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Supporting Information

Single Cell Transcriptome Analysis

Uncovers Intra-tumoral Heterogeneity and

Underlying Mechanisms for Drug Resistance in

Hepatobiliary Tumor Organoids

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Supplementary Figure.1
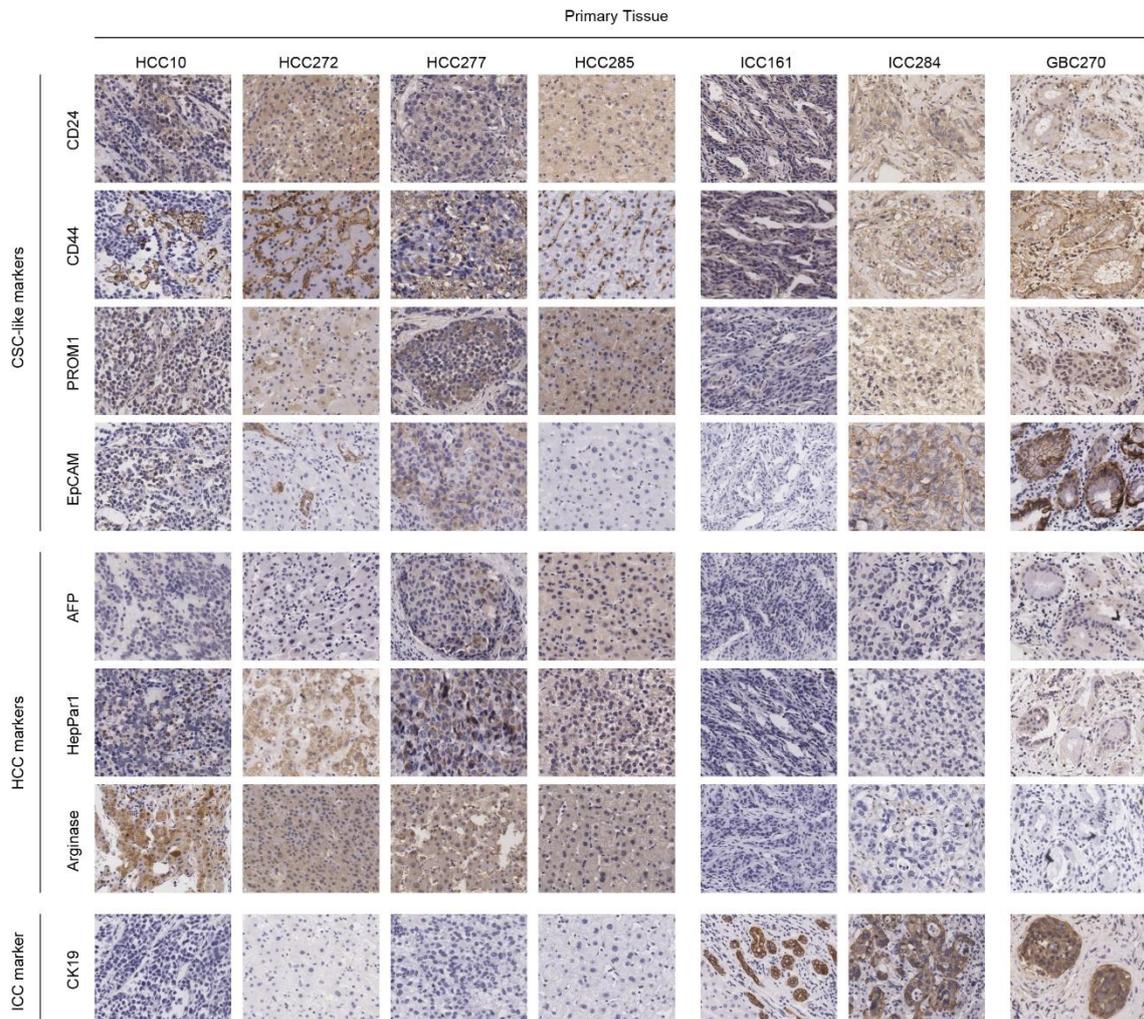
Supplementary Figure.1. Expression of CSCs-like markers and specific tumoral markers in hepatobiliary tumor tissues.

