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REVIEW

MicroRNA in HCC: Biomarkers and Therapeutic Targets

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ABSTRACT

Hepatocellular carcinoma (HCC) is a malignant tumor with high morbidity and mortality. At present, diagnostic methods such as imaging observation, serum testing and tissue biopsy, as well as treatment methods such as surgical resection, radiotherapy, and chemotherapy have certain limitations in clinical interventions for HCC due to the complex pathogenesis and drug resistance of liver cancer, which seriously affect the survival and prognosis of patients. As a large-scale cytokine, microRNA (miRNA) plays an important role in regulating various life activities of cells. Extensive evidence proved that certain miRNAs are specifically expressed in the tissues and blood of HCC patients, and some of them have been confirmed as important factors that can participate in the regulation of key signaling pathways in cancer cells. For this reason, these miRNAs have great potential in clinical diagnosis and treatment of HCC, and can improve the limitations of conventional diagnosis and treatment. Our paper reviews the research on miRNA biomarkers and targets in HCC in recent years, and aims to provide new ideas for the diagnosis and treatment of HCC.

KEYWORDS

HCC; miRNA; diagnosis; treatment; review

1 Introduction

Hepatocellular carcinoma (HCC) is one of the malignant tumors with the highest incidence, and one of the three high-fatal cancers in the world [1–3]. Statistics show that about 60% of HCC patient progress to the middle and advanced stages at the time of treatment, and the 5-year survival rate of HCC patients is generally lower than 10% [4,5]. HCC is divided into primary and secondary according to the origin of the lesion. Primary HCC cancer refers to the cancerous transformation of liver epithelial or mesenchymal tissue cells, which in turn forms a type of HCC with high incidence and high malignancy [6]; secondary HCC refers to malignant tumor cells invasion into liver by breast, prostate, and ovarian cancer or gastric cancer and indirectly cause liver cell canceration [7]. With the improvement of technology, the level of diagnosis and treatment of HCC has been greatly improved. Contrast-enhanced ultrasound, nuclear imaging, CT and other imaging diagnostic technologies, as well as the application of serum-specific marker detection technologies, can effectively locate and characterize the lesions of HCC patients [8]. Local ablation techniques, surgical resection, radiotherapy, and chemotherapy are also commonly used to clear

the patient's lesions [9]. However, due to the high degree of malignancy and recurrence of liver cancer, conventional treatment methods barely achieve the desired results. miRNA is an important type of non-coding RNA in cells, which can participate in a variety of life activities such as cell proliferation, differentiation, autophagy, and apoptosis [10]. At present, there are more than 2000 kinds of human miRNAs that have been discovered, and 60% of mRNAs have been confirmed to contain miRNA binding regions, and about 30% of mRNAs can be directly targeted and regulated by the corresponding miRNAs [11–13]. In addition, extensive evidences show that certain miRNAs can participate in the formation and development of cancer by targeting the expression levels of protocarcinoma and tumor suppressor genes in cells. At the same time, recent studies have also pointed out that certain miRNAs can serve as potential biomarkers in clinical interventions for HCC, which can effectively improve the diagnosis and treatment efficiency [14,15]. This paper reviews the scientific research progress of miRNA in HCC in recent years, aiming to provide a certain reference for the targeted therapy of HCC.

2 Overview of miRNA

miRNA is an endogenous non-coding RNA that is usually transcribed by RNA polymerase II or III to form primary miRNA, which is then split, transported out of the nucleus and cleaved by Drosha/DGCR8 complex, Exportin5-Ran-GTP complex and Dicer enzymes respectively to form mature miRNA. Finally, RISCs complex binds to the target protein mRNA with the RISCs complex, and regulates the expression level of the target protein in the cell by means of transcriptional inhibition, thereby participating in the regulation of cell life activities [16]. Hoelscher et al. [17] found that miR-128 plays a key role in the development of zebrafish heart. It can control the differentiation of cardiac progenitor cells by regulating the expression levels of various factors, and the knockout of miR-128 will promote the expression of transcription factors such as Isl1, Sfrp5 and Hcn4. Meanwhile, it inhibits the expression of Irx4, a key factor in the development of cardiac progenitor cells, and can reduce the beating frequency of early cardiomyocytes by up-regulating the expression of MyL2 in ventricular cardiomyocytes. Wei et al. [18] found that the expression level of miR-378a-3p in muscle was significantly higher than that of other tissues, and miR-378a-3p could inhibit the proliferation of myoblasts and promote their differentiation by targeting the expression of HDAC4. These studies indicate that miRNAs play an important role in biological development.

