

225

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 (< 2 year) recurrence. At the opposite, proliferative HCCs include *Extracellular Matrix-* and *STEM-type* HCCs with bad outcomes. *Periportal-*, *Extracellular Matrix-* and *STEM-type* HCCs distribute across a spectrum which ranges from hepatocyte-like to stem/progenitor-like phenotypes. In contrast, *Perivenous-type* HCCs deviate from that spectrum because they express β -catenin (*CTNNB1*) target genes (Hepatology 2017, doi:10.1002/hep.29254). Thus, it is not clear how phenotypic diversity contributes to cancer aggressiveness in *Perivenous-type* HCCs. **Aim:** To explore the impact of phenotypic diversity in the outcome of *Perivenous-type* HCCs. **Methods:** First, to confirm the specificity of our previous 5-gene score used to predict *CTNNB1* mutations (Hepatology 2017, doi:10.1002/hep.29254), we retrovirally 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 the 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.

Disclosures:

The following people have nothing to disclose: Romain Desert, Christelle Reynès, Robert Sabatier, Damien Grégoire, Florian Rohart, Frédéric Canal, Marie Sicard, Mireille Desille, Stephanie Renaud, Bruno Turlin, Laurent Sulpice, Damien Bergeat, Bruno Clement, Kim-Anh Lê Cao, Orlando Musso

226

The incidence of hepatocellular carcinoma is not increased in individuals with chronic hepatitis C after SVR with interferon-free regimens compared with interferon-containing regimens: an ERCHIVES study

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Background: Sustained virologic response (SVR) after interferon-based treatment for chronic hepatitis C virus (HCV) infection has been strongly associated with decreased incidence of hepatocellular carcinoma (HCC). Surprisingly, several recent studies have reported higher rates of HCC in individuals treated with direct-acting antivirals (DAAs). However, making definitive conclusions has been challenging due to the heterogeneous populations and methodologies of these reports. We sought to determine whether DAA use is associated with increased rates of incident HCC in our large, well-characterized cohort. **Methods:** Using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database, we identified 17,836 patients with chronic HCV and did not have a prior diagnosis of HCC. Patients were divided into 3 groups based on treatment: (a) pegylated interferon + ribavirin (IFN) (n=3,534); (b) DAA-only (n=5,829); and (c) no treatment (n=8,643). Additional analyses were performed on subgroups of DAA-only treatment, including sofosbuvir/simeprevir (SOF/SMV) and sofosbuvir/ledipasvir (SOF/LDV). Predictors of HCC were identified using multivariate Cox proportional hazards analysis. HCC-free survival in cirrhotics was assessed by Kaplan-Meier analysis. **Results:** SVR was achieved by 66.6% and 96.2% of the IFN and DAA groups, respectively. Among all treated patients, the risk of HCC was not higher in the DAA group compared to the IFN group (HR 1.16; [95% CI: 0.79, 1.71]). Among cirrhotics who achieved SVR, neither the HCC incidence rate nor HCC-free survival were significantly different in the DAA group compared to the IFN group (21.2 vs. 22.8 per 1000 patient years; $p=0.78$; and log-rank $p=0.17$, respectively). Untreated cirrhotics had a significantly higher HCC incidence rate (45.3 per 1000 patient years) compared to those treated with IFN or DAAs ($p = 0.03$). Further, both groups of treated patients had significantly longer HCC-free survival compared to untreated