Lefter 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 al¹, 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 IncRNAs in oncogenesis is currently of great interest and several studies focused on their implications². 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 (IncRNAs) have been explored to analyze their roles. IncRNAs 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 functions3. Nuclear IncRNAs 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 IncRNAs 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 IncRNAs 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 processes⁵⁻⁷. Well-described examples for functionally important IncRNAs are HOTAIR, HULC, TERC, HOXA-AS2, CASC2, HOXD-AS1, PVT1, SPRY4-IT1, MALAT1, DREH, CCAT2.

This evidence suggests that a better understanding of how IncRNAs exert their functions in hepato-carcinogenesis could be useful in finding some solutions for liver cancer treatment. After the detection of IncRNAs expression (especially in the earlier phases of the disease), some strategies of IncRNAs-based treatment should be taken into account. The control of IncRNAs levels could open the way to a more target-specific therapy counteracting the epigenetic modifications guided by IncRNAs 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 al¹ 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

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, IncRNA00673 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 IncRNAs 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 IncRNA00673. 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 HCC⁸⁻¹².

Conflict of Interest

The Authors declare that they have no conflict of interests.

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