Editorial

Therapeutic targeting of alternative splicing to inhibit hepatocellular carcinoma metastasis

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Hepatocellular carcinoma (HCC) had the fourth highest mortality rate worldwide and was the sixth most common cancer type among various carcinomas in 2018, accounting for 8.2% and 4.7% of all carcinomas, respectively (1). HCC is generated predominantly due to the causative factors including chronic infection with hepatitis B virus or hepatitis C virus, long-term consumption of aflatoxin-contained foods, alcohol abuse, obesity, smoking and type 2 diabetes with a geographic variation (2). In addition, several genetic factors are involved in the development of HCC, including activation of oncogenes and inactivation of tumor suppressor genes (3-5). Sorafenib, a tyrosine kinase inhibitor (TKI) of multiple targets [such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and rapidly accelerated fibrosarcoma (RAF) kinase], is the first-line FDA-approved agent for systemic therapy of advanced HCC patients. Sorafenib prescription still had some limitations in that individual patient's response varied to a large extent with only about 8 months increase of overall survival (OS) and in that disruption of its multiple target pathways did not effectively prevent HCC recurrence and/or metastasis (6,7). More recently, other TKIs, including regorafenib, lenvatinib and cabozantinib, have shown an improved therapeutic index in terms of increase in OS of advanced HCC patients (8). However, these agents are blocking the biological activities of similar target genes and its related signaling pathways. Thus, it is urgently needed to identify other target genes or pathways that could be explored for next-line treatment options.

Poor prognosis of HCC was derived from high rates of metastasis and post-operative recurrence (9,10). Therefore, identification of new targets functionally associated with HCC metastasis is essential to prevent secondary tumor formation. Previous reports evidenced that the expressions of heterogeneous nuclear ribonucleoprotein (HNRNP) family members, as vital members of spliceosome, are upregulated in various types of tumors, such as colorectal cancer and glioblastoma, and contribute to tumorigenesis and metastasis (11,12). Alternative splicing (AS) is an important process for expanding gene-expression patterns and abnormal expression of splicing factor induced the abnormal AS patterns detected in tumors (13). HNRNPM, a member of HNRNP family, was identified as a biomarker for colorectal cancer and an important player for promoting breast cancer metastasis (14,15). Recently, Qiao *et al.* defined HNRNPM gene as a poor prognostic marker for OS of HCC patients and showed that inhibition of HNRNPM expression suppresses HCC cell growth and migration via inactivation of ERK and AKT signaling (16). It was previously reported that ERK is functionally associated with *NEK2* that positively regulates Wnt/β-catenin signaling to promote cancer growth and stemness (17,18). Inhibition of *NEK2* expression suppressed ERK phosphorylation in cancer cells (19). Those previous evidences may partially explain how silencing of HNRNPM expression could

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induce the observed HCC phenotypic changes.

Meanwhile, identification of novel therapeutic targets that are functionally connected to HCC stemness will provide useful information for developing next-line treatment pipelines to prevent secondary tumor formation and to overcome sorafenib resistance. AKT/β-catenin signaling is a well-known key regulatory pathway as well for cancer cell proliferation and maintenance of stemness (20). One of molecular mechanisms underlying the acquired resistance to sorafenib was activation of AKT signaling (7). Thus, Qiao *et al.* (16) provided a possibility that targeting HNRNPM could be used as a combinatorial therapy with sorafenib to overcome therapeutic resistance and to inhibit tumor relapse after treatment.

Future studies could be directed toward two ways. First, it would be interesting to find out a specific regulatory way how HNRNPM, as a subunit of spliceosome, controls the expressions or activities of ERK and AKT. By doing so, precise mode of action of future-developing HNRNPM inhibitor could be provided. Second, it would be also interesting to observe if the inactivation of ERK and AKT/β-catenin pathway was generally induced in parental HCC cell culture and isolated cancer stem cell (CSC) portion in which were received with a HNRNPM-specific small interfering RNA (siRNA). Taken together, targeting of HNRNPM could be a next-line treatment strategy for elimination of both tumor cells and CSCs, suppressing growth and metastatic potential of the HCC microenvironment.

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