Editorial

Cancer prevention through miRNAs: miR-206 prevents the initiation and progression of hepatocellular carcinoma by attenuating c-MET signaling and cell-cycle progression via cyclin D1 and CDK6

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Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is one of the most common cancers worldwide, with over 80% of cases diagnosed in developing countries in sub-Sahara Africa and Southeast Asia (1). In the United States alone, HCC incidence has more than tripled over the past three decades due to an increased prevalence of liver cirrhosis, which is the major risk factor for HCC. The most common causes of liver cirrhosis, and subsequent HCC development, are chronic infections with hepatitis B and C virus (HBV, HCV), chronic alcoholic liver disease, and non-alcoholic fatty liver disease (2). The incidence-to-mortality ratio of HCC is ~1.16, with more than 700,000 people being diagnosed with HCC, and over 600,000 deaths due to HCC, each year worldwide (1,2). The overall 5-year survival rate of HCC is just 17.7% [2008–2014] (3), demonstrating the aggressive nature of this disease. Treatment options for HCC are still quite limited, with the multi-kinase inhibitor, sorafenib, as the standard-of-care for first-line HCC. Recently, the multi-kinase inhibitor lenvatinib has shown promise in a Phase 3 trial (4,5). The multi-kinase inhibitor regorafenib (6) and the immune checkpoint inhibitor nivolumab (5) are approved for patients who have progressed on sorafenib. New approaches are still needed for effective HCC treatment.

Our understanding of non-coding RNA, RNA which does not code for protein, is rapidly expanding. Interestingly, coding RNA actually represents the minority of RNA species in the cell, with ~75% of the genome transcribed into RNA but only ~2% translated into protein (7,8). This has led to a revision of the "central dogma", first proposed by Crick in 1958 (9). MicroRNAs (miRNAs) are a family of small (21–25 nucleotides) non-coding single-stranded RNAs that negatively regulate gene expression at the translational level (10). miRNAs function primarily by binding to the 3'UTR (untranslated region) of specific mRNAs leading to either their degradation or translational inhibition. miRNAs were initially discovered as temporally-regulated RNAs that controlled developmental transitions in C. elegans (10). However, since their discovery in 1993, it has become increasingly evident that miRNAs are not limited to regulation of developmental events; rather, miRNAs have both diverse expression patterns and physiological functions. Specifically, in the context of cancer, miRNAs are frequently deregulated; and are functionally categorized as either tumor suppressor miRNAs (tsmiRs) or oncogenic miRNAs (oncomiRs) based on the balance of pathways they regulate.

A number of miRNAs have been shown to play important roles in regulating the development and progression of HCC. OncomiRs, including miR-21, miR-221/222, and miR-224 are found consistently upregulated in HCC cell lines and patient tumors. miR-21 promotes proliferation, migration and invasion in HCC cells through repression of the tumor suppressor PTEN (11), and use of anti-miR-21 *in vivo* represses HCC xenograft growth (12). miR-221 has been shown to increase proliferation of HCC cells through direct targeting of cyclin-dependent kinase inhibitors CDKN1B (p27) and CDKN1C (p57) (13) and use of anti-miR-221 *in vivo* inhibits growth and metastasis

