Coordinated Activities of Multiple Myc-Dependent and Myc-Independent Biosynthetic Pathways in Hepatoblastoma

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Running Title: *Coordinated Biosynthetic Pathways in Hepatoblastoma*

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SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure S1. Expression of potential Myc surrogates in WT and KO hepatocytes and HBs. *A*, Transcript levels for the indicated genes was obtained from RNA seq data performed on WT and KO HBs. *B*, Immuno-blotting for the indicated proteins of WT and KO livers (L) and HBs (T)

Supplemental Figure S2. Structure and function of ETC complexes in livers and HBs. *A*, Top panel: Representative BNGE of ETC complexes from paired WT and KO livers (L) and HBs (T) stained with Coomassie Blue. Bottom panels: Representative examples of *in situ* enzymatic activities for ETC complexes I, III, IV and V. SC=super-complexes composed of varying stoichiometries of Complexes I, II and IV. *B*, Quantification of relative specific activities of *in situ* enzymatic activities after normalizing to total protein content. N=4-7 samples/group. Note that Complex II assays were performed upon total mitochondrial lysates as *in situ* gel-based assays proved unreliable(1,2).

Supplemental Figure S3. Low-magnification transmission electron micrographs of WT and KO livers (L) and HBs (T). *A*, Representative photos (magnification x 10,000) emphasizing the relative paucity of mitochondria (white arrows) in HBs. *B*, Quantification of mitochondrial

number and size in WT livers and tumors.

Supplemental Figure S4. RNA seq analysis of differential gene expression in WT and KO HBs. Red=up-regulated; green=down-regulated. The transcripts depicted here represent all those identified with $q<0.05$ after correction for false discovery rates.

Supplemental Figure S5. Transcripts encoding RPs. The depicted heat map is same as shown in Figure 3*B*. Absolute levels of expression are included.

Supplemental Figure S6. Transcripts encoding proteins involved in the regulation of translation**.** The depicted heat map is the same as shown in Figure 3*A* and includes members involved in signaling by eIF2, eIF4, p70S6K and mTOR(3,4). Absolute levels of expression are indicated thus permitting a direct comparison of transcript level differences among WT and KO hepatocytes and HBs. Note the ~11-25-fold down-regulation in both WT and KO HBs of transcripts encoding eIF4EBP3, a negative regulator of pre-initiation complex formation.

Supplemental Figure S7. Transcripts encoding glycolytic enzymes. *A,* The depicted heat map is the same as shown in Fig. 3*C*. Absolute levels of expression are included. *B,* The glycolytic pathway depicting key enzymes encoded by transcripts listed in *A.*

Supplemental Figure S8. IPA of the top categories of transcript variation between WT and KO HBs. We have previously shown that several of these pathways, which regulate functions associated with white blood cells, including "granulocyte adhesion and diapedesis" and "leukocyte extravasation signaling" are likely to be up-regulated in KO livers in response to the accumulation of lipids by hepatocytes (1). Excluding these and the already discussed pathways pertaining to protein translation, 8 of the remaining pathways (asterisks) were associated with lipid, sterol and eicosanoid biosynthesis.

Supplemental Figure S9. Differential expression of transcripts related to fatty acid biosynthesis. The data are taken from the heat map depicted in Figure 4*A* with actual levels of expression indicated. ND=not detected.

Supplemental Figure S10. Differential expression of transcripts related to FAO. The data are taken from the heat map depicted in Figure 4*B* with actual levels of expression indicated

Supplemental Figure S11. Differential expression of transcripts related to cholesterol biosynthesis. The data are taken from the heat map depicted in Figure 4*C* with actual levels of expression indicated.

Supplemental Figure S12. Reduced conversion of glutamine to α-ketoglutarate. *A,* In the liver Slc1A5 is the major glutamine transporter, whereas Gls2 and Glud1 catalyze the sequential two step deamination of glutamine to α-ketoglutarate. Glud1 also catalyzes the conversion of oxaloacetate and pyruvate to α-ketoglutarate via the actions of Got1/2 and Gpt, respectively. *B,* Transcript levels encoding each of the above-mentioned enzymes in WT and KO livers and HBs. Each bar represents the mean of five individual RNAseq results +/- 1 S.E. *C,* Immunoblots for Gls2 and Glud1 in WT and KO livers and HBs. *D,* The conversion of glutamine to α-ketoglutarate via the actions of Gls2 and Glud1. Each result was normalized to equivalent protein concentrations.

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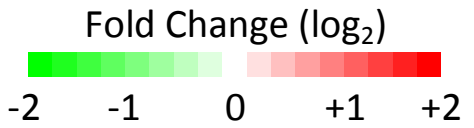
Supplemental Table S1. Antibodies utilized in the current study

Antibody	Species	Vendor and ID no.	Dilution used
Myc	Rabbit	Cell Signaling(13987)	1:1,000
N-Myc	Rabbit	Santa Cruze(sc791)	1:500
L-Myc	Rabbit	Santa Cruze(sc790)	1:1,000
AMPK	Rabbit	Cell Signaling (3532)	1:1,000
pAMPK (Thr172)	Rabbit	Cell Signaling (4188)	1:1,000
Histone H3	Rabbit	Cell Signaling (9715)	1:1,000
Glutaminase 2	Rabbit	Abcam(ab113509)	1:1,000
Glutamine dehydrogenase	Rabbit	Cell signaling(12793)	1:1,000
Acetyl-histone-H3 (K9/K14)	Rabbit	Santa Cruz (sc8655-R)	1:500
GAPDH	Mouse	Sigma-Aldrich(G8795)	1:20,000
HRP anti-mouse	Horse	Cell Signaling(7076)	1:10,000
HRP anti-ribbit	Goat	Cell Signaling(7074)	1:5,000
Alexa Fluor 488 anti-rabbit	Goat	Thermo Fisher(A-11008)	1:1,000