3 miRNA is Involved in the Formation and Development of HCC

The formation and development of cancer cells are usually related to changes in the activities of multiple signaling pathways. Carcinogenesis of HCC usually involves changes in various intracellular signaling pathways such as PI3K/AKT, WNT/β-catenin, JAK/STAT, and activation or inactivation of these pathways can directly affect the proliferation, migration, invasion of cancer cells and drug resistance [19,20]. During these processes, certain miRNAs are significantly abnormally expressed in HCC cells, and these miRNAs can bind to the mRNAs of key factors in certain signaling pathways, thereby participating in intracellular signal transduction by changing the expression levels of these factors in the cell. And ultimately it can affect the proliferation, invasion or apoptosis of HCC cells [21,22]. Yang et al. [23] found that compared with normal liver cells, the expression level of miR-802 in liver cancer cell lines such as Hep3B, Huh7, SMMC-7721 and Bel-7402 was significantly up-regulated, and miR-802 could be targeted inhibit the expression of zinc finger protein 521 to promote the up-regulation of RunX2 and activate the PI3KK/AKT signaling pathway, consequently promoting the proliferation, metastasis and invasion of HCC cells. Wu et al. [24] demonstrated that miR-660-5p is significantly highly expressed in a variety of HCC cell lines, and miR-660-5p can directly target the 3 non-coding region of the tumor suppressor gene YWHAH and inhibit its mRNA translation. Thus, the PI3K/AKT signaling pathway is activated by down-regulating the protein level of YWHAH to induce the proliferation and migration of HCC cells. In the absence of miR-660-5, YWHAH knockout can also activate the

PI3K/AKT pathway to promote the proliferation of HCC cells such as HCCLM3, HepG2 and Huh-7. In addition, some studies have shown that the down-regulation of certain miRNA levels will also promote the formation and development of HCC. Yu et al. [25] pointed out that compared with normal liver cells THLE-3, the expression level of miR-642 in HCC cells such as Huh7 and HCCLM3 was significantly down-regulated, and the lack of miR-642 would promote the up-regulation of SEMA4C protein levels and the activation of p38/MAPK signaling pathway, thus inhibiting the apoptosis of these HCC cells. All these studies have shown that the dysregulation of miRNAs can greatly increase the malignancy of cancer cells, which is directly related to the various bad behaviors of cancer.

