Hepatocellular carcinoma is one of the deadliest types of cancer. Despite improvements in treatment over the past few decades, patient survival remains poor and there is an urgent need for development of targeted therapies. MicroRNAs represent a class of small RNAs, frequently deregulated in human malignancies. We are reviewing the role of microRNA in the development of primary hepatocellular carcinoma and its use as a biomarker for early diagnosis and clinical treatment. First, we describe the current incidence and possible causes of the incidence of hepatocellular carcinoma, followed by the introduction of microRNA synthesis, maturation and function, and finally we explain the role of microRNA in the development of hepatocellular carcinoma and its clinical value as a biological marker in the diagnosis and treatment of liver cancer. A comprehensive analysis of cellular microRNA is a benefit for early diagnosis of hepatocellular carcinoma and early clinical intervention, and microRNA is considered by some to be a key target of gene therapy to control the occurrence and development of hepatocellular carcinoma. (Adv Clin Exp Med 2016, 25, 5, 971–975).

Key words: microRNA, HCC, occurrence, development, biomarkers.
of HCC patients is only a few months [6]. About 90% of patients have varying degrees of liver cirrhosis. The high risk factors of HCC, such as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol abuse, hemochromatosis psychosis and so on, may lead to a chronic liver disease, then with progression to cirrhosis, eventually leading to the occurrence of HCC [1, 2, 7].

The Biosynthesis, Maturation and Function of microRNA

MicroRNA is a class of endogenous, small RNA, with a length of about 20–24 nucleotides. In the nucleus, the transcription of microRNA was mainly by polymerase II. The process of transcription was as follows. First, at the beginning of transcription, microRNA evolved into primary microRNA (PRI-microRNA) under the effect of polymerase II. Then PRI-microRNA forms one or more hairpin structures of individual microRNA precursor (pre-microRNA) under the action of the enzyme family of RNase III. Pre-microRNA was firstly cleavage by specific Drosha, Dicer and Argonaute and other endogenous enzymatic and then fully or partially complementarily bind to the target gene mRNA 3’-UTR region which then results in negative regulation of target gene expression by degradation of the target mRNA or inhibition of post-transcriptional translation. Next, the microRNA was untied into two strands. One has been binds mRNA 3’-UTR, was selectivity binding silencing complex (RISC) induced by RNA protein and finally becomes mature microRNA under the effect of the regulation gene. The other strand is rapidly degraded, eventually producing one or more functions of microRNAs [8–10]. MicroRNAs do not encode proteins. Though microRNAs are to modulate associated with gene expression at the level of transcription or translation. So microRNAs are involved in a variety of biological processes, such as development, proliferation, differentiation and apoptosis, etc. It has been reported that several microRNAs can regulate the same gene, or by a combination of several microRNAs to regulate the expression of one gene [11, 12]. Lewis et al. [13] reported that microRNAs regulate one-third of the human genes. The regulation of microRNAs may be through the relevant enzymes, promoter hypermethylation and microRNA’s absence of a target gene binding site [14].

The Role of microRNA in the Occurrence and Development of HCC

The occurrence and development of HCC through genes down-regulated a variety of molecular pathways, including p53, RAS/MAPK, PI3K/Akt/mTOR, Wnt/β-cateninβ, MET, Myc gene, transforming growth factor-β, resulting in molecular genetic and epigenetic histological changes. Particularly, abnormal expression of microRNAs affects these critical cancer-related pathways [15]. It is reported that sustained micro RNA-122 [16–19], microRNA-101 [20, 21] down-regulated and microRNA-21 [22], microRNA-221 [23] up-regulated in the occurrence of hepatocellular carcinoma seems to be particularly important.

