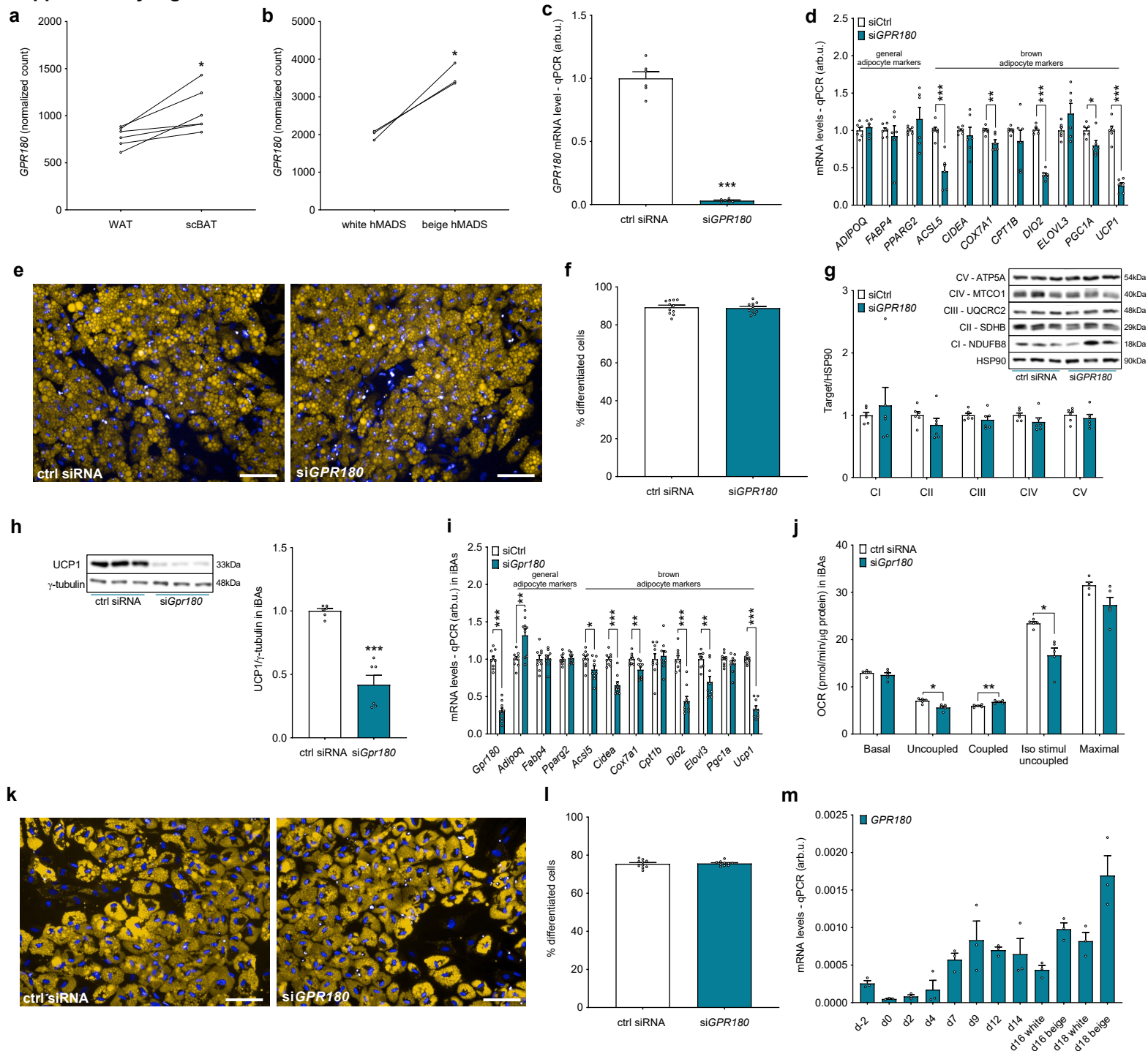


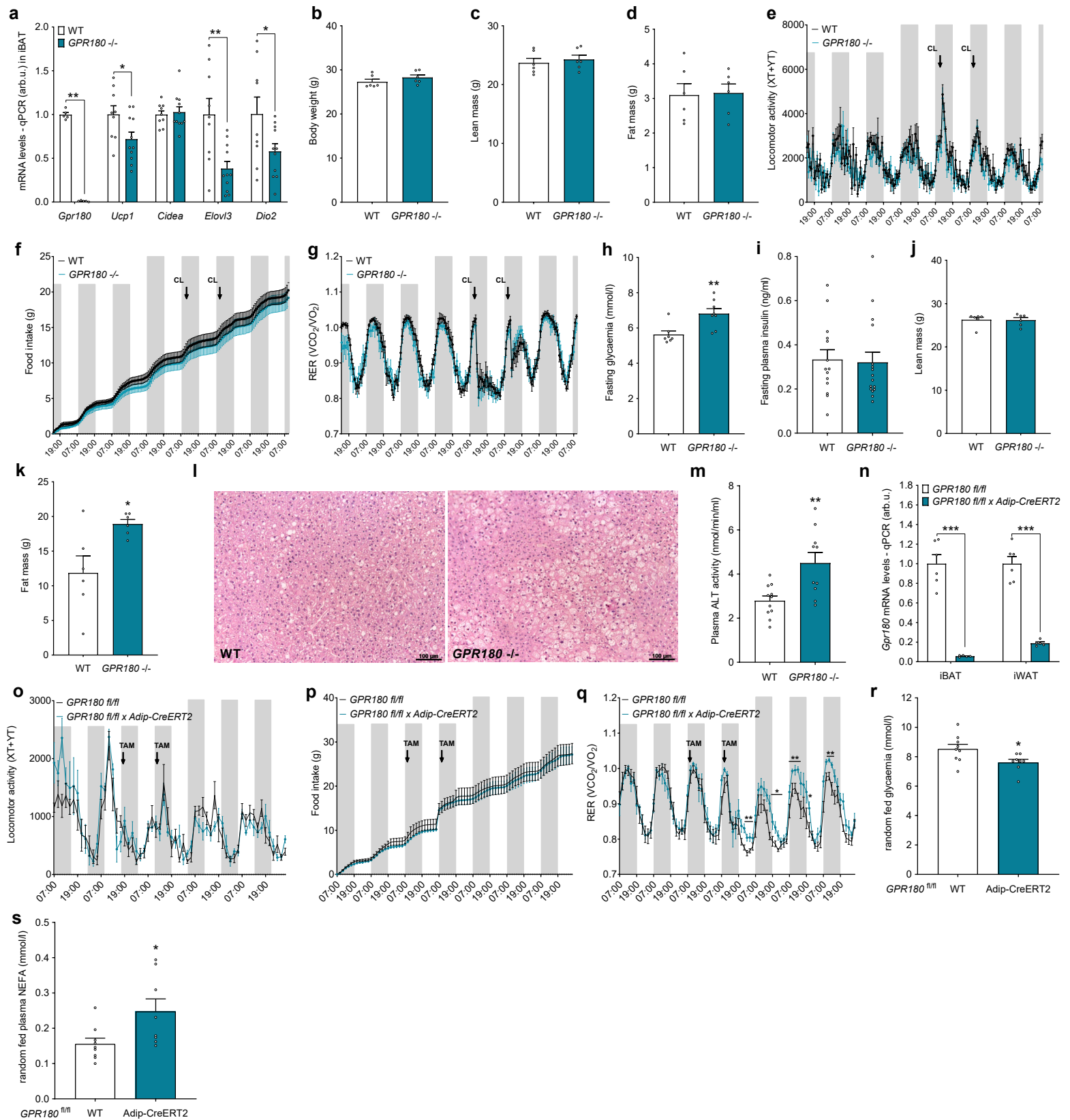
Supplementary Figure 1



Supplementary Fig. 1 (related to Fig. 1): GPR180 is upregulated in BAT and required for brown phenotype in both human and murine adipocytes.