of HepG2 xenografts (14). Its homologous miRNA, miR-222, induces apoptosis resistance, and enhances migration and invasion by modulating the expression of PTEN and the metallopeptidase inhibitor TIMP3 (15). miR-224 is nearly undetectable in normal liver tissue, but is increased in benign liver tumors and furthermore in HCC, reaching levels up to 20-fold in HCC compared to normal liver (16). miR-224 has also been reported to promote HCC migration and invasion through direct repression of the HOXD10 homeobox transcription factor. HOXD10 down-regulation by miR-224 led to upregulation of phospho-PAK4 and MMP-9, promoting cell invasion (17). In contrast to these HCC promoting miRNAs, tumor suppressor miRNAs, such as miR-122 and miR-26a are downregulated in HCC, and have been shown to oppose functions essential for HCC cancer cells. miR-122 constitutes ~70% of the miRNA content in the normal adult liver and is a marker of hepatocyte-specific differentiation. miR-122 is lost in poor-prognosis HCCs, which follow HBV infection; and its loss correlates with increased proliferative index and decreased apoptotic index of tumors (18). A number of genes involved in the regulation of HCC tumorigenesis and metastasis are regulated by miR-122. These include, but are not limited to, RHOA, VEGF, HIF1A, VIM, SRF, and IGF1R (18,19). Inhibition of miR-122 in HCC cells was found to suppress the hepatic phenotype and conferred increased metastatic properties to cells (18). Moreover, restoration of miR-122 decreased growth and metastasis of HCC cells *in vivo* (20). miR-26a is down-regulated in HCC and is significantly associated with tumor recurrence and metastasis (21). miR-26a has been shown to suppress tumor growth and metastasis in *in vivo* mouse models of HCC by negatively regulating the IL-6, Stat3, and HGF-c-MET pathways (21,22); as well as increasing the biogenesis of tumor suppressor miRNA, let-7 (23). Recently, miR-26a was found to repress both c-Myc and the epigenetic modifier EZH2. Adeno-associated virus delivery of miR-26a down-regulated c-Myc and EZH2 and inhibited tumor growth and metastasis in a DEN (diethylnitrosamine)-induced model of HCC (24), suggesting that miR-26a has promise as a therapeutic microRNA.

The recent study by Wu *et al.* focuses on miR-206, a well-known tumor suppressor microRNA. miR-206 is a member of the miR-1 family of muscle-specific miRNAs known as "myomiRs", and plays an important role in skeletal muscle development and function (25). Beyond this developmental context, a plethora of studies have found that miR-206 is downregulated in various cancers and has tumor suppressor properties in clear-cell renal carcinoma (26), lung cancer (27), rhabdomyosarcoma (28), endometrial endometrioid carcinoma (29), and breast cancer (30,31). Previous studies on miR-206 in HCC by Pang *et al.* revealed that miR-206 expression is significantly lower in HCC cell lines compared to the normal hepatocyte cell line, L02 (32). Overexpression of miR-206 was found to significantly attenuate HCC cell proliferation, induce cell cycle arrest and apoptosis, and inhibit cell migration (32,33). These studies also identified Notch3, Hes1, Bcl-2, MMP-9, and CDK9 as mRNAs that miR-206 regulates to achieve its tumor suppressor effects. The current comprehensive study by Wu *et al.* builds on these findings and highlights the therapeutic potential of miR-206 using systemic delivery in several mouse models of liver cancer, driven by disease-relevant perturbations, as discussed below.

Amplification of the c-MYC oncogene is a frequent genetic alteration in HCC, occurring in 48% of cases; and is significantly associated with poor prognosis in HCC patients (34). Accordingly, overexpression of c-Myc in mice via hydrodynamic injection leads to aggressive liver tumors, most closely resembling human hepatoblastomas (35). Activation of the AKT/mTOR pathway is common in HCC, with loss of the negative regulator, PTEN, observed in ~50% of HCCs (36). Activation of the Ras/MAPK pathway is nearly universal in HCC, with >93% of HCCs demonstrating Ras mutations (37). Interestingly, co-expression of Myr-Akt and N-Ras-V12 in mice via hydrodynamic injection leads to rapid development of aggressive HCC, more pronounced than either oncogene alone (38). Wu *et al.* utilized both the c-Myc and Akt/Ras models to gain insight into human HCC. They first profiled global miRNA expression in livers of wildtype, c-Myc, and AKT/Ras mice and identified 12 miRNAs that were expressed in wild type livers but were undetectable in tumors of both c-Myc and AKT/Ras mice. To translate these findings to human HCC, they measured the expression of the 12 miRNAs in normal human hepatocyte cells and four HCC cell lines. They found that miR-206 was the only miRNA undetectable in tumors of both c-Myc and AKT/Ras mice and also significantly reduced in HCC cell lines compared to normal liver cells. Notably, miR-206 was also significantly reduced in a cohort of 31 human HCC tumors, compared to adjacent normal tissue, suggesting that miR-206 may play an important role in the pathogenesis of HCC.

