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The Diagnostic and Prognostic Potential of MicroRNAs for Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (also termed hepatocarcinoma) is the third cancer-related cause of death worldwide. To our knowledge, markers such as α -fetoprotein display poor performance in the early diagnosis and prognosis prediction of hepatocarcinoma. MicroRNAs are an evolutionarily conserved class of small noncoding single-stranded RNA typically consisting of 18–24 nucleotides. They have been reported to act as tumor suppressors or oncogenes via reversely regulating gene expression. Recent evidence has revealed that microRNAs, especially in body fluids such as the blood and urine, display important diagnostic and prognostic potential for hepatocarcinoma. Here, we reviewed currently available data on microRNAs and hepatocarcinoma, with emphasis on the biogenesis and function of microRNAs and their potential diagnostic and prognostic value for hepatocarcinoma. We also discussed the clinical utility perspectives of microRNAs in hepatocarcinoma and possible challenges.

Keywords: hepatocarcinoma, microRNA, diagnosis, prognosis

1. Introduction

Hepatocarcinoma, also termed as hepatocellular carcinoma (HCC) or liver carcinoma, is the most common primary liver malignant disease in adults [1]. One of the most striking features of this malignant tumor is the wide variation in its incidence in different parts of the world. In areas of high incidence, such as China, hepatocarcinoma is among the leading cause of cancer-correlated deaths in recent years, with an annual incidence of approximately 40 per 100,000 [2, 3]. However, the countries in the low incidence, such as the USA, have only 2.3% of cancer-related deaths in

past decades. Globally, hepatocarcinoma is the fifth most common cancer among males and the eighth most common among females [1]. Furthermore, the incidence of this tumor generally increases with age, although there are geographic and gender differences. The precise reasons for this difference is not known, but growing evidence has exhibited that multiple factors including chronic viral hepatitis B (HBV) and C (HCV), aflatoxin (such as aflatoxin B1) exposure, hepatic cirrhosis, obesity, diabetes, and vitamin D deficiency play an important role [4–6]. Although the molecular mechanism of hepatocarcinoma has been unclear, these hepatocarcinoma patients with early diagnosis often have good prognosis with more than 50% of five overall survival rate [6]. This is mainly because they benefit from the curative treatment such as curative resection and orthotopic liver transplantation [6]. However, if patients are lately diagnosed, the cumulative 5-year survival rate remarkably reduces to less than 10%, and tumor recurrence risk noticeably increases (about 70–80% of 5-year recurrence rate). Thus, it is very urgent to identify specific and sensitive markers for early diagnosing hepatocarcinoma at a curative stage, monitoring recurrence of tumor, and predicting prognosis of tumor [6].

Currently, the early diagnosis of hepatocarcinoma is based on the following two classes of methods: imaging examination which mainly consists of ultrasonography, magnetic resonance imaging, and computed tomography and serological tests such as serum α -fetoprotein (AFP) [4, 7]. Although advances in imaging technologies have significantly improved the early screening of hepatocarcinoma, these methods are so costly and unsatisfactory in early diagnosis that is not suitable for daily clinical practice [4, 7]. About serological methods, AFP is the most widely utilized marker for the diagnosis and prognosis prediction of hepatocarcinoma. However, this biomarker is limited because of its modest accuracy (with sensitivity of 40–65% and specificity of 87–96%) and about 30–40% of the false-negative rate for patients with early-stage hepatocarcinoma [8]. Additionally, serum AFP levels of some benign hepatic lesions, such as liver nodular hyperplasia, inflammation lesions of liver, and liver fibrotic cirrhosis, may give false-positive results [8]. Therefore, the reliability of this biomarker to determine hepatocarcinoma is inadequate because of its low sensitivity and specificity.

Emerging evidence has exhibited a correlation between dysregulation of microRNAs and development of hepatocarcinoma. Particularly, microRNAs are characterized by high stability in body fluids (including the blood and urine) and tissue specific in expression patterns, indicative of microRNAs in body fluids acting as potentially novel and ideal biomarkers for hepatocarcinoma diagnosis and prognosis prediction [8–16].

This review attempts to briefly review currently available data on microRNAs and hepatocarcinoma, with emphasis on (1) the biogenesis and function of microRNA, (2) potential diagnostic and prognostic value for hepatocarcinoma, and (3) the different value for hepatocarcinoma induced by different causes. Additionally, we summarized the clinical applicative perspectives and potential challenges of microRNAs in hepatocarcinoma.

2. MicroRNA biogenesis and function

Previous several reports have thoroughly reviewed biogenesis and function of microRNAs [8, 11, 17–29]. In brief, microRNAs are an evolutionarily conserved class of small noncoding

single-stranded RNA typically consisting of 18–24 nucleotides. Originally, they are first transcribed by the RNA polymerase enzyme II into a kind of primary production named as primary microRNA that is characterized by long nucleotide sequences, 5'-cap structure, and 3'-poly-A tail, resembling protein-coding mRNAs. Then, primary microRNAs form a hairpin-shaped stem-loop structure and are processed into microRNA precursors (usually containing 60–70 nucleotides) by the microprocessor complex (consisting of DGCR8/Pasha and Drosha). After that, their precursors are transported to the cytoplasm and treated into a short double-strand duplex structure by another RNase endonuclease III (also called Dicer). Finally, the duplex structure (also called microRNA-microRNA*) is unwound into mature microRNAs by helicases. To date, it has been identified that there are more than 1800 microRNAs in the mammalian genome (miRDatabase) (**Figure 1**) [30]. Functionally, microRNAs are involved in regulating the expression of their

Figure 1. Biosynthesis and functions of microRNA. In the nucleus, the microRNA genes are transcribed into primary microRNAs by RNA polymerase II (Pol II). The primary microRNAs are then cleaved by Drosha and DGCR8 and produce their precursor molecules (also named as precursor microRNA). After that, the precursor molecules are transported to the cytoplasm by Exportin-5 and Ran-GTP and undergo final processing step including the cleavage by Dicer and the formation of stem-loop duplex molecule structure which contains the single-stranded mature microRNA molecule and a microRNA* fragment. Finally, the duplex molecule structure is incorporated into the RNA-induced silencing complex (RISC), the microRNA* fragments are degraded, and mature microRNA molecules are formed. The mature microRNAs can display genic regulation role via recognizing and binding to the 3'-untranslated region of their target genes' mRNAs. *Note:* This figure is plotted according to ScienceSlides (version#2016).

targeting genes via recognizing and integrating into the 3'-untranslated region of these genes' mRNAs. On the basis of perfect or imperfect base-base complementarity of microRNAs-their targeting mRNA binding, one microRNA specifically regulates the expression of multiple mRNAs, and at the same time, one mRNA might be inhibited by multiple microRNAs. This indicates the specificity and diversity of microRNAs regulating gene expression. In the past decades, microRNAs are emerged as important players in a very wide range of physiological processes including cell differentiation, cell proliferation and apoptosis, cycle regulation, survival, detoxification, physiological timing, metabolism, angiogenesis, hormone secretion, and DNA damage repair (**Figure 1**). Furthermore, growing evidence has shown that microRNAs can also display a role in the etiology and pathogenesis of various cancers by targeting many oncogenes or tumor inhibitive genes (**Figure 1**) [24, 27, 29–32]. Recent several reports have exhibited that some microRNAs involve in the tumorigenesis and procession of hepatocarcinoma and may become new potential markers for hepatocarcinoma diagnosis and prognosis [24, 27, 29, 31, 32].

3. MicroRNAs as novel biomarkers for hepatocarcinoma diagnosis

3.1. Diagnostic potential of single microRNA for hepatocarcinoma

With increasing incidence and death rate of hepatocarcinoma, it is very expected to identify one or several diagnostic biomarkers (with both high sensitivity and specificity) such as microRNAs for this malignancy. Growing evidence has shown that the expression change of all microRNAs in the peripheral blood may have a unique advantage because they exhibit tissue specificity and relative stability and can also provide some specific cues for early and small hepatocarcinoma [8–14]. Until now, more than 30 circulating microRNAs have been identified to have diagnostic potential for hepatocarcinoma (**Table 1**). For example, microRNA-122 has been reported as a hepatic-specific microRNA, accounting for 70% of the total microRNAs in hepatic tissues. This microRNA, a high conservative microRNA between vertebrate species, is indicative of a regulator of fatty acid metabolism and playing a critical role in liver homeostasis and tumorigenesis [19, 33, 34]. Increasing evidence has shown that elevated serum amount of microRNA-122 is positively associated with the severity of hepatic diseases including hepatitis, fatty- and alcohol-related liver damage, and drug-induced hepatotoxicity [35–39]. Interestingly, this increasing serum expression of microRNA-122 is noticeable and indicated that it could serve as a potential biomarker for the detection of patients with hepatocarcinoma from healthy controls with about 85% of the area under the receiver operating characteristic curve (AUC), 80% of sensitivity, and 80% of specificity [40, 41]. These results indicate that the dysregulated miR-122 in the peripheral blood may be used as a potential marker for hepatocarcinoma diagnosis. Results from retrospective studies have suggested that the microRNA-200 family (consisting of microRNA-200a and microRNA -200b) is also a promising biochemical biomarker for hepatocarcinoma diagnosis because of its deregulation during the development of both hepatic fibrosis and hepatocarcinoma [42, 43]. The elevated plasma levels of microRNA-21 can distinguish patients with hepatocarcinoma from cases with chronic hepatitis (with 61.1% of sensitivity and 83.3% of specificity) or healthy controls (the corresponding sensitivity and specificity are 87.3 and 92.0%, respectively) [44]. This suggests that this biomarker may have higher diagnostic potential than AFP. Some

