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## Transcriptional reprogramming that persists after clearance of oncogenic hepatitis C virus

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## Transcriptional reprogramming 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.