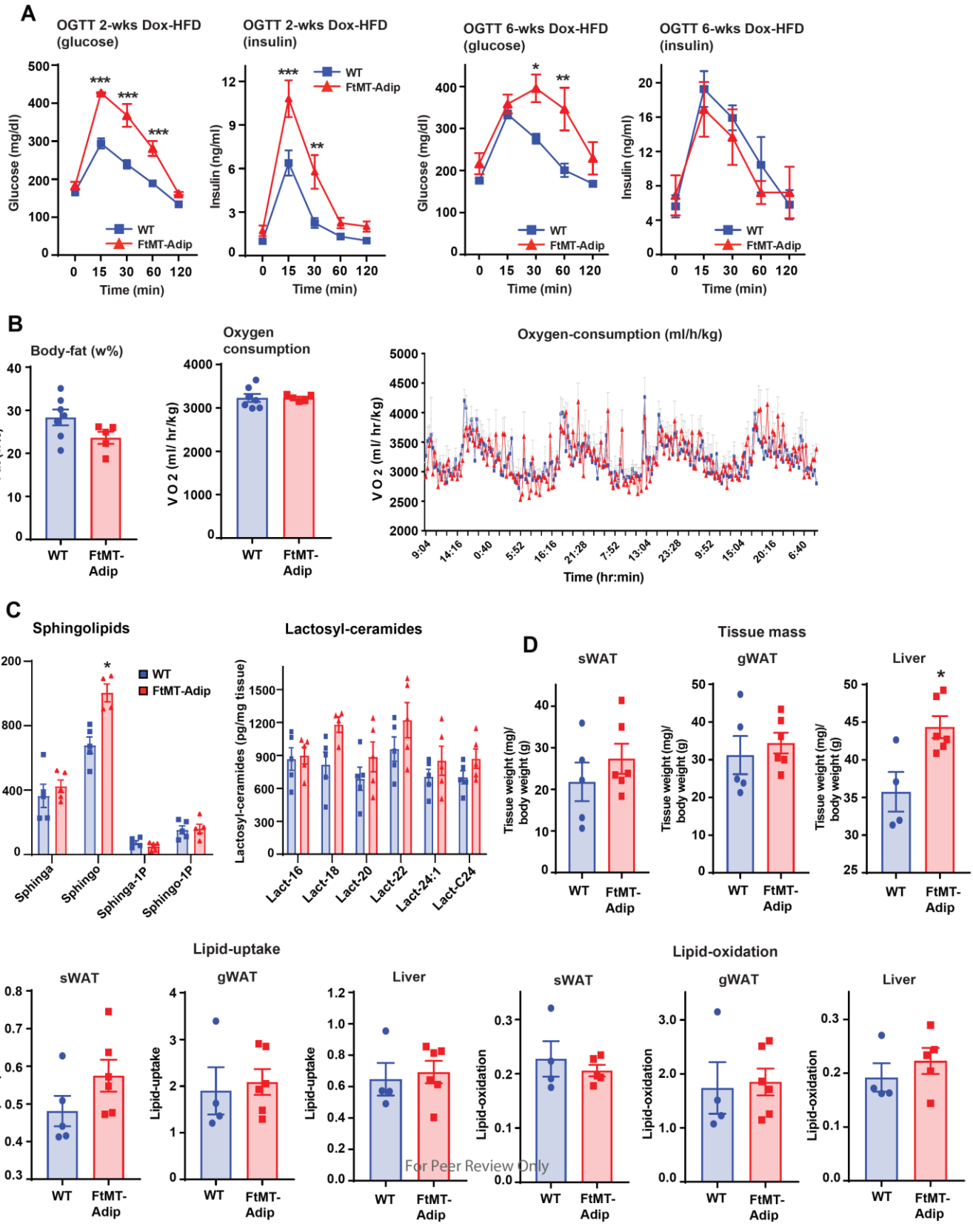
SUPPLEMENTARY DATA

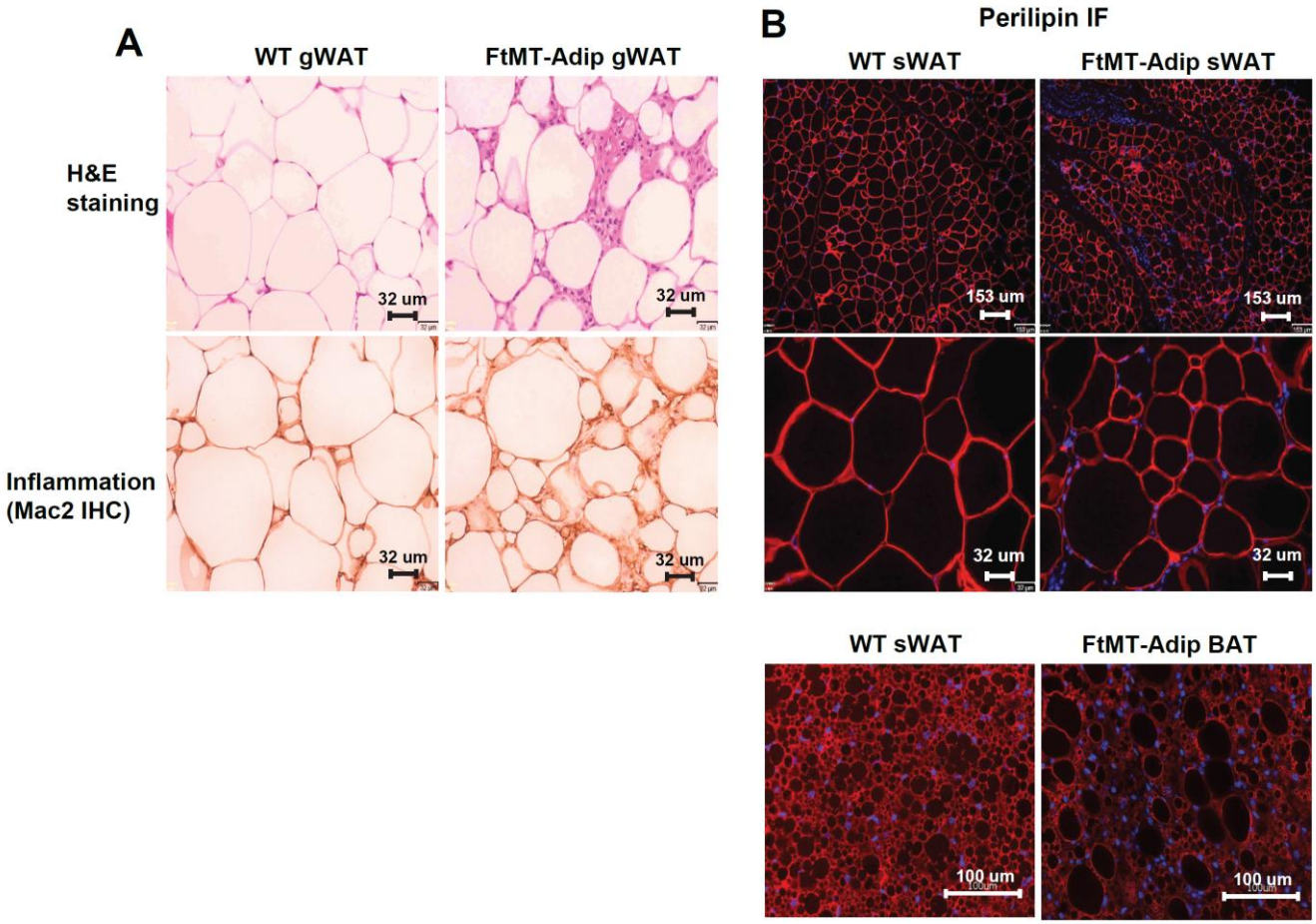
Supplementary Figure 1. Glucose tolerance, energy expenditure and lipid-uptake and oxidation measurements in FtMT-Adip mice.