MicroRNAs	Source	Diagnostic relevance	Expression level	AUC (95% CI)	Sen (%)	Spe (%)	Refs
miR-12	Serum	HCCs (n = 101) vs. HCs (n = 89)	Upregulated	0.87 (0.81–0.93)	84.0	75.3	[41]
miR-122	Serum	HCCs (n = 101) vs. HCs (n = 89)	Upregulated	0.79 (0.71–0.86)	70.7	69.1	[41]
miR-223	Serum	HCCs (n = 101) vs. CHCs (n = 89)	Upregulated	0.86 (0.80–0.92)	80.0	76.5	[41]
miR-12	Serum	HCCs (n = 101) vs. HCs (n = 48)	Upregulated	0.91 (0.84–0.97)	80.0	95.6	[41]
miR-122	Serum	HCCs (n = 101) vs. HCs (n = 48)	Upregulated	0.93 (0.88–0.98)	80.0	91.2	[41]
miR-223	Serum	HCCs (n = 101) vs. HCs (n = 48)	Upregulated	0.88 (0.81–0.94)	80.0	75.0	[41]
miR-122	Serum	HCCs (n = 70) vs. HCs (n = 34)	Upregulated	0.87 (0.79–0.95)	81.6	83.3	[40]
miR-122	Serum	HCCs (n = 70) vs. CHCs (n = 45)	Upregulated	0.63 (0.52–0.74)	77.6	57.8	[40]
miR-21	Plasma	HCCs (n = 126) vs. HCs (n = 50)	Upregulated	0.77	61.1	83.3	[44]
miR-21	Plasma	HCCs (n = 126) vs. CHCs (n = 30)	Upregulated	0.95	87.3	92.0	[44]
miR-143	Serum	HCCs (n = 95) vs. CTLs (n = 245)	Upregulated	0.80 (0.68–0.92)	73.0	83.0	[46]
miR-215	Serum	HCCs (n = 95) vs. CTLs (n = 245)	Upregulated	0.82 (0.72–0.97)	80.0	91.0	[46]
miR-10b	Serum	HCCs (n = 27) vs. HCs (n = 50)	Upregulated	0.85 (0.76–0.94)	/	/	[51]
miR-10b	Serum	HCCs (n = 27) vs. CLDs (n = 31)	Upregulated	0.73 (0.60–0.86)	/	/	[51]
miR-106b	Serum	HCCs (n = 27) vs. HCs (n = 50)	Upregulated	0.82 (0.72–0.91)	/	/	[51]
miR-106b	Serum	HCCs (n = 27) vs. CLDs (n = 31)	Upregulated	0.71 (0.57–0.84)	/	/	[51]
miR-181a	Serum	HCCs (n = 27) vs. HCs (n = 50)	Upregulated	0.89 (0.81–0.97)	/	/	[51]
miR-181a	Serum	HCCs (n = 27) vs. CLDs (n = 31)	Upregulated	0.81 (0.70–0.92)	/	/	[51]
miR-206	Serum	HCCs (n = 261) vs. HCs (n = 173)	Upregulated	0.62 (0.55–0.68)	48.1	78.8	[52]
miR-143-3p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Upregulated	0.76 (0.70–0.80)	68.1	83.3	[52]
miR-433-3p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Upregulated	0.74 (0.67–0.80)	79.3	64.4	[52]
miR-1228-5p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Upregulated	0.55 (0.44–0.60)	79.3	27.8	[52]
miR-199a-5p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Downregulated	0.64 (0.57–0.71)	59.3	66.7	[52]

MicroRNAs	Source	Diagnostic relevance	Expression level	AUC (95% CI)	Sen (%)	Spe (%)	Refs
miR-122-5p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Downregulated	0.70 (0.63–0.77)	48.9	82.2	[52]
miR-192-5p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Downregulated	0.70 (0.62–0.77)	71.9	75.6	[52]
miR-26a-5p	Serum	HCCs (n = 261) vs. HCs (n = 173)	Downregulated	0.76 (0.70–0.82)	68.9	74.4	[52]
miR-206	Serum	HCCs (n = 261) vs. CCs (n = 233)	Upregulated	0.69 (0.62–0.77)	77.8	68.9	[52]
miR-143-3p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Upregulated	0.66 (0.60–0.73)	60.7	72.7	[52]
miR-433-3p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Upregulated	0.64 (0.58–0.71)	56.4	67.4	[52]
miR-1228-5p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Upregulated	0.54 (0.47–0.61)	66.7	47	[52]
miR-199a-5p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Downregulated	0.59 (0.52–0.66)	59.3	57.6	[52]
miR-122-5p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Downregulated	0.75 (0.69–0.81)	48.9	90.2	[52]
miR-192-5p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Downregulated	0.69 (0.62–0.75)	54.8	83.3	[52]
miR-26a-5p	Serum	HCCs (n = 261) vs. CCs (n = 233)	Downregulated	0.74 (0.68–0.81)	60.7	90.9	[52]
miR-16	Serum	HCCs (n = 105) vs. CTLs (n = 188)	Downregulated	/	72.1	88.8	[14]
miR-199	Serum	HCCs (n = 105) vs. CTLs (n = 188)	Downregulated	/	62.9	93.5	[14]
miR-199a	Serum	HCCs (n = 105) vs. CTLs (n = 188)	Downregulated	/	78.1	64.5	[14]
miR-375	Serum	HCCs (n = 78) vs. HCs (n = 156)	Downregulated	0.64 (0.56–0.74)	/	/	[53]
miR-199a-3p	Serum	HCCs (n = 78) vs. HCs (n = 156)	Downregulated	0.88 (0.83–0.94)	/	/	[53]
miR-30c-5p	Plasma	HCCs (n = 8) vs. CTLs (n = 86)	Upregulated	/	/	/	[54]
miR-223-3p	Plasma	HCCs (n = 8) vs. CTLs (n = 86)	Downregulated	/	/	/	[54]
miR-202c-3p	Plasma	HCCs (n = 8) vs. CTLs (n = 86)	Upregulated	/	/	/	[54]
miR-17-57	Plasma	HCCs (n = 8) vs. CTLs (n = 86)	Upregulated	/	/	/	[54]
miR-4651	Serum	AHCCs (n = 279) vs. HCs (n = 338)	Upregulated	0.89 (0.86–0.92)	78.1	99.1	[55]
miR-4651	Serum	AHCCs (n = 279) vs. AHCs (n = 292)	Upregulated	0.82 (0.78–0.85)	78.1	85.3	[55]
miR-4651	Serum	AHCCs (n = 279) vs. ALCs (n = 32)	Upregulated	0.80 (0.71–0.88)	78.1	81.2	[55]

MicroRNAs	Source	Diagnostic relevance	Expression level	AUC (95% CI)	Sen (%)	Spe (%)	Refs
miR-4651	Serum	AHCCs (n = 279) vs. CTLs (n = 662)	Upregulated	0.85 (0.82–0.88)	78.1	92.1	[55]
miR-143	Serum	HCCs (n = 131) vs. HCs (n = 122)	Downregulated	0.83	80.3	82.4	[56]
miR-125b	Plasma	HCCs (n = 64) vs. HCs (n = 56)	Downregulated	0.89	90.0	80.0	[57]
miR-125b	Plasma	HCCs (n = 64) vs. CHBs (n = 63)	Downregulated	0.96	90.0	90.0	[57]
miR-125b	Plasma	HCCs (n = 64) vs. CCs (n = 59)	Downregulated	0.96	90.0	90.0	[57]
miR-150	Serum	HCCs (n = 120) vs. CHBs (n = 110)	Downregulated	0.88 (0.84–0.93)	79.1	76.5	[58]
miR-150	Serum	HCCs (n = 120) vs. HCs (n = 120)	Downregulated	0.93 (0.90–0.96)	82.5	83.7	[58]
miR-106b	Plasma	HCCs (n = 47) vs. CTLs (n = 61)	Upregulated	0.81	0.7	0.8	[59]
miR-200a	Serum	HCCs (n = 22) vs. HCs (n = 15)	Downregulated	0.82 (0.69–0.97)	/	/	[60]
miR-200a	Serum	HCCs (n = 22) vs. CCs (n = 22)	Downregulated	0.73 (0.56–0.89)	/	/	[60]
miR-143	Serum	HCCs (n = 95) vs. CHCs (n = 118)	Upregulated	0.62 (0.51–0.76)	78.0	64.0	[46]
miR-215	Serum	HCCs (n = 95) vs. CHCs (n = 118)	Upregulated	0.80 (0.67–0.95)	78.0	89.0	[46]
miR-143	Serum	HCCs (n = 95) vs. HCs (n = 127)	Upregulated	0.80 (0.68–0.92)	78.0	89.0	[46]
miR-215	Serum	HCCs (n = 95) vs. HCs (n = 127)	Upregulated	0.82 (0.72–0.97)	80.0	91.0	[46]
miR-101	Serum	HCCs (n = 67) vs. HCs (n = 30)	Downregulated	0.79 (0.69–0.87)	76.1	70.0	[61]
miR-483-5p	Serum	HCCs (n = 49) vs. HCs (n = 49)	Upregulated	0.91	75.5	89.8	[62]
miR-122a	Plasma	HCCs (n = 85) vs. HCs (n = 85)	Downregulated	0.71	70.6	67.1	[63]
miR-618	Urine	HCCs (n = 32) vs. CTLs (n = 74)	Upregulated	0.66	64.0	68.0	[47]
miR-650	Urine	HCCs (n = 32) vs. CTLs (n = 74)	Downregulated	0.65	72.0	58.0	[47]
miR-126	tumor tissue	HCCs vs. CAs	Upregulated	/	/	/	[48]

Abbreviation: miR, microRNA; HCCs, cases with hepatocarcinoma; CTLs, non-HCC controls (including healthy control and other nontumor controls); HCs, healthy controls; CCs, controls with liver cirrhosis; CHBs, patients with chronic hepatitis B; CLDs, cases with nontumor chronic liver diseases; Sen, sensitivity; Spe, specificity; AUC, the area under the receiver operating characteristic curve; CI, confidence interval; Refs, references.

Table 1. The microRNAs as diagnostic biomarkers for hepatocarcinoma.

other serum microRNAs, such as microRNA-15b, microRNA-130b, miR-143, and miR-215, are additional potential biomarkers that are significantly dysregulated in hepatocarcinoma [45, 46]. Noticeably, these biomarkers also exhibit their diagnostic potential for patients with early-stage hepatocarcinoma and/or negative-status AFP [45, 46].

