Hepatocellular Carcinoma Column: Editorial

Decoding hepatocellular carcinoma: the promise of microRNAs

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Abstract: MicroRNAs (miRNAs) may play an important role in the development and progression of hepatocellular carcinoma (HCC). Understanding the mechanism of specific miRNAs may provide opportunity for development of biomarkers and novel therapeutics in hepatocellular carcinoma which are desperately needed.

Keywords: Hepatocellular carcinoma (HCC); hepatocyte growth factor (HGF); vascular endothelial growth factor (VEGF); MET; microRNAs (miRNAs)

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer with rising incidence and mortality worldwide. While advances in surgical, transplantation, and regional therapies have made an impact in treatment, the highly vascular nature of the tumor and tendency to metastasize make systemic treatment necessary for the majority of patients. In the past five years, molecularly targeted therapies have been developed with modest success. Most notably, sorafenib (Nexavar), an oral multi-kinase inhibitor of the vascular endothelial growth factor receptor (VEGFR) demonstrated improved survival (1). Unfortunately, the benefit of sorafenib is short-lived, and despite numerous clinical trials, no other VEGF-targeting agent has clearly shown efficacy in randomized studies (2-4). Therefore, it is essential to understand drivers of HCC other than the classic VEGF pathway.

MicroRNAs (miRNAs) have been implicated in multiple biological pathways and dysregulation of miRNAs has been shown in many human tumors, including HCC (5). Specifically miR-26a has previously been shown to be downregulated in metastatic HCC patient samples when compared to non-metastatic samples, indicating that the target of miR-26a may be involved in tumor migration and invasion (6). The target mRNA, however was unknown. In the study by Yang *et al*. (7) , the authors identified hepatocyte growth factor (HGF) as the target of miR-26a and showed that expression of miR-26a can result in *in vitro* inhibition of proliferation and migration as well as *in vivo* inhibition of angiogenesis in mice. They demonstrate that miR-26a acts as a tumor suppressor by targeting HGF and subsequent down-regulation of the HGF-MET signaling proteins and VEGFA. Increased expression of miR-26a correlated with decreased expression of VEGFA and decreased microvessel density, indicating that miR-26a functions to inhibit angiogenesis. Moreover, the authors show that the expression of miR-26a is an independent prognostic marker for overall survival and time to recurrence in HCC patients. Patients with high HGF levels, low miR-26a levels, high VEGFA, and high microvessel density had worse overall survival and a higher likelihood of tumor recurrence compared to patients with low HGF levels.

Tissue biomarkers are sorely lacking for HCC. The ability to make the diagnosis of HCC without a biopsy has hindered the ability to develop prognostic and predictive markers for our patients. Levels of miR-26a may serve as a prognostic marker and should be explored as a possible predictor for response to inhibition of angiogenesis. In order to confirm these data and identify new biomarkers, tissue studies must be incorporated into clinical trials of HCC. Recently, the association of benefit in patients with MET-high tumors treated with tivantinib, an inhibitor of

the MET pathway, demonstrates that a biopsy can be quite revealing in HCC (8).

Even more intriguing than its role as a biomarker, miR-26a could be a new opportunity for treatment of HCC. Ultimately, if miRNAs can be delivered successfully in the clinic, mimics of miR-26a should lead to inhibition of proliferation, migration and angiogenesis. The mechanism would be postulated to be complementary to both MET and VEGF inhibition. A cancer-targeting miRNA mimic of another miRNA, miR-34 (MRX34), is in phase I clinical trials in HCC and recruiting patients (NCT01829971). MicroRNA therapy is an unproven frontier in drug development, but we have learned from experience that successful HCC treatment will require a radical new approach.

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