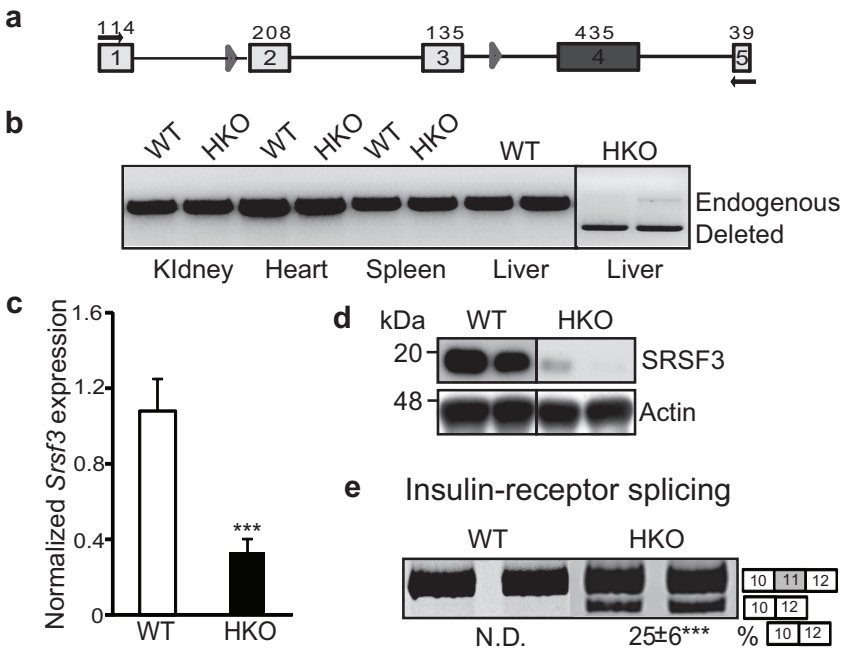
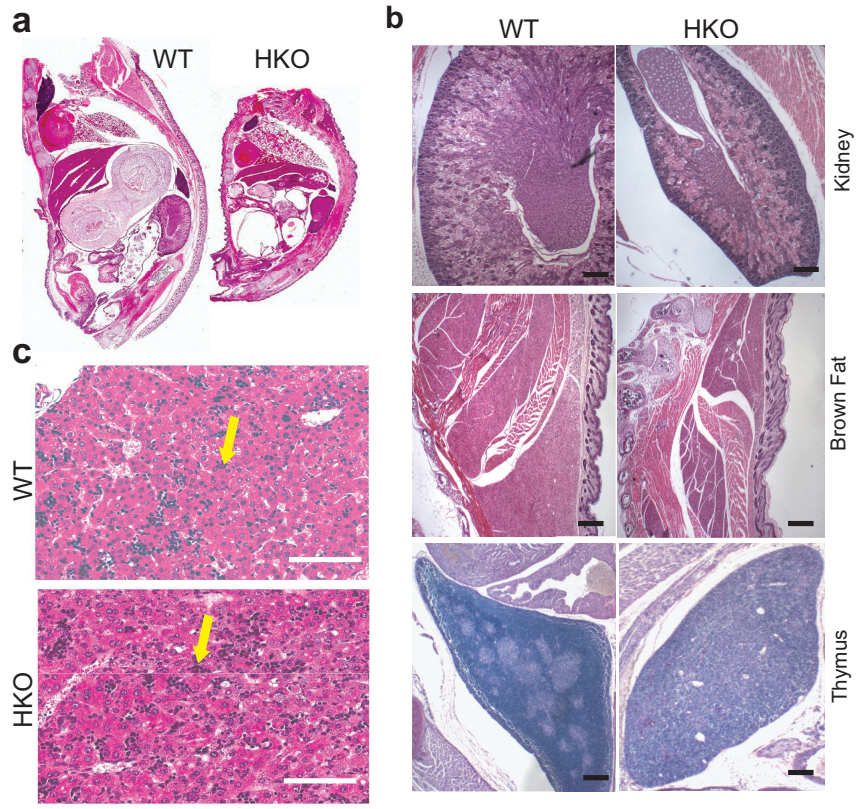
Supplementary Figure S1. Characterization of SRSF3HKO mice.



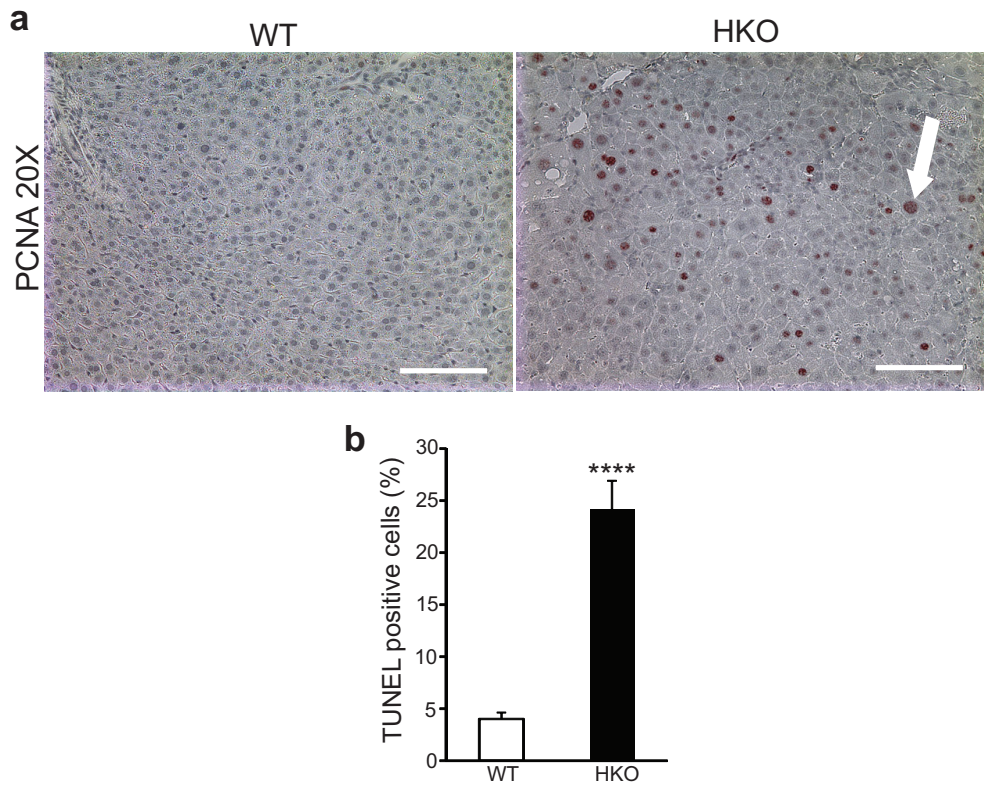
(a) Structure of the SRSF3 cassette present in flox:flox mice with primer sites for RT-PCR. LoxP sites are marked by arrowheads. (b) RT-PCR analysis of the RNA from mice with indicated genotypes. Total RNAs from the indicated tissues were prepared from 4 weeks old mice. The SRSF3 deleted allele is smaller than the endogenous due to the lack of the floxed exon 2 and 3 sequences (343 nt). (c) Q-PCR analysis of *Srsf3* expression in WT and HKO liver. Results are means ± SEM, n=6, p***=0.005 (d) Quantification of SRSF3 protein expression in hepatocytes by immunoblotting. Blots were stripped and reblotted for actin as a loading control. (e) Representative gel electrophoresis of RT-PCR product from two individuals from each group showing SRSF3 dependent insulin receptor exon 11 alternative splicing. Below the gel, the percentage of exon exclusion is shown.

