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Research on the application of microRNA in hepatocellular carcinoma

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Abstract. The digestive tract frequently develops the malignant tumor known as hepatocellular carcinoma (HCC). A variety of liver diseases can develop into HCC and therefore a therapeutic approach is required. Extracellular vesicles known as exosomes are released by a number of cells and contain a wide range of active substances, including lipids, proteins, RNA, and DNA. microRNA is a type of RNA that accelerates apoptosis by participating in the regulation of downstream gene translation. Studies have shown that exosomal micrornas regulate HCC. Exosomal microRNAs have been proven in studies which regulate HCC. Exosomal micrornas may therefore be particular biomarkers for HCC metastases and early diagnosis as well as possible therapeutic targets. The utilization of exosomal micrornas in HCC is employed as biomarkers for early diagnosis and may trigger cancer cell apoptosis through the PI3K-AKT channel or MAPKs/ERK channel to produce therapeutic effects. Exosomal micrornas are briefly detailed in this paper.

Keywords: microRNAs, HCC, exosomes, application.

1. Introduction

As a new research hotspot, exosomes have become a potential effective way for disease diagnosis and treatment due to their wide distribution in the body and ease of acquisition. Exosomes are found in a variety of bodily fluids, including blood and urine, and the biomarkers they contain are easy to find and less dangerous. Exosomes can be employed as effective tumor-targeting vectors to transport medications to proximal or distal cells due to their tiny size, high stability, good biocompatibility, and safety. Exosomes can be administered into the body orally, intravenously, intraperitoneally, subcutaneously, nasally, or intravenously. The current research is no more than these three: the first is the study of exosome miRNA as a biomarker; the second is to explore the function of miRNA in exosomes, not limited to markers; and the third is the mechanism of miRNA action on distant cells or tissues. Starting from microRNA, researchers have determined whether a certain tissue or cell contains a functional miRNA and whether it can be secreted into other distant cells or tissues through exosomes to exert its function. According to the literature review, the research methods are very similar, looking for biological phenotypes and selecting samples. Exosomes were collected and total RNA or miRNA were extracted. Differentially expressed mirnas were screened by high-throughput sequencing. Using qPCR and other methods to verify screening, by studying the application of microRNA in HCC, the limitations of treatment can be improved, and measures can be taken to treat it at an early stage.

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2. Related Concepts

2.1. Overview of HCC

A type of liver cancer brought on by liver cells is called hepatocellular carcinoma. 90% of all primary liver cancers are this prevalent primary cancer. The disease is mostly caused by genetics, chronic hepatitis B, hepatitis C virus infection, and other causes. Liver cancer has a poor prognosis and a high rate of metastasis and recurrence. Therefore, effective treatment strategies will represent a significant advancement in their care.

2.2. Overview of exosomes

Different types of cells can generate exosomes, which are natural drug carriers in both healthy and diseased conditions. It is mostly made of polyvesicular bodies, which are produced by the invagination of lysosomal microparticles within cells and expelled into the extracellular matrix after the fusing of the polyvesicular outer membrane with the cell membrane. Exosomes are a diverse collection of bioactive molecules that can be categorized as lipids (including cholesterol, sphingomyelin, phosphatidylserine, and other lipids), proteins (including oncoproteins, tumor suppressor proteins, transcription regulators), proteins, DNA, RNA, and single-stranded DNA. Exosomes are utilised in a range of malignancies, including hepatocellular carcinoma, according to an increasing number of studies.

2.3. Overview of microRNA

A form of RNA called a miR, which has a length of 20 to 24 nucleotides, can target and control downstream genes, influence several pathophysiological processes, and then take part in the onset and progression of several kinds of diseases.In exosomes, miR is stably present and can be picked up by distant or nearby cells as well as the systemic circulation, which is extremely helpful in the detection and evaluation of cancer. MiR has been discovered to be helpful in the early detection of HCC.

3. Early detection and prognostic biomarkers

Hepatocellular carcinoma frequently misses the ideal treatment window since it typically has no distinct early symptoms. Therefore, early detection is a crucial requirement for HCC treatment effectiveness. In most high-risk groups nowadays, serum alpha-fetoprotein (AFP) and ultrasonography (US) are commonly used for the early identification of liver cancer.

Numerous microRNAs (miRNAs) have been reported to have significantly increased levels in the serum of people with hepatocellular carcinoma (HCC). Here are some examples of their experimental results: There is an urgent need for innovative methods for the diagnosis of hepatocellular carcinoma (HCC). The use of microRNAs (miRNAs) as disease biomarkers is gaining popularity. MiR-21 expression in serum exosomes from patients with HCC or chronic hepatitis B (CHB) was studied by Wang Hao, Hou Lei, Li An, and others. They discovered that exosomal miR-21 may be used as a potential biomarker for HCC diagnosis [1]. The results of the other two trials using RNA sequencing, analysis, and qPCR revealed that miR-122 and miR-215-5p can be employed for HCC early detection [2, 3]. Exosomes of miRNA-96 have been identified as diagnostic biomarkers for HCC patients by Wang S, Yang Y, Sun L, Qiao G, et al. Based on the aforementioned information, the exosomes of HCC patients can also be used to predict their prognosis [4].High amounts of Mir-210-3p (miR-2110) were reported in the serum of hepatocellular carcinoma (HCC) patients, and Lin XJ, Fang JH, Yang XJ, et al. noticed that exosomal miR-210 may be transported into endothelial cells via targeting, thereby boosting the development of tumor blood vessels. His look can be used to make a preliminary HCC diagnosis [5]. The levels of serum exosomal miR-18a, miR-221, miR-222, and miR-224 in HCC patients were considerably greater than those in CHB or LC patients, according to research by Sohn W, Kim J, Kang SH, et al. Therefore, it is implied that new serological biomarkers for HCC can be identified using serum exosomal microRNAs [6]. By injecting liver cancer serum into two groups of rats, Nakano T, Chen IH, Wang CC, et al. discovered that exosomal miR-92b may be utilized to predict the probability of HCC recurrence following transplantation [7]. In summary, if we want to make an early diagnosis of

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hepatocellular carcinoma, we can use PCR technology and mathematical analysis for the miRNA level in serum exosomes of patients, such as the AUC area, and compare it with CHB or LC patients. If it is higher than their values, we can infer that the patient has HCC.

