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Letter to the Editor

Promotion of proliferation and metastasis of hepatocellular carcinoma by LncRNA00673 based on the targeted-regulation of notch signaling pathway

Dear Editor,

we read with great interest the paper by Dr. Chen et al[1], recently published in European Review for Medical and Pharmacological Sciences and titled ''Promotion of proliferation and metastasis of hepatocellular carcinoma by LncRNA00673 based on the targeted-regulation of notch signaling pathway''. Authors concluded that lncRNA00673 is highly expressed and may be a potential target for the treatment of Hepatocellular Carcinoma (HCC). Moreover, according to authors, it can promote the proliferation and metastasis of HCC by the regulation of Notch signaling pathway. We congratulate the authors for their interesting work.

The role of lncRNAs in oncogenesis is currently of great interest and several studies focused on their implications[2]. In the last years, increasing evidence showed that non-coding RNAs represent functional molecules participating in different physiological and pathological processes. In addition to small non-coding RNAs (small nuclear RNAs, small nucleolar RNAs, microRNAs, piwi-interacting RNAs, small interfering RNAs) that were well characterized for their function, more recently long non-coding RNAs (lncRNAs) have been explored to analyze their roles. lncRNAs show a lot of similarities with mRNAs, even if generally expressed at a lower level, and can localize in specific compartments of the cell. Based on their localization, they can exert different biological functions[3]. Nuclear lncRNAs are mainly involved in the recruitment of transcriptional factors or chromatin modifiers (both DNA and histone modifying enzymes), thanks to their ability to be structured in functional domains able to interact with proteins[2,4,5]. Cytoplasmic lncRNAs exert other functions at post-transcriptional levels by controlling the stability of messenger RNAs or by sequestering miRNAs acting as competing for endogenous RNAs (ceRNAs). miRNAs and lncRNAs are often dysregulated in pathological conditions. Notably, respect to liver cancer, it has been reported that non-coding RNAs play a primary role in hepatocarcinogenic processes[5-7]. Well-described examples for functionally important lncRNAs are HOTAIR, HULC, TERC, HOXA-AS2, CASC2, HOXD-AS1, PVT1, SPRY4-IT1, MALAT1, DREH, CCAT2.

This evidence suggests that a better understanding of how lncRNAs exert their functions in hepato-carcinogenesis could be useful in finding some solutions for liver cancer treatment. After the detection of lncRNAs expression (especially in the earlier phases of the disease), some strategies of lncRNAs-based treatment should be taken into account. The control of lncRNAs levels could open the way to a more target-specific therapy counteracting the epigenetic modifications guided by lncRNAs recruiting chromatin-remodeling complexes at specific loci. As a result, cells could re-acquire their polarity, the epithelial phenotype, the adhesion to the other cells, while losing invasive and migratory properties.

Recently, Chen et al[1] reported that lncRNA00673, a 2275bp long non-coding RNA, plays a role in tumour biology. In non-small-cell lung cancer cells, it is expressed at high levels and is able to interact with both LSD1 on the promoter of NCALD, thus, promoting cell proliferation, and PRC2 on the regulatory regions of HOXA5. Specifically, they show that lncRNA00673 is expressed at high levels in liver tumour samples and in HCC cell lines compared to control. More interestingly, the depletion of lncRNA00673 through an RNA interference approach on

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HCC cell lines displays that this non-coding RNA is involved in the maintenance of tumour cells proliferation since cells transfected with siRNAs were retarded in G0-G1 phase. Additionally, lncRNA00673 depletion induces an increase in the apoptotic rate while diminishing the metastatic and invasive capacities and the expression of Notch pathway genes.

This work confirms that lncRNAs play a central role in tumor cell proliferation, apoptosis, epithelial to mesenchymal transition (EMT) by regulating different pathways, such as Notch pathway in the case of lncRNA00673. The understanding of the molecular players and processes involved in HCC onset and development could represent the starting point to prevent a liver tumor, by identifying molecular markers, and to develop new therapies for HCC treatment.

In summary, since currently adopted staging systems do not include any tumor-specific biological prognostic factors, further studies on intracellular pathways and tumor-stroma cross-talk are needed to improve diagnosis and management of HCC[8-12].

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Chen H, Liu JZ, Hu GJ, Shi LL, Lan T. Promotion of proliferation and metastasis of hepatocellular carcinoma by LncRNA00673 based on the targeted-regulation of notch signaling pathway. Eur Rev Med Pharmacol Sci 2017; 3412-3420.

2) Battistelli C, Cicchini C, Santangelo L, Tramontano A, Grassi L, Gonzalez FJ, de Nonno V, Grassi G, Amicone L, Tripodi M. The Snail repressor recruits EZH2 to specific genomic sites through the enrollment of the lncRNA HOTAIR in epithelial-to-mesenchymal transition. Oncogene 2017; 36: 942-955.

3) Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013; 152: 1298-1307.

4) Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010; 464: 1071-1076.

5) Amicone L, Citarella F, Cicchini C. Epigenetic regulation in hepatocellular carcinoma requires long noncoding RNAs. Biomed Res Int 2015; 2015: 473942.

6) Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 2015; 47: 199-208.

7) Gong J, He XX, Tian DA. Emerging role of microRNA in hepatocellular carcinoma (Review). Oncol Lett 2015; 9:1027-1033.

8) Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, Di Sandro S, Quintini C, Codeluppi M, Tirelli U,Gerunda GE. Don't deny liver transplantation to HIV patients with hepatocellular carcinoma in the highly active antiretroviral therapy era. J Clin Oncol 2006; 24: e26-27.

9) Magistri P, Tarantino G, Ballarin R, Berretta M, Pecchi A, Ramacciato G, Di Benedetto F. The evolving role of local treatments for HCC in the third millennium. Anticancer Res 2017; 37: 389-401.

10) Magistri P, Tarantino G, Ballarin R, Coratti A, Di Benedetto F. Robotic liver surgery is the optimal approach as bridge to transplantation. World J Hepatol 2017; 9: 224-226.

11) Canzonieri V, Alessandrini L, Caggiari L, Perin T, Berretta M, Cannizzaro R, De Re V. Hepatocellular carcinoma: anoverview of clinico-pathological and molecular perspectives. WCRJ 2015; 2: e485.

12) Berretta S, Fisichella R, Spartà D, Lleshi A, Nasti G. Primary liver cancer: clinical aspects, prognostic factors and predictive response to therapy WCRJ 2015; 2: e561.

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