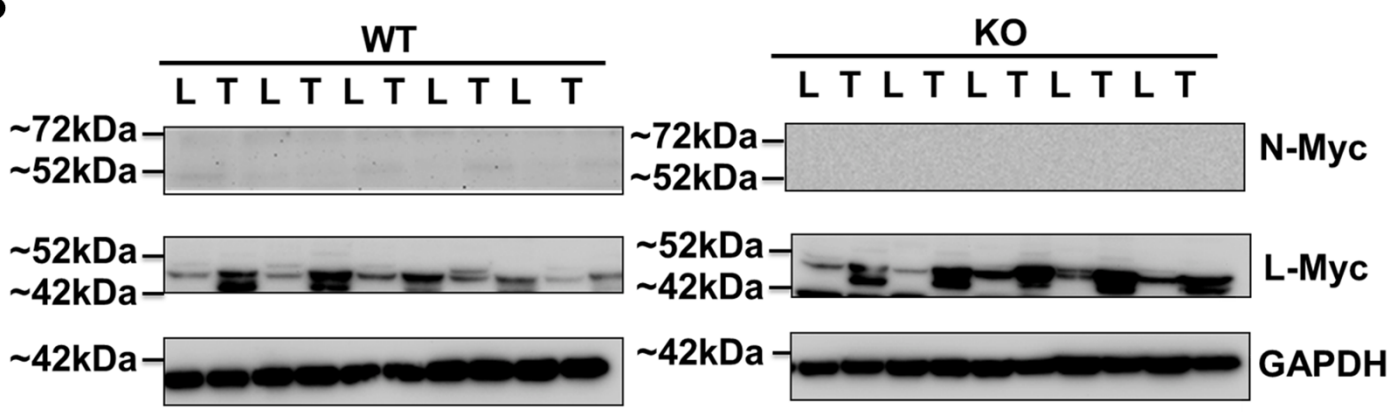
Supplemental Fig. S1

A

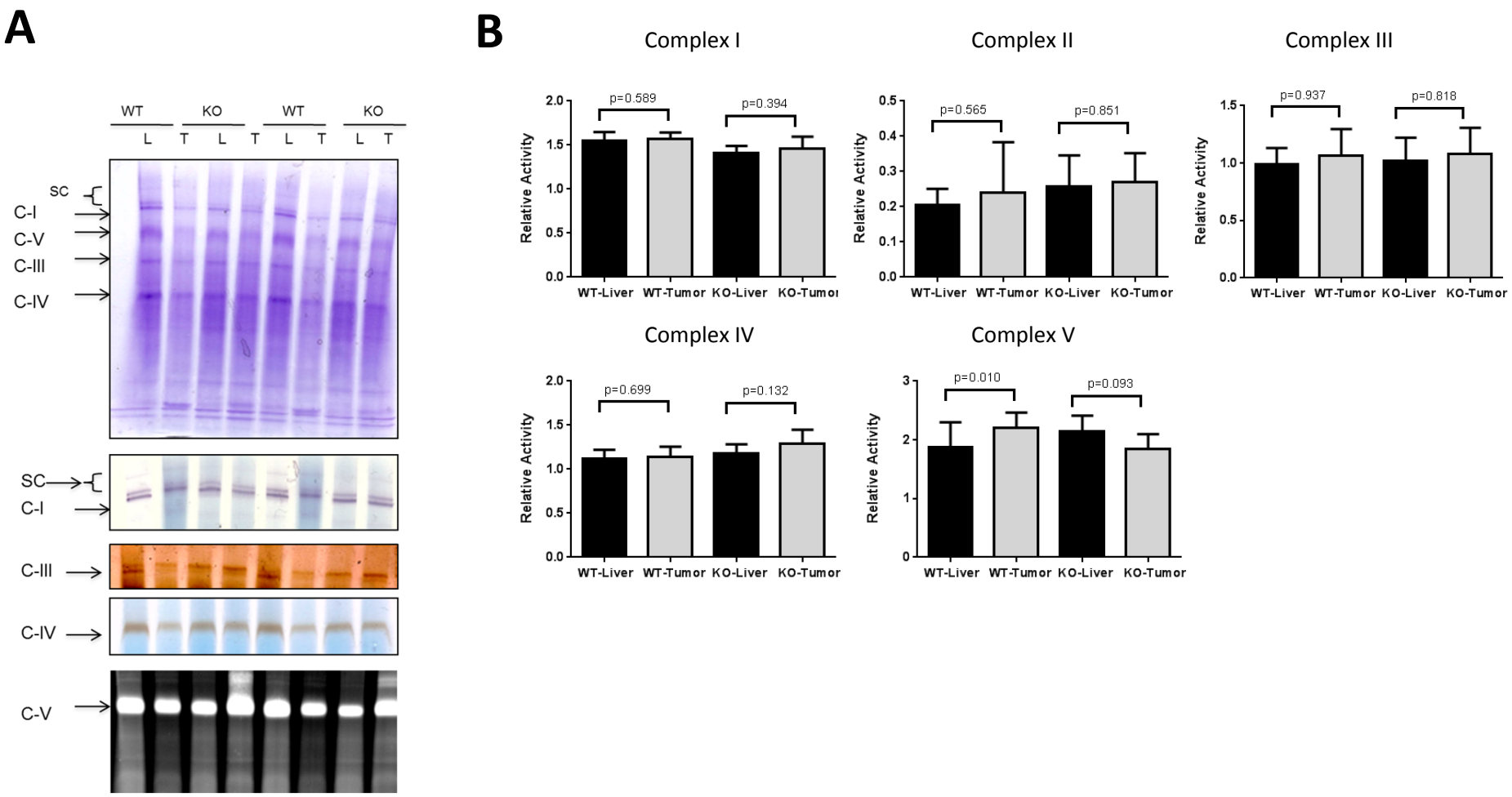
Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO				
		WT		KO		Hepatocyte		Tumor		
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value
18109	MycN	2.66579	0.0005	4.9589	0.0495	-0.44572	1	0.15	1	0.00005
17869	Myc	2.71304	0.001	1.9223	0.001	2.48272	0.00005	9.669	0.00005	0.00005
16918	MycL1	1.02645	0.1528	-0.1244	0.7672	-0.08056	0.56465	2.1	0.56465	0.00065
107771	Bmyc	3.24755	0.004	4.0193	0.0011	0.02518	0.9872	0.596	0.9872	0.0204
17187	Max	1.32828	0.0003	1.0313	0.0001	-0.06986	0.6689	1.171	0.6689	0.30865
17428	Mnt	1.75034	0.0018	2.0488	< 0.0001	0.23179	0.24975	0.955	0.24975	0.8384
29808	Mga	1.43572	0.0012	-7.5744	0.2938	-8.90309	0.56055	1.077	0.56055	0.5515
17119	Mxd1	2.0956	0.0137	2.0085	0.0002	0.18613	0.4201	1.209	0.4201	0.24585
17859	Mxi1(Mxd2)	0.72251	0.0021	0.2568	0.2875	0.00215	0.9735	1.383	0.9735	0.0418
17121	Mxd3	5.01446	0.0001	5.0623	< 0.0001	0.243	0.81725	1.145	0.81725	0.8958
17122	Mxd4	0.3774	0.2197	0.4551	0.1366	-0.08549	0.6747	0.893	0.6747	0.6504
17120	Mad1l1	0.81785	0.0196	1.1574	0.0018	0.2543	0.203	0.943	0.203	0.82065
56150	Mad2l1	3.94556	0.003	3.9472	0.0678	-0.36914	0.3595	0.773	0.3595	0.3518
20425	SHMT1	-0.131	0.6498	-0.199	0.2951	-0.02056	0.79875	1.033	0.79875	0.83415
68632	Myct1	1.02037	0.4076	1.0469	0.4377	0.02111	0.9783	0.996	0.9783	0.7778
15361	HMGA1	-0.0123	0.9768	-0.6635	0.1475	-0.24419	0.43215	1.326	0.43215	0.4766
21428	Mlx	0.63471	0.0086	0.362	0.0773	-0.1768	0.33125	1.069	0.33125	0.58905
208104	Mlxip (MondoA)	1.89311	0.0003	1.8463	< 0.0001	0.31356	0.1257	1.284	0.1257	0.1483
58805	Mlxipl (Chrebp)	0.28983	0.2877	0.8266	0.0165	0.43805	0.00755	0.934	0.00755	0.65565



B



Supplemental Fig. S2



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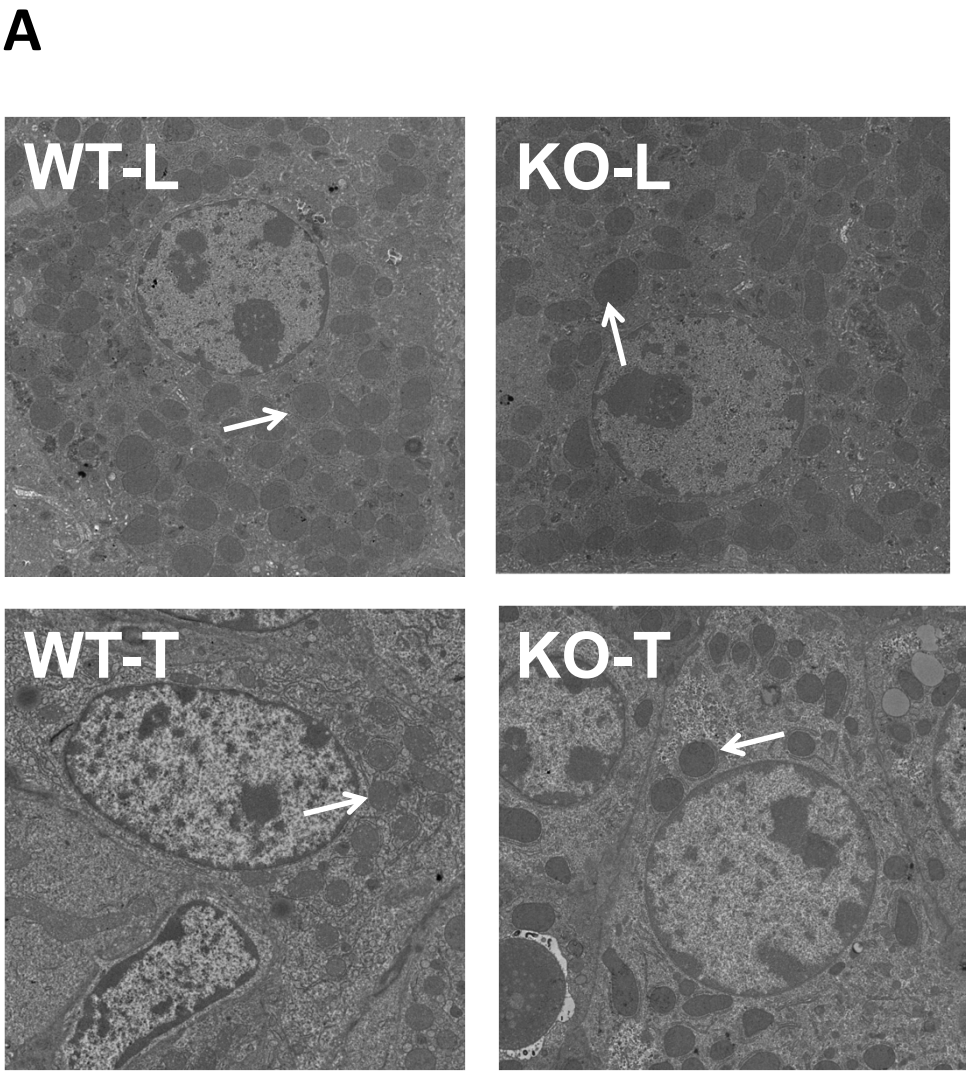