Expression of GPR180 in (a) human fat tissues (n=6; p=0.0167) and (b) human beige and white adipocytes (n=3;p=0.0236). (c) Knockdown efficiency of siRNAs targeting GPR180 in mature beige hMADS cells (n=6; p<0.0001). (d) Gene expression of general and brown adipocyte markers in human beige adipocytes with ablated GPR180 (n=6; *ACSL5* p=0.0003; *COX7A1* p= 0.0062; *DIO2* p<0.0001; *PGC1A* p=0.0209; *UCP1* p<0.0001). (e) Representative images with scale bar 100 μ m and (f) quantification of cell differentiation following GPR180 knockdown in beige hMADS cells (n=11; p=0.7484), lipid droplets in yellow (LD540), nuclei blue (Hoechst). Experiment was repeated 3 times independently with similar results. (g) Representative blots and quantification of OXPHOS proteins in beige hMADS cells (n=6; CII p=0.5978; CIII p=0.2228; CIII p=0.2977; CIV p=0.1724; CV p=0.5228). Effect of Gpr180 knockdown in murine immortalized brown adipocytes on (h) UCP1 protein (n=6; p<0.0001), (i) expression of general and brown adipocyte marker genes (n=9; *Gpr180* p<0.0001; *Adipoq* p=0.0032; *Acs15* p=0.0389; *Cidea* p<0.0001; *Cox7a1* p=0.0071; *Dio2* p<0.0001; *Elovl3* p=0.0020; *Ucp1* p<0.0001) and (j) mitochondrial respiration (n=5; uncoupled p=0.0271; coupled p=0.0093; iso stimul uncoupled p=0.0486). (k) Representative images with scale bar 100 μ m and (l) quantification of cell differentiation following GPR180 knockdown in undifferentiated preadipocytes (n=10; p=0.7917), lipid droplets in yellow (LD540), nuclei blue (Hoechst). Experiment was repeated 3 times independently with similar results. (m) GPR180 expression during time-course of hMADS cells differentiation. Data are shown as mean \pm SEM. Statistical significance was calculated using paired Student's t test (Fig. a and b), unpaired two-sided Student's t test (Fig. c-i and l) and two-way ANOVA with Sidak post-hoc test (Fig. j) and indicated as * p < 0.05, ** p < 0.01 and *** p < 0.001. ACSL5, Acyl-CoA synthetase long chain family member 5; ADIPOQ, Adiponectin; ATP5A, ATP synthase F1 subunit alpha; CIDEA, Cell death inducing DFFA like effector a; COX7A1, Cytochrome c oxidase subunit 7a1; CPT1 β , Carnitine palmitoyltransferase 1 β ; DIO2, Iodothyronine deiodinase 2; ELOVL3, Fatty acid elongase 3; FABP4, Fatty acid binding protein 4; GPR180, G protein coupled receptor 180; hMADS, human multipotent adipose derived stem cells; HSP90, Heat shock protein 90; MTCO1, Mitochondrially encoded cytochrome c oxidase1; NDUFB8, NADH:ubiquinone oxidoreductase subunit B8 PGC1A, PPAR γ coactivator 1 α ; PPARG2, Peroxisome proliferator activated receptor gamma; scBAT, supraclavicular brown adipose tissue; SDHB, Succinate dehydrogenase complex iron sulfur subunit B; UCP1, Uncoupling protein 1; UQCRC2, Ubiquinol-cytochrome c reductase core protein 2; WAT, white adipose tissue.

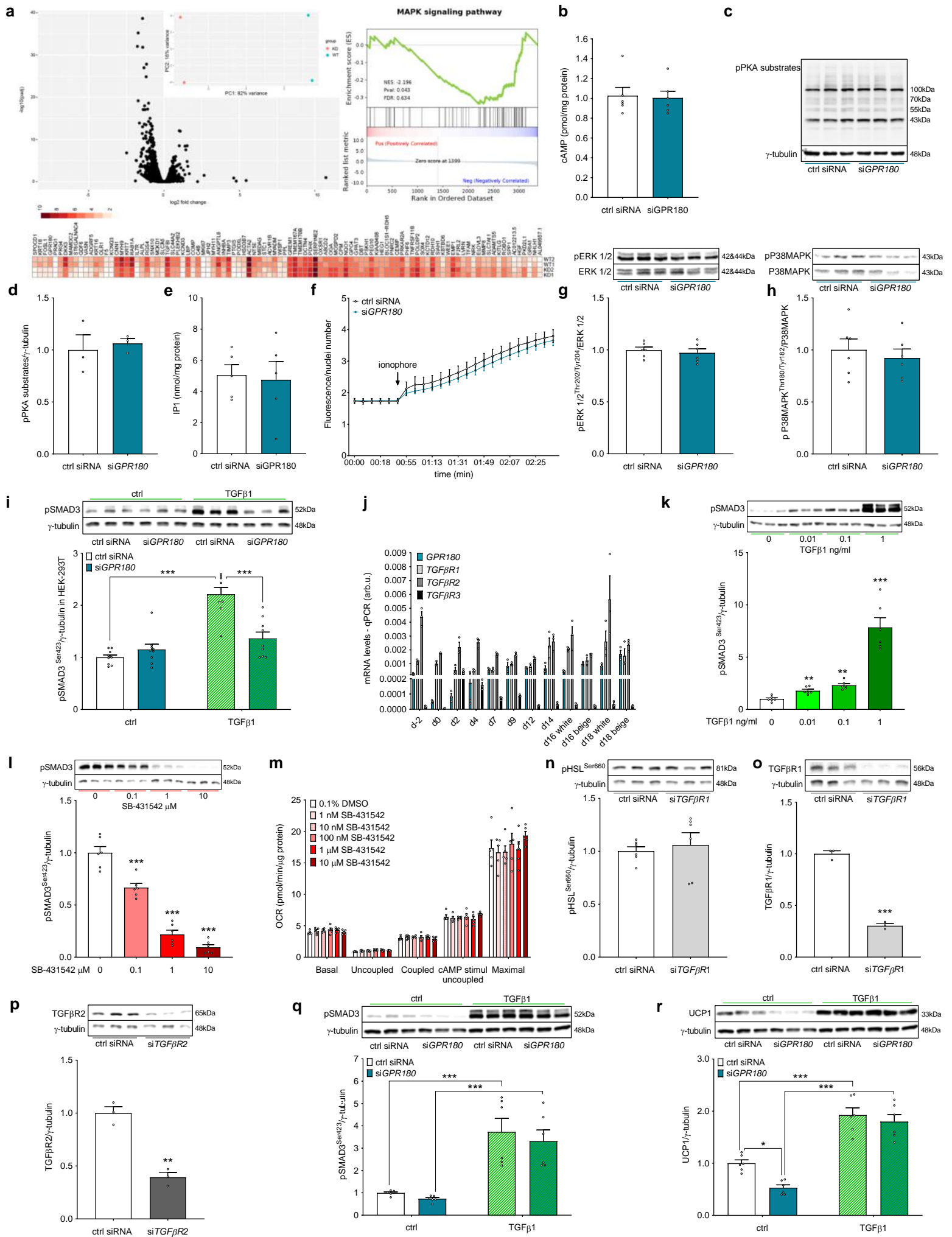
Supplementary Figure 2



Supplementary Figure 2 (related to Fig. 2): Metabolic derangements in GPR180 knockout mice