Wu, Tao, and colleagues next investigated the mRNA targets of miR-206, to provide mechanistic insight into how miR-206 regulates HCC pathogenesis. They identified the

Met receptor tyrosine kinase (c-MET), cyclin D1 (CCND1), and cyclin-dependent kinase 6 (CDK6) as targets of miR-206, and hypothesized that miR-206 was able to prevent HCC by modulating both c-MET signaling, which has been previously implicated in HCC tumor growth when co-expressed with Myr-Akt (39), and cell-cycle progression. Using a luciferase reporter assay they demonstrated that miR-206 directly binds to the 3'UTRs of CCND1, c-MET, and CDK6, and that overexpression of miR-206 decreased both mRNA and protein levels of CCND1, c-MET, and CDK6 in HepG2 cells and in livers of mice overexpressing miR-206. This is in agreement with previous studies which reported that c-MET (28,40-44) and CCND1 (41,45,46) are targets of miR-206. To investigate the functional consequences of miR-206 re-introduction in HCC cells of different backgrounds, the authors overexpressed miR-206 in Huh7, SNU449, and MHCC97-H cell lines. They found that miR-206 overexpression prevented colony formation, significantly delayed G_1/S progression of the cell cycle, and strongly suppressed proliferation while also inhibiting growth of these cells as subcutaneous xenografts. Importantly, the authors subsequently showed that repression of CCND1, CDK6, and c-MET is required for miR-206's inhibitory effect on colony formation, proliferation, and growth as tumors *in vivo*, using a collection of "target protector" (TP) morpholinos to prevent miR-206 binding. This strongly suggests that the functional effects of miR-206 in HCC are due, at least in part, to downregulation of these three targets.

Finally, Wu and colleagues investigated the effects of miR-206 over-expression in the c-Myc and ATK/Ras models. As previously reported, the authors found that 100% of c-Myc and AKT/Ras control mice died from lethal tumor burden within 6 to 8 weeks (35-38). However, c-Myc and AKT/Ras mice over-expressing miR-206 remained healthy and had no evidence of liver tumors during this time period. miR-206 over-expressing mice also had reduced liver expression of *Ccnd1*, *Cdk6*, and *c-Met*, in agreement with the authors' findings discussed above. Interestingly, while *c-MET* or *Cdk6* cDNA over-expression (lacking miR-206 binding site) rescued tumor growth in both cMyc and AKT/Ras mice, overexpression of Ccnd1 failed to rescue tumor growth in either model. This suggests that in these models, Ccnd1 repression by miR-206 may not contribute to tumor growth. However, more study is needed as there are a number of papers which implicate Ccnd1, or pathways which impinge on Ccnd1, in HCC (47,48).

Over the past few decades, miRNAs have emerged as promising therapeutic strategies for cancer (49). This is largely due to the fact that miRNA mimics and inhibitors (known as antagomiRs) are small in size, potentially circumventing *in vivo* delivery issues. Furthermore, since miRNAs are known to have multiple mRNA targets, as seen in this study, they provide the potential to simultaneously modulate multiple key players in a pathway, possibly leading to more robust beneficial effects. To address translation, the authors investigated the therapeutic potential of miR-206 for the treatment of HCC. In order to resemble clinical conditions, the authors first induced HCC tumor growth for two weeks, and then treated mice intravenously with a hepatocyte-specific miR-206 minicircle episomal DNA vector, which due to its small size, may offer several advantages. Treatment with miR-206 significantly repressed both the growth of HCC and the expression of *Ccnd1*, *Cdk6*, and *c-Met* in c-Myc mice. However, surprisingly, miR-206 failed to attenuate tumor growth in AKT/Ras mice, and when the authors measured expression levels of miR-206, *Ccnd1*, *Cdk6*, and *c-Met* in these mice, they were unchanged compared to control, suggesting that poor delivery of miR-206 in the AKT/Ras model may have explained the lack of response. In order to address this, Wu, Tao, and colleagues attempted to increase delivery efficiency of miR-206 by using a miR-206 mimic that is much smaller than the miR-206 minicircle vector. This mimic was also chemically modified to increase its stability and transfection efficiency. Similar to their previous experiment, tumors formation was induced for 2 weeks followed by intravenous treatment with the miR-206 mimic. The authors observed that miR-206 treatment provided a significant anti-tumor effect, and significantly reduced mRNA levels of *Ccnd1*, *Cdk6*, and *c-MET* in the c-Myc mouse model of HCC, but no attenuation of tumor growth or changes in mRNA target expression was observed in the AKT/Ras model. This again appears to be due to a delivery issue, as miR-206 was not elevated in the livers of AKT/Ras mice. The authors speculate that the rapid growth of AKT/Ras tumors prevented efficient miR-206 delivery.

