



Supplementary Figure 1: Mitochondria regulators are inhibited and lipid/lipogenic pathways are dramatically upregulated in fasted 6-mo *Pcyt2*^{-/-}. Immunoblot analysis of lipid pathways in fasted *Pcyt2*^{+/+} and *Pcyt2*^{-/-} (n=4). Data are presented as mean ± SD. **p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001.

Supplementary table 1. Primer Sequences and melting temperatures (T_m) for polymerase chain reaction (PCR) using mouse hepatic RNA.

Gene	Primer Forward 5'-3'	Primer Reverse 5'-3'	T _m (°C)
TGH	GCTGGGTCCAGGACAACATT	GCGCAGGCAATGAACCATAA	59
LPL	GCTCGCACGAGCGCTCCATT	CCTCGGGCAGGGTGAAGGGAA	59
ATGL	CAACGCCACTCACATCTACGG	GGACACCTCAATAATGTTGGCAC	57
PPAR α	GCTCACAGAATTTGCCAAGG	GTCATCCAGTTCTAAGGCATTG	57
PPAR γ	CAGAAGTGCCTTGCTGTGGGG	CTTGGCTTTGGTCAGCGGG	57
CTL-1	GAACGCTCTGCGAGTGGCTGC	CGGCTTTAGCTCTCGGGCGT	49
PCYT1	ATGCACAGAGTTCAGCTAAAG	GGGCTTACTAAAGTCAACTTCAA	50
PSS1	CTGTTGTGCAATGGTGGTGG	GGCTGGCTTGGAACACAAAG	59.5
PSS2	GAGTGGCTGTCCCTGAAGAC	TCGTAGATCTCACGCATGGC	59
PSD	GTTTGCTGTCACGTGCCTGTG	CAGTGCAAGCCACATACGGG	59.5
PEMT	TGTTTGTGCTGTCCAGCTTC	TTCCAAAGATCCTTCATGGC	52
BHMT	TGGATTGGAACCCCGAGTTG	GGTGTGCATGTCCAAACCAC	59
TNF α	ACAGAAAGCATGATCCGCGA	GCTACAGGCTTGTCACCTCGAA	56
TNFR	AAAGGGCACCTTTACGGCTT	GTGACATTTGCAAGCGGAGG	56
IL-10	TCTTGCACTACCAAAGCCACA	TTGGCAACCCAAGTTAACCCT	57
IL-6	GCCTTCTTGGGACTGATGCT	TGGAAATTGGGGTAGGAAGGAC	56
TGF β 1	AGGAGACGGAATACAGGGCT	CCACGTAGTAGACGATGGGC	57
TGF β 3	ATGACCCACGTCCCCTATCA	ACTCTGCCCGGAACAGATTG	57
IFNY	CGGCACAGTCATTGAAAGCC	TGCATCCTTTTTTCGCCTTGC	57
GAPDH	ACCACAGTCCATGCCATCAC	TCCACCACCCTGTTGCTGTA	58

Abbreviations: ACC-acetyl-CoA carboxylase, Akt-protein kinase B, AMPK-AMP-activated protein kinase, ANGPTL4-angiopoietin-like 4, ANOVA-analysis of variance, ATGL-adipose triglyceride lipase, ATP-adenosine triphosphate, AUC-area under the curve, BCA-bicinchoninic acid, BMI-body mass index, BSA-bovine serum albumin, CD68- cluster of differentiation 68, CDP-cytidine diphosphate, CMP-cytidine monophosphate, COX-2-cyclooxygenase-2, CTL-1-choline transporter-like protein 1, CTP-cytidine triphosphate, DAG-diacylglycerol, EGR1-early growth response protein 1, EIF2 α - Eukaryotic Initiation Factor 2 alpha, EK-ethanolamine kinase, EPT-CDP-ethanolamine:1,2-diacylglycerol ethanolamine-phosphotransferase, ERK- Extracellular signal-regulated kinase, ET/Pcyt2-CTP-phosphoethanolamine cytidyltransferase, ETKO- CTP-phosphoethanolamine cytidyltransferase knock out, Etn-ethanolamine, FA-fatty acid, FBS-fetal bovine serum, FOXO1- Forkhead Box O1, G6Pase-glucose 6-phosphate, G6PDH-glucose 6-phosphate dehydrogenase, GAPDH- glyceraldehyde 3-phosphate dehydrogenase, GK-glucokinase, GTT-glucose tolerance test, H&E-hematoxylin and eosin, HK-hexokinase, INF γ -interferon gamma, IR-insulin receptor, IRS1-insulin receptor substrate 1, JNK- c-Jun N-terminal kinases, Keap1-kelch-like ECH-associated protein 1, L-Pk-liver pyruvate kinase, LSC- liquid scintillation counting, LXR-liver X receptor, MAM-ER mitochondria associated membranes, MAPK- Mitogen-activated protein kinase, mRNA-messenger ribonucleic acid, mTORC1/2-mammalian target of rapamycin complex 1/2, NAD-nicotinamide adenine dinucleotide, NADPH/NADP⁺-nicotinamide adenine dinucleotide phosphate, NAFLD-non-alcoholic fatty liver disease, NASH-nonalcoholic steatohepatitis, NF- κ B-nuclear factor kappa-light-chain-enhancer of activated B cells, NIH- National Institutes of Health, Nrf2-nuclear factor erythroid 2-related factor 2, PAS-periodic acid-Schiff reagent, PC-phosphatidylcholine, PDK-phosphoinositide-dependent kinase-1, PE-phosphatidylethanolamine, PEMT-PE N-methyltransferase, PEPCK-phosphoenolpyruvate carboxykinase, PEtn-phosphoethanolamine, PGC1 α - Peroxisome proliferator activated receptor gamma coactivator 1 alpha, Pi-inorganic phosphate, PI3K-phosphoinositide 3-kinase, PKA- protein kinase A, PKC-protein kinase C, PPAR-peroxisome proliferator-activated receptor, PS-phosphatidylserine, PSD-phosphatidylserine decarboxylase,