Supplementary Figure S2. Phenotype of SRSF3HKO mice at 2 days old.



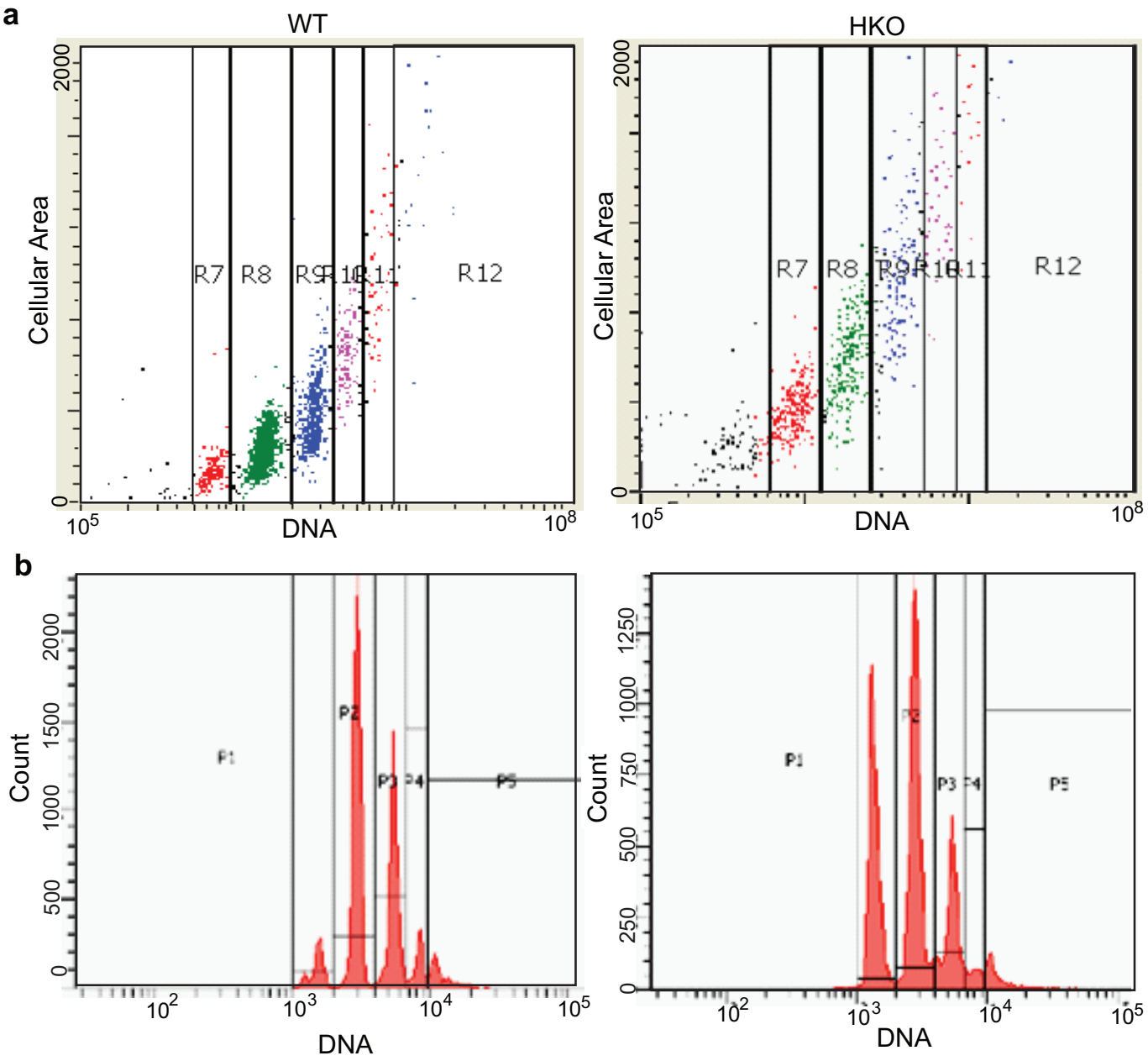
(a) Representative section from the whole body of SRSF3HKO and WT mice at 2 days old. Mice were fixed in Bouin's fixative after decapitation and stained with H&E. Magnification is 4X. (b) H&E staining of whole body showing that kidney and thymus development is impaired in SRSF3HKO mice. Brown fat mass is also less in HKO mice. Magnification is 4X. Scale bar, 100 μm. (c) H&E stained liver sections show the presence of dark condensed hematopoetic cells (yellow arrows) in both WT and and HKO mice. Magnification is 20X. Scale bar, 100 μm.

Supplementary Figure S3. SRSF3HKO liver shows increased expression of proliferation marker and apoptosis.



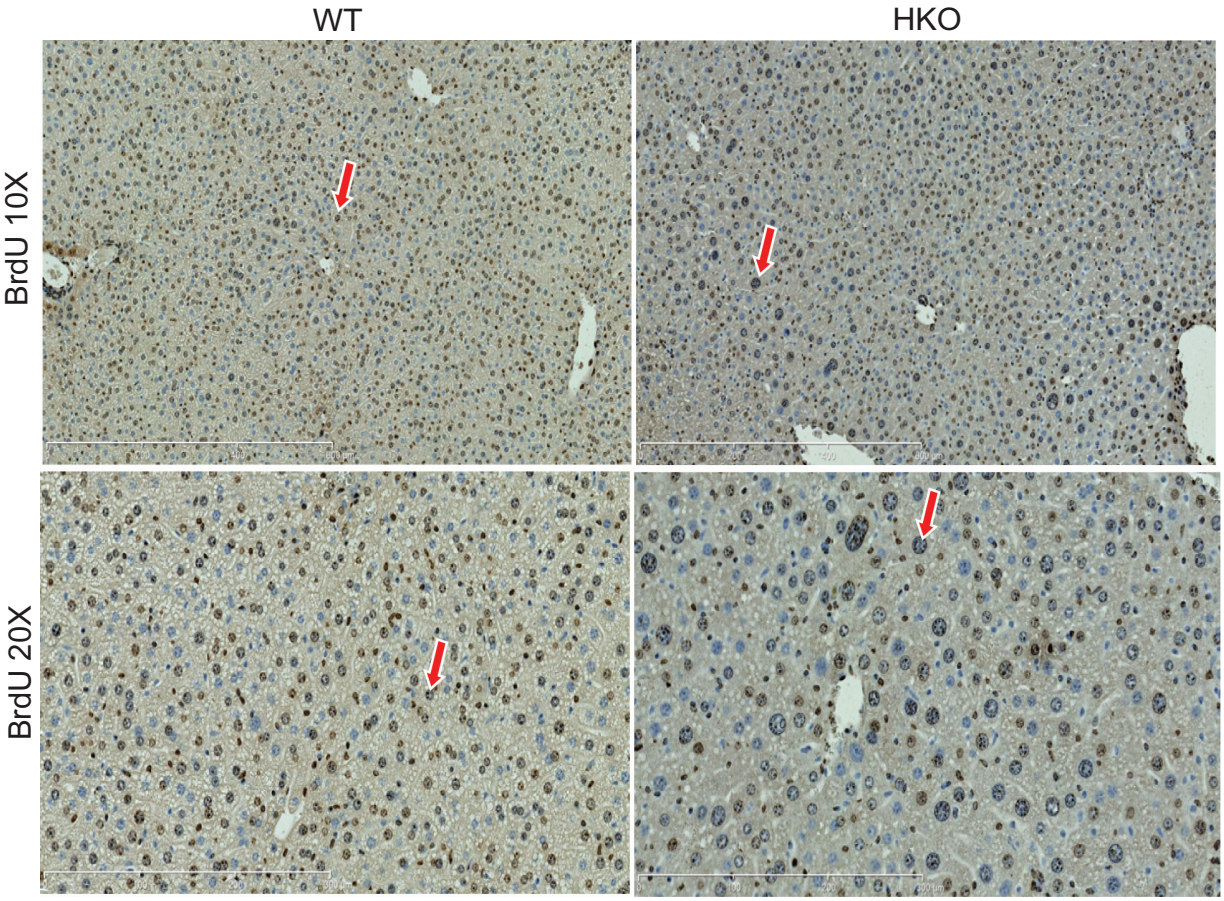
(a) Increased expression of the cell proliferation marker PCNA (marked by white arrow) is observed in SRSF3HKO liver compared to wild-type liver. Scale bar, 100 μm. **(b)** Quantification of TUNEL positive cells (mean ± s.e.m.) from six different fields from three different mice. Statistical significance assessed by Student's t-test, ****p<0.0001.

