Supplemental data.

Slu7 is essential for liver differentiation, metabolism and quiescence.

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Inventory of Supplemental Data

Methods.

Tissue samples.

Samples from cirrhotic livers (6 from patients with chronic hepatitis C virus infection and 6 from alcoholic patients) and HCC tissues were from individuals undergoing partial hepatectomy or liver transplantation. Healthy liver tissue was obtained from individuals with normal or minimal changes in the liver. Samples were collected at surgery of digestive tumors or from percutaneous liver biopsy performed because of mild alterations of liver function. Patients were recruited according to our national and institutional guidelines.

Cell culture and transfections.

The human HCC cell lines PLC/PRF/5, HepG2 and Hep3B, and HepaRG cells, were cultured as described (1, 2). HepaRG cells were from BioPredic (Rennes, France). pEGFP-SLU7 expression vector was generously provided by Dr. Ast (Department of Human Molecular Genetics & Biochemistry, Sackler Medical School, Tel Aviv University, Tel Aviv, Israel) (3). pCB6-HNF4 expression vector was generously provided by Dr. Weiss (Institut Pasteur, Paris, France). Transfections of pEGFP-SLU7, pCB6-HNF4, and pCB6 and pEGFP empty plasmids were performed with Lipofectamine 2000 from Invitrogen. Mouse hepatocytes were isolated as described (4).

Microarray hybridization

Cells transfected with siGL or siSLU7 in triplicates were harvested with TRIzol Reagent (Invitrogen) and the RNA was extracted according to the manufacturer's instructions. As a last step of the extraction procedure, the RNA was purified with the RNeasy Mini-kit (Qiagen, Hilden, Germany). Before cDNA synthesis, RNA integrity from each sample was confirmed on Agilent RNA Nano LabChips (Agilent Technologies).

The sense cDNA was prepared from 300 ng of total RNA using the Ambion® WT Expression Kit. The sense strand cDNA was then fragmented and biotinylated with the Affymetrix GeneChip® WT Terminal Labeling Kit (PN 900671). Labeled sense cDNA was hybridized to the Affymetrix Human Exon 1.0 ST microarray according

to the manufacturer protocols and using GeneChip® Hybridization, Wash and Stain Kit. Genechips were scanned with the Affymetrix GeneChip® Scanner 3000. Data were deposited at the Gene Expression Omnibus with accession number GSE54090.

Gene expression data analysis

The probeset-level analysis was carried out using only the subset of core probe sets from the Exon Array corresponding to the most confident ones (18708 probe sets). Both background correction and normalization were done using RMA (Robust Multichip Average) algorithm (5). Then, a filtering process was performed to eliminate low expression probe sets. Applying the criterion of an expression value greater than 64 in at least 2 samples for each experimental condition (siGL, siSLU7), 11834 probe sets were selected for further analysis. R/Bioconductor {Gentleman:2006vy} was used for preprocessing and statistical analysis. LIMMA (Linear Models for Microarray Data) (6) was used to find out the probe sets that showed significant differential expression between experimental conditions. Genes were selected as significant using a criteria of B>0.

Alternative splicing (AS) data analysis

AltAnalyze (7) was run with default parameters in order to identify alternative exons. Briefly, this analysis consists in expression summarization of microarrays with RMA, low level probe set filtering and alternative exon analysis statistics calculation (splicing-index and MiDAS (8)). After RMA normalization and gene expression statistics analysis, AltAnalyze filters probe sets to identify those that align to a single Ensembl gene and that match user defined expression and DABG p-value thresholds. Using the splicing index (SI) method (9), AltAnalyze calculates the likelihood of AS for all Ensembl genes with one or more constitutive probe sets. Two probability estimates for alternative exon regulation are calculated, MiDAS and SI, by performing a t-test of the normalized exon expression values (exon probe set expression divided by constitutive expression) between siGL and siSLU7 sample groups. The filters for identifying alternative exons were a SI fold change of 0.1, SI p-value = 0.05 and MiDAS p-value=0.05.

Functional and pathway analysis

Functional enrichment analysis of Gene Ontology (GO) categories was carried out using standard hypergeometric test (10). The biological knowledge extraction was complemented through the use of Ingenuity Pathway Analysis (Ingenuity Systems, www.ingenuity.com), which database includes manually curated and fully traceable data derived from literature sources.

Immunohistochemical stainings.

Immunohistochemical detection of SLU7 and Ki67 in paraffin-embedded mouse liver tissues was carried out using a rabbit polyclonal antibody against SLU7 (Santa Cruz) and a rabbit monoclonal antibody against Ki67 (Thermo Scientific).

RNA isolation and PCR.

Total RNA from liver tissue and cell lines was extracted using the automated Maxwell system from Promega. Reverse transcription was performed as described (1). Multiplex PCR of SRSF3 was carried out as reported (11). Real time PCRs were performed with iQ SYBR Green supermix (BioRad) in a CFX96 system from BioRad as previously described (1). Gene expression was normalized relative to that of the housekeeping genes RPLP0 or β-ACTIN as described (1). Primers used in the study are listed in Table S3. When possible primers were designed on conserved sequences in mouse and human.

Western blot and chromatin immunoprecipitation (ChIP) analyses.

HCC cells and liver tissues were lysed and homogenates were subjected to Western blot analysis as reported (1). For ChIP assay PLC/PRF/5 cells were transfected with siSLU7 and siGL duplexes and after 48 h were treatment for 30 minutes with 10 μ M forskolin. For crosslinking of DNA and proteins cells were treated with 1% formaldehyde for 10 min before quenching with 0.125M glycine. Cells were harvested in ice-cold PBS with proteases inhibitors. Cells were pelleted and disrupted using a potter homogenizer in lysis buffer (3 mM MgCl2, 10 mM NaCl, 10 mM Tris-HCl pH 7.4, 0.1 % NP40). Nuclei were collected by centrifugation at 5000 rpm during 5 min and then resuspended in Nuclear Extraction Buffer (50 mM Tris-HCl pH 8.1, 10 mM EDTA, 1% SDS). Lysates were sonicated on ice to yield 200-800

bp DNA fragments. After centrifugation at 14000 rpm for 10 min, supernatant was collected and frozen at -80°C to obtain the chromatin. One mg of protein were used per IP, pre-cleared with magnetic beads (Dynabeads, Invitrogen) for two hours, then diluted 1/4 in IP dilution buffer (0.01 % SDS, 1.1 % Triton-X100, 1.2 mM EDTA, 16.7 mM Tris-HCl pH 8.1, 167 mM NaCl) and incubated overnight at 4°C with 5 μg of either SLU7 (BD), CBP and RNA polymerase II antibodies or 5 μg nonspecific IgGs (Table S4). Immuno-complexes were precipitated by incubation for 2 hours with protein G-conjugated magnetic beads. Immunoprecipitates were washed sequentially with IP wash buffer II (1% Triton, 2 mM EDTA, 20 mM Tris pH 8.1, 500 mM NaCl), wash buffer III (0.25 M LiCl, 1% NP40, 1% Na-Deoxycholate, 1 mM EDTA, 10 mM Tris pH 8.1) and TE before eluting in 1% SDS/0.1 M NaHCO3. Cross-linking was reversed by heating to 65°C for 4 hours and treating with proteinase K for 1 h at 45°C. Finally, DNA was purified by phenol/chloroform extraction. PEPCK and NR4A2 proximal promoter regions were amplified using specific primers (Supplementary Table 3). Independent ChIP assays were performed at least two times in duplicates.