Recently, some evidence has also exhibited that microRNAs in urine samples and liver tissues have screening potential for hepatocarcinoma (**Table 1**). Actually, the detection of five deregulated microRNAs, including microR-618, microRNA-625, microRNA-650, microRNA-532, and miR-516-5P, in the urine samples has already been used for screening patients with the early and small hepatocarcinoma from these with risk factors such as chronic virus hepatitis, liver cirrhosis, and dysplasia [47]. Barshack et al. [48] investigated differential diagnosis potential of microRNAs for discriminating hepatocarcinoma from metastatic tumors in the liver using custom microarray expression technique. In their study, they tested the distributed features of microRNAs among 144 tumor samples with or without metastatic adenocarcinoma and similar hepatocarcinoma in the morphology and immune types and found that microR-141 and microR-200c can promote non-hepatic epithelial phenotypes while microRNA-126 displays hepatic epithelial phenotypes. Higher expression of microRNA-126 is further shown in these tissue samples with hepatocarcinoma. Therefore, the change profiles of microRNAs in body fluids (such as urine) and tumor tissues may represent a kind of gold biomarkers for such cancers as liver carcinoma.

However, the specificity of a single microRNA identifying hepatocarcinoma is relatively poor. For example, the serum level of aforementioned liver-specific microRNA-122 is upregulated not only among cases with hepatocarcinoma but also among these with chronic virus hepatitis, liver cirrhosis, and fatty liver diseases caused by alcohol or non-alcohol [49, 50]. Evidence has shown that serum microRNA-122 does not discriminate patients with hepatocarcinoma from these with chronic hepatitis, although higher expression is observed among cancer cases [40, 41]. This indicates that more investigations on the basis of large size of samples and the prospective randomized controlled trials should help us for addressing these concerns.

3.2. Diagnostic potential of microRNA panel for hepatocarcinoma

Because hepatocarcinoma is a multifactor-induced highly complex malignant disease with heterogeneous feature, a combination of multiple microRNAs in place of a single microRNA may have higher accuracy for hepatocarcinoma discrimination. Several circulating microRNA panels have been reported to have higher early diagnostic value for hepatocarcinoma (**Table 2**) [47, 51, 52, 64–70]. For example, Lin et al. [70] preformed a three-stage study consisting of the discovery stage (including 6 cases with hepatocarcinoma and 8 cases with chronic hepatitis B), the training stage (including 108 cases with hepatocarcinoma, 51 cases with chronic hepatitis B, 47 cases with liver cirrhosis, and 51 healthy controls), and the validation stage (including 229 patients with hepatocarcinoma and 424 controls with or without nontumor liver diseases). In the first stage, they identified 31 different serum microRNAs between individuals with hepatocarcinoma and those with chronic hepatitis B using the TaqMan Array technique. Next, they validated these different microRNAs and constructed diagnostic panel containing miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, and miR-505 on the basis of logistic regression model. Finally, the established serum microRNA panel was tested among

MicroRNA panel	Source	AUC (95% CI)	Sen (%)	Spe (%)	Diagnostic relevance	Refs
miR-10b + miR-106b + miR-181a	Serum	0.94 (0.89–0.99)	/	/	HCCs (n = 27) vs. HCs (n = 50)	[51]
miR-10b + miR-106b + miR-181a	Serum	0.91 (0.80–0.97)	/	/	HCCs (n = 27) vs. CLDs (n = 31)	[51]
miR-206 + miR-143-3p + miR-433-3p + miR-1228-5p + miR-199a-5p + miR-122-5p + miR-192-5p + miR-26a-5p	Serum	0.89 (0.85–0.94)	82.8	83.3	HCCs (n = 261) vs. HCs (n = 173)	[52]
miR-206 + miR-143-3p + miR-433-3p + miR-1228-5p + miR-199a-5p + miR-122-5p + miR-192-5p + miR-26a-5p	Serum	0.89 (0.84–0.94)	81.6	84.6	HCCs (n = 261) vs. CCs (n = 233)	[52]
miR-122 + miR-192 + miR-21 + miR-223 + miR-26a + miR-27a + miR-801	Plasma	0.86 (0.83–0.90)	68.6	90.1	HCCs (n = 204) vs. CTLs (n = 303)	[64]
miR-122 + miR-192 + miR-21 + miR-223 + miR-26a + miR-27a + miR-801	Plasma	0.89 (0.85–0.92)	81.8	83.5	HCCs (n = 196) vs. CTLs (n = 194)	[64]
miR-27b-3p + miR-192-5p	Serum	0.84 (0.78–0.89)	0.7	0.9	HCCs (n = 91) vs. CTLs (n = 91)	[65]
miR-92-3p + miR-107 + miR-3126-5p	Serum	0.97 (0.95–0.99)	/	/	HCCs (n = 115) vs. HCs (n = 40)	[66]
88-miRNA	Serum	1.00 (0.97–1.00)	100.0	99.2	HCCs (n = 261) vs. CCs (n = 233)	[67]
miR214-5p + miR-125b + miR-1269 + miR-375	Serum	0.95	96.9	83.2	HCCs (n = 224) vs. HCs (n = 84)	[68]
miR-122 + miR-885-5p + miR-29b	Serum	1.00	/	/	HCCs (n = 192) vs. HCs (n = 96)	[69]
miR-29a + miR-29c + miR-133a + miR-143 + miR-145 + miR-192 + miR-505	Serum	0.82 (0.77–0.87)	74.5	89.9	HCCs (n = 153) vs. CTLs (n = 199)	[70]
miR-29a + miR-29c + miR-133a + miR-143 + miR-145 + miR-192 + miR-505	Serum	0.88 (0.82–0.95)	85.7	91.1	HCCs (n = 49) vs. CTLs (n = 90)	[70]
miR-618 + miR-650	Urine	0.69	58.0	75.0	HCCs (n = 32) vs. CTLs (n = 74)	[47]

Abbreviation: miR, microRNA; HCCs, cases with hepatocarcinoma; CTLs, non-HCC controls (including healthy control and other nontumor controls); HCs, healthy controls; CCs, controls with liver cirrhosis; CHBs, patients with chronic hepatitis B; CLDs, cases with nontumor chronic liver diseases; Sen, sensitivity; Spe, specificity; AUC, the area under the receiver operating characteristic curve; CI, confidence interval; Refs, references.

Table 2. The microRNA panel as diagnostic biomarkers for hepatocarcinoma.

individuals from the training and validation cohorts. These data identified seven microRNAs and constructed a serum microRNA panel with an increasing diagnostic accuracy for hepatocarcinoma [AUC = 0.826 (0.771–0.880) for training set and 0.817 (0.769–0.865) and 0.884 (0.818–0.951) for two different validation sets, respectively]. Interestingly, a nest case-control study has further proved that this panel could be used to detect preclinical hepatocarcinoma as well as small-size, early-stage, and α -fetoprotein-negative disease.

Similarly, Jiang et al. [59] and Zhou et al. [64] also attempted to identify possible combination of different microRNAs for increasing diagnostic accuracy of hepatocarcinoma on the basis of different controls with or without liver diseases. They found that the panel consisting of miR-10b, miR-106b, and miR-181a as well as the combination of miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a, and miR-801 can improve detection of hepatocarcinoma. These reports indicate that the panel of microRNAs may have better performance than a single-microRNA assay.

3.3. Diagnostic potential of microRNAs binding with AFP for hepatocarcinoma

AFP has been regarded as the most important marker for hepatocarcinoma screening and diagnosis, ever since it was identified in the peripheral blood samples from patients with hepatocarcinoma in 1964 [8, 71, 72]. However, this marker is relatively unsatisfactory because of its low sensitivity and specificity. This is mainly because only 60–80% of cases with hepatocarcinoma show positive AFP, whereas about 40% of cirrhotic patients also exhibit different degree increasing level of serum AFP [73, 74]. Thus, AFP may not be a reliable hepatocarcinoma marker, especially for early-stage and/or AFP-negative hepatocarcinoma. On the basis of low sensitivity and specificity of AFP for hepatocarcinoma diagnosis, the American Association for the Study of Liver Disease Practice Guidelines has thrown it away for prognostic surveillance and tumor diagnosis [75]. However, recent studies have displayed that the combination of AFP in the peripheral blood and microRNAs in body fluids may improve the sensitivity and specificity of hepatocarcinoma diagnosis and increase their diagnostic potential [14, 47, 55, 58, 65–67, 69, 70, 76].

For example, Wu et al. [55] investigated the joint diagnostic value of serum microRNA-4651 and AFP for hepatocarcinoma in 279 hepatocarcinoma patients, 324 controls with liver injury, and 338 healthy controls. Their results imply that serum microRNA-4651 has higher expression level among cases with hepatocarcinoma (AUC of 0.85; sensitivity of 78.1% and specificity of 92.1%); this increasing expression also displays higher diagnostic potential than AFP at cutoff of 20 ng/mL (AFP20) (AUC = 0.80, sensitivity = 61.3%, and specificity = 98.8%) and of 400 ng/mL (AFP400) (AUC = 0.72, sensitivity = 43.0%, and specificity = 100.0%). Noticeably, the combination of serum microRNA-4651 with AFP significantly improves the discrimination power between patients with hepatocarcinoma and with chronic nontumor liver injury (AUC = 0.90, sensitivity = 83.2%, and specificity = 97.1%). Similar findings have also been observed in the analyses of combination of serum AFP and other microRNAs, such as miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, miR-505, miR-16, miR-195, and miR-199a [14, 47, 58, 65–67, 69, 70, 76]. Altogether, these data suggest that the combination of microRNAs with AFP may improve diagnostic potential of hepatocarcinoma.