Supplementary Table 2 for Fig 2A. Downregulated pathways in 2-mo *Pcyt2*^{+/-} liver

Figure 2A-a: MGI Mammalian Phenotype level 4, 2019

Term	Overlap Combined Score	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds Ratio
1. MP:0002628 hepatic steatosis	19/206 3.0408255347593585	29.84444911985981	5.464855551992962E-5	0.06394902276836688	0	0
ANK1;ELOVL5;NOS3;PEX11A;MAT1A;GNMT;HADHB;LGALS3;POR;PGRMC1;ACADL;ACX1;ACADM;ALDOB;APOB;PARGC1A;PNPLA2;SIDT2;SLC25A13						
2. MP:0005309 increased circulating ammonia level	5/14 0	16.422018348623855	5.9793382672619803E-5	159.69781517242902	OAT;CPS1;ARG1;ASL;ASS1	0.06394902276836688
3. MP:0011501 increased glomerular capsule space	5/20 0	9.850152905198776	3.929038056401208E-4	77.2443646666549	INVS;GLIS3;SCTR;GNE;UOX	0.23151917642846842
4. MP:0009355 increased liver triglyceride level	10/84 0	4.011785282971724	4.3294843651887503E-4	31.070843428097586	GYS2;FADS2;LGALS3;PGRMC1;PANK1;PEX11A;LPIN2;SIDT2;SLC25A13;PNPLA2	0.23151917642846842
5. MP:0009815 decreased prostaglandin level	4/13 0	13.117557251908398	6.584952774437638E-4	96.09336361432368	FADS2;NOS3;LPAR3;FADS1	0.28170427969044215
6. MP:0002118 abnormal lipid homeostasis	13/141 0	3.0206196787925697	7.970780246633689E-4	21.550786252056398	ARSA;PCYT2;CYP4A14;ADIPOR2;CYP7A1;HADHB;ACADL;EHHADH;ANGPTL4;SLC37A4;PPARGC1A;MFSD2A;PNPLA2	0.284158315792491
7. MP:0005584 abnormal enzyme/coenzyme activity	14/171 0.4962944438385961	0	0.001624151990121633	2.6522095492025874	GKD;PANK1;GPT2;KMO;KLF15;ASS1;SLK;ACADL;CES1E;TMBIM1;ME1;ASL;LPIN2;PNPLA2	17.03453047198098
8. MP:0000598 abnormal liver morphology	17/233 0	2.344561266874351	0.001924728975720663	14.660471529834393	INVS;ONECUT2;ARG1;EPO;UNC93B1;NOS3;ASPSCR1;MAT1A;CYP7A1;CRKL;GNMT;LGALS3;ACOX1;CTH;ALDOB;MFSD2A;SIDT2	0.5146244098833123
9. MP:0005311 abnormal circulating amino acid level	6/43 0.6416566712394823	0	0.0026998176910497155	4.793841314515127	OAT;ARG1;CTH;ASL;KLF15;ASS1	28.353514961655737
10. MP:0000609 abnormal liver physiology	10/110 0	2.9647149460708784	0.003436208878611819	16.819973708379674	AS3MT;EPO;PANK1;ELOVL5;ACOX1;NOS3;MAT1A;PPARGC1A;CYP7A1;RAD18	0.7223244186275055

