

# CircMTO1: a novel regulator of hepatocellular carcinoma progression

Xuechao Wan, Yao Li

State Key Laboratory of Genetic Engineering, School of Life Science, Fudan University, Shanghai 200433, China

Correspondence to: Yao Li. State Key Laboratory of Genetic Engineering, School of Life Science, Fudan University, Shanghai 200433, China.

Email: yaoli@fudan.edu.cn.

*Provenance:* This is an invited Editorial commissioned by Section Editor Dr. Chunlin Ou, MD, PhD (Cancer Research Institute of Central South University, Changsha, China).

*Comment on:* Han D, Li J, Wang H, *et al.* Circular RNA circMTO1 acts as the sponge of microRNA-9 to suppress hepatocellular carcinoma progression. *Hepatology* 2017;66:1151-64.

Submitted Nov 27, 2017. Accepted for publication Dec 05, 2017.

doi: 10.21037/tcr.2017.12.15

View this article at: <http://dx.doi.org/10.21037/tcr.2017.12.15>

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 circMTO1 overexpression 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<sup>Gln</sup>, mt-tRNA<sup>Glu</sup>, and mt-tRNA<sup>Lys</sup> (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.

### Acknowledgements

**Funding:** This work was supported by a grant 31571330 from the National Natural Science Foundation of China, and Project SKLGE-1608 supported by the Research Fund of the State Key Laboratory of Genetic Engineering, Fudan University.

### Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

### References

- Salzman J, Gawad C, Wang PL, et al. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One* 2012;7:e30733.
- Ashwal-Fluss R, Meyer M, Pamudurti NR, et al. circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell* 2014;56:55-66.
- Hentze MW, Preiss T. Circular RNAs: splicing's enigma variations. *EMBO J* 2013;32:923-5.
- Chen LL, Yang L. Regulation of circRNA biogenesis. *RNA Biol* 2015;12:381-8.
- Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 2013;495:333-8.
- Salzman J, Chen RE, Olsen MN, et al. Cell-type specific features of circular RNA expression. *PLoS Genet* 2013;9:e1003777.
- Kong Z, Wan X, Zhang Y, et al. Androgen-responsive circular RNA circSMARCA5 is up-regulated and promotes cell proliferation in prostate cancer. *Biochem Biophys Res Commun* 2017;493:1217-23.
- Tian M, Chen R, Li T, et al. Reduced expression of circRNA hsa\_circ\_0003159 in gastric cancer and its clinical significance. *J Clin Lab Anal* 2017. [Epub ahead of print].
- Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
- Yao Z, Luo J, Hu K, et al. ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. *Mol Oncol* 2017;11:422-37.
- Shang X, Li G, Liu H, et al. Comprehensive Circular RNA profiling reveals that hsa\_circ\_0005075, a new circular rna biomarker, is involved in hepatocellular carcinoma development. *Medicine (Baltimore)* 2016;95:e3811.
- Yu L, Gong X, Sun L, et al. The Circular RNA Cdr1as act as an oncogene in hepatocellular carcinoma through targeting miR-7 Expression. *PLoS One* 2016;11:e0158347.
- Xu L, Zhang M, Zheng X, et al. The circular RNA ciRS-7 (Cdr1as) acts as a risk factor of hepatic microvascular invasion in hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2017;143:17-27.
- Fu L, Yao T, Chen Q, et al. Screening differential circular RNA expression profiles reveals hsa\_circ\_0004018 is associated with hepatocellular carcinoma. *Oncotarget* 2017;8:58405-16.
- Qin M, Liu G, Huo X, et al. Hsa\_circ\_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. *Cancer Biomark* 2016;16:161-9.
- Han D, Li J, Wang H, et al. Circular RNA circMTO1 acts as the sponge of microRNA-9 to suppress hepatocellular carcinoma progression. *Hepatology* 2017;66:1151-64.
- Salmena L, Poliseno L, Tay Y, et al. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* 2011;146:353-8.
- Xiao Y, Jiao C, Lin Y, et al. lncRNA UCA1 Contributes to Imatinib Resistance by Acting as a ceRNA Against miR-16 in Chronic Myeloid Leukemia Cells. *DNA Cell Biol* 2017;36:18-25.

19. Wu Q, Yan H, Tao SQ, et al. XIAP 3'-untranslated region as a ceRNA promotes FSCN1 function in inducing the progression of breast cancer by binding endogenous miR-29a-5p. *Oncotarget* 2017;8:16784-800.
20. Gao XH, Li J, Liu Y, et al. ZNF148 modulates TOP2A expression and cell proliferation via ceRNA regulatory mechanism in colorectal cancer. *Medicine (Baltimore)* 2017;96:e5845.
21. Zhang S, Zhu D, Li H, et al. Characterization of circRNA-Associated-ceRNA Networks in a senescence-accelerated mouse prone 8 brain. *Mol Ther* 2017;25:2053-61.
22. Peng L, Yuan XQ, Li GC. The emerging landscape of circular RNA ciRS-7 in cancer (Review). *Oncol Rep* 2015;33:2669-74.
23. Li F, Zhang L, Li W, et al. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. *Oncotarget* 2015;6:6001-13.
24. Wang X, Yan Q, Guan MX. Combination of the loss of cmm5U34 with the lack of s2U34 modifications of tRNA<sup>Lys</sup>, tRNA<sup>Glu</sup>, and tRNA<sup>Gln</sup> altered mitochondrial biogenesis and respiration. *J Mol Biol* 2010;395:1038-48.
25. Glazar P, Papavasileiou P, Rajewsky N. circBase: a database for circular RNAs. *RNA* 2014;20:1666-70.

**Cite this article as:** Wan X, Li Y. CircMTO1: a novel regulator of hepatocellular carcinoma progression. *Transl Cancer Res* 2018;7(Suppl 1):S44-S46. doi: 10.21037/tcr.2017.12.15