



A role for lnc-DILC in liver cancer stem cells

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As the sixth most common malignant tumor, the mortality rate of hepatocellular carcinoma (HCC) is the second highest worldwide (1). Despite the great amount of progress regarding the diagnosis and treatment for HCC in recent years, the long-term survival of HCC patients remains unsatisfactory. Dismal prognosis and frequent recurrence of HCC has limited patients' survival (2). Therefore, new targets for HCC diagnosis and treatment and the strategy for research on HCC are required to be adjusted efficiently. Liver cancer stem cells (LCSCs) have the ability of self-renewal and multi-directional differentiation, which are considered to be the origin of HCC initiation, propagation, metastasis, relapse and chemo-resistance (3). However, the regulatory mechanism of LCSCs is still unclear. It is constructive to study the molecular mechanism of LCSCs in the pathogenesis of HCC progression. At the same time, finding new therapeutic targets regarding LCSCs is also significant. Recent studies found that long non-coding RNAs (lncRNAs), present widely in eukaryotes, are involved in the regulation of diverse physiological and pathological processes in various cancers. Some evidence has indicated that lncRNAs participate in the regulation of the occurrence and development of HCC (4), and play a role in the maintenance and differentiation of the HCC cells (5). However, there are still lots of gaps between the function and mechanism of lncRNAs in LCSCs.

We read a study carried out by Wang X *et al.* published in *Journal of Hepatology* (6), which identified the lnc-DILC (lncRNA downregulated in LCSCs) through high-throughput lncRNA microarray screening. The study not only elucidated biological function and molecular mechanism of lnc-DILC in LCSCs expansion both *in vitro* and *in vivo* experiments, but also explored the feasibility of using it as a marker and therapeutic target for HCC prognosis. The researchers found the lnc-DILC held a

suppressive role in regulating the self-renewal of LCSCs, as the deletion of lnc-DILC was shown to enhance the expansion of LCSCs while overexpression of it suppressed the propagation. Experiments *in vivo* showed that lnc-DILC could inhibit the tumorigenicity of LCSCs and the growth of xenografted tumours bearing mice. It was confirmed that lnc-DILC regulated the IL-6/STAT3 autocrine signaling pathway by binding to the IL-6 promoter to inhibit the proliferation of LCSCs, which was proved through pull-down assay. Similarly, the influences on IL-6 transcription, STAT3 activation and LCSC expansion initiated by lnc-DILC depletion or lnc-DILC overexpression could be abrogated by the oligoribonucleotide mimics and an oligodeoxynucleotide decoy of lnc-DILC. The studies also found that lnc-DILC could mediate the crosstalk between IL-6/STAT3 cascade and TNF- α /NF- κ B signaling pathway, which was an organic connection between the liver inflammatory microenvironment and LCSCs. Furthermore, their clinical studies showed that patients with low expression of lnc-DILC had significantly poorer prognosis compared to those with high expression of lnc-DILC. The researchers believed that their findings put forward a new theory of the molecular mechanism underlying LCSCs pathologic activities and the regulatory role of lncRNAs, and provided strong evidence for lncRNAs serving as new prognostic markers and therapeutic targets for HCC.

Recently, a number of studies on lncRNAs and LCSCs have been reported, most of which are correlated to the increased expression of lncRNAs in LCSCs. Lately, Wang Y *et al.* found another elevated expression lncRNA—lncRNA TCF7 in human HCC and LCSCs by transcriptome microarray, which played a significant role in promoting self-renewal and propagation of LCSCs by activating Wnt signaling pathway (7). Meanwhile, it has been reported that lncRNA HOTAIR could inhibit the expression of SETD2

through inhibiting the binding of CREB, P300 and RNA polII with the SETD2 promoter for further enhancement of the malignant growth of LCSCs (8). The study of Guo *et al.* showed that lncRNA ICR combined ICAM-1 mRNA to form an RNA complex for enhancing the stability of ICAM-1 mRNA, which promoted the stemness of ICAM-1⁺ LCSCs. The elevated expression of ICR and ICAM-1 in HCC tissues was associated with the occurrence of portal vein tumor thrombus (PVTT) and poor clinical prognosis (9). It was also found that the expression of lncRNA DANCR in LCSCs was significantly increased, and overexpression of lncRNA DANCR could enhance the stemness and tumor formation ability of HCC cells, while the knockdown of lncRNA DANCR could weaken the stemness, which was closely related to the prognosis of patients with HCC (10). At present, original discoveries and therapeutic designs towards lncRNAs in LCSCs have become a hot spot and new direction in the diagnosis and treatment of HCC. We have identified that the lncRNAs serve as key modulators in the maintenance and differentiation of LCSCs, but the molecular mechanisms and regulatory roles of lncRNAs in LCSCs are still in their infancy.

The findings of Wang X *et al.* firmly showed us the suppressive role of lnc-DILC in LCSCs propagation, and opened a new way for us to explore the mechanism and function between lncRNAs and LCSCs, which was a big step forward in the study of lncRNAs in HCC (6). In the future, lnc-DILC may not only serve as a possible prognostic marker of HCC, but also as a potential therapeutic target towards LCSCs. However, the molecular mechanism and biological effect of lncRNAs, including the regulatory suppression mechanism for lnc-DILC in LCSCs, is worth to be confirmed and clarified. Future researches are expected to combine lncRNAs with known signaling molecules, miRNAs, transcription factors and epigenetic regulatory factors in LCSCs to complete and modify the lncRNAs regulation network in LCSCs, which might as well require the developments in new theories and techniques. All these work will be helpful for a more comprehensive understanding of the occurrence and propagation of HCC. Most importantly, it can bring new directions and new targets for the diagnosis and treatment of HCC.

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