

Letter to the Editor

Comment on: MiR-877-5p suppresses cell growth, migration and invasion by targeting cyclin dependent kinase 14 and predicts prognosis in hepatocellular carcinoma

Dear Editor,

We analyzed with great interest the article of Yan et al¹ concerning miR-877-5p role in both clinical and mechanism of hepatocellular carcinoma (HCC). The authors found that the expression of miR-877-5p was downregulated in HCC tissues or cell lines and associated with histologic grade, TNM stage and lower survival rate. They also identified CDK14 as the target of miR-877-5p, which can thus be marked as tumor suppressor in HCC.

The miRNAs role has also been investigated in other studies, either on animals or cell models. In this sense, Wang et al² evaluated the miR-300 role on HCC cells and tissues. This study showed that the miR-300 down-regulation increased the invasiveness of HCC cells and promoted the epithelial-mesenchymal transition (EMT) in both HCC tissues and cells lines.

More in depth, miR-300 inhibited the EMT-mediated migration and invasion of HCC cells through FAK modulation and the PI3K/AKT signaling pathway.

In this scenario, Visalli et al³ identified a novel three-miRNA signature, (miR-371-5p, miR-373 and miR-543), which seems to be involved in the apoptosis mechanism mediated by Caspase-8 (Casp-8). Findings underlined that miR-371-5p, miR-373 and miR-543 were overexpressed in HCC tissues and markedly downregulated Casp-8 expression. Conversely, the selective suppression of those miRNA significantly increased Casp-8 levels and the reduction of programmed cell necrosis.

Callegari et al⁴ studied the miR-199a-3p, a miRNA highly expressed in normal liver, by mimic molecules assayed in the TG221 mouse, a transgenic model highly predisposed to the development of liver cancer. The ectopic expression of miR-199a-3p mimics induced a significant reduction of both number and size of HCC lesions. Furthermore, the anti-tumor activity of miR-199a-3p mimics was similar to Sorafenib, a kinase inhibitor used in HCC therapy⁵. The evaluation, through cell line or mouse models, of specific signaling pathway could be useful in the acknowledgment of several up-regulated genes and proteins involved in drug resistance⁶. The "miR-na topic" could represent an important point of view concerning HCC, considering the poor prognosis and limited therapeutic options⁷. However, the range between cell and animal experimentation and the prospective clinical application still seems to be far. In the end, prevention through the evaluation of molecular markers⁸, and the identification of main risk factors, particularly viral⁹ and metabolic¹⁰⁻¹³, could be still considered the best strategy.

Conflict of interest

The authors declare no conflicts of interest.

References

- 1) YAN TH, QIU C, SUN J, LI WH. MiR-877-5p suppresses cell growth, migration and invasion by targeting cyclin dependent kinase 14 and predicts prognosis in hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci* 2018; 22: 3038-3046.
- 2) WANG R, YU Z, CHEN F, XU H, SHEN S, CHEN W, CHEN L, SU Q, ZHANG L, BI J, ZENG W, LI W, HUANG X, WANG Q. miR-300 regulates the epithelial-mesenchymal transition and invasion of hepatocellular carcinoma by targeting the FAK/PI3K/AKT signalling pathway. *Biomed Pharmacother* 2018; 103: 1632-1642.

- 3) VISALLI M, BARTOLOTTA M, POLITO F, OTERI R, BARBERA A, ARRIGO R, DI GIORGIO RM, NAVARRA G, AGUENNOUZ M. miRNA expression profiling regulates necroptotic cell death in hepatocellular carcinoma. *Int J Oncol* 2018 May 17. doi: 10.3892/ijo.2018.4410. [Epub ahead of print]
- 4) CALLEGARI E, D'ABUNDO L, GUERRIERO P, SIMIONI C, ELAMIN BK, RUSSO M, CANI A, BASSI C, ZAGATTI B, GIACOMELLI L, BLANDAMURA S, MOSHIRI F, ULTIMO S, FRASSOLDATI A, ALTAVILLA G, GRAMANTIERI L, NERI LM, SABBIONI S, NEGRINI M. miR-199a-3p modulates MTOR and PAK4 pathways and inhibits tumor growth in a hepatocellular carcinoma transgenic mouse model. *Mol Ther Nucleic Acids* 2018; 1; 11: 485-497.
- 5) BERRETTA M, RINALDI L, DI BENEDETTO F, LLESHI A, DE RE V, FACCHINI F, DE PAOLI P, DI FRANCIA R. Angiogenesis inhibitors for the treatment of hepatocellular carcinoma. *Front Pharmacol* 2016; 7: 428.
- 6) RINALDI L, MILIONE S, PORTA G, SINISCALCHI LI, FRANCI G, DI FRANCIA R. Inhibition of the JNK signaling pathway increases sensitivity of hepatocellular carcinoma cells to cisplatin by down-regulating expression of P-glycoprotein. *Eur Rev Med Pharmacol Sci* 2016; 20: 2947-2949.
- 7) DI BENEDETTO F, TARANTINO G, ERCOLANI G, BACCARANI U, MONTALTI R, DE RUVO N, BERRETTA M, ADANI GL, ZANELLO M, TAVIO M, CAUTERO N, TIRELLI U, PINNA AD, GERUNDA GE, GUARALDI G. Multicenter italian experience in liver transplantation for hepatocellular carcinoma in HIV-infected patients. *Oncologist* 2013; 18: 592-599.
- 8) BIONDI A, MALAGUARNERA G, VACANTE M, BERRETTA M, D'AGATA V, MALAGUARNERA M, BASILE F, DRAGO F, BERTINO G. Elevated serum levels of chromogranin A in hepatocellular carcinoma. *BMC Surg* 2012; 12 Suppl 1: S7.
- 9) ADINOLFI LE, NEVOLA R, RINALDI L, ROMANO C, GIORDANO M. Chronic hepatitis C virus infection and depression. *Clin Liv Dis* 2017 ;21: 517-534.
- 10) LONARDO A, NASCIBENI F, MAURANTONIO M, MARRAZZO A, RINALDI L, ADINOLFI E. Non-alcoholic fatty liver disease: evolving paradigms. *World J Gastroenterol* 2017; 23: 6571-6592.
- 11) RINALDI L, NASCIBENI F, GIORDANO M, MASETTI C, GUERRERA B, AMELIA A, FASCIONE MC, BALLESTRI S, ROMAGNOLI D, ZAMPINO R, NEVOLA R, BALDELLI E, IULIANO N, ROSATO V, LONARDO A, ADINOLFI LE. Clinical features and natural history of cryptogenic cirrhosis compared to hepatitis C virus-related cirrhosis. *World J Gastroenterol* 2017; 23: 1458-1468.
- 12) DI FRANCIA R, RINALDI L, TROISI A, DI BENEDETTO F, BERRETTA M. Effect of anti-oxidant agents in patients with hepatocellular disease. *Eur Rev Med Pharmacol Sci* 2015; 19: 3993-3995.
- 13) DI MARTINO S, RAINONE A, MAROTTA G, MAZZARELLA M, PUGLIESE S, RINALDI L. Nutraceutical agents with hepatoprotective effects in cancer patients. *WCRJ* 2016; 3: e788.

P.C. Pafundi¹, A. Caturano¹, G. Franci²

¹Department of Medical Surgical, Neurological, Metabolic and Aging Sciences,
University of Campania "Luigi Vanvitelli", Naples, Italy

²Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy