# O-GlcNAc transferase acts as a critical nutritional node for the control of liver homeostasis

Paula Ortega-Prieto, Lucia Parlati, Fadila Benhamed, Marion Regnier, Isadora Cavalcante, Mélanie Montabord, Rachel Onifarasoaniaina, Maryline Favier, Natasa Pavlovic, Julie Magusto, Michèle Cauzac, Patrick Pagesy, Jérémie Gautheron, Chantal Desdouets, Sandra Guilmeau, Tarik Issad, Catherine Postic

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**Supplementary figure legends**

**Fig. S1. Physiological parameters in 4 week-old $\mathbf{OGT^{LWT}}$ and $\mathbf{OGT^{LKO}}$ mice**. Male liver-specific *Ogt* knockout ($OGT^{LKO}$) and control floxed littermates ($OGT^{LWT}$) mice were studied 4 weeks after birth. **A.** Fasting blood glucose (5 hours) (mmol/L). **B**. Glucose tolerance test. The area under the curve (AUC) is shown. **C**. Pyruvate tolerance test. The area under the curve (AUC) is shown. **D**. Insulin tolerance test. The area under the curve (AUC) is shown. **E**. Western blot analysis of Foxo1 (whole lysate), Foxo1O-GlcNAcylation levels (WGA) and global O-GlcNAcylation in liver of $OGT^{LWT}$ and $OGT^{LKO}$ mice. Actin was used as loading control. Three representative samples are presented per condition. **F**. Relative expression levels of gluconeogenic genes normalized to TBP. Data are shown as Mean ± SEM of 6-8 male mice. *P < 0.05; **P < 0.01; ***P<0.001 by unpaired Student t-test (Mann-Whitney U test).

**Fig. S2. Liver injury and cell identity assessment in $\mathbf{OGT^{LKO}}$ mice.** Male liver-specific *Ogt* knockout ($OGT^{LKO}$) and control floxed littermates ($OGT^{LWT}$) mice were studied 8 weeks after birth in the fed state. **A**. Relative expression of *Oga* normalized to TBP **B**. Relative expression levels of proliferation markers normalized to TBP. **C**. Western blot analysis of proliferation markers. Three representative samples are shown. Actin was used as a loading control. **D**. Liver section of mice without macroscopic nodular phenotype stained with HE, Sirius red and OGT. **E**. Serum levels of aspartate aminotransferase (AST), total and direct bilirubin and alkaline phosphatase (ALP) in mice 8 weeks after birth. **F.** Representation of hepatoblast differentiation into hepatocytes or cholangiocytes. Markers used for cell characterization are represented under each cellular type. **G**. Relative expression of cell identity markers in livers from $OGT^{LWT}$ compared to $OGT^{LKO}$ mice at 4 and 8 weeks. TBP was used as a housekeeping gene. **H**. Liver sections of 8 week-old mice stained with HNF4α, SOX9 and

Krt19 antibodies. Scale bars = 100 μm on the two upper sections. Detailed zoom is shown in the bottom sections with a scale bar = 50μm. PV: Portal vein. CV: Central vein. Data are represented as Mean ± SEM of 8-10 mice at 4 weeks and 13-15 mice at 8 weeks. **P < 0.01; ***P < 0.001 by unpaired Student t-test (Mann-Whitney U test) comparing $OGT^{LWT}$ and $OGT^{LKO}$ at the same age (Panels A, B, E). **P <0.01; ***P <0.001 by two-way ANOVA followed by Bonferroni post hoc test (panel G).

**Fig. S3. Female $OGT^{LKO}$ mice exhibit severe liver damage.**

Female liver-specific *Ogt* knockout ($OGT^{LKO}$) and control floxed littermates ($OGT^{LWT}$) mice were studied 8 weeks after birth in the fed state. **A**. Fed blood glucose (mmol/L), body (g), liver and spleen weights are shown. Liver and spleen weight are represented as percentage of body weight. **B**. Relative expression levels of *Ogt* normalized to TBP. **C**. Western blot analysis of OGT and CHOP protein content in liver of $OGT^{LWT}$ and $OGT^{LKO}$ mice. Four representative samples are shown. Actin was used as a loading control. **D**. Liver sections stained with hematoxylin-eosin (HE), Sirius red, αSMA, OGT, Ki67 and SOX9. Scale bars = 100 μm. **E**. Relative expression levels of inflammatory markers normalized to TBP. **F**. Relative expression levels of fibrosis markers normalized to TBP. **G**. Relative expression levels of oxidative stress markers normalized to TBP. **H**. Serum levels of alanine aminotransferase (ALT). Data are shown as Mean ± SEM of 5 female mice per condition. *P < 0.05; **P < 0.01; ***P < 0.001; ****P<0.0005 by unpaired Student t-test (Mann-Whitney U test).

**Fig. S4. Heatmaps of oxidative stress, necroptosis, DNA repair and extracelular matrix.**

**A.** Microarray results of genes involved in oxidative stress. **B**. Microarray results of genes involved in necroptosis. **C**. Microarray results of genes involved in DNA repair. **D**. Microarray results of significant changing genes involved in extracellular matrix formation. Genes found significantly different (either down or up-regulated) between $OGT^{LWT}$ and $OGT^{LKO}$ are indicated by an asterisk (*). Differentially expressed (DE) gene cut-off was set for a fold change $\geq |2|$ and False discovery rate (FDR) p-value $< 0.05$.

**Fig. S5. Kinetics of inflammation, oxidative stress and ER stress markers in liver of OGT$^{LWT}$ and OGT$^{LKO}$ mice.** Male liver-specific *Ogt* knockout (OGT$^{LKO}$) and control floxed littermates (OGT$^{LWT}$) mice were studied 2, 4 or 8 weeks after birth in the fed state. **A**. Western blots showing protein content in whole liver lysates of inflammation (Phospho-JNK and total JNK), ER stress (CHOP) markers. Actin and/or HSP90 were used as loading controls. **B**. Relative expression levels of oxidative stress markers and of *Chop* normalized to TBP. Data are represented as Mean ± SEM of 6 mice per group age. *$P < 0.05$; ***$P < 0.001$; ****$P < 0.0005$ by two-way Anova followed by Bonferroni post hoc test.

**Fig. S6. Persistent fibrosis and liver injury in 12 weeks and 12 months old OGT$^{LKO}$ mice.** Liver-specific *Ogt* knockout (OGT$^{LKO}$) and control floxed littermates (OGT$^{LWT}$) mice were studied 12 weeks and 12 months after birth in the fed state. **A.** Liver and spleen weights are shown and are represented as percentage of body weight. **B**. Relative expression levels of oxidative stress and inflammatory markers normalized to TBP. **C**. Liver sections stained with hematoxylin-eosin (HE) and F4/80. Scale bars = 100 µm. **D**. Serum levels of alanine aminotransferase (ALT) of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). Data are shown as Mean ± SEM of 18-20 individual male and female mice at 12 weeks and 12 months. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ and ****$P < 0.0005$ by two-way ANOVA followed by Bonferroni post hoc test.

**Fig. S7. Low carbohydrate high fat (LCHF) diet improves oxidative stress, ER stress and DNA damage but not fibrosis in OGT$^{LKO}$ mice. A.** Liver-specific *Ogt* knockout

($OGT^{LKO}$) and control floxed littermates ($OGT^{LWT}$) mice were weaned (at 3 weeks of age) on a low carbohydrate high fat (LCHF in % of calories: 21% of carbohydrates, 60% of fat, 19% of proteins) diet and sacrificed 5 weeks later in the fed state. **B.** Body weight (g), liver and spleen weights are shown. Liver and spleen weights are represented as percentage of body weight. **C**. Serum concentrations of β-hydroxybutyrate. **D**. Relative expression levels of *Chop* normalized to TBP. **E**. Serum levels of Cxcl1. Data are shown as Mean ± SEM of 4-12 mice (males and females). *P < 0.05; ***P < 0.001; ****P< 0.0005 by two-way ANOVA followed by Bonferroni post hoc test.

**Fig. S8. Ketogenic diet (KD) improves oxidative stress, ER stress, DNA damage, hepatic fibrosis and liver injury in $OGT^{LKO}$ mice. A.** Liver-specific *Ogt* knockout ($OGT^{LKO}$) and control floxed littermates ($OGT^{LWT}$) were weaned (at 3 weeks of age) on a ketogenic diet (KD: 1% of carbohydrates, 94% of fat, 5% of protein) and sacrificed 5 weeks later in the fed state. **B**. Body weight (g), liver and spleen weights are shown. Liver and spleen weights are represented as percentage of body weight. **C**. Serum concentrations of β-hydroxybutyrate**. D**. Relative expression levels of *Chop* normalized to TBP. Data are shown as Mean ± SEM of 4-8 mice (males and females). ***P < 0.001; ****P < 0.0005 by two-way ANOVA followed by Bonferroni post hoc test.

**Fig. S9. Lipidomic analysis in liver of $OGT^{LWT}$ and $OGT^{LKO}$ mice fed on SD, LCHF or KD diets.** **A**. Heat map of lipid species in liver from $OGT^{LWT}$ and $OGT^{LKO}$ mice fed at weaning for 5 weeks with a LCHF diet. Specific clusters are indicated. **B**. Heat map of lipid species in liver from $OGT^{LWT}$ and $OGT^{LKO}$ fed for 5 weeks at weaning with a KD diet. Specific clusters are indicated. Data are shown as Mean ± SEM of 4-12 mice (males and females).