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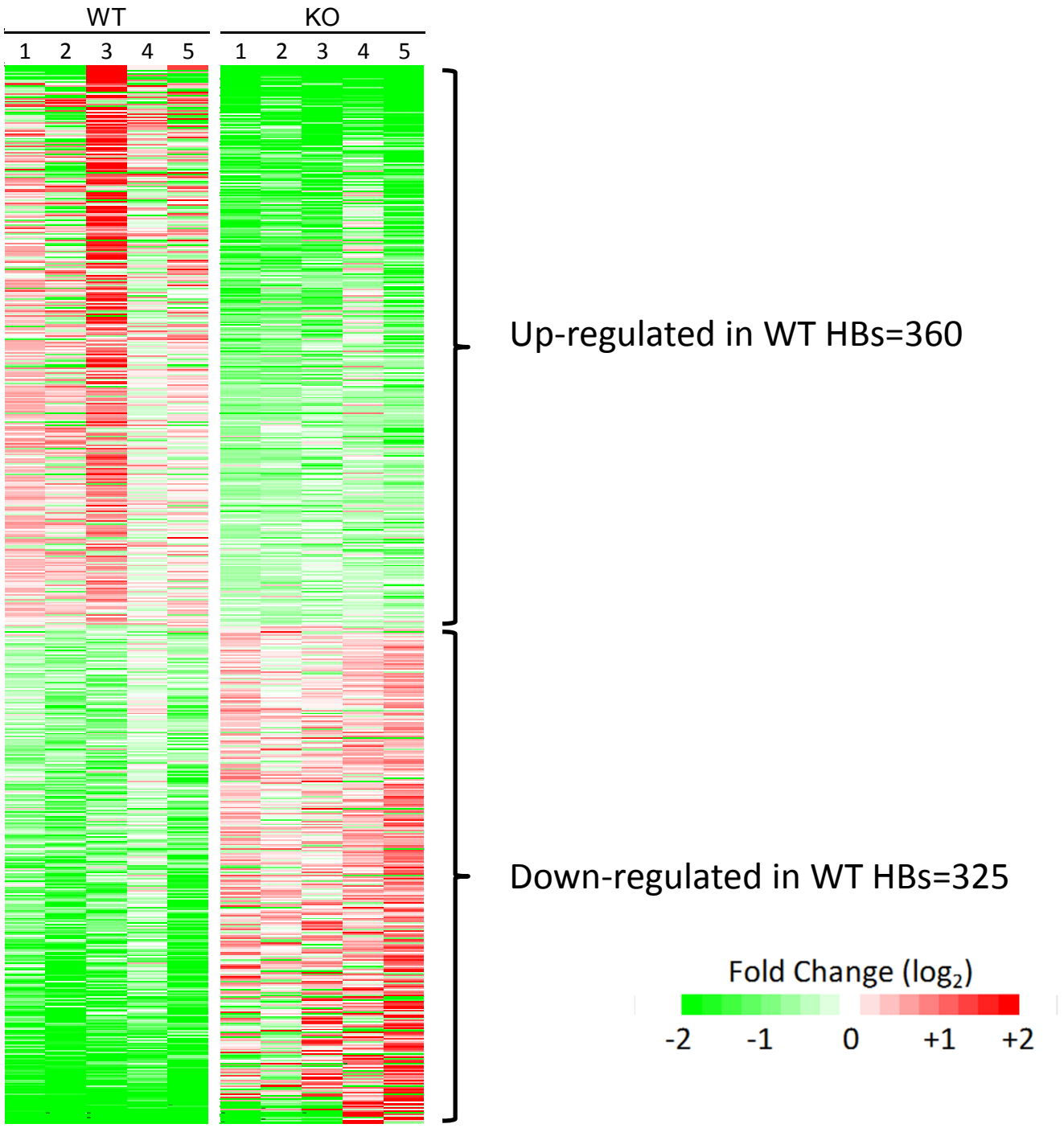
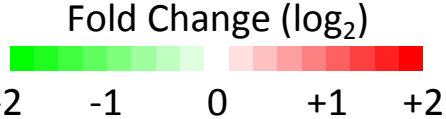


