ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 January 26; 11(3): 487-718

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
January 26, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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World J Clin Cases 2023 January 26; 11(3): 528-533

DOI: 10.12998/wjcc.v11.i3.528

ISSN 2307-8960 (online)

MINIREVIEWS

Exosomal miRNA in early-stage hepatocellular carcinoma

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Luo L, China; Mohammed HA, Saudi Arabia; Wang ZX, China

Received: October 28, 2022
Peer-review started: October 28, 2022
First decision: December 19, 2022
Revised: December 26, 2022
Accepted: January 5, 2023
Article in press: January 5, 2023
Published online: January 26, 2023

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Abstract

The incidence and mortality of hepatic carcinoma (HCC) remain high, and early diagnosis of HCC is seen as a key approach in improving clinical outcomes. However, the sensitivity and specificity of current early screening methods for HCC are not satisfactory. In recent years, research around exosomal miRNA has gradually increased, and these molecules have emerged as attractive candidates for early diagnosis and treatment of HCC. This review summarizes the feasibility of using miRNAs in peripheral blood exosomes as early diagnostic tools for HCC.

Key Words: Hepatic carcinoma; Early diagnosis; Exosomal miRNA; Biomarker

Core Tip: The prognosis of hepatic carcinoma (HCC) is poor and surgical resection is the only potential radical cure. Early diagnosis of HCC is a key approach in improving clinical outcomes. However, the sensitivity and specificity of current early screening methods for HCC are not satisfactory. Exosomal miRNAs have become a candidate for early diagnosis and treatment of HCC. This review summarizes the feasibility of using miRNAs in peripheral blood exosomes as early diagnostic tools for HCC.

Citation: Wu ZQ, Zhu YX, Jin Y, Zhan YC. Exosomal miRNA in early-stage hepatocellular carcinoma. *World J Clin Cases* 2023; 11(3): 528-533
URL: https://www.wjgnet.com/2307-8960/full/v11/i3/528.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i3.528

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, with the seventh highest incidence and second highest mortality among all malignant cancer types[1,2]. About 905000 patients are newly diagnosed with liver cancers each year around the world, with 75% of these being accounted for by HCC alone, and altogether causing about 830000 deaths[3]. Infection with hepatitis B virus (HBV) is the most common cause of HCC, and more than half of the world's new cases of HCC were detected in China[4]. The high incidence and mortality of HCC pose a significant threat to the health of Chinese people and place a heavy burden on society[5].

It is considered that the best stage for treatment of HCC is Stage I, or subclinical liver cancer[6]. However, HCC symptoms in this period are not obvious, and most patients are not diagnosed until the middle or late stages. Therefore, development of more effective screening methods that allow earlier detection of HCC represents an important research focus. The five-year survival rate for patients with early-stage HCC is more than 70%, but this rate drops to less than 12.5% for patients with advanced HCC[7].

Tumor markers represent one approach for the early diagnosis of HCC, allowing earlier detection of primary tumors, recurrent tumors, and metastatic tumors than other methods. Yet, the accuracy of prediction and diagnosis achieved by tumor markers could still be improved, and such improvements would confer parallel improvements in prognosis and patient outcomes (Table 1)[8-12]. Alpha-fetoprotein (AFP), which has been widely used as a marker for HCC diagnosis and monitoring, is not highly sensitive to early HCC, and may also be increased in patients without HCC but with chronic viral hepatitis and cirrhosis[13]. As such, AFP can lead to misdiagnoses or unclear clinical interpretation, particularly if detected alone[14]. Despite the obvious limitations of using AFP as an early screening marker for HCC, its ubiquity has precluded its replacement by other clinical markers. At present, a variety of molecular markers are used in the diagnosis of HCC, but they all have the problems of low sensitivity and insufficient specificity. The sensitivity of AFP-L3, a glycoform of AFP, for the diagnosis of early HCC is less than 28%[15]. Another biomarker, protein induced by vitamin K absence II (PIVKA II), is also relatively insensitive for diagnosing early HCC[7]. Therefore, it is an urgent research direction to identify tumor markers with high sensitivity and specificity for the early diagnosis of HCC.