Co-immunopreciptitation.

For co-immunoprecipitation PLC cells were lysed with cold 1% Nonidet P-40 lysis buffer as described (12) and incubated with anti-SLU7 (BD) or IgG chemically coupled to protein G Dynabeads. Western blots for RNA pol II, CBP, SLU7, pCREB were performed as described above.

References

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Supplementary figures

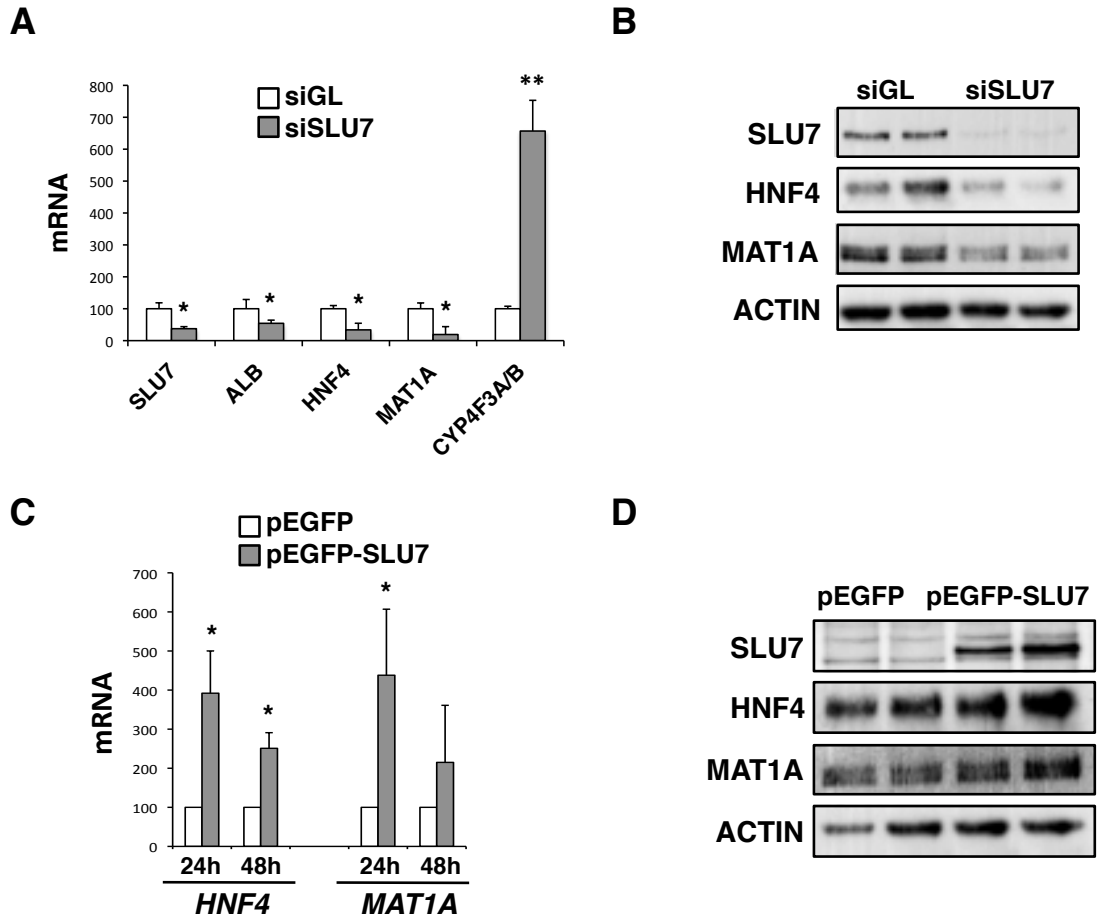

Figure S1. *Slu7 modulates the expression of adult and fetal markers in HepG2 cells*. (**A**) qPCR analysis of the expression of adult (albumin, *HNF4*, *MAT1A*) and fetal (*CYP4F3A/B* splice variants ratio) marker genes in HepG2 cells transfected with control (siGL) or SLU7-specific (siSLU7) siRNAs. * $P<0.05$, ** $P<0.01$ *vs* siGL. (**B**) Representative western blot analyses of SLU7, HNF4α and MAT1A protein levels in HepG2 cells transfected with siGL or siSLU7 siRNAs. (**C**) qPCR analysis of the expression of *HNF4α* and *MAT1A* genes in HepG2 cells transfected with control (pEGFP) and SLU7 (pEGFP-SLU7) expression vectors. * $P<0.05$ *vs* cells transfected with control vector pEGFP. (**D**) Representative western blot analyses of SLU7, HNF4α and MAT1A protein levels in HepG2 cells transfected with control (pEGFP) and SLU7 (pEGFP-SLU7) expression vectors. Actin protein levels are shown as loading and specificity control.

A

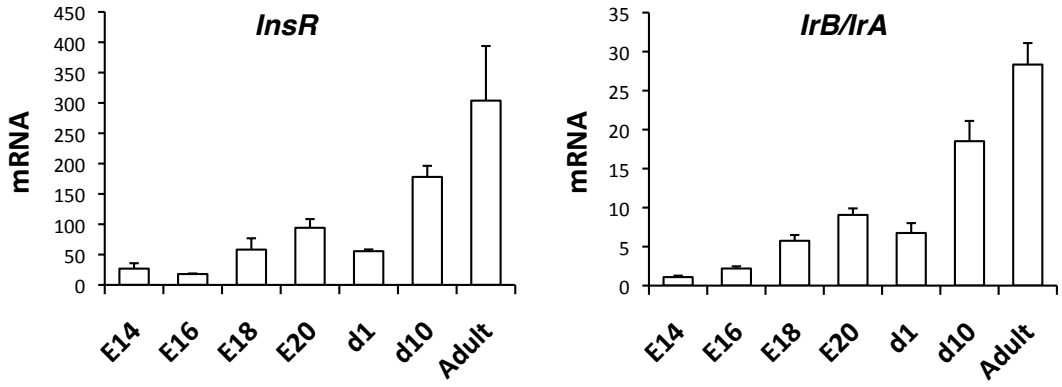

Figure S2. *The expression of insulin receptor is developmentally regulated in mouse liver*. qPCR analysis of the expression of the insulin receptor (*InsR*) and the ratio of the splicing isoforms *IrB/IrA* in fetal and postnatal mouse liver at the indicated developmental stages and post-partum days.