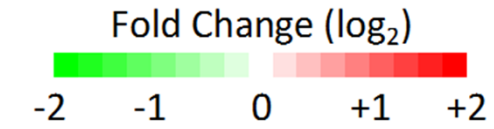
Supplemental Fig. S5

Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
67945	Rpl41	1.74219	0.013	1.02487	0.00383	0.100198	0.39875	1.762	0.39875	0.00455																		
100043813	Rps27rt	2.09551	0.0202	1.15726	0.00812	0.056166	0.66135	1.992	0.66135	0.00195																		
20084	Rps18	2.11274	0.0029	1.28879	0.00032	0.223376	0.1333	2.067	0.1333	0.00175																		
20054	Rps15	1.33649	0.0108	0.72165	0.00068	0.340651	0.6729	1.939	0.6729	0.52035																		
110954	Rpl10	1.85765	0.0009	1.55574	0.00041	0.167644	0.3207	1.385	0.3207	0.1424																		
20068	Rps17	1.68703	0.0028	1.0089	0.00033	0.22934	0.1344	1.876	0.1344	0.00095																		
20042	Rps12	2.28065	0.0125	1.51676	< 0.0001	0.449116	0.0039	2.318	0.0039	0.0002																		
19921	Rpl19	1.53045	0.0078	0.83389	0.0004	0.123076	0.4045	1.765	0.4045	0.00735																		
56040	Rplp1	2.66364	0.0016	2.07392	< 0.0001	0.472522	0.00355	2.088	0.00355	0.0002																		
54217	Rpl36	1.61067	0.0052	0.70447	0.00186	0.227923	0.11785	2.195	0.11785	0.00005																		
19943	Rpl28	1.48677	0.0059	0.98724	0.00056	0.306342	0.05035	1.748	0.05035	0.002																		
67671	Rpl38	2.60447	0.0025	2.15956	< 0.0001	0.384099	0.1794	1.776	0.1794	0.0094																		
16898	Rps2	1.74688	0.0003	1.13719	< 0.0001	0.226015	0.16665	1.785	0.16665	0.0129																		
27176	Rpl7a	1.38018	0.0028	0.83954	0.00025	0.256764	0.1068	1.738	0.1068	0.00375																		
57808	Rpl35a	1.69688	0.0157	1.0127	0.00021	0.162245	0.27615	1.798	0.27615	0.00195																		
67025	Rpl11	1.57876	0.0024	0.77767	0.00016	0.086553	0.5007	1.85	0.5007	0.00085																		
20044	Rps14	1.6692	0.0112	1.01062	0.0091	0.255373	0.1098	1.884	0.1098	0.00065																		
268449	Rpl23a	1.93063	0.0012	1.28436	0.00024	0.166011	0.24815	1.756	0.24815	0.0024																		
19989	Rpl7	1.6019	0.0029	1.08698	0.00024	0.22153	0.16025	1.666	0.16025	0.0095																		
67186	Rplp2	1.63461	0.0027	1.0565	0.00059	0.217391	0.1253	1.736	0.1253	0.00095																		
20090	Rps29	2.53911	0.0012	2.02321	< 0.0001	0.150395	0.32895	1.587	0.32895	0.0072																		
20091	Rps3a1	1.59241	0.0022	1.04024	0.00215	0.255234	0.1025	1.75	0.1025	0.0067																		
19951	Rpl32	2.19745	0.005	1.43277	0.00022	0.343341	0.0256	2.155	0.0256	0.00025																		
66483	Rpl36al	0.92267	0.0016	0.70093	0.00042	0.012281	0.8677	1.176	0.8677	0.2374																		
66489	Rpl35	2.05064	0.0057	1.23634	0.00045	0.188207	0.1831	2.003	0.1831	0.0002																		
319195	Rpl17	1.89206	0.0062	1.00947	0.00159	0.089673	0.46075	1.962	0.46075	0.00075																		
26961	Rpl8	1.28486	0.0023	0.7675	0.00168	0.302078	0.0572	1.765	0.0572	0.00225																		
76846	Rps9	1.97104	0.002	1.31237	0.00267	0.231217	0.1405	1.853	0.1405	0.003																		
66475	Rps23	1.77085	0.0053	0.95742	0.00153	0.137047	0.38695	1.933	0.38695	0.0003																		
27370	Rps26	1.68378	0.0028	1.16168	0.00052	0.195824	0.188	1.645	0.188	0.002																		
54127	Rps28	2.12041	0.0022	1.44362	0.00071	0.184605	0.20625	1.817	0.20625	0.0003																		
20116	Rps8	2.05902	0.0013	1.35833	< 0.0001	0.363082	0.01875	2.09	0.01875	0.0002																		
20088	Rps24	1.98352	0.013	1.10472	0.0014	0.229743	0.11045	2.156	0.11045	0.00075																		
67427	Rps20	2.49369	0.0018	1.7487	< 0.0001	0.295155	0.0473	2.056	0.0473	0.0001																		
66481	Rps21	2.23749	0.0072	1.50663	< 0.0001	0.271297	0.079	2.003	0.079	0.00015																		
67891	Rpl4	1.61068	0.0002	1.18015	0.00014	0.230254	0.1455	1.581	0.1455	0.027																		
67097	Rps10	2.07134	0.0023	1.30424	0.00032	0.181946	0.1986	1.931	0.1986	0.0004																		
78294	Rps27a	1.99383	0.0036	1.42859	0.00072	0.241549	0.1217	1.749	0.1217	0.00615																		
20103	Rps5	2.05641	0.0019	1.26435	0.0002	0.263351	0.08075	2.078	0.08075	0.00005																		
20102	Rps4x	2.17124	0.0007	1.71412	0.00034	0.264421	0.10355	1.649	0.10355	0.0106																		
11837	Rplp0	1.83843	0.0003	0.98377	0.00037	0.176374	0.2726	2.043	0.2726	0.001																		
75617	Rps25	2.01932	0.0024	1.22144	< 0.0001	0.119157	0.3484	1.888	0.3484	0.0013																		
22121	Rpl13a	1.94853	0.0035	1.19295	0.00026	0.291974	0.0526	2.067	0.0526	0.0005																		
27207	Rps11	2.33255	0.0051	1.63598	< 0.0001	0.165624	0.2839	1.818	0.2839	0.0015																		
19896	Rpl10a	1.77114	0.0013	1.21732	0.00056	0.457647	0.0027	2.016	0.0027	0.00005																		
20005	Rpl9	2.30176	0.0087	1.26433	0.00013	0.079603	0.61875	2.169	0.61875	0.0006																		
16785	Rpsa	1.41231	0.0039	0.81404	0.00318	0.38076	0.0175	1.971	0.0175	0.0023																		
65019	Rpl23	1.73509	0.0022	1.14351	0.00016	0.302914	0.0493	1.859	0.0493	0.0015																		
20055	Rps16	2.44975	0.0027	1.72279	< 0.0001	0.185389	0.21475	1.882	0.21475	0.00115																		
19899	Rpl18	1.55491	0.0014	1.00864	0.00037	0.251092	0.12025	1.738	0.12025	0.0012																		
19981	Rpl37a	2.00037	0.0049	1.3962	< 0.0001	0.213597	0.16075	1.763	0.16075	0.0017																		
20104	Rps6	1.69347	0.0016	0.89144	0.00026	0.233779	0.1429	2.05	0.1429	0.0008																		
19944	Rpl29	1.63768	0.0015	1.26438	0.00013	0.266978	0.07125	1.559	0.07125	0.00715																		
19982	Rpl36a	1.98979	0.0021	1.20114	0.00032	0.276614	0.06285	2.093	0.06285	0.00005																		
68193	Rpl24	2.04682	0.0013	1.42191	< 0.0001	0.136107	0.35205	1.695	0.35205	0.00215																		
19988	Rpl6	1.73442	0.0023	1.04296	< 0.0001	0.283617	0.0712	1.966	0.0712	0.00155																		
269261	Rpl12	2.90071	0.0006	2.13782	< 0.0001	0.642592	0.0001	2.649	0.0001	0.00005																		
67941	Rps27l	1.7259	0.0007	1.16863	< 0.0001	-0.103017	0.6051	1.37	0.6051	0.0296																		
20115	Rps7	1.97007	0.0017	1.31342	0.00019	0.306413	0.04495	1.949	0.04495	0.0005																		
76808	Rpl18a	1.31887	0.0045	0.71531	0.00232	0.315223	0.0426	1.891	0.0426	0.0008																		
19942	Rpl27	1.50664	0.0041	0.92063	0.00037	0.237077	0.11145	1.769	0.11145	0.00035																		
26451	Rpl27a	1.63563	0.0059	0.89713	0.00045	0.150095	0.28685	1.851	0.28685	0.00105																		
68052	Rps13	2.18696	0.0031	1.44984	0.00015	0.130747	0.38155	1.825	0.38155	0.0002																		
270106	Rpl13	2.45774	0.0009	1.82114	< 0.0001	0.304868	0.0359	1.92	0.0359	0.00095																		
67248	Rpl39	3.46759	0.0029	2.73678	< 0.0001	0.254295	0.09425	1.979	0.09425	0.00065																		
20085	Rps19	2.77847	0.0047	1.87531	0.00012	0.261472	0.09265	2.242	0.09265	0.00005																		
100503670	Rpl5	1.87107	0.0034	1.02984	0.00089	0.228633	0.15895	2.099	0.15895	0.0006																		
27367	Rpl3	2.40379	0.0003	1.71992	0.00022	0.219001	0.1239	1.87	0.1239	0.0031																		
114641	Rpl31	1.88806	0.0063	1.21842	< 0.0001	0.292333	0.0922	1.948	0.0922	0.0005																		
67281	Rpl37	1.43394	0.0052	0.84897	0.00218	0.350414	0.01925	1.912	0.01925	0.0001																		
67115	Rpl14	2.3849	0.0013	1.66753	< 0.0001	0.156164	0.33345	1.832	0.33345	0.0013																		
19933	Rpl21	1.70883	0.0026	1.19313	< 0.0001	0.213398	0.1585	1.658	0.1585	0.00965																		
27050	Rps3	1.94591	0.0048	1.0488	0.00116	0.122737	0.4252	2.028	0.4252	0.0008																		
66480	Rpl15	2.13242	0.001	1.5799	< 0.0001	0.16765	0.2666	1.647	0.2666	0.0042																		
19934	Rpl22	1.84833	0.0019	1.11797	0.00019	0.090653	0.5041	1.767	0.5041	0.0004																		
68028	Rpl22l1	4.39441	0.0042	3.96383	0.00028	0.219485	0.26615	1.569	0.26615	0.00335																		
267019	Rps15a	2.07121	0.0039	1.4534	0.00021	0.295542	0.04285	1.883	0.04285	0.00015																		
66229	Rpl7l1	0.82176	0.0002	0.75425	0.00182	-0.042336	0.8213	1.018	0.8213	0.78355																		
100502825	Rpl37rt	2.36308	0.0012	1.79788	0.00025	0.382375	0.0254	1.929	0.0254	0.26255																		
19941	Rpl26	-1.4476	0.0046	-2.88015	0.00055	-0.24838	0.81335	2.272	0.81335	0.36375																		
66184	Rps4l	0.59039	0.1298	0.52428	0.46055	-0.322224	0.3566	0.837	0.3566	0.6444																		
19946	Rpl30	0.32393	0.3979	-0.02033	0.95771	0.102759	0.94055	1.363	0.94055	0.6044																		
66538	Rps19bp1	1.36929	0.0015	1.42024	< 0.0001	0.136743	0.50045	1.061	0.50045	0.65835																		
68436	Rpl34	1.9497	0.0004	1.34676	0.00043	-0.071527	0.9081	1.445	0.9081	0.7491																		
57294	Rps27	6.6621	0.0173	6.25532	0.04831	-0.090668	0.9542	1.245	0.9542	0.69765																		