RELATIONSHIP BETWEEN RNA AND HCC

In recent years, non-coding RNA has attracted ever-increasing attention in the field of biological medicine. Our understanding of these RNA molecules has progressed rapidly, yielding a new understanding of cellular life and providing new opportunities for the diagnosis and treatment of various diseases. Among such non-coding RNA, the most extensively studied, to date, is microRNA (miRNA) - a class of small non-coding single-stranded RNA molecules containing 19-25 nucleotides. They are formed from double-stranded RNA precursors composed of 70-100 nucleotides in a hairpin structure. The sequences of miRNA are highly conserved across different species, suggesting that these very small molecules may play important roles in various cellular processes such as development, proliferation, differentiation, and apoptosis[16]. Significant differences in miRNA expression profiles have also been identified in some diseases[17,18], indicating that miRNA may be used as biomarkers for the diagnosis and prognosis of such diseases, including malignant tumors. Due to their structure, miRNAs can stably exist in the blood circulation, but the form of miRNAs in the circulation is not clear. Since RNA exposed to the blood is degraded within a short period of time, some researchers have pointed out that the stable existence of miRNAs in plasma must indicate the presence of protective macromolecules. Increasing evidence has shown that the main components of such protective macromolecular complexes are exosomes[19].

The correlation between miRNA and HCC was first proposed by Murakami, who analyzed the expression of microRNAs in tumor and adjacent tissues of HCC patients, as well as the liver tissues of hepatitis patients. It was found that miRNA-99a was positively correlated with the degree of pathological differentiation of HCC, while miRNA-20, miRNA-18 and pre-miRNA-18 were negatively correlated with the differentiation of HCC and positively correlated with the occurrence of HCC[20]. Since then, additional studies have confirmed close associations between miRNAs and HCC. These miRNAs can be roughly divided into two categories: "non-liver-specific miRNAs," such as miRNA-21, miRNA-221/222, and let-7, which are abnormally expressed in various tumors such as liver cancer, pancreatic cancer, and lung cancer[21-23], and "liver-specific miRNAs," which are only abnormally expressed in HCC. An example of a liver-specific miRNA is miRNA-122, which is up-regulated in HCC and suppresses the expression of the proto-oncogene c-myc through transcriptional activators[24]. Studies have shown that miRNA-122 is up-regulated in 70% of human liver cancer tissues and 100% of liver cancer cell models[25].

HCC is the result of multiple genetic mutations, which can occur in oncogenes or tumor suppressor genes, growth factors or their receptors, and myriad signaling pathways controlling cellular prolif-

Table 1 Biomarkers for the diagnosis of hepatocellular carcinoma

Biomarker	Ref.	Country	Sensitivity (%)	Specificity (%)
AFP	Trevisani *et al*[8]	Italy	60	90
DCP	Feng *et al*[9]	China	83	91
AFP-L3	Toyoda *et al*[10]	Japan	41	85
GP73	Marrero *et al*[11]	United States	62	88
miR-21-5p	Ghosh *et al*[12]	India	74	68

AFP: Alpha-fetoprotein; DCP: Des-γ-carboxyprothrombin.

eration or behavior. Gene mutations also play a very important role in the progression of a tumor. When the expression of a gene or a class of molecules is silenced or enhanced, the possibility of tumorigenesis is present[26], and microRNA is gradually becoming the focus of this kind of research. miRNAs - small RNA molecules with very simple structures that regulate hundreds of mRNAs - play an unusual role in gene expression networks. Abnormally expressed miRNA may play a role similar to oncogenes such as myc or tumor suppressor genes such as p53, inducing or inhibiting liver tumorigenesis according to the specific cellular function of the target gene or genes regulated by that specific miRNA[27]. Meanwhile, and critically, miRNA can also influence the therapeutic effects of chemotherapy and intervene in the process of drug tolerance[28,29].