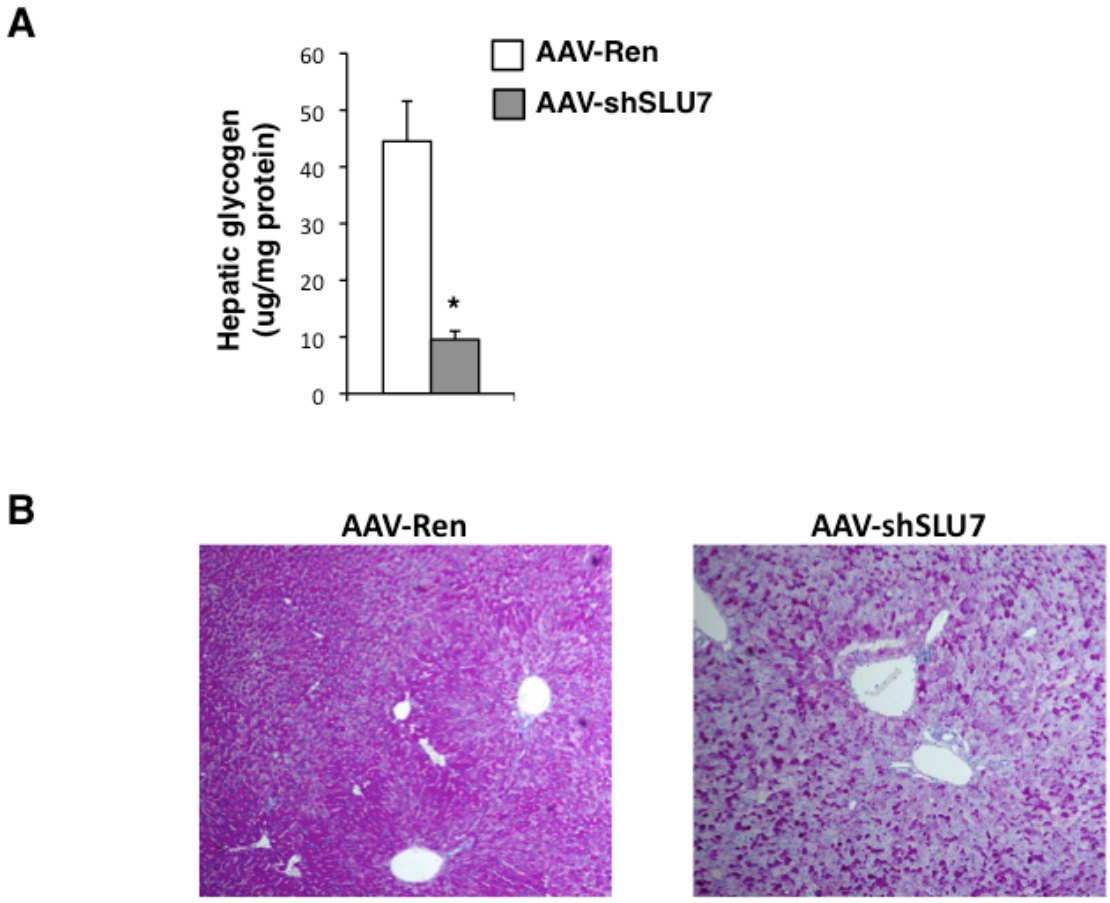

Figure S3. *Slu7 depletion in mouse liver results in reduced intrahepatic glycogen stores*. (**A**) Biochemical quantification of hepatic glycogen levels in mice infected with control (AAV-Ren) or *Slu7* targeting (AAV-shSLU7) adeno-associated viruses. (**B**) Representative periodic acid-Schiff (PAS) staining for glycogen in liver sections from mice infected with control (AAV-Ren) or *Slu7* targeting (AAV-shSLU7) adeno-associated viruses.