Figure 2b: GO Biological Process 2018

1. fatty acid metabolic process (GO:0006631)	15/106 0	2.017310155131874E-6	0.0029175606462129217	4.927138079311993	64.6132350140058	CPT1A;ABCD3;ACSM3;GPX4;ELOVL4;ACSL1;PLA2G1B;ADIPOR2;ACOX1;FASN;PCCB;ACOT1;ACADM;PPARGC1A;LPIN2
2. organonitrogen compound biosynthetic process (GO:1901566)	20/181 0.0029175606462129217	0	2.3576247646165025E-6	3.7286521058719466	48.31533669439376	OAT;GOT1;ELOVL4;ELOVL5;ARG1;GSTO1;GPT2;ASNS;FURIN;GPHN;ASS1;ALDH3A2;GLUD1;CPS1;VAPA;VAPB;ASL;CEPT1;LPIN2;MFSD2A

3. fatty acid oxidation (GO:0019395) 10/50 4.397605834839108E-6 0.003628024813742264 0
0 7.434899845916795 91.70540258718638
HADHB;ALDH3A2;ABCD3;ACADL;ACOX1;EHHADH;ACADM;ACAD11;ADIPOR2;PPARGC1A

4. fatty acid beta-oxidation (GO:0006635) 9/50 3.2408985307256655E-5 0.019556789706896935 0
0 6.51782363977486 67.37523081898888
HADHB;ABCD3;ACADL;ACOX1;EHHADH;ACADM;ACAD11;DECR2;CRAT

5. alpha-linolenic acid metabolic process (GO:0036109) 5/13 3.950866607453926E-5
0.019556789706896935 0 0 18.47572629969419 187.3252137256421
FADS2;ELOVL5;ACSL1;ACOX1;FADS1

6. regulation of primary metabolic process (GO:0080090) 15/139 5.5823126258719955E-5
0.023027039581721982 0 0 3.6096849328791825 35.35080804066797
CPT1A;PSMD12;ACSL1;PSMD13;PEX11A;CYP7A1;GLIPR1;PSMB4;ACOX1;CARM1;ME1;HMGCS2;ACADM;ANGPTL
4;FADS1

7. regulation of lipid metabolic process (GO:0019216) 12/100 1.1019524030597333E-4
0.038961888536754856 0 0 4.057819305887312 36.97994960002394
CPT1A;GLIPR1;ACSL1;ACOX1;PEX11A;CARM1;ME1;HMGCS2;ACADM;ANGPTL4;CYP7A1;FADS1

8. fatty acid catabolic process (GO:0009062) 9/65 2.6656374259770733E-4 0.07207968712770826
0 0 4.7682692307692305 39.24236539435219
HADHB;ALDH3A2;ABCD3;ACADL;EHHADH;PCCB;ACADM;ACAD11;LPIN2

9. carnitine metabolic process (GO:0009437) 4/11 3.203541650120367E-4 0.07207968712770826
0 0 16.867175572519084 135.71470152266448 CPT1A;ACADL;ACADM;CRAT

10. urea cycle (GO:0000050) 4/11 3.203541650120367E-4 0.07207968712770826 0 0
16.867175572519084 135.71470152266448 CPS1;ARG1;ASL;ASS1

11. arginine metabolic process (GO:0006525) 4/11 3.203541650120367E-4 0.07207968712770826
0 0 16.867175572519084 135.71470152266448 CPS1;NOS3;ARG1;ASS1

12. phosphatidylethanolamine metabolic process (GO:0046337) 5/20 3.929038056401208E-4
0.078613615737343850 0 9.850152905198776 77.2443646666549
PCYT2;ETNK2;HRASLS5;CEPT1;LPIN2

13. long-chain fatty acid metabolic process (GO:0001676) 8/55 4.129200018527152E-4
0.078613615737343850 0 5.044677582769553 39.30942261235577
FADS2;CPT1A;ACADL;ACSL1;ELOVL5;ACOX1;ACOT1;FADS1

14. mitochondrial transport (GO:0006839) 13/135 5.277643310456708E-4 0.09330119423843108 0
0 3.170164441963153 23.924789492261766
PNPT1;BAD;TIMM9;BNIP3;AIP;ATP5C1;ATP5G3;ATP5L;PINK1;GRPEL1;SLC25A20;SLC25A22;SLC25A13
ELOVL5;ACOX1;ACOT1

Supplementary Table 3 for Figure 2B. Upregulated pathways in 2-mo *Pcyt2*^{-/-} liver