Supplementary Figure S4. Quantification of cell size and DNA content.



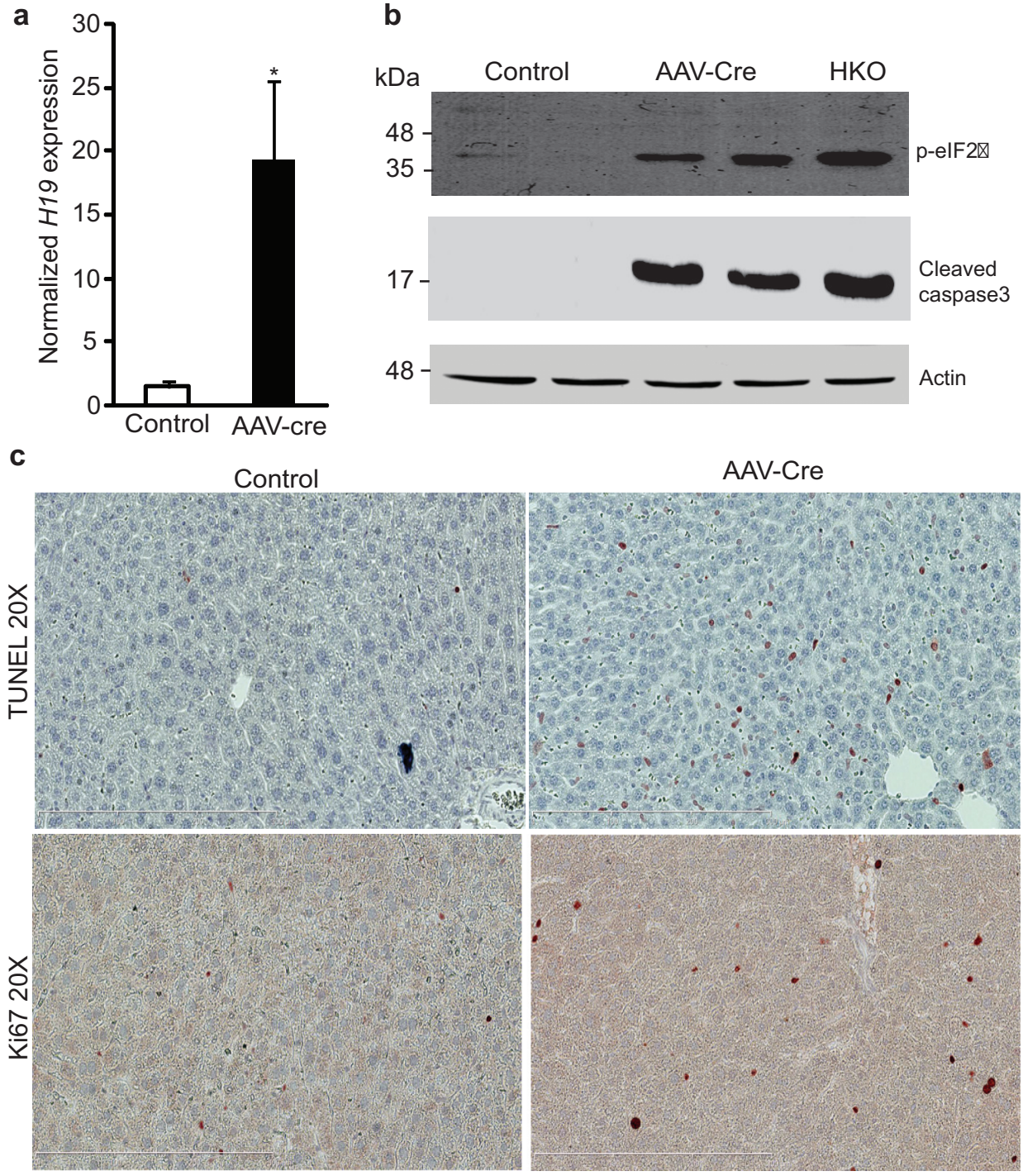
(a) Quantification of laser scanning cytometry. Plots show cell counts binned and colored for DNA content (x-axis, Long Red Integral) against cellular area (y-axis). Note more diffuse size distribution for R7, R8, R9 and R10. **(b)** Quantification of DNA content by flow cytometry. Plots show propidum iodide fluorescence (x-axis) versus cell count (y-axis). Peaks are gated for 2n, 4n, 8n and 16n content.

Supplementary Figure S5. SRSF3HKO liver regenerate like WT after partial hepatectomy.



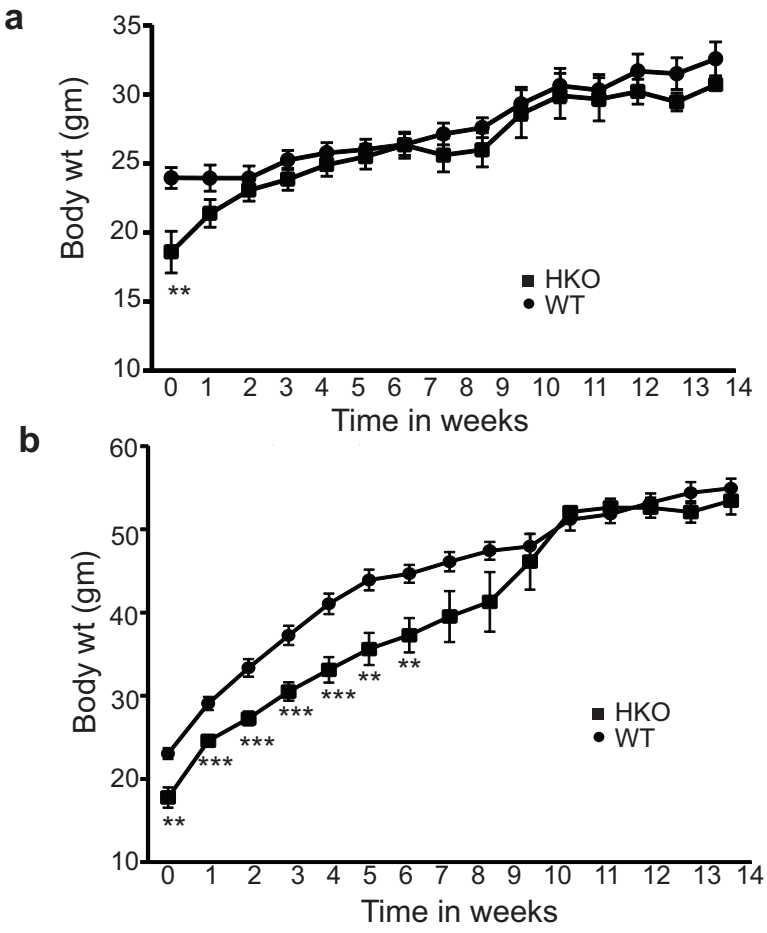
BrdU immunostaining for liver sections after 36 hr. of partial hepatectomy. BrdU stained brown cells are indicated by arrows. Scale bar, 600 μm.

