World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i11.1530

World J Hepatol 2015 June 18; 7(11): 1530-1540
ISSN 1948-5182 (online)

REVIEW

MicroRNAs dysregulation in hepatocellular carcinoma: Insights in genomic medicine

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Author contributions: All the authors equally contributed to this work.

Conflict-of-interest: Authors have no conflict of interests related to this manuscript. All authors have contributed equally in the realization of this manuscript.

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Received: September 17, 2014
Peer-review started: September 20, 2014
First decision: November 27, 2014
Revised: December 22, 2014
Accepted: May 8, 2015
Article in press: May 11, 2015
Published online: June 18, 2015

Abstract

Hepatocellular carcinoma (HCC) is the leading primary liver cancer and its clinical outcome is still poor. MicroRNAs (miRNAs) have demonstrated an interesting potential to regulate gene expression at post-transcriptional level. Current findings suggest that miRNAs deregulation in cancer is caused by genetic and/or epigenetic, transcriptional and post-transcriptional modifications resulting in abnormal expression and hallmarks of malignant transformation: aberrant cell growth, cell death, differentiation, angiogenesis, invasion and metástasis. The important role of miRNAs in the development and progression of HCC has increased the efforts to understand and develop mechanisms of control overt this single-stranded RNAs. Several studies have analyzed tumoral response to the regulation and control of deregulated miRNAs with good results *in vitro* and *in vivo*, proving that targeting aberrant expression of miRNAs is a powerful anticancer therapeutic. Identification of up and/or down regulated miRNAs related to HCC has led to the discovery of new potential application for detection of their presence in the affected organism. MiRNAs represent a relevant new target for diagnosis, prognosis and treatment in a wide variety of pathologic entities, including HCC. This manuscript intends to summarize current knowledge regarding miRNAs and their role in HCC development.

Key words: Hepatocellular carcinoma; MicroRNAs; Regulation; Therapeutic targets

Core tip: MicroRNAs are implicated in the control of gene expression which enable them a relevant new target for diagnosis, prognosis and treatment in a wide variety of pathologic entities, including hepatocellular carcinoma (HCC). This manuscript represents an attempt to summarize current knowledge regarding miRNAs and

their role in HCC development.

Lyra-González I, Flores-Fong LE, González-García I, Medina-Preciado D, Armendáriz-Borunda J. MicroRNAs dysregulation in hepatocellular carcinoma: Insights in genomic medicine. *World J Hepatol* 2015; 7(11): 1530-1540 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i11/1530.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i11.1530

INTRODUCTION

Hepatocellular carcinoma (HCC) is the leading primary liver cancer and represents the fifth most common cause of cancer in men, the seventh in women, and is considered the third most frequent cause of cancer-related death worldwide[1]. Almost 85% of new cases occur in developing countries, with highest incidence in areas located in sub-Saharan Africa, east and southeast Asia but also Melanesia and Micronesia/Polynesia; whereas low-incidence areas include northern and Western Europe and North America[1,2]. Nonetheless, clinical outcome of HCC is still poor, which can be attributed to lack of reliable markers for early diagnosis, resistance to treatment, tumor recurrence, and metastasis. Recent evidence suggests a rising incidence of HCC-related deaths in the United States, and during the last two decades, the incidence of HCC in this country has tripled with no difference in 5-year survival rate (12%)[3,4].

HCC develops within an established background of chronic liver disease like cirrhosis due to hepatitis B virus (HBV) and/or HCV, non-alcoholic steatohepatitis, autoimmune hepatitis, iron overload syndromes, diabetes, alcohol abuse, smoking, oral contraceptive use and aflatoxin exposure[5-8].

HCC is believed to be a multistep process, though despite an increasing knowledge of molecular mechanisms inducing hepatocarcinogenesis, poor prognosis of HCC patients reflects the failure to block and reverse the steps of molecular transformation[9,10].

Up to now, alpha-fetoprotein (AFP) along with ultrasounds every 6-12 mo remains as the most commonly used approach to monitoring patients at high risk for HCC[6,11]. Unfortunately the use of both diagnostic tools not only fails to increase detection rates, but also raises false positive uncertainties[12].

