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Discussion on the Correlation between miRNA and the Regulatory Mechanism of Hepatocellular Carcinoma Cells

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Abstract:

Hepatocellular carcinoma, ranking as the sixth most prevalent malignant neoplasm globally, is characterized by a propensity for rapid proliferation and a high tendency to metastasize to distant sites within the body. microRNAs control the expression of liver cancer cells by targeting specific mRNA sequences. At present, miRNAs have made a lot of progress in the early detection and continuous tracking of liver cancer cells, as well as in creating ways to diagnose liver cancer using blood samples. However, there is still a big gap in the research on using miRNAs for the prompt identification and intervention for hepatic carcinoma. To identify unique effects resulting from miRNAs on how liver cancer is regulated, this study looked at the regulatory mechanisms of miRNAs and paid special attention to specific miRNAs like miR-590-5p. Outcomes demonstrated approach could modulate growth dynamics, migratory behavior, metastatic potential among cancerous hepatic cells, hence participating in the early diagnosis of liver cancer. This study aims to summarize and analyze the regulatory pathways of miRNAs in liver cancer, Aiming to contribute pertinent knowledge to the exploration of the early-stage diagnosis and treatment for malignant hepatic tumors.

Keywords:-microRNA; hepatocellular carcinoma; proliferation; migration; invasion

I. Introduction

HCC is a major influence in raising the mortality rate related to cancerous illnesses. Its pathogenesis is complex and it accounts for over 90% of all primary liver cancers [1]. During the year 2020, the global incidence of new cases was estimated to be around one million, with a high degree of malignancy and metastasis rate. According to the data from the Global Cancer Registry, as of 2022, HCC ranks sixth among all malignant tumors, with about 830,000 people dying from liver cancer each year. HCC is highly malignant and prone to proliferation, migration and invasion. Early diagnosis is difficult, and about 70% of patients

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are diagnosed with advanced liver cancer.

In recent years, microRNAs have become a focus in the research on the mechanisms of HCC and clinical diagnosis due to their fundamental part in the orchestration of gene expression is played by. These tiny non-coding RNA molecules carry out their regulatory actions by binding to the 3'-non-coding part at the end of their intended target genes, which subsequently leads to either the destabilization and breakdown of the corresponding mRNA or the prevention of its translation into protein. participating in Biological events encompassing cellular growth expansion and programmed cellular self-destruction. Research findings indicate that there exists an aberrant manifestation of miRNA levels within hepatocellular carcinoma (HCC) tissues is not only directly related to tumor occurrence and development, but also can Exert an impact on the initiation and progression of liver carcinoma through the modulation of pivotal signal communication pathways and epigenetic modifications.

The application of miRNA in the early diagnosis of HCC has demonstrated unique advantages. Compared with traditional markers such as alpha-fetoprotein (AFP) and imaging examinations, miRNA has high stability and tissue specificity. For instance, the liquid biopsy technology based on exosomal miRNA, by enriching liver cancer-specific miR-21 and miR-122, can increase the sensitivity of early HCC detection to 90% and the specificity to 92%, which is significantly superior to the sensitivity of AFP.

This article aims to provide readers with a comprehensive review of the regulatory mechanisms following aspects pertaining to miRNA within the proliferation, migration as well as invasion of HCC, and focuses on its potential in early diagnosis. The significance of this study lies in: (1) clarifying the molecular mechanisms by which miRNA regulates the development of HCC through the PI3K-AKT, EMT and autophagy pathways, providing new ideas for diagnosis and treatment; (2) evaluating the clinical diagnostic value of miRNA as a biological marker, promoting the construction of a precise diagnosis and treatment system. Multi-dimensional analysis of the biological functions and research prospects of miRNA provides a theoretical basis for the molecular classification and individualized treatment of HCC, and helps to transform the prevention and treatment of liver cancer towards "precise intervention".