Supplementary Figure S6. AAV-cre liver shows increased expression of *H19*, increased ER stress and increased apoptosis and proliferation.



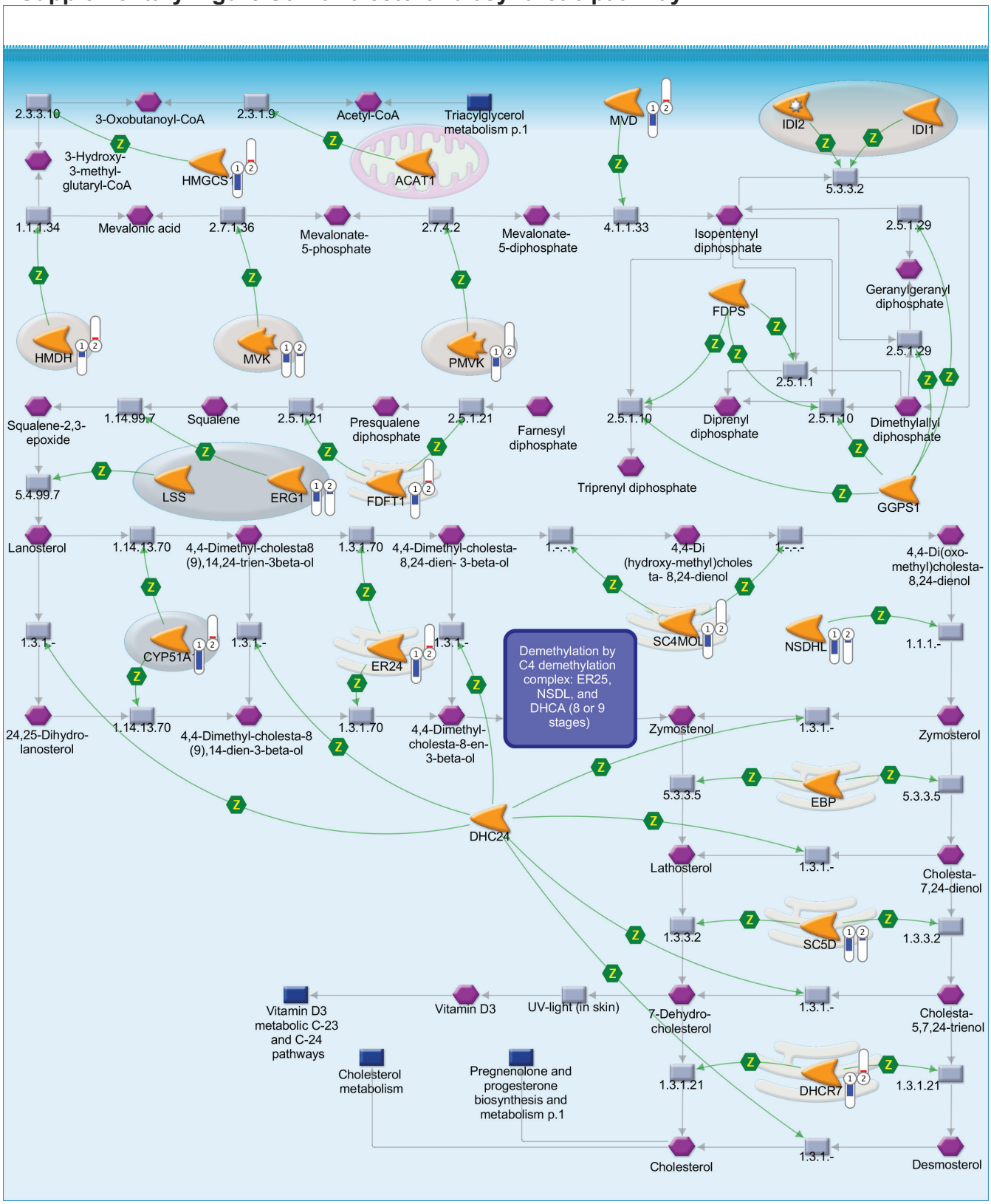
(a) Increased expression of *H19* mRNA is observed in AAV-cre liver compared to control liver. Results are means ± SEM, n=3-4 **(b)** Immunoblotting for phospho-eIF2a and cleaved caspase 3 with actin control are shown. **(c)** TUNEL staining and ki-67 immunostaining show increased number of apoptotic (red stain) and proliferating (red stain) cells in liver of AAV-cre infected mice. Scale bar, 600 μm.

Supplementary Figure S7. Body weight of WT and SRSF3HKO mice.



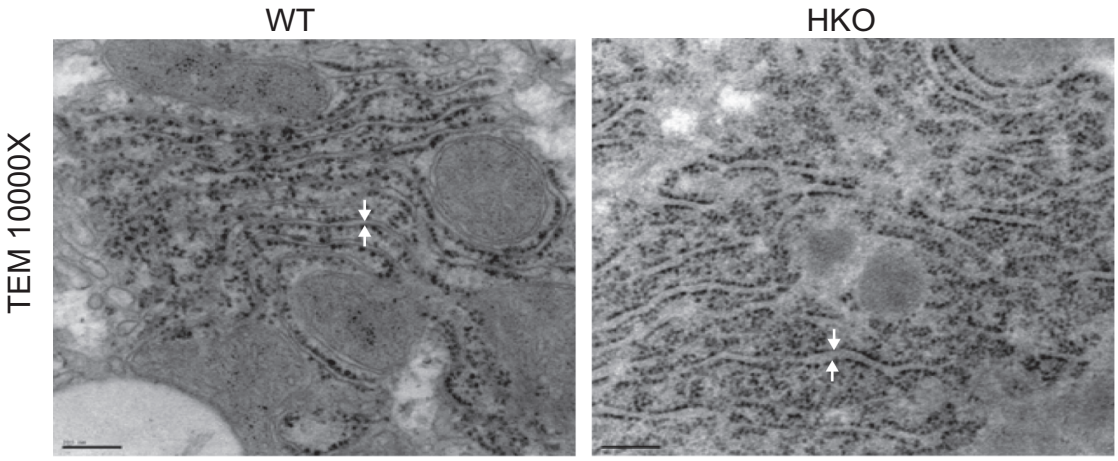
(a) Mice fed low fat control diet or **(b)** high-fat diet for 14 weeks. Statistical significance assessed by Student's t-test, Results are means ± SEM. In all panels, n=2-8 per group, **p<0.01,***p<0.001.

Supplementary Figure S8: Cholesterol biosynthetic pathway.