4. Prognostic potential of microRNA for hepatocarcinoma

In the past decades, growing evidence has exhibited that microRNAs can act as prognostic biomarkers for hepatocarcinoma [56, 77–101], and **Table 3** summarizes these significantly affecting hepatocarcinoma outcomes. Functionally, the microRNAs affect hepatocarcinoma prognosis

MicroRNAs	Source	Expression level	Prognostic significance	HR (95%CI)	Refs
miR-122	Serum	Upregulated	Increasing levels correlate with poor OS	OS, 0.08 (0.03–0.22)	[120]
miR-1	Serum	Upregulated	Increasing levels correlate with poor OS	OS, 0.45 (0.23–0.86)	[121]
miR-122	Serum	Upregulated	Correlated with clinical chemistry parameters of hepatic necroinflammation, liver function, and synthetic capacity	/	[121]
miR-221	Serum	Upregulated	(1) Correlated with tumor size, cirrhosis, and tumor stage; (2) increasing levels decreased survival rate	/	[122]
miR-4651	Serum	Upregulated	Increasing levels correlate with poor OS and RFS	OS, 2.67 (1.61–4.42) RFS, 3.62 (1.49–8.81)	[55]
miR-1268a	Tumor tissues	Upregulated	Increasing levels correlate with poor OS and RFS	OS, 2.44 (1.82–3.23) RFS, 2.86 (2.08–3.85)	[115]
miR-24	Tumor tissues	Upregulated	Increasing levels correlate with poor OS and RFS	OS, 3.58 (2.34–5.46) RFS, 4.75 (2.66–8.47)	[77]
miR-429	Tumor tissues	Upregulated	Increasing levels correlate with poor OS and RFS	OS, 4.64 (2.56–8.41) RFS, 6.94 (3.19–15.08)	[78]
miR-143	Serum	Downregulated	Decreasing levels correlate with poor OS and RFS	/	[56]
miR-9	Tumor tissues	Upregulated	Increasing levels correlate with poor OS and RFS	/	[123]
miR-92b	Tumor tissues, serum	Upregulated	Increasing levels promoting tumor metastasis	/	[102]
miR-150	Serum	Downregulated	Increasing levels correlate with poor OS	0.45 (0.23–0.85)	[58]
miR-21	Serum	Upregulated	Increasing levels correlate with poor OS	2.23 (1.33–3.74)	[76]
20-miRNA signature	Tumor tissues	10 downregulated and 20 upregulated miRNAs	6 were risk factors and 14 were protective factors	OS, 2.75 (1.58–4.79)	[124]
miR-221	Tumor tissues	Upregulated	Increasing expression promotes metastasis-free survival	/	[125]

MicroRNAs	Source	Expression level	Prognostic significance	HR (95%CI)	Refs
miR-96	Tumor tissues	Upregulated	Increasing expression correlates with poor RFS	/	[126]
miR-92a	Tumor tissues	Downregulated	Decreasing expression correlates with poor RFS	RFS, 1.60 (1.00–2.50)	[79]
miR-22	Tumor tissues	Downregulated	Decreasing expression correlates with poor RFS	/	[80]
miR-500	Serum	Upregulated	Decreasing expression correlates with tumor resected	/	[127]
miR-375	Tumor tissues	/	Decreasing expression correlates with poor RFS	RFS, 3.273	[81]
miR-148b	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	OS, 1.86 (1.23–2.98)	[82]
miR-101	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS and RFS	RFS, 2.56 (1.32–5.69) OS, 3.27 (1.18–6.92)	[83]
miR-19a	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS and RFS	/	[84]
miR-210	Tumor tissues	Upregulated	Increasing expression correlates with poor OS	/	[80]
miR-224	Tumor tissues	Upregulated	Increasing expression correlates with poor OS and RFS	/	[85]
miR-29	Tumor tissues	Downregulated	Decreasing expression correlates with poor and RFS	/	[86]
miR-139-5p	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	/	[87]
miR-1	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS and RFS	OS, 2.79	[88]
miR-199b-5p	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	/	[89]
miR-130b	Tumor tissues	Upregulated	Increasing expression correlates with poor OS and RFS	RFS, 4.00 (1.58–7.90) OS, 2.52 (1.02–7.90)	[90]
miR-9	Tumor tissues	Upregulated	Increasing expression correlates with poor OS and RFS	/	[91]
miR-25	Tumor tissues	Upregulated	Increasing expression correlates with poor OS and RFS	RFS, 1.62 OS, 2.18	[92]
let-7	Tumor tissues	Upregulated	Increasing expression correlates with poor OS	/	[93]

MicroRNAs	Source	Expression level	Prognostic significance	HR (95%CI)	Refs
miR-30a	Tumor tissues	Downregulated	Decreasing expression correlates with poor RFS	RFS, 3.2 (1.5–6.8)	[94]
miR-99a	Tumor tissues	Downregulated	Decreasing expression correlates with poor RFS	RFS, 1.60 (1.00–2.50)	[79]
miR-106b	Tumor tissues	Upregulated	Increasing expression correlates with poor OS	OS, 2.00 (1.13–6.98)	[95]
miR-130a	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	OS, 2.22 (1.10–4.46)	[96]
miR-19b	Tumor tissues	/	Increasing expression correlates with good OS	OS, 0.45 (0.24–0.85)	[97]
miR-148a	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	/	[98]
miR-372	Tumor tissues	Upregulated	Increasing expression correlates with poor OS and RFS	RFS, 6.83 OS, 9.53	[99]
miR-630	Tumor tissues	Downregulated	Increasing expression correlates with good OS and RFS	OS, 0.71 (0.26–1.92) RFS, 0.66 (0.33–1.35)	[100]
miR-100	Tumor tissues	Downregulated	Decreasing expression correlates with poor OS	OS, 1.66 (1.32–2.82)	[101]

Abbreviation: miR, microRNA; OS, overall survival; RFS, tumor recurrence-free survival; HR, hazard ratio; CI, confidence interval; Refs, references.

Table 3. The microRNAs as prognostic biomarkers for hepatocarcinoma.

via the following pathways: (1) promoting cancerous growth and proliferation [77, 78, 80, 83, 89, 98, 99, 102–113], (2) inhibiting cancerous apoptosis [77, 78, 86, 99, 101, 107–109, 111, 112, 114], (3) increasing microvessel density in the tumor tissues [77, 115], (4) affecting cell cycles [24, 25, 27, 28, 116–119], (5) increasing the risk of tumor metastasis [77, 115], and (6) decreasing the sensitivity of cancer cells to anticancer drugs [115]. For example, Lu et al. [115] investigated the prognostic potential of microRNA-1268a for hepatocarcinoma in 411 patients with hepatocarcinoma. Their results imply that microRNA-1268a expression in the cancerous tissues is significantly related to tumor features including tumor volume, stage and grade, and microvessel density. Results from multivariable factors analyses based on Cox regression models show that microRNA-1268a expression is independent of other known prognostic factors for hepatocarcinoma. Furthermore, transarterial chemoembolization (TACE) treatment can improve the prognosis of hepatocarcinoma patients with low microRNA-1268a expression, but not for those with high microRNA-1268e expression. These data imply that the dysregulation of microRNA-1268a can modify the response of cancer cells to antidrugs. Their following studies prove that upregulated microRNA-1268a inhibited while its downregulation enhanced doxorubicin

(an anticancer drug)-induced the death of tumor cells. Similarly, Liu et al. [77] and Huang et al. [78] investigated the roles of microRNAs, such as microRNA-24 and microRNA-429, in the tumorigenesis of liver cancer on the basis of analyses of hepatocarcinoma samples and genic toxicity induced by aflatoxin B1 and found the dysregulation of these microRNAs increased microvessel density and mutation frequency of TP53 gene possibly resulting from the loss of DNA repair capacity. Taken together, these reports indicate that microRNAs in body fluids and cancerous tissues may be important candidate biomarkers for hepatocarcinoma prognosis.

5. Further direction

In the past decades, the advance in pathological mechanisms of microRNAs regulating tumorigenesis and procession of hepatocarcinoma holds great promise for identifying whether microRNAs in body fluids (such as blood and urine) act as novel early diagnostic and prognostic biomarkers for this malignancy. However, we are still far from a comprehensive view of this kind of potentials. Although some hepato-specific microRNAs have been identified, microRNAs in body fluids may be from hemocytes and vascular endothelial cells and others from tissues and organs with high blood flow as well as hepatocarcinoma. This kind of heterogeneous origin indicates that the dysregulation of tumor-specific microRNA signatures may be concealed by microRNAs from other origins. Furthermore, well-standardized protocols of testing microRNAs have not been constructed or confirmed on the basis of the prospective, randomized controlled trials. Disclosing the different diagnostic and prognostic potential of microRNAs will greatly benefit our constructing high accurate diagnostic and prognostic models for hepatocarcinoma and will shed important light on the early diagnosis, tumor monitoring, and prognosis prediction for individuals with risk factors.

6. Summary

To conclude, the advances in technologies, including microarray PCR technology, high-throughput sequencing, and mass spectrometry, make it possible to identify new markers for hepatocarcinoma diagnosis and prognosis. On the whole, the microRNAs are a class of attractive markers and may replace known traditional serum markers such as AFP on the basis of the following reasons. First, because many circulating microRNAs is highly stable and readily detected in patients with hepatocarcinoma, they may have higher diagnostic potential (with high AUCs, sensitivity, and specificity) for hepatocarcinoma than AFP. Second, some microRNAs appear in the urine and can be utilized for screening patients with high-risk factors of hepatocarcinoma. Third, some dysregulated microRNAs in the body fluids can change with the different stages of hepatocarcinoma, indicative of their potential in monitoring tumor recurrence. Finally, different expressions of microRNAs are useful for treatment strategies such as TACE selection. Taken together, the dysregulated microRNAs in body fluids (including urine and blood) may be a kind of promised biomarkers for liver carcinoma diagnosis and prognosis because they are early detected and easily monitored.

