Editorial

Circular RNA YAP1: a new player in gastric cancer

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Gastric cancer (GC) is a frequently diagnosed malignant tumour in which cancer cells form in lining of the stomach. It represents the fourth most common cancer worldwide and the 5-year survival is 54–58% in Japan and South Korea, and below 40% in other countries (1). The poor prognosis is mainly due to the high incidence of recurrence (2). Accordingly to the US National Cancer Institute (NCI; https://www.cancer.gov), there are six standard treatments currently used in GC including surgery, chemotherapy, radiation therapy, chemo-radiation, targeted therapy and immunotherapy. GC is mostly asymptomatic until it progresses to advanced stages when it is often diagnosed (2). Hence, it comes the need to discover new cancer biomarkers for the early detection of the tumour and personalized treatments.

Recently, circular RNAs (circRNAs) have come to the spotlight for their role in the occurrence and development of cancer (3-5), including GC (6-8). circRNAs are an abundant class of endogenous RNAs, characterized by a single-stranded covalently closed loop structure without 5' end caps or 3' poly (A) tails (9,10). This characteristic makes circRNAs resistant to exonuclease RNase R and more stable than the corresponding linear RNA isoforms (9,10).

Liu *et al.* described the role of a new circular RNA, circYAP1, in GC. The authors selected this circular RNA using CircNet, a public database that provides tissue-specific circRNA expression profiles (http://syslab5.nchu.edu.tw/CircNet/). No explanation is given about the selection of this particular circular RNA, although the value of the study is not particularly affected by this lack. The authors used a good range of techniques to characterize the function of circYAP1, including Real time PCR, FISH, circRNA *in vivo* precipitation and lentiviral-based approach. They also used different cell-based phenotype assays such as proliferation, colony formation and invasion assay and *in vivo* models.

The circYAP1 expression level was initially assessed by real time PCR in 17 patients. CircYAP1 resulted down regulated in this first group of patients and this trend was confirmed by FISH assay in an additional group of 80 GC samples. Interestingly, circYAP1 behaves as an independent prognostic factor for overall survival in GC.

Mechanistically, Liu *et al.* found that circYAP1 worked as a sponge for miR-367-5p. CircRNAs can bind miRNAs through a miRNA response element (MRE) and negatively regulate their activity (9).

The authors used two cell lines to define the putative miRNAs sponged by circYAP1 and in both they found that the miR-367-5p was significantly up-regulated following circYAP1 overexpression. MiR-367 is known to behave like an oncogene. It was found up-regulated in non-small cell lung cancer (NSCLC) and associated with unfavourable prognosis (11). Another study showed that miR-367 induces epithelial-to-mesenchymal transition (EMT) and promotes invasion and metastasis of pancreatic cancer cells through the Smad7-TGFb pathway (12).

MiRNAs potentially sponged by circYAP1 were identified using the two databases, CircNet and CircInteractome (13). Since the two databases are relatively new, as well as the study of circRNAs in human diseases, it would have been useful a more detailed explanation about the methods the authors used to combine the data from the two databases and select the common miRNAs coming from the analysis. Nevertheless, by circRNA *in vivo* precipitation

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and FISH analysis, the authors showed compellingly the sponging effect of circYAP1 on miR-367-5p. As well as miR-367-5p, other miRNAs, i.e., miR-1200, miR-330-5p, miR-513a-3p and miR-513c-3p, were selected as putative circYAP1 targets. The miR-1200 and miR-367-5p were the only two miRNAs significantly up-regulated by circYAP1 overexpression in the AGS cells instead miR-367-5p was the only miRNA up-regulated in the MKN cells. The selection of the two cell lines used led to the selection of the miR-367-5p but we cannot exclude that other miRNAs are targets of circYAP1 in GC.

The authors showed that circYAP1 overexpression suppressed AGS and MNK45 cell growth inducing an arrest of the cell population in G1 phase. This effect could be reversed when the cells were co-transfected with miR-367-5p mimic. On the same line, also colony formation assay and invasion assay brought to a similar result whit the effect of circYAP1 overexpression rescued by miR-367-5p. As expected, the authors obtained the opposite cellular phenotype upon the circYAP1 knockdown. These data further reinforce the circYAP1 sponging action on miR-367-5p that authors already showed by RNA precipitation and FISH analysis.

To define the molecular model involving circYAP1 in GC, the authors focused on miR-367-5p target genes. They found that p27 Kip1 (p27) was the best potential miR-367-5p target. P27 is a member of the cyclin-dependent kinase inhibitor (CDKI) family and regulates cell cycle, cell motility, apoptosis, cell adhesion, neuron differentiation, cell signalling and ion transport (14,15). P27 is frequently deregulated in cancer and this condition is associated with a poor prognosis in most human cancers including GC (14,16). The authors concluded the work with mice *in vivo* model. MKN-45 cells overexpressing circYAP1 generated a tumour in nude mice, which volume was significantly smaller than those grown after injection of control cells.

CircYAP-1 derives from the Yes-associated protein 1 (YAP1) locus. YAP1 is encoded by the *YAP* gene that is located in the human chromosome 11q22a (17,18). YAP1 is a transcriptional co-activator of TEAD family factors through which determine the main functions of Hippo pathway (19). Hippo pathway is a conserved regulator of organ size and it has an important role in cancer (19).

Since other studies showed that YAP1 plays important role in GC (20,21), the authors should have worked more on the comparison between circYAP1 and YAP1. It would be interested to understand if the circRNA and its host gene have the same behaviour among the patients selected for the study and if they are able to determine the same phenotype *in vitro* and *in vivo*. CircRNAs can have different functions of their host genes depending on the specific disease context (5).

In conclusion, Liu *et al*. describe a new circRNA1, circYAP1 that could be used as new molecular target in GC. Since circYAP1 is an independent prognostic factor in GC, it can be also considered a promising cancer biomarker. Based on their biochemical features, including their high stability and resistance to the RNase R activity, circRNAs are likely to become the favourite biomarkers in human diseases. Moreover, circRNAs show cell-, tissue- and developmental-stage specific patterns of expression. They are also present in accessible body fluids such as saliva, plasma and blood representing the ideal candidates for the application of non-invasive diagnostic methods (22,23). CircRNAs show great potential as source of molecular biomarkers for the early cancer diagnosis, prediction of response to antitumor therapy and disease prognosis, and for the prediction of disease recurrence and post-treatment monitoring.

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Footnote

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