**Supplementary table legends**

**Table S1. Differentially expressed genes at 4 weeks**

**Table S2. Differentially expressed genes at 8 weeks**

**Table S3. Differentially expressed genes common to 4 and 8 weeks**

**Table S4. List of primers used for qPCR**

**Supplementary figures**

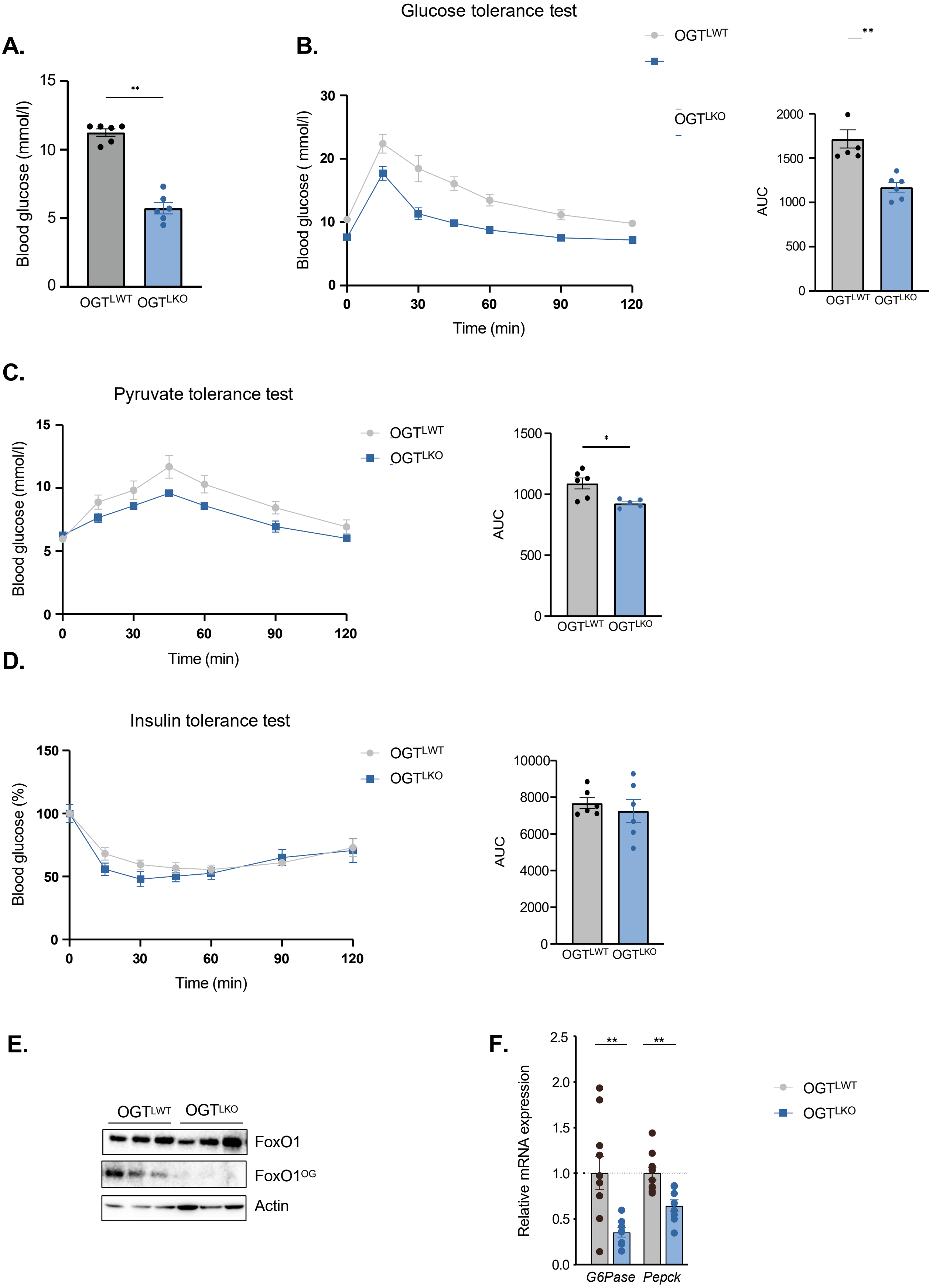
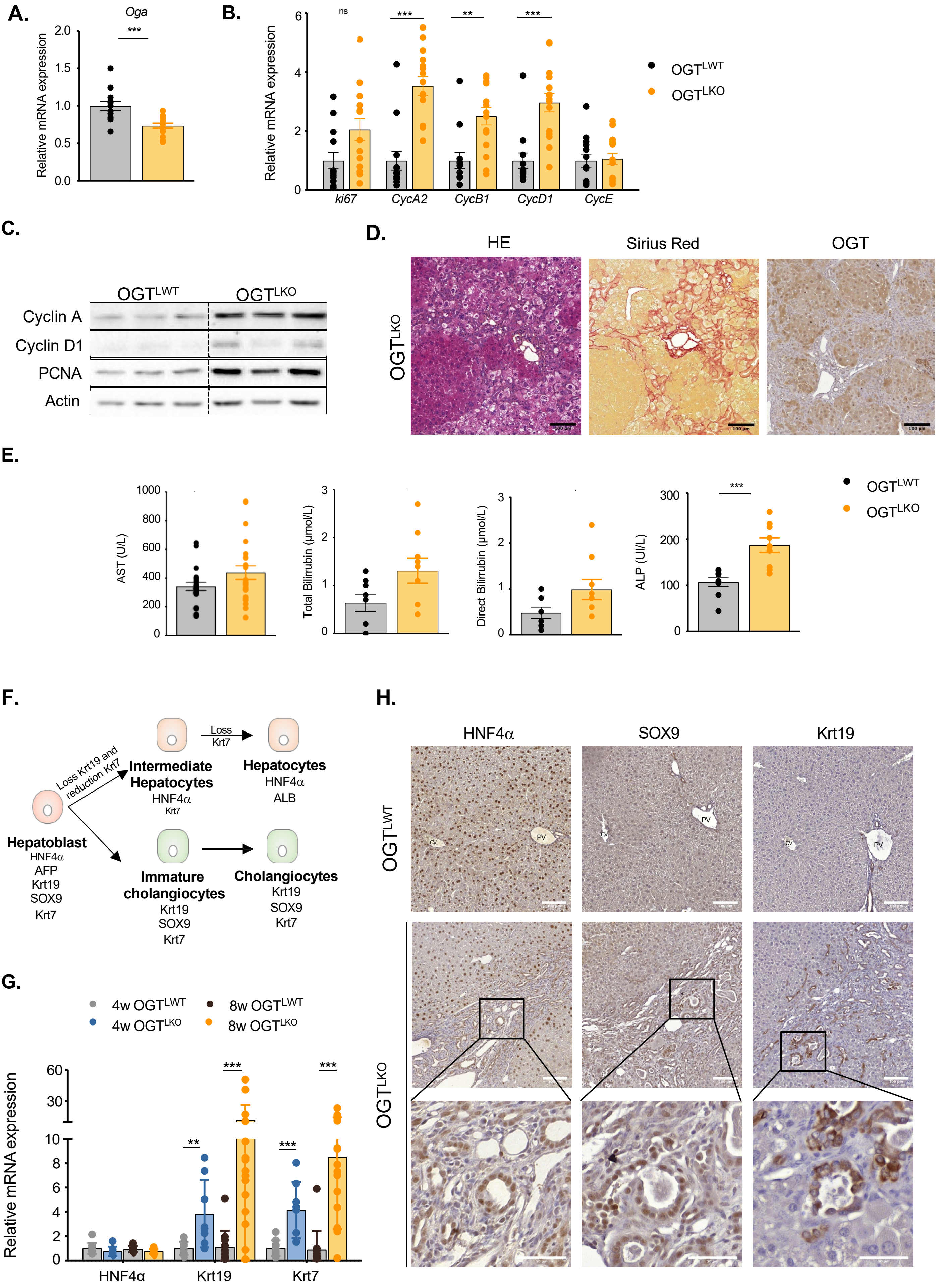



**Fig. S1**



A.
Oga
Relative mRNA expression
B.
Relative mRNA expression
ki67
CycA2
CycB1
CycD1
CycE
OGTLWT
OGTLKO
C.
Cyclin A
Cyclin D1
PCNA
Actin
D.
HE
Sirius Red
OGT
E.
AST (U/L)
Total Bilirubin (µmol/L)
Direct Bilirubin (µmol/L)
ALP (UI/L)
F.
Loss Krt19 and reduction Krt7
Loss Krt7
Intermediate Hepatocytes
HNF4α
Krt7
Hepatocytes
HNF4α
ALB
Hepatoblast
HNF4α
AFP
Krt19
SOX9
Krt7
Immature cholangiocytes
Krt19
SOX9
Krt7
Cholangiocytes
Krt19
SOX9
Krt7
G.
4w OGTLWT
4w OGTLKO
8w OGTLWT
8w OGTLKO
Relative mRNA expression
HNF4α
Krt19
Krt7
H.
HNF4α
SOX9
Krt19
OGTLWT
OGTLKO