4 miRNA Serves as a Diagnostic Marker for HCC

Currently, the diagnosis of HCC mainly adopts methods such as detecting the level of AFP in the patient's serum, observing the size of the tumor through imaging equipment, and detecting markers in pathological tissues through sampling [26–28]. Yet, the expression of AFP in the serum of some HCC patients lacks specificity, which cannot accurately reflect the true condition of the patient; imaging detection is not effective in identifying and positioning the lesions in early HCC patients; tissue biopsy needs to invade the patient's body for sampling, which is easy to cause the metastasis of tumors [29–31]. Studies have shown that compared with adjacent tissues, some miRNAs in HCC cells have significant abnormal expression, and the differential expression profiles of miRNAs are also specific in different cancers. Wang et al. [32] compared miRNA expression differences in 387 liver cancer patient tissues and 62 adjacent tissues in the TCGA cancer database and found that miR-199a-3p, miR-199b-3p, miR-139-5p, miR-139-3p, miR-424-3p, miR-1269b and miR-1269a are significantly correlated with HCC, and miR-139-5p can be used as a biomarker to effectively predict the three-year survival rate of HCC patients. Shohda et al. [33] analyzed the expression level of miRNA in the tissues of 40 patients with HCC and found that compared with the adjacent tissues, miR-615 was significantly down-regulated in HCC tissues, while miR-484, miR-524-5p and miR-628 were significantly up-regulated. These studies show that compared with normal tissues, miRNA is specifically abnormally expressed in HCC tissues, so it can be used as a potential marker for clinical diagnosis. In addition, the acquisition of miRNA is relatively easy, and miRNA samples of patients can be obtained through non-invasive methods such as serum collection, which can reduce the cost of diagnosis and greatly lower the risk of tumor metastasis. Bai et al. [34] selected 10 HCC patients as the research subjects. By analyzing the miRNA differential expression profiles of the patients' plasma, excised adjacent cancer and HCC tissues, they found that the overall expression level of miRNA in HCC tissues was significantly up-regulated, while miR-486-5p of HCC is markedly down-regulated compared with adjacent tissues, and the TCGA clinical database shows that miR-100-5p, miR-10a-5p and miR-99a-5p have a notable correlation with the 5-year survival rate of patients.

Chronic hepatitis B virus (HBV) infection is one of the main risk factors for HCC, and the current lack of effective treatment for HBV-related HCC results in a higher recurrence rate and poor prognosis after treatment. Wang et al. [35] analyzed miRNA microarray of 32 HBV-positive and 24 HBV-negative patients with HCC and adjacent tissue and found that miR-150, miR-342-3p, miR-663, miR-20b, miR-92a-3p, miR-376c-3p, and miR-92b have remarkable abnormal expression in HBV-positive HCC tissues. And further enrichment of the KEGG signaling pathway revealed that these miRNAs are notably correlated with 11 factors such as AGO2, TP53, CCND1 that are associated with HCC development. Weis et al. [36] analyzed miRNA expression levels in HCC tissues and serum of HBV-positive patients by miRNA microarray and found that the expression levels of miR-112-5p and miR-151a-5p were significantly down-regulated in patients' serum, while miR-486-5p is significantly up-regulated, which is remarkably different from that of patients with liver cirrhosis. It is further believed that miR-112-5p, miR-151a-5p and miR-486-5p can be used as diagnostic markers for HBV-positive HCC patients. These studies show that certain miRNAs have specificity in the tissues and serum of HBV-positive and negative

HCC patients, which may be related to the pathogenesis of HCC mediated by HBV, so they can be used as specific diagnostic markers to distinguish HCC categories.

5 miRNA Serves as a Therapeutic Target for HCC

miRNAs play a major role in cell life activities, and enormous studies have confirmed that the abnormal expression of certain miRNAs is specific in HCC, and can participate in the proliferation, metastasis and apoptosis of HCC cells through various signal transduction pathways [37–39]. And the interference with the expression level of miRNA can effectively prevent or delay the malignant development of cancer cells by inhibiting proliferation, promoting apoptosis, and inhibiting aerobic glycolysis. Therefore, these miRNAs have great value in clinical targeted therapy of HCC. Ni et al. [40] found that compared with normal liver cells, the expression level of miR-515-5p was significantly down-regulated in HCC cells such as HepG2 and Heh-7, while overexpression of miR-515-5p in HCC cells would cause down-regulation of IL6 and inactivation of the JAK/STAT signaling pathway mediated by HCC, accordingly, inhibiting the proliferation and invasion of HCC cells. Wang et al. [41] found that miR-383 can significantly reduce the luciferase activity of wild-type IL-7, while overexpression of miR-383 in HCC cells such as HepG2 and Heh-7 can cause the down-regulation of IL7 and promote the inactivation of STAT3 signal pathway, consequently promoting the apoptosis of HCC cells.