However, there are several issues to be noted. First, research on the diagnostic and prognostic potential of microRNAs is still in the early stages, and challenges are noticeable in the clinical utilization of significant microRNAs. Second, in spite of these biomarkers that are discussed well, their therapeutic potential still remains unclear. Finally, although the diagnostic and prognostic potential of microRNAs is well evaluated on the basis of retrospective case-control studies, results from the prospective, randomized controlled trials are absent. Finally, because of the polygenic feature for hepatocarcinoma development, it is essential for a panel of biomarkers to determine high-risk individuals. Thus, the advances in the fields of microRNAs including their origins, stability, detection strategies, variant characteristics, and biofunctions in hepatocarcinoma will progress microRNAs in body fluids to become possible tools for hepatocarcinoma diagnosis and prognosis in the future.

Conflicts of interest and source of funding

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Abbreviations

AFP	α -fetoprotein
AFB1	aflatoxin B1
AUC	the area under the receiver operating characteristic curve
CT	computed tomography
HBV	hepatitis virus B
HCC	hepatocellular carcinoma
HCV	hepatitis virus C
MRI	magnetic resonance imaging

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References

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA: a Cancer Journal for Clinicians*. 2017;**67**:7-30. DOI: 10.3322/caac.21387
- [2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, XQ Y, He J. Cancer statistics in China, 2015. *CA: a Cancer Journal for Clinicians*. 2016;**66**:115-132. DOI: 10.3322/caac.21338
- [3] Long J, Luo GP, Xiao ZW, Liu ZQ, Guo M, Liu L, Liu C, Xu J, Gao YT, Zheng Y, Wu C, Ni QX, Li M, Yu X. Cancer statistics: Current diagnosis and treatment of pancreatic cancer in shanghai, China. *Cancer Letters*. 2014. DOI: 10.1016/j.canlet.2014.01.004
- [4] Page AJ, Cosgrove DC, Philosophe B, Pawlik TM. Hepatocellular Carcinoma: Diagnosis, Management, and Prognosis. *Surgical Oncology Clinics of North America*. 2014;**23**:289-311. DOI: 10.1016/j.soc.2013.10.006
- [5] Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology*. 2014. DOI: 10.1002/hep.27388
- [6] Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, Caturelli E, Zoli M, Borzio F, Trevisani F, Cancer g IL. Prognosis of untreated hepatocellular carcinoma. *Hepatology*. 2014. DOI: 10.1002/hep.27443

- [7] Nault JC. Pathogenesis of hepatocellular carcinoma according to aetiology. *Best Practice & Research. Clinical Gastroenterology*. 2014;**28**:937-947. DOI: 10.1016/j.bpg.2014.08.006
- [8] Tsuchiya N, Sawada Y, Endo I, Saito K, Uemura Y, Nakatsura T. Biomarkers for the early diagnosis of hepatocellular carcinoma. *World Journal of Gastroenterology*. 2015;**21**: 10573-10583. DOI: 10.3748/wjg.v21.i37.10573
- [9] Hung CH, TH H, SN L, Kuo FY, Chen CH, Wang JH, Huang CM, Lee CM, Lin CY, Yen YH, Chiu YC. Circulating microRNAs as biomarkers for diagnosis of early hepatocellular carcinoma associated with hepatitis B virus. *International Journal of Cancer*. 2016;**138**:714-720. DOI: 10.1002/ijc.29802
- [10] Huang JT, Liu SM, Ma H, Yang Y, Zhang X, Sun H, Zhang X, Xu J, Wang J. Systematic review and meta-analysis: Circulating miRNAs for diagnosis of Hepatocellular carcinoma. *Journal of Cellular Physiology*. 2016;**231**:328-335. DOI: 10.1002/jcp.25135
- [11] Zhang YC, Xu Z, Zhang TF, Wang YL. Circulating microRNAs as diagnostic and prognostic tools for hepatocellular carcinoma. *World Journal of Gastroenterology*. 2015; **21**:9853-9862. DOI: 10.3748/wjg.v21.i34.9853
- [12] Chang-Hao Tsao S, Behren A, Cebon J, Christophi C. The role of circulating microRNA in hepatocellular carcinoma. *Frontiers in Bioscience (Landmark Ed)*. 2015;**20**:78-104
- [13] Yang Y, Zhu R. Diagnostic value of circulating microRNAs for hepatocellular carcinoma. *Molecular Biology Reports*. 2014;**41**:6919-6929. DOI: 10.1007/s11033-014-3578-7
- [14] KZ Q, Zhang K, Li H, Afdhal NH, Albitar M. Circulating microRNAs as biomarkers for hepatocellular carcinoma. *Journal of Clinical Gastroenterology*. 2011;**45**:355-360. DOI: 10.1097/MCG.0b013e3181f18ac2
- [15] Wong KF, Xu Z, Chen J, Lee NP, Luk JM. Circulating markers for prognosis of hepatocellular carcinoma. *Expert Opinion on Medical Diagnostics*. 2013;**7**:319-329. DOI: 10.1517/17530059.2013.795146
- [16] Zhao X, Yang Z, Li G, Li D, Zhao Y, Wu Y, Robson SC, He L, Xu Y, Miao R, Zhao H. The role and clinical implications of microRNAs in hepatocellular carcinoma. *Science China. Life Sciences*. 2012;**55**:906-919. DOI: 10.1007/s11427-012-4384-x
- [17] Lyra-Gonzalez I, Flores-Fong LE, Gonzalez-Garcia I, Medina-Preciado D, Armendariz-Borunda J. MicroRNAs dysregulation in hepatocellular carcinoma: Insights in genomic medicine. *World Journal of Hepatology*. 2015;**7**:1530-1540. DOI: 10.4254/wjh.v7.i11.1530
- [18] Cardin R, Picciocchi M, Bortolami M, Kotsafti A, Barzon L, Lavezzo E, Sinigaglia A, Rodriguez-Castro KI, Rugge M, Farinati F. Oxidative damage in the progression of chronic liver disease to hepatocellular carcinoma: An intricate pathway. *World Journal of Gastroenterology*. 2014;**20**:3078-3086. DOI: 10.3748/wjg.v20.i12.3078
- [19] Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. *Current Biology*. 2002;**12**:735-739
- [20] Saunders MA, Liang H, Li WH. Human polymorphism at microRNAs and microRNA target sites. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**:3300-3305. DOI: 10.1073/pnas.0611347104

- [21] Griffiths-Jones S. The microRNA registry. *Nucleic Acids Research*. 2004;**32**:D109-D111. DOI: 10.1093/nar/gkh023
- [22] Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Research*. 2006;**34**:D140-D144. DOI: 10.1093/nar/gkj112
- [23] Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. *Developmental Biology*. 2007;**302**:1-12. DOI: 10.1016/j.ydbio.2006.08.028
- [24] Wojcicka A, de la Chapelle A, Jazdzewski K. MicroRNA-related sequence variations in human cancers. *Human Genetics*. 2014;**133**:463-469. DOI: 10.1007/s00439-013-1397-x
- [25] van Rooij E. The art of microRNA research. *Circulation Research*. 2011;**108**:219-234. DOI: 10.1161/CIRCRESAHA.110.227496
- [26] Sontheimer EJ. Assembly and function of RNA silencing complexes. *Nature Reviews. Molecular Cell Biology*. 2005;**6**:127-138. DOI: 10.1038/nrm1568
- [27] Schwabe RF, Wang TC. Targeting liver cancer: First steps toward a miRacle? *Cancer Cell*. 2011;**20**:698-699. DOI: 10.1016/j.ccr.2011.11.021
- [28] Ranganathan K, Sivasankar V. MicroRNAs - biology and clinical applications. *Journal of Oral and Maxillofacial Pathology*. 2014;**18**:229-234. DOI: 10.4103/0973-029X.140762
- [29] Lynam-Lennon N, Maher SG, Reynolds JV. The roles of microRNA in cancer and apoptosis. *Biological Reviews of the Cambridge Philosophical Society*. 2009;**84**:55-71. DOI: 10.1111/j.1469-185X.2008.00061.x
- [30] Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*. 2004;**116**:281-297. DOI: S0092867404000455 [pii]
- [31] Kumar A. MicroRNA in HCV infection and liver cancer. *Biochimica et Biophysica Acta*. 1809;**2011**:694-699. DOI: 10.1016/j.bbagr.2011.07.010
- [32] Boeri M, Pastorino U, Sozzi G. Role of microRNAs in lung cancer: microRNA signatures in cancer prognosis. *Cancer Journal*. 2012;**18**:268-274. DOI: 10.1097/PPO.0b013e318258b743
- [33] Celton-Morizur S, Desdouets C. Liver physiological polyploidization: MicroRNA-122 a key regulator. *Clinics and Research in Hepatology and Gastroenterology*. 2017;**41**:123-125. DOI: 10.1016/j.clinre.2016.07.006
- [34] Hsu SH, Delgado ER, Otero PA, Teng KY, Kutay H, Meehan KM, Moroney JB, Monga JK, Hand NJ, Friedman JR, Ghoshal K, Duncan AW. MicroRNA-122 regulates polyploidization in the murine liver. *Hepatology*. 2016;**64**:599-615. DOI: 10.1002/hep.28573
- [35] Cho HJ, Kim JK, Nam JS, Wang HJ, Lee JH, Kim BW, Kim SS, Noh CK, Shin SJ, Lee KM, Cho SW, Cheong JY. High circulating microRNA-122 expression is a poor prognostic marker in patients with hepatitis B virus-related hepatocellular carcinoma who undergo radiofrequency ablation. *Clinical Biochemistry*. 2015;**48**:1073-1078. DOI: 10.1016/j.clinbiochem.2015.06.019

