Gene regulatory network analysis on snRNAseq revealed key regulators for hepatocellular carcinoma progression

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Many clinical researchers have developed targeted therapy and immunotherapy for the case of advanced stage of hepatocellular carcinoma (HCC). However, the molecular mechanisms of HCC development still need to be investigated to improve the response rate of those therapies. Here, we generated single nucleus RNA sequencing (snRNAseq) data from biopsy samples of six patients with Barcelona Clinic Liver Cancer (BCLC) advanced C stage. We first found that the gene expression heterogeneity in hepatocytes were mainly dissected by vascular invasion. To identify the key regulators of malignant progression of hepatocytes, we applied TENET, a gene regulatory network (GRN) inference tool based on pseudotime-ordered single cell expression. TENET predicts that MLXIPL and CUX1 are the top two regulators and regulate each other. This finding was comprehensively validated by overexpression and knockdown of those two regulators in various HCC cell lines. This study suggested that GRN analysis with single cell transcriptomics may provide new therapeutic targets for HCC.