Recent studies have demonstrated evidence that anomalous expression of specific miRNAs are implicated in a broad spectrum of human ailments, including rheumatic diseases[13-15], diabetes/insulin resistance[16-18], cardiovascular disease[19-21], renal disease[22] and a wide variety of cancers[23].

Last but not least, the aim of this review is to provide an update in the field of miRNAs and their application in different aspects of HCC.

MIRNAS OVERVIEW AND ITS ROLE IN CANCER DEVELOPMENT

MicroRNAs (miRNAs) are defined as non-coding single-stranded RNAs (ssRNAs) of 19-25 nucleotides in length that are generated from endogenous hairpin-shaped transcripts[24]. MiRNAs were first reported by Lee *et al*[25], who described a small noncoding RNA encoded by the lin-4 locus associated to the developmental timing of the nematode *Caenorhabditis elegans*. Since that moment, thousands of miRNAs have been identified in a wide variety of organisms, including mammals and specifically humans. Actually, we know that about 3% of human genes encode miRNAs and more than 1500 miRNA genes have been predicted or experimentally shown to play critical roles in normal cellular functions[26-28].

Up to date, miRNAs have demonstrated an interesting potential to regulate gene expression at post-transcriptional level, binding through partial complementarity to target mRNAs, and mainly leading to mRNA degradation or translation inhibition[29]. Imperfect base pairing between miRNAs and mRNAs is common and enables miRNAs to regulate a broad, but specific set of genes[30].

The first evidence of the involvement of miRNAs in human cancer was reported in chronic lymphocytic leukemia (CLL) patients in 2002, when Calin *et al*[31] showed miR-16-1 and miR-15a deletion in chromosome 13q14 in more than 59% of CLL patients. Recently, miRNAs alterations have been described in different types of cancer, including CLL, acute promyelocytic leukemia, acute myeloid leukemia, multiple myeloma, monoclonal gammopathy of undetermined significance, non-Hodgkin lymphoma, breast cancer, esophageal cancer, gastric cancer, clear-cell kidney cancer, cervical cancer, and others[23].

Current findings suggest that miRNAs deregulation in cancer is caused by genetic and/or epigenetic, transcriptional, and post-transcriptional modifications resulting in abnormal expression and hallmarks of malignant transformation: aberrant cell growth, cell death, differentiation, angiogenesis, invasion and metastasis[32,33]. This knowledge has established miRNAs as potential diagnostic biomarkers or even as new therapeutic targets in the fight against cancer.

The difficulty of miRNA target prediction and biological validation has been a major obstacle to miRNA research. Experimental identification of miRNAs is difficult to isolate by cloning due to low expression, low stability, tissue specificity and problems in cloning procedures[34].

MIRNAS IN HCC

As discussed before, miRNAs have important functions in cancer development because of their relevant role in regulation of cell proliferation, avoidance of apoptosis

(cell perpetuation) and metastasis.

Recently, the identification of up and/or down regulated miRNAs related to HCC has led to the discovery of new potential application for detection of their presence in the affected organism. Up to now, every week appears new evidence of miRNAs with potential effect on carcinogenesis; therefore, in this review we expose the most relevant findings on the field of miRNAs in HCC. To provide an easy comprehension of the data, we have classified our findings based in the up or down regulation status of the most relevant minas implicated in HCC development[35].

Up-regulated miRNAs in HCC

The role of several miRNAs has been studied in other malignances, this is the case of miR-181a which is associated with malignancies such as chronic lymphocytic leukemia and acute myelogenous leukemia[36], and has been linked to improved survival and decrease recurrence in gliomas, where it seems to be an inhibitor of oncogenesis and tumor growth with importance in the development of epithelial cell adhesion molecule$^+$/AFP$^+$ HCC associated with increased metastases and poor survival. Bhattacharya *et al*[37] analyzed the role of osteopontin (OPN) in HCC, and their findings suggested that OPN confer a prometastatic phenotype to cancer cell lines. Recent findings have described that miR-181 are up-regulated in hepatic stem cell populations and HCC cells with progenitor cell features, implying that miR-181 functions in maintaining an undifferentiated state of hepatic progenitor cells. In this regard, evidence suggests that miR-181 may activate hepatic progenitor cells and HCCs through two cellular signaling pathways: (1) blockage of HCC cell differentiation through inhibition of GATA6 or CDX2, two transcriptional activators regulating hepatocyte differentiation; and (2) activation of Wnt/β-catenin pathway by down-regulating NLK, a Wnt/β-catenin signaling inhibitor[38].