Genes with altered expression in SRSF3HKO livers compared to WT littermates are shown with expression data as columns beside the icons. Proteins are shown in yellow, enzyme activities with corresponding E.C. numbers are shown as grey boxes, biosynthetic intermediates are shown in purple. Green arrows indicate that a protein is involved in the indicated enzyme activity. Column 1 is the expression data corresponds to SRSF3HKOmice, column 2 to WT mice.

Supplementary Figure S9. Rough ER morphology in WT and SRSF3HKO liver by transmission electron microscopy.



Scale bar represents 200 nm. Width of RER lumen is marked by white arrows.

Supplementary Table S1
Non-Mendelian inheritance of genotypes

	Alb-Cre -ve	Alb-Cre +ve
SRSF3 (LoxP/+)	85	95
SRSF3 (LoxP/LoxP)	80	17*

*p<0.0001 by Fisher's exact test or Chi-squared test. Numbers in the table define the number of mice per genotype.

Supplementary Table S2
Basic Metabolic Parameters in SRSF3HKO and WT mice

	WT	**SRSF3HKO**
Albumin (g/dl)	3±0.23	2.18±0.2*
Anion Gap	36±0	49±4.3*
Bilirubin Total (mg/dl)	0.2±0	0.9±0.31
BUN (mg/dl)	21±1.8	22.5±2.5
Total Protein (g/dl)	4.65±0.25	3.65±0.21*
Fasting insulin (ng/ml)	0.13±0.02	0.17±0.03
LDL (mg/dl)	0	0
Creatinine	0.16±0.01	0.2±0.03
Calcium	10.5±0.6	7.8±0.7*

Metabolic parameters were assessed on male 4 week old mice (n=4 per group) fed ad libitum on normal chow. Values represent mean±SEM. Statistical significance between WT and SRSF3HKO was assessed by student t test, *$p<0.05$.

Supplementary Table S3
Hematology analysis in SRSF3HKO and WT mice

	WT	SRSF3HKO
White Blood Cells (K/µl)	1.96±0.22	2.66±0.37
Leukocytes (K/µl)	1.57±0.19	2.06±0.43
Neutrophils (K/µl)	0.22±0.04	0.35±0.09
Monocytes (K/µl)	0.15±0.02	0.21±0.03
Eosinophils (K/µl)	0.01±0.006	0.02±0.01
Red Blood Cells (M/µl)	7.4±0.4	8.1±0.2
Hemoglobin (g/dL)	10.7±0.5	10.3±0.7
RBC Distribution Width (%)	21.2±0.6	25.2±0.8***
Mean Corpuscular Hemoglobin Volume (g/dL)	27.9±0.9	25.4±0.6*
Platelets (K/µl)	90±32	158±79

Analysis was performed on female 4-week old mice (n=4 & 8 for HKO and WT) fed ad libitum on normal chow. Values are mean±SEM. Statistical significance between WT and HKO was determined by student t test, *$p<0.05$, ***$p<0.001$.

Supplementary Table S4:
Clusters of Enriched Pathways and Process by DAVID (exon dataset)

Annotation Cluster 1: 3 terms	Enrichment Score: 6.08				
Term	Count	%	P-Value	Fold	FDR
GO:0006631~fatty acid metabolic process	30	3.15	7.09E-08	3.15	1.25E-04
lipid metabolism	23	2.41	1.01E-06	3.39	1.43E-03
fatty acid metabolism	14	1.47	7.71E-06	4.59	1.10E-02
Annotation Cluster 2: 12 terms (top 3 shown)	Enrichment Score: 5.72				
Term	Count	%	P-Value	Fold	FDR
GO:0031090~organelle membrane	79	8.29	3.23E-09	2.00	4.51E-06
GO:0031967~organelle envelope	60	6.30	3.58E-09	2.28	5.01E-06
GO:0031975~envelope	60	6.30	4.13E-09	2.27	5.77E-06
Annotation Cluster 3: 12 terms (top 3 shown)	Enrichment Score: 4.76				
Term	Count	%	P-Value	Fold	FDR
GO:0001882~nucleoside binding	128	13.43	1.97E-07	1.56	3.07E-04
GO:0001883~purine nucleoside binding	127	13.33	2.48E-07	1.56	3.85E-04
GO:0030554~adenyl nucleotide binding	125	13.12	4.70E-07	1.55	7.30E-04
Annotation Cluster 4: 6 terms (top 3 shown)	Enrichment Score: 4.59				
Term	Count	%	P-Value	Fold	FDR
GO:0031974~membrane-enclosed lumen	94	9.86	1.24E-06	1.64	1.74E-03
GO:0070013~intracellular organelle lumen	91	9.55	1.69E-06	1.65	2.37E-03
GO:0043233~organelle lumen	91	9.55	1.88E-06	1.64	2.62E-03
Annotation Cluster 5: 5 terms (top 3 shown)	Enrichment Score: 4.31				
Term	Count	%	P-Value	Fold	FDR
GO:0000267~cell fraction	55	5.77	6.70E-06	1.89	9.36E-03
GO:0005626~insoluble fraction	49	5.14	2.05E-05	1.91	2.86E-02
GO:0042598~vesicular fraction	23	2.41	7.33E-05	2.59	1.02E-01
Annotation Cluster 6: 8 terms (top 3 shown)	Enrichment Score: 3.43				
Term	Count	%	P-Value	Fold	FDR
GO:0042579~microbody	18	1.89	1.00E-05	3.55	1.40E-02
GO:0005777~peroxisome	18	1.89	1.00E-05	3.55	1.40E-02
peroxisome	16	1.68	7.82E-05	3.34	1.11E-01
Annotation Cluster 7: 4 terms (top 3 shown)	Enrichment Score: 3.23				
Term	Count	%	P-Value	Fold	FDR
GO:0051186~cofactor metabolic process	24	2.52	6.43E-05	2.55	1.13E-01
GO:0006732~coenzyme metabolic process	20	2.10	1.40E-04	2.70	2.46E-01
GO:0051188~cofactor biosynthetic process	13	1.36	2.44E-03	2.76	4.20E+00
Annotation Cluster 8: 15 terms (top 3 shown)	Enrichment Score: 2.50				
Term	Count	%	P-Value	Fold	FDR
GO:0048037~cofactor binding	31	3.25	2.70E-06	2.60	4.20E-03
GO:0050662~coenzyme binding	23	2.41	3.30E-05	2.73	5.13E-02
Flavoprotein	15	1.57	5.89E-04	2.91	8.35E-01
Annotation Cluster 9: 23 terms (top 3 shown)	Enrichment Score: 2.33				
Term	Count	%	P-Value	Fold	FDR
mmu02010:ABC transporters	13	1.36	5.17E-06	5.04	6.33E-03
IPR003439:ABC transporter-like	13	1.36	8.54E-06	4.93	1.42E-02
IPR017871:ABC transporter, conserved site	13	1.36	6.36E-05	4.08	1.06E-01
Annotation Cluster 10: 4 terms (top 3 shown)	Enrichment Score: 2.31				
Term	Count	%	P-Value	Fold	FDR
IPR006903:Protein of unknown function DUF618	4	0.42	3.69E-03	11.48	5.96E+00
IPR008942:ENTH/VHS	6	0.63	4.78E-03	5.24	7.67E+00
IPR006569:Regulation of nuclear pre-mRNA protein	4	0.42	5.68E-03	10.05	9.05E+00

Supplementary Table S5: GeneGo Enrichment analysis report (exon dataset)