MicroRNAs and Occurrence of HCC

MicroRNAs whose expression is increased in tumors may be considered as oncogenes. Apoptosis is a major obstacle that must be addressed in the process of malignant tumor transformation and progression. These oncogene microRNAs usually promote tumor development by negatively inhibiting tumor suppressor genes and/or genes that control cell differentiation or apoptosis. Many miRNA genes have been found that are significantly over-expressed in different cancers. The evolution of tumor cells is to evade apoptosis so that they stay away from the tumor monitoring system to survive. Many signals induced apoptosis concentrated in the mitochondria, and then release a powerful catalyst for apoptosis – cytochrome C. The Bcl-2 protein family, whose members have apoptosis (BIM, BMF, Bax, Bak, Bid) or anti-apoptotic (Bcl-2, Bcl-W, Bcl XL, Mcl-1) function in the regulation of mitochondrial death signal transduction plays an important role. It has been reported that abnormal microRNAs in tumor cells can help evade the action of the Bcl-2 family to escape apoptosis [24]. It is reported that HBsAg suppresses the expression of MICA and MICB to prevent the NKG2D-mediated elimination of HCC cells. The process is through unregulated microRNA-133 and down-regulated microRNA-9 [25]. So the occurrence of HCC could be the risk factors’ abnormal regulation of the expression of certain microRNAs.
MicroRNAs and Metastasis of HCC

Invasion and metastasis are the two most critical signs of cancer and usually are the main causes of death, especially in patients of hepatocellular carcinoma. The high rate of tumor recurrence, mainly due to the intrahepatic metastasis of cancer cells, is the main problem involved in the survival of patients with hepatocellular carcinoma after curative resection. Identification and understanding of the mechanisms associated with transfer are very important for the treatment of HCC metastasis. More and more upstream regulator genes related to tumor metastasis, such as pre-transfer microRNA and anti-metastatic microRNA, are found to have an important role in the invasion and metastasis of HCC. Genome-wide screening has identified that miR-134 acts as a metastasis suppressor by targeting integrin beta 1 in hepatocellular carcinoma [26]. microRNA-21, which can change the focal adhesion kinase (FAK) expression and phosphorylation of MMP2 and MMP9 matrix metalloproteinase, together with the downstream regulator of PTEN, participate in the metastasis and invasion of tumor cells. A recent discovery of PTEN is that PTEN participates in the occurrence and development of liver cancer [28]. A report also shows that many expressions of microRNAs are sensitive to doxorubicin and vincristine [19]. In a mouse model for the treatment of hepatocellular carcinoma by microRNAs, no toxicity was observed. MicroRNA-21 as a target of antagonism or microRNA-181b may be effective in improving the efficacy of the treatment. By contrast, down-regulation of onco-miR-221 can be a good strategy. MicroRNA replacement therapy of primary HCC has been applied in a mouse model and the demonstrated systems complementing microRNA-6a, -122 and -124 can reduce tumorigenesis and metastasis of HCC [33, 34]. By contrast, the inhibition of onco-miR-221 can prolong survival and shrink the volume of a tumor [35, 36]. With the progress of targeted gene therapy, microRNAs can be useful as a potential therapeutic target for HCC, because microRNA is involved in the occurrence and development of HCC. However, this hypothesis needs to be tested in clinical patients with hepatocellular carcinoma. Furthermore, chemotherapy will kill normal cells and result in significant toxicity to patients. In a mouse model for the treatment of hepatocellular carcinoma by microRNAs, no toxicity was observed. MicroRNA-21 as a target of antagonism or microRNA-181b may be effective in improving the efficacy of the treatment. By contrast, down-regulating the expression of multidrug resistant (MDR) proteins to restore the contents of microRNA-122 in hepatoma cells, will make hepatoma cells more sensitive to doxorubicin and vincristine [19].

To sum up, the results of the present studies show that many expressions of microRNAs are varied in HCC. Therefore, controlling the occurrence and development of liver cancer by directly targeting control of a large number of the key genes in hepatoma cells is a great development of potential treatment options for improving clinical outcomes. At the same time, comprehensive analysis of the expression levels of microRNAs in liver cells may have certain significance in the classification and diagnosis of early HCC. For more information from the genome-wide association
studies, through the auxiliary of a high-resolution single nucleotide polymorphism (SNP) research platform and next-generation sequencing technologies, we can find abnormal microRNA expression earlier in patients with hepatocellular carcinoma. Meanwhile, some abnormal expressions of micro-RNAs associated with tumors may be applied to the development of chemotherapeutic agents. As a consequence, future laboratory research and clinical research should attach great importance to the aspects of micro-RNAs for the early diagnosis and treatment of HCC, and the potential for better clinical application in the treatment of patients with hepatocellular carcinoma.

References


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