MiR-21 overexpression is found in HCC cells and has been linked to inhibition of apoptosis and promotion of cell proliferation. Connolly *et al*[39], studied the role of miR-21 in cell invasion and migration, and found that overexpression of this miRNA increases matrix metalloproteinase-9 (MMP-9) activity in multiple cell lines. These findings described the role of MMP-9 expression with invasive and/or metastasic phenotypes of tumors. Other mechanism of metastases identified the role of tumor suppressor RECK, in conjunction with RHOB, in regulating the *in vitro* metastatic properties, being associated with poor prognosis[39].

MiR-151 is localized within intron 22 of focal adhesion kinase (FAK), which is often overexpressed in human tumors and promotes cancer cell invasion and metastasis. A study carried-out by Ding *et al*[40] found that suppression of p53 can increase the expression of both FAK and miR-151 simultaneously, suggesting that p53 may be a potential transcriptional regulator for FAK and miR-151 in liver cancer cells. Other description made by this team revealed that *RhoGDIA* is a direct and functional target for miR-151, which once suppresses *RhoGDIA* expression activate Rac1, Cdc42 and Rho GTPases, and this inhibitory effect may work synergistically with FAK signaling to promote cell motility and invasion. This situation indicates that it may be a general mechanism for the metastasis of human cancer cells.

Upregulation of miR-191 after hepatocyte injury has been linked with extensive changes in gene expression. The most affected pathways are transforming growth factor beta (TGF-β) and mitogen-activated protein kinases (MAPK) which play a significant role in hepatocarcinogenesis. TGF-β pathway regulates cell proliferation, differentiation, and adhesion. While MEPK signaling pathway is also involved in diverse cellular processes such as cell survival, differentiation, and proliferation[41].

Overexpression of miR-221 is present in almost 71% of HCC and plays an important role in HCC development due to its ability to modulate the expression of the oncogenic proteins c-kit and cyclin-dependent kinase inhibitors CDKN1B/p27 and CDKN1C/p57, promoting cancer cell proliferation. Dysregulation of CDKN1B/p27 exhibits a relevant prognostic significance, being associated with advanced tumor staged, poor survival and recurrence of small HCC. Whereas CDKN1C/p57, has been linked with higher biological aggressiveness, advanced stage, poor differentiation, larger size, portal invasion and high proliferative activity[42]. Other studies showed that miR-221 dysregulation alters G1/S transition inhibitors, where p27 and p21 proteins are frequently down-regulated in HCC, while TGF-β proteins were frequently up-regulated. These alterations lead in loss of control of the transition G1/S in HCC cells, which result in cellular proliferation and metastasis improvement[43]. Furthermore, new evidence suggests a wider role of miRNA in HCC[44], and recently Gramantieri *et al*[45], described how throughout a pro-apoptotic molecule called Bmf, miR-221 can simultaneously affect proliferation and apoptosis. Bmf is involved in the balance of pro-apoptotic and anti-apoptotic stimuli in Bcl-2/Bcl-xL-induced apoptosis and also seems to follow TGF-β up-regulation[45].

MiR-224 over-expression found in HCC tissues suggests its key role in the malignant phenotype of hepatocarcinoma cells. Recent findings affirmed that miR-224 can modulate cell proliferation and has an important role in cell migration and invasion. Alteration of molecules PAK4 and MMP-9 are considered as the misbalance responsible of the carcinogenic role of miR-224[46].

MiR-183 in the liver acts as negative regulator of programmed cell death 4 (PDCD4) molecule acting at posttranscriptional level which has been found to inhibit activator protein-1 (AP-1) mediated trans-activation and to induce expression of the cyclin-dependent kinase inhibitor p21. MiR-183 up-regulation and subsequent loss of PDCD4 improves cell growing and thereby facilitates cancer development[47]. PDCD4 down-regulation was

