World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i33.5439

World J Gastroenterol 2013 September 7; 19(33): 5439-5445
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Epigenetics of hepatocellular carcinoma: Role of microRNA

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Supported by VA Merit Award, project ID 1171590; NCI Cancer Prevention RO3 Grant, CA150081-03 to Khare S; Raymond E and Vaona H Peck Chair in Cancer Research to Ibdah JA
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Received: May 14, 2013 Revised: July 3, 2013
Accepted: July 19, 2013
Published online: September 7, 2013

Abstract

Hepatocellular carcinoma (HCC) represents a major form of primary liver cancer in adults. MicroRNAs (miRs), small non-coding single-stranded RNAs of 19-24 nucleotides in length, negatively regulate the expression of many target genes at the post-transcriptional and/or translational levels and play a critical role in the initiation and progression of HCC. In this review we have summarized the information of aberrantly expressed miRs in HCC, their mechanism of action and relationship to cancer. The recent advances in HCC research reveal that miRs regulate expression of various oncogenes and tumor suppressor genes, thereby contributing to the modulation of diverse biological processes including proliferation, apoptosis, epithelial to mesenchymal transition and metastasis. From a clinical viewpoint, polymorphisms within miR-binding sites are associated with the risk of HCC. Polymorphisms in miR related genes have been shown to correlate with survival or treatment outcome in patients. Furthermore, the review focuses on the potential role of miRs as novel biomarkers and their translational applications for diagnosis and therapy in HCC. With further insights into miR deregulation in HCC, it is expected that novel miR-based therapeutics will arise. Also, we orient the readers to other reviews that may provide better understanding of miR research in HCC.

Key words: MicroRNA; Cancer; Hepatocellular carcinoma; Biomarker; Polymorphism

Core tip: This review provides the relationship between microRNA (miR) and hepatocellular carcinoma and speculates on the progress that will be achieved through ongoing research. A research effort to identify genetic polymorphisms associated with cancer is emphasized. The review highlights that miR-based therapeutics, and diagnostic and prognostic systems should be used for patients.

Khare S, Zhang Q, Ibdah JA. Epigenetics of hepatocellular carcinoma: Role of microRNA. *World J Gastroenterol* 2013; 19(33): 5439-5445 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i33/5439.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i33.5439

INTRODUCTION

Liver cancer is the second and sixth leading cause of cancer related-death in males and females respectively. Hepatocellular carcinoma (HCC) that accounts for most of the primary liver cancers is the fifth most frequently diagnosed cancer worldwide. Early detection of HCC is needed because the best indicator of prognosis is based on the stage of the disease. About 90% of HCC cases arise from cirrhosis and the disease is strongly associated with several risks factors, including hepatitis B and C

infections, alcohol abuse, primary biliary cirrhosis, autoimmune hepatitis and nonalcoholic steatohepatitis[1]. Epigenetic changes in microRNAs (miRs) and their target gene expression may provide tools and opportunities for detection and therapeutic intervention in HCC.

MiRs, a class of non-coding RNAs with lengths of 19- to -25 nucleotides (nt), act as post-transcriptional regulators by binding to 3'-untranslated region (3'UTR) of target messenger RNA (mRNA). MiRs function as endogenous suppressor of gene expression by inducing either mRNA degradation or translational repression. The promoters of *MiR* genes are regulated by transcription factors, co-activators, enhancers and suppressors similar to protein coding genes. Thus, proto-oncogene c-myc[2,3] and tumor suppressor p53[4] transactivate miRs in HCC. In a genomic cluster the individual miRs are often expressed at different times from the same pri-miR. Pri-miRs are transcribed in the nucleus into a 70-100 nt hairpin-shaped structure and the process is catalyzed by Drosha, which is associated with cofactor DGCR8 and other proteins. After translocation to the cytoplasm by Exportin5, miRs are cleaved into a 19-25 nt miR duplex by enzyme Dicer. One strand of the duplex is then incorporated into the RNA-induced silencing complex (RISC) for its mRNA targets. MiRs function as endogenous suppressor of gene expression by binding of RISC to the 3'UTR of target mRNAs and inducing either mRNA degradation or translational repression. The mRNA degradation is induced if miR binds completely or almost completely, however, if the binding is incomplete, miR represses translation of mRNA. Each step of the process is well regulated, and dysfunction at any level can result in inappropriate miR functions. Gene silencing is the most methodically studied role of miRs, however, they can up-regulate gene transcription during cell cycle arrest and, therefore, overexpression of miRs in human cancers hinted to probable oncogenic functions of miRs. As discussed earlier a direct binding of miR to 5'UTR or promoter of the target genes activate rather inhibit gene expression[5].