(a) Expression of *Gpr180* (n=5; p<0.0001) and selected brown adipocyte markers in iBAT of male *GPR180* knockout mice and their wild type littermates (WT n=9 and *GPR180*^{-/-} n=11; p=0.0365 for *Ucp1*, p=0.7231 for *Cidea*, p=0.0041 for *Elovl3*, p=0.0484 for *Dio2*) housed at RT and fed chow diet. (b) Body weight (p=0.2587), (c) lean (p=0.5936) and (d) fat mass (p=0.8833) of animals housed at RT and fed chow diet (n=6). Effect of *Gpr180* deletion on (e) locomotor activity (p=0.1839), (f) cumulative food intake (p=0.4613) and (g) respiratory exchange ratio (p=0.5832) (n=6). CL-316.243 (0.1 mg/kg/day) was administered intraperitoneally at indicated time points. (h) Blood glucose (WT n=7, *GPR180*^{-/-} n=8; p=0.0059) and (i) plasma insulin level (WT n=14, *GPR180*^{-/-} n=16; p=0.8441) in chow fed mice fasted for 6h prior to blood sampling. Body composition, (j) lean mass (p=0.9303) and (k) fat mass (p=0.0195) of mice housed at RT and challenged with HFD for 12 weeks (n=6). (l) Representative images of haematoxylin and eosin stained liver sections (10x magnification with scale bar 100 μ m, experiment was repeated twice independently with similar results) and (m) plasma alanine-aminotransferase activity (p=0.0033) in global *GPR180* knockouts after 12 weeks of HFD feeding regimen at RT (WT n=11, *GPR180*^{-/-} n=10). (n) Knockout efficiency in iBAT (p<0.0001) and iWAT (p<0.0001) of male adipocyte specific *GPR180* (*aGPR180*) knockouts and fl/fl controls (fl/fl control n=6 and *aGPR180* knockout n=5) 2 weeks after tamoxifen (TAM) gavage (2mg/animal) in two consecutive days. Effect of *GPR180* ablation in mature adipocytes on (o) locomotor activity (p=0.0538), (p) food intake (p=0.7565) and (q) respiratory exchange ratio (p=0.0132) in *aGPR180* knockouts (n=5) and fl/fl controls (n=6). Random fed (r) glycaemia (p=0.0309) and (s) plasma free fatty acids level (p=0.0265) in *aGPR180* knockouts (n=8) and fl/fl controls (n=9) on 3rd day after tamoxifen induced knockout. Data are presented as mean \pm SEM. Statistical analysis was performed using two-sided Student's t test (Fig. a-e, h-n, r and s) or two-way ANOVA with repeated measurements followed by Sidak post-hoc test (Fig. e-g, o-q). Significance is indicated as * p < 0.05, ** p < 0.01 and *** p < 0.001. ALT, Alanine aminotransferase; CIDEA, Cell death inducing DFFA like effector a; CL, CL-316,243; DIO2, Iodothyronine deiodinase 2; ELOVL3, Fatty acid elongase 3; GPR180, G protein coupled receptor 180; iBAT, interscapular brown adipose tissue; iWAT, inguinal white adipose tissue; NEFA, non-esterified fatty acids; RER, respiratory exchange ratio; RT, room temperature; TAM, tamoxifen; UCP1, Uncoupling protein 1; WT, wild type.