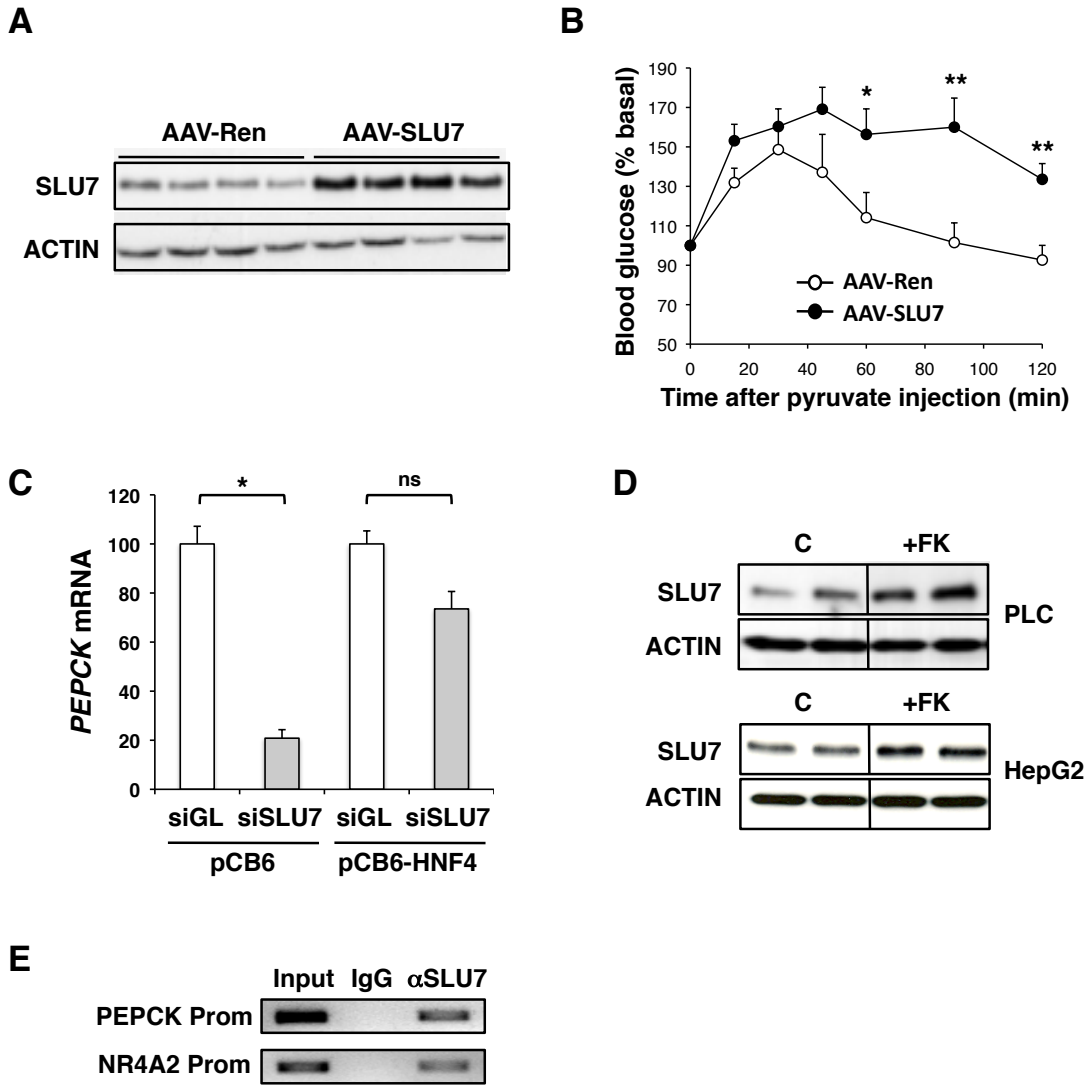

Figure S4. (**A**) AAV-mediated overexpression of SLU7 in mouse liver. Representative blot showing SLU7 protein levels in livers from mice infected with control AAV (AAV-Ren) and SLU7-expressing AAV (AAV-SLU7). (**B**) Hepatic glucose production after pyruvate challenge in AAV-Ren and AAV-SLU7 mice. * P<0.05, ** P<0.01 *vs* AAV-Ren. (**C**) *HNF4α* overexpression attenuates the effect of SLU7 knockdown on *PEPCK* mRNA levels. HepaRG cells were initially transfected with control (siGL) or SLU7-specific (siSLU7) siRNAs, 24 h afterwards cells were transfected with control (pCB6) or HNF4α expressing (pCB6-HNF4) vectors. *PEPCK* mRNA levels were analyzed by qPCR 24 h after the second transfection. * P<0.05 *vs* siGL/pCB6 control. (**D**) SLU7 expression is induced upon forskolin treatment. PLC/PRF/5 and HepG2 cells were treated for 4 hours with 10μM forskolin (FK) and SLU7 and actin expression was assayed by western blot. The lanes were run in the same gel but were non-contiguous. (**E**) ChIP assay of the binding of SLU7 to the *PEPCK* and *NR4A2* promoters in PLC/PRF/5 cells. PCR-amplified DNA fragments corresponding to the *PEPCK* and *NR4A2* gene promoters were resolved in agarose gels.

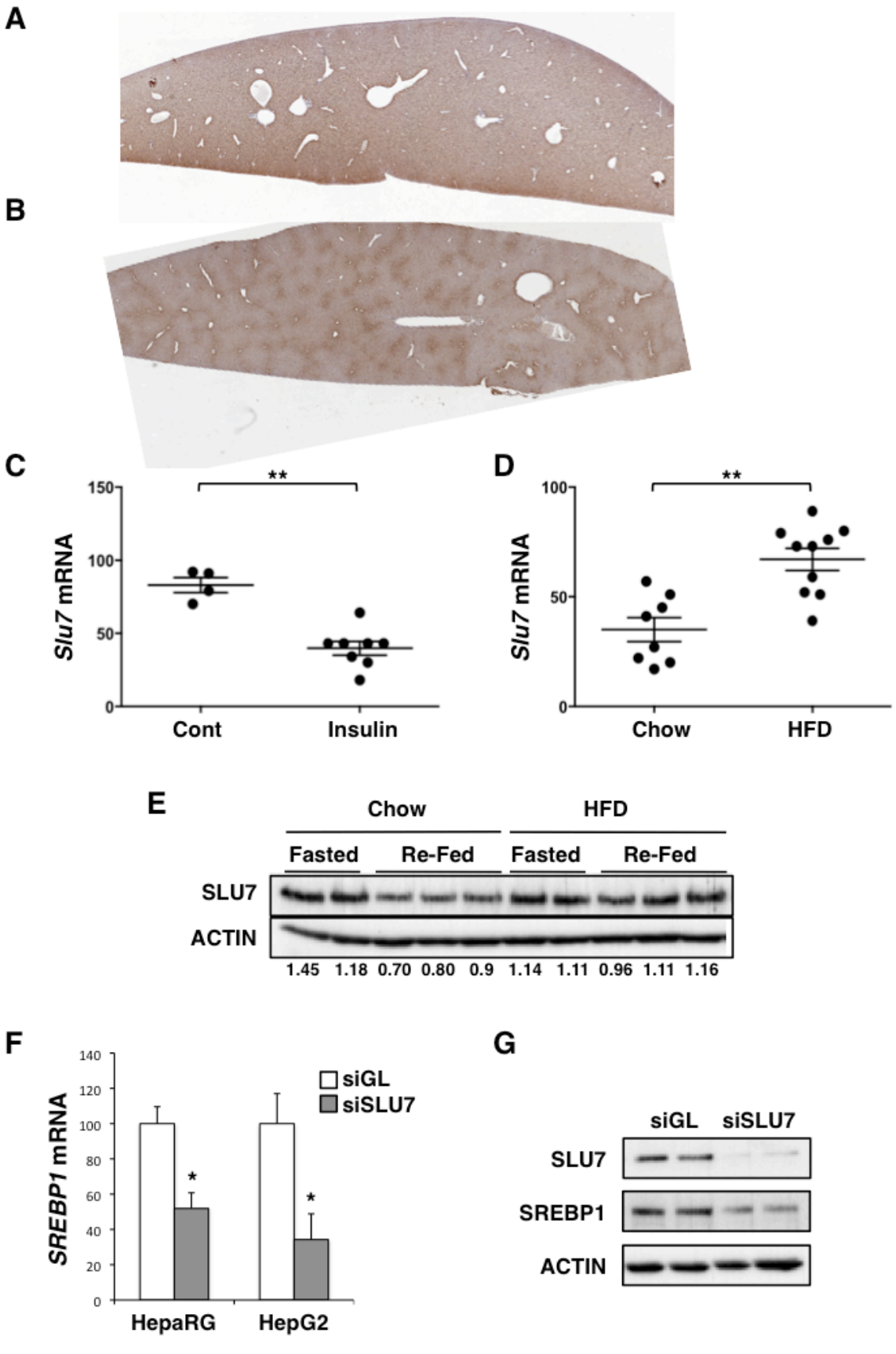
A
B
C
Slu7 mRNA
150
100
50
0
**
Cont
Insulin
D
Slu7 mRNA
100
50
0
**
Chow
HFD
E
Chow
HFD
Fasted
Re-Fed
Fasted
Re-Fed
SLU7
ACTIN
1.45 1.18 0.70 0.80 0.9 1.14 1.11 0.96 1.11 1.16
F
SREBP1 mRNA
140
120
100
80
60
40
20
0
siGL
siSLU7
*
*
HepaRG
HepG2
G
siGL
siSLU7
SLU7
SREBP1
ACTIN