(A) Glucose and insulin levels during an OGTT on WT and FtMT-Adip mice following 2-weeks (left) or 6-weeks (right) of Dox-HFD feeding. n = 5. **(B)** Metabolic cage analyses showing body-fat composition (w%) (left) and oxygen-consumption rates (VO2) (ml/h/kg) in WT and FtMT-Adip mice post 3-weeks Dox-HFD feeding. n = 5-7. **(C)** Sphingolipid (sphinganine, sphingosine, sphinganine-1-phosphate and sphingosine-1-phopshate) and lactosyl-ceramide (lactosyl-16, 18, 20, 22, 24:1 and C24) levels in WT and FtMT-Adip mice following 1-week of Dox-HFD feeding. n = 4-5. **(D)** Tissue-mass, 3H-triolein lipid-uptake, and lipid-oxidation in sWAT, gWAT and liver tissues of WT and FtMT-Adip mice. n = 4-6. Data are shown as mean ± s.e.m. *****$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

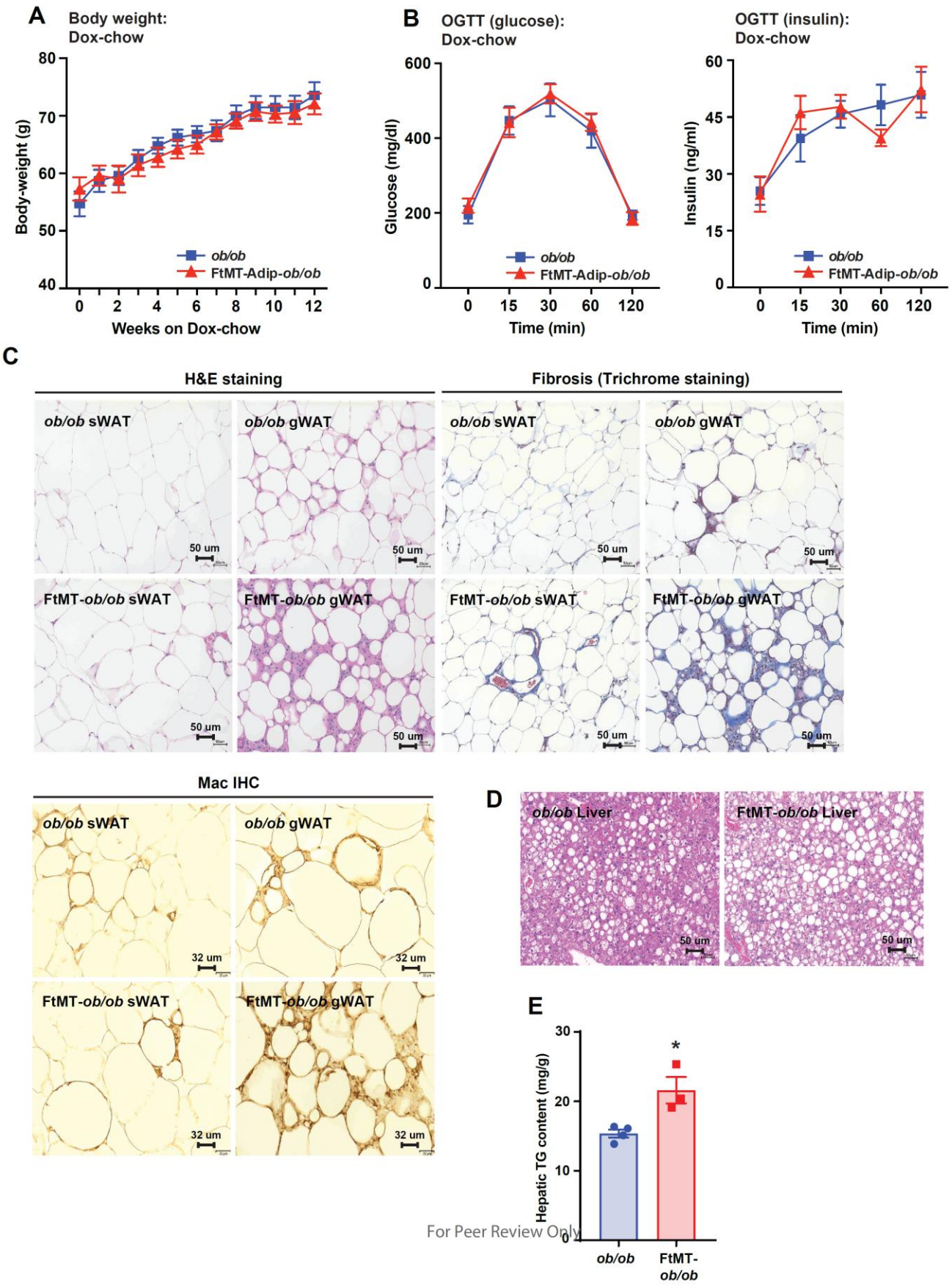
Supplementary Figure 2. Representative images of fibrotic alterations and adipocyte cell viability following FtMT induction in fat.
(A) Representative images of H&E staining (top) and Mac2 IHC staining (bottom) of gWAT from WT and FtMT-Adip mice following 16-weeks of Dox-HFD feeding. Scale bar = 32 μm. **(B)** Representative images of perilipin IF staining of sWAT and BAT from WT and FtMT-Adip mice post 16 weeks Dox-HFD feeding. Scale bars = 153 μm, 32 μm and 100 μm.