3.1. HCC develops, differentiates and metastasizes

According to literature review, the differentiation and metastasis of HCC cannot be separated from two channels, namely PI3K-AKT channel and MAPKs/ ERK channel, which subsequently induce cell apoptosis. The role played by the two channels in this process will be discussed in detail next.

3.2. Through the PI3K-AKT pathway

The PI3K-AKT pathway is an intracellular signal transduction route that reacts to extracellular inputs to support angiogenesis, cell growth, survival, and proliferation. The primary genes involved in this process are phosphatidylinositol 3-kinase (PI3K) and AKT/protein kinase b, and as a result, this pathway is called after these two genes. This mechanism is regulated by serine or threonine phosphorylation of a number of downstream substrates. As a direct downstream target and functional mediator of miR-155 in HCC cells, we discovered AT-rich interactive domain 2 (ARID2). Modifications to ARID2 expression reversed the effects of miR-155 on HCC cell proliferation, cell cycle, and death. By changing Cyclin D1 and p27, critical elements of the cell cycle machinery, researchers showed that Akt phosphorylation plays a significant role in the operation of miR-155. In addition, miR-155 downregulation was found to inhibit HCC tumor growth by inhibiting the Akt signaling pathway. As a result of their research, it was shown that miR-155 accelerated tumor growth in HCC by concentrating on the ARID2-mediated Akt phosphorylation pathway [8]. Another study revealed that miR-23a-3p inhibited T cell activity and promoted the metastasis of cancer cells by controlling PD-L1 expression via the PTEN-phosphatilylinositol 3-kinase protein kinase B (AKT) pathway [9]. Another group of researchers examined the function of APLN through ectopic expression and silencing. The results showed that APLN overexpression was common in HCC, and Through the APLN receptor, APLN triggered the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. The oncogenic involvement of APLN in HCC is revealed by increased expression of phosphorylated glycogen synthase kinase 3 (p-GSK3) and cyclin D1 [10].

3.3. Through the MAPKs/ ERK pathway

The regulation of cell proliferation, differentiation, apoptosis, migration, and other processes is greatly influenced by the ERK1/2 signaling system. When external signals such as growth factors and mitogens bind to the receptor, the receptor tyrosine kinase activity is activated, and the signal is transmitted to the small gtpase Ras through downstream adapter proteins. Ras changes from GDP-binding to GTP-binding, and phosphorylates the threonine and tyrosine residues on ERK1/2, activating MEK1/2 in the process. Activated ERK1/2 further activates nuclear transcription factors or cytoplasmic proteins and produces a series of changes. MiR-320a levels were found to be considerably lower in exosomes produced from CAF after microRNA (miRNA) sequencing was done on exosomes from various sources. It was proven that mesenchymal cells can transmit miRNA to HCC cells using exogenous miRNA. Studies have demonstrated that miR-320a can function as an anti-tumor miRNA by binding to its downstream direct target PBX3, which prevents HCC cells from proliferating, migrating, and metastasizing. By preventing the activation of the MAPK pathway, which can cause the epithelial-mesenchymal transition, up-regulate the expression of CDK2 and MMP2, and enhance cell proliferation and metastasis, the miR-320a-PBX3 pathway slows the growth of tumors. When CAFs were combined with MHCC97-H cells in a xenograft experiment, miR-320a was overexpressed in the CAFs, which could prevent tumorigenesis [11]. Studies have revealed that overexpressing miR-9-3p lowers HCC cells' viability and proliferation while upregulating ERK1/2 [12].

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3.4. Induction of apoptosis

In the HCC microenvironment, transfer between exosomes can induce or inhibit tumor growth and metastasis [13]. Two studies confirm this. According to one study, miR-451a was downregulated based on miRNA expression and TCGA analysis, and TargetScan, GSEA analysis, and the Uniprot database were used to predict LPIN1 as the miRNA's target. Real-time PCR and a dual luciferase experiment were then used to corroborate the findings: Human umbilical vein endothelial cells (HUVECs) and liver cancer cell lines can both be made to undergo apoptosis by exosomal miR-451a, which can also prevent HUVEC migration, tube formation, and vascular permeability [14]. The link between ATP7A and mir-139 was investigated using luciferase reporter assay, Western blot, and real-time quantitative reverse transcription PCR by identifying and documenting the expression of mir-139. MiR-139 was discovered to be a strong inhibitor of OC cell invasion, colony formation, proliferation, and migration. Additionally, it greatly reduced the production of proteins linked to cell death, the death of OC cells, and the release of exosomes [15].

4. Conclusion

Exosomal microRNA plays an essential part in the environmental regulation of HCC occurrence and development and is implicated in the pathological process of many cancers, including HCC. Exosomal microRNA is a potentially useful biomarker for HCC diagnosis, prediction, prognosis, and real-time treatment response monitoring. This article discusses the function of exosomal microRNAs in HCC and demonstrates how exosomes may be used clinically to diagnose and treat various illnesses. The results described in this article are currently known, and their roles may be further discovered through subsequent studies. Future liver cancer detection and treatment will be based on a better understanding of the role of exosomal micrornas, and this is very likely to result in a significant advancement.

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