- [36] Kumar S, Chawla YK, Ghosh S, Chakraborti A. Severity of hepatitis C virus (genotype-3) infection positively correlates with circulating microRNA-122 in patients sera. *Disease Markers*. 2014;**2014**:435476. DOI: 10.1155/2014/435476
- [37] van der Meer AJ, Farid WR, Sonneveld MJ, de Ruiter PE, Boonstra A, van Vuuren AJ, Verheij J, Hansen BE, de Knecht RJ, van der Laan LJ, Janssen HL. Sensitive detection of hepatocellular injury in chronic hepatitis C patients with circulating hepatocyte-derived microRNA-122. *Journal of Viral Hepatitis*. 2013;**20**:158-166. DOI: 10.1111/jvh.12001
- [38] Arataki K, Hayes CN, Akamatsu S, Akiyama R, Abe H, Tsuge M, Miki D, Ochi H, Hiraga N, Imamura M, Takahashi S, Aikata H, Kawaoka T, Kawakami H, Ohishi W, Chayama K. Circulating microRNA-22 correlates with microRNA-122 and represents viral replication and liver injury in patients with chronic hepatitis B. *Journal of Medical Virology*. 2013;**85**:789-798. DOI: 10.1002/jmv.23540
- [39] Ding X, Ding J, Ning J, Yi F, Chen J, Zhao D, Zheng J, Liang Z, Hu Z, Du Q. Circulating microRNA-122 as a potential biomarker for liver injury. *Molecular Medicine Reports*. 2012;**5**:1428-1432. DOI: 10.3892/mmr.2012.838
- [40] Qi P, Cheng SQ, Wang H, Li N, Chen YF, Gao CF. Serum microRNAs as biomarkers for hepatocellular carcinoma in Chinese patients with chronic hepatitis B virus infection. *PLoS One*. 2011;**6**:e28486. DOI: 10.1371/journal.pone.0028486
- [41] Xu J, Wu C, Che X, Wang L, Yu D, Zhang T, Huang L, Li H, Tan W, Wang C, Lin D. Circulating microRNAs, miR-21, miR-122, and miR-223, in patients with hepatocellular carcinoma or chronic hepatitis. *Molecular Carcinogenesis*. 2011;**50**:136-142. DOI: 10.1002/mc.20712
- [42] Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, Shimotohno K. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. *Oncogene*. 2006;**25**:2537-2545. DOI: 10.1038/sj.onc.1209283
- [43] Hung CS, Liu HH, Liu JJ, Yeh CT, Chang TC, CH W, Ho YS, Wei PL, Chang YJ. MicroRNA-200a and -200b mediated hepatocellular carcinoma cell migration through the epithelial to mesenchymal transition markers. *Annals of Surgical Oncology*. 2013;**20**(Suppl 3):S360-S368. DOI: 10.1245/s10434-012-2482-4
- [44] Tomimaru Y, Eguchi H, Nagano H, Wada H, Kobayashi S, Marubashi S, Tanemura M, Tomokuni A, Takemasa I, Umeshita K, Kanto T, Doki Y, Mori M. Circulating microRNA-21 as a novel biomarker for hepatocellular carcinoma. *Journal of Hepatology*. 2012;**56**:167-175. DOI: 10.1016/j.jhep.2011.04.026
- [45] Liu AM, Yao TJ, Wang W, Wong KF, Lee NP, Fan ST, Poon RT, Gao C, Luk JM. Circulating miR-15b and miR-130b in serum as potential markers for detecting hepatocellular carcinoma: A retrospective cohort study. *BMJ Open*. 2012;**2**:e000825. DOI: 10.1136/bmjopen-2012-000825
- [46] Zhang ZQ, Meng H, Wang N, Liang LN, Liu LN, SM L, Luan Y. Serum microRNA 143 and microRNA 215 as potential biomarkers for the diagnosis of chronic hepatitis and hepatocellular carcinoma. *Diagnostic Pathology*. 2014;**9**:135. DOI: 10.1186/1746-1596-9-135

- [47] Abdalla MA, Haj-Ahmad Y. Promising candidate urinary MicroRNA biomarkers for the early detection of Hepatocellular carcinoma among high-risk hepatitis C virus Egyptian patients. *Journal of Cancer*. 2012;**3**:19-31
- [48] Barshack I, Meiri E, Rosenwald S, Lebanony D, Bronfeld M, Aviel-Ronen S, Rosenblatt K, Polak-Charcon S, Leizerman I, Ezagouri M, Zepeniuk M, Shabes N, Cohen L, Tabak S, Cohen D, Bentwich Z, Rosenfeld N. Differential diagnosis of hepatocellular carcinoma from metastatic tumors in the liver using microRNA expression. *The International Journal of Biochemistry & Cell Biology*. 2010;**42**:1355-1362. DOI: 10.1016/j.biocel.2009.02.021
- [49] Vliegenthart ADB, Berends C, Potter CMJ, Kersaudy-Kerhoas M, Dear JW. MicroRNA-122 can be measured in capillary blood which facilitates point-of-care testing for drug-induced liver injury. *British Journal of Clinical Pharmacology*. 2017;**83**:2027-2033. DOI: 10.1111/bcp.13282
- [50] Qiao DD, Yang J, Lei XF, Mi GL, Li SL, Li K, CQ X, Yang HL. Expression of microRNA-122 and microRNA-22 in HBV-related liver cancer and the correlation with clinical features. *European Review for Medical and Pharmacological Sciences*. 2017;**21**:742-747
- [51] Jiang L, Cheng Q, Zhang BH, Zhang MZ. Circulating microRNAs as biomarkers in hepatocellular carcinoma screening: A validation set from China. *Medicine (Baltimore)*. 2015;**94**:e603. DOI: 10.1097/MD.0000000000000603
- [52] Tan Y, Ge G, Pan T, Wen D, Chen L, Yu X, Zhou X, Gan J. A serum microRNA panel as potential biomarkers for hepatocellular carcinoma related with hepatitis B virus. *PLoS One*. 2014;**9**:e107986. DOI: 10.1371/journal.pone.0107986
- [53] Yin J, Hou P, Wu Z, Wang T, Nie Y. Circulating miR-375 and miR-199a-3p as potential biomarkers for the diagnosis of hepatocellular carcinoma. *Tumour Biology*. 2015;**36**:4501-4507. DOI: 10.1007/s13277-015-3092-0
- [54] Oksuz Z, Serin MS, Kaplan E, Dogen A, Tezcan S, Aslan G, Emekdas G, Sezgin O, Altintas E, Tiftik EN. Serum microRNAs; miR-30c-5p, miR-223-3p, miR-302c-3p and miR-17-5p could be used as novel non-invasive biomarkers for HCV-positive cirrhosis and hepatocellular carcinoma. *Molecular Biology Reports*. 2015;**42**:713-720. DOI: 10.1007/s11033-014-3819-9
- [55] XM W, Xi ZF, Liao P, Huang HD, Huang XY, Wang C, Ma Y, Xia Q, Yao JG, Long XD. Diagnostic and prognostic potential of serum microRNA-4651 for patients with hepatocellular carcinoma related to aflatoxin B1. *Oncotarget*. 2017. DOI: 10.18632/oncotarget.16027
- [56] Zhang J, Lin H, Wang XY, Zhang DQ, Chen JX, Zhuang Y, Zheng XL. Predictive value of microRNA-143 in evaluating the prognosis of patients with hepatocellular carcinoma. *Cancer Biomarkers*. 2017;**19**:257-262. DOI: 10.3233/CBM-160357
- [57] Chen S, Chen H, Gao S, Qiu S, Zhou H, Yu M, Tu J. Differential expression of plasma microRNA-125b in hepatitis B virus-related liver diseases and diagnostic potential for hepatitis B virus-induced hepatocellular carcinoma. *Hepatology Research*. 2017;**47**:312-320. DOI: 10.1111/hepr.12739

- [58] Yu F, Lu Z, Chen B, Dong P, Zheng J. microRNA-150: A promising novel biomarker for hepatitis B virus-related hepatocellular carcinoma. *Diagnostic Pathology*. 2015;**10**:129. DOI: 10.1186/s13000-015-0369-y
- [59] Jiang L, Li X, Cheng Q, Zhang BH. Plasma microRNA might as a potential biomarker for hepatocellular carcinoma and chronic liver disease screening. *Tumour Biology*. 2015;**36**:7167-7174. DOI: 10.1007/s13277-015-3446-7
- [60] Dhayat SA, Husing A, Senninger N, Schmidt HH, Haier J, Wolters H, Kabar I. Circulating microRNA-200 family as diagnostic marker in Hepatocellular carcinoma. *PLoS One*. 2015;**10**:e0140066. DOI: 10.1371/journal.pone.0140066
- [61] Xie Y, Yao Q, Butt AM, Guo J, Tian Z, Bao X, Li H, Meng Q, Lu J. Expression profiling of serum microRNA-101 in HBV-associated chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. *Cancer Biology & Therapy*. 2014;**15**:1248-1255. DOI: 10.4161/cbt.29688
- [62] Shen J, Wang A, Wang Q, Gurvich I, Siegel AB, Remotti H, Santella RM. Exploration of genome-wide circulating microRNA in hepatocellular carcinoma: MiR-483-5p as a potential biomarker. *Cancer Epidemiology, Biomarkers & Prevention*. 2013;**22**:2364-2373. DOI: 10.1158/1055-9965.EPI-13-0237
- [63] Luo J, Chen M, Huang H, Yuan T, Zhang M, Zhang K, Deng S. Circulating microRNA-122a as a diagnostic marker for hepatocellular carcinoma. *OncoTargets and Therapy*. 2013;**6**:577-583. DOI: 10.2147/OTT.S44215
- [64] Zhou J, Yu L, Gao X, Hu J, Wang J, Dai Z, Wang JF, Zhang Z, Lu S, Huang X, Wang Z, Qiu S, Wang X, Yang G, Sun H, Tang Z, Wu Y, Zhu H, Fan J. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. *Journal of Clinical Oncology*. 2011;**29**:4781-4788. DOI: 10.1200/JCO.2011.38.2697
- [65] Zhu HT, Liu RB, Liang YY, Hasan AME, Wang HY, Shao Q, Zhang ZC, Wang J, He CY, Wang F, Shao JY. Serum microRNA profiles as diagnostic biomarkers for HBV-positive hepatocellular carcinoma. *Liver International*. 2017;**37**:888-896. DOI: 10.1111/liv.13356
- [66] Zhang Y, Li T, Qiu Y, Zhang T, Guo P, Ma X, Wei Q, Han L. Serum microRNA panel for early diagnosis of the onset of hepatocellular carcinoma. *Medicine (Baltimore)*. 2017;**96**:e5642. DOI: 10.1097/MD.00000000000005642
- [67] Long XR, Zhang YJ, Zhang MY, Chen K, Zheng XFS, Wang HY. Identification of an 88-microRNA signature in whole blood for diagnosis of hepatocellular carcinoma and other chronic liver diseases. *Aging (Albany NY)*. 2017;**9**:1565-1584. DOI: 10.18632/aging.101253
- [68] Elemeery MN, Badr AN, Mohamed MA, Ghareeb DA. Validation of a serum microRNA panel as biomarkers for early diagnosis of hepatocellular carcinoma post-hepatitis C infection in Egyptian patients. *World Journal of Gastroenterology*. 2017;**23**:3864-3875. DOI: 10.3748/wjg.v23.i21.3864
- [69] Zekri AN, Youssef AS, El-Desouky ED, Ahmed OS, Lotfy MM, Nassar AA, Bahnassey AA. Serum microRNA panels as potential biomarkers for early detection of hepatocellular carcinoma on top of HCV infection. *Tumour Biology*. 2016;**37**:12273-12286. DOI: 10.1007/s13277-016-5097-8

