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Transcriptional reprograming that persists after clearance of oncogenic hepatitis C virus

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Background: The risk of HCV-related HCC development persists even after sustained virologic response (SVR) to antiviral therapies. Clinical studies have suggested that naturally occurring mutations in HCV genome are associated with post-SVR HCC. In our previous study, the oncogenic HCV clones induced cancer-related molecular pathways in differentiated hepatocyte-like cells (J Hepatol 63;1323,2015). However, underlying molecular mechanisms are still unknown.
Objectives: Identify persistent transcriptional dysregulation after clearance of the oncogenic HCV strains in cell-based model.
Methods: Differentiated matured hepatocyte-like cells were infected with the oncogenic HCV or wild-type clone. After establishment of infection, cells were treated with direct-acting antivirals (DAAs) or DMSO. After cessation of the DAA treatment, the drugs were washed out. Residual HCV was determined by HCV RNA quantification with qPCR , NS5A protein quantification with flow cytometry, and tissue culture infectious dose 50 assay (TCID50) for infectivity. Modulation of our previously reported HCC risk gene signature was measured.
Results: In the DAA-treated cells after the washout period, HCV RNA levels reduced to approximately 5%, and NS5A positive cells were reduced to <0.5%. TCID50 was undetectable, indicating that HCV was completely cleared and there was residual virus with replication and infection capability. Analysis of the HCC risk signature has revealed that a subset of genes in the signature were persistently upregulated or downregulated even after the washout of DAAs, suggesting that the genes represent the molecular dysregulation driving post-SVR carcinogenesis.
Conclusions: Our cell-based analysis suggested possible drivers of post-SVR HCC.