Term	Overlap Combined Score	P-value Genes	Adjusted P-value	Old P-value	Old Adjusted P-value	Odds	Ratio
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Elsevier Pathway Collection

1.	AngiopietinR -> STAT Signaling	3/8	6.695238747960458E-4	0.30440483811407787	0		
	0	24.976119402985073	182.54905138092414	ANGPT4;ANGPT2;LCK			
2.	AngiopietinR -> FOXO Signaling	3/9	9.86725569251468E-4	0.30440483811407787	0		
	0	20.812366737739872	144.04485859125822	ANGPT4;ANGPT2;FOXO1			
3.	GUCY2C in Intestinal Ion and Fluid Homeostasis	3/12	0.002451382720992579				
	0.504167712950807	0	0	13.872778962331202	83.39070376195338		
	SLC9A3;GUCA2B;GUCA2A						
4.	Genes with Mutations Associated with Urolithiasis	2/6	0.007828126089712499				
	0.8517865161452929	0	0	20.770212765957446	100.73619909675153		
	CASR;SLC34A1						
5.	IGF1R -> CEBPA/FOXO1A Signaling	2/9	0.017926636569026717	0.8517865161452929	0		
	0	11.866869300911855	47.72223035652416	IGF2;FOXO1			
6.	Dioxin Role in Endometriosis	2/11	0.0265489417774117	0.8517865161452929	0		
	0	9.228841607565013	33.489301013599345	ARNT;CYP1B1			
7.	Glioblastoma, Proneural Subtype	2/11	0.0265489417774117	0.8517865161452929	0		
	0	9.228841607565013	33.489301013599345	SOX2;TCF4			
8.	Hematopoietic Cell Lineage: B-cell (mouse)	4/49	0.028152708219656288	0.8517865161452929			
	0	0	3.700474833808167	13.211108582205329	ANGPT2;EBF1;ID3;DNMT		
9.	Endocannabinoids Role in Sleep Regulation	2/12	0.031368464329064434	0.8517865161452929			
	0	0	8.305531914893617	28.753354580170335	NAPEPLD;DAGLB		
10.	Dioxin Induced Chloracne (Hypothesis)	2/12	0.031368464329064434	0.8517865161452929			
	0	0	8.305531914893617	28.753354580170335	EPGN;ARNT		

BioPlanet 2019

1.	Proepithelin conversion to epithelin and wound repair control	2/8	0.014162203067316765				
	0.9300147537850102	0	0	13.845390070921987	58.94229858120675		
	CELA3B;CELA1						
2.	Binding of RNA by insulin-like growth factor 2 mRNA binding proteins (IGF2BPs/IMPs/VICKZs)	2/8	0.014162203067316765	0.9300147537850102	0	0	13.845390070921987
	58.94229858120675			IGF2;ACTB			
3.	Activation of pro-caspase 8	2/9	0.017926636569026717	0.9300147537850102	0		
	0	11.866869300911855	47.72223035652416	CASP8;TNFSF10			
4.	Transport of inorganic cations/anions and amino acids/oligopeptides	6/95	0.02500765895155889				
	0.9300147537850102	0	0	2.812219703910884	10.37307807197569		
	SLC9A3;SLC6A19;SLC7A8;SLC34A1;SLC7A11;SLC12A6						
5.	Glutathione biosynthesis and recycling	2/11	0.0265489417774117	0.9300147537850102			
	0	0	9.228841607565013	33.489301013599345	GCLC;CNDP2		
6.	G-protein activation	3/28	0.02763591893096248	0.9300147537850102	0	0	
	4.990106609808103		17.90769090377881	GNAZ;GNB4;GNG12			
7.	Homologous recombination	3/29	0.030298923376566384	0.9300147537850102	0		
	0	4.797933409873709	16.776660748174137	POLD3;TOP3B;XRCC3			

8. **Myometrial relaxation and contraction pathways** 8/155 0.03098226588517045
0.9300147537850102 0 0 2.2731644381890685 7.897746830699842
GUCY1A3;RGS2;PKIA;GNB4;GUCA2B;GNG12;ACTB;GUCA2A
9. **SODD/TNFR1 signaling pathway** 2/12 0.031368464329064434 0.9300147537850102 0
0 8.305531914893617 28.753354580170335 CASP8;MADD
10. **Amino acid transport across the plasma membrane** 3/31 0.0360143368120434
0.9300147537850102 0 0 4.454766981419433 14.806924553684793
SLC6A19;SLC7A8;SLC7A11