Supplemental Fig. S6

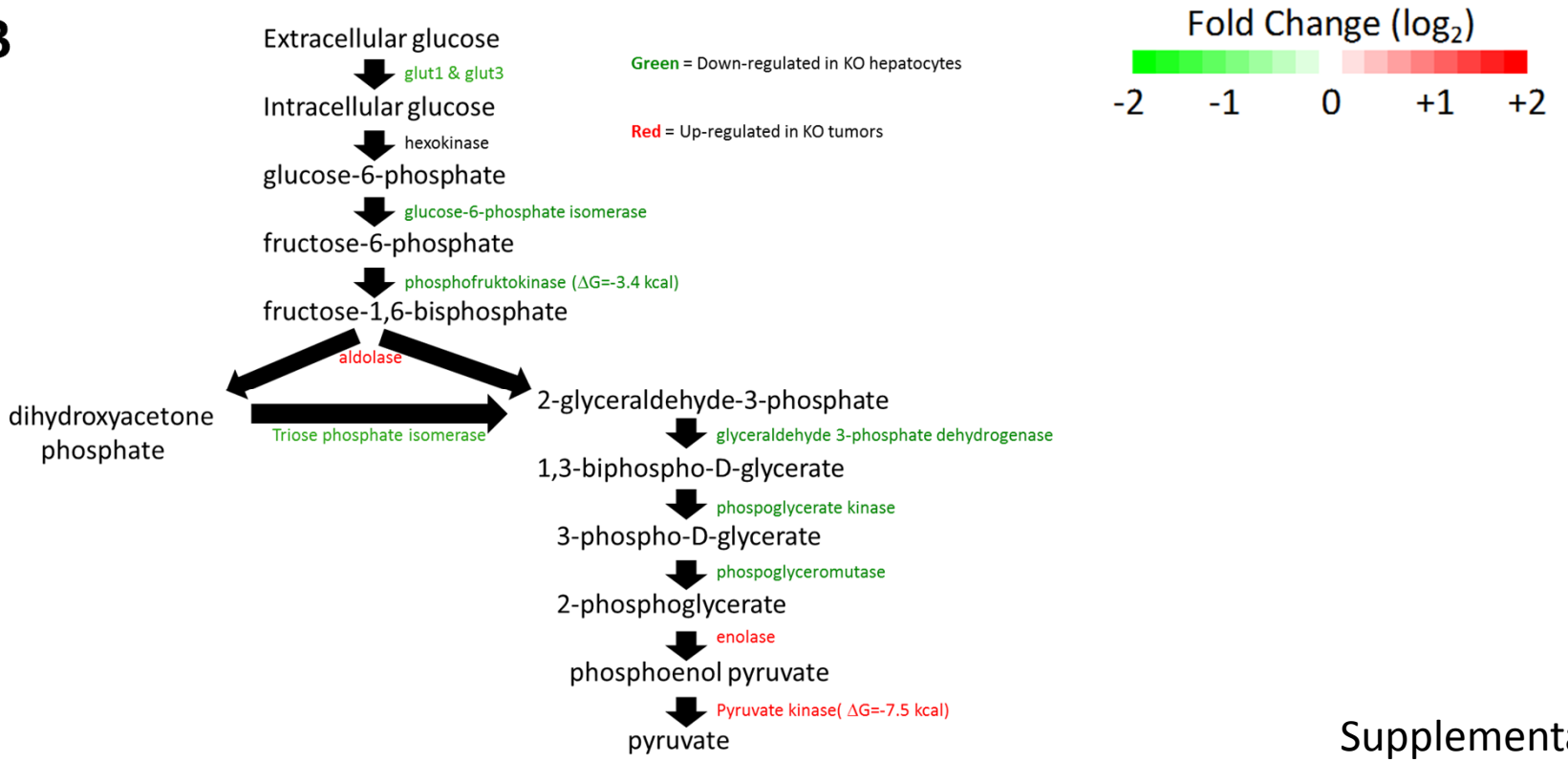
Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
381404	Pabpc1l	5.18419	0.0044	5.44632	0.0014	-0.487956	1	0.595	1	1																		
12877	Cpeb1	3.60576	0.0006	3.86504	< 0.0001	0.134924	0.57265	0.917	0.57265	0.63645																		
66892	Eif4e3	3.30828	0.002	3.64597	< 0.0001	-0.318557	0.217	0.635	0.217	0.0193																		
208691	Eif5a2	3.18944	0.0001	4.09914	0.03338	0.789505	1	0.92	1	1																		
13666	Eif2ak3	2.36478	0.0006	2.73397	< 0.0001	0.051071	0.7085	0.802	0.7085	0.1845																		
66085	Eif3f	1.83995	0.0003	1.59386	0.0001	0.205563	0.2084	1.368	0.2084	0.03335																		
16418	Eif6	1.7709	0.0003	1.61567	0.0002	0.068107	0.62815	1.167	0.62815	0.24445																		
27103	Eif2ak4	1.66115	0.0001	1.90368	< 0.0001	0.051175	0.80485	0.876	0.80485	0.543																		
19106	Eif2ak2	1.56325	0.0054	1.38913	0.00022	-0.22614	0.2213	0.965	0.2213	0.9113																		
74203	Eif4enif1	1.54449	0.0001	1.17337	0.00031	-0.035643	0.9691	1.262	0.9691	0.5489																		
245474	Dkc1	1.45613	0.0131	1.48565	0.00023	0.232899	0.47105	1.151	0.47105	0.65855																		
226982	Eif5b	1.40429	0.0001	1.38709	< 0.0001	0.064316	0.65395	1.058	0.65395	0.65185																		
67204	Eif2s2	1.308	0.0027	1.00081	0.0005	0.086927	0.52175	1.314	0.52175	0.0555																		
68135	Eif3h	1.2953	0.0036	0.67602	0.00484	-0.098261	0.5891	1.435	0.5891	0.0148																		
13685	Eif4ebp1	1.28911	0.0042	0.73167	0.00967	0.179898	0.23065	1.667	0.23065	0.00075																		
56347	Eif3c	1.26837	0.0014	1.1763	0.00023	0.051679	0.74695	1.105	0.74695	0.4966																		
13681	Eif4a1	1.26802	0.0001	1.07561	0.00246	0.10727	0.4779	1.231	0.4779	0.2294																		
98221	Eif3m	1.26096	0.0035	0.83999	0.00085	0.044256	0.75875	1.381	0.75875	0.0259																		
16341	Eif3e	1.14567	0.0012	0.68289	0.00491	0.078112	0.5846	1.455	0.5846	0.00725																		
54196	Pabpn1	1.13078	0.0039	1.64202	< 0.0001	0.514931	0.0042	1.003	0.0042	0.9615																		
13669	Eif3a	1.12092	0.0018	1.22362	0.00015	0.192415	0.22535	1.064	0.22535	0.61375																		
13665	Eif2s1	1.11395	0.0034	0.87035	0.00404	-0.076339	0.66695	1.123	0.66695	0.30255																		
192170	Eif4a3	1.11412	0.0004	1.16742	0.00019	-0.01933	0.84395	0.951	0.84395	0.88675																		
229317	Eif2a	1.08897	0.0008	0.79767	0.00077	0.134344	0.7067	1.343	0.7067	0.50565																		
26905	Eif2s3x	1.08087	0.0021	1.05913	0.00081	0.087628	0.59635	1.079	0.59635	0.5039																		
16865	Eif2d	1.07727	0.0002	1.06373	0.00076	0.090473	0.5123	1.075	0.5123	0.52285																		
54709	Eif3i	1.05754	0.0035	0.37621	0.03789	0.04637	0.72375	1.656	0.72375	0.00075																		
20918	Eif1	0.99224	0.0004	0.731	0.01625	0.047096	0.86015	1.238	0.86015	0.22545																		
18458	Pabpc1	0.97786	0.001	0.87378	0.00158	0.337305	0.03755	1.358	0.03755	0.0565																		
217715	Eif2b2	0.94981	0.0032	0.74883	0.00039	0.073033	0.6451	1.209	0.6451	0.1702																		
73830	Eif3k	0.89395	0.0135	0.50165	0.00101	0.096759	0.5041	1.404	0.5041	0.0168																		
53356	Eif3g	0.88924	0.0033	0.79203	0.00031	0.099563	0.55925	1.146	0.55925	0.29265																		
56717	Mtor	0.8912	0.0269	1.08441	0.00038	0.157115	0.38675	0.975	0.38675	0.89835																		
13690	Eif4g2	0.84925	0.0098	0.99134	0.00172	-0.022613	0.86865	0.892	0.86865	0.67695																		
22384	Eif4h	0.84096	0.0037	0.84816	0.00018	-0.011214	0.9054	0.987	0.9054	0.9829																		
66711	Sbds	0.76935	0.0024	0.36713	0.1107	-0.083208	0.66225	1.247	0.66225	0.10385																		
224045	Eif2b5	0.74574	0.0009	0.66133	0.0012	0.075137	0.64175	1.117	0.64175	0.36885																		
13664	Eif1a	0.73861	0.0032	0.77716	0.00181	0.168335	0.25915	1.094	0.25915	0.4171																		
276770	Eif5a	0.68884	0.0046	0.39079	0.05671	0.012764	0.8643	1.24	0.8643	0.1675																		
230721	Pabpc4	0.65381	0.015	0.31733	0.14409	0.373499	0.0282	1.636	0.0282	0.0012																		
26987	Eif4e2	0.63721	0.0002	0.52102	0.00247	-0.059228	0.80365	1.04	0.80365	0.67365																		
27979	Eif3b	0.62351	0.0087	0.65144	0.00074	0.26852	0.08245	1.181	0.08245	0.2347																		
223691	Eif3l	0.5532	0.0027	0.47252	0.03367	0.006755	0.90065	1.062	0.90065	0.56505																		
78655	Eif3j1	0.53259	0.029	0.38252	0.07399	0.004449	0.9396	1.113	0.9396	0.5093																		
108067	Eif2b3	0.51112	0.0316	0.24144	0.17994	0.193109	0.2942	1.378	0.2942	0.0708																		
209354	Eif2b1	0.46272	0.0191	0.37733	0.03552	0.092252	0.5617	1.131	0.5617	0.3859																		
13667	Eif2b4	0.46276	0.0006	0.61481	0.0016	0.162229	0.27765	1.007	0.27765	0.8645																		
231207	Cpeb2	-0.79246	0.0288	-0.3848	0.15123	0.250075	0.1413	0.897	0.1413	0.601																		
108112	Eif4ebp3	-3.45449	0.0051	-4.48411	0.00885	-0.045688	0.6816	1.978	0.6816	0.00015																		



