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Two Distinct Stem Cell-like Subtypes Of Resectable Hepatocellular Carcinoma With Clinical Significance And Their Therapeutic Potentials

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Background : Hepatocellular carcinoma (HCC) is among the most common cancers worldwide. Stem cell-like characteristics, which drive early recurrence and therapy resistance, contribute significantly to poor prognosis even in the early stage with resectability. Therefore, a precise adjuvant treatment strategy for high-risk patients showing stem cell-like features is mandatory in the early stage HCC after surgical resection.

Methods : We integrated and analyzed gene expression data from human fetal liver cells and primarily resectable HCC tumors (n = 1231). We uncovered two clinically and biologically distinct hepatic stem cell (HS) subtypes, potential biomarkers associated with, and a possible new therapeutic intervention for these subtypes.

Results : By analyzing single-cell gene expression data from human fetal liver cells, we identified 609-, 2538-, and 1139-gene signatures for gestational 10-week fetal liver cells, 17-week fetal liver cells, and mature hepatocytes, renamed the gene signatures specific to the 10- and 17-week cells hepatic stem cell type 1 (HS1) and hepatic stem cell type 2 (HS2), respectively. The HS1 subtype was associated with the worst overall survival, the HS2 subtype exhibited moderate overall survival, and the DH subtype exhibited the best overall survival ($P < 0.001$). The HS1 subtype showed higher rates of TP53 and RB1 mutations, while the HS2 subtype showed frequent IL6ST and CDKN2A mutations. Both HS subtypes showed high immune dysfunction with exclusion scores, suggesting that patients with either HS subtype would not benefit substantially from immunotherapy. YAP1 was highly activated in the HS1 subtype. Since YAP1 regulates HS and is associated with poor prognosis in HCC, we next examined the potential interaction of other transcription regulators with YAP1 by integrating the downstream target genes of each of the transcription regulators. JQ1 significantly reduced the viability and migration of HCC cells and tumor size in the patient-derived xenograft (PDX) mouse suggesting that JQ1 can inhibit the growth and invasion of HCC cells by suppressing YAP1.

Conclusions : Importantly, the HS1 subtype, which has a poor prognosis, appears to be sensitive to BET inhibitors. The newly identified serum markers associated with these subtypes may provide opportunities to develop marker-based clinical trials in the adjuvant setting. Furthermore, the potential marker genes we identified are well-preserved in PDX models, which shows promise for the development of accurate disease models for preclinical study.

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