Analogous to the protein-coding genes, epigenetic mechanisms, for example, CpG island hypermethylation[6-8] and histone modifications[9] also regulate miR expression in HCC. MiRs that are transcribed from CpG islands undergo DNA hypermethylation-coupled repression due to binding of the transcriptional repressor methyl CpG binding proteins. Epigenetic regulation of miRs might be more common than reported so far as approximately 16% of the annotated human miRs are located within 1000 bp of a CpG island. To date, more than 1000 human miRs have been identified and each miR control hundreds of genes. It has been suggested that miRs regulate the translation rate of more than 60% of protein coding genes.

ABERRANT EXPRESSION OF MICRORNAS IN HCC

MiRs play a central role in basic biological processes such as cellular differentiation, proliferation, apoptosis, migration and invasion. MiR expression profiles are different between normal tissue and derived tumors and between distinct tumor types. Protein coding genes of cell cycle, apoptosis, and metastasis are direct targets of miRs in HCC[10]. Microarray studies have identified a number of miRs that are either up-or down-regulated[11]. Down-regulation of subsets of miRs is a common finding in HCC, indicating that some of these miRs may act as putative tumor suppressor genes. Restoration of tumor suppressive miRs leads to cell cycle block, increased apoptosis and reduced tumor angiogenesis and metastasis by inhibiting migration and invasion. On the contrary, onco-miRs that are up-regulated in HCC potentially target many tumor suppressive genes. Experimental suppression of onco-miRs helps restoring expression of tumor suppressive genes that initiates apoptosis and inhibits cell proliferation, angiogenesis and metastasis in HCC. In general, to investigate the role of deregulated miRs in HCC, miR expression vectors and mature miR mimics or inhibitors (antagomirs) are transfected in HCC cell lines. Further, to confirm the target genes of respective miRs, 3'UTR luciferase vectors (empty luciferase vector or luciferase vector containing wild-type or mutant-type target gene 3' UTR) are utilized for reporter assays. Major down- and up-regulated miRs and their target genes in HCC are discussed in Table 1.

CLINICAL SIGNIFICANCE AND TRANSLATIONAL APPLICATIONS OF MICRORNAS IN HCC

Single nucleotide polymorphism in miRs

Single nucleotide polymorphisms (SNPs) in miRs and their targets have been associated with risk of various cancers. Due to the stringent recognition requirement needed by the miR and the binding region on its target gene, it is rather conceivable that SNPs could have functional implications on the post-transcriptional regulation of target genes. An SNP could either weaken a known miR target or create a sequence match to the miR that was not previously associated with the given mRNA. Changes in the expression pattern of a gene could therefore influence a person's risk of disease. Polymorphisms in miR-34b-c/rs4938723[12], miR-101-1/rs7536540[13], miR-101-2/rs-12375841[13], miR-106b-25/rs99985[14] and miR-196a-2/rs11614913[15] are positively associated with HCC. On the contrary, miR-371-373/rs3859501[16] and miR-149c/rs2292832[17] are negatively associated with HCC risk. Also, a positive association of HCC risk has been demonstrated with polymorphisms in miR target genes IL-1/rs3783553 (miR-122 and miR-378)[18], -TrCP/rs16405 (miR-920)[19], IFNAR1/rs17875871 (miR-1231)[20], ErbB4/rs6147150 (miR-let-7c)[21] and COL1A2/rs3917 (miR-let-7g)[22].

miRs as biomarkers in HCC

miRs are prognostic markers of HCC. Down-regulation

Table 1 Down-regulated microRNA in hepatocellular carcinoma and their characteristics

