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Journal of Advances in Medicine Science

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ARTICLE

Advances in miRNA Research in Hepatocellular Carcinoma

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ARTICLE INFO

Article history
Received: 18 February 2024
Revised: 23 February 2024
Accepted: 30 March 2024
Published Online: 30 June 2024

Keywords:
Hepatocellular carcinoma
miRNA

ABSTRACT

Globally, Hepatocellular carcinoma (HCC) is recognized as a major malignant tumor, being the 6th most common in terms of occurrence and ranking third in mortality rates among all cancer types. Within China, HCC is noted as the fourth most prevalent cancer and the second most common cause of cancer-related fatalities. The difficulty in managing HCC stems from its tendency to remain undetected due to a lack of symptoms in the early stages, along with the current lack of both effective diagnostic techniques and treatments for chemotherapy.

MiRNA, also referred to as microRNA, is a type of non-coding RNA typically consisting of 19-22 nucleotides in length. Upon binding to the mRNA of target genes, it functions to suppress mRNA translation or induce mRNA degradation, thereby exerting regulatory control over gene expression. Recent research increasingly suggests the pivotal involvement of miRNA in the onset and progression of primary hepatic cells. Studies exploring the association between miRNA and primary hepatic cell carcinoma hold substantial clinical significance in elucidating the pathogenesis, facilitating diagnosis, and advancing treatment modalities for liver cancer.

1. Introduction

Hepatocellular carcinoma (HCC), a prevalent malignant tumor, poses a significant mortality risk. The global incidence of liver cancer continues to escalate[1]. Among primary liver cancers, hepatocellular carcinoma stands as the most prevalent, constituting approximately 90% of cases, while intrahepatic cholangiocarcinoma and mixed hepatocellular carcinoma contribute to a mere 10%[2,3]. In some developing regions of Asia, hepatitis B virus (HBV) emerges as the primary culprit for HCC[4]. Early-stage HCC lacks clinical significance and specific serum markers, resulting in challenges for timely intervention. As HCC advances to later stages, the optimal window for effective treatment diminishes, emphasizing the critical importance of early detection[5]. Hence, there is an urgent need for a reliable serum biomarker to facilitate early diagnosis, treatment initiation, and enhanced prognosis for liver cancer patients.

MicroRNAs (miRNAs), small non-coding single-stranded RNAs within the human body, orchestrate diverse biological activities by modulating downstream target genes[6,7]. In recent years, the progressively unveiled significance of miRNAs has shed light on their role in tumor development, including breast cancer[8], prostate cancer[9], colon cancer[10], and more. A substantial body of literature has emerged, exploring the potential of miRNAs in cancer diagnostics and targeted drug research. This article provides a comprehensive overview of miRNAs and their involvement in the development of hepatocellular carcinoma (HCC). The objective is to deepen our under-

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 DOI: https://doi.org/10.26549/jams.v7i1.15782

standing of the mechanisms underlying HCC development and establish the groundwork for utilizing miRNAs as molecular markers for HCC and potential targets for drug intervention.

2. miRNA biology

In 1993, Ambros Laboratories reported the cloning and developmental function of the first microRNA: lin-4, marking a pivotal moment in gene exploration[11]. In 2000, Reinhart et al. demonstrated that another small non-coding RNA, called let-7 (for lethal-7), serves as a crucial regulator in the developmental time series of stem cells in the cryptic nematode Cryptomeria japonica[12-14]. Notably, let-7 was also identified as the first miRNA discovered in humans[14-16]. However, the miRase miRNA database currently catalogues 38,589 mature miRNAs, with over 2,000 sequences representing unique human miRNA genes. In recent years, an increasing number of genes have become implicated in developmental, physiological, and pathological processes[17].