II. miRNA and its expression regulation mechanism

Micro ribonucleic acid possesses a length that spans approximately 18 to 25 nucleotides. It is initially synthesized starting with DNA sequences and resulting in pre-miRNA, and subsequently undergoes additional processing to form the precursor (pre-miRNA) and a mature miRNA of approximately 20-24 nucleotides [2]. The regulatory function of miRNA in gene expression is accomplished across RISC. As shown in Figure 1, after The Fully Processed microRNA is covalently coupled with RISC, the miRNA activates the complex in a specific way, enabling it to target specific mRNAs. By promoting mRNA degradation, specifically when they are completely complementary or nearly complementary, it can guide the degradation of mRNA or reduce mRNA translation. Specifically, when The miRNA attaches to the mRNA's 3'UTR, a key move in miRNA-regulated post-transcriptional gene expression., it will hinder the translation process but not affect the stability of the mRNA [3]. Through these two mechanisms, it affects gene expression, thereby influencing key biological events include cell expansion, trait acquisition, regulated cell self-destruction, and EMT. Moreover, the mechanism of promoting degradation is more widespread in animals than the mechanism of inhibiting translation. Therefore, it can be concluded that miRNA and its downstream mRNA exert a significant influence in tumor occurrence and maturation.

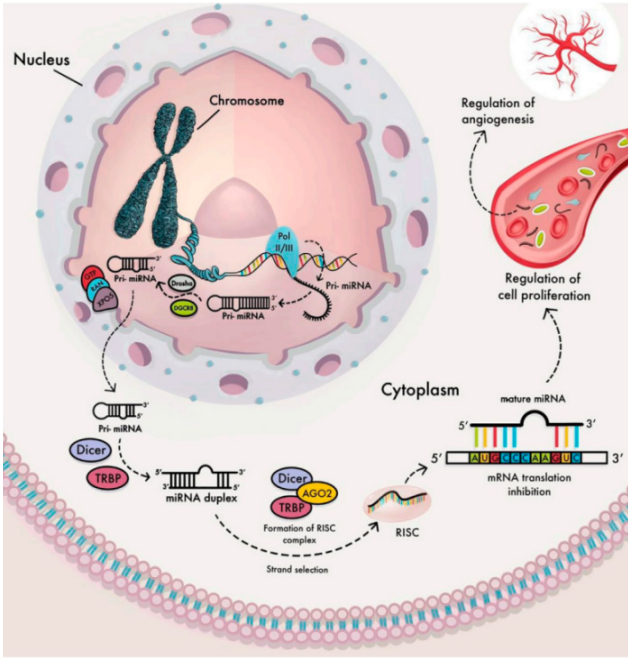

Figure 1. The miRNA biological occurrence pathway [3].

III. The regulatory role of miRNA in

HCC

A. The Regulatory Influence Exerted by miRNA on the Multiplicative Process of Liver Cancer Cells

miR-590-5p and miR-590-3p exert a facilitative influence on the proliferative capacity of liver cancer cells. Tumor cell proliferation is a process where cancer cells undergo abnormal cell division, resulting in uncontrollable increase in cell numbers. Proliferation ability is the foundation for tumor occurrence, development, migration, etc. Generally, the characteristics of tumor cell proliferation include uncontrolled nature (losing the regulation of cell division), rapidity (dividing at a speed far exceeding that of normal cells), and anti-apoptosis (escaping programmed cell death while proliferating).

miR-590-5p and miR-590-3p are two mature strands formed by the processing of the same precursor miRNA (pre-miR-590), located at the 3' end and 5' end of the precursor respectively. Their expression levels in liver cancer tumor tissues are significantly higher than those in adjacent tissues, enhancing the survival ability of liver cancer cells and promoting cell proliferation (as shown in Figure 2). Research findings indicate that the two strands hold significant positions at the start and during the extending process of hepatic neoplastic disease.