Expression of CSCs-like markers implied the CSCs heterogeneity within different hepatobiliary tumor. Particularly, *CD44*-positive cells were significantly increased in HCC272, which is consistent with analysis from scRNA-seq. In addition, diverse tumor subtypes were identified distinctly with specific expression of corresponding tumoral markers.

Supplementary Figure.2
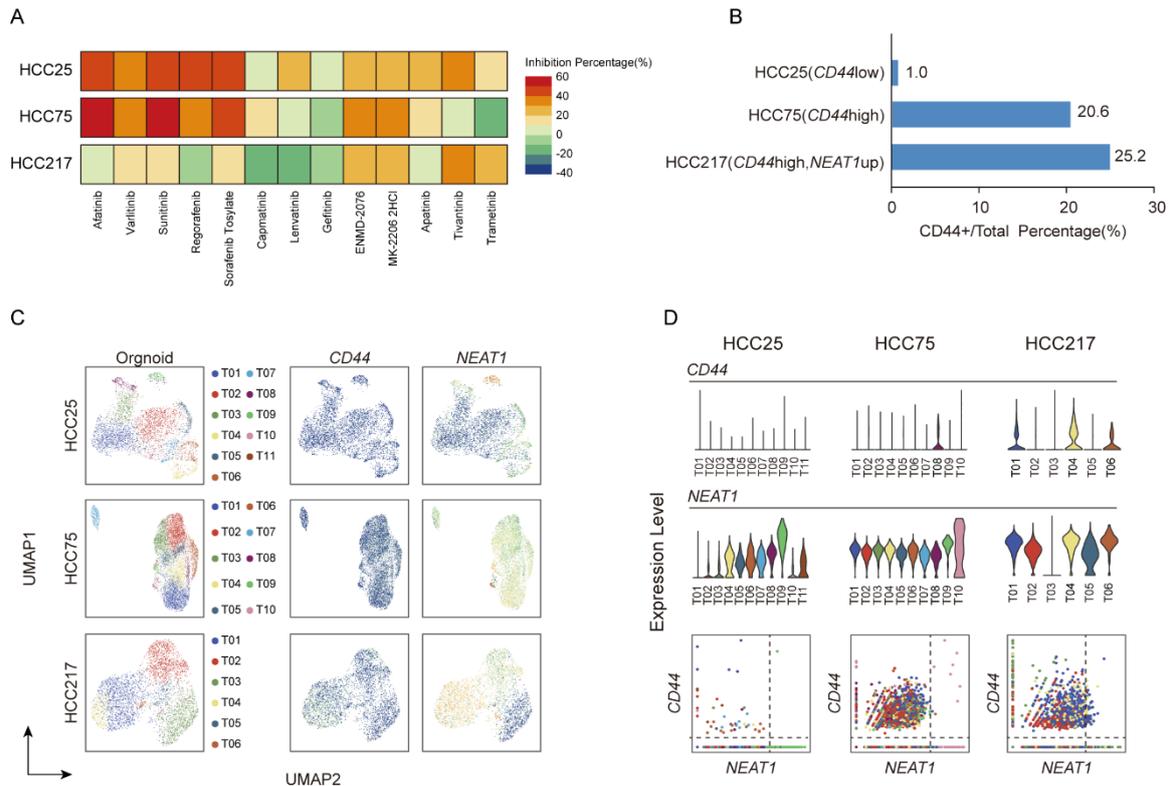
Supplementary Figure.2. *CD44* **and** *NEAT1* **common expressed in one cluster may confer to the resistant phenotype in HCC217.**

(A) Heatmap shows inhibition ratio of 13 drugs in 3 organoid lines. Detailed drug information was listed in Supplementary Table 3. Data were presented as mean of multiple independently repeated inhibition ratios.

(B) Bar plot shows the proportion of *CD44*$^+$ cells in individual organoids.

(C) UMAP plot of all the single cells in individual organoids, and cells marked by *CD44* and *NEAT1* in each organoid. Color key from blue to yellow indicates relative expression levels from low to high.

(D) Violin plots and scatterplots depict the expression of *CD44* and *NEAT1* within clusters in each organoid.