**Fig. S2**

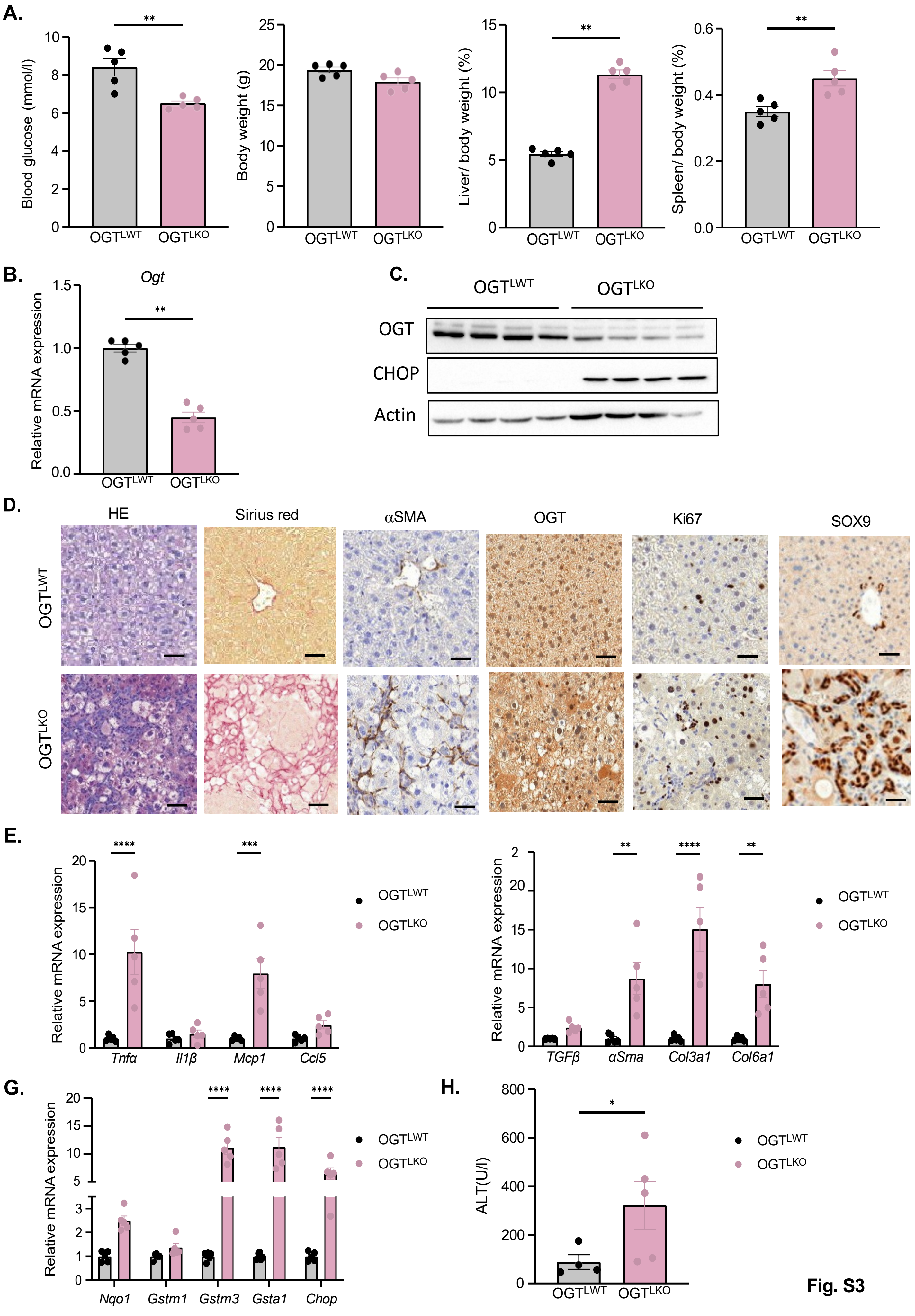

A.
Blood glucose (mmol/l)
Body weight (g)
Liver/ body weight (%)
Spleen/ body weight (%)
OGT^LWT
OGT^LKO
B.
Ogt
Relative mRNA expression
C.
OGT
CHOP
Actin
D.
HE
Sirius red
αSMA
Ki67
SOX9
E.
Tnfα
Il1β
Mcp1
Ccl5
TGFβ
αSma
Col3a1
Col6a1
G.
Nqo1
Gstm1
Gstm3
Gsta1
Chop
H.
ALT(U/l)

Fig. S3

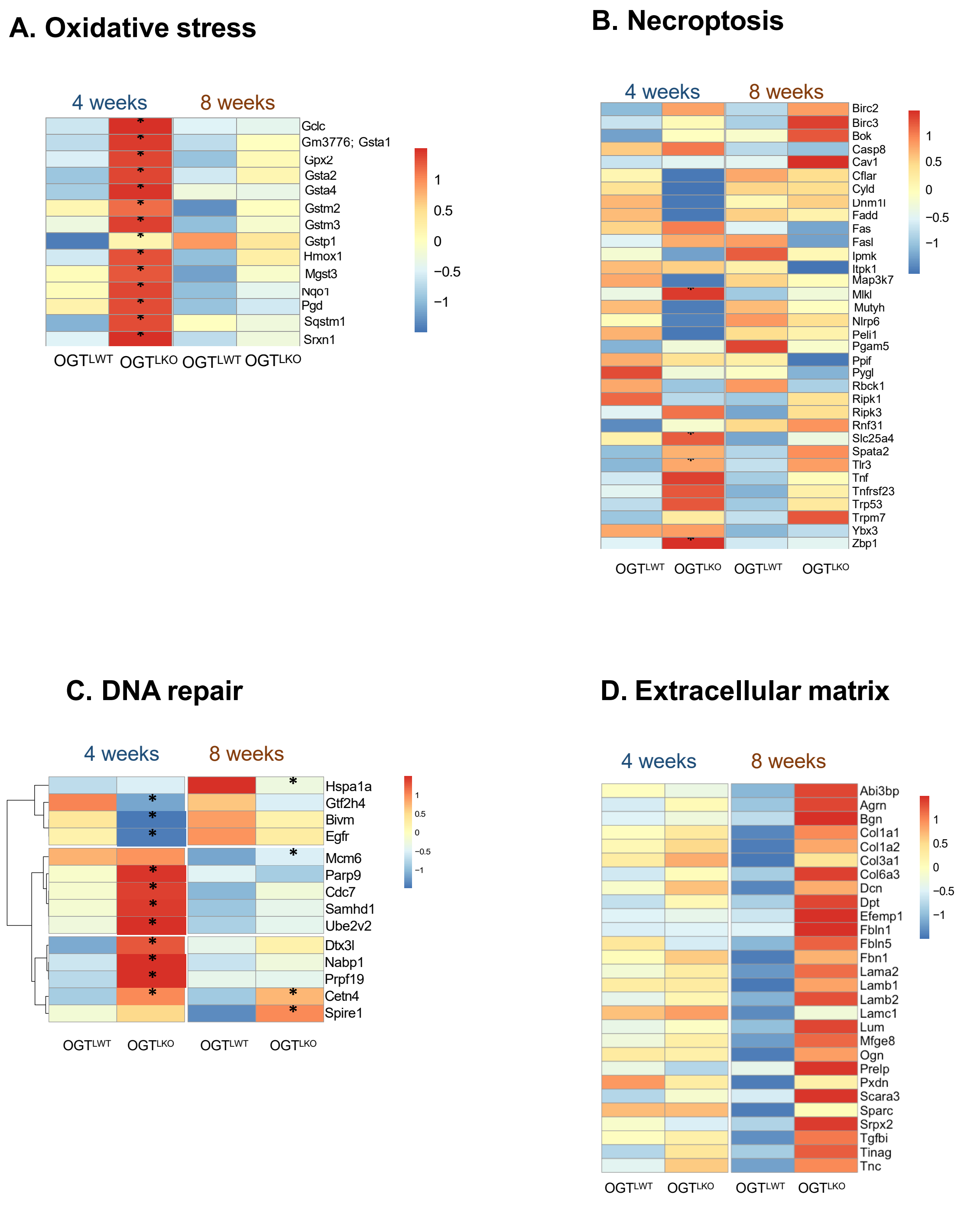

A. Oxidative stress
4 weeks
8 weeks
Gclc
Gm3776; Gsta1
Gpx2
Gsta2
Gsta4
Gstm2
Gstm3
Gstp1
Hmox1
Mgst3
Nqo1
Pgd
Sqstm1
Srxn1
OGTLWT OGTLKO OGTLWT OGTLKO
1
0.5
0
−0.5
−1
B. Necroptosis
4 weeks
8 weeks
Birc2
Birc3
Bok
Casp8
Cav1
Cflar
Cyld
Dnm1l
Fadd
Fas
Fasl
Ipmk
Itpk1
Map3k7
Mlkl
Mutyh
Nlrp6
Peli1
Pgam5
Ppif
Pygl
Rbck1
Ripk1
Ripk3
Rnf31
Slc25a4
Spata2
Tlr3
Tnf
Tnfrsf23
Trp53
Trpm7
Ybx3
Zbp1
OGTLWT OGTLKO OGTLWT OGTLKO
1
0.5
0
−0.5
−1
C. DNA repair
4 weeks
8 weeks
Hspa1a
Gtf2h4
Bivm
Egfr
Mcm6
Parp9
Cdc7
Samhd1
Ube2v2
Dtx3l
Nabp1
Prpf19
Cetn4
Spire1
OGTLWT OGTLKO OGTLWT OGTLKO
1
0.5
0
−0.5
−1
D. Extracellular matrix
4 weeks
8 weeks
Abi3bp
Agrn
Bgn
Col1a1
Col1a2
Col3a1
Col6a3
Dcn
Dpt
Efemp1
Fbln1
Fbln5
Fbn1
Lama2
Lamb1
Lamb2
Lamc1
Lum
Mfge8
Ogn
Prelp
Pxdn
Scara3
Sparc
Srpx2
Tgfbi
Tinag
Tnc
OGTLWT OGTLKO OGTLWT OGTLKO
1
0.5
0
−0.5
−1