MiRNAs are a class of small, non-coding, single-stranded RNA molecules containing 19-25 nucleotides. miRNAs bind to the 3' end of the target mRNA molecule in response to the interaction of a number of proteins, resulting in either inhibition of translation or specific cleavage of the mRNA molecule induced by the interaction of the target mRNA with the target gene[18,19]. One of the most common modes of cleavage known to date is that miRNAs proceed in an incomplete complementary form with the target gene, thereby blocking it from the target mRNA without causing any interference with its stability, thus preventing its translation from proceeding. miRNAs mainly regulate mRNAs as as initiating or repressing factors involved in tumourigenesis and progression[20-22] . The fact that miRNAs are highly conserved across different species makes this simple class of miRNAs have very critical functions in life activities.

Since their discovery, miRNAs have garnered significant attention in basic medical research, owing to their profound regulatory effects on gene expression and widespread distribution in human tissues and body fluids[18-20]. This characteristic renders miRNAs promising diagnostic markers and therapeutic targets in clinical practice. Notably, miRNAs are actively and passively secreted by tissue cells, and those circulating in the bloodstream exhibit remarkable stability, unaffected by factors such as repeated freezing, pH changes, or RNA degradation. Furthermore, studies indicate minimal gender and inter-individual variations in miRNA expression levels in peripheral blood. These findings underscore the potential of peripheral blood miRNAs as superior diagnostic and therapeutic tools. Presently, the utilization of miRNAs in diverse disease contexts is expanding[23].

3. miRNA expression and mechanism of action in cancer

The miRNA-mediated regulation of gene expression induces cellular stress in response to environmental changes, such as starvation, hypoxia, oxidative stress, and DNA damage[24-26]. This phenomenon is closely associated with human diseases, particularly cancer. MiRNAs involved in cancer regulation can be categorized into oncogenes (oncomiRs) and tumor suppressors. OncomiRs are up-regulated in cancer, suppressing their target oncogenes, while tumor suppressors are down-regulated in malignant tumors, leading to the overexpression of their target oncogenes. Approximately 50% of miRNAs are located at "fragile sites" in the genome, and many of them undergo amplification or deletion in cancer[27-28].

Numerous miRNAs have been identified to be associated with cancer, with a single miRNA exerting effects on multiple cancer types. For instance, the oncogene MiR-155, a validated immune system oncogene[29-30], has been implicated in nasopharyngeal carcinoma and breast cancer in recent studies[31]. In vitro experiments have demonstrated that the overexpression of miR-155 influences the expression of transforming growth factor-beta receptor 2 (TGFβR2), subsequently impacting the proliferation and metastasis of gastric cancer cells[32,33]. Similarly, miR-21 is another miRNA exhibiting elevated expression in various cancers. In ovarian cancer, miR-21 interacts with the 3'-UTR of PTEN mRNA[34]. In lung cancer, miR-21-5p directly targets SMAD7, resulting in a significant up-regulation of SMAD7 in lung cancer tissues[35]. Additionally, the MiR-17~92 family has been demonstrated to be up-regulated in various cancers[36].

MiR-15 and miR-16 function as oncogenes and are located within the intron of the non-protein coding gene LEU2. They act as tumor suppressors in approximately 68% of B-cell chronic lymphocytic leukemia (B-CLL) cases and are associated with lymphoma of the condyloma, multiple myeloma, and prostate cancer[37,38]. The miR-34 family comprises miR-34a and miR-34b/c, which are direct transcriptional targets of p53 and are downregulated in various cancers, including acute myeloid leukemia[39,40]. Conversely, in prostate cancer[41], breast cancer[42], and renal cancer[43], miR-34 has been found to be upregulated, resulting in tumor suppression by inhibiting cell cycle regulation, promoting apoptosis, and reducing cell invasion and proliferation[44].

DOI: https://doi.org/10.26549/jams.v7i1.15782

4. Mechanisms of miRNA action in hepatocellular carcinoma

In conclusion, miRNAs exert a critical role in the progression of hepatocellular carcinoma and its related diseases. On one hand, they can be targeted to impact viral transcription, as exemplified by miR-199-3p and miR-201, which can inhibit HBV replication[45]. Moreover, HCV possesses two miR-5-binding sites at the RNA 122′UTR of its genome, and binding of the miR-122/Ago2 complex to these sites can stabilize viral RNA and inhibit its degradation[45,46]. On the other hand, miRNAs can also contribute to liver protection or influence the progression of hepatocellular carcinoma by modulating hepatic fibrosis, hepatic lipid metabolism, hepatic inflammation, alcoholic liver disease, and non-alcoholic liver disease.