- [70] Lin XJ, Chong Y, Guo ZW, Xie C, Yang XJ, Zhang Q, Li SP, Xiong Y, Yuan Y, Min J, Jia WH, Jie Y, Chen MS, Chen MX, Fang JH, Zeng C, Zhang Y, Guo RP, Wu Y, Lin G, Zheng L, Zhuang SM. A serum microRNA classifier for early detection of hepatocellular carcinoma: A multicentre, retrospective, longitudinal biomarker identification study with a nested case-control study. *The Lancet Oncology*. 2015;**16**:804-815. DOI: 10.1016/S1470-2045(15)00048-0
- [71] Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. *Annals of Internal Medicine*. 2003;**139**:46-50
- [72] Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, Domenicali M, De Notariis S, Roda E, Bernardi M. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: Influence of HBsAg and anti-HCV status. *Journal of Hepatology*. 2001;**34**:570-575
- [73] Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, Reddy KR, Harnois D, Llovet JM, Normolle D, Dalhgren J, Chia D, Lok AS, Wagner PD, Srivastava S, Schwartz M. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology*. 2009;**137**:110-118. DOI: 10.1053/j.gastro.2009.04.005
- [74] Spangenberg HC, Thimme R, Blum HE. Serum markers of hepatocellular carcinoma. *Seminars in Liver Disease*. 2006;**26**:385-390. DOI: 10.1055/s-2006-951606
- [75] Zinkin NT, Grall F, Bhaskar K, Otu HH, Spentzos D, Kalmowitz B, Wells M, Guerrero M, Asara JM, Libermann TA, Afdhal NH. Serum proteomics and biomarkers in hepatocellular carcinoma and chronic liver disease. *Clinical Cancer Research*. 2008;**14**:470-477. DOI: 10.1158/1078-0432.CCR-07-0586
- [76] Wang X, Zhang J, Zhou L, Lu P, Zheng ZG, Sun W, Wang JL, Yang XS, Li XL, Xia N, Zhang N, Dou KF. Significance of serum microRNA-21 in diagnosis of hepatocellular carcinoma (HCC): Clinical analyses of patients and an HCC rat model. *International Journal of Clinical and Experimental Pathology*. 2015;**8**:1466-1478
- [77] Liu YX, Long XD, Xi ZF, Ma Y, Huang XY, Yao JG, Wang C, Xing TY, Xia Q. MicroRNA-24 modulates aflatoxin B1-related hepatocellular carcinoma prognosis and tumorigenesis. *BioMed Research International*. 2014;**2014**:482926. DOI: 10.1155/2014/482926
- [78] Huang XY, Yao JG, Huang HD, Wang C, Ma Y, Xia Q, Long XD. MicroRNA-429 modulates hepatocellular carcinoma prognosis and tumorigenesis. *Gastroenterology Research and Practice*. 2013;**2013**:804128. DOI: 10.1155/2013/804128
- [79] Li D, Liu X, Lin L, Hou J, Li N, Wang C, Wang P, Zhang Q, Zhang P, Zhou W, Wang Z, Ding G, Zhuang SM, Zheng L, Tao W, Cao X. MicroRNA-99a inhibits hepatocellular carcinoma growth and correlates with prognosis of patients with hepatocellular carcinoma. *The Journal of Biological Chemistry*. 2011;**286**:36677-36685. DOI: 10.1074/jbc.M111.270561

- [80] Zhang J, Yang Y, Yang T, Liu Y, Li A, Fu S, Wu M, Pan Z, Zhou W. microRNA-22, down-regulated in hepatocellular carcinoma and correlated with prognosis, suppresses cell proliferation and tumourigenicity. *British Journal of Cancer*. 2010;**103**:1215-1220. DOI: 10.1038/sj.bjc.6605895
- [81] Zhou N, Wu J, Wang X, Sun Z, Han Q, Zhao L. Low-level expression of microRNA-375 predicts poor prognosis in hepatocellular carcinoma. *Tumour Biology*. 2016;**37**:2145-2152. DOI: 10.1007/s13277-015-3841-0
- [82] Zhang Z, Zheng W, Hai J. MicroRNA-148b expression is decreased in hepatocellular carcinoma and associated with prognosis. *Medical Oncology*. 2014;**31**:984. DOI: 10.1007/s12032-014-0984-6
- [83] Zhang Y, Guo X, Xiong L, Kong X, Xu Y, Liu C, Zou L, Li Z, Zhao J, Lin N. MicroRNA-101 suppresses SOX9-dependent tumorigenicity and promotes favorable prognosis of human hepatocellular carcinoma. *FEBS Letters*. 2012;**586**:4362-4370. DOI: 10.1016/j.febslet.2012.10.053
- [84] Zhang Y, Guo X, Li Z, Li B, Li Z, Li R, Guo Q, Xiong L, Yu L, Zhao J, Lin N. A systematic investigation based on microRNA-mediated gene regulatory network reveals that dysregulation of microRNA-19a/Cyclin D1 axis confers an oncogenic potential and a worse prognosis in human hepatocellular carcinoma. *RNA Biology*. 2015;**12**:643-657. DOI: 10.1080/15476286.2015.1022702
- [85] Zhan M, Li Y, Hu B, He X, Huang J, Zhao Y, Fu S, Lu L. Serum microRNA-210 as a predictive biomarker for treatment response and prognosis in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. *Journal of Vascular and Interventional Radiology*. 2014;**25**:1279-1287 e1271. DOI: 10.1016/j.jvir.2014.04.013
- [86] Xiong Y, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH, Zhuang SM. Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. *Hepatology*. 2010;**51**:836-845. DOI: 10.1002/hep.23380
- [87] Wang Z, Ding Q, Li Y, Liu Q, Wu W, Wu L, Yu H. Reanalysis of microRNA expression profiles identifies novel biomarkers for hepatocellular carcinoma prognosis. *Tumour Biology*. 2016;**37**:14779-14787. DOI: 10.1007/s13277-016-5369-3
- [88] Wang X, Huang Y, Zhuang H, Qian Y, Zhao Q, Yang L, Gu H, Chen J, Guo R, Liu Y. Downregulation of MicroRNA-1 is associated with poor prognosis in Hepatocellular carcinoma. *Clinical Laboratory*. 2015;**61**:1331-1336
- [89] Wang C, Song B, Song W, Liu J, Sun A, Wu D, Yu H, Lian J, Chen L, Han J. Underexpressed microRNA-199b-5p targets hypoxia-inducible factor-1alpha in hepatocellular carcinoma and predicts prognosis of hepatocellular carcinoma patients. *Journal of Gastroenterology and Hepatology*. 2011;**26**:1630-1637. DOI: 10.1111/j.1440-1746.2011.06758.x
- [90] Wang WY, Zhang HF, Wang L, Ma YP, Gao F, Zhang SJ, Wang LC. High expression of microRNA-130b correlates with poor prognosis of patients with hepatocellular carcinoma. *Diagnostic Pathology*. 2014;**9**:160. DOI: 10.1186/s13000-014-0160-5