Figure S5. Representative immunostainings of SLU7 in liver sections from fed (**A**) and 12 h fasted (**B**) mice. (**C**) Effect of insulin treatment (1 nM, 12 h) on the expression of *Slu7* in primary cultured mouse hepatocytes as analyzed by qPCR. ** $P<0.01$ *vs* control. (**D**) qPCR analysis of *Slu7* gene expression in the liver of mice fed a control diet (Chow) or a high fat diet (HFD). ** $P<0.01$ *vs* Chow diet. (**E**) *SLU7* protein levels in the livers of mice fed a control diet (Chow) or a high fat diet (HFD) for 5 months, and then either fasted for 12 h or fasted and subsequently re-fed for 4 h. Representative western blots are shown. Numbers indicate the densitometric quantification of the bands using actin signal as internal control. (**F**) qPCR analysis of *SREBP1* gene expression in HepaRG and HepG2 cells 48 h after transfection with control (siGL) or SLU7-specific (siSLU7) siRNAs. * $P<0.05$ *vs* siGL. (**G**) Representative western blot analysis of SLU7 and SREBP1 protein levels in HepG2 cells 48 h after transfection with control (siGL) or SLU7-specific (siSLU7) siRNAs.

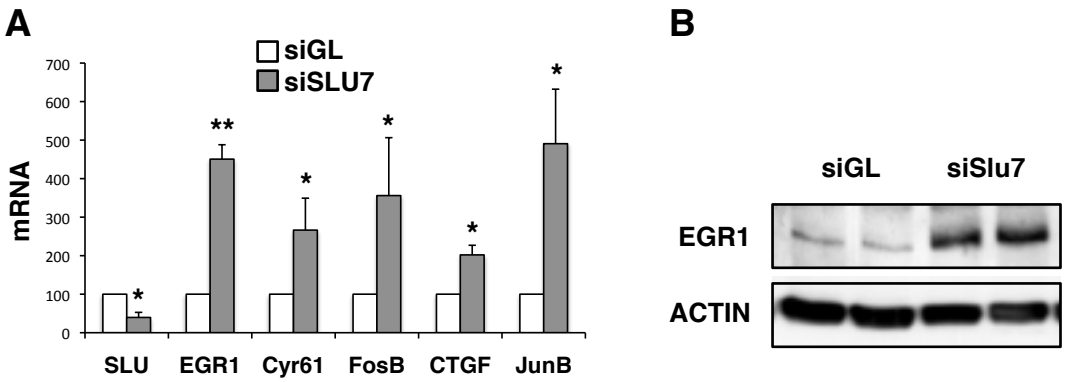

Figure S6. *Slu7 knockdown triggers proliferation-related gene expression in HepG2 cells.* (**A**) qPCR analysis of the expression of cell cycle and proliferation-related genes in HepG2 cells transfected with control (siGL) or SLU7-specific (siSLU7) siRNAs. * $P<0.05$, ** $P<0.01$ *vs* siGL. (**B**) Western blot analysis of EGR1 in HepG2 cells transfected with control (siGL) or SLU7-specific (siSLU7) siRNAs. Actin protein levels are shown as controls. Representative blots are shown.

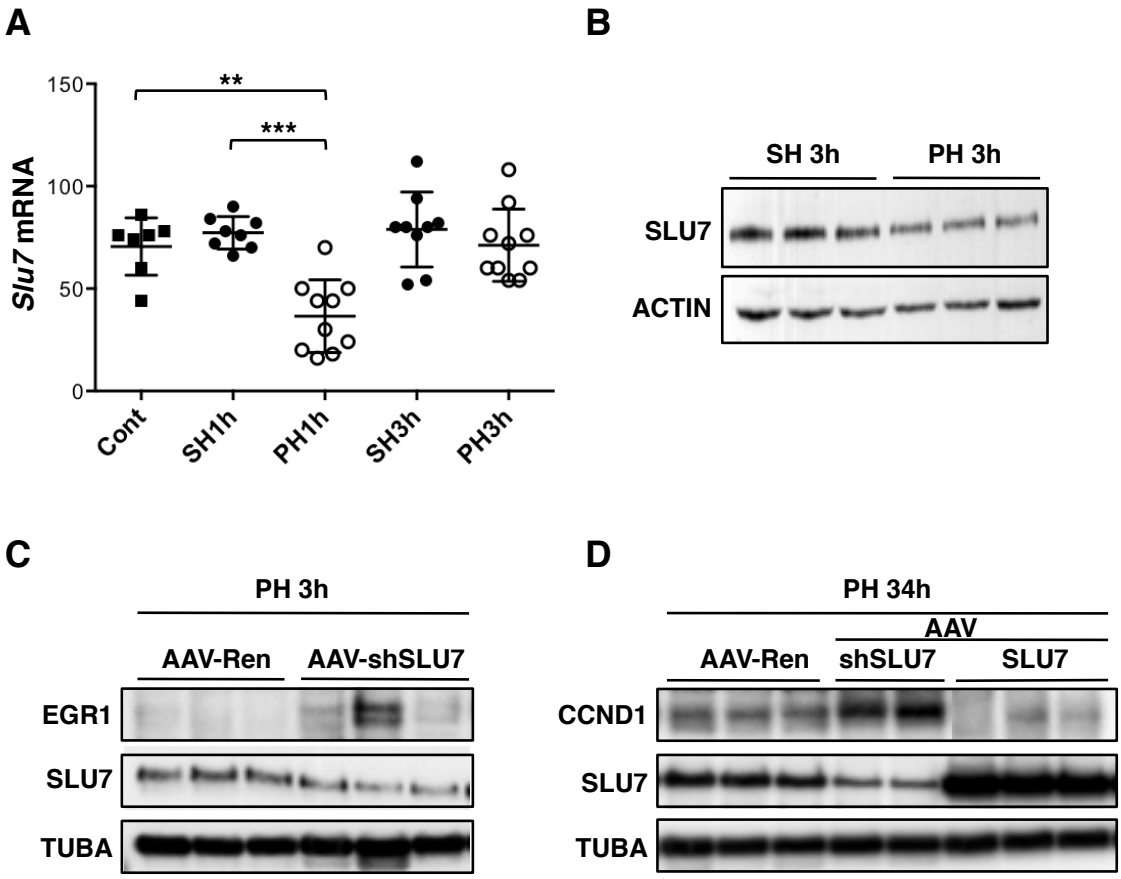

Figure S7. (**A**) qPCR analysis of Slu7 gene expression in the liver of control mice (Cont), sham-operated mice (SH) and partially hepatectomized mice (PH) at the indicated time points after the interventions. ***P*<0.01 and ****P*<0.001. (**B**) Western blot analysis of SLU7 protein levels in the liver of control sham-operated mice (SH) or partially hepatectomized mice (PH) 3 h after the interventions. Representative blots are shown. Actin protein levels are shown as loading and specificity controls. (**C**) Western blot analysis of EGR1 protein levels in the livers of mice infected with control (AAV-Ren) or *Slu7* targeting (AAV-shSLU7) adeno-associated viruses 3h after patial hepatectomy (PH). SLU7 protein levels are also shown to demonstrate the efficacy of AAV-shSLU7. Representative blots are shown. Tubulin (TUBA) protein levels are shown as loading controls. (**D**) Western blot analysis of cyclin D1 (CCND1) protein levels in the liver of mice infected with control (AAV-Ren), Slu7 targeting (AAV-shSLU7) or SLU7 expressing (AAV-SLU7) adeno-associated viruses 34 h after partial hepatectomy (PH). SLU7 protein levels are also shown to demonstrate the efficacy of the AAV-shSLU7 and AAV-SLU7 viral vectors. Representative blots are shown. Tubulin (TUBA) protein levels are shown as loading controls.