**Fig. S4**

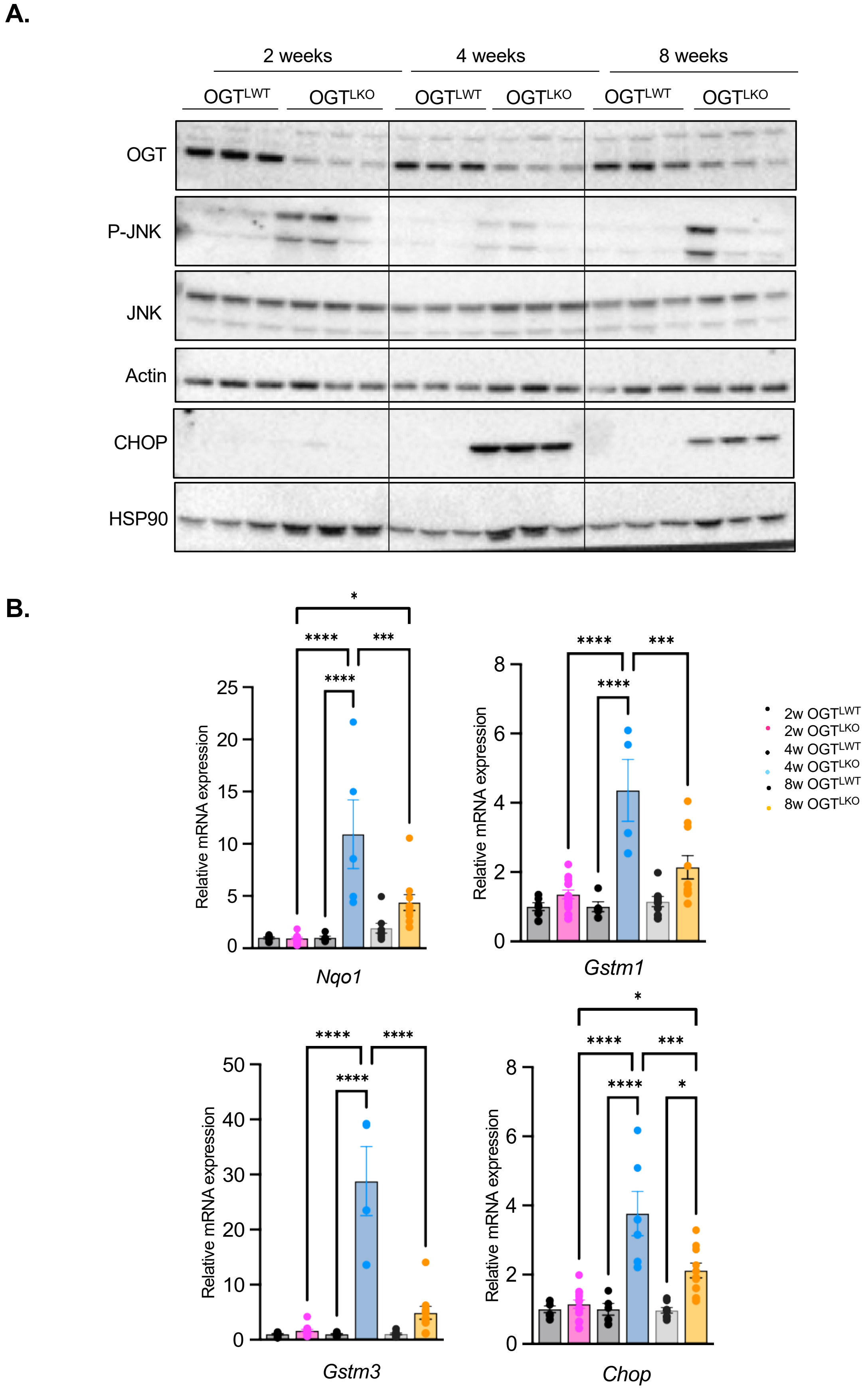

A.
2 weeks
4 weeks
8 weeks
OGTLWT
OGTLKO
OGT
P-JNK
JNK
Actin
CHOP
HSP90
B.
Relative mRNA expression
Nqo1
Gstm1
Gstm3
Chop
2w OGTLWT
2w OGTLKO
4w OGTLWT
4w OGTLKO
8w OGTLWT
8w OGTLKO

**Fig. S5**

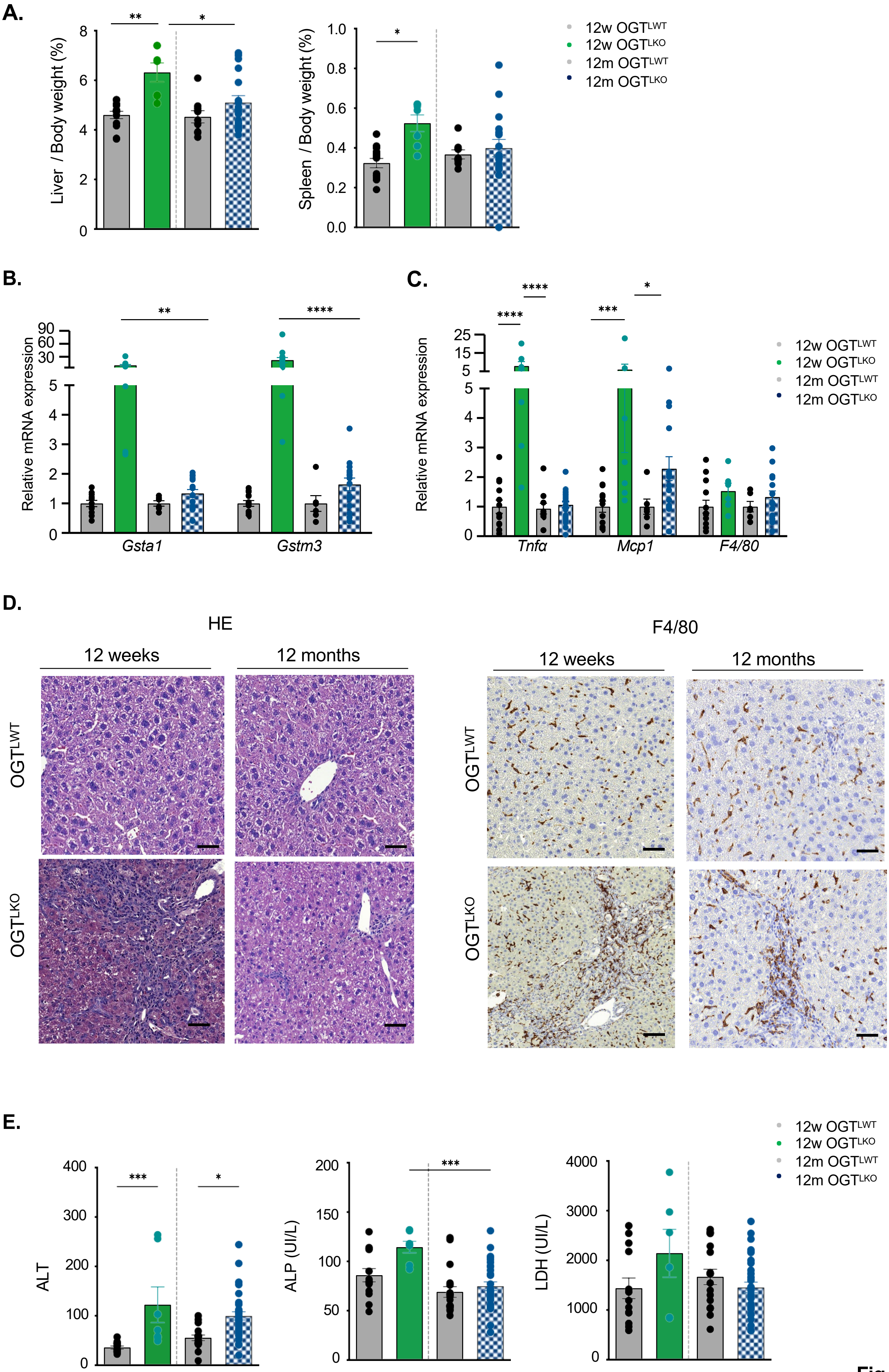

A.
Liver / Body weight (%)
Spleen / Body weight (%)
12w OGT^LWT
12w OGT^LKO
12m OGT^LWT
12m OGT^LKO
B.
Relative mRNA expression
Gsta1
Gstm3
C.
Tnfα
Mcp1
F4/80
D.
HE
F4/80
12 weeks
12 months
OGT^LWT
OGT^LKO
E.
ALT
ALP (UI/L)
LDH (UI/L)

Fig. S6

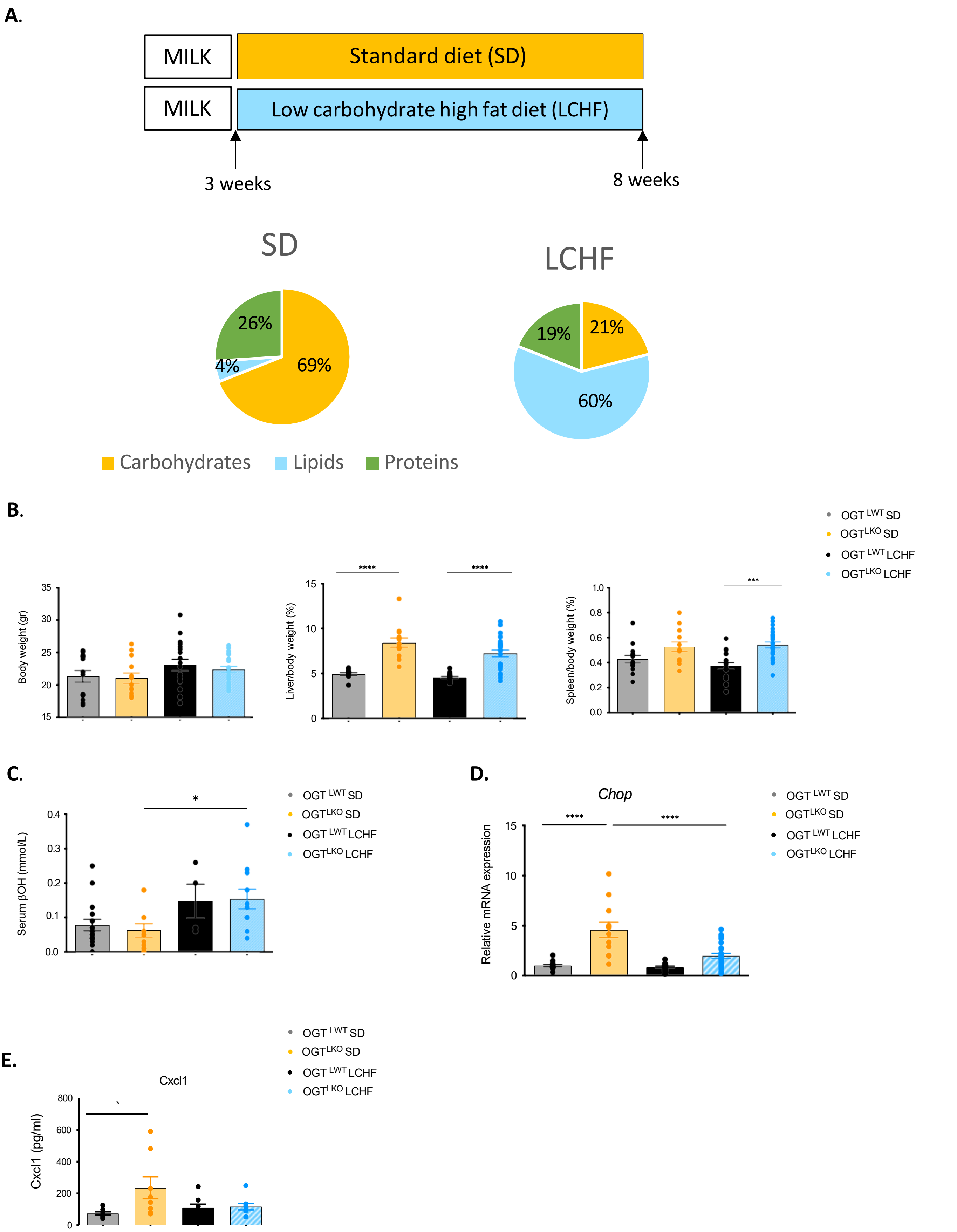

A.
MILK
Standard diet (SD)
MILK
Low carbohydrate high fat diet (LCHF)
3 weeks
8 weeks
SD
26%
4%
69%
LCHF
19%
21%
60%
Carbohydrates
Lipids
Proteins
B.
Body weight (gr)
Liver/body weight (%)
Spleen/body weight (%)
C.
Serum βOH (mmol/L)
D.
Chop
Relative mRNA expression
E.
Cxcl1
Cxcl1 (pg/ml)
OGT LWT SD
OGTLKO SD
OGT LWT LCHF
OGTLKO LCHF