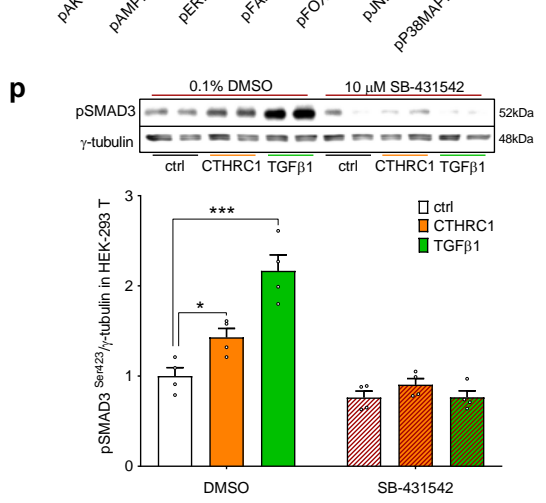
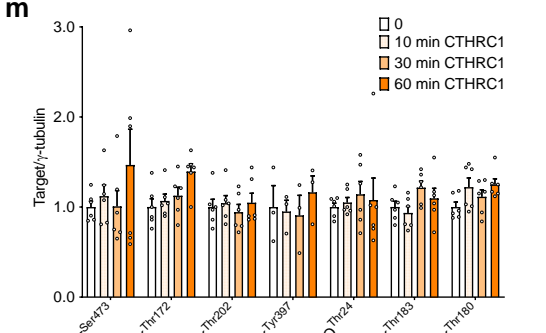
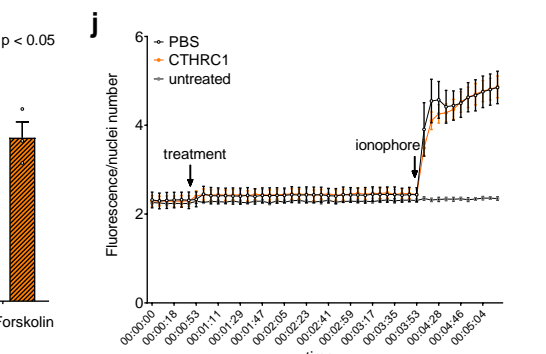
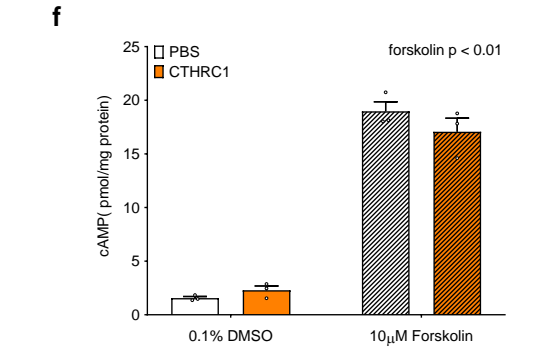
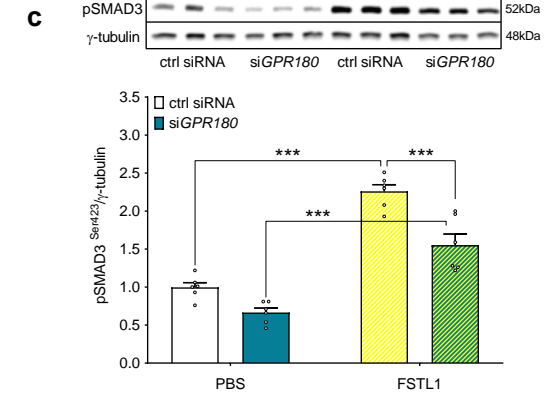
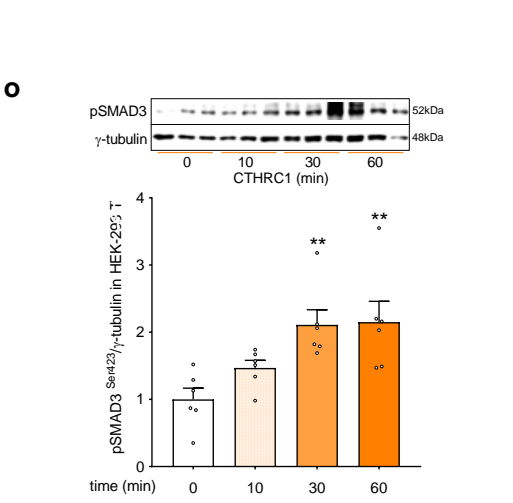
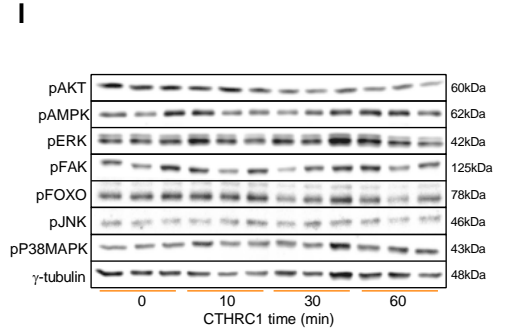
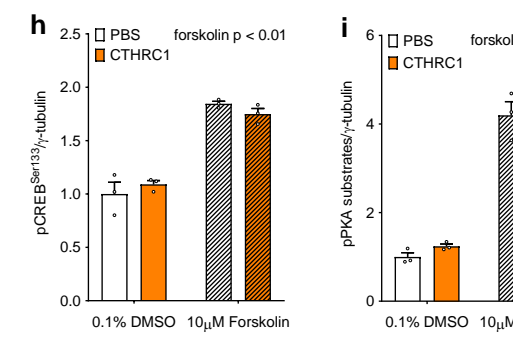
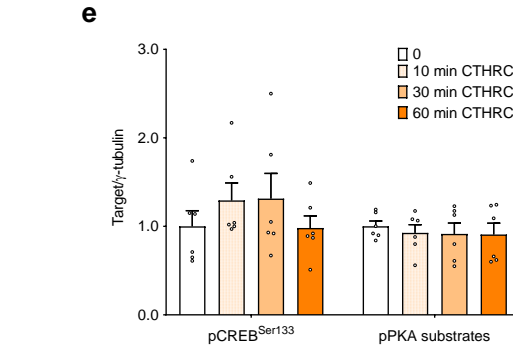
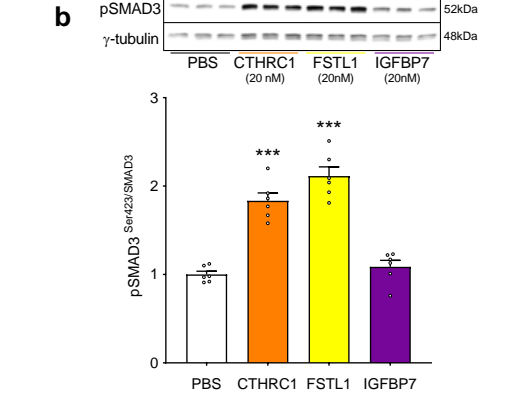
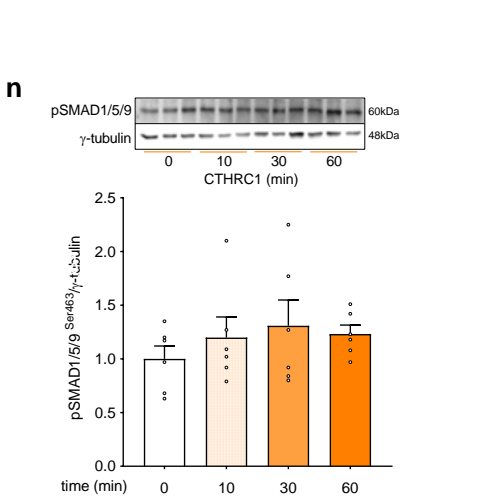
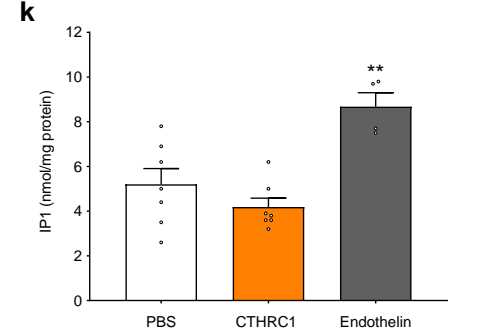
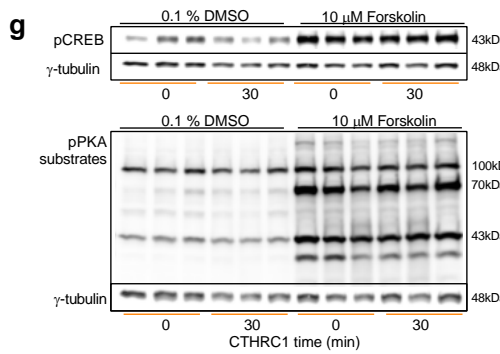
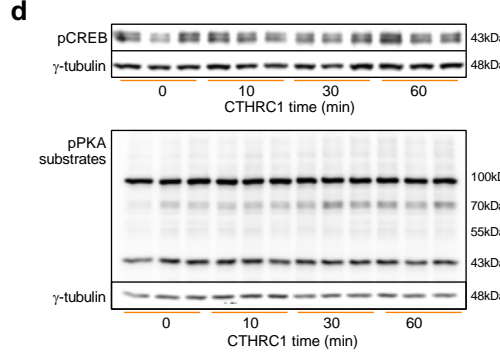
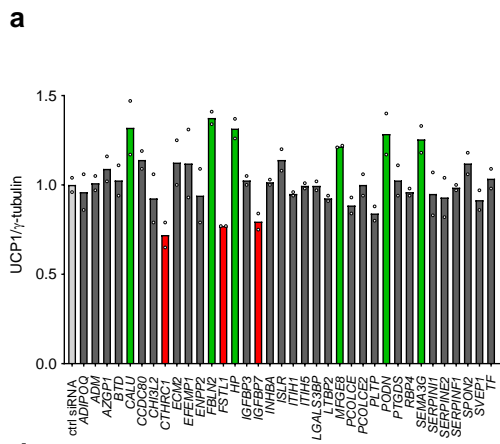
Supplementary Figure 3



Supplementary Fig. 3 (related to Fig. 3): GPR180 is not a GPCR but a component of TGF β signalling pathway