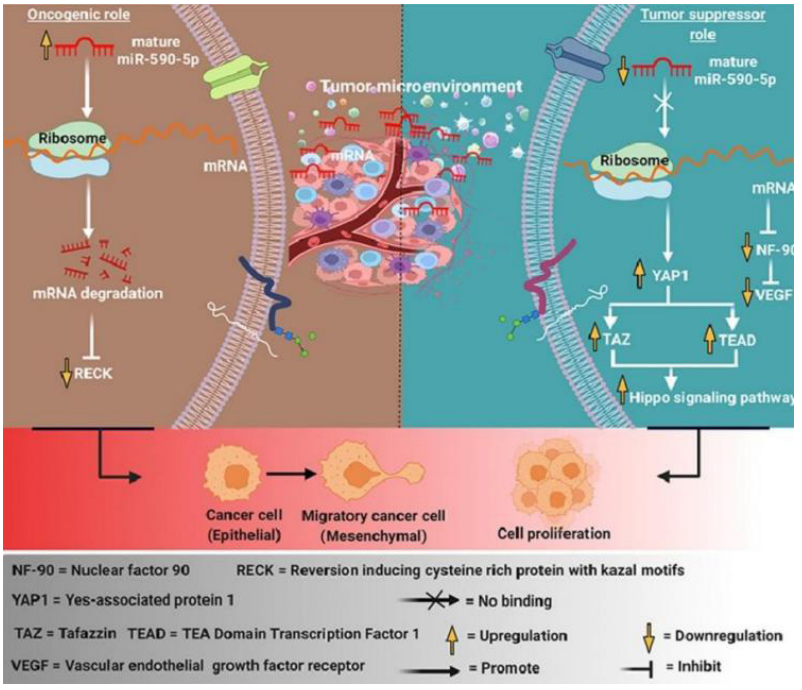

Figure 2. The role played by miR-590-5p in the tumorigenic mechanism [4].

miR-590-5p is capable of diminishing the expression magnitude of the apoptotic protein PDCD4(by competitively binding to the RNA binding site of RNA helicase elF4A through the MA3 domain [5], inhibiting its activity, suppressing the formation of the ribosomal initiation complex, and thereby inhibiting the synthesis of oncogenic proteins such as cell cycle proteins and anti-apoptotic proteins). This enables the cells to acquire anti-apoptotic ability, and the acquisition of anti-apoptotic ability is one of the main steps in the occurrence of cancer. PDCD4 inhibits tumor occurrence by inducing cell apoptosis. miR-590-5p can down-regulate the expression of PDCD4, inhibit the translation of PDCD4 protein, prevent cell apoptosis, and thereby promote cell survival.

miR-590-3p promotes cell proliferation by inhibiting the expression of the tumor suppressor gene PTEN (tumor suppressor protein). PTEN is a protein mainly responsible for regulating the PI3K/AKT signaling pathway. It dephosphorylates PIP3 into PIP2, thereby reducing the phosphorylation level of AKT1-S473 and inactivating it, disrupting the PI3K-AKT-mediated signal-transmission route. In clinical practice, the abnormality of this pathway is closely related in relation to the advancement and therapeutic resistance exhibited by diverse cancer types, including but not limited to breast carcinoma and prostate adenocarcinoma. Inhibitors targeting this pathway (such as Alpelisib) have been employed for the therapeutic management of particular mutant variants of breast carcinoma. While miR-590-3p indirectly activates the PI3K/AKT signaling pathway by inhibiting PTEN, miR-590-5p along with miR-590-3p exert a highly significant regulatory influence on the oncogenesis and cellular multiplication of

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liver cells.

B. The Modulatory Influence Exerted by miRNA on the Migratory Capability of Hepatic Carcinoma Cells

miR-34a has an suppressive influence on the migratory capacity of hepatic carcinoma cells and is expressed at a low level in tumor cells. Tumor cell migration referswith regard to the capability of malignant tumor cells for actively move at the molecular and cellular levels. This migration usually involves changes in cell morphology (such as the formation of pseudopods), a decrease in cell adhesion ability, and invasion of surrounding tissues. The migration mechanisms mainly include EMT, chemokine guidance, and cytoskeleton reorganization, etc.

miR-34a is a type of miRNA. Its main function is to inhibit mRNA translation and regulate cell cycle and apoptosis.When miR-34a is activated, it can stop tumor cells from migrating [6]. Several studies have indicated that the amount of miR-34a in liver cancer is much less than that in the nearby healthy tissues.miR-34a takes part in the growth and change of liver cancer and is strongly related with how malignant the malignancy is.

