Editorial

Crosstalk between circular RNAs and microRNAs in tumorigenesis

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Liver cancer is the fifth most common cancer worldwide and the second leading cause of cancer-related mortality, resulting in approximately 750,000 deaths annually (1). Hepatocellular carcinoma (HCC) accounts for 70–90% of all cases of liver cancer (2). Although significant advances have been made toward understanding its causal mechanisms, the 5-year risk of HCC recurrence still exceeds 70% (3). The low survival rate of HCC patients is widely attributed to postsurgical recurrence and metastases of primary tumours (1). Furthermore, the progression and development of HCC involve multiple genes and pathways that are induced by cellular conditions such as oxidative stress and a tumour microenvironment (4). In addition, hypoxia and inflammation act in concert with various molecular events. There is an urgent need for effective strategies to screen for and detect early-stage HCC, thereby improving the long-term survival of HCC patients.

Tumour biomarkers represent a promising tool for early tumour diagnosis, determination of disease severity, monitoring high-risk populations, evaluation of treatment and prognosis, formulation of individualized therapies, and investigation of disease course (4-6). At the beginning of the post-genomic era, after the completion of Human Genome Project (HGP), non-coding RNA (ncRNA) received substantial research attention in various fields (7). In 2006, the Nobel Prize was awarded for the discovery of small interfering RNA (siRNA) (8), increasing the interest in ncRNAs, including circular RNAs (circRNAs), in biomedical research. CircRNAs were recognized as a novel type of endogenous ncRNAs. These are usually produced either from exons or introns by a back-splicing reaction, thereby forming covalently closed continuous loops without 5' or 3' tails (9-10). Because circRNAs are stable, conserved, abundant, and showed strong tissue- and cell-specific expression (11), they have recently received more research attention than microRNAs (miRNAs) or long ncRNAs (lncRNAs). In the past decade, thousands of circRNAs have been discovered to be differentially expressed in many human diseases. They play vital regulatory roles in many physiological processes (e.g., cell proliferation, apoptosis, differentiation, and survival) that are similar to the roles of gene transcriptional and expression regulators, protein/peptide translators, miRNA sponges, and RNA-binding protein (RBP) sponges (12,13). Studies have shown that aberrant expression of circRNAs such as Hsa_circ_0001649 (14), ciRS-7 (Cdr1as) (15), circRNA_000839 (16), and circRNA-100338 (17) is associated with metastasis and tumorigenesis and can be used to diagnose or determine the prognosis of HCC. However, the expression, dysregulation, function, and mechanism of circRNAs in HCC still remain elusive.

A recent study by Han *et al.* (18), reported in *Hepatology*,

clearly and comprehensively demonstrated the association of circRNAs and HCC tumorigenesis. In this study, the authors examined the down-regulation of a novel circRNA, circMTO1 (hsa_circRNA_0007874/hsa_circRNA_104135), by analysing the expression of human circRNAs in seven pairs of HCC tissues and corresponding normal liver tissues, and found that circMTO1 was closely associated with disease outcome. The mechanism through which circMTO1 suppresses HCC progression may involve the circRNA-miRNA-mRNA axis, with circMTO1 acting as a sponge for oncogenic miR-9 and inhibiting its activity, as well as promoting p21 expression, the target of miR-9. This study introduced a novel strategy for the treatment of HCC, with circMTO1 potentially serving as a predictor of low survival rates in patients with HCC. However, in our opinion, the conclusion drawn by Han *et al.* should be validated for the following reasons. Firstly, although the authors showed using RIP circMTO1 pull-down assays that circMTO1 can enrich miR-9, we cannot conclude that circMTO1, expressed endogenously at a low level, sponges miR-9 in cancer. Secondly, the circRNA-miRNA-mRNA complex is known to bind to AGO2, thereby inducing the degradation of the RNA-induced silencing complex (RISC); however, in this study, there was little evidence of circMTO1 sponging of miR-9. Finally, figure 6 of this paper is the poor evidence to reflect figures 1–5 to suggest that circMTO1 sponges miR-9 to suppress the progression of HCC, because there was no confirmatory experiment that followed.

In summary, Han *et al.* not only showed that circMTO1 could act as a clinical biomarker for HCC patients but also suggested that reversing the loss of circRNA expression may be exploited as a cancer therapy. With the development and application of RNA sequencing technology and next-generation sequencing, many new circRNAs have been identified. Because of their unique structure, circRNAs are highly stable in diseased tissues, serum, and cells. Further, circRNAs are easy to screen, more stable than miRNAs and lncRNAs, and can be extracted and detected with higher sensitivity and specificity than proteins. Therefore, circRNAs have served as novel diagnostic biomarkers for and therapeutic targets in many human diseases. In cancer research, circRNAs have been recognised as a "new star", because an increasing number of circRNAs have been reported to be associated with the development and progression of cancer. However, circRNA research has faced two recent challenges. On the one hand, it is necessary to validate new-found circRNAs by RNA sequencing of human tissues or cells to determine whether they are functional and whether the functional circRNAs are specifically associated with one or more diseases. On the other hand, the functions of circRNAs *in vivo* remain a question because appropriate and convenient *in vivo* models are not available. Therefore, there is a long road from scientific research to clinical application (19,20). We believe that technological advances would eventually help clarify the function and mechanism of these circRNAs, which would in turn lead to the development of novel strategies for the early screening and therapy of cancer.

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