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A New Treatment Method in Hepatocellular Carcinoma by MicroRNAs

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Abstract

Objectives: Hepatocellular carcinoma (HCC) is considered as the most incidence form of cancer in the human liver and the main reason for worldwide cancer death. In addition, HCC is a common form of cancer in Africa and Asia and a global health issue. Thus, efforts should be made to improve treatment strategies and prognosis in HCC for recognizing novel prognostic and predictive markers.

Methods: The present study reviewed recently published studies that were identified from the National Institutes of Health's PubMed database, Latin American Literature in Health Sciences, and Scientific Electronic Library Online. To this end, several key terms were searched, including "hepatocellular carcinoma" AND "diagnosis" AND "hepatic resection", miRNA, and Mesh (Medical Subject Headings) consisting of miRNA "hepatocellular carcinoma".

Results: Both physiological and pathological processes such as development can be altered by the function and expression modifying of miRNA. The findings revealed that miR-101, miR-106, miR-130a, miR-515-5p, miR-199a, and miR-34a-5p have a considerable connection with tumor size in HCC patients.

Conclusions: In general, several reports indicated that more than half of the miRNAs genes are located in cancer-associated genomic regions or fragile sites. Considering the reports regarding the important roles of miRNAs in cancer, their potential as prognostic or diagnostics markers is confirmed by a long list of studies and miRNA markers that could be used for cancer diagnosis are becoming available

Keywords: Hepatocellular carcinoma, miRNA, Molecular targets

Introduction

Hepatocellular carcinoma (HCC) is a common form of cancer in Africa and Asia and a global health issue. Accordingly, it is necessary to make efforts to improve treatment strategies and prognosis in HCC in order to recognize novel prognostic and predictive markers (1). In addition, HCC is a multifactorial and heterogeneous neoplasm with some genomic variations.

Potential therapeutic treatment is required for 40% of patients (i.e., resection, transplantation, or local ablation) and 20% for chemotherapy (2). Further, HCC is a global health issue (3, 4).

The rising occurrence of hepatitis C infections is regarded as the main reason for HCC in western countries. HCC has intricated molecular pathogenesis chromosomal aberrations, along with different genetic and epigenetic modifications, and molecular pathway disruption might be implicated in each of these abnormalities.

Methods

In this study, recently published studies were reviewed, which were identified from the National Institutes of Health's PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), Latin American Literature in Health Sciences, and Scientific Electronic Library Online. For this purpose, some key terms were searched, consisting of "hepatocellular carcinoma" AND "diagnosis" AND "hepatic resection", miRNA, and Mesh (Medical Subject Headings) including miRNA hepatocellular carcinoma.

Results and Discussion

Synopsis of Molecular Pathogenesis

HCC molecular pathogenesis is multifaceted. In 80% of cases, HCC found in the liver appears normal, but it is abnormal in noncirrhotic and cirrhotic livers as the consequence of various environmental risk factors. The molecular pathway of HCC formation and progression is not clear. Various studies have attempted to unravel the molecular pathway that consists of the cancer invasion process and metastasis.

This process involves different variations, chromosomal deviance, gene mutations, and modified molecular pathways (3), the details of which are shown in Figure 1. Gene expression modification is the major event that is

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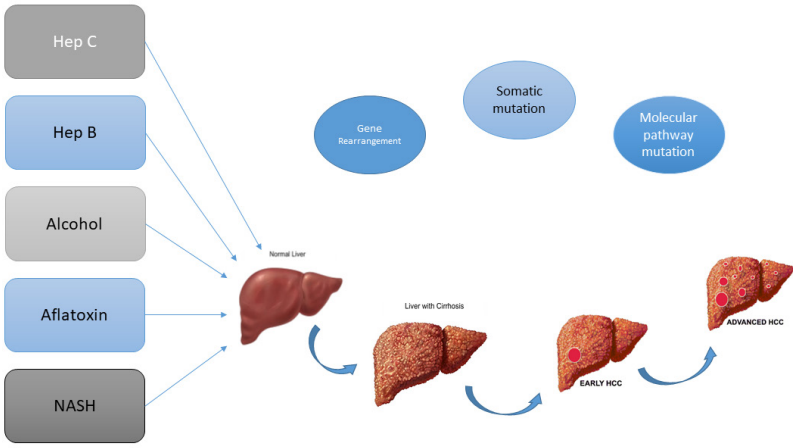

Figure 1. Different Risk Factors of Hepatocellular Carcinoma.

accrued in HCC. The Ras pathway modification triggers cell proliferation and survival. Further, different growth factors such as EGF and IGF-1 attach to their receptors (e.g., EGFR and IGF-1R) and induce Ras activation, which consecutively activates craft, mitogen-activated protein kinase (MEK), and extracellular signal-regulated kinase (ERK). It should be mentioned that RAS-mitogen-activated protein kinase and PI3K-AKT kinase signaling pathways are activated in chronic liver diseases and HCC (5).