#	Enrichment of Pathway Maps	pValue
1	Immune response_Gastrin in inflammatory response	5.59E-07
2	Cytoskeleton remodeling_Cytoskeleton remodeling	6.72E-07
3	Immune response_Lectin induced complement pathway	3.27E-06
4	Immune response_Classical complement pathway	6.07E-06
5	Development_Gastrin in cell growth and proliferation	6.12E-06
6	Development_Angiotensin signaling via PYK2	6.56E-06
7	Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling	1.01E-05
8	Development_Ligand-independent activation of ESR1 and ESR2	1.01E-05
9	Development_Beta-adrenergic receptors transactivation of EGFR	1.29E-05
10	Development_Alpha-2 adrenergic receptor activation of ERK	3.54E-05

#	Enrichment of Process Networks	pValue
1	Development_Regulation of angiogenesis	1.47E-06
2	Protein folding_Response to unfolded proteins	3.73E-06
3	Cell adhesion_Cell junctions	7.74E-06
4	Immune response_Phagocytosis	3.35E-05
5	Inflammation_Amphoterin signaling	7.24E-05
6	Inflammation_Protein C signaling	7.66E-05
7	Cell cycle_G1-S Interleukin regulation	2.10E-04
8	Signal Transduction_TGF-beta, GDF and Activin signaling	2.38E-04
9	Cell cycle_G1-S Growth factor regulation	4.26E-04
10	Transcription_Nuclear receptors transcriptional regulation	4.93E-04

#	Enrichment of Metabolic Networks	pValue
1	1,2-dioleoyl-sn-glycerol_3-phosphate pathway	2.25E-04
2	1,2-didocosahexaenoyl-sn-glycerol_3-phosphate pathway	3.66E-04
3	1,2-didocosapentaenoyl-sn-glycerol_3-phosphate pathway	6.64E-04
4	Lipid metabolism_Triacylglycerol metabolism	1.46E-03
5	Sphingomyelin pathway	1.58E-03
6	Ceramide pathway	2.87E-03
7	Lipid metabolism_n-6 Poliunsaturated fatty acid biosynthesis	4.00E-03
8	O-hexanoyl-(L)-carnitine pathway	6.41E-03
9	2-oleoyl-glycerol_3-phosphate pathway	6.70E-03
10	Glycine pathway	7.94E-03

Supplementary Table S6
Clusters of terms significantly enriched by DAVID (expression dataset)

Annotation Cluster 1: 14 terms (top 3 shown)	Enrichment Score: 9.56				
Term	Count	%	Fold	P-Value	FDR
GO:0008202~steroid metabolic process	46	5.18	6.05	4.53E-23	7.94E-20
GO:0008610~lipid biosynthetic process	52	5.86	3.86	7.60E-17	2.00E-13
GO:0006694~steroid biosynthetic process	25	2.82	7.45	6.32E-15	1.11E-11
Annotation Cluster 2: 24 terms (top 3 shown)	Enrichment Score: 5.60				
Term	Count	%	Fold	P-Value	FDR
GO:0042598~vesicular fraction	32	3.60	3.70	4.60E-10	6.33E-07
GO:0005792~microsome	31	3.49	3.71	8.66E-10	1.19E-06
GO:0009055~electron carrier activity	34	3.83	3.43	9.56E-10	1.49E-06
Annotation Cluster 3: 4 terms (top 3 shown)	Enrichment Score: 5.53				
Term	Count	%	Fold	P-Value	FDR
GO:0042579~microbody	20	2.25	4.05	3.60E-07	4.95E-04
GO:0005777~peroxisome	20	2.25	4.05	3.60E-07	4.95E-04
peroxisome	18	2.03	4.02	1.88E-06	2.67E-03
Annotation Cluster 4: 4 terms (top 3 shown)	Enrichment Score: 5.29				
Term	Count	%	Fold	P-Value	FDR
GO:0016053~organic acid biosynthetic process	24	2.70	3.60	1.74E-07	3.05E-04
GO:0046394~carboxylic acid biosynthetic process	24	2.70	3.60	1.74E-07	3.05E-04
GO:0006633~fatty acid biosynthetic process	14	1.58	3.66	9.86E-05	1.73E-01
Annotation Cluster 5: 4 terms (top 3 shown)	Enrichment Score: 5.19				
Term	Count	%	Fold	P-Value	FDR
GO:0051186~cofactor metabolic process	30	3.38	3.49	7.51E-09	1.32E-05
GO:0006732~coenzyme metabolic process	22	2.48	3.26	3.44E-06	6.03E-03
GO:0051188~cofactor biosynthetic process	15	1.69	3.49	8.65E-05	1.51E-01
Annotation Cluster 6: 10 terms (top 3 shown)	Enrichment Score: 5.13				
Term	Count	%	Fold	P-Value	FDR
GO:0005739~mitochondrion	114	12.84	1.82	1.97E-10	2.71E-07
GO:0031090~organelle membrane	69	7.77	1.80	2.37E-06	3.26E-03
mitochondrion	67	7.55	1.82	2.81E-06	4.00E-03
Annotation Cluster 7: 8 terms (top 3 shown)	Enrichment Score: 4.79				
Term	Count	%	Fold	P-Value	FDR
GO:0016229~steroid dehydrogenase activity	14	1.58	9.82	2.79E-10	4.33E-07
GO:0033764~steroid dehydrogenase activity	11	1.24	9.73	4.84E-08	7.52E-05
IPR002225:3-beta hydroxysteroid dehydrogenase	6	0.68	14.48	2.20E-05	3.62E-02
Annotation Cluster 8: 5 terms (top 3 shown)	Enrichment Score: 3.76				
Term	Count	%	Fold	P-Value	FDR
Flavoprotein	18	2.03	3.75	5.10E-06	7.26E-03
GO:0050662~coenzyme binding	23	2.59	2.93	1.13E-05	1.76E-02
FAD	17	1.91	3.35	4.33E-05	6.16E-02
Annotation Cluster 9: 4 terms (top 3 shown)	Enrichment Score: 3.44				
Term	Count	%	Fold	P-Value	FDR
mmu00830:Retinol metabolism	16	1.80	3.85	1.02E-05	1.25E-02
mmu00982:Drug metabolism	14	1.58	3.05	5.18E-04	6.35E-01
mmu00980:Metabolism of xenobiotics by cyto P450	13	1.46	3.22	5.40E-04	6.61E-01
Annotation Cluster 10: 6 terms (top 3 shown)	Enrichment Score: 3.35				
Term	Count	%	Fold	P-Value	FDR
mitochondrion	67	7.55	1.82	2.81E-06	4.00E-03
GO:0044429~mitochondrial part	49	5.52	1.97	8.65E-06	1.19E-02
transit peptide	40	4.50	1.88	2.03E-04	2.88E-01

Supplementary Table S7
GeneGo Enrichment analysis report (expression dataset)

#	Enrichment of Pathway Maps	pValue
1	Immune response_Classical complement pathway	1.29E-09
2	Immune response_Lectin induced complement pathway	5.08E-08
3	Linoleic acid / Rodent version	2.32E-05
4	Cholesterol Biosynthesis	6.16E-05
5	Regulation of metabolism_Triiodothyronine and Thyroxine signaling	6.60E-04

#	Enrichment of Process Networks	pValue
1	Inflammation_Complement system	5.05E-07
2	Blood coagulation	3.84E-06
3	Inflammation_IL-6 signaling	3.04E-04
4	Development_Blood vessel morphogenesis	2.63E-03
5	Regulation of metabolism_Bile acid regulation of lipid metabolism	2.86E-03