Reactome 2016

1. **TRAIL signaling** Homo sapiens R-HSA-75158 2/7 0.010789024695074069
0.9999952869426106 0 0 16.61531914893617 75.25453371818327
CASP8;TNFSF10
2. **Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPs/IMPs/VICKZs) bind RNA** Homo sapiens R-
HSA-428359 2/8 0.014162203067316765 0.9999952869426106 0 0
13.845390070921987 58.94229858120675 IGF2;ACTB
3. **Thromboxane signaling through TP receptor** Homo sapiens R-HSA-428930 3/23
0.016287439904619384 0.9999952869426106 0 0 6.239232409381663
25.689172355795996 **TBXA2R;GNB4;GNG12**
4. **CASP8 activity is inhibited** Homo sapiens R-HSA-5218900 2/11 0.0265489417774117
0.9999952869426106 0 0 9.228841607565013 33.489301013599345
CASP8;TNFSF10
5. **Regulation by c-FLIP** Homo sapiens R-HSA-3371378 2/11 0.0265489417774117
0.9999952869426106 0 0 9.228841607565013 33.489301013599345
CASP8;TNFSF10
6. **Dimerization of procaspase-8** Homo sapiens R-HSA-69416 2/11 0.0265489417774117
0.9999952869426106 0 0 9.228841607565013 33.489301013599345
CASP8;TNFSF10
7. **G-protein activation** Homo sapiens R-HSA-202040 3/28 0.02763591893096248
0.9999952869426106 0 0 4.990106609808103 17.90769090377881
GNAZ;GNB4;GNG12
8. **Transport of inorganic cations/anions and amino acids/oligopeptides** Homo sapiens R-HSA-425393
6/99 0.029844089887825203 0.9999952869426106 0 0 2.69071023120587
9.449151304645508 **SLC9A3;SLC6A19;SLC7A8;SLC34A1;SLC7A11;SLC12A6**
9. **mRNA 3'-end processing** Homo sapiens R-HSA-72187 4/51 0.03201949066091937
0.9999952869426106 0 0 3.5426441171122023 12.191692586029836
FYTTD1;FIP1L1;CPSF3;SRSF11
10. **Post-Elongation Processing of Intron-Containing pre-mRNA** Homo sapiens R-HSA-112296 4/51
0.03201949066091937 0.9999952869426106 0 0 3.5426441171122023
12.191692586029836 FYTTD1;FIP1L1;CPSF3;SRSF11,CASP8;TNFSF10

GO Biological Processes 2018

1. **negative regulation of blood vessel endothelial cell migration (GO:0043537)** 5/31
7.333995806897917E-4 0.9359433242991512 0 0 8.030802174271125
57.96488353811351 **ANGPT4;ANGPT2;TBXA2R;MMRN2;MEOX2**
2. **negative regulation of cell migration involved in sprouting angiogenesis (GO:0090051)** 3/14
0.003916065051671796 0.9359433242991512 0 0 11.34929249854623
62.905359703868335 **TBXA2R;MMRN2; MEOX2**

3.	membrane lipid catabolic process (GO:0046466)	2/8	0.014162203067316765				
	0.9359433242991512	0	0	13.845390070921987	58.94229858120675		
	PPT1;CYP1B1						
4.	negative regulation of protein polymerization (GO:0032272)	3/22	0.014410698981294951				
	0.9359433242991512	0	0	6.567949725058916	27.846690544326467		
	DYRK1A;HIP1R;PFN2						
5.	negative regulation of sprouting angiogenesis (GO:1903671)	3/22	0.014410698981294951				
	0.9359433242991512	0	0	6.567949725058916	27.846690544326467		
	TBXA2R;MMRN2;MEOX2						
6.	regulation of epidermal growth factor-activated receptor activity (GO:0007176)	3/24					
	0.01829466228131285	0.9359433242991512	0	0	5.9418215047212914		
	23.77409499159111 EPGN;NCK2;EREG						
7.	RNA catabolic process (GO:0006401)	4/43	0.01829529208018193	0.9359433242991512			
	0	0	4.271093578785886	17.089121702331116	RNASEH2B;DIS3L;RNASE6;HSPA1A		
8.	positive regulation of nuclear division (GO:0051785)	3/25	0.020432949995376072				
	0.9359433242991512	0	0	5.671447955030045	22.065372194915977		
	EPGN;IGF2;EREG						
9.	positive regulation of epidermal growth factor-activated receptor activity (GO:0045741)	2/10					
	0.022062059633939514	0.9359433242991512	0	0	10.382978723404255		
	39.59960002889824 EPGN;EREG						
10.	negative regulation of cardiac muscle hypertrophy (GO:0010614)	2/11	0.0265489417774117				
	0.9359433242991512	0	0	9.228841607565013	33.489301013599345		
	RGS2;FOXO1						