A

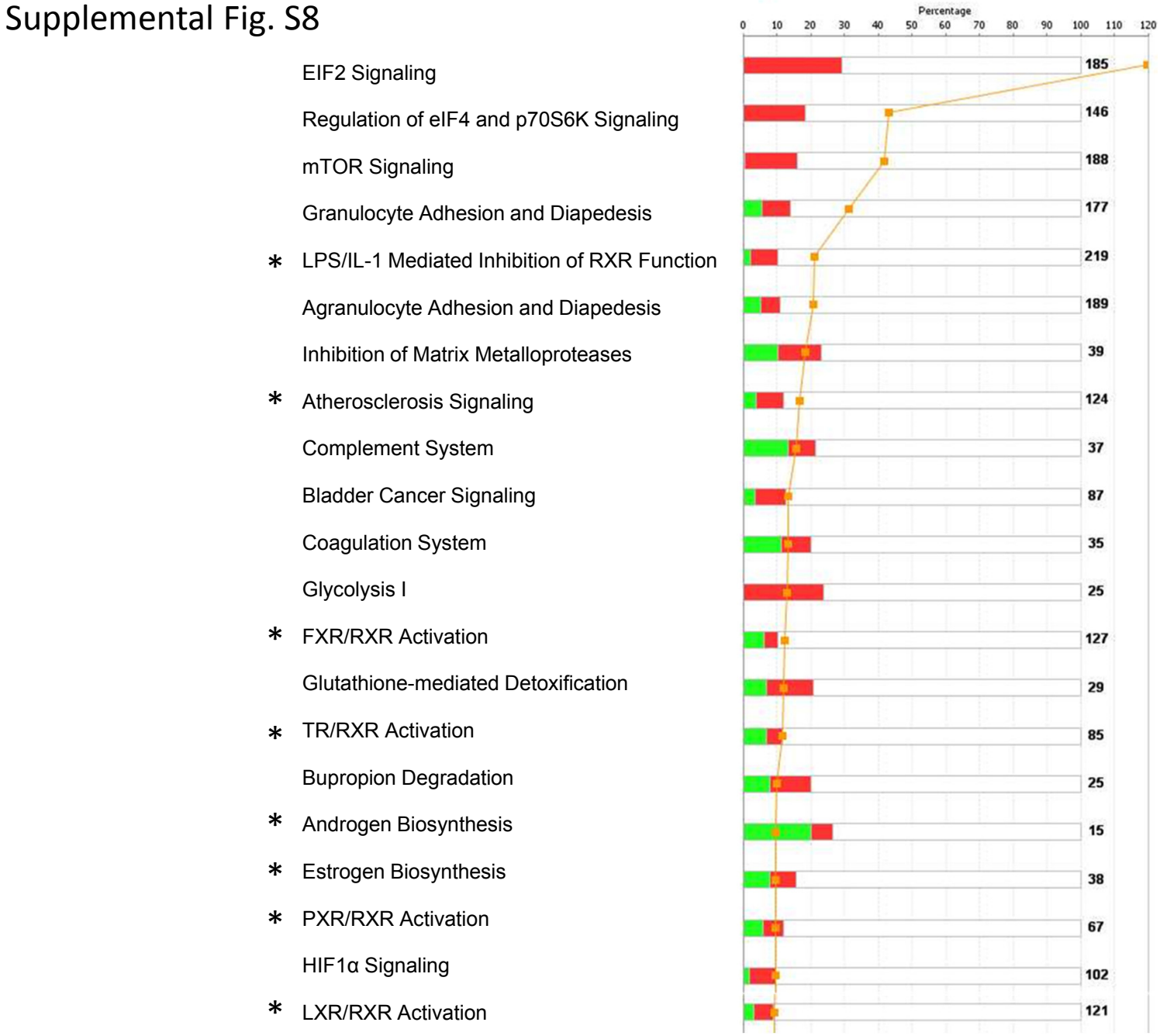
Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold D	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
20525	SLC2A1	1.58506	0.1198	0.47423	0.19863	0.20369	0.1633	2.487	0.1633	0.00005																		
20526	SLC2A2	1.31565	0.0258	0.51479	0.12053	-0.524995	0.0025	1.211	0.0025	0.22935																		
20527	SLC2A3	4.85613	0.1233	4.83753	0.00706	1.387674	1	2.651	1	0.00805																		
20528	SLC2A4	6.07493	0.0198	6.56371	< 0.0001	0.619948	1	1.095	1	0.78																		
15275	HK1	3.63795	0.0783	2.5991	0.02999	-0.191743	1	1.799	1	0.02255																		
15277	HK2	5.75422	0.045	4.49358	0.00307	-0.606021	1	1.574	1	0.0651																		
212032	HK3	3.03876	0.0134	3.53789	0.01232	0.679162	1	1.133	1	0.5318																		
14751	GPI1	1.46372	0.0015	0.71571	0.00077	0.150086	0.30745	1.864	0.30745	0.0002																		
18641	PFKL	2.57103	0.0066	2.04986	< 0.0001	0.131595	0.50285	1.572	0.50285	0.0022																		
18642	PFKM	0.15914	0.5869	0.505	0.03512	0.219948	0.3057	0.916	0.3057	0.7656																		
56421	PFKP	4.07116	0.0243	3.0525	0.00121	-0.121706	1	1.862	1	0.1705																		
11674	ALDOA	1.84761	0.0628	0.54645	0.00773	0.121555	0.3214	2.681	0.3214	0.00005																		
230163	ALDOB	-1.16576	0.002	-1.51574	0.00099	-0.20247	0.47945	1.108	0.47945	0.6644																		
11676	ALDOC	3.64566	0.0012	2.65665	< 0.0001	-0.552653	0.019	1.353	0.019	0.05335																		
14433	GAPDH	-0.04584	0.8477	-0.72266	0.0124	-0.019563	0.9564	1.577	0.9564	0.0145																		
14447	GAPDHS	3.1865	0.0059	3.77327	0.00029	0.976888	1	1.31	1	0.4964																		
18655	PGK1	0.47065	0.2311	-0.47368	0.02162	-0.053085	0.7048	1.855	0.7048	0.0003																		
12183	BPGM	0.02313	0.8975	-0.0589	0.72372	0.06457	0.77035	1.107	0.77035	0.4815																		
18648	PGAM1	0.77814	0.0288	0.2355	0.26493	0.063955	0.6586	1.523	0.6586	0.0077																		
13806	ENO1	0.07807	0.853	-0.592	0.11035	-0.079343	0.75145	1.506	0.75145	0.1079																		
433182	ENO1B	1.79967	0.0014	1.13356	0.00137	0.009521	0.81115	1.597	0.81115	0.22245																		
13808	ENO3	1.17718	0.0213	1.61451	0.00492	0.702704	0.0042	1.202	0.0042	0.40945																		
18770	PKLR	1.78039	0.0679	1.09927	0.00254	-0.428274	0.00815	1.192	0.00815	0.2756																		
18746	PKM	5.48674	0.0598	3.72967	0.00661	0.029697	0.9775	3.45	0.9775	0.00005																		
18597	PDHA1	0.32312	0.1644	0.158	0.46156	0.036679	0.77515	1.15	0.77515	0.29025																		
68263	PDHB	-0.13949	0.49	-0.29326	0.14184	-0.059054	0.7536	1.068	0.7536	0.5415																		