Table 1 Upregulated miRNAs in hepatocellular carcinoma

MiRNA	Cellular process	Ref.
MiR-10a	Epithelial to mesenchymal transition and metastasis	[50]
MiR-130a	Drug resistance	[51]
MiR-135a	Metastasis	[52]
MiR-143	Metastasis	[53]
MiR-155	Proliferation and tumorigenesis	[54]
MiR-18a	Proliferation	[55]
MiR-181b	Cell growth, tumorigenesis and metastasis	[56]
MiR-182	Metastasis	[57]
MiR-183	Apoptosis	[47]
MiR-21	Metastasis and drug resistance	[39,58,59]
MiR-210	Metastasis, apoptosis and proliferation	[60,61]
MiR-216a	Tumorigenesis	[62]
MiR-221	Apoptosis, proliferation and angiogenesis	[42,45,63,64]
MiR-224	Metastasis, proliferation and apoptosis	[65-67]
MiR-23a	Gluconeogenesis	[68]
MiR-373	Cell cycle	[69]
MiR-301a	Metastasis	[70]
MiR-490-3p	Epithelial to mesenchymal transition	[71]
MiR-519d	Proliferation, invasion and apoptosis	[72]
MiR-550a	Metastasis	[73]
MiR-590-5p	Metastasis and proliferation	[74]
MiR-615-5p	Cell growth and migration	[75]
MiR-657	Proliferation	[76]
MiR-96	Proliferation	[77,78]
MiR-222	Metastasis	[79]

MiRNAs: MicroRNAs.

previously recognized in human colorectal cancer and melanoma[48,49].

Other up-regulated miRNAs related to hepatocarcinogenesis are included in Table 1.

Down-regulated miRNAs in HCC

MiR-122 is highly abundant in liver, accounting for 70% of total liver miRNA reported[80-82]. Previous reports had shown its positive regulation of lipid metabolism and disease, but recent knowledge has established an important role of miR-122 in hepatocarcinoma/hepatoma, acting as tumor suppressor gene frequently down-regulated in HCC cell lines and correlated with clinical parameters as etiology, tumor size and differentiation grade. Recent findings suggest that miR-122 inhibits and controls all characteristic properties of cancer cells such as cell cycle, clonogenic survival, anchorage-independent growth, migration, invasion, epithelial-mesenchymal transition and mutagenesis[83-85]. The mechanisms of this dysregulation are unknown, but studies have provided genes and molecules implicated which include ADAM10, Igf1R, SRF, peroxiredoxin 2, members of the septin family like SEPT2 and SEPT9, vimentin, MMP-7, Aldoase A, the muscle isoform of pyruvate kinase (PKM2), and cyclin G1[83-87]. Coulouarn *et al*[88] showed that repression of miR-122 was characteristic of HCC displaying either a hepatoblast, c-Met or late TGF-β signature; these results showed that HCC cell lines exhibit a more invasive phenotype once decreased miR-122 expression is present. Other study correlated high AFP level with more aggressive properties of HCC. These findings correlated also with lower rates of recurrence-free survival and lower overall survival due to increased expression of CUX1, a direct target of miR-122[89].

Decreased levels of miR-26 in HCC have been associated with poor prognosis and are considered predictive of therapeutic response to interferon-α. Recent studies have reported that animals treated systemically with miR26 presented tumor regression. Recent studies elucidated the role of miR-26 in hepatocyte proliferation confirming that E2 promotes liver cancer cells growth *via* the E2-ERα pathway and suggested that miR-26 significantly down-regulates ERα preventing hepatoma cell growth, suggesting anti-carcinogenic activities in women[90,91]. Also, miR-26 directly or indirectly regulates expression of a wide variety of genes by down-regulating AFP, PCNA, PR, CEA, nuclear factor-κB and interleukin-6 or increasing P53 and PTEN[90-92].

MiR-34a has been considered a direct transcriptional target of p53 and is commonly reduced or deleted in HCC and other cancers[93]. To date, there are more than 34 proteins altered by miR-34a down-regulation, which include LMNA, ALDH2, MACF1, LOC100129335, GFAP and c-Met as targets of miR-34a with a crucial role in hepatocarcinogenesis[94]. Likewise, down-regulation of miR-34 has shown to down-regulate CyclinD1-CDK6 complex, which is one of the critical positive regulators during G1/S phase transition and a major checkpoint for cell progression. These alterations proved that miR-34a deregulation has the capacity to increase adhesion of tumoral cells to regional lymph nodes improving metastasis[95,96].