GO Human phenotype

1.	Narrow forehead (HP:0000341)	5/65	0.018581530379705388	0.811679484707992	0		
	0	3.4739471805852964	13.845719353687516				
	CSPP1;NPHP1;DYRK1A;TCF4;SLC12A6						
2.	Hypoalphalipoproteinemia (HP:0003233)	2/10	0.022062059633939514	0.811679484707992			
	0	0	10.382978723404255	39.59960002889824	ALMS1;PPP1R3A		
3.	Asthma (HP:0002099)	4/51	0.03201949066091937	0.811679484707992	0	0	
	3.5426441171122023	12.191692586029836	CASP8;CDSN;ALMS1;LIFR				
4.	Rhabdomyosarcoma (HP:0002859)	2/13	0.03650249782103007	0.811679484707992	0		
	0	7.550096711798839	24.99364828626234	PMS2;FOXO1			
5.	Insulin-resistant diabetes mellitus (HP:0000831)	2/13	0.03650249782103007				
	0.811679484707992	0	0	7.550096711798839	24.99364828626234		
	ALMS1;PPP1R3A						
6.	Polydipsia (HP:0001959)	2/14	0.04193358005675239	0.811679484707992	0	0	
	6.920567375886525	21.94974443882456	CASR;NPHP1				
7.	Abnormal drinking behavior (HP:0030082)	2/14	0.04193358005675239	0.811679484707992			
	0	0	6.920567375886525	21.94974443882456	CASR;NPHP1		
8.	Complement deficiency (HP:0004431)	2/15	0.04764489483849146	0.811679484707992			
	0	0	6.387888707037643	19.444604146539334	CFH;C8A		
9.	Maternal diabetes (HP:0009800)	2/15	0.04764489483849146	0.811679484707992	0		
	0	6.387888707037643	19.444604146539334	SOX2;PPP1R3A			
10.	Hyperuricemia (HP:0002149)	2/16	0.05362025129539057	0.811679484707992	0		
	0	5.931306990881459	17.353986796469474	ALMS1;PPP1R3A			

Supplementary Table 4 for Fig. 3A Downregulated pathways in 6-mo *Pcvt2*^{-/-} liver

Fig. 3A-a KEGG pathway Mouse

Term	Overlap Combined Score	P-value Adjusted Genes	Old P-value	Old Adjusted P-value	Odds Ratio
1. Insulin signaling pathway	17/139 0	3.3542736653252626E-27 125.65685543964233	7659.986902198042	5.36683786452042E-25	
		INS1;PRKCI;MAP2K1;PKLR;BRAF;PIK3R2;SORBS1;CBL;GCK;PTPRF;HK2;ACACA;PIK3CA;SOS1;RAF1;FBP1;PCK2			
2. Chronic myeloid leukemia	8/76 10	1.6651543929129943E-12 75.49525616698293	2047.5146387729324	1.3321235143303954E-10	
		MAP2K1;PIK3CA;BRAF;PIK3R2;SOS1;RAF1;CBL;BCL2L1			
3. FoxO signaling pathway	9/132 0	3.2306236031537076E-12 48.385365853658534	1280.1967477703968	1.523046855804862E-10	
		INS1;MAP2K1;PIK3CA;BRAF;PIK3R2;SOS1;RAF1;IGF1R;PCK2			
4. ErbB signaling pathway	8/84 0	3.8076171395121555E-12 67.52122241086587	1775.4042067411829	1.523046855804862E-10	
		MAP2K1;PIK3CA;BRAF;PIK3R2;SOS1;RAF1;CBL;NCK1			
5. Prostate cancer	8/97 0	1.2397993514637874E-11 57.62087712939471	1447.0611181639738	3.4869852094777943E-10	0
		INS1;MAP2K1;PIK3CA;BRAF;PIK3R2;SOS1;RAF1;IGF1R			
6. mTOR signaling pathway	9/154 10	1.3076194535541728E-11 40.99862068965517	1027.4347719136917	3.4869852094777943E-10	
		INS1;MAP2K1;PIK3CA;GRB10;BRAF;PIK3R2;SOS1;RAF1;IGF1R			
7. Prolactin signaling pathway	7/72 0	8.15064064653917E-11 66.95769230769231	1555.4499238974392	1.86300357635181E-9	0
		INS1;MAP2K1;PIK3CA;PIK3R2;SOS1;RAF1;GCK			
8. AMPK signaling pathway	8/126 9	1.0351024557091974E-10 43.396391470749045	997.7416474812381	1.9441581916696194E-9	
		INS1;PIK3CA;PPARG;PIK3R2;FBP1;ACACA;IGF1R;PCK2			
9. Glioma	7/75 63.994025735294116	1.0935889828141608E-10 1467.7916758179063		1.9441581916696194E-9	0
		MAP2K1;PIK3CA;BRAF;PIK3R2;SOS1;RAF1;IGF1R			
10. Proteoglycans in cancer	9/203 0	1.5584661687681132E-10 30.567525773195875	690.2804159933993	2.493545870028981E-9	0
		MAP2K1;PIK3CA;FRS2;BRAF;PIK3R2;SOS1;RAF1;CBL;IGF1R			