B



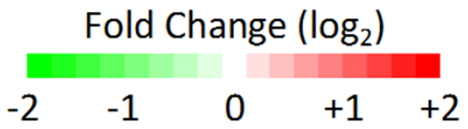
Supplemental Fig. S7

Supplemental Fig. S8

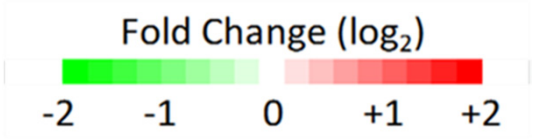


Supplemental Fig.S9

Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
99035	Olah	ND	0.0099	ND	0.40708	ND	1	1.895	1	1																		
20250	Scd2	5.35496	0.0357	6.44417	0.32818	-0.260133	1	0.392	1	0.00675																		
14104	Fasn	2.73821	0.03	2.61305	0.00181	-0.280659	0.11165	0.898	0.11165	0.59545																		
107476	Acaca	1.98298	0.0341	2.11802	< 0.0001	0.187243	0.21625	1.037	0.21625	0.7744																		
76267	Fads1	1.52696	0.0037	1.6504	0.00061	-0.238732	0.15505	0.778	0.15505	0.2096																		
104112	Acly	1.42411	0.0483	1.26471	0.05286	-0.500834	0.0032	0.789	0.0032	0.2267																		
70757	Hacd2	0.66957	0.0055	0.85006	0.00118	0.033325	0.8002	0.903	0.8002	0.62485																		
106529	Tecr	0.56436	0.0296	0.75321	0.00332	-0.047017	0.7814	0.849	0.7814	0.354																		
30963	Hacd1	0.39742	0.0233	0.78949	0.0056	0.178589	0.29595	0.862	0.29595	0.55785																		

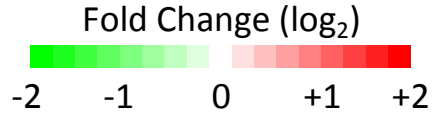


Supplemental Fig. S10



Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
74147	Ehhadh	-4.69984	0.0002	-4.89661	0.00086	-0.202551	0.4964	0.996	0.4964	0.95085																		
14080	Fabp1	-3.21805	0.0005	-2.34599	0.00041	-0.07713	0.9063	0.518	0.9063	0.01485																		
233799	Acsm2	-2.65395	0.0007	-2.5866	< 0.0001	0.2681	1	1.149	1	1																		
14081	Acsl1	-2.3982	0.0007	-1.9572	< 0.0001	0.375276	0.1015	0.955	0.1015	0.8478																		
12896	Cpt2	-2.20244	< 0.0001	-1.91881	< 0.0001	0.137434	0.3786	0.904	0.3786	0.5696																		
74114	Crot	-2.09681	0.0005	-1.21864	0.00161	-0.341977	0.10025	0.429	0.10025	0.00005																		
26458	Slc27a2	-2.1144	0.0001	-2.08631	0.00016	-0.041647	0.8519	0.953	0.8519	0.865																		
11430	Acox1	-1.80057	0.0002	-1.57285	0.00047	0.02523	0.87805	0.869	0.87805	0.5746																		
380660	Acss3	-1.72074	0.0361	-2.72278	0.00162	-0.331179	0.06485	1.592	0.06485	0.1478																		
15108	Hsd17b10	-1.60104	0.0014	-2.04163	0.00184	-0.116746	0.5121	1.252	0.5121	0.12085																		
102632	Acad11	-1.5458	0.001	-1.81782	0.00021	-0.038293	0.7997	1.176	0.7997	0.27855																		
15488	Hsd17b4	-1.54413	0.001	-1.52095	0.00062	-0.078614	0.6472	0.932	0.6472	0.76775																		
19299	Abcd3	-1.51993	0.0007	-1.09915	0.003	0.049411	0.80245	0.773	0.80245	0.1727																		
66841	Etfdh	-1.482	0.0019	-1.50617	0.00325	-0.189096	0.3181	0.892	0.3181	0.5895																		
113868	Acaa1a	-1.44485	< 0.0001	-1.48206	< 0.0001	0.04794	0.9511	1.061	0.9511	0.4505																		
66968	Plin5	-1.07797	0.0057	-1.24646	0.00465	0.161276	0.5212	1.257	0.5212	0.12415																		
12908	Crat	-1.0062	0.007	-0.70602	0.01287	0.192267	0.2783	0.928	0.2783	0.67975																		
117147	Acsm1	-0.9854	0.0001	-0.32766	0.1413	-0.045606	0.9381	0.614	0.9381	0.00255																		
13177	Eci1	-0.97036	0.0003	-1.24581	0.00053	-0.148768	0.4287	1.092	0.4287	0.434																		
57279	Slc25a20	-0.75599	0.0049	-0.8824	0.00052	-0.020293	0.8712	1.076	0.8712	0.5382																		
67460	Decr1	-0.7347	0.0006	-1.01293	0.00055	-0.195973	0.2857	1.059	0.2857	0.5782																		
231086	Hadhb	-0.73054	0.0081	-1.18479	0.00092	-0.142966	0.39655	1.241	0.39655	0.141																		
11364	Acadm	-0.69135	0.019	-1.02661	0.00703	-0.169137	0.389	1.122	0.389	0.4391																		
110446	Acat1	-0.6913	0.0363	-0.76832	0.03091	-0.201074	0.2925	0.918	0.2925	0.7131																		
97212	Hadha	-0.64952	0.0176	-0.94508	0.00709	-0.160878	0.38765	1.098	0.38765	0.4939																		
11370	Vlcad	-0.61564	0.0072	-0.82947	0.00185	-0.084541	0.6499	1.094	0.6499	0.53145																		
11409	Acads	-0.57986	0.0065	-0.83731	0.00261	-0.111812	0.5105	1.106	0.5105	0.41435																		
110826	Etfb	-0.49086	0.0185	-0.74422	< 0.0001	-0.052003	0.80355	1.15	0.80355	0.34875																		
56690	Mlycd	-0.48684	0.0126	-0.41436	0.04417	0.134405	0.36105	1.044	0.36105	0.72185																		
52538	Acaa2	-0.29102	0.0398	-0.47696	0.02354	-0.116966	0.59385	1.049	0.59385	0.7166																		
71767	Tysnd1	-0.2925	0.035	0.00589	0.95477	0.237408	0.2645	0.959	0.2645	0.89585																		
110842	Etfa	0.64941	0.0081	0.39828	0.03279	-0.181821	0.273	1.049	0.273	0.654																		
20524	Slc25a17	0.69042	0.0384	0.57609	0.01353	0.00174	0.97285	1.084	0.97285	0.47795																		
93747	Echs1	0.8075	0.0016	0.31174	0.07582	-0.261467	0.1088	1.176	0.1088	0.24755																		
56717	Mtor	0.8912	0.0269	1.08441	0.00038	0.157115	0.38675	0.975	0.38675	0.89835																		
13167	Dbi	0.93892	0.0006	0.93983	0.00206	-0.281529	0.1605	0.822	0.1605	0.42845																		
16367	Irs1	1.37787	0.0435	1.95467	< 0.0001	-0.146844	0.48335	0.606	0.48335	0.00285																		
384783	Irs2	1.49735	0.018	2.03768	0.0111	0.486816	0.0296	0.964	0.0296	0.8997																		
50790	Acsl4	2.12521	0.0013	1.67699	0.00038	-0.271484	0.1025	1.13	0.1025	0.30415																		
74205	Acsl3	2.57542	0.0002	2.6476	< 0.0001	-0.286615	0.1682	0.78	0.1682	0.16845																		
69123	Eci3	4.66984	0.0004	4.14286	< 0.0001	-0.162466	1	1.287	1	1																		
68738	Acss1	5.31256	0.0092	4.81661	0.00778	0.153057	1	1.568	1	0.2064																		

