Investigation and Distinction of Energy Metabolism in Proliferating Hepatocytes and Hepatocellular Carcinoma Cells

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Abstract

Metabolic rewiring is a hallmark of both hepatic regeneration and malignant transformation, complicating the identification of cancer-specific traits. This study aimed to distinguish the metabolic profiles of proliferating hepatocytes and hepatocellular carcinoma (HCC) cells through integrated analyses of mRNA and protein expression, along with functional characterization. We compared non-malignant Upcyte® hepatocytes (HepaFH3) cultured under proliferative and confluent conditions with primary human hepatocytes, primary human hepatoma cells, and hepatoma cell lines. Proliferating HepaFH3 cells exhibited features of metabolic reprogramming, including elevated glycolysis, increased HIF1A expression, and ketone body accumulation, while maintaining low c-MYC expression and reduced BDH1 levels, distinguishing them from malignant models. In contrast, HCC cells showed upregulation of HK2, c-MYC, and BDH1, reflecting a shift toward aggressive glycolytic and ketolytic metabolism. Functional assays supported the transcript and protein expression data, demonstrating increased glucose uptake, elevated lactate secretion, and reduced glycogen storage in both proliferating and malignant cells. These findings reveal that cancer-like metabolic changes also occur during hepatic regeneration, limiting the diagnostic utility of individual metabolic markers. HepaFH3 cells thus provide a physiologically relevant in vitro model to study regeneration-associated metabolic adaptation and may offer insights that contribute to distinguishing regenerative from malignant processes. Our findings highlight the potential of integrated metabolic profiling in differentiating proliferation from tumorigenesis.