**Fig. S7**

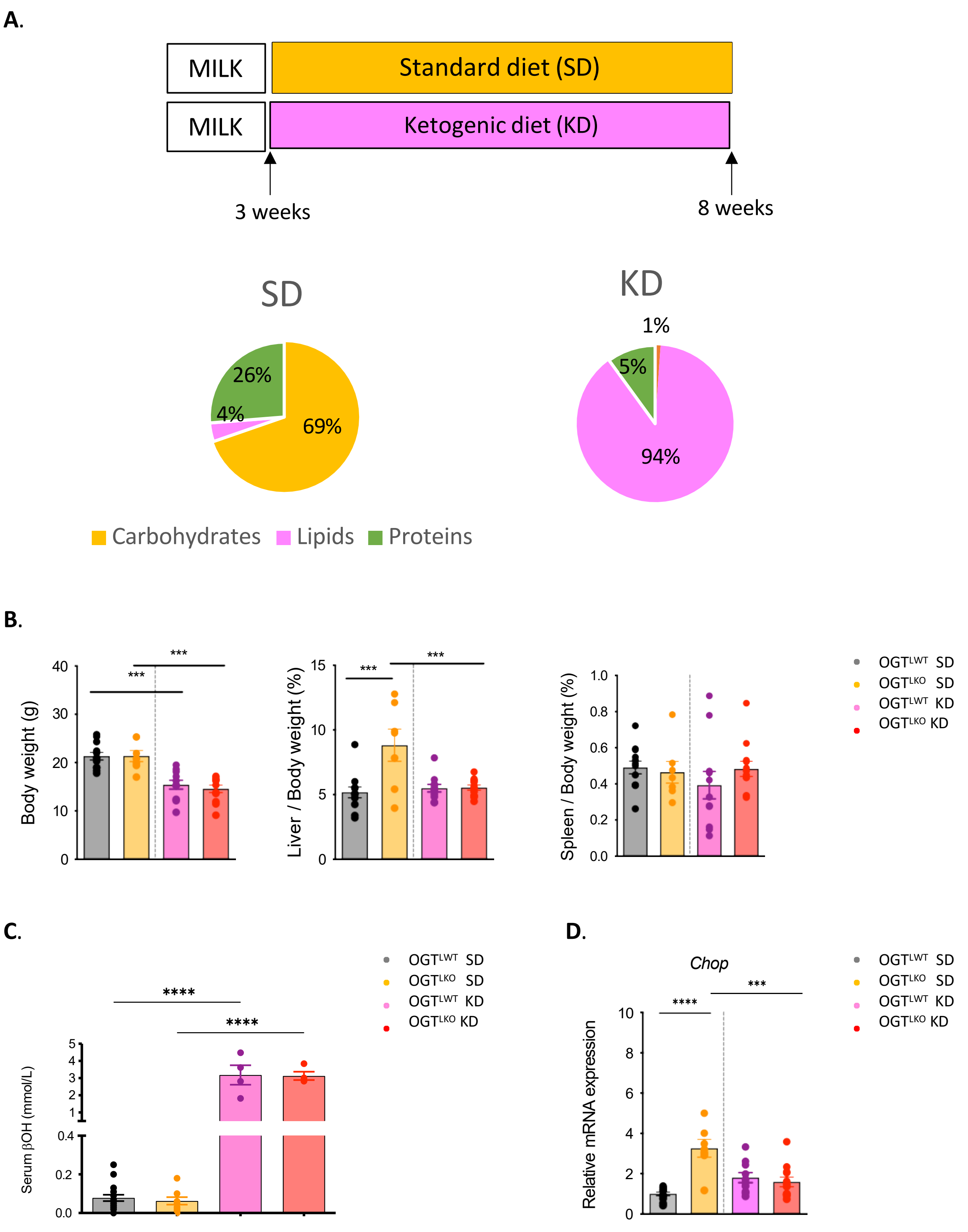
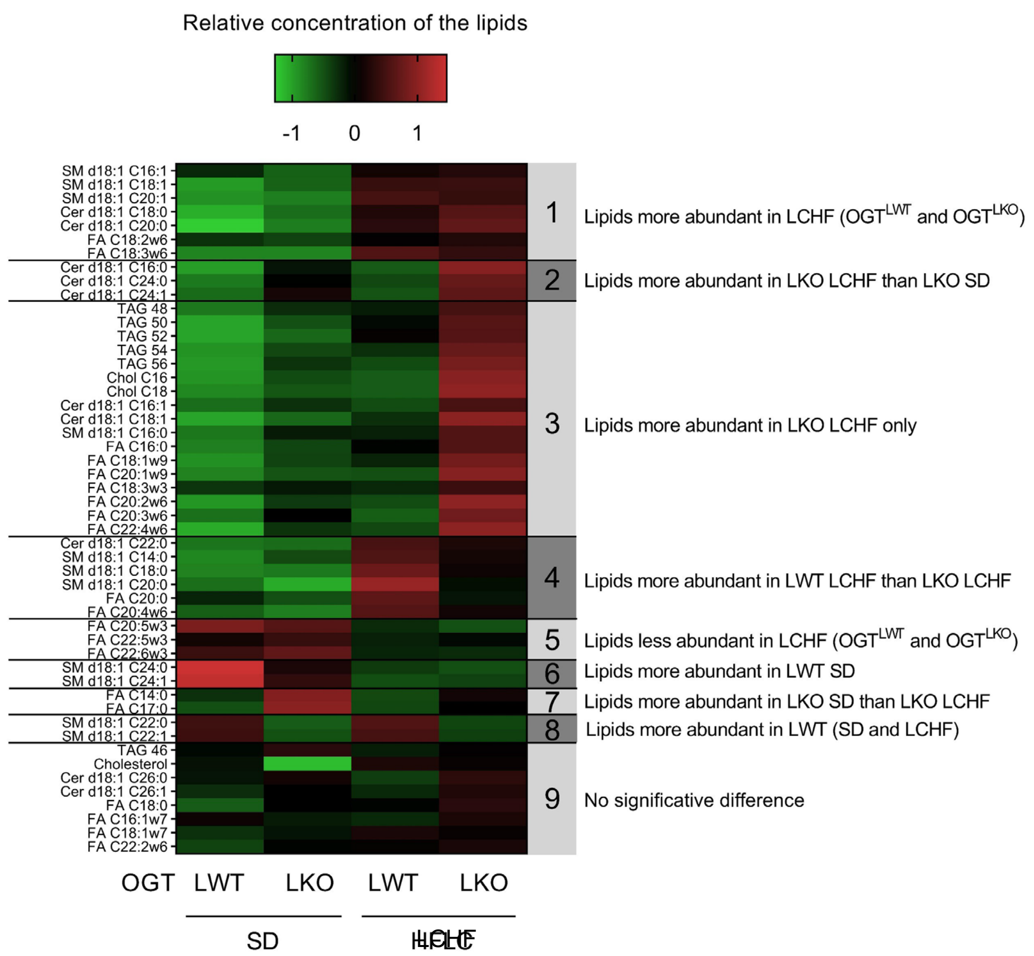

A.
MILK
Standard diet (SD)
MILK
Ketogenic diet (KD)
3 weeks
8 weeks
SD
26%
4%
69%
KD
1%
5%
94%
Carbohydrates
Lipids
Proteins
B.
Body weight (g)
***
***
Liver / Body weight (%)
***
***
Spleen / Body weight (%)
OGTLWT SD
OGTLKO SD
OGTLWT KD
OGTLKO KD
C.
Serum βOH (mmol/L)
****
****
OGTLWT SD
OGTLKO SD
OGTLWT KD
OGTLKO KD
D.
Chop
Relative mRNA expression
****
***
OGTLWT SD
OGTLKO SD
OGTLWT KD
OGTLKO KD

