Hierarchical cluster analysis of integrated gene expression data from hepatic progenitor cells

Panel A. Dendrogram and heat-map overview of the two-way hierarchical cluster analysis of gene expression data from 109 samples (9 rat samples from fetal hepatoblasts (HB) and adult hepatocytes (HC), 39 mouse hepatocellular carcinomas (HCC) from 5 different mouse models, and 61 HCC from Chinese individuals), using 80 orthologous genes. Columns represent individual samples and rows represent each gene. Each cell in the matrix represents the expression level of a gene feature in an individual sample. Red and green in cells reflect high and low expression levels, respectively, as indicated in the scale bar (log2-transformed scale). Colored bars between dendrogram and heat-map represent rat, mouse, and human samples, as indicated at the bottom of diagram.

Panel B. Kaplan-Meier plot of overall survival of individuals with the HB and HC subtypes of HCC from hierarchical clustering analysis of integrated gene expression data. P = 0.001, log-rank test. +, censored data. By applying two independent gene expression signatures, it was possible to divide individuals with HCC into three subgroups characterized by statistically significant differences in clinical outcome. These findings support the notion that multiple molecular pathways dictate development and different clinical outcomes of HCC.

Abstract: The variability in the prognosis of individuals with hepatocellular carcinoma (HCC) suggests that HCC may comprise several distinct biological phenotypes. These phenotypes may result from activation of different oncogetic pathways during tumorigenesis and/or from a different cell of origin. We addressed whether the transcriptional characteristics of HCC can provide insight into the cellular origin of the tumor. We integrated gene expression data from rat fetal hepatoblasts and adult hepatocytes with HCC from human and mouse models. Individuals with HCC who shared a gene expression pattern with fetal hepatoblasts had a poor prognosis. The gene expression program that distinguished this subtype from other types of HCC included markers of hepatic oval cells, suggesting that HCC of this subtype may arise from hepatic progenitor cells. Analyses of gene networks showed that activation of AP-1 transcription factors in this newly identified HCC subtype might have key roles in tumor development.

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