HCC Different Risk Factors

The sequence of molecular procedures related to cirrhosis and preneoplastic stages of HCC has not been distinguished. Genetic modification accumulation in stem cells or mature hepatocytes channels the cirrhotic liver to cancer.

Genetic damaging is severely affected by hepatitis C (HCV) and B (HBV) viruses. An increase in transforming growth factor (TGF)-alpha and insulin-like growth factor-2 (IGF-2) could promote hepatocyte proliferation in chronic HCV-infected cases. Various studies recommended that HCV centre protein acts as Wnt (Wingless-related integration site) ligand, activates Ras signaling, and inactivates the p53 pathway (6,7). Furthermore, the nonrandom DNA integration of HBV in chronic HBV infection activates the promoter of oncogenes, DNA rearrangement, and chromosomal instability (8,9). Some molecules such as p53, rat sarcoma virus oncogene (RAS), wingless-type (Wnt), and TGF-β pathway are commonly discovered to be genetically or epigenetically modified in HCC (10,11), related data are depicted in Figure 2. Modified molecular pathways in HCC activate these pathways, and promote cell proliferation and trigger angiogenesis, invasion, and metastasis by binding "Fibroblast growth factor" (FGF), "hepatocyte growth factor" (HGF), "platelet-derived growth factor" (PDGF), TGF-α, "epidermal growth factor" (EGF), and "vascular endothelial growth factor" (VEGF) to their cell surface receptors (12). Moreover, Wnt/β-catenin is another signaling pathway that is commonly activated in the hepatocarcinogenesis and activates the stabilization of β-catenin and promotes its translocation to the nucleus.

Additionally, Wnt/β-catenin interacts with T-cell-specific transcription factor (TCF/LEF) transcription factors, which thus activate the transcription of target genes counting c-myc, c-met, cyclin D1, VEGF, metalloproteases, and the other genes (13,14). Similarly, Wnt-β-catenin is one of the molecular pathways that is aberrantly activated throughout some mechanisms in HCC. β-catenin N-terminus deletions or mutations were discovered in 12%–26% of HCCs and the epigenetic alterations of the E-cadherin gene, along with the loss of function mutations at the AXIN1 or AXIN2 genes was found in 8%-13% of HCCs. Beta-catenin stabilization is also influenced by the Erk-primed inactivation of GSK-3β or the action of HBV-X protein. Liver adenomas are probably related to the mutations of the β-catenin gene (15).

The overexpression of MET proto-oncogene (i.e., the HGF receptor) was reported in 40%-70% of HCCs (16). Similarly, the overexpression of PDGF and its receptor as

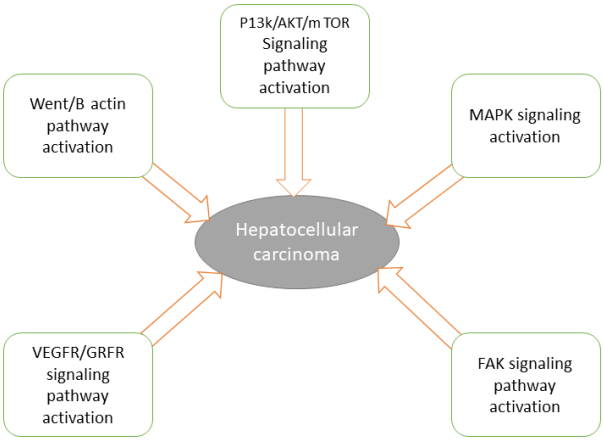

Figure 2. Modificated Molecular Pathways in Hepatocellular Carcinoma.

well as RAS overexpression, which is associated with the HCC pathogenesis, were demonstrated in HCC (16).

In addition, the overexpression of FGF and VEGF results in angiogenic and invasive phenotypes of HCC (17). According to Toyokuni et al (18), genomic and mitochondrial DNA damage, oxidative stress, and chronic inflammation which occur at the HCC preneoplastic stages might cause genetic aberrations (allelic deletions) and epigenetic alterations (aberrant methylation). The consequence for HCC patients is still poor despite the development of various therapies (19). This is mainly because HCC often deteriorates owing to intrahepatic and distant metastases following therapeutic surgical disconnection or transplantation (20). It should be noted that no potential biomarker is discovered for the early diagnosis and prognosis of HCC and only about 30% to 40% of HCC patients are treated effectively.