Collectively, the data presented by Wu, Tao *et al.* provides strong evidence that miR-206 opposes HCC growth by negatively regulating CCND1, CDK6, and c-MET (*Figure 1*). Furthermore, since the majority of HCC patients demonstrate perturbations in CCND1, CDK6, and/or c-MET, this suggests that miR-206 may hold therapeutic potential as a treatment for HCC. The authors acknowledge that more insight is needed into HCC-relevant miR-206 targets and will pursue an unbiased analysis of miR-206

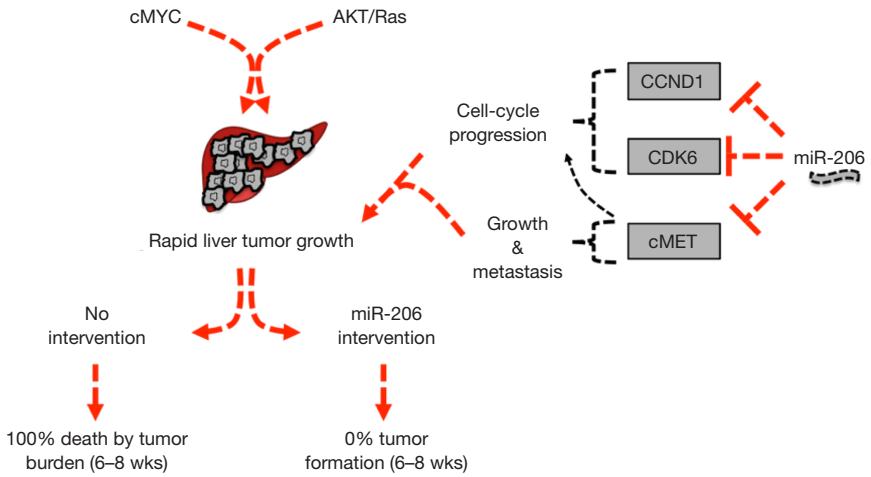

Figure 1 miR-206 in HCC pathogenesis. Over-expression of the cMYC or AKT/Ras oncogenes via hydrodynamic injection in mice leads to rapid formation of HCC resulting in death within 6–8 weeks due to lethal tumor burden. Mice treated with miR-206 show no evidence of liver tumor formation at the 6–8 weeks' time point. The effects of miR-206 are achieved, at least in part, by down-regulation of the c-MET receptor tyrosine kinase, which regulates growth signaling and metastasis, and cell-cycle regulators CCND1 and CKD6, which promote progression through the cell-cycle. miR-206, microRNA-206; CCND1, cyclin D1; CDK6, cyclin dependent kinase 6.

targets to construct the miR-206 "targetome". Further studies will also be needed to address the durability of the tumor suppressor effects of miR-206 *in vivo*, as well as the effect of miR-206 on HCC metastasis (50). Which tumor suppressor microRNA(s) to pursue is also a key question, as the authors previously demonstrated that miR-101 over-expression dramatically inhibits tumor development in the c-Myc and AKT/Ras models (51). This raises the question of whether there is benefit in co-delivery of promising microRNAs. Finally, challenges to efficient delivery will need to be addressed with innovative approaches. In summary, Wu, Tao *et al.* have characterized miR-206 as a robust tumor suppressor microRNA with promise for HCC treatment. This miRNA is added to an expanding list of noncoding RNAs relevant for cancer biology.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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