#	Enrichment of Diseases	pValue
1	Metabolism, Inborn Errors	2.87E-11
2	Hyperinsulinism	7.16E-11
3	Calculi	1.09E-10
4	Hyperlipidemias	1.58E-10
5	Insulin Resistance	1.59E-10

#	Enrichment of Metaboic Networks	pValue
1	Steroid metabolism_Cholesterol biosynthesis	2.29E-05
2	1,2-didocosapentaenoyl-sn-glycerol_3-phosphate pathway	6.85E-03
3	GalNAcbeta1-3Gal pathway	7.87E-03
4	1,2-dioleoyl-sn-glycerol_3-phosphate pathway	8.43E-03
5	1,2-didocosahexaenoyl-sn-glycerol_3-phosphate pathway	1.16E-02

#	Enrichment of Processes	pValue
1	small molecule metabolic process	3.68E-51
2	lipid metabolic process	1.91E-43
3	metabolic process	2.57E-40
4	steroid metabolic process	6.20E-39
5	organic acid metabolic process	1.36E-34

#	Liver toxicity endpoint processes	pValue
1	Cholestasis, development_liver	1.35E-07
2	Steatosis, development_liver	3.38E-07
3	Hypertrophic organ growth_liver	2.83E-02
4	Phospholipidosis, development_liver	5.35E-02
5	Inflammation, development	7.73E-02

#	Toxicity by Liver maps	pValue
1	Ligand-Dependent Transcription of Retinoid-Target genes	1.07E-04
2	Cholesterol Biosynthesis	2.33E-04
3	Regulation of lipid metabolism	3.06E-04
4	Regulation of metabolism_Triiodothyronine and Thyroxine signaling	3.26E-04
5	Immune response_IFN alpha/beta signaling pathway	6.67E-04

Supplementary Table S8
Transcription Factors underlying expression changes

Principal Transcription Factors by Network Analysis

#	Network	Total nodes	Seed nodes	p-Value	zScore
1	SP1	222	221	0.00E+00	124.25
2	HNF4-alpha	216	215	0.00E+00	122.54
3	c-Myc	131	130	7.94E-244	95.07
4	ESR1	110	110	1.41E-207	87.78
5	CREB1	110	109	1.25E-203	86.97
6	C/EBPbeta	105	104	4.21E-194	84.93
7	p53	101	100	1.72E-186	83.26
8	AP-1	99	98	1.09E-182	82.41
9	EGR1	86	86	7.30E-162	77.6
10	Androgen receptor	85	84	3.82E-156	76.23
11	GCR-alpha	83	82	2.31E-152	75.3
12	c-Jun	83	82	2.31E-152	75.3
13	GATA-1	77	76	4.93E-141	72.45
14	SREBP1	75	74	2.91E-137	71.48
15	RelA (p65 NF-kB)	75	74	2.91E-137	71.48
16	YY1	71	70	9.98E-130	69.49
17	SP3	71	70	9.98E-130	69.49
18	HIF1A	70	69	7.61E-128	68.99
19	HNF1-alpha	68	67	4.40E-124	67.96
20	USF1	65	64	1.91E-118	66.4

Over-connected Transcription Factors by Interactome Analysis

#	Transcription Factor	Actual	Expected	Ratio	p-value	z-score
1	HNF1alpha	68	22.2	3.063	1.476E-16	10.07
2	SREBP1	45	11.87	3.791	1.043E-14	9.901
3	HNF4alpha	191	107.4	1.778	4.148E-16	8.793
4	SREBP2	19	3.473	5.471	9.95E-10	8.538
5	SP1	207	128.9	1.606	6.577E-13	7.609
6	NFIA	38	13.45	2.825	8.121E-09	6.898
7	HNF3beta	41	16.48	2.487	8.101E-08	6.233
8	C/EBPbeta	76	39.04	1.947	2.004E-08	6.188
9	Oct-1	55	27.21	2.021	6.058E-07	5.533
10	HNF1beta	17	5.011	3.392	9.892E-06	5.492
11	PXR	18	5.539	3.25	1.009E-05	5.432
12	NFIB	29	11.39	2.547	3.944E-06	5.373
13	PPARalpha	26	9.847	2.64	6.425E-06	5.294
14	EGR1	64	34.29	1.867	1.191E-06	5.292
15	C/EBPalpha	58	30.16	1.923	1.493E-06	5.276
16	NFIC	32	13.36	2.395	4.765E-06	5.253
17	HNF3alpha	22	7.781	2.827	0.000011	5.236
18	STAT5B	20	6.77	2.954	1.423E-05	5.22
19	CREB1	91	54.95	1.656	1.336E-06	5.135
20	GCRalpha	62	34.16	1.815	4.331E-06	4.969

Supplementary Table S9
Sequences for primers

Gene	Forward (5'-3')	Reverse (5'-3')	Use in this study
Srsf3	cgtgacgccgcgagacgagaa	ctgctccggctcgggaaaagc	RT-PCR
Dhcr7	tccaagaaggtgccattact	agtaatggcaccttcttgga	RT-PCR
Hmgcs1	ctgcggtctccttgctttgct	tccagcatctacaccatcgta	RT-PCR
Ern1	catgctcaaggacatggcta	tcccaacaatcaccattctg	RT-PCR
Hnf1α	ctggagaacctcagcccaga	ggttcctacgccccttctta	RT-PCR
INSR	catgctcaaggacatggcta	tttctcaaatggcctgtgctcctc	RT-PCR
Ern1	ggctGAATTCtgggccctacagaagtgtaa	gatcGGATCCtaagccagatggaagatgg	Cloning
Xbp1	aaacagagtagcagcgcagactgc	ggatctctaaaactagaggcttggtg	RT-PCR

Restriction sites for enzymes are marked in uppercase in Ern1 primers used for cloning.

Supplementary Table S10
Sequences for Q-PCR primers

Gene	Forward (5'-3')	Reverse (5'-3')
Srsf3	tcgtcgtcctcgagatgatt	ctccttcttggggatctgc
Afp	cctatgcccctcccccattc	ctcacaccaaagcgtcaacacatt
H19	atgtcttcatttctccctatagcc	gtcatcctcgccttcagtg
Alb	agtgttgtgcagaggctgac	ttctccttcacaccatcaagc
Gys2	ccagacaaattccacctagagc	gggcctgggatacttaaagc
Pygl	cagaagatccgagagggatg	aagggtttccatgcctgag
Pklr	gtggaggcttccttcaagtg	aggtcggtagcgagacagaa
G6pc	tctgtcccggatctaccttg	gaaagtttcagccacagcaa
Gck	ctggatgacagagccaggat	gctggaactctgccaggat
Pah	acattgagaaactggccaca	cccagcaccatatgccttta
Pkm2	atgctggagagcatgatcaagaagccacgc	caacatccatggccaagtt
Pck1	atgtgtgggcgatgacatt	aacccgttttctgggttgat
Hnf1α	cgcctccaccctggttat	actccccatgctgttgatg
Hnf1β	atccccagcaatctcagaac	tgggaggtgttgaggctct
Hnf4α	ccaagaggtccatggtgttt	ccgagggacgatgtagtcat
Onecut1	agaccttccggaggatgtg	ttgctctttccgtttgcag
E2f8	tcagcccaaacaacagtgg	gcagactgctcagcctctaag
Cebpα	aaacaacgcaacgtggaga	gcggtcattgtcactggtc
Foxa1	gaacagctactacgcggaca	cggagttcatgttgctgaca
Cebpζ	agggcaagaatggcttctc	tccaaagtagccagcataagg
Atf3	gctggagtcagttaccgtcaa	cgcctccttttcctctcat
ZHX2	aaggaactcacagcagacactg	gcacagacaattgtaactgtagca
Igf1	tcggcctcatagtacccact	acgacatgatgtgtatctttattgc
Igfals	ggccagctctgtacaaggaa	cagaaagccagaagcaccac
Igfbp2	gcgggtacctgtgaaaagag	cctcagagtggtcgtcatca
Ghr	ttgtagttatattttcaaagcagcaaa	agaagatctggatcaatccctttt
Hmgcs1	cagggtctgatccccttg	cagagaactgtggtctccaggt
Hmgcr	cgtaagcgcagttccttcc	ttgtagcctcacagtccttgg
Dhcr7	gcttcaggcaggcacttaga	ggatttcgaagccatcagg
Scap	tggctacttcaccctcgtg	acaccaggcccacaacag
SREBP2	acctagacctcgccaaaggt	gcacggataagcaggtttgt
SREBP1	ggttttgaacgacatcgaaga	cgggaagtcactgtcttggt
Cat	ccttcaagttggttaatgcaga	caagtttttgatgccctggt
Scd1	ttccctcctgcaagctctac	cagagcgctggtcatgtagt
Dgat2	ggcgctacttccgagactac	tggtcagcaggttgtgtgtc
Acc2	tgaatctcacgcgcctacta	ttgtgttctcggcctctctt
Edem1	ggtcttcgaagctacgataagg	gggctgtttggaatcagttatta

