Phenotypic diversity spanning the spectrum of hepatocyte differentiation impacts the outcome of patients with β-catenin-mutated hepatocellular carcinomas.

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Background: Hepatocellular carcinomas (HCCs) are heterogeneous tumors that display a spectrum of molecular phenotypes. Non-proliferative, well-differentiated HCCs have favorable outcomes, preserve metabolic liver zonation programs and include two mutually exclusive subclasses: Periportal-type (wild-type β-catenin) and Perivenous-type (mutant β-catenin). Periportal-type HCCs have the lowest potential for early recurrence (<2 year). Periportal-type, extracellular matrix- and stem-type HCCs are characterized by the presence of stem/progenitor-like cells. Periportal-type HCCs can be further divided into two mutually exclusive subclasses: Hepatocyte-like (wild-type β-catenin) and Hepatocyte-like-like (mutant β-catenin). Hepatocyte-like-like HCCs have the lowest potential for early recurrence (<2 year).

Methods: First, to confirm the specificity of our previous 5-gene score used to predict CTNNB1 mutations (Hepatology 2017, doi:10.1002/hep.29524), we retrospectively transduced mutant (T41A) CTNNB1 to well-differentiated, hepatocyte-like human HCC cells (HepaRG cell line). Then, we predicted CTNNB1 mutations in a 242-HCC transcriptomic dataset (GSE14520) and analyzed 12509 genes by Cox-PLS combined to genetic algorithms to allow feature selection. Cell proliferation was assessed in an independent series of 72 CTNNB1-Sanger-sequenced HCCs by immunohistochemistry for MKI67. Results: HepaRG cells expressing mutated CTNNB1 confirmed the specificity of the mutation markers GLUL, LGR5, HAL, VNN1 and ODAM. Analysis of 72 HCCs showed that cell proliferation rates were low in tumors with mutated CTNNB1 (Sanger-sequenced or predicted) or with high GLUL staining. As expected, high cell proliferation was associated with HCC recurrence (p = 0.007). However, neither GLUL staining nor CTNNB1 mutation rates were associated with recurrence in 242-HCC dataset, CTNNB1 was predicted to be mutated in 63 and wild-type in 179 tumors. Discriminant analyses revealed the phenotypic diversity of HCCs with mutated CTNNB1, which ranged from well-differentiated tumors with hepatocyte-like features to HCCs expressing a stem/progenitor-like cell program. Thus, HCCs with mutated CTNNB1 could develop substantial cancer stem/progenitor cell subpopulations overtime.

Conclusions: Albeit non-proliferative, HCCs with mutant CTNNB1 may evolve toward an undifferentiated phenotype with bad outcome, which justifies early HCC detection.

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