(a) Analysis of differentially expressed genes following GPR180 knockdown in beige hMADS cells with top 50 regulated genes shown in the bottom. DESeq2 detects DE genes based on a generalised linear model using the negative binomial distribution. The p-values obtained by Wald test were corrected by Benjamini–Hochberg multiple testing procedure. Effect of GPR180 knockdown on (b) cAMP (n=5; p=0.8448), (c, d) phospho-PKA substrates (n=3; p=0.7010) (e) IP1 (n=5; p=0.8349) and (f) calcium levels in beige hMADS cells (n=5; p=0.5480). Phosphorylation of kinases (g) ERK (at Threonine 202; p=0.5960) and (h) P38MAPK (at Threonine 180; p=0.5758) in beige hMADS cells with ablated GPR180 (n=6). (i) Effect of acute (1 hour) TGF β 1 stimulus (1ng/ml) on SMAD3 phosphorylation (at Serine 423) in HEK-293T in combination with GPR180 silencing (n=9; p<0.0001 for ctrl siRNA ctrl vs ctrl siRNA TGF β 1; p<0.0001 for ctrl siRNA TGF β 1 vs siGPR180 TGF β 1). (j) Expression of genes encoding GPR180 and individual TGF β receptors in time course of hMADS cells differentiation (n=3). (k) Phosphorylation of SMAD3 (at Serine 423) in response to long-term (72 hours) TGF β 1 treatment of hMADS cells (n=6; p=0.0022 for 0.01 ng/ml, p=0.001 for 0.1 ng/ml and p<0.0001 for 1ng/ml). Effect of long-term TGF β 1 pharmacological inhibition (72 hours) on (l) SMAD3 phosphorylation (at Serine 423) (n=6; p<0.0001 for all comparisons) and (m) mitochondrial respiration (n=5; p=0.5209). (n) Phosphorylated HSL (at Serine 660) in beige hMADS cells with ablated TGF β 1R1 (n=6; p=0.6598). Knockdown efficiency after (o) TGF β 1R1 (p<0.0001) and (p) TGF β 2R2 siRNA mediated silencing (n=3; p=0.0014). Effect of long-term (72 hours) TGF β 1 treatment (1ng/ml) on (q) phosphorylated SMAD3 (at Serine 423; p=0.0005 for TGF β 1 treatment within ctrl siRNA and p=0.0009 for TGF β 1 treatment within siGPR180) and (r) UCP1 protein in beige adipocytes lacking GPR180 (n=6; p=0.0316 for ctrl siRNA ctrl vs siGPR180 ctrl; p<0.0001 for ctrl siRNA ctrl vs ctrl siRNA TGF β 1 and p<0.0001 for siGPR180 ctrl vs siGPR180 TGF β 1). Data are presented as mean \pm SEM. Statistical analysis was performed using two-sided Student's t test (Fig. b-e, g, h, n-p), one-way (Fig. k and l) or two-way ANOVA (Fig. f, i, m, q and r) with Dunnett's and Sidak post-hoc test, respectively. Significant differences are indicated as * p < 0.05, ** p < 0.01 and *** p < 0.001. cAMP, cyclic adenosine monophosphate; DMSO, dimethyl sulfoxide; ERK, Extracellular signal regulated kinase; GPR180, G protein coupled receptor 180; HSL, Hormone sensitive lipase; IP1, inositol monophosphate; MAPK, Mitogen-activated protein kinase; OCR, oxygen consumption rate; PKA, Proteinkinase A; SMAD3, Mothers against decapentaplegic homolog 3; TGF β 1, Transforming growth factor β 1; TGF β 1R1, Transforming growth factor β receptor type 1; TGF β 2R2, Transforming growth factor β receptor type 2; TGF β 3R3, Transforming growth factor β receptor type 3; UCP1, Uncoupling protein 1.

Supplementary Figure 4

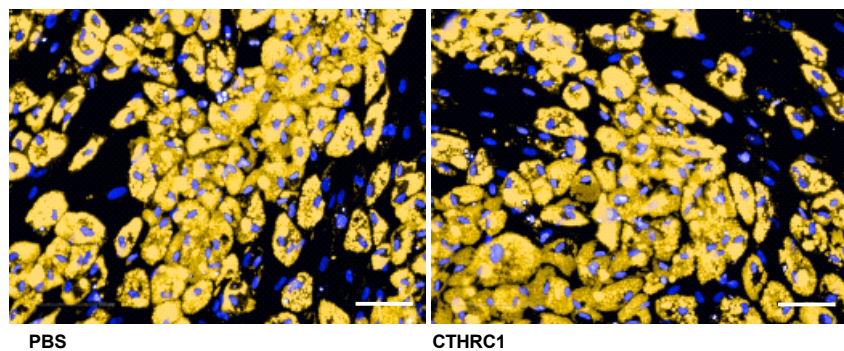


Supplementary Fig. 4 (related to Fig. 4): CTHRC1 does not activate GPCR mediated signalling

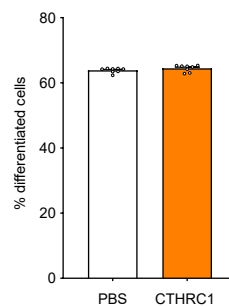
(a) Screening aimed to identify secreted molecules regulating UCP1 protein expression based on siRNA-mediated silencing of individual target genes; $\geq 20\%$ upregulation in green, $\geq 20\%$ downregulation in red (n=2). (b) Representative blot and quantification of SMAD3 phosphorylation (at Serine 423) in beige hMADS cells in response to CTHRC1, FSTL1 and IGFBP7 (20nM; 1 hour) treatment (n=6; p<0.0001 for both CTHRC1 and FSTL1). (c) Representative blot and quantification of SMAD3 phosphorylation (at Serine 423) in beige hMADS cells in response to FSTL1 treatment (20nM; 1 hour) combined with *GPR180* knockdown (n=6; p<0.0001 for ctrl siRNA PBS vs ctrl siRNA FSTL1; p<0.0001 for si*GPR180* PBS vs si*GPR180* FSTL1 and p=0.0002 for ctrl siRNA FSTL1 vs si*GPR180* FSTL1). (d) Representative blots and (e) quantification of short-term CTHRC1 treatment (500ng/ml) on phosphorylation of CREB (at Serine 133; p=0.5261) and phospho-PKA substrates (p=0.9142) in human beige adipocytes starved for 2h prior the treatment (n=6). (f) Cyclic AMP levels in basal and forskolin (10 μ M) pre-treated cells in response to acute CTHRC1 (500ng/ml) treatment (n=3; forskolin p=0.0028, siRNA p=0.2746). (g) Representative blots and quantification of CTHRC1 action on phosphorylation of (h) CREB (at Serine 133; forskolin p=0.0100, siRNA p=0.972) and (i) phospho-PKA substrates (forskolin p=0.0130, siRNA p=0.5663) in beige adipocytes starved for 2h prior the treatment (n=3). Effect of acute CTHRC1 treatment (500ng/ml) on (j) intracellular calcium level (n=4; p=0.9453) and (k) IP1 accumulation (n=7; p=0.3558 for CTHRC1 and p=0.0035 for Endothelin). (l) Representative blots and (m) quantification of phosphorylation of various kinases in time course of CTHRC1 treatment (500ng/ml) of beige adipocytes (n=6; p=0.4427 for AKT, p=0.0522 for AMPK; p=0.8326 for ERK; p=0.8075 for FAK; p=0.9190 for FOXO1; p=0.1127 for JNK and p=0.117 for P38MAPK). (n) SMAD1/5/9 phosphorylation (n=6; p=0.6248) in hMADS cells in response to CTHRC1 (500 ng/ml). (o) Effect of CTHRC1 stimulation (500ng/ml) on SMAD3 phosphorylation (at Serine 423) in HEK-293T cells (n=6; p=0.0046 for 30 min and p=0.0034 for 60 min). (p) Effect of short-term (1 hour) CTHRC1 stimulus on SMAD3 phosphorylation (at Serine 423) in HEK-293T cells pre-treated for 2h with TGF β R1 kinase inhibitor SB-431542 (n=4; p=0.0259 for CTHRC1 in DMSO and p<0.0001 for TGF β 1 within DMSO). Data are presented as mean \pm SEM. Statistical significance was calculated using one- (Fig. b, e, k, m-o) or two-way ANOVA (Fig. c, f, h-j and p) with Dunnett's and Sidak post-hoc test, respectively and is indicated as * p < 0.05, ** p < 0.01 and *** p < 0.001. AKT, AKT serine/threonine kinase 1; AMPK, Protein kinase AMP-activated catalytic subunit alpha 2; cAMP, cyclic adenosine monophosphate; CREB, cAMP responsive element binding protein 1; CTHRC1, Collagen triple helix repeat containing 1; DMSO, dimethyl sulfoxide; ERK, Extracellular signal regulated kinase; FAK, Protein tyrosine kinase 2; FOXO, Forkhead box O; FSTL1, Follistatin like 1; GPR180, G protein coupled receptor 180; IGFBP7, Insulin like growth factor binding protein 7; IP1, inositol monophosphate; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; PBS, phosphate buffered saline; PKA, Protein kinase A; SMAD3, Mothers against decapentaplegic homolog 3; TGF β 1, Transforming growth factor β 1.