miRs	Targets	Characteristics
Down-regulated		
miR-1	ET1	Proliferation[52]
miRs-7a, -7b, -7c, -7d, -7f-1, -7d	Caspase-3, HMGA2, C-myc, Bcl-xl	Proliferation, apoptosis[2,23,53-58]
miR-101	Mcl-1, SOX-9, EZH2, EED, DNMT3A	Proliferation, apoptosis[59-61]
miRs-122	Bcl-w, ADAM-1, Wnt-1	Angiogenesis, apoptosis, Metastasis[45,62-64]
miR-125a, -125b	MMP11, SIRT7, VEGF-A, LIN28B2, Bcl-2, Mcl-1, Bcl-w	Angiogenesis, apoptosis, metastasis, proliferation[65-70]
miR-139	c-Fos, Rho-kinase-2	Metastasis[30,71]
miR-145	IRS1-2, OCT4	Insulin-like growth factor pathway, Stem-like cells tumorigenicity[31,72]
miR-195	CDK6, E2F3, cyclinD1	Proliferation, apoptosis, tumorigenicity[73,74]
miR-199a-3p, -199-5p	c-Met, mTOR, PAK4, DDR1, caveolin-2	Proliferation, autophagy, metastasis[9,75-78]
miRs-214	HDGF, catenin	Proliferation, angiogenesis, metastasis[79-81]
Up-regulated		
miR-10a	EphA4, CADM1	EMT, metastasis[33,82]
miR-21	Pten, RhoB, PDCD4	Drug Resistance, metastasis[49,83-85]
miR-221	Bmf, DDIT4, Arnt, CDKN1B/p27, CDKN1C/p57	Angiogenesis, apoptosis, proliferation[86-89]
miRs-224	Yin Yang1/Raf-1 kinase, NFκB pathways, apoptosis inhibitor-5	Proliferation, apoptosis, metastasis[90-93]

miRs: MicroRNAs; EMT: Epithelial-mesenchymal transition.

of miR-let-7g[23], -22[24], -26[25], -29[26], -99a[27], -122[28], -124[29], -139[30], -145[31] and -199b[32] is associated with poor prognosis, increased risk of aggressive tumor recurrence and shorter disease free survival. Similarly, up-regulation of HCC associated miRs-10b[33], -17-5p[34], -21[35], -135a[36], -155[37], -182[38], -221[35], and -222[35,39] is linked to poor prognosis. Studies have shown that miRs are protected from enzymatic cleavage by RNAse in blood and therefore miR expression profile in serum or plasma could also be utilized as novel diagnostic markers. More than 20 miRs in serum and/or plasma have been associated with HCC detection. The expression profile of miRs-500, -92a, -25, -375 and let-7f could identify HCC cases from controls[40-43]. Furthermore, Zhou *et al*[44] demonstrated that miR-122, -192, -21, -223, -26a, -27a and-801a helped detecting early-stage HCC with high diagnostic accuracy.

miRs as therapeutic targets in HCC

Tumor suppressive miRs that are expressed in normal liver, however, are down-regulated in tumor tissues during tumorigenesis and metastasis. For treatment, a good strategy would be to replenish such miRs systemically in HCC patients. Such miR replacement therapies have been demonstrated in the case of miRs -26a[3], -122[45], and -124[46] in mice models of HCC. Conversely, suppression of oncomir-221[47,48] by antagomirs resulted in prolonged survival and reduction of tumors. As targeted gene therapies are gaining interest in cancer treatment, miR as a therapeutic target would be more efficient since single miR can control multiple deranged genes in HCC. However, this hypothesis is yet to be tested in HCC patients. Further, chemotherapeutics kill normal cells and pose significant toxicities in cancer patients, a non-discriminatory behavior of chemotherapy drugs. In mice models, as discussed above, no such toxicity was observed when miRs were used to treat HCC. In this regard, miRs also influence sensitivity of tumors to anticancer drugs. Tumors with high expression of oncomiR-21[49] and -181b[50] were resistant to IFN-5FU combination therapy and doxorubicin treatment respectively. A strategy to suppress these miRs by antagomirs might be useful in increasing drug efficacy. Similarly, studies have demonstrated that restoration of tumor suppressive miR-122[51] makes HCC cells more sensitive to Sorafenib treatment *via* down-regulation of multidrug resistance genes.

CONCLUSION

miRs control expression of many target genes in HCC. miR profiling reveals molecular mechanisms of pathogenesis and hidden visions into early detection and treatment of HCC. Hundreds of miRs have been identified to date; however, computer models suggest there may be hundreds more. There are several online tools available for researchers and clinicians to identify and predict the targets of miRs. As research continues to verify *in silico* predictions, miR profiling will be a prominent tool for identification of differentially expressed miRs in HCC. More information from genome-wide association studies, assisted by high resolution SNP arrays and the next-generation sequencing technology, is anticipated to identify increasing number of polymorphisms in HCC specific miRs and their 3'UTR targets. For future studies, we should consider miRs and their regulatory networks in order to comprehend the complex processes underlying HCC transformation.

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ISSN 1007-9327