**ATOH8 Depletion Can Reprogram Non-Cancer Stem Cells into Cancer Stem Cells in Hepatocellular Carcinoma**

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**Abstract**

HCC is one of the most common solid tumors in the world with extremely poor prognosis, with the CSCs at the apex. In CSC study, one important unclear question is whether this hierarchical structure is reversible, i.e., whether a non-CSC can be reprogrammed into a CSC? In the present study, we characterized a stemness regulator, Atonal Homolog 8 (ATOH8), which was frequently down-regulated in HCC. Down-regulation of ATOH8 was significantly associated with poor outcome and differentiation of HCC. Functional study demonstrated the strongest tumor suppressive functional role of this gene. Further study found ATOH8 to efficiently repress transcription activity of stemness-associated genes. In both HCC clinical samples and HCC cell lines, absent expression of ATOH8 was frequently observed in CD133+ HCC CSCs subset. Knockdown of ATOH8 by RNAi could induce CD133+ cells into CD133+ cells, which possessed CSC properties. Therapeutically, re-introduction of ATOH8 into HCC cells can increase the chemo-sensitivity of cancer cells, which has immense potential as a novel therapy in HCC treatment.

**CD133+ cells induced by ATOH8 depletion possessed properties of CSC**

**ATOH8 increased the chemosensitivity of HCC cells.**

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**Figure 1:** A schematic representation of xenograft tumorigenesis and treatment with ATOH8-SFU and CDDP in nude mice. A 1 mm3 xenograft piece was subcutaneously implanted in 6-8 weeks old nude mice individually. When the tumor reached approximately 1 cm in diameter, the nude mice were divided into 5 groups (6 mice per group). (a) Representative images of xenograft tumors in nude mice after different treatment. The tumor growth curves of each group of mice were summarized (*, P < 0.05, **, P < 0.01, Student's t-test).