When miR-34a is overexpressed, it exhibits the potential to impede the cellular vitality and migratory behavior of liver-derived malignant cells. Bcl-2 plays a role in the downstream target of miR-34a. It can participate in the initiation stage of cell apoptosis, combine with pro-apoptotic proteins such as Bax (inhibiting their oligomerization to maintain the integrity of the mitochondrial membrane), by preventing the increase of mitochondrial outer membrane permeability (MOMP), inhibiting factors involved in apoptosis, like cytochrome C, are let out from the mitochondria, thereby achieving the effect of anti-apoptosis. In liver cancer cells, If miR-34a is overexpressed, it can stop Bcl-2 from being made by targeting, thereby inhibiting when the PI3K/AKT pathway is activated, it causes a drop in the activity of MMPs and inhibiting EMT, and further reducing the migratory capability of hepatic carcinoma cells [7].

C. The Way miRNA Regulates the Ability of Liver Cancer Cells to Spread into Surrounding Tissues

miR-424-5p can stop or slow down the invasive ability of liver cancer cells and is expressed at a low level within hepatic carcinoma cells. The migratory-invasive attribute of liver-derived malignant cells corresponds to the dynamic sequence in which liver cancer cells break through the surrounding tissue barriers (such as the basement membrane, extracellular matrix, etc.) from the initial tumor locus and progressively disseminate into surrounding tissues, blood vessels or lymphatic vessels. This step is the key to the initiation of liver cancer cell metastasis.

When it comes to liver cancer, miR-424-5p often serves as a factor that can stop tumors from growing. It can manage gene expression by linking up with the 3'UTR part of the mRNA of the gene it's aiming at and is usually expressed at a low level in liver cancer cells. It exerts corresponding effects by targeting genes such as CLDN6 and HMGA1 [8].

CLDNs are a type of tight junction proteins located on the cell membrane. Their main function is to form tight junction structures between cells, regulate the permeability of cells, and maintain the polarity and barrier function of epithelial and endothelial cells. Regarding liver cancer, miR-424-5p usually plays the role of a factor that helps prevent tumor growth.

CLDN6 predominantly shows an affiliation with the emergence of intercellular barriers and the modulation within signaling cascades. It is highly expressed in liver cancer cells. Through its own phosphorylation sites, it recruits the Src family tyrosine kinases, promoting their autophosphorylation and subsequently activating the downstream STAT3 signaling pathway. Once the signaling pathway is activated, it triggers an elevation in the synthesis levels of matrix metalloproteinases, specifically MMP-2 and MMP-9. This then helps liver cancer cells spread more easily.

If there's an increased transcriptional activity of miR-424-5p, it can stop Hepatic carcinoma cells from being as invasive. CLDN6 is the downstream target gene by this microRNA. In liver tumor cells, it directly links up with the 3'UTR part of CLDN6 mRNA. This connection then messes up the normal process of turning CLDN6 mRNA into protein, so there's less CLDN6 protein. It can even turn back the epithelial-mesenchymal transition. This makes it harder for hepatocellular carcinoma (HCC) cells to be invasive. When miR-424-5p is over-expressed, it elicits an elevation in the expression level of epithelial marker E-cadherin whilst curtailing the presence of mesenchymal markers N-cadherin along with Vimentin. Because of this, epithelial-mesenchymal transition is reversed, and liver cancer cells aren't as able to invade [9].