Supplementary Figure 5

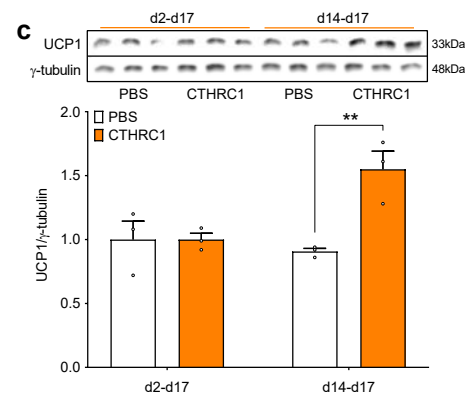
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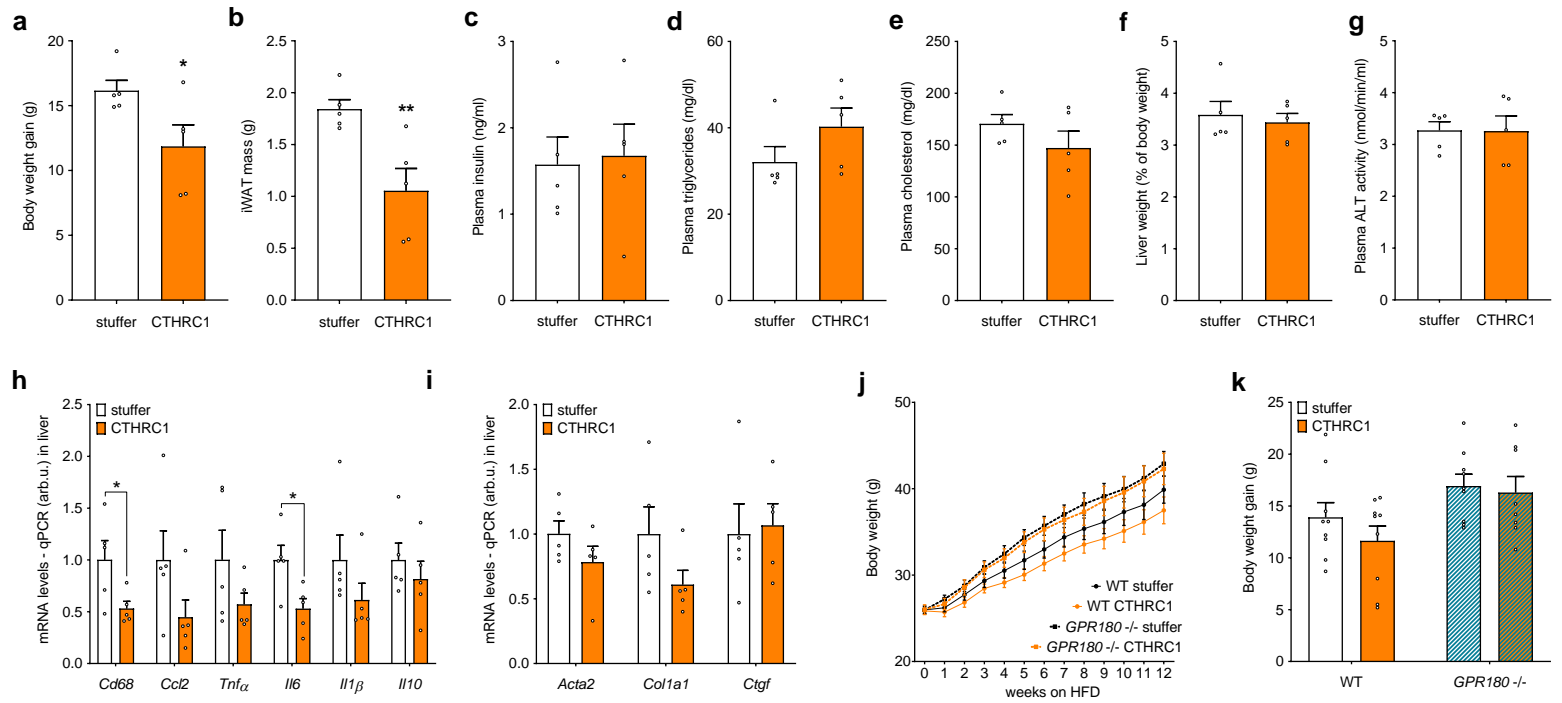
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Supplementary Fig. 5 (related to Fig. 5): CTHRC1 does not affect adipocyte formation

(a) Representative images and (b) quantification of the CTHRC1 (500ng/ml) effect on adipocyte differentiation (n=8; p=0.1805); staining of lipid droplets (yellow) and nuclei (blue); scale bar 100 μ m, the experiment was repeated three times independently. (c) Effect of CTHRC1 treatment (500ng/ml) on beige adipocyte formation (treatment day 2-17) and adipocyte browning (treatment day 14-17) (n=3; p=0.0147 for CTHRC1 within d14-d17). Data are shown as mean \pm SEM. Statistical analysis was performed by unpaired two-sided Student's t test (Fig. b) and two-way ANOVA with Sidak post-hoc test (Fig. c). Significance is indicated as * p < 0.05, ** p < 0.01 and *** p < 0.001. CTHRC1, Collagen triple helix repeat containing 1; PBS, phosphate buffered saline; UCP1, Uncoupling protein 1.