Recently, it has been demonstrated that miR-29b is capable of repressing tumor angiogenesis, invasion and metastasis in normal subjects by suppressing MMP-2. Data provided by Fang *et al*[97], suggest that miR-29b deregulation result in enhanced MMP-2 level in the tumor microenvironment, which in turn activates vascular endothelial growth factor receptor-2 (VEGFR-2) in endothelial cells promoting angiogenesis. Conclusions provided by Fang *et al*[97], showed inhibitory effects on invasion and metastasis and established MMP-2 as a relevant protein implicated in tumoral growth and metastasis.

MiR-145 forms a double negative feedback loop with key stemness factors OCT4, SOX2, and KLF. And, at the same time, OCT4 binds to the miR-145 promoter and suppresses its expression. Down-regulation of miR-145 in human embryonic stem cells impairs its differentiation and enhances stem cell self-renewal, these findings suggest an important role of miR-145 in carcinogenesis[98]. A study published by Gao *et al*[99], studied the role of miR-145 in hepatocarcinogenesis and they concluded that down-regulation of miR-145 favors cellular proliferation and migration, suggesting that miR-145 acts as a negative regulator of HCC development.

The analysis of miR-199 down-regulation showed new specific targets like CD44, a member of trans-

Table 2 Downregulated microRNAs in hepatocellular carcinoma

MiRNA	Cellular process	Ref.
Let-7a	Apoptosis and proliferation	[107,108]
Let-7b	Apoptosis and proliferation	[109]
Let-7c	Apoptosis, proliferation and cell growth	[110-112]
Let-7d	Apoptosis and proliferation	[107]
Let-7f-1	Apoptosis and proliferation	[107]
Let-7g	Apoptosis and metastasis	[113-115]
MiR-1	Proliferation	[116]
MiR-34a	Metastasis	[96]
MiR-101	Apoptosis and DNA methylation	[110,117,118]
MiR-122	Apoptosis, metastasis and angiogenesis	[119-122]
MiR-124	Proliferation	[123]
MiR-125a	Proliferation, metastasis and metabolism	[124-126]
MiR-125b	Proliferation, metastasis, angiogenesis, apoptosis and histone modification	[110,125-127]
MiR-139	Metastasis	[128,129]
MiR-138	Cell cycle	[130]
MiR-145	Cell growth and tumorigenesis	[131]
MiR-195	Tumorigenesis, cell cycle and apoptosis	[132,133]
MiR-199a-3p	Drug resistance and cell growth	[101,134]
MiR-199a-5p	Invasion and autophagy	[135]
MiR-200a	Proliferation and metastasis	[136]
MiR-203	Proliferation	[137]
MiR-214	Cell growth, metastasis and angiogenesis	[138,139]
MiR-219-5p	Proliferation	[140]
MiR-223	Proliferation	[141]
MiR-26a/b	Cell cycle	[142]
MiR-29a	Proliferation	[143]
MiR-34a	Metastasis	[96,144]
MiR-375	Autophagy	[145]
MiR-376a	Apoptosis and proliferation	[146]
MiR-449	Proliferation and apoptosis	[147]
MiR-450a	Proliferation	[148]
MiR-520b	Cell growth and proliferation	[149]
MiR-7	Tumorigenesis and metastasis	[150]

MiRNAs: MicroRNAs.

membrane glycoproteins which acts mainly as receptor of hyaluronic acid, being involved in cell-cell interactions, cell adhesion and migration. Studies have demonstrated that inhibition of CD44 enhances apoptosis and improves chemosensitivity, diminishes tumorigenesis and invasion[100]. Interestingly, miR-199 also plays a relevant role in regulation of mammalian target of rapamycin (mTOR) which stands a key role in cell growth, protein translation, metabolism, cell invasion and apoptosis; and c-Met, a proto-oncogene involved in a biological "invasive growth" that result from stimulation of cell motility, invasion, and protection from apoptosis[101,102].

Up-regulation of MKi67 is considered an important risk factor for pathologies in breast, prostate and others cancers like meningiomas, but Hou *et al*[103] found that higher levels in human HCC cells contribute to malignant phenotype. This study recently published showed that in normal situations, miR-519 suppresses cellular growth by MKi67 due to direct binding of the miRNA to an identified target site in the MKi67 3'-UTR where mutation of this region abolishes this effect.