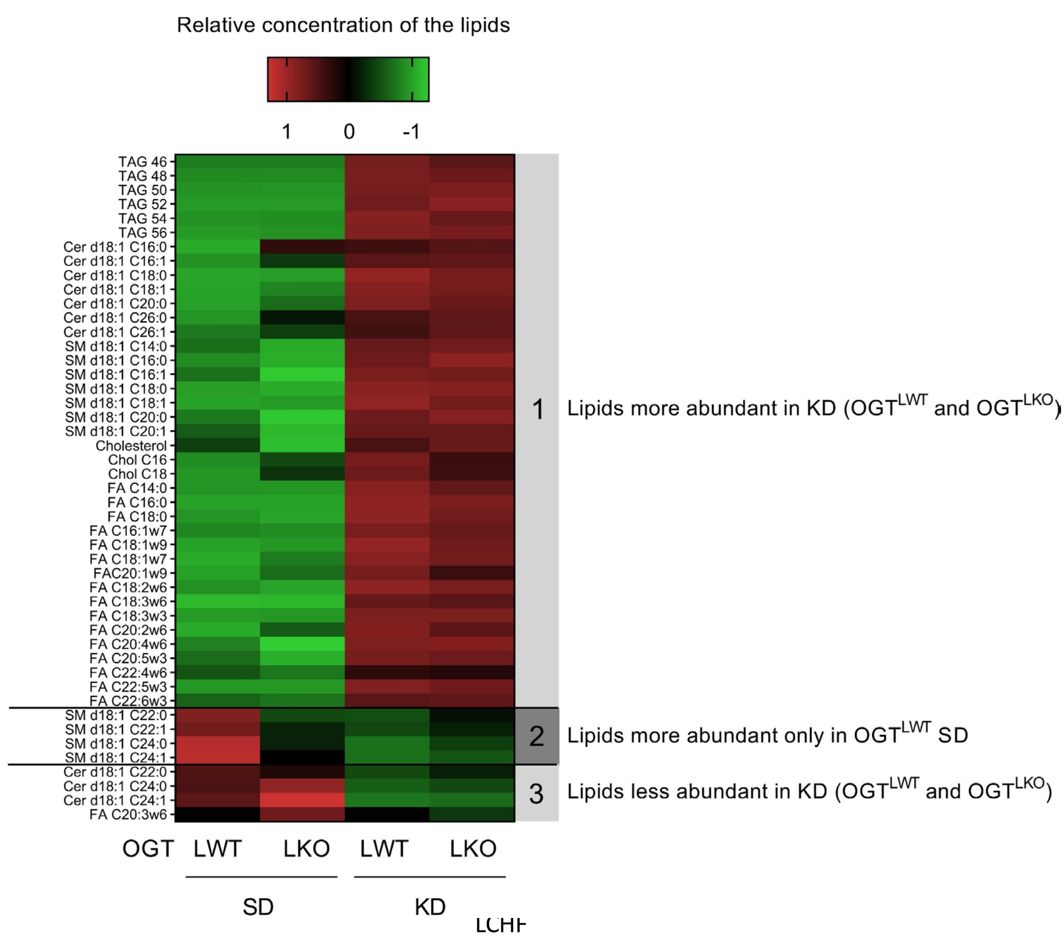
Fig. S8

**A.**



Relative concentration of the lipids
-1
0
1
SM d18:1 C16:1
SM d18:1 C18:1
SM d18:1 C20:1
Cer d18:1 C18:0
Cer d18:1 C20:0
FA C18:2w6
FA C18:3w6
Cer d18:1 C16:0
Cer d18:1 C24:0
Cer d18:1 C24:1
TAG 48
TAG 50
TAG 52
TAG 54
TAG 56
Chol C16
Chol C18
Cer d18:1 C16:1
Cer d18:1 C18:1
SM d18:1 C16:0
FA C16:0
FA C18:1w9
FA C20:1w9
FA C18:3w3
FA C20:2w6
FA C20:3w6
FA C22:4w6
Cer d18:1 C22:0
SM d18:1 C14:0
SM d18:1 C18:0
SM d18:1 C20:0
FA C20:0
FA C20:4w6
FA C20:5w3
FA C22:5w3
FA C22:6w3
SM d18:1 C24:0
SM d18:1 C24:1
FA C14:0
FA C17:0
SM d18:1 C22:0
SM d18:1 C22:1
TAG 46
Cholesterol
Cer d18:1 C26:0
Cer d18:1 C26:1
FA C18:0
FA C16:1w7
FA C18:1w7
FA C22:2w6
1 Lipids more abundant in LCHF (OGT^LWT and OGT^LKO)
2 Lipids more abundant in LKO LCHF than LKO SD
3 Lipids more abundant in LKO LCHF only
4 Lipids more abundant in LWT LCHF than LKO LCHF
5 Lipids less abundant in LCHF (OGT^LWT and OGT^LKO)
6 Lipids more abundant in LWT SD
7 Lipids more abundant in LKO SD than LKO LCHF
8 Lipids more abundant in LWT (SD and LCHF)
9 No significative difference
OGT LWT LKO LWT LKO
SD
LCHF


**B.**



Relative concentration of the lipids
1
0
-1
TAG 46
TAG 48
TAG 50
TAG 52
TAG 54
TAG 56
Cer d18:1 C16:0
Cer d18:1 C16:1
Cer d18:1 C18:0
Cer d18:1 C18:1
Cer d18:1 C20:0
Cer d18:1 C26:0
Cer d18:1 C26:1
SM d18:1 C14:0
SM d18:1 C16:0
SM d18:1 C16:1
SM d18:1 C18:0
SM d18:1 C18:1
SM d18:1 C20:0
SM d18:1 C20:1
Cholesterol
Chol C16
Chol C18
FA C14:0
FA C16:0
FA C18:0
FA C16:1w7
FA C18:1w9
FA C18:1w7
FAC20:1w9
FA C18:2w6
FA C18:3w6
FA C18:3w3
FA C20:2w6
FA C20:4w6
FA C20:5w3
FA C22:4w6
FA C22:5w3
FA C22:6w3
SM d18:1 C22:0
SM d18:1 C22:1
SM d18:1 C24:0
SM d18:1 C24:1
Cer d18:1 C22:0
Cer d18:1 C24:0
Cer d18:1 C24:1
FA C20:3w6
1 Lipids more abundant in KD (OGT^LWT and OGT^LKO)
2 Lipids more abundant only in OGT^LWT SD
3 Lipids less abundant in KD (OGT^LWT and OGT^LKO)
OGT LWT LKO LWT LKO
SD
KD
LCHF


**Fig. S9**

## Supplementary tables

**Table S1. DE genes at 4 weeks.**

| | | | |
|---|---|---|---|
| 0610010F05Rik | C6 | Dhx38 | Gcdh |
| 0610011F06Rik | Calml4 | Dhx58 | Gclc |
| 1110012L19Rik | Car5a | Dixdc1 | Gcsh |
| 1700001C19Rik | Car5b | Dlg3 | Gde1 |
| 1700024P16Rik | Cbr1 | Dnaic1 | Gdpd1 |
| 1810011O10Rik | Cbr3 | Dnajc2 | Gipc2 |
| 2010003K11Rik | Ccbl1 | Dnajc4 | Gm10639 |
| 9130409I23Rik | Ccdc120 | Dnpep | Gm10768; Abcc2 |
| A1bg | Ccl19 | Dnttip2 | Gm11437 |
| Abca3 | Ccl2 | Dpm3 | Gm13139; Znf41-ps |
| Abcb8 | Ccrl2 | Dpyd | Gm13248 |
| Abhd14b | Cd200r1 | Dtx3l | Gm13251 |
| Abhd15 | Cd5l | Dusp10 | Gm18853 |
| Abhd6 | Cdc7 | Dynll1 | Gm1966 |
| Acad12 | Cdk11b | Ear12; Ear2; Ear3 | Gm2a |
| Acot1 | Cdkl5 | Echdc1 | Gm3776; Gsta1 |
| Acot3 | Cenpp | Eda2r | Gm4794 |
| Acot4 | Ces1d | Eif2ak2 | Gm4952 |
| Acsl1 | Ces1e | Eif2d | Gm4955 |
| Acss2 | Ces1f | Eif6 | Gm7120 |
| Adar | Ces3b | Elovl3 | Gm8074 |
| Adgrf1 | Cidec | Elp4 | Gpi1 |
| Adra1b | Cisd1 | Emc10 | Gpr155 |
| Afm | Cldn12 | Enox2 | Gpr35 |
| Afp | Clec2d | Enpep | Gpt |
| Agpat5 | Clpb | Entpd5 | Gpx2 |
| AI464131 | Cmbl | Epas1 | Grb7 |
| Aida | Cmpk2 | Epb41l4b | Grem2 |
| Akr1c12 | Cmtm6 | Ephx1 | Gsta2 |
| Akr1c13 | Cnnm2 | Epsti1 | Gsta4 |
| Akr1c19 | Cnpy2 | Etfdh | Gstk1 |
| Aldh6a1 | Coa3 | F11 | Gsto1 |
| Aph1c | Cops7b | Fabp5 | Gstp1 |
| Apol9a | Cox19 | Fam131c | Gstp2 |
| Apol9b | Crip2 | Fam20a | Gstt1 |
| Apom | Cryz | Fam210b | Gstt3 |
| Apon | Cxcl10 | Fam60a | Gtf2h4 |
| Arhgap6 | Cxcl9 | Fam98a | Gtf2ird2 |
| Arrdc4 | Cyp2a22 | Fastkd2 | Guf1 |
| Aspdh | Cyp2a5; Cyp2a4 | Fbxo36 | Gvin1 |
| Aspg | Cyp2c40 | Fbxo4 | Gzmd; Gzme |
| Asrgl1 | Cyp2c69 | Fcgrt | H2-Ke6 |

| | | | |
|---|---|---|---|
| Atat1 | Cyp2d37-ps | Fetub | H2-L; H2-D1 |
| Atf3 | Cyp2f2 | Fgf21 | H2-Q1 |
| Atp2b2 | Cyp2j5 | Fgfr4 | H2-Q4 |
| Atp5e | Cyp2u1 | Fhit | H2-Q5 |
| Atp6v1d | Cyp4a31 | Foxo1 | H2-Q7; H2-Q9 |
| B4galnt1 | Cyp4a32 | Foxp1 | H2-Q8; H2-Q6 |
| Bax | Cyp4f15 | Ftsj3 | H2-T10 |
| BC021614 | Cyp4f17 | Fzd8 | H2-T22; H2-T9 |
| BC089597 | Dapk1 | Gabrb3 | Hacl1 |
| Bcl2a1a | Dbt | Galnt10 | Hao2 |
| Bcl2a1d | Dcxr | Galnt4 | Hcfc1r1 |
| Bivm | Ddit3 | Gamt | Heatr1 |
| Bmp1 | Ddx58 | Gbp10; Gbp6 | Herc6 |
| Bmp8b | Ddx60 | Gbp11 | Hes6 |
| Bnip3 | Decr2 | Gbp2b; Gbp5 | Hgfac |
| Borcs8 | Defb1 | Gbp3 | Hint2 |
| Bphl | Dhx33 | Gbp4 | Hmox1 |
| Brix1 | Dhx37 | Gbp9 | Hn1 |

