# Supplementary Tables

**Table S1.** Lipid composition of HCV particles obtained fromScholtes et al[1](#_ENREF_1).

**Table S2.** Antimetabolites that inhibit HCV assembly and validations from the literature.

**Table S3.** Metabolites that were removed from the model before running the Reporter Subnetwork algorithm.

# Supplementary Figures

**Figure S1. Systems biology approaches are used to study the interactions between hepatocytes and HCV.** (A)Diagram describing how HCV particles are assembled from *iHepatocytes2322* resources. The black and gray arrows represent *iHepatocytes2322* and *iHCV* reactions, respectively. AAs, amino acids; DAG, diacylglycerolipids; NNs, DNA and RNA nucleotides; LPA, lysophosphatidic acid; NS5B, HCV RNA polymerase; PA, phosphatidate; TAG, triglycerolipid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; and SM, sphingomyelin. (B) Diagram describing the antimetabolite algorithm for a metabolite *m1*. The FBA maximizes the HCV assembly reaction where the flux values (*v1 … v6*) for all reactions (*R1...R6*) involving *m1* are constrained to zero. (C) Diagram describing the Reporter Metabolite algorithm for metabolite *m1*. The *Z* score was calculated from the adjusted *P*-value (*q1 … q6*) for each gene associated with reactions *R1... R6*. (D) Diagram describing the Reporter Subnetwork algorithm. The reaction graph is extracted from the GEM, where the nodes are reactions and the edges describe two nodes that share at least one metabolite. The reactions *R1...R6* are fully connected because they share the metabolite *m1*. The *Zscore (Z1 … Z8)* was calculated for each reaction from its *q*-value for genes associated with these reactions. The Reporter Subnetwork analysis identifies highly scored subnetworks in a connective manner (*R1*, *R6* and *R7*) using a simulated annealing algorithm.

**Figure S2. Acyl-carnitine metabolites are significantly changed in the dysplastic nodule and early HCC stages.** The colored area represents the negative logarithm of the *P*-value of a reported metabolite.

**Figure S3. DNA methylation probes for the *BBOX1* and *BCAT1* genes with delta beta values = 0.1 (adjusted *P*-value < 0.05).** Red and green circles are the average beta values for probes across all of the cancer and normal TCGA samples, respectively. Blue and gray rectangles indicate that the probe is in the promoter region and gene body region, respectively. The bold black line in the rectangle indicates that this probe is a CpG island.

**Figure S4. Oncoprint for the *ASH1L*, *METTL13*, *SMYD2*, *TARBP1,* *SMYD3*, *GNPAT* and *PPOX* genes obtained from cBioPortal[2](#_ENREF_2" \o "Gao, 2013 #111)** (see the link:<http://www.cbioportal.org/index.do?cancer_study_list=lihc_tcga&cancer_study_id=lihc_tcga&genetic_profile_ids_PROFILE_MUTATION_EXTENDED=lihc_tcga_mutations&genetic_profile_ids_PROFILE_COPY_NUMBER_ALTERATION=lihc_tcga_gistic&genetic_profile_ids_PROFILE_MRNA_EXPRESSION=lihc_tcga_rna_seq_v2_mrna_median_Zscores&Z_SCORE_THRESHOLD=2.0&data_priority=0&case_set_id=lihc_tcga_log2CNA&case_ids=&patient_case_select=sample&gene_set_choice=user-defined-list&gene_list=GNPAT%0D%0APPOX%0D%0AASH1L%0D%0AMETTL13%0D%0ASMYD2%0D%0ATARBP1%0D%0ASMYD3%0D%0A%0D%0A%0D%0A%0D%0A%0D%0A%0D%0A%0D%0A%0D%0A&clinical_param_selection=null&tab_index=tab_visualize&Action=Submit>**)**

**Figure S5. Oxidative stress reactions and the role of SLC7A6 in transporting amino acids and citrate to the cell are integrated with gene expression in early HCC.** (A) Oxidative stress reactions were reported in the Reporter Subnetwork analysis of the early HCC stage. **(B)** Biosynthesis of TCA metabolites from extracellular citrate using *SLC7A6*.Blue, red and black arrows indicate that the gene(s) associated with this reaction are downregulated, upregulated and unregulated (adjusted *P*-value > 0.05), respectively. The reaction is also unregulated if it involves both upregulated and downregulated genes.

SupplementaryData

**Supplementary Data 1.** Zip file containing the model *iHepatocytes2322* with *iHCV* in Excel and XML formats and the MATLAB code used to run the antimetabolite analysis.

**Supplementary Data 2.** Reported metabolic GO terms in the four stages: cirrhosis, dysplastic nodule, early HCC, and advanced HCC.

**Supplementary Data 3.** R code used to analyze the CNVs, DNA methylation and microRNA samples from TCGA. The DNA methylation code is adopted from Phipson and Oshlack.[3](#_ENREF_3)

**Supplementary Data 4.** Description of TCGA samples used in the CNV, DNA methylation and microRNA analyses.

**Supplementary Data 5.** Reported metabolites in the four stages: cirrhosis, dysplastic nodule, early HCC, and advanced HCC.

**Supplementary Data 6.** Zip file containing the XML description for thehighly scored subnetworks in the four stages: cirrhosis, dysplastic nodule, early HCC, and advanced HCC. The unzipped files can be opened with Cytoscape.

**Supplementary Data 7.** Integration of the reactions involved in the highly scored subnetworks in early HCC with CNV and the gene expression profiles.

**Supplementary Data 8.** Integration of the reactions involved in the carnitine shuttle with the gene expression profiles.

**Supplementary Data 9.** Integration of the reactions containing AKG in the model with the gene expression profiles.

**Supplementary Data 10.** Integration of the reactions containing SAH in the model with the gene expression profiles.

**Supplementary Data 11.** Gene expression of the NADPH oxidase genes.

**Supplementary Data 12.** Integration of the gene expression profiles with the reactions associated with SLC7A6 and all of the reactions reported in the figures.

**Supplementary Data 13.** List of Ensembl genes reported in the proteomic HCV study[4](#_ENREF_4).

**Supplementary Data 14.** Zip file containing the source code for our MATLAB GUI.

**References**

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2. J. Gao, B. A. Aksoy, U. Dogrusoz, G. Dresdner, B. Gross, S. O. Sumer, Y. Sun, A. Jacobsen, R. Sinha, E. Larsson, E. Cerami, C. Sander and N. Schultz, *Science Signaling*, 2013, **6**, pl1-pl1.

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4. D. L. Diamond, J. M. Jacobs, B. Paeper, S. C. Proll, M. A. Gritsenko, R. L. Carithers, A. M. Larson, M. M. Yeh, D. G. Camp, R. D. Smith and M. G. Katze, *Hepatology*, 2007, **46**, 649-657.