Supplementary Table 1: IPA OF SPLICING DATA SET			
MOLECULAR AND CELLULAR FUNCTION	**Nr. Genes**	**p-Value**	**Associated genes**
RNA Post-Transcriptional Modification	36	6,12E-12	AHCYL1,CDC42,CLK4,DDX39A,DDX41,DDX5,EIF4A1,EIF4B,FASTK,GRSF1,HNRNPC,HNRNPD,HNRNPH1,HNRNPH3,HNRNPK,HNRNPU,IVNS1ABP,MBNL1,NUP98,RBM25,RBM3,RBM4,RBMX,RNPS1,RPL5,RPS24,RPS7,SFPQ,SNRNP200,SON,SRSF2,SRSF3,SRSF7,THOC6,TRA2B,U2AF1
Gene Expression	77	7,37E-08	AGRN,ATF2,BCLAF1,BIRC5,CDC42,CDK5RAP2,CDK5RAP3,CHUK,CIAO1,CIRBP,CITED2,COL4A2,CSE1L,CUX1,DDX5,DNMT1,DUSP1,EIF2B5,EIF3L,EIF4B,EIF4G1,EIF4G2,EWSR1,FN1,GAPDH,GNB2L1,GPS2,GSTP1,HDAC5,HDAC6,HNRNPC,HPN,ID3,IVNS1ABP,JAK3,LRP1,MBD1,MCM7,MGEA5,MRPL19,NACA,NEDD8,NFYC,PPIE,PPM1A,PPM1L,PRKAB1,PRKAR1A,PTK2,RBM3,RBM4,RBMX,RNPS1,RPAIN,RPL13A,RPS24,RPS4X,RPS6KB2,RPS9,SEC61A1,SETDB1,SFPQ,SIRT1,SQSTM1,SUB1,TCEA2,TCFL5,TGM2,TOM1L1,TRAF6,TROVE2,VAPA,YAF2,YWHAB,ZNF24,ZNF263,ZNF292
Cell Death and Survival	126	1,40E-05	ABCA1,ACSL4,ADH5,AGAP2,AGRN,ALDOC,ANXA11,ANXA4,ATF2,ATP2A2,ATP5A1,AXL,BCLAF1,BECN1,BIRC5,CBS,CCT3,CD99,CDC42,CDK5RAP3,CHUK,CIRBP,CITED2,COL4A2,COL5A3,CSE1L,CYFIP2,DDX41,DDX5,DFFA,DPP8,DPYD,DUSP1,DUSP9,DYNC1H1,EEF1A1,EGLN3,EIF2B5,EIF4G1,EIF4G2,ERCC5,EWSR1,FAH,FASTK,FDFT1,FN1,FNTA,GAPDH,GBA2,GNB2L1,GPI,GPS2,GSTP1,HDAC5,HDAC6,HK2,HNRNPC,HNRNPK,HNRNPU,HPN,HYAL1,ID3,IDE,ITGB3BP,IVNS1ABP,IVNSABP,JAK3,LIMK2,LRP1,MAP4,MBD1,MICAL1,MYH9,NCL,NDRG1,NEDD8,NQO2,OAZ1,PCBP2,PKM,PLXNB1,PPIA,PPM1A,PPP1R15A,PRKAB1,PRKAR1A,PTK2,PTPRF,PTRH2,RABGGTB,RASSF1,RBM25,RBM3,RGN,RPS6KB2,SETDB1,SIRT1,SLC1A2,SLC2A3,SLX4,SOD1,SON,SPAG16,SPTBN1,SQSTM1,SRSF2,STMN1,STOML2,SUB1,SUN1,SYVN1,TACC1,TGM2,TICAM2,TNFRSF21,TPM1,TPT1,TRAF6,UBR4,VAPA,VCL,VCP,VIM,WBP1,YWHAB
Cellular Growth and Proliferation	136	6,48E-05	ACSL4,AGAP2,AGRN,ANXA11,ASGR1,ATF2,ATP2A2,ATP5A1,AXL,BCCIP,BCLAF1,BECN1,BIRC5,CBS,CCT3,CD99,CDC16,CDC42,CGRRF1,CHUK,CIAO1,CIRBP,CITED2,COL4A2,COPS3,CSE1L,CTNND1,CUX1,DDX5,DNMT1,DUSP1,DUSP9,DYNC1H1,EEF1A1,EEF1B2,EGLN3,EIF4A1,EIF4B,EIF4G1,EIF4G2,EML4,EWSR1,EXOSC9,FAH,FDFT1,FLOT2,FN1,FNTA,GLA,GLTSCR2,GNB2L1,GPI,GSTP1,H19,HDAC5,HDAC6,HK2,HNRNPC,HNRNPD,HNRNPK,HNRNPU,HPN,HYAL1,ID3,IDE,IVNS1ABP,JAK3,LOX,LRP1,MBD1,MCM7,MFSD12,MGEA5,MSI2,MVD,MYH9,NACA,NCL,NDFIP1,NDRG1,NQO2,NRD1,NUP98,OAZ1,PCBP4,PFKP,PKM,PLEKHA1,PLXNB1,PPIA,PPM1A,PPP1R15A,PRKAB1,PRKAR1A,PRMT1,PRRC2C,PTK2,PTPRF,RABEP1,RASSF1,RBM3,RPAIN,RPL23A,RPS15A,RPS4X,RPS6KB2,RPS9,SEC61A1,SHMT2,SIRT1,SLC12A4,SLC1A2,SLX4,SOD1,