Supplementary Figure 6



Supplementary Fig. 6 (related to Fig. 6): CTHRC1 ameliorates metabolic disturbances in obesity through GPR180

(a) Body weight gain ($p=0.0472$) and (b) iWAT mass ($p=0.0096$) in mice overexpressing CTHRC1 under HFD feeding regimen ($n=5$). Circulating levels of (c) insulin ($p=0.8390$), (d) triglycerides ($p=0.1829$) and (e) cholesterol ($p=0.2453$) following AAV-mediated CTHRC1 overexpression in male C57BL/6N mice ($n=5$). Effect of CTHRC1 overexpression on (f) liver weight ($p=0.6503$), (g) plasma ALT activity ($p=0.9678$) and the expression of (h) inflammatory ($p=0.0443$ for *Cd68* and $p=0.0280$ for *Il6*) and (i) fibrotic markers ($p=0.2029$ for *Acta2*; $p=0.1378$ for *Col1a1* and $p=0.8185$ for *Ctgf*) in livers of mice fed with HFD ($n=5$). (j) Body weight ($p=0.0616$ for treatment) and (k) body weight gain ($p=0.3022$ for treatment) in wild type and global *GPR180* knockout mice on HFD with stuffer or CTHRC1 overexpression ($n=9$ for all experimental groups except *GPR180*^{-/-} CTHRC1 with $n=8$). Data are shown as mean \pm SEM. Statistical significance was calculated using two-sided Student's *t* test (Fig. a-i) or two-way ANOVA with repeated measurement (Fig. j and k) and Sidak post-hoc test. Significant differences are indicated as * $p < 0.05$ and ** $p < 0.01$. ACTA2, Alpha smooth muscle actin; ALT, Alanine aminotransferase; CCL2, monocyte chemoattractant protein-1; CD68, Cd68 antigen; COL1A1, Collagen type 1 alpha 1; CTGF, Connective tissue growth factor; CTHRC1, Collagen triple helix repeat containing 1; GPR180, G protein coupled receptor 180; HFD, high fat diet; IL1 β , Interleukin 1 β ; IL10, Interleukin 10; IL6, Interleukin 6; iWAT, inguinal white adipose tissue; TNF α , Tumor necrosis factor α ; WT, wild type.

Supplementary Table 1 (related to Figure 7): Metabolic profile of individuals with detectable circulating CTHRC1.

parameter	group with detectable circulating CTHRC1	group with circulating CTHRC1 below the limit of detection	p value
age (y)	37.7 ± 1.6	44.8 ± 1.3	0.0008
BMI (kg/m ²)	26.7 ± 0.7	29.4 ± 0.6	0.0028
waist circumference (cm)	98.1 ± 2.1	103.6 ± 1.7	0.0452
fat (%)	23.6 ± 1.0	27.9 ± 0.9	0.0019
adipocyte diameter (µm)	103.9 ± 2.7	116.9 ± 2.3	0.0004
hepatic lipids	5.6 ± 2.5	12.4 ± 2.1	0.0388
extramyocellular lipids	776.0 ± 99.0	1393.3 ± 152.7	0.0010
TAG (mmol/l)	1.3 ± 0.2	1.9 ± 0.1	0.0022
HDL cholesterol (mmol/l)	1.37 ± 0.04	1.27 ± 0.03	0.0300
fasting insulin (mIU/l)	7.44 ± 1.12	10.52 ± 0.93	0.0400
M value (mg/kg BW/min)	6.4 ± 0.4	4.5 ± 0.3	0.0007

Supplementary Table 2: Sequence of siRNAs used in the functional studies (siRNA pools) and secretome screening (single siRNA)

Gene symbol	Species	Sense siRNA sequence
<i>GPR180</i>	Human	#1 CCAGAUUCCGUCUCCACAA #2 GCUGGUUCAGCUUUAGCUA #3 GCGACUACCAAAGAGACAA
<i>CTHRC1</i>	Human	#1 GCUGUCAGCGUUGGUAUUU #2 CCCAACUACAAGCAGUGUU #3 GGAUGUUGCUAUCUGGGUU
<i>TGFβR1</i>	Human	#1 GAACAGAAGUUAAGGCCAA #2 CCAUCUUCACAUGGAGAUU #3 CGAGAUAGGCCGUUUGUAU
<i>TGFβR2</i>	Human	#1 GCAAGACGCGGAAGCUCAU #2 GCUCUGGUGCUCUGGGAAA #3 GAACAUAACACUAGAGACA
<i>SMAD2</i>	Human	#1 GCAGAACTATCTCCTACTA #2 GGAGAAACCTTCCATGCAT #3 GCCACGGTAGAAATGACAA
<i>SMAD3</i>	Human	#1 GCGTGAATCCCTACCACTA #2 GCCATCCATGACTGTGGAT #3 CCGCATGAGCTTCGTCAA
<i>Gpr180</i>	Mouse	#1 CCAUGCACACCAUCUAAAA #2 GCUAGGAGUGCCUCUCAUA #3 GCUCUCCUCAGUAACGCUA
Non-targeting control siRNA pool	-	#1 UGGUUUACAUGUCGACUAA #2 UGGUUUACAUGUUUUCUGA #3 UGGUUUACAUGUUUUCUA
<i>ADIPOQ</i>	Human	GAUUGGAGACUUACGUUACUA
<i>ADM</i>	Human	UCGCGUCGGAGUUUCGAAA
<i>AZGP1</i>	Human	CCAGGGAGGACAUCUUUAU
<i>BTD</i>	Human	GCAUGCCUAGUAGCUGUUU
<i>CALU</i>	Human	UCACUGUGGAUGAGCUCAA
<i>CCDC80</i>	Human	GCCUCAUCCUAAGCUGAU
<i>CHI3L2</i>	Human	GGAGGGUACCUGUUUGGUU
<i>CTHRC1</i>	Human	GCUGUCAGCGUUGGUAUUU
<i>ECM2</i>	Human	GCAGAGGAGGAGACAGAAA
<i>EFEMP1</i>	Human	CCACCAAAGAUGCGUGAAU
<i>ENPP2</i>	Human	CCAAUUAUCCAGGGAUUAU
<i>FBLN2</i>	Human	GUCGUGUGAGUCCAAUCCUAA
<i>FSTL1</i>	Human	GCAGUAAUGGCAAGACCUA
<i>HP</i>	Human	GGUUCGCUACCAGUGUAAGAA
<i>IGFBP3</i>	Human	CCAGCUCCAGGAAAUGCUA
<i>IGFBP7</i>	Human	CCUCAUCUGGAACAAGGUA
<i>INHBA</i>	Human	CCGAGGAAGUGGGCUUAAA

<i>ISLR</i>	Human	CCCUCCAAUUGCUCUAAGAU
<i>ITIH1</i>	Human	GCCGUUACAGCAGAUGGAA
<i>ITIH5</i>	Human	GCAAGUACGAGCACAGCAU
<i>LGALS3BP</i>	Human	GCGUGAACGAUGGUGACAU
<i>LTBP2</i>	Human	GCACCAACCACUGUAUCAA
<i>MFGE8</i>	Human	CCUGGAGAAUGGGAACAUI
<i>PCOLCE</i>	Human	GCACCUUGCAGAGCAACUU
<i>PCOLCE2</i>	Human	GGAUGUGUACAAUGGCCAU
<i>PLTP</i>	Human	GCAAAGAAGGCCACUUCUA
<i>PODN</i>	Human	GCUCAGCCACACACAACUA
<i>PTGDS</i>	Human	GGGUGAGUUAAAGGAGAA
<i>RBP4</i>	Human	CCAGACUCUGAUUCAUUA
<i>SEMA3G</i>	Human	CCGUCUGUGUGUACCACAU
<i>SERPINI1</i>	Human	GCUGACUUGUCAGUGAAUA
<i>SERPINE2</i>	Human	GCCTCTTTCCGGCTGTGAC
<i>SERPINF1</i>	Human	GCGAACAGAAUCCAUCAUU
<i>SPON2</i>	Human	UCUCGUUUGUGGUGCGCAU
<i>SVEP1</i>	Human	GCACAUGUGUGAAAGGAUU
<i>TF</i>	Human	GGUUUGGUGUAUGAUGCUU