The high recurrence rate and high fatality rate of HCC are closely related to the tolerance of HCC cells to chemotherapy drugs. Commonly used chemotherapy drugs include sorafenib, doxorubicin, 5-fluorouracil, etc., and the resistance of HCC cells to these drugs leads to poor prognosis and recurrent adverse reactions after receiving clinical chemotherapy [42,43]. However, the drug resistance mechanism of HCC cells is very complicated, including drug pumping caused by the up-regulation of certain transporters in the cell, inactivation of the apoptosis signaling pathway induced by down-regulation of key tumor suppressor genes such as p53, and the enhancement of damage repair ability of cancer cell DNA, the increase of cell autophagy and the activation of cancer stem cells [44–48]. With the in-depth research on the mechanism of miRNAs involved in the formation and development of cancer cells, more and more evidences show that the abnormal expression of certain miRNAs is closely related to drug resistance in HCC cells. As a standard targeted therapeutic agent for HCC approved by the FDA, sorafenib has shown a satisfactory outcome in the treatment of HCC worldwide. However, the HCC cells in most HCC patients eventually develop resistance to sorafenib, which is inseparable from the abnormal expression of certain miRNAs. He et al. [49] found that miR-21 can inhibit the autophagy of HCC cells by targeting inactivation of the PTEN/AKT signaling pathway, thereby increasing the sensitivity of cancer cells to sorafenib. Pollutri et al. [50] found in mouse models that the expression level of miR-494 was significantly up-regulated in mouse HCC stem cells, and miR-494 could promote the autophagy of cancer cells to enable mouse HCC to resistant to sorafenib. It is then concluded that the combination of sorafenib and miR-494 can improve the poor prognosis of HCC caused by drug resistance. Recently, a research group found that the maternal miRNA, miR-27a-3p, in obese mouse mothers that is passed on to their offspring, increasing susceptibility to liver cancer and elevating the odds of HCC developing in offspring, down multiple generations, this study pointed to a future therapeutic target [51]. All these suggest that the intervention of certain miRNA expression can significantly improve the killing effect of chemotherapeutic drugs on HCC cells, and also reflect that miRNAs have broad application prospects in future clinical chemotherapy.

6 Summary

As an important type of non-coding RNA in cells, miRNA can participate in a variety of life activities such as cell proliferation, differentiation and apoptosis. The abnormal expression of some miRNAs is also closely related to the formation and development of cancer. Although substantial evidence has enhanced the understanding of miRNAs, the regulatory mechanism of miRNAs in HCC due to the complexity of

cancer mechanisms is still not clear, which needs more in-depth research to clarify. Current review discussed that certain miRNAs can be used as specific markers or targets in HCC, and these miRNAs may play a huge role in clinical diagnosis, target drug development, and drug target combined chemotherapy in the future as the research deepens.

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Appendix

Summary of HCC related miRNAs

Name	Function	Mechanism
miR-802	Promotion of the proliferation, metastasis and invasion of HCC cells.	Inhibition of zinc finger protein 521 expression to promote the up-regulation of RunX2 and activate the PI3KK/AKT signaling pathway.
miR-660-5p	Down-regulation of miR-660-5p promotes the formation and development of HCC.	Directly target the 3' non-coding region of the tumor suppressor gene YWHAH and inhibit its mRNA translation.
miR-642	Down-regulation of miR-642 inhibits HCC apoptosis.	Promotion of the up-regulation of SEMA4C protein levels and the activation of p38/MAPK signaling pathway.
miR-139-5p	A biomarker to effectively predict the three-year survival rate of HCC patients.	Significantly correlated with HCC.
miR-515-5p	Overexpression of miR-515-5p inhibits the proliferation and invasion of HCC cells.	Down-regulation of IL6 and inactivation of the JAK/STAT signaling pathway mediated by HCC.
miR-383	Overexpression of miR-383 promotes HCC cell apoptosis.	Down-regulation of IL7 and inactivation of STAT3 signal pathway.
miR-21	Increasing the sensitivity of cancer cells to sorafenib.	Inhibition of the autophagy of HCC cells by targeting inactivation of the PTEN/AKT signaling pathway.
miR-494	Promotion of HCC cell autophagy.	Enable mouse HCC to resistant to sorafenib.