Regarding the use of miRNAs as molecular markers for tumors, miRNA-21 has gained attention as the first miRNA used in the clinic[30]. Many studies have confirmed that miRNA-21 is an oncogene, promoting liver tumor growth and metastasis by inhibiting the tumor suppressor genes PTEN and MAP2K3[31,32]. In 2012, Tomimaru *et al*[33] found that expression of miRNA-21 was increased in the plasma and tumor tissues of HCC patients, and that there was a correlation between them. Further investigation revealed that plasma miRNA-21 had clinical application value and could be used to diagnose HCC. Several additional studies have also shown that various miRNAs can be used for the diagnosis or prognosis of HCC patients. For example, serum miRNA-122 can also be used as a tumor marker for the diagnosis of HCC[34], while miRNA-125 and miRNA-233 can further be used for the early diagnosis of HCC patients who are HBV-positive[35]. miR-140 can also be used to determine the prognosis of HCC patients[36].

EXOSOMAL MIRNA IN HCC

The stability of miRNAs in plasma depends on exosomes. Exosomes are bilayer lipid membrane-coated vesicles with diameters of about 30-100 nm that can be released out of the cell and into the blood, urine, saliva, and other body fluids. It is generally believed that exosomes are composed of such lipid molecules as well as myriad amino acids and proteins, among which the common markers of exosomes have been identified as CD9, CD63, CD81, CD82, and others[37]. Nucleic acids in exosomes include mRNA, DNA, miRNA and other non-coding RNAs. Exosomes can carry these functional substances between cells and mediate communication between cells, thus regulating protein synthesis, cellular proliferation and differentiation, antiviral activity, and myriad other physiological and pathological activities.

Exosomal miRNAs have multiple potential functions in cell-to-cell communication. As such, they can be used to detect pathophysiological changes in the body, track changes in tumors, and aid in the diagnosis and prognosis of various diseases[38]. Down-regulation of exosomal miRNA expression has been shown to play a certain role in the mechanism of tumorigenesis[39]. Because exosomes and their contents (mainly miRNAs) can reflect the state of the cell they were released from – including whether that cell was of a tumorigenic or healthy state - exosomal miRNAs may hold a high value in the clinical diagnosis of tumors[40]. Detection of exosomes derived from tumor cells and their miRNA levels may become a novel biological tool with clinical potential and utility in people at high risk of cancer[41].

Protein and miRNA profiles in exosomes produced by HCC cells have been shown to be significantly different from those produced by normal cells[42,43]. Such exosomes can be ingested and internalized by other cells to deliver genes with certain functions[44]. Similar to the screening of serum tumor markers for liver cancer, exosomal miRNA can also be used as a valuable, non-invasive biomarker to distinguish the type and grade of liver inflammation, and then assist in the early diagnosis of liver cancer. Studies have also shown that circulating miRNAs may become biomarkers for HCC diagnosis due to the large number of miRNA variants in HCC cells[45]. Ghosh *et al*[12] identified a liver-specific exosomal miRNA, miR-21-5p, as an early circulating diagnostic marker for HCC with low AFP. The sensitivity, specificity, and accuracy of miR-21-5p differential diagnosis of HCC are 74%, 68%, and 71%,

respectively.

CONCLUSION

In conclusion, although many miRNAs have been identified as tumor markers for early diagnosis of liver cancer in recent years, most of them have some defects and deficiencies, meaning that there is no clear consensus on which one or few miRNAs can improve the early diagnostics of HCC. Remaining challenges include a lack of further study on the specificity and sensitivity of target miRNAs in the diagnosis of liver cancer, a lack of robust clinical comparison between candidate miRNAs and the current tumor marker, AFP, and an expensive and cumbersome detection method for target miRNAs in HCC patients. As increased attention is placed upon exosomal miRNAs and their application at home and abroad, it is necessary and urgent to fully explore and realize the potential for exosomal miRNAs in the early diagnosis and treatment of liver cancer in clinical practice.

FOOTNOTES

Author contributions: Wu ZQ and Zhu YX designed and reviewed the manuscript; Wu ZQ, Zhu YX, and Jin Y wrote the paper; All authors read and approved the manuscript; Wu ZQ and Zhu YX contributed equally to this work.

Supported by the Quzhou Science and Technology Guided Project Planning, No. 2019133.

Conflict-of-interest statement: We declare that we have no conflict of interest related to this work.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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