Searching for new molecular targets is the primary goal of HCC therapy. For example, E-cadherin is expressed in most normal epithelial cells which can be classified as a tumor suppressor. Further, E-cadherin down-regulation can lead to dedifferentiation and invasiveness in human carcinomas is found in aggressive breast carcinoma.

In some solid tumors, the E-cadherin expression promotes intraepithelial expansion and invasiveness such as HCC metastasis (21) and the loss of E-cadherin is detected in aggressive breast carcinoma.

E-cadherin expression is favorable for intraepithelial expansion and invasiveness in some solid tumors such as the intrahepatic metastasis of HCC (22). Furthermore, microRNAs are connected with tumor development such as HCC and the modifications of microRNA expression are related to various types of cancer (23). These miRNAs, which act directly as the repressors of gene expression, reside in fragile sites and genomic regions related to cancer (24). The abnormal expression of several miRNAs was discovered in human hepatocarcinogenesis. Nevertheless, no effective biomarkers have yet been discovered for the early detection of HCC.

About 30% to 40% of HCC patients were treated effectively. New biomarkers are required for the accurate diagnosis, prognosis, and treatment of HCC. Moreover, microRNAs (miRNAs) are essential regulators with an important function in the regulation of gene expression in numerous biological functions and considerably affect the post-transcriptional regulation of gene expression. Additionally, miRNAs affect numerous cellular processes such as differentiation, proliferation, and cell death, as well as many physiological and pathological operations (23). In addition, miRNAs are connected with tumor development such as Hc and the modifications of microRNA expression were related to various types of cancer. These miRNAs act directly as the repressors of gene expression and reside in fragile sites and genomic regions associated with cancer. The abnormal expression of several miRNAs was discovered in human hepatocarcinogenesis (24). Further, miRNA dysregulation in cancer is connected with various pathological features such as human malignancies, cardiovascular, and metabolic diseases.

Certain earlier findings linked the implication of miRNA modification in cancer and tumor suppressor genes and oncogenes. The prior evidence of miRNAs enrolment in cancer was that functional miRNA binding sequences can locate in the 3′-untranslated region (UTR) of the target mRNA but can happen within the 5′-UTR or coding region.

Disregulation of miRNAs have been reported in a variety of cancers. The prior evidence regarding the identification of miR-15a and miR-16-1 at human chromosome 13q14a was the first direct participation of miRNAs in cancer, which is frequently lost in chronic lymphocytic leukemia (25).

miR-15a and miR-16-1 are identified at human chromosome 13q14, and are frequently lost in chronic lymphocytic leukemia (26). The targeting of miR-15a and miR-16-1 to the minimal region of 13q14 loss of heterozygosity in lymphocytic leukemia proposed that these miRNAs attend as the tumor suppressor factor in this region together with the reports that these miRNAs target anti-apoptotic *Bcl-2* oncogene. Furthermore, Ras oncogene suppressed by the let-7 family members often under-expressed in lung cancer was another well-documented discovery. In contrast to the tumor-suppressive miRNAs, in several cancers, some miRNAs are up-regulated and function similar to oncogenes (e.g., miR-17-92 cluster), which are typically up-regulated in lymphoma and breast cancer.

C-Myc protein induces miR-17-92 cluster that has proliferative and anti-apoptotic activity (27).

Deregulated miRNAs in cancer could function as tumor suppressors or promoters through targeting oncogenes and tumor suppressor genes, respectively. An evidence presented the relationship between the p53 tumor suppressor pathway and the miRNA-mediated gene regulatory system (28). Moreover, a novel function of p53 is unraveled when it facilitates miRNA maturation in primary miRNA transcripts.

The tumor-suppressor gene p53 affects the cell cycle arrest and apoptosis by up-regulating the transcription of miR-34 (29).

Some cancer characteristics such as drug resistance, angiogenesis, and metastasis are related to the miRNA function dysregulation of miRNA associated with HCC. Additionally, the yield of mature miRNA covers multiple steps each of which has an influence on the final amount or final mature miRNA.

The first step initiates with the pri-miRNA transcription, which can be regulated by transcription factors or genes that are dysregulated in HCC and then bind to the sequence located upstream in the promoter region.

Epigenetic mechanisms (e.g., histone deacetylation and DNA methylation) could be affected by miRNA silencing.

For example, the methylation of miR-124 and miR-203 genes in HCC cell lines silenced their expression. The mature miRNA cleaves out by the Dicer.

