precise mechanisms, the cellular pathways that the viral infection or cancer cells alter in the different steps of the infection and/or tumor evolution. The knowledge will allow developing powerful targeted therapeutical strategies. The significance of miRNAs in antiviral immunity and liver carcinogenesis emphasizes their values as therapeutic targets for HBV infection and HBV-induced HCC. MiR-122 and miR-18a are of particular interest. They are both released in the blood and could be used as potential non-invasive biomarkers for HBV-related HCC screening (Liu et al. 2009; Waidmann et al. 2012; Li et al. 2012). Some other reports suggest using a miRNA panel in order to improve the specificity of the test (Li et al. 2010; Zhou et al. 2011). In addition with the current routinely used markers such as HBV surface antigen, HBV extracellular antigen and alanine aminotransferase, 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 work of Ura's group is valuable. 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 (Ura et al. 2009). The HBV infection alters mostly the pathways related to signal transduction, inflammation and natural killer toxicity, DNA damage, recombination, and cell death (Fig. 7.6), while HCV infection modifies those involved in immune response involving antigen presentation, cell cycle and cell adhesion (Ura et al. 2009).

Moreover, 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 collaborators on the liver cancer (Kota et al. 2009). 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.

## 7 Concluding Remarks

MiRNAs have emerged as novel key players in the control of gene expression in cells. Investigations of their profiling have unveiled specific miRNA deregulations in tumors and in condition of viral infection. On the viral point of view, the deregulated 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 is trying to get rid of the intruder and that become

deregulated. In both cases, the viral infection leads to the alteration of miRNA expression by RSSs that can trigger tumorigenesis. Several oncogenic viruses, especially herpesviruses like EBV and KSHV, encode their own miRNAs to modify both cellular and viral gene expression (Pfeffer et al. 2004). This step is crucial for their latency phase. On the other hand, HPV, HBV and HCV do not express viral miRNAs but can affect the host miRNA pathway. The present and future knowledge about miRNA will broaden our understanding of the pathogenesis of oncogenic viruses and most certainly allow developing efficient oncogenic viral therapies.

**Acknowledgements** The authors would like to thank Servier Medical Art for their image bank used to create the illustrations.

## References

Abend JR, Uldrick T, Ziegelbauer JM (2010) Regulation of tumor necrosis factor-like weak inducer of apoptosis receptor protein (TWEAKR) expression by Kaposi's sarcoma-associated herpesvirus microRNA prevents TWEAK-induced apoptosis and inflammatory cytokine expression. J Virol 84(23):12139–12151

Alajez NM, Lenarduzzi M, Ito E, Hui AB, Shi W, Bruce J et al (2011) MiR-218 suppresses nasopharyngeal cancer progression through downregulation of survivin and the SLIT2-ROBO1 pathway. Cancer Res 71(6):2381–2391

Amoroso R, Fitzsimmons L, Thomas WA, Kelly GL, Rowe M, Bell AI (2011) Quantitative studies of Epstein-Barr virus-encoded microRNAs provide novel insights into their regulation. J Virol 85(2):996–1010

Appel N, Schaller T, Penin F, Bartenschlager R (2006) From structure to function: new insights into hepatitis C virus RNA replication. J Biol Chem 281(15):9833–9836

Arataki K, Hayes CN, Akamatsu S, Akiyama R, Abe H, Tsuge M et al (2013) Circulating microRNA-22 correlates with microRNA-122 and represents viral replication and liver injury in patients with chronic hepatitis B. J Med Virol 85(5):789–798

Au Yeung CL, Tsang TY, Yau PL, Kwok TT (2011) Human papillomavirus type 16 E6 induces cervical cancer cell migration through the p53/microRNA-23b/urokinase-type plasminogen activator pathway. Oncogene 30(21):2401–2410

Backes S, Shapiro JS, Sabin LR, Pham AM, Reyes I, Moss B et al (2012) Degradation of host microRNAs by poxvirus poly(A) polymerase reveals terminal RNA methylation as a protective antiviral mechanism. Cell Host Microbe 12(2):200–210

Baer R, Bankier AT, Biggin MD, Deininger PL, Farrell PJ, Gibson TJ et al (1984) DNA sequence and expression of the B95-8 Epstein-Barr virus genome. Nature 310(5974):207–211

Bai S, Nasser MW, Wang B, Hsu SH, Datta J, Kutay H et al (2009) MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. J Biol Chem 284(46):32015–32027

Baltimore D, Boldin MP, O'Connell RM, Rao DS, Taganov KD (2008) MicroRNAs: new regulators of immune cell development and function. Nat Immunol 9(8):839–845

Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. Cell 136(2):215–233

Barth S, Pfuhl T, Mamiani A, Ehses C, Roemer K, Kremmer E et al (2008) Epstein-Barr virus-encoded microRNA miR-BART2 down-regulates the viral DNA polymerase BALF5. Nucleic Acids Res 36(2):666–675

Bellare P, Ganem D (2009) Regulation of KSHV lytic switch protein expression by a virus-encoded microRNA: an evolutionary adaptation that fine-tunes lytic reactivation. Cell Host Microbe 6(6):570–575

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