In liver tissues, oncogenic factors are present. miR-221 is one of the most highly expressed miRNAs in HCC tissues; its overexpression increased the tumorigenicity of hepatic progenitor cells expressing p53-/-myc. In addition, miR-221 overexpression stimulated the growth of tumourigenic murine hepatic progenitor cells targeting DNA damage-inducible transcript 4 (mTOR pathway regulator DDIT4)[47]. miRNA-21 contributes to hepatocarcinogenesis through the promotion of collagen synthesis and fibrogenesis in the extracellular matrix in the liver[48], and the expression level of miRNA-21 was increased in both serum and tissues[49,50], and the expression level was significantly correlated with tumour progression significantly correlated[51]. Correspondingly, oncogenic factors exist in the liver. In HCC, miR-1, which targets MCL101, is downregulated, thereby inducing apoptosis and delaying tumour progression[52], miR-29 plays an important role as an oncogenic factor in various cancers[53], an in vivo HCC study found that the inhibitory effect of miR-29 was due to the suppression of IGF2BP1 proliferation, migration and invasion in HCC cells[54]. Cheng et al.[55] demonstrated that miR-122 is a significant factor in HCC tissues and cells. 122 was significantly inhibited in HCC tissues and cell lines and targeted IGF-1R, ADAM10 and pyruvate kinase M2 (PKM2). And when miR-122 expression was elevated, it reversed the oncogenicity and could hinder the development of HCC in mice. miR-342-3p expression in hepatocellular carcinoma cells showed a significant reduction in cell proliferation, migration and colony formation. Monocarboxylate transporter protein 1 (MCT1) was identified as a bona fide target of miR-342-3p in HCC[56].

5. miRNA as a diagnostic marker for hepatocellular carcinoma

There have been many discoveries of biomarkers that can be used for cancer diagnosis. For example, CEA (carcinoembryonic antigen) can be used as a diagnostic marker for colon cancer, increased PSA (prostate-specific antigen) in prostate cancer has obvious diagnostic significance, as well as AFP and PIVKA-II in hepatocellular carcinoma[57].However, HCC markers are often not able to achieve simple and effective diagnosis, and the significance of persistently increased AFP in the diagnosis of HCC is quite clear, but it is impossible for the general public to monitor AFP for a long time. Long-term monitoring of AFP has been reported to be negative in about one-third of HCC patients. PIVKA-II is often used in the assessment of HCC after surgical treatment [58]. MiRNAs can be released into the body fluids after necrosis, apoptosis and rupture of the cell, or released into the body fluids in tumors, allowing miRNAs to be easily detected and analyzed in both normal and cancerous cells[59]. So miRNAs have greater application prospects in tumor diagnosis[60].In addition miRNAs have certain tissue specificity. In human tissue biopsies of different organs, the expression of miRNAs has certain differences[61]. Hong Z et al[61] investigated the potential utility of circulating miR-122 and let-7 in the diagnosis of early hepatocellular carcinoma, and their sensitivity was comparable to that of AFP based on the serum levels of patients with precancerous nodules of HBV and early hepatocellular carcinoma. Circulating miRNAs are stable in peripheral blood, and miRNAs in tissues will show specificity and therefore are more useful biomarkers for circulating miRNA assessment of HCC.

6. Summary and outlook

MiRNAs serve not only as markers for clinical diagnosis but also as independent prognostic factors and discriminators between early and late tumor stages in certain cancers. Furthermore, they play a crucial role in molecular targeted therapy and tumor immunotherapy[62]. Presently, miRNA mimics are employed to supplement tumor suppressor miRNAs or inhibit tumors using anti-miRs. However, further in-depth studies are required to translate this therapeutic approach into clinical practice.

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