| | | | | |
|---|---|---|---|---|
| Hpn | Mb21d1 | Pak1ip1 | Rars | Sp4 |
| Hps4 | Mccc2 | Pank1 | Rbbp9 | Spats2 |
| Hs3st3b1 | Mest | Papss2 | Rdh11 | Sqle |
| Hsbp1l1 | Mgam | Paqr9 | Rdh16 | Sqstm1 |
| Hsd11b1 | Mgea5 | Parp12 | Reep6 | Srd5a2 |
| Hsd17b7 | Mgll | Parp14 | Rfc2 | Srxn1 |
| Hsd3b1 | Mitd1 | Parp9 | Rgs1 | Sstr2 |
| Hspb1 | Mlkl | Pbld1 | Rhoc | St6galnac6; St6galnac4 |
| Hspbap1 | Mlxipl | Pcca | Rhod | Stab2 |
| Htra2 | Mmab | Pccb | Rnf213 | Stard4 |
| Hykk | Mmachc | Pcid2 | Rnf34 | Stat2 |
| Ifi35 | Mmp13 | Pde9a | Rock2 | Steap2 |
| Ifi44 | Mndal | Pdk1 | Rpn2 | Stx2 |
| Ifih1 | Mpst | Pdxk | Rsad2 | Sult2a8 |
| Ifit1 | Mpv17l2 | Pecr | Rtp4 | Sult3a1 |
| Ifit1bl1 | Mrpl24 | Peg10 | Saa3 | Suox |
| Ifit2 | Mrpl34 | Pex7 | Samhd1 | Tcp11l2 |
| Ifit3 | Ms4a4b | Pfdn2 | Scap | Tesk2 |
| Ifit3b | Ms4a6b | Pgd | Scnn1a | Tfdp2 |
| Igfals | Msmo1 | Phf11a | Sec11c | Thoc6 |
| Il22ra1 | Mterf3 | Phf11b | Sell | Thtpa; Zfhx2os |
| Il2rg | Mup-ps19; Mup20 | Phkg2 | Selo | Timm21 |
| Impact | Mup20 | Phyhd1 | Sema4g | Tlcd2 |
| Inmt | Mut | Pik3c2g | Serf1 | Tlr1 |
| Irak1; Mir718; Mir5132 | Mx1 | Pkd2l2 | Serpine2 | Tlr2 |
| Irf7 | Mx2 | Pklr | Serpinf1 | Tlr3 |
| Irs2 | Myc | Plek | Serpinf2 | Tm2d2 |
| Isg15 | Myo5c | Pm20d1 | Sesn3 | Tmem184c |
| Isoc2a | Myo6 | Pmvk | Sfxn1 | Tmem256 |
| Itih1 | N4bp2 | Pnpo | Sfxn5 | Tmem43 |
| Ivd | Nabp1 | Polr3g | Sgsm1 | Tmem53 |
| Kdelc1 | Naglu | Ppfibp2 | Shb | Tmem97 |
| Kif3a | Nampt | Ppm1k | Shmt1 | Tmprss2 |
| Kitl | Ncald; Gm15941 | Prkra | Slc10a5 | Tnfrsf12a |
| Klf12 | Ndufa3 | Prlr | Slc11a1 | Tnfsf10 |
| Klf9 | Ndufaf3 | Prodh2 | Slc15a3 | Tor1b |
| Klk1b4 | Ndufv3 | Prpf19 | Slc16a10 | Tor3a |
| Klkb1; Cyp4v3 | Neto2 | Prpsap1 | Slc16a12 | Tox |
| Kptn | Nit2 | Prr14 | Slc16a2 | Tprkb |
| Krt18 | Nop56; Snord57 | Prss8 | Slc20a1 | Trim30a |
| Krt20 | Nqo1 | Prune | Slc22a28 | Trim34b; Trim34a |
| Krt8 | Nr1i3 | Psmb8 | Slc22a30 | Trmt10a |

| | | | | |
|---|---|---|---|---|
| Lage3 | Nr5a2 | Psmd5 | Slc25a23 | Tsc22d3 |
| Lgals3bp | Nrg1 | Psmd8 | Slc25a42 | Tsku |
| Lilr4b | Nt5dc1 | Ptcd3 | Slc25a51 | Ttc36 |
| Lin7a | Nt5e | Pter | Slc29a1 | Ttc38 |
| Lmf1 | Nudt19 | Ptgr1 | Slc35b4 | Ttll7 |
| Lonp1 | Nudt2 | Ptprc | Slc35c2 | Uap1l1 |
| Lrp11 | Nup133 | Pvr | Slc35d1 | Ube2v2 |
| Lrrc3 | Nup62cl | Pwp2 | Slc35e3 | Ugdh |
| Lrsam1 | Nxt2 | Pxmp2 | Slc44a1 | Ugp2 |
| Lsg1 | Oaf | Pxmp4 | Slc47a1 | Ugt2a3 |
| Ly6a | Oas1a | Pydc3 | Slc4a7 | Ugt3a1 |
| Ly6c1 | Oas1g | Pydc4 | Slc6a12 | Ugt3a2 |
| Ly6c2 | Oasl2 | Pygo1 | Slfn5 | Ulk2 |
| Lyar | Odf3b | Pyhin1 | Slfn8 | Uqcr10 |
| Mafb | Ogfrl1 | Qdpr | Slpi; Mir7678 | Urm1 |
| Man2b2 | Ogt | Qsox1 | Snrpa1 | Uroc1 |
| Map2k6 | Orm1 | Rab11fip2 | Sox6 | Usp18 |
| Marchf2 | Pafah2 | Rabac1 | Sp100 | Vps28 |

Vps51; Tm7sf2
Vwa8
Wfdc2
Wfdc21
Wfdc3
Xaf1
Xdh
Yeats4
Yif1a
Zbp1
Zcchc24
Zcwpw1
Zfand4
Zfp65
Zfp729a
Zfp729b
Zpr1

**Table S2. DE genes at 8 weeks.**

| | | | | | |
|---|---|---|---|---|---|
| 1600002H07Rik | Atp8a1 | Clstn1 | Epha3 | Gpm6a | Klf6 |
| 1700011H14Rik | Axl | Cmtm3 | Epha7 | Gpm6b | Klhl13 |
| 1700047I17Rik2 | B4galt6 | Cmtm3 | Ephx4 | Gpr65 | Krt19 |
| 2210013O21Rik | Bambi | Col1a1 | Erich5 | Gpx3 | Krt7 |
| 2610305D13Rik | Bcam | Col1a2 | Etl4 | Gsn | Lama2 |
| 6720489N17Rik | Bcl2 | Col3a1 | Ets2 | Gstm2 | Lamb1 |
| Aadat | Bgn | Col6a3 | Ezr | Gucy1a3; Mir7010 | Lamb2 |
| Abcd2 | Bicc1 | Cox18 | Fam105a | H2-Ab1 | Lamc1 |
| Abhd2 | C1qb | Cptp | Fam107a | H2-DMb1 | Lbh |
| Abi2 | C1qc | Creb3l1 | Fam177a | H2-M2 | Ldb1 |
| Abi3bp | C1qtnf7 | Crtap | Fam180a | Heph | Ldhd |
| Abr | C3ar1 | Csf1r | Fam19a2 | Hexa | Lgi2 |
| Ace | Cacnb3 | Csrp1 | Fam205a2 | Hexb | Lgmn |
| Acot9 | Cadm4 | Ctgf | Fam47e | Hgf | Lhfp |
| Acsf2 | Capn8 | Ctsk | Fbln1 | Hist1h2ak | Loxl1 |
| Actg1; Mir6935 | Car2 | Cttnbp2nl | Fbln5 | Hnf4g | Loxl2 |
| Adamts1 | Casc4 | Cxcr4 | Fbn1 | Hnrnpa1 | Lpar1 |
| Adamts2 | Casp12 | Cygb | Fcgr3 | Hpgds | Lpl |
| Adamts5 | Cav2 | Cyp7b1 | Fcna | Hsd3b4 | Lrrcc1 |
| Adamts9 | Cbx6 | Cyp8b1 | Fermt1 | Hsd3b4 | Ltbp4 |
| Adamtsl2 | Ccdc3 | Cysltr1 | Fgfr3 | Htra1 | Lum |
| Add1; Mir7036b | Ccdc80 | D17H6S56E-5 | Fgl2 | Icosl | Ly86 |
| Adgre5; Mir1668 | Ccdc88a | Dab2 | Fhl2 | Idh2 | Lyz2 |
| Adgrg1 | Ccnd1 | Dcdc2a | Flrt2 | Ifi27l2a | Macc1 |
| Adgrg6 | Cd14 | Dcn | Fmo2 | Ifi27l2b | Mamdc2 |
| Adh6-ps1 | Cd163 | Ddah2 | Foxq1 | Ifi30 | Mamld1 |
| Aebp1 | Cd24a | Ddit4l | Frzb | Ifngr1 | Map3k1 |
| Agpat4 | Cd300lh | Ddr2 | Fut10 | Ift57 | Map4k4 |
| Agrn | Cd300lh | Ddx26b | Fxyd5; Mir7050 | Igf1r | Marcks |
| Ahnak; Mir6367 | Cd34 | Dkk3 | Fzd1 | Igfbp3 | Mark1 |
| AI506816 | Cd36 | Dnal1 | G2e3 | Igfbp7 | Mbnl3 |
| Aldh1a2 | Cd52 | Dock10 | G6pdx | Ikbip | Mboat1 |
| Angpt1 | Cd68 | Dpt | Gabra3 | Il10rb | Mcm6 |
| Ankrd1 | Cd74; Mir5107 | Dpy19l3 | Gabrp | Islr | Meis2 |
| Ano1 | Cdh6 | Dpysl2 | Galnt3 | Itga3 | Mfge8 |
| Ano6 | Cdk14 | Efemp1 | Gas6 | Itga8 | Mgat4a |
| Antxr1 | Cerk | Efhd2 | Gdf10 | Itga9 | Mid1 |
| Anxa13 | Chchd7 | Efnb2 | Gem | Itgb5 | Mir3962 |
| Anxa2 | Chst15 | Egflam | Gfpt2 | Itgb6 | Mir6950 |
| Anxa3 | Cib3 | Ehd2 | Gja1 | Itgb8 | Mir7025 |
| Aoah | Clca3a1; Clca1 | Ehf | Gldn | Itgbl1 | Mir7677 |
| Apobec3 | Clca3a2; Clca2 | Elf4 | Gm10052 | Itm2c | Mmp14 |

| | | | | | |
|---|---|---|---|---|---|
| App | Cldn4 | Emb | Gm10600 | Itpr3 | Mmp2 |
| Arg2 | Cldn7 | Emp1 | Gm11710 | Itpripl2 | Moxd1 |
| Arhgdib | Cldn8 | Emp2 | Gm11711 | Jag1 | Mrc2 |
| Arhgef6 | Clec4n | Emp3 | Gm11711 | Jchain | Ms4a4a |
| Arpc1b | Clic1 | Eng | Gm609 | Kalrn | Ms4a4d |
| Art4 | Clic6 | Enho | Gng2 | Kcnma1 | Muc1 |
| Atp2b4; Mir6903 | Clmp | Enkur | Golm1 | Kifc3 | Mxra8 |
| Atp6v0d2 | Cln6 | Epcam | Gpc3 | Klf5 | Myadm |