Supplemental Fig. S11



Gene ID	Gene Symbol	Tumor vs Hepatocyte				WT vs KO					Hepatocytes								HBs									
		WT		KO		Hepatocyte		Tumor			WT				KO				WT					KO				
		Log2 Diff	P value	Log2 Diff	P value	Log2 Diff	P value	Fold Di	Log2 Diff	P value	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	3	4	5
13123	Cyp7b1	-4.69176	0.0035	-3.84353	0.00189	0.057426	0.61205	0.578	0.61205	0.01435																		
13116	Cyp46a1	-3.13295	0.0002	-3.21851	0.00077	-0.027761	0.85195	1.041	0.85195	1																		
72999	Insig2	-2.27149	0.0018	-2.37479	0.00022	0.167093	0.45835	1.206	0.45835	0.1541																		
15360	Hmgcs2	-1.96508	0.0018	-1.89364	0.00022	-0.013229	0.9421	0.943	0.9421	0.8547																		
23957	Nr0b2	-1.32013	0.0215	-1.38126	0.08547	0.307678	0.1966	1.291	0.1966	0.1571																		
16816	Lcat	-0.84829	0.0131	-1.24703	0.00285	-0.14052	0.3894	1.196	0.3894	0.24795																		
103161	Apof	-0.73738	0.0097	-0.63008	0.01772	-0.363376	0.048	0.722	0.048	0.12005																		
235623	Scap	-0.63596	0.0063	-0.40151	0.03305	0.09964	0.565	0.911	0.565	0.6404																		
100017	Ldlrap1	0.70334	0.0409	0.81264	0.00209	0.030078	0.8882	0.947	0.8882	0.7862																		
110611	Hdlbp	0.72112	0.0106	0.76611	0.00425	-0.063155	0.7467	0.928	0.7467	0.7761																		
59045	Stard3	0.98662	0.0001	1.13156	< 0.0001	0.145908	0.4208	1.001	0.4208	0.90035																		
56453	Mbtps1	1.18164	0.0011	1.53386	< 0.0001	0.102599	0.47785	0.841	0.47785	0.32035																		
19015	Ppard	1.23726	0.0002	2.30311	0.01337	0.213385	0.4449	0.554	0.4449	0.00555																		
266781	Snx17	1.25744	< 0.0001	1.00424	0.0001	-0.066626	0.74565	1.138	0.74565	0.3586																		
105787	Prkaa1	1.38677	< 0.0001	1.42798	0.0006	0.023447	0.9046	0.988	0.9046	0.9092																		
223920	Soat2	1.52572	0.0222	1.12866	0.03278	-0.0575	0.884	1.265	0.884	0.14525																		
109754	Cyb5r3	1.59613	0.0003	1.63545	< 0.0001	-0.042179	0.83	0.945	0.83	0.8129																		
56050	Cyp39a1	1.66853	0.0102	1.10627	0.00806	0.110725	0.8545	1.594	0.8545	0.00215																		
208665	Akr1d1	1.73908	0.0058	0.90323	0.06929	-0.348424	0.0292	1.402	0.0292	0.04																		
74754	Dhcr24	1.821	0.0313	1.95487	0.00033	-0.129997	0.5085	0.833	0.5085	0.4719																		
13360	Dhcr7	1.92583	0.0469	2.1447	0.02204	-0.218559	0.14345	0.738	0.14345	0.09185																		
16835	Ldlr	2.09415	0.0102	1.96252	< 0.0001	-0.330091	0.12035	0.871	0.12035	0.4274																		
68603	Pmvk	2.11278	0.0108	2.0422	0.00135	-0.147214	0.43645	0.948	0.43645	0.8304																		
20788	Srebf2	2.75327	0.0014	2.69949	< 0.0001	-0.239857	0.15315	0.879	0.15315	0.47005																		
208715	Hmgcs1	3.08099	0.0464	3.1741	0.00453	-0.190476	0.3517	0.822	0.3517	0.4532																		
14137	Fdft1	3.11175	0.0015	3.04767	0.00014	-0.211196	0.74915	0.903	0.74915	0.8661																		
11307	Abcg1	3.18142	0.0032	2.87338	0.01114	-0.130011	1	1.131	1	0.388																		
17855	Mvk	3.28413	0.0013	2.85063	< 0.0001	-0.443164	0.0631	0.993	0.0631	0.9888																		
13121	Cyp51	3.58826	0.0167	3.07326	0.00923	-0.749737	0.00015	0.85	0.00015	0.4335																		
224829	Trerf1	3.74865	0.0035	6.32225	0.00022	2.254213	1	0.801	1	1																		
15357	Hmgcr	3.84437	0.0351	2.75865	0.00063	-0.3521	0.0677	1.663	0.0677	0.0041																		
20652	Soat1	3.95286	0.024	3.9682	0.00568	0.339443	1	1.252	1	0.24045																		
18194	Nsdhl	4.12098	0.0118	3.98212	0.01021	-0.465654	0.03875	0.797	0.03875	0.21195																		
319554	Idi1	4.37905	0.0405	3.52211	0.00564	-1.144443	0.00005	0.819	0.00005	0.33755																		
20787	Srebf1	4.39789	0.0002	3.88437	< 0.0001	-0.44145	0.054	1.051	0.054	0.7064																		
231070	Insig1	4.48608	0.0037	3.83662	0.00019	-0.690207	0.0004	0.972	0.0004	0.94495																		
192156	Mvd	4.59952	0.0082	4.58838	0.00154	-0.168466	0.87175	0.897	0.87175	0.54165																		
110196	Fdps	4.80717	0.0066	4.53193	0.00272	-0.541933	0.0091	0.831	0.0091	0.39905																		
20660	Sorl1	6.57623	0.0026	6.65822	0.00044	-0.238193	1	0.801	1	0.3603																		
100102	Pcsk9	6.85811	0.0044	6.07238	0.00019	-0.563855	0.0791	1.166	0.0791	0.3206																		
22359	Vldlr	7.40272	0.0003	5.53473	0.01518	-1.838679	1	1.021	1	0.8566																		
237636	Npc1l1	∞	0.0173	3.29972	0.00187	ND	1	2.575	1	1																		

Supplemental Fig. S12