Supplementary Methods

Hematology Analysis

Hematology analysis was performed by the UCSD Murine Hematology and Coagulation Core Laboratory using un-clotted blood from SRSF3HKO and WT mice.

Analysis of Microarray data

Expression data from exon array were analyzed by three methods: 1) data were normalized by RMA and analyzed by ANOVA using Exon Array Analyzer; 2) data were normalized by RMA and analyzed by ANOVA using X-Ray (Biotique Systems, Reno, NV); and 3) un-normalized raw data was analyzed using a Bayesian variance modeling approach in VAMPIRE using a FDR of 0.05. Lists of significant genes by the three approaches were imported into GeneSpring (Agilent) for visualization. A Venn diagram was generated to show the overlap and genes that were significant by at least two approaches were combined to give the final list of 895 genes whose expression was significantly altered. Analysis of exon utilization was performed in Exon Array Analyzer and X-Ray after RMA normalization and in GeneSpring after PLIER normalization. The overlap of the approaches was visualized by Venn Diagram in GeneSpring as before and genes that showed significant exon bias by at least two approaches were combined to give the final list of 956 genes that showed significant alteration of exon utilization. Genes in the altered expression list were subjected to gene ontology mapping using VAMPIRE's Goby or DAVID (NIAID), or mapped to pathway, disease, process and toxicity maps using GeneGo's Metacore software (St. Joseph, MI). The gene list was also used for network analysis in MetaCore to identify transcription factors that might drive expression of these genes. The individual networks for liver-enriched transcription factors were merged to create a global network that included HNF4α, HNF1α, SREBP1, STAT1, C/EBPα, C/EBPβ, ESR1, GCRα and CREB1. A similar global network was created for non-liver-specific transcription factors including Sp1, p53, c-Myc, AP-1 and E2F1. Similarly, interactome analysis in MetaCore was used to highlight transcription factors that were over-connected in the dataset, i.e. that had more connections than expected. Genes in the altered splicing list were subjected to pathway and process mapping using Metacore software, and for gene ontology mapping using Metacore and DAVID.

Antibodies used for immunoblotting and imunohistochemistry

Antibodies used for immunoblotting : anti SFRS3 rabbit polyclonal antibody (1:3000 dilutions, ab73891,abcam), anti-XBP-1 (M-186) rabbit polyclonal antibody (1:100 dilutions, Santa Cruz Biotechnology), anti-actin mouse monoclonal antibody (1:5000 dilutions, abcam), anti-β-tubulin rabbit polyclonal antibody (1:1000 dilutions, Santa Cruz Biotechnology), anti-HNF1 alpha rabbit polyclonal antibody (N1N3, 1:2000 dilutions, GeneTex), anti-ATF6 mouse monoclonal antibody (Clone 70B1413.1) (1:500 dilutions, Imgenex), anti-IRE1α rabbit monoclonal antibody (1:1000 dilutions, Cell Signaling Technologies) anti-cleaved caspase-3 (Asp175) (5A1E) rabbit

monoclonal antibody (1:1000 dilutions, Cell Signaling Technologies), anti-total/phospho-eif2alpha (1:1000 dilutions, Cell Signaling Technologies), anti-GRP78 rabbit polyclonal antibody (1:1000 dilutions, Cell Signaling Technologies), anti-GRP94 rabbit polyclonal antibody (1:1000 dilutions, Cell Signaling Technologies), anti-phospho-PERK rabbit polyclonal antibody (1:1000 dilutions, Cell Signaling Technologies). The following antibodies were used for immunohistochemistry: anti-Ki67 (1:100 dilutions, ab15580, abcam), anti-CD45 (1:100 dilutions, ab10558, abcam), anti-PCNA (1:100 dilutions, ab2624, abcam).

Partial hepatectomy and BrdU staining

Partial hepatectomy was performed using 3 months old SRSF3HKO and their WT littermates according to the method of Mitchell et al.[53]. 36 hrs after partial hepatectomy, mice were injected intraperitoneally with bromodeoxyuridine (BrdU) labeling reagent according to the manufacturer's instruction (Invitrogen). Animals were sacrificed and liver was hervested 2 h after injection. BrdU immunostaining was performed with formalin fixed liver sections according to the manufacturer's instruction (Invitrogen).

In vivo administration of AAV-cre virus

To determine the effect of adeno-associated virus (AAV) mediated recombination in adult liver , 9-12 weeks old Srsf3flox/flox mice were intravenously (I.V.) injected with a total of 2 $X10^{12}$ particles of AAV-Cre-GFP (Serotype 2, Signagen Lab) in a final volume of 100 µl with a 27-gauge needle via tail vein. The mice were sacrificed at 4 weeks after the injection and liver was harvested for analysis of gene and protein expression and immunohistochemistry.

Transmission electron microscopy

Perfused liver from one month old SRSF3HKO and littermate control mice were immersed in modified Karnovsky's fixative (2.5% glutaraldehyde and 2% paraformaldehyde in 0.15 M sodium cacodylate buffer, pH 7.4) postfixed in 1% osmium tetroxide in 0.15 M cacodylate buffer and stained en bloc in 2% uranyl acetate. Samples were dehydrated in ethanol, embedded in Durcupan epoxy resin (Sigma-Aldrich), sectioned at 50 to 60 nm on a Leica UCT ultramicrotome, and picked up on Formvar and carbon-coated copper grids. Sections were stained with 2% uranyl acetate and Sato's lead stain. Grids were viewed using a JEOL 1200EX II (JEOL, Peabody, MA) transmission electron microscope and photographed using a Gatan digital camera (Gatan, Pleasanton, CA). Processing of the liver for electron microscopy was performed by UCSD electron microscopy core.

Supplementary References

53. Mitchell, C. & Willenbring, H. A reproducible and well-tolerated method for 2/3 partial hepatectomy in mice. *Nat Protoc* **3**, 1167-1170, 80 (2008).