Dicer expression is altered in many cancers. This results in miRNA dysregulation and may lead to cancer phenotype. Eventually, some modifications (e.g., differential polyadenylation modifications) affect the stability of the mature miRNA molecule. miR-122, as a liver-specific miRNA, is selectively 30-adenylated polymer which is destabilized in fibroblasts because of poly (A) polymerase GLD-2 depletion.

Furthermore, the alterations of the miRNA processing and the risk of HCC are related to miRNA polymorphisms.

A miRNA polymorphism involves a single nucleotide polymorphism in the miRNA gene that can affect miRNA, processing, or target recognition.

Moreover, medicated miRNA dysregulation was found in a large variety of HCC And hepatocarcinogenesis associated with the expression level of miR-26.miR-122 expression was related to hepatocarcinogenesis.

HCC therapeutic options are limited and solely offered for early-stage HCC patients. As a result, the identification of novel treatment options is necessary. Thus, new targets for non-conventional treatment will necessarily take advantage of progress on the molecular pathogenesis of HCC.

The abnormal expression of several miRNAs was also discovered in hepatocarcinogenesis and miRNA dysregulation was associated with the pathology of HCC.

Additionally, altered expression of miRNAs were related to cancer-associated pathways, signifying a direct role in liver tumorigenesis. For instance, the up-regulation of mir-221 and mir-21 could endorse cell cycle progression, reduce cell death, and induce angiogenesis and invasion.

miRNAs were also connected with other pathological issues such as secretion by the child stage, cholesterol reverse transport, and tumor size. Evidence suggests that miR-10, miR-106b, miR-130, miR-16-5p, and miR-34a -5p had a considerable connection with tumor size in HCC patients.

HCC miRNA Biomarkers Within Different Ethnic Groups

HCC patients have a specific genomic pattern in different geographic regions, for instance, in Asia as the highest HCC prevalent region. HCC miRNA biomarkers based on the patient's ethnicity are defined in Figure 3, which points to the high risk or elevated frequency of HCC in China.

Tumor Suppressor/Oncogene-miR

Tumor suppressor, high expression in tissues consisting of miR-150-5p and miR-29a-5p and low expression of miR-101-3p, miR-126-3p, miR-127-3p, miR-139-5p, and miR-214-3p played tumor-suppressor roles and could be used as diagnostic biomarkers for HCC.

The circulating miR-101-3p, miR-122-5p, miR-125b-5p, miR-139-5p, miR-150-5p, miR-16-5p, miR-181a-5p, miR-199a-3p, miR-199a-5p, miR-203a-3p, miR-21-5p, miR-22-3p, miR-29b-3p, miR-375, and let-7b-5p are correlated with the tumor suppressor and could be considered as potential biomarkers for differentiating HCC from healthy ones, and are used as prognostic indicators for HCC (30).

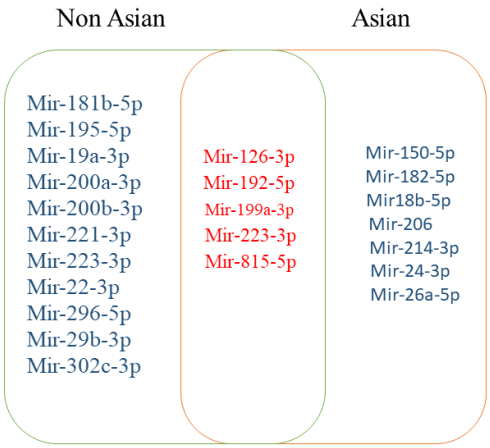

Figure 3. Hepatocellular Carcinoma miRNA Biomarkers in Different Ethnic Groups.

Conclusions

Several reports indicated that more than half of the miRNAs genes are located in cancer-associated genomic regions or fragile sites. As miRNAs important roles in cancer are reported, their potential as prognostic or diagnostics markers is evidenced by a long list of studies. In addition, miRNA markers that could be used for cancer diagnosis are becoming available (31). For example, miR-10b is up-regulated in metastatic breast cancer cells. Once a reliable miRNA marker is chosen, it is expected to yield easy and accurate tools for cancer diagnosis. Further, microRNA profiling could potentially be used as diagnostic markers for screening asymptomatic populations (32).

Accordingly, large carefully designed cohorts, including the data within a similar type of cancer are necessary for comparison and validation. At least invasive methods for collecting blood, saliva, and urine are extremely important for the development of reliable and cost-effective miRNA-based technologies for routine use in the clinics for early cancer prognosis.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by Tabriz University of medical Sciences (Ethics No. IR.TBZMED.REC.1396.941).

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