- [91] Sun J, Fang K, Shen H, Qian Y. MicroRNA-9 is a ponderable index for the prognosis of human hepatocellular carcinoma. *International Journal of Clinical and Experimental Medicine*. 2015;8:17748-17756
- [92] ZX S, Zhao J, Rong ZH, Geng WM, YG W, Qin CK. Upregulation of microRNA-25 associates with prognosis in hepatocellular carcinoma. *Diagnostic Pathology*. 2014;9:47. DOI: 10.1186/1746-1596-9-47
- [93] Shi W, Zhang Z, Yang B, Guo H, Jing L, Liu T, Luo Y, Liu H, Li Y, Gao Y. Overexpression of microRNA let-7 correlates with disease progression and poor prognosis in hepatocellular carcinoma. *Medicine (Baltimore)*. 2017;96:e7764. DOI: 10.1097/MD.00000000000007764
- [94] Liu Z, Tu K, Liu Q. Effects of microRNA-30a on migration, invasion and prognosis of hepatocellular carcinoma. *FEBS Letters*. 2014;588:3089-3097. DOI: 10.1016/j.febslet.2014.06.037
- [95] Li BK, Huang PZ, Qiu JL, Liao YD, Hong J, Yuan YF. Upregulation of microRNA-106b is associated with poor prognosis in hepatocellular carcinoma. *Diagnostic Pathology*. 2014;9:226. DOI: 10.1186/s13000-014-0226-4
- [96] Li B, Huang P, Qiu J, Liao Y, Hong J, Yuan Y. MicroRNA-130a is down-regulated in hepatocellular carcinoma and associates with poor prognosis. *Medical Oncology*. 2014;31:230. DOI: 10.1007/s12032-014-0230-2
- [97] Hung CL, Yen CS, Tsai HW, YC S, Yen CJ. Upregulation of MicroRNA-19b predicts good prognosis in patients with hepatocellular carcinoma presenting with vascular invasion or multifocal disease. *BMC Cancer*. 2015;15:665. DOI: 10.1186/s12885-015-1671-5
- [98] Heo MJ, Kim YM, Koo JH, Yang YM, An J, Lee SK, Lee SJ, Kim KM, Park JW, Kim SG. microRNA-148a dysregulation discriminates poor prognosis of hepatocellular carcinoma in association with USP4 overexpression. *Oncotarget*. 2014;5:2792-2806. DOI: 10.18632/oncotarget.1920
- [99] Gu H, Guo X, Zou L, Zhu H, Zhang J. Upregulation of microRNA-372 associates with tumor progression and prognosis in hepatocellular carcinoma. *Molecular and Cellular Biochemistry*. 2013;375:23-30. DOI: 10.1007/s11010-012-1521-6
- [100] Chen WX, Zhang ZG, Ding ZY, Liang HF, Song J, Tan XL, Wu JJ, Li GZ, Zeng Z, Zhang BX, Chen XP. MicroRNA-630 suppresses tumor metastasis through the TGF-beta- miR-630-slug signaling pathway and correlates inversely with poor prognosis in hepatocellular carcinoma. *Oncotarget*. 2016;7:22674-22686. DOI: 10.18632/oncotarget.8047
- [101] Chen P, Zhao X, Ma L. Downregulation of microRNA-100 correlates with tumor progression and poor prognosis in hepatocellular carcinoma. *Molecular and Cellular Biochemistry*. 2013;383:49-58. DOI: 10.1007/s11010-013-1753-0
- [102] Zhuang LK, Yang YT, Ma X, Han B, Wang ZS, Zhao QY, Wu LQ, Qu ZQ. MicroRNA-92b promotes hepatocellular carcinoma progression by targeting Smad7 and is mediated by long non-coding RNA XIST. *Cell Death & Disease*. 2016;7:e2203. DOI: 10.1038/cddis.2016.100

- [103] Zhang H, Sheng C, Yin Y, Wen S, Yang G, Cheng Z, Zhu Q. PABPC1 interacts with AGO2 and is responsible for the microRNA mediated gene silencing in high grade hepatocellular carcinoma. *Cancer Letters*. 2015;**367**:49-57. DOI: 10.1016/j.canlet.2015.07.010
- [104] Yao M, Wang L, Yao Y, HB G, Yao DF. Biomarker-based MicroRNA therapeutic strategies for Hepatocellular carcinoma. *Journal of Clinical and Translational Hepatology*. 2014;**2**:253-258. DOI: 10.14218/JCTH.2014.00020
- [105] Yao M, Wang L, Qiu L, Qian Q, Yao D. Encouraging microRNA-based therapeutic strategies for Hepatocellular carcinoma. *Anti-Cancer Agents in Medicinal Chemistry*. 2015;**15**:453-460
- [106] Wei L, Lian B, Zhang Y, Li W, Gu J, He X, Xie L. Application of microRNA and mRNA expression profiling on prognostic biomarker discovery for hepatocellular carcinoma. *BMC Genomics*. 2014;**15**(Suppl 1):S13. DOI: 10.1186/1471-2164-15-S1-S13
- [107] Miao HL, Lei CJ, Qiu ZD, Liu ZK, Li R, Bao ST, Li MY. MicroRNA-520c-3p inhibits hepatocellular carcinoma cell proliferation and invasion through induction of cell apoptosis by targeting glypican-3. *Hepatology Research*. 2014;**44**:338-348. DOI: 10.1111/hepr.12121
- [108] Lu Y, Yue X, Cui Y, Zhang J, Wang K. MicroRNA-124 suppresses growth of human hepatocellular carcinoma by targeting STAT3. *Biochemical and Biophysical Research Communications*. 2013;**441**:873-879. DOI: 10.1016/j.bbrc.2013.10.157
- [109] Khare S, Zhang Q, Ibdah JA. Epigenetics of hepatocellular carcinoma: Role of microRNA. *World Journal of Gastroenterology*. 2013;**19**:5439-5445. DOI: 10.3748/wjg.v19.i33.5439
- [110] Hu X, Feng Y, Sun L, Qu L, Sun C. Roles of microRNA-330 and its target gene ING4 in the development of aggressive phenotype in Hepatocellular carcinoma cells. *Digestive Diseases and Sciences*. 2017;**62**:715-722. DOI: 10.1007/s10620-016-4429-2
- [111] Hu S, Ran Y, Chen W, Zhang Y, Xu Y. MicroRNA-326 inhibits cell proliferation and invasion, activating apoptosis in hepatocellular carcinoma by directly targeting LIM and SH3 protein 1. *Oncology Reports*. 2017;**38**:1569-1578. DOI: 10.3892/or.2017.5810
- [112] He XX, Chang Y, Meng FY, Wang MY, Xie QH, Tang F, Li PY, Song YH, Lin JS. MicroRNA-375 targets AEG-1 in hepatocellular carcinoma and suppresses liver cancer cell growth in vitro and in vivo. *Oncogene*. 2012;**31**:3357-3369. DOI: 10.1038/onc.2011.500
- [113] Chen SY, Ma DN, Chen QD, Zhang JJ, Tian YR, Wang ZC, Cai H, Lin Y, Sun HC. MicroRNA-200a inhibits cell growth and metastasis by targeting Foxa2 in hepatocellular carcinoma. *Journal of Cancer*. 2017;**8**:617-625. DOI: 10.7150/jca.17394
- [114] Zhang X, Tang W, Chen G, Ren F, Liang H, Dang Y, Rong M. An encapsulation of gene signatures for Hepatocellular carcinoma, MicroRNA-132 predicted target genes and the corresponding overlaps. *PLoS One*. 2016;**11**:e0159498. DOI: 10.1371/journal.pone.0159498
- [115] YL L, Yao JG, Huang XY, Wang C, XM W, Xia Q, Long XD. Prognostic significance of miR-1268a expression and its beneficial effects for post-operative adjuvant transarterial chemoembolization in hepatocellular carcinoma. *Scientific Reports*. 2016;**6**:36104. DOI: 10.1038/srep36104

- [116] Aguda BD. Modeling microRNA-transcription factor networks in cancer. *Advances in Experimental Medicine and Biology*. 2013;**774**:149-167. DOI: 10.1007/978-94-007-5590-1_9
- [117] Rossi JJ. New hope for a microRNA therapy for liver cancer. *Cell*. 2009;**137**:990-992. DOI: 10.1016/j.cell.2009.05.038
- [118] Zhang G, Wang Q, Xu R. Therapeutics based on microRNA: A new approach for liver cancer. *Current Genomics*. 2010;**11**:311-325. DOI: 10.2174/138920210791616671
- [119] Zhu Z, Zhang X, Wang G, Zheng H. Role of MicroRNAs in Hepatocellular carcinoma. *Hepatitis Monthly*. 2014;**14**:e18672. DOI: 10.5812/hepatmon.18672
- [120] Xu Y, Bu X, Dai C, Shang C. High serum microRNA-122 level is independently associated with higher overall survival rate in hepatocellular carcinoma patients. *Tumour Biology*. 2015;**36**:4773-4776. DOI: 10.1007/s13277-015-3128-5
- [121] Koberle V, Kronenberger B, Pleli T, Trojan J, Imelmann E, Peveling-Oberhag J, Welker MW, Elhendawy M, Zeuzem S, Piiper A, Waidmann O. Serum microRNA-1 and microRNA-122 are prognostic markers in patients with hepatocellular carcinoma. *European Journal of Cancer*. 2013;**49**:3442-3449. DOI: 10.1016/j.ejca.2013.06.002
- [122] Li J, Wang Y, Yu W, Chen J, Luo J. Expression of serum miR-221 in human hepatocellular carcinoma and its prognostic significance. *Biochemical and Biophysical Research Communications*. 2011;**406**:70-73. DOI: 10.1016/j.bbrc.2011.01.111
- [123] Liu Y, Liu H, Yang L, Wu Q, Liu W, Fu Q, Zhang W, Zhang H, Xu J, Gu J. Loss of N-Acetylgalactosaminyltransferase-4 orchestrates Oncogenic MicroRNA-9 in Hepatocellular carcinoma. *The Journal of Biological Chemistry*. 2017;**292**:3186-3200. DOI: 10.1074/jbc.M116.751685
- [124] Wei R, Huang GL, Zhang MY, Li BK, Zhang HZ, Shi M, Chen XQ, Huang L, Zhou QM, Jia WH, Zheng XF, Yuan YF, Wang HY. Clinical significance and prognostic value of microRNA expression signatures in hepatocellular carcinoma. *Clinical Cancer Research*. 2013;**19**:4780-4791. DOI: 10.1158/1078-0432.CCR-12-2728
- [125] Yoon SO, Chun SM, Han EH, Choi J, Jang SJ, Koh SA, Hwang S, Yu E. Deregulated expression of microRNA-221 with the potential for prognostic biomarkers in surgically resected hepatocellular carcinoma. *Human Pathology*. 2011;**42**:1391-1400. DOI: 10.1016/j.humpath.2010.12.010
- [126] Sato F, Hatano E, Kitamura K, Myomoto A, Fujiwara T, Takizawa S, Tsuchiya S, Tsujimoto G, Uemoto S, Shimizu K. MicroRNA profile predicts recurrence after resection in patients with hepatocellular carcinoma within the Milan criteria. *PLoS One*. 2011;**6**:e16435. DOI: 10.1371/journal.pone.0016435
- [127] Yamamoto Y, Kosaka N, Tanaka M, Koizumi F, Kanai Y, Mizutani T, Murakami Y, Kuroda M, Miyajima A, Kato T, Ochiya T. MicroRNA-500 as a potential diagnostic marker for hepatocellular carcinoma. *Biomarkers*. 2009;**14**:529-538. DOI: 10.3109/13547500903150771