			SPTBN1,SQSTM1,SRSF2,SRSF3,STARD10,STMN1,TACC1,TACC2,TBC1D3F,TGM2,TICAM2,TNFRSF21,TOM1L1,TPM1,TPM2,TPT1,TRAF6,VCL,VCP,VIM,WNK1,ZFYVE21
Carbohydrate Metabolism	16	2,92E-04	ABCA1,AKR1A1,ALDOC,GALT,GAPDH,GPI,HK2,LYPLA2,MGEA5,PFKL,PFKP,PKM,SIRT1,SLC1A2,SLC2A3,SORBS1
Cell cycle	55	6,21E-04	AXL,AXL,BCCIP,BIRC5,CDC16,CDC42,CDK5RAP3,CHUK,CIRBP,CITED2,COL4A2,COX4I1,CSE1L,CUX1,DNMT1,DUSP1,DUSP9,EIF4G2,EWSR1,FN1,FNTA,GNB2L1,GPI,GPS2,HNRNPD,ID3,IVNS1ABP,JAK3,KIF2A,MAP4,MCM7,NDRG1,PCBP4,PPM1A,PPP1R15A,PRKAR1A,PRMT1,PTK2,PTPRF,RASSF1,RBM3,RPL5,RPS15A,SIRT1,SOD1,SRSF2,STMN1,SUN1,TACC2,TBC1D3F (includes others),TPM2,VCP,YWHAB,ZWINT
Lipid Metabolism	10	6,21E-04	ABCA1,ACOT11,ANXA6,GBA2,GLA,LYPLA2,MAP4,SIRT1,STMN1,VIM

Supplementary Table 2: IPA OF EXPRESSION DATA SET			
MOLECULAR AND CELLULAR FUNCTION	**Nr. Genes**	**p-Value**	**Associated genes**
Carbohydrate Metabolism	31	3,35E-06	ACADVL,ADM,ANGPTL4,APOC3,ATP2A2,CA9,CRH,GATM,HK1,HK2,IGF1R,INPP5F,INPPL1,INSIG1,ITPR3,LGALS1,NNMT,PCK1,PCK2,PFKL,PFKP,PGK1,PGM1,PLA2G16,PNPLA6,PRKAG2,PRKCA,SCD,SIRT1,SMAD3,SORBS1
Cell Death and Survival	43	9,17E-05	ACLY,ADM,ALKBH3,ATF1,ATP2A2,AXL,BNIP3L,CA9,CD24,CDH1,COL18A1,CRH,CYFIP2,DDIT4,FN1,GJA1,GLI1,HDAC6,HK1,HK2,HLF,HNRNPA1,HPN,IGF1R,IQGAP2,ITPR3,LGALS1,MAGED1,NDRG1,NEDD9,PDCD6IP,PLA2G16,PNPLA6,PRDM2,PRKAB1,PRKCA,RBBP6,SCD,SIRT1,SLC7A11,SMAD2,SMAD3,VIM
Cell cycle	16	1,24E-04	ACTN4,CD24,CDH1,CRH,FN1,GJA1,GLI1,HAVCR1,IGF1R,INF2,LGALS1,NDRG1,PRKCA,PRMT1,SMAD2,SMAD3
Cellular Growth and Proliferation	47	1,24E-04	A2M,ACLY,ACTN4,ADM,ALKBH3,ANGPTL4,ATP2A2,AXL,CA9,CD24,CDCA8,CDH1,COL18A1,CRH,CTNND1,DYNC1H1,FN1,FSCN1,GJA1,GLI1,HDAC6,HK1,HK2,HNRNPA1,HPN,IGF1R,INPP5F,IQGAP2,ITGA3,LGALS1,MAGED1,NDRG1,NEDD9,PDCD6IP,PDE4A,PFKP,PLAC8,PRKCA,PRMT1,RBBP6,SIRT1,SLC7A11,SMAD2,SMAD3,TAF7,ZFP36
Lipid Metabolism	46	1,96E-04	ABCC2,ACADVL,ACLY,ADM,ANGPTL4,AP3M2,APOC3,ATP2A2,CAV2,CLDN16,COL18A1,CRH,CYP4F12,CYP4F3,DLAT,DYNC1H1,FAF2,FDPS,FN1,GATM,GFER,HLF,IGFR1,INPP5F,INPPL1,INSIG1,INSIG2,ITGA3,LGALS1,MYH9,NEDD4L,PCK1,PDCD6IP,PLA2G16,PNPLA6,PRKAB1,PRKAG2,PRKCA,RELN,SCD,SIRT1,SLC25A1,SMAD2,SMAD3,SORBS1,VIM
RNA Post-Transcriptional Modification	2	1,40E-02	ALKBH3,HNRNPA1