| | | | |
|---|---|---|---|
| Mybl1 | Pcdhgc3 | Rbl1 | Tmem229b |
| Myh9 | Pcdhgc4 | Rbm3 | Tmem45a |
| Myo1d | Pcdhgc5 | Rbms1 | Tmem47 |
| Myo7a | Pde1a | Rbms3 | Tmsb10 |
| Nav1 | Pdgfc | Rbp1 | Tmsb4x |
| Ncam1 | Pdgfd | Rcn1 | Tnc |
| Ncoa7 | Pdgfra | Rgs2 | Tnfrsf19 |
| Ndrg1 | Pdgfrb | Rhob | Tns1 |
| Nedd9 | Pdzk1ip1 | Rhoj | Tns3 |
| Nek5 | Pea15a | Rnasel | Tox3 |
| Ngfrap1 | Pear1 | Robo1 | Tpm4 |
| Nipal1 | Phactr2 | Robo2 | Tpr |
| Nipal2 | Phlda1 | Rragd | Trib1 |
| Nmnat1 | Phldb2 | Rtn4 | Trove2 |
| Nox4 | Pirb | S100a11 | Tspan3 |
| Npcd | Pisd-ps3 | Scara3 | Tspan8 |
| Npr2 | Pkd2 | Scarf2 | Ttc3 |
| Nptxr | Pkhd1 | Sccpdh | Tuba1a |
| Nt5c3b | Plat | Scd2; Mir5114 | Ucp2 |
| Nudt7 | Pld4 | Sdr9c7 | Ugt2b38 |
| Obp2a | Plekha2 | Selenbp2 | Unc5b |
| Ogn | Plekho1 | Selm | Veph1 |
| Olfml3 | Plet1 | Selplg | Vgll3 |
| Osmr | Plk2 | Sema3c | Vim |
| Pacs1 | Plod2 | Sema3f | Wbp5 |
| Pam | Plp2 | Sema5a | Wfdc15b |
| Pamr1 | Plxdc2 | Sema6a | Wls |
| Parm1 | Plxna4 | Septin11 | Wwc2 |
| Parp8 | Ppic | Septin8 | Zeb2; Mir5129 |
| Pawr | Ppp1r9b | Serpinb6a | |
| Pbk | Prelp | Serpinh1 | |
| Pcdhga1 | Prex2 | Sestd1 | |
| Pcdhga10 | Prkch | Sftpd | |
| Pcdhga11 | Prom1 | Sh2d4a | |
| Pcdhga12 | Prr15l | Sh3kbp1 | |
| Pcdhga2 | Prrg1 | Tgfb2 | |
| Pcdhga3 | Ptger4 | Tgfb3 | |
| Pcdhga4 | Ptgfrn | Tgfbi | |
| Pcdhga5 | Ptpn13 | Thbs1 | |
| Pcdhga6 | Ptpn14 | Thbs2 | |
| Pcdhga7 | Ptprm | Tiam2 | |
| Pcdhga8 | Ptprs | Timp2 | |

| | | |
|---|---|---|
| Pcdhga9 | Pxdn | Timp3 |
| Pcdhgb1 | Rab27b | Tinag |
| Pcdhgb2 | Rab31 | Tlr4 |
| Pcdhgb4 | Rab8b | Tlr7 |
| Pcdhgb5 | Ralgds | Tm4sf1 |
| Pcdhgb6 | Rarres1 | Tmem106a |
| Pcdhgb7 | Rasef | Tmem173 |
| Pcdhgb8 | Rassf9 | Tmem189 |

**Table S3. DE genes common to 4 and 8 weeks.**

9230110C19Rik
9930111J21Rik1; 9930111J21Rik2
9930111J21Rik2
Abcb1a
Adora1
Aebp2
AI607873
Ajuba
Alcam
Anxa5
Bcl2a1b; Bcl2a1a
Capsl
Ccl22
Ccr2
Cd180
Cd44
Cd53
Cd63
Cd9
Cetn4
Chic1
Clec12a
Clec7a
Csprs
Ctss
Cxcl16
Cybb
Elovl7
Epb41l4a
Evi2a; Evi2b; Gm21975
F2rl1
Fads3
Fgf1
Flna
Fn3krp
Glipr1
Gm13212
Gm2399
Gm3934
Gm5431
Gm9844
Gpnmb
Ifi204
Ifi27
Iqgap1
Laptm5
Lenep; Flad1
Lifr
Lilrb4a
Ly6e
Mgst3
Mmp12
Mnda
Mpv17l
Ms4a4c
Ms4a6c
Ms4a6d
Ms4a7
Myl12a
Myof
Nid1
Npnt
Ntrk2
P2ry4
Pafah1b3
Phf11d; Phf11c
Pla2g7
Plac8
Plekhb1
Pygb
Retsat
Samd9l
Septin6
Sirpa
Slamf7
Slamf9
Slc22a26
Slc25a45
Slfn2
Spi1
Tceal8
Tcf24
Tlr13
Tmem176b

Gstm3
H2-Aa
H2-DMb2
H2-Eb1
Haus8
Hcls1
Ido2
Ifi203
Tmem19
Tnfaip3
Vcam1

**Table S4. Primer sequences.**

| Name | Sequence |
|---|---|
| **Ccl5 F** | CTG ACC CTG TAT AGC TTC CCT |
| **Ccl5 R** | GGG ATT ACT GAG TGG CAT CC |
| **Chop F** | AAG GAG AAG GAG CAG GAG AAC |
| **Chop R** | GGT ACA CTT CCG GAG AGA CAG |
| **Col3a1 F** | CTGTAACATGGAAACTGGGGAAA |
| **Col3a1 R** | CCATAGCTGAACTGAAAACCACC |
| **Col6a1 F** | CTGCTGCTACAAGCCTGCT |
| **Col6a1 R** | CCCCATAAGGTTTCAGCCTCA |
| **CycA2 F** | TGC CTT CAC TCA TTG CTG GA |
| **CycA2 R** | TGT GGC GCT TTG AGG TAG GT |
| **CycB1 F** | TGC CTT TGT CAC GGC CTT AG |
| **CycB1 R** | GGA AAT TCT TGA CAA CGG TG |
| **CycD F** | GCG TAC CCT GAC ACC AAT CTC |
| **CycD R** | CTC CTC TTC GCA CTT CTG CTC |
| **CycE F** | CAGAGCAGCGAGCAGGAGA |
| **CycE R** | CAGCTGCTTCCACACCACTG |
| **F4/80 F** | CTT TGG CTA TGG GCT TCC AGT C |
| **F4/80 R** | GCA AGG AGG ACA GAG TTT ATC GTG |
| **Gpx3 F** | GCC ATT TGG CTT GGT CAT TC |
| **Gpx3 R** | TGG GGA GTA TCT CCG AGT TC |
| **Gpx4 F** | GCA CGA ATT CTC AGC CAA GG |
| **Gpx4 R** | CAA ACT GGT TGC AGG GGA AG |
| **Gclc F** | CTG CAC ATC TAC CAC GCA GT |
| **Gclc R** | TTC ATG ATC GAA GGA CAC CA |
| **Gss F** | GAAGCAGCTCGAAGAACTGG |
| **Gss R** | AGCACTGGGTACTGGTGAGG |
| **Gsta1 F** | CCA GAG CCA TTC TCA ACT A |
| **Gsta1 R** | TGC CCA ATC ATT TCA GTC AG |
| **Gstm1 F** | CTACCTTGCCCGAAAGCAC |
| **Gstm1 R** | ATGTCTGCACGGATCCTCTC |
| **Gstm3 R** | TGA AGG CCA TCC CTG AGA AA |
| **Gstm3 F** | CTT GGG AGG AAG CGG CTA CT |
| **Gstm5 R** | AGA TAC ATC GCA CGC AAG CA |
| **Gstm5 F** | CCA TGT GAA TTT CCC CAG GA |
| **Hnf4α F** | TGCCTGCCTCAAAGCCAT |
| **Hnf4α R** | CACTCAGCCCCTTGGCAT |
| **HO-1 F** | GTCAAGCACAGGGTGACAGA |
| **HO-1 R** | ATCACCTGCAGCTCCTCAAA |
| **Il-1β F** | GGGCCTCAAAGGAAAGAATC |
| **Il-1β R** | TACCAGTTGGGGAACTCTGC |

| | |
|---|---|
| **KI67 F** | AGG ATG GAA GCA AGC CAA CA |
| **KI67 R** | GGC CCT TGG CAT ACA CAA AA |
| **Krt7 F** | CACCCGGAATGAGATTGCG |
| **Krt7 R** | GCACGCTGGTTCTTCAAGGT |
| **Krt19 F** | TGCTGGATGAGCTGACTCTG |
| **Krt19 R** | AATCCACCTCCACACTGACC |
| **Mcp1 F** | TGAATGTGAAGTTGACCCGT |
| **Mcp1 R** | AGAAGTGCTTGAGGTGGTTG |
| **Nq01 F** | AGC GTT CGG TAT TAC GAT CC |
| **Nq01 R** | AGT ACA ATC AGG GCT CTT CTC G |
| **Nrf2 F** | TTC TTT CAG CAG CAT CCT CTC CAC |
| **Nrf2 R** | ACA GCC TTC AAT AGT CCC GTC CAG |
| **Oga F** | TTCACTGAAGGCTAATGGCTCCCG |
| **Oga R** | TGTCACAGGCTCCGACCAAGT |
| **Ogt F** | TCGCACAGCTCTGTCAAAAA |
| **Ogt R** | GCCCTGGGTCGCTTGGAAGA |
| **Phgdh F** | GGAGGAGATCTGGCCTCTCT |
| **Phgdh R** | GCACACCTTTCTTGCACTGA |
| **αSma F** | TGA CCC AGA TTA TGT TTG AGA CC |
| **αSma R** | CCA GAG TCC AGC ACA ATA CCA |
| **Tbp F** | CCCCACAACTCTTCCATTCT |
| **Tbp R** | GCAGGAGTGATAGGGGTCAT |
| **Tgf} F** | TGAGTGGCTGTCTTTTGACG |
| **Tgf} R** | AGTGAGCGCTGAATCGAAAG |
| **Tnfα F** | TGGGAGTAGACAAGGTACAACC |
| **Tnfα R** | CATCTTCTCAAAATTCGAGTGAC |
| | |