Editorial

CircMTO1: a novel regulator of hepatocellular carcinoma progression

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Circular RNAs (circRNAs), a unique class of RNA, were transcribed from protein-coding genes or non-coding genes by RNA polymerase II and engendered by backsplicing (1,2). CircRNAs are characterized by forming a covalently closed continuous loop which have no 5'–3' polarity and polyA tail (3,4). Compared to linear RNAs, circRNAs were stable, abundant and showed a cell-type-specific, tissue-specific and stage-specific expression pattern (5,6). Previous studies had showed that circRNAs played important roles in many biological processes in different types of cancers, such as prostate (7), and gastric (8) cancer.

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, especially in China (9). Emerging evidences suggested circRNAs could also act as diagnostic and therapeutic biomarkers for HCC treatment (10-15). For example, hsa_circ_0001649 (15) and hsa_circ_0004018 (14) were found to be down-regulated while Cdr1as (12,13) and circ_0005075 (11) were upregulated in HCC. Yao *et al.* also found circZKSCAN1 could inhibit HCC cell growth, migration, and invasion (10). Therefore, identification of deregulated circRNAs as novel biomarkers for HCC is of great importance.

In the issue of the Hepatology, Han *et al.* (16) reported a novel circRNA circMTO1 was decreased in HCC by using the circRNA microarray. The expression of circMTO1 was found to be significantly down-regulated in 87.4% HCC tissues. Moreover, the authors demonstrated decreased circMTO1 expression in HCC tissues was significantly correlated with poor prognosis of HCC patients. These results indicated the potential important regulatory roles of circMTO1 in HCC.

Of note, although circRNA were found to be widely dysregulated in human cancers, the mechanism of circRNA underlying cancer progression remained largely unclear. CeRNA hypothesis, which was proposed by Salmena *et al.* (17) in 2011, indicated that pseudogenes, long noncoding RNAs (lncRNAs), and mRNAs can act as miRNA "sponges" and promote miRNA targets expression. The crosstalk among different types of RNAs played crucial roles in human diseases (18-21). Previous reports had showed circRNAs [such as ciRS-7 (22) and circ-ITCH (23)] could also serve as ceRNAs, however, no relevant studies were reported in HCC. In Han *et al.*'s study (16), authors for the first time found circMTO1 in HCC acted as a competitive endogenous RNA (ceRNA) by binding to microRNA-9 to up-regulate p21.

Moreover, Han *et al.* performed functional experiments to reveal the potential roles of circMTO1 in HCC. CircMTO1 silencing could significantly promote HCC cell proliferation and invasion, whereas circMTO1overexpression promoted apoptosis of HCC cells. More important, miR-9 inhibitor significantly blocked the circMTO1 silencing-mediated promotion of proliferation, indicated the important roles of circMTO1-miR-9 axis in HCC cells.

Another intriguing meaning of this study was to broaden the function of *MTO1* gene. MTO1 encodes an enzyme, which increases the accuracy and efficiency of mtDNA translation by catalyzing the 5-carboxymethylaminomethylation of the wobble uridine base in three mitochondrial tRNAs, including mt-tRNA^{Gln}, mt-tRNA^{Glu}, and mt-tRNA^{Lys} (24).

As we all known, circMTO1 was encoded by the *MTO1* gene and engendered by backsplicing. From Han *et al.*'s report, we knew that circMTO1 played the different roles of MTO1 by sponging miR-9 in HCC. This study provided novel insights for the prevention of HCC progression. According to TCGA data, only about 20,000 proteins were expressed, however, more than 70,000 circRNAs were existed in human tissues (25). Exploring the functions of circRNAs in diseases will provide useful information for diagnosis and treatment.

In conclusion, the study by Han *et al.* showed circMTO1 acted as the sponge of microRNA-9 to suppress HCC progression, which also provided a novel insight for the prevention of HCC progression. Despite this promising finding, much work remains to be done to explore novel diagnostic and therapeutic biomarkers for HCC.

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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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