Supplementary Table 3: Primers used in the study

Gen	Species	Forward (5'-3')	Reverse (5'-3')
AcadVL	mouse	CGAGCTGGGTGGTTTGGGCC	GATGGAGGCTACATCGGATCC
ACC	human/mouse	GCATGTCTGGCTTGCACCTAG	CATCTTAATGTATTCTGCATTGGC
ACLY	human/mouse	TCCTTGACTTGGCGGCCAAGG	CTTGGCATAGTCATAGGTCTG
AFP	human	GATAAGTTTAGCTGACCTGG	CTGTTGCTGCCTTTGTTTGG
Afp	mouse	GCCATGAAGTGGATCACACC	CTCCTCGGTGGCTTCCGGAA
ALB	human	CTTTGGCACAATGAAGTGG	CATAGGTTTCACGAAGAGTTGC
Alb	mouse	GAAGTGGGTAACCTTTCTCC	ACAGCAGTCAGCCAGTTCACC
ATF3	human/mouse	CGGATGTCCTCTGCGCTGG	GACTCTTTCTGCAGGCACTC
CCNA2	human/mouse	CCATTCATGTGGATGAAGCAG	CATTTAACCTCCATTTCCCTAAGGTA
CCNB2	human/mouse	GAGGATGTCTCCATGAAGGAAGAG	GTCCATTTATATCTCTTCCATCTAAG
CCND1	human/mouse	TGGAACACCAGCTCCTGTGC	TCCAGGTAGTTCATGGCCAG
ChERBP	human/mouse	CGCCGCACAGCGACTCGCTG	CACCTCGATGCGCCGCTTCC
CYP4F3-IsoA	human	TCCTGGCCTGGACCTATACC	GAGCAAAGAGCACAGGCTTG
CYP4F3-IsoB	human	TCCTGGCCTGGACCTATACC	GAGGCGTTGATGACAGACCG
Egr1	mouse	TCACCCACCATGGACAACTA	AGCGGCCAGTATAGGTGAT
EGR1	human	ATGGACAACTACCCTAAGCTGG	ATGGCACTGCGCAGCTCAGG
FASN	human/mouse	AGCCATGGAGGAGGTGGTGAT	GTGTGCCTGCTTGGGGTGGAC
FOXM1	human/mouse	GGAGAATTGTCACCTGGAGCAG	GAAGGAGACCTTGCCATTGGCAG
G6PC	human/mouse	AGACTCCCAGGACTGGTTCATC	GCCCATGGCATGGCCAGAGGG
G6pt	mouse	GGATCCTGGTTTTAGGAGCCG	GCCACCCAGAAGGCTGTGCTC
GCK	human/mouse	GTAGAGCAGATCCTGGCAGAG	TTCACCAGCATCACCCTGAAG
Gls1	mouse	CAGGGTCTGTTACCTAGCTTGG	CTTTGTCTAGCATGACACCATCTG
Gls2	mouse	ATCCCTATCCACAAGTTCACC	GATCCACATGGCCCGTGAACTC
GYS2	human/mouse	CAGGTGCATTTTGGAAGATGGC	CTGCCATTCATGGAATTGGGC
H19	human	TGCCTCAGCGTTCGGGCTGG	GACCCGCTTCTTGCCGCAGC
HK2	human/mouse	TTGACCAGTATCTCTACCACATGCG	CAATGTGGTCAAACAGCTGGG
HMGCR	human/mouse	TAGCAAAGTTTGCCCTCAGTTC	TGCCAAATTGGACGACCCTC
HNF4a	human/mouse	GAAGAACCACATGTACTCCTGC	TTGATGGAGGGCAGGCTGCTG
Hnf4a-P1	mouse	GCGTGGGTAGGGGAGAATGC	CCGGTCGCCACAGATGGCGC
Hnf4a-P2	mouse	ATGGTCAGTGTGAACGCGCCC	CCGGTCGCCACAGATGGCGC
hnRNPA1	human/mouse	TGGCTAGTGCTTCATCCAGC	ATCATTGTAGCTTCCACCAC
Insig1	mouse	GCGGAATGTCACGCTCTTCC	CTGGCGTGGTTGATGCCAACG
Insig2A	mouse	CCCTCAATGAATGTACTGAAGGATT	GGCCGAGGTGACTCCGTCTCTC
Insig2B	mouse	CCGGGCAGAGCTCAGGAT	GGCCGAGGTGACTCCGTCTCTC
InsR-A	mouse	GGTTTTTGTCCCCAGGCCATCCC	CTTCAGGCATGGTCCGGGCAC
InsR-B	mouse	CAATGGTGCCGAGGACAGTAG	CTTCAGGCATGGTCCGGGCAC
INSR	human/mouse	GCCACTATCGACTGGTCCCG	CAGCGCCAGTCCTGGAAGTG
LPK	human/mouse	GCACTGCCTTCTTCCAGCAGC	GGTGTCCAGGGCGATGGCCAC
MAT1A	human	TCTTCATGTTCACATCGGAG	TGCACTCCTCTGTCTCGTCG
Mat1A	mouse	TTCTCTAAGTGAAGAGGGAGC	CCTTGGCAGAGTCGTCATAG
Mat2A	mouse	ATGCTGTCCTTGATGCAC	GCGTAACCAAGGCAATG
NOR1	human/mouse	AGACTTTCCATCAGGTCAAACACTGC	CTTTGGTTCTTTTAACCCATGTC
NURR1	human/mouse	GTCTGATCAGTGCCCTCGTCAG	GCTGATTCAAAAAGCAGGTCTTGG
PEPCK	human/mouse	AGCCTGCCCCAGGCAGTGAGG	CATGCACCCTGGGAACCTGGC
PEPCK Promoter	human	GGTTGAGGGCTCGAAGTCTCC	CTGTGGAAAAGAATAGCCCTGC
PKM2	human/mouse	GCTGAAGGCAGTGATGTGGCC	CACTGCAGCACTTGAAGGAGGC
PYGL	human/mouse	ATGGAAACCCTTGGGAGAAG	CAGCCTGAATGTAGTCTCCAAC
RPLP0	human/mouse	AACATCTCCCCCTTCTCCTT	GAAGGCCTTGACCTTTTCAG
Scd1	mouse	CATCACAGCCGGGGCTCATCGCC	CAAGCAGCCAACCCACGTGAG
SRSF3	human	TCGTGATTCCTGTCCATTGG	TCATCTCGAGGGCGACGAC
SRSF3-ISO1	human/mouse	GTGGCTGCCGTGTAAGAGTGG	TCTCTTCTCCTATCTCTAGAAAG
SRSF3-ISO2	human/mouse	GTGGCTGCCGTGTAAGAGTGG	CTGACGACTGGCCAGCCTGG
SLU7	human/mouse	GAAGAAGGAGCTAGAAGAACAG	CTTCCCATCATAGTCAAACATCAG
SREBP1	human/mouse	CACTTCATCAAGGCAGACTC	CGGTAGCGCTTCTCAATGGC
Wt1	mouse	GGAATCAGATGAACCTAGGAG	CGTTTCTCACTGGTTTCAGATGCTG

Supplementary Table 4: Antibodies used in the study			
Antibody	**Method**	**Origin**	**Reference**
Actin	WB (1º)	Sigma Chemical Co	A2066
p-Akt (Ser 473)	WB (1º)	Cell Signaling	9271
Cyclin A (H-432)	WB (1º)	Santa Cruz	sc-751
Cyclin B1 (H-433)	WB (1º)	Santa Cruz	sc-752
Cyclin D1 (72-13G)	WB (1º)	Santa Cruz	sc-4550
CREB (48H2)	WB (1º)	Cell Signaling	9197
p-CREB (Ser 133) (87G3)	WB/ChIP	Cell Signaling	9198
c-myc	WB (1º)	Sigma Chemical Co	M4439
Egr1 (C-19)	WB (1º)	Santa Cruz	sc-189
p-GSK3 b (Ser 9)	WB (1º)	Cell Signaling	9336
HXK II (H-95)	WB (1º)	Santa Cruz	sc-28889
hnRNPA1 (9H10)	WB (1º)	ABCAM	ab5832
HNF4a	WB (1º)	Santa Cruz	sc-8987
Insulin receptor b (4B8)	WB (1º)	Cell Signaling	3025
Ki67	IHQ	Thermo Scientific	RM9106
MAT I/II/III (H-300)	WB (1º)	Santa Cruz	sc-32929
PEPCK-C (I-17)	WB (1º)	Santa Cruz	sc-74823
PKM2	WB (1º)	Cell Signaling	3198
PCNA (PC-10)	WB (1º)	Santa Cruz	sc-56
RNA polimerase II	WB/ChIP	Millipore	17-620
SREBP-A (2A4)	WB (1º)	Santa Cruz	sc-13551
Slu7	WB/ChIP	BD TrasnductionLlaboratories	612605
Slu7 (L-16)	IHQ	Santa Cruz	sc-10829
SRSF3 (SRp20) (7B4)	WB (1º)	Santa Cruz	sc-13510
Tubulin	WB (1º)	Sigma Chemical Co	T6074
WT-1 (C-19)	WB (1º)	Santa Cruz	SC-192
anti-IgG goat-HRP	WB (2º)	Santa Cruz	sc-2020
anti-IgG rabbit-HRP	WB (2º)	Sigma Chemical Co	A0545
anti-IgG mouse-HRP	WB (2º)	Sigma Chemical Co	A0168
IgG rabbit	ChIP	Santa Cruz	sc-2027
IgG mouse	ChIP	Santa Cruz	sc-2025