Fig. 3A-b GO Biological process

1.	cellular response to insulin stimulus (GO:0032869)	9/110	6.091506918849882E-13	6.091506918849882E-13	
		3.9533879903335734E-10	0	58.99009900990099	
		1659.1974499768214 PRKCI;PKLR;PPARG;PIK3R2;SORBS1;SOS1;GCK;IGF1R;PCK2			

2. response to insulin (GO:0032868) 7/71 7.368534951486453E-11
2.3910895917573538E-8 0 0 68.00732421875
1586.693647227742 PRKCI;PKLR;PPARG;PIK3R2;SORBS1;GCK;PCK2
3. cellular response to peptide hormone stimulus (GO:0071375) 7/110
1.6693108435580462E-9 3.6112757915639067E-7 0 0
42.17415048543689 852.375638700225
PRKCI;PKLR;PPARG;PIK3R2;SORBS1;GCK;PCK2
4. cellular glucose homeostasis (GO:0001678) 5/33 4.9264155952384554E-9
7.993109303274394E-7 0 104.69012605042016
2002.581216558548 PIK3R2;HK2;GCK;IGF1R;PCK2
5. transmembrane receptor protein tyrosine kinase signaling pathway (GO:0007169)
9/396 5.352640065119736E-8 6.947726804525419E-6 0
15.173643410852714 254.0536899204188
PIK3CA;FRS2;PIK3R2;SORBS1;SOS1;CBL;FRS3;IGF1R;NCK1
6. insulin receptor signaling pathway (GO:0008286) 5/67 1.9104003837882453E-
7 2.066416415130952E-5 0 47.19876660341556
730.2018668253547 PIK3CA;PIK3R2;SORBS1;SOS1;IGF1R
7. pyruvate metabolic process (GO:0006090) 4/46 1.8986985018884242E-6
1.760364753893696E-4 0 54.201360544217685
714.067255553722 PKLR;GCK;HK2;PCK2
8. glycolytic process (GO:0006096) 3/23 1.1816441035959648E-5
5.842794088959005E-4 0 83.0875 942.7123277486376
PKLR;HK2;GCK
9. glucose homeostasis (GO:0042593) 4/74 1.287349249979027E-5
5.842794088959005E-4 0 32.475102040816324
365.6806971932668 PPARG;PIK3R2;GCK;HK2
10. axon guidance (GO:0007411) 5/158 1.3383789991443453E-5
5.842794088959005E-4 0 19.038831218762013
213.64360263511566 DOK2;PIK3CA;GRB10;FRS2;SOS1

Supplementary Table 5 for Fig. 3B Upregulated pathways in 6-mo *Pcyt2*^{+/-} liver