IV. Using miRNAs to detect liver cancer at an early stage

The fields of medicine and biological knowledge are experiencing rapid updates. Nowadays, numerous studies have shown that by leveraging the advantages of miRNA in regulating liver cancer cells based on previous experience and technology, it is possible to diagnose early-stage

liver cancer more efficiently and conveniently at an earlier stage. Wen Y et al. conducted tests on blood serum derived from multiple clinical individuals, screened microRNAs with altered expression levels through TLDA chips with a large number of plasma and tissue samples, verified their liver origin through tissue samples, validated the diagnostic efficacy of candidate miRNAs through qRT-PCR, and employed technical means such as combining model construction, based on criteria such as expression differences, validation of the stem cell prototype, and consistent expression trends in plasma and tissue. They identified four miRNAs, That is, miR-20a-5p, miR-320a, miR-324p, and miR-375 showed a clear increase in their expression in hepatocellular carcinoma patients' plasma as biological markers for early diagnosis of HCC [10]. The main advantages include high sensitivity and specificity, non-invasive detection suitable for large-scale screening, dynamic monitoring capabilities, and potential for combined diagnosis. Prior to this, the methods for early diagnosis of liver cancer were mostly APF detection, imaging detection, and liver biopsy.

A. Positive Aspects of microRNAs (miRNAs) in Catching Liver Cancer at an Early Stage

The technology of detecting miRNA using real-time fluorescence quantitative method has been well established, making it relatively easy to screen out miRNAs with high sensitivity and strong specificity as the target molecules for diagnosing liver cancer; miRNAs have a nano-scale protective structure. Whether miRNAs are at room temperature (25°C) or repeatedly frozen and thawed in a -80°C refrigerator, or in the presence of widespread RNA and DNA enzymes in nature, miRNAs will not be degraded. Therefore, miRNAs still express stably under extreme conditions [11]; This detection is a non-invasive test that does not require invasive tissue puncture or complex examination procedures. It only requires collecting routine body fluid samples such as the patient's blood to complete the test. It is easy to perform and causes little harm to the body, so it is suitable for regular screening of high-risk populations and short-term postoperative detection.

B. Application of miRNA in the Early Diagnosis of Primary HCC

The diagnosis of HCC is mainly carried out by detecting abnormal indicators in serum, tissues, and through ultrasound examinations. Although the detection rate is high, most patients have already reached the middle or advanced stage of it. So, it is extremely important to locate a diagnostic way that can diagnose HCC at an early stage and is also inexpensive. CaoLL et al. used artificial intelligence to diagnose HCC through ultrasound and assess the severity of HCC. However, using artificial intelligence for ultrasound diagnosis of HCC has a strong delay nature and cannot timely diagnose early-stage HCC.

miRNA has made certain progress in the early diagnosis of HCC. Tadokoro and his team conducted a detailed analysis and found that the abnormal overexpression of oncogenic miR-21, the decreased expression of tumor-suppressive miR-122, and the changed expression of exosomal miR-214 were related to the development of hepatocellular carcinoma (HCC). They also explained how these miRNAs worked during the start and growth of HCC. By checking the miRNA abundance within the serum sample as a method to diagnose HCC early, the diagnosis was much more accurate than using the traditional AFP test. Their study results showed that the amount of oncogenic miRNA in the serum of HCC patients was much higher, while the amount of tumor-suppressive miRNA was much lower in HCC. Because the abnormal expression of miRNA can be detected 34.5-50.5 months before clinical diagnosis, so it can provide valuable time [12].

V. Conclusion

This research indicated that several microRNAs have the potential to influence the gene expression patterns of liver-derived malignant cells through influencing their proliferation, migration and invasion. Therefore, it is indicated that miRNA may regulate the expression of liver cancer cells through the above three ways, and the regulatory effect is very obvious. And due to this efficient regulatory mechanism, miRNA holds potential for application in the early-stage detection of liver cancer, thereby addressing a void in the research of miRNA application in tumors. However, this study still has certain limitations. One is that the sample size is too small; the other is that the instability of RNA is relatively high, and there are still certain difficulties in specific applications. In the future, more in-depth research should be conducted at the genomic and biological application levels to explore breakthroughs in precise tumor treatment.

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