MiR-152 down-regulation was described as a cause of aberrant DNA methylation by targeting DNMT1, and is inversely correlated with DNMT1 expression in HCC. DNMT1 is necessary and sufficient for maintaining global methylation and aberrant CpG island methylation in human cancer cells contributing to pathogenesis of HCC[104].

Recently, an inverse correlation between miR-338 and smoothened (SMO) expression has been elucidated by Huang *et al*[105], where miR-338 showed an important role in suppressing HCC metastasis through down-regulating SMO. MMP-9 expression is increased in HCC, correlates with metastasis and advanced tumor stages, and this study has demonstrated that SMO siRNA can abolish MMP-9 expression. These results indicate that miR-338 suppresses the invasiveness of liver cancer through down-regulation of SMO-induced MMP-9 expression[105].

MiR-101 has been shown to be down-regulated in different tumors like breast, lung and pituitary adenoma, but Li *et al*[106] have demonstrated that its under-expression also has an important role in cell invasion and migration in HCC. This oncogenic activity is attributed to FBJ murine osteosarcoma (FOS), which in normal tissues is negatively regulated by miR-101 at posttranscriptional level *via* a specific target site within the 3'-UTR. Down-regulation of miR-101 may contribute to the high expression level of FOS protein, which activates the AP-1 family of transcription factors (c-fos and c-jun). Both, c-fos and c-jun can induce epithelial-mesenchymal transition, a hallmark of metastasis and invasive growth associated with loss of cell polarity in epithelial cells. Therefore, according with Li *et al*[106] regulation of miR-101 could be a potentially suitable candidate for anticancer therapy.

Additional down-regulated miRNAs are included in Table 2.

DISCUSSION

Thus far, more than 800 human miRNAs have been described and speculations about the total number of human miRNAs have exceeded 1000[106]. In human cancer, every type of tumor shows a miRNA profile significantly different compared with normal cells from the same tissue.

Single nucleotide polymorphisms in miRs and their targets have been associated with risk of various cancers because changes in the expression pattern of a gene could therefore influence a person's risk of illness. Noteworthy, miRs are considered promising prognostic markers of HCC. Some studies have shown that miRs are protected from enzymatic cleavage by RNAses in blood, and therefore their expression profile in serum or plasma could also be utilized as novel diagnostic and prognostic markers[151,152].

Taking into account all this great deal of data, miRNAs issue is one of the most complex topics in oncology due to its wide range of actions as either oncogenes or tumor-suppressors genes in HCC. These facts have led investigators to device two approaches for developing miRNA-based therapies: antagonists and/or mimics[30].

The important role of miRNAs as players in the development and progression of HCC has increased the efforts to understand and develop mechanisms of control overt this ssRNAs. In the last years, several studies have been designed to analyze tumoral response to the regulation and control of deregulated miRNAs with good results *in vitro* and *in vivo,* proving that targeting aberrant expression of miRNAs is a powerful anticancer therapeutic[9]. Recent data showed that tumor suppressive miRs expressed in normal liver are down-regulated in tumor tissues during tumorigenesis and metastasis. Hence, a potentially plausible strategy would be to replenish those miRs systemically in HCC patients (miR-181, miR-29, miR-221, miR-122, miR-29, miR-199, *etc*.) to restore altered pathways balance, and stimulate and/or increase cellular mechanisms to regulate cell proliferation, cell cycle regulation, cell migration and invasion and apoptosis[35].

One of the biggest challenges to translate this knowledge to humans resides that every miRNA may target several mRNAs[78]. This situation empowers selective delivery a crucial issue, which calls for alternate targeted delivery strategy more refined and accurate. The use of viral vectors represents a promising approach[5].

CONCLUSION

MiRNAs are implicated in the control of gene expression which enable them a relevant new target for diagnosis, prognosis and treatment in a wide variety of pathologic entities, including HCC. This manuscript represents an attempt to summarize current knowledge regarding miRNAs and their role in HCC development.

We believe that miRNA is one of the most promising and challenging opportunities to classify and attack cancer. However, translation of knowledge from experimental models to humans remains as a critical point due to the wide and different range of effects caused by each miRNA from cell to cell. Thus, cell-specific delivery most be improved to increase tumoral-specificity and then be considered as a potential therapy in human cancer.

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P- Reviewer: Chuang WL, Yang J **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Liu SQ

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