Supplementary Table 3: Oligo duplexes targeting human *GPR180* gene used for generation HEK293T stable cell line with receptor deletion.

duplex	Oligonucleotide sequence
hGPR180gRNA1	FWD: CACCGactcgaagtggccgatgcgc REV: AAACgcgcatcggccacttcgagtC
hGPR180gRNA2	FWD: CACCGtgccccgcagggtcttacc REV: AAACgggtaagaccctgcggggcaC
hGPR180gRNA3	FWD: CACCGcggccaccagcagcacgtga REV: AAACtcacgtgctgctggtggccgC
hGPR180gRNA4	FWD: CACCGgacgccccagggccagcgc REV: AAACatgcgctggccctgggcgtcC
hGPR180gRNA5	FWD: CACCGctgtggcctcacgtgctgc REV: AAACgcagcacgtgagggccacagC
hGPR180gRNA6	FWD: CACCGacgtgctgctggtggccgca REV: AAACtgccggccaccagcagcacgtC

Supplementary Table 4: Sequence of qPCR primers used in the study.

Gene symbol	Species	Primer sequence
<i>ACSL5</i>	Human	FWD: AAGAAGGACAGGGACTCGTG REV: AGCAGCAGGAAATTCAGACC
<i>ADIPOQ</i>	Human	FWD: GGTGAGAAGGGTGAGAAAGGA REV: TTTCACCGATGTCTCCCTTAG
<i>B2M</i>	Human	FWD: CGCTCCGTGGCCTTAGC REV: AATCTTTGGAGTACGCTGGATAGC
<i>CIDEA</i>	Human	FWD: GGCAGGTTACGTGTGGATA REV: GAAACACAGTGTTTGGCTCAAGA
<i>COX7A1</i>	Human	FWD: TGACATCCCGTTGTACCTGAAG REV: ACAGTGCCGCCAGACA
<i>CPT1B</i>	Human	FWD: AAACAGTGCCAGGCGGTC REV: CGTCTGCCAACGCCTTG
<i>DIO2</i>	Human	FWD: TCGATGCCTACAAACAGGTG REV: TGGCTCCCTCAGCTATCTTC
<i>ELOVL3</i>	Human	FWD: AACCTGCAAGGGCCTCTC REV: ATAATGCCCCACATCCTCAC
<i>FABP4</i>	Human	FWD: AACCTTAGATGGGGGTGTCTGGT REV: ACGCCTTTCATGACGCATTCCACC
<i>GPR180</i>	Human	FWD: CCAGATGCCGAAGGGAAT REV: GGAGGAAAAGAACTCATGTAACC
<i>PGC1A</i>	Human	FWD: CAGCCTCTTTGCCCAGATCTT REV: TCACTGCACCACTTGAGTCCAC
<i>PPARG2</i>	Human	FWD: CGTGGCCGCAGAAATGA REV: TCAAAGGAGTGGGAGTGGTC
<i>RPL13A</i>	Human	FWD: GGACCGTGCGAGGTATGCT REV: ATGCCGTCAAACACCTTGAG A
<i>UCP1</i>	Human	FWD: AGGTCCAAGGTGAATGCC REV: GCGGTGATTGTTCCAGGA
<i>Acs15</i>	Mouse	FWD: ACAACCAGTCTGTGGGGATT REV: GGTCATTGTTCTTCTGGAAAGC
<i>Acta2</i>	Mouse	FWD: ACTGGGACGACATGGAAAAG REV: GTTCAGTGGTGCCTCTGTCA
<i>Adipoq</i>	Mouse	FWD: ACCATGCTCTACGTGCTGTG REV: CGATTGTCAGTGGATCTGACG
<i>Ccl2</i>	Mouse	FWD: CATCCACGTGTTGGCTCA REV: GATCATCTTGCTGGTGAATGAGT
<i>Cd68</i>	Mouse	FWD: CACAGTGGACATTCATGGCG REV: GCAAGAGAAACATGGCCCGA
<i>Cidea</i>	Mouse	FWD: ACTTCCTCGGCTGTCTCAATGTCA REV: TCAGCAGATTCTTAACACGGCCT
<i>Cpt1b</i>	Mouse	FWD: AGTCATGGTGGGCAACTAAC REV: TGCTTGCACATTTGTGTTCTT
<i>Coll1a1</i>	Mouse	FWD: CATGTTCACTTTGTGGACCT REV: GCAGCTGACTTCAGGGATGT
<i>Cox7a1</i>	Mouse	FWD: CAGCGTCATGGTCAGTCTGT REV: AGAAAACCGTGTGGCAGAGA

<i>Ctgf</i>	Mouse	FWD: TGACCTGGAGGAAAACATTAAGA REV: AGCCCTGTATGTCTTCACACTG
<i>Dio2</i>	Mouse	FWD: GAACCATGAAGCCAACGACT REV: CTCCTCCTAGATGCCTACAAAC
<i>Elovl3</i>	Mouse	FWD: GGCATAATTGTTACCTGATTTCAGG REV: GATGGTTCTGGGCACCATCTT
<i>Fabp4</i>	Mouse	FWD: GATGCCTTTGTGGGAACCT REV: CAACAGTAGCATCCTGAGCCCT
<i>Gpr180</i>	Mouse	FWD: CAGAGATGGGCTAGGAGTGC REV: GCCCATAACAGGCTCAGAA
<i>Il1b</i>	Mouse	FWD: AGTTGACGGACCCCAAAG REV: AGCTGGATGCTCTCATCAGG
<i>Il10</i>	Mouse	FWD: GTAGAAGTGATGCCCCAGGC REV: AAATCGATGACAGCGCCTCAG
<i>Il6</i>	Mouse	FWD: GCTACCAAACCTGGATATAATCAGGA REV: CCAGGTAGCTATGGTACTCCAGAA
<i>Pgc1a</i>	Mouse	FWD: ACCCAAAGGATGCGCTCTCGTT REV: TGCGGTGTCTGTAGTGGCTTGATT
<i>Pparg2</i>	Mouse	FWD: GCATGGTGCCTTCGCTGA REV: TGGCATCTCTGTGTCAACCATG
<i>Tbp</i>	Mouse	FWD: GAAGCTGCGGTACAATTCCAG REV: CCCCTTGTACCCTTCACCAAT
<i>Tnfa</i>	Mouse	FWD: CAGGGGCCACCACGCTCTTC REV: TACGACGTGGGCTACAGGCTTGTC
<i>Ucp1</i>	Mouse	FWD: GGGCATTTCAGAGGCAAATCAGCTT REV: AACTGCCACACCTCCAGTCATTA