Background Primary hepatocellular carcinoma (HCC) is one of the most common malignancies all over the world. However, the mechanism of HCC initiation and development remains unclear. In our previous work, high-throughput microarray assay in HCC samples followed by bioinformatic analysis suggested that Metallothionein1G (MT1G) might be one of the key factors in HCC. In this study, we aim to clarify the biological function of MT1G and validate its potential to be utilised as a biomarker in HCC.

Methods We detected the MT1G expression in paired HCC samples and cell lines by both RT-qPCR and Western blot. MSP (Methylation specific PCR) and BGS (Bisulfite genomic sequencing) were performed to evaluate methylation status of MT1G in HCC. TCGA (The Cancer Genome Altas) data analysis was used to validate the results from our samples. The functional significance of MT1G was investigated by overexpression or knockdown in vivo and in vitro. Kaplan-Meier survival analysis was performed using TCGA data to estimate the clinical value of MT1G expression and methylation status in HCC.

Results MT1G was inactivated in 4 of 6 HCC cell lines. The expression of MT1G was downregulated in cancer tissues compared with the adjacent non-tumour tissues (p<0.001). The gene expression of MT1G was closely correlated to the promoter methylation status. The MT1G expression in silenced HCC cell lines could be restored by demethylation agent. Ectopic re-expression of MT1G by stable transfection in SMMC7721 and Hep3B cells inhibited colony formation (p<0.001), suppressed cell motility and invasiveness (p<0.05), accompanying with up-regulation of E-cadherin; and down-regulation of PCNA, MMP2, MMP13 and Vimentin. Xenograft tumour assay in nude mice also revealed that MT1G could markedly decrease tumour weights and volumes in vivo (p<0.001). Survival analysis revealed that hypermethylation of MT1G predicts good outcomes of HCC patients.

Conclusions Our results demonstrate that MT1G promoter methylation directly mediates the transcription down-regulation and commonly occurs in HCC. MT1G gene can act as a functional tumour suppressor in liver carcinogenesis by playing an important role in the depression of cell proliferation, migration and invasion.

CIRCULAR RNA CIRC5379–6 PERFORMS FUNCTIONS IN INHIBITING TUMORIGENESIS AND METASTASIS OF HEPATOCELLULAR CARCINOMA VIA THE REGULATION OF PPARα

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Background Circular RNAs (circRNAs) are considered as RNA molecules in loop structure and was reported as a potential novel biomarker for hepatocellular carcinoma (HCC). Peroxisome proliferator-activated receptor alpha (PPARα) is a suppressor of HCC via direct targeting nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway according to our previous study, whereas their relationship in the modulation of pathogenesis processes in HCC is still unclear. The aim of this study was to determine the circRNAs those perform functions in regulating the gene PPARα and thereby regulate the pathogenesis processes in HCC.

Methods The candidate circRNAs were firstly validated in structure via the RNase R treatment, amplification of specific convergent and divergent primers, and Sanger sequencing. After over-expressing the circRNAs in HCC cell lines and further validation of the cell viability assay, the circRNA correlated to PPARα was obtained. Functional analysis of the
candidate circRNA was performed *in vitro* and *in vivo*, including cell viability assay, colony formation assay, cell cycle analysis, apoptosis array and Matrigel migration and invasion assay. Differences between experimental groups and control groups were analysed using the paired t-test and Wilcoxon test.

**Results** Of the seven-candidate circRNAs, Circ5379–6 was verified to be correlated positively to PPARα. Overexpression of circ5379–6 lead to up-regulation of PPARα and it thereby suppressed the cell proliferation, inhibited the cell migration and invasion. The most obvious effect of circ5379–6 expression should be the induction of cell apoptosis in the HCC cell lines. Matrix metalloprotein 9 (MMP-9) was down-regulated expressed while Vimentin, N-Cadherin and E-Cadherin were up-regulated expressed in the tumour generated by the cells with circ5379–6 overexpression. Furthermore, the overexpression of circ5379–6 effectively inhibited the tumorigenesis and metastasis of HCC according to the *in vivo* studies in nude mice.

**Conclusions** Circ5379–6 acts as an effective tumour inhibitor of HCC via regulating the level of PPARα. It suggests that induction of Circ5379–6 expression may utilise as a potential therapeutic method for HCC.

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**POKEMON OVER-EXPRESSION ACCELERATES THE PROGRESSION OF NAFLD VIA INCREASING LIPID DROPLET DEPOSIT IN HEPATOCYTE**

Jingping Zhou*, Zhongshan Hospital Affiliated to Xiamen University, China

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**Background** Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of metabolic syndrome and is characterised by the accumulation of lipid droplets. Pokemon (PFI-1/ZATB7A) is an important proto-oncogene which is involved in cancer development and adipogenic gene expression. The aim of our study is to explore the role of Pokemon in the development and progression of NAFLD.

**Methods** C57BL/6 mice were fed with normal chow (NC) or high-fat diet (HFD) for 16 weeks to induce NAFLD. Pokemon mRNA and protein were detected by RT-PCR and Western blot as well as immunohistochemistry. NAFLD cell models were established by oleic acid, and si-Pokemon hepatic cancer cell lines were also constructed by plko lentiviral system. The NaFLD models were also constructed by plko lentiviral system.

**Results** Mice fed with HFD for 16 weeks showed increased body weight, liver weight, liver-to-body weight ratio as well as increased lipid accumulation as shown by H and E staining and Oil Red O staining consistent with the establishment of NAFLD. The Pokemon mRNA as determined by RT-PCR and protein expression as determined by Western blot and immunohistochemistry were significantly upregulated in mice fed with HFD compared with the NC group (p<0.01). The upregulated Pokemon was accompanied by increased serum TNF-α, IL-6, triglyceride, cholesterol and MDA levels in HFD group (p<0.01). For *in vitro* study, Pokemon and SREBP-1 protein expression in HepG2 were increased in a concentration-dependent manner when treated with oleic acid (p<0.01). SREBP-1 and FAS mRNA expression were also increased which could be counteracted by pokemon silencing. Knockdown of Pokemon by siRNA in HepG2 cells showed decreased lipid accumulation, triglyceride content, suppressed mRNA expression of lipogenic genes including FASN, SREBP, SCD-1, HMGCR and genes related with oxidation metabolism including Cpt1 and Acadm.

**Conclusions** Pokemon promotes NAFLD progression via increasing lipid accumulation and repressing free acids oxidation.