Wiki Pathway 2019 Mouse

Term	Overlap Combined Score	P-value	Adjusted P-value Genes	Old P-value	Old Adjusted P-value	Odds Ratio
1. Insulin Signaling WP65	16/159 110.88671328671329	7.480853932910914E-25	6160.009786612667 PTPN1;PRKCI;JUN;SHC1;PDPK1;SLC2A1;PIK3R2;PIK3R1;FOS;AKT2;RPS6KA1;EIF4EBP1;AKT1;MAPK1;GRB2;RAF1	6160.009786612667	5.685448989012295E-23	0
2. EGFR1 Signaling Pathway WP572	14/178 0	3.724366304165368E-20	3437.096004828217 CEBPB;PRKCI;JUN;SHC1;ARAF;PIK3R2;PIK3R1;FOS;RPS6KA1;AKT1;MAPK1;GRB2;KRAS;RAF1	3437.096004828217	1.4152591955828397E-180	0
3. Focal Adhesion-PI3K-Akt-mTOR-signaling pathway WP2841	15/324 8.633713839088465E-17	0	0 SREBF1;PDPK1;SLC2A1;IRS2;PIK3R2;PIK3R1;VEGFA;AKT2;AKT3;EIF4EBP1;AKT1;MAPK1;GRB2;KRA	45.43458159963014	4.11453478524301E-18	1818.8374386403746
4. Focal Adhesion WP85	13/185 65.03943377148634	4.544059915309719E-18	2597.200899846062 JUN;SHC1;PDPK1;ARAF;PIK3R2;PIK3R1;VEGFA;AKT2;AKT3;AKT1;MAPK1;GRB2;RAF1	2597.200899846062	8.633713839088465E-17	0
5. IL-6 signaling Pathway WP387	11/99 0	1.3368163335801963E-17	3861.2762999138718 CEBPB;JUN;SHC1;EIF4EBP1;AKT1;MAPK1;PIK3R2;GRB2;PIK3R1;FOS;RAF1	3861.2762999138718	2.031960827041898E-16	0
6. IL-5 Signaling Pathway WP151	10/69 0	2.860656750433226E-17	4942.888408930943 JUN;SHC1;RPS6KA1;AKT1;MAPK1;PIK3R2;GRB2;KRAS;PIK3R1;RAF1	4942.888408930943	3.623498550548752E-16	0
7. Integrin-mediated Cell Adhesion WP6	10/100 0	1.4039043292691922E-15	2904.620706154356 SHC1;PDPK1;AKT2;AKT3;ARAF;AKT1;MAPK1;PIK3R2;GRB2;RAF1	2904.620706154356	1.5242389860636944E-14	0
8. ESC Pluripotency Pathways WP339	10/118 0	7.737110119024626E-15	2297.6353532769176 JUN;AKT2;AKT3;ARAF;AKT1;MAPK1;PIK3R2;GRB2;FOS;RAF1	2297.6353532769176	7.350254613073394E-14	0
9. IL-2 Signaling Pathway WP450	9/76 0	8.772632206983754E-15	3204.024749007802 SHC1;AKT1;MAPK1;IRS2;PIK3R2;GRB2;KRAS;PIK3R1;RAF1	3204.024749007802	7.408000530341836E-14	0
10. Novel Jun-Dmp1 Pathway WP3654	7/26 0	2.1117806814715364E-14	7978.746344732662 JUN;RRAS;ARAF;MAPK1;KRAS;FOS;RAF1	7978.746344732662	1.6049533179183675E-130	0

Jensen Diseases

1. Hyperglycemia	11/108 90.11835051546392	3.621127000780859E-17	3411.6249295109155 PTPN1;SREBF1;JUN;G6PC;LEP;SLC2A1;AKT1;IRS2;PPARG;RETN;VEGFA	3411.6249295109155	5.540324311194714E-15	0
2. Hyperinsulinism	7/54 102.28833455612619	5.48763317803716E-12	2652.1855444627995 SREBF1;G6PC;SLC2A1;AKT1;IRS2;PPARG;RETN	2652.1855444627995	4.1980393811984273E-100	0
3. Fatty liver disease	7/85 61.5393457117595	1.4704016405222077E-10	1393.2701928314445 SREBF1;ACOX1;LEP;AKT1;IRS2;PPARG;RETN	1393.2701928314445	7.49904836666326E-9	0

4.	Arthritis	8/186	1.1652877018418393E-9	4.4572254595450357E-8	0	0	
			31.759229534510432	653.2968102506449			
			JUN;LEP;AKT1;MAPK1;PPARG;RETN;FOS;VEGFA				
5.	Cancer	9/300	2.2503138803435725E-9	6.885960473851332E-8	0	0	
			22.534936998854526	448.72008525522403			
			PRKCI;JUN;AKT2;ARAF;AKT1;RRAS2;KRAS;FOS;RAF1				
6.	Lipodystrophy	4/28	1.7546733069703368E-7	4.474416932774359E-6	0	0	
			103.85416666666667	1615.5359919124223			
			SREBF1;LEP;PPARG;RETN				
7.	Neutropenia	4/72	8.334015310359583E-6	1.778082598445152E-4	0	0	
			36.5735294117647	427.7334679739925			
			G6PC;ERCC1;KRAS;VEGFA				
8.	Diabetes mellitus	4/74	9.297163913438704E-6	1.778082598445152E-4	0	0	35.525
			411.5855862039443	AKT2;LEP;PPARG;RETN			
9.	Noonan syndrome	2/5	3.1392977135267624E-5	5.336806112995496E-4	0	0	0
			391.3921568627451	4058.3164477642435			
			KRAS;RAF1				
10.	Lung disease	4/119	6.057300576276312E-5	9.148899989723336E-4	0	0	21.575
			209.52909068321378	JUN;AKT1;PPARG;VEGFA			