SUPPLEMENTARY DATA

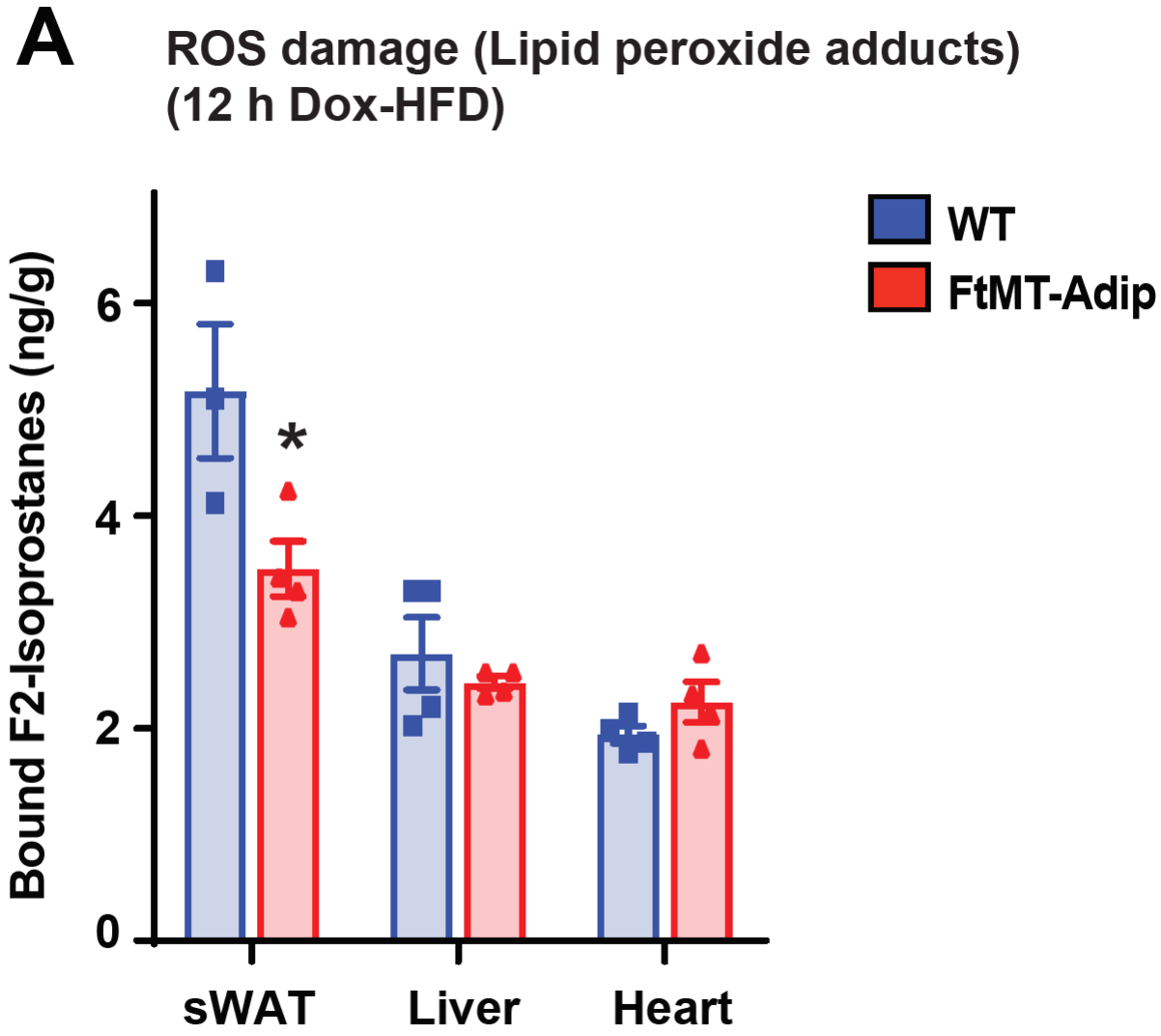
Supplementary Figure 3. Fat-specific induction of FtMT in Dox-chow-diet fed *ob/ob* mice. **(A)** Body-weights (g) of C57/BL6 *ob/ob versus* FtMT-Adip-*ob/ob* mice during Dox-chow (600 mg/kg) feeding. n = 5. **(B)** Glucose (left) and insulin (right) levels during an OGTT on *ob/ob* and FtMT-Adip-*ob/ob* mice following 6-weeks of Dox-chow feeding. n = 5. **(C)** Representative images of H&E staining (top left), Trichrome staining (top right) and Mac2 IHC (bottom) of sWAT and gWAT from *ob/ob* and FtMT-Adip-*ob/ob* mice following 12-weeks Dox-chow feeding. Scale bars = 50 μm and 32 μm. **(D)** Representative images of H&E stained livers and **(E)** hepatic TG content of *ob/ob* and FtMT-Adip-*ob/ob* mice following 12-weeks Doxchow feeding. n = 3-4. Scale bars = 50 μm. Data are shown as mean ± s.e.m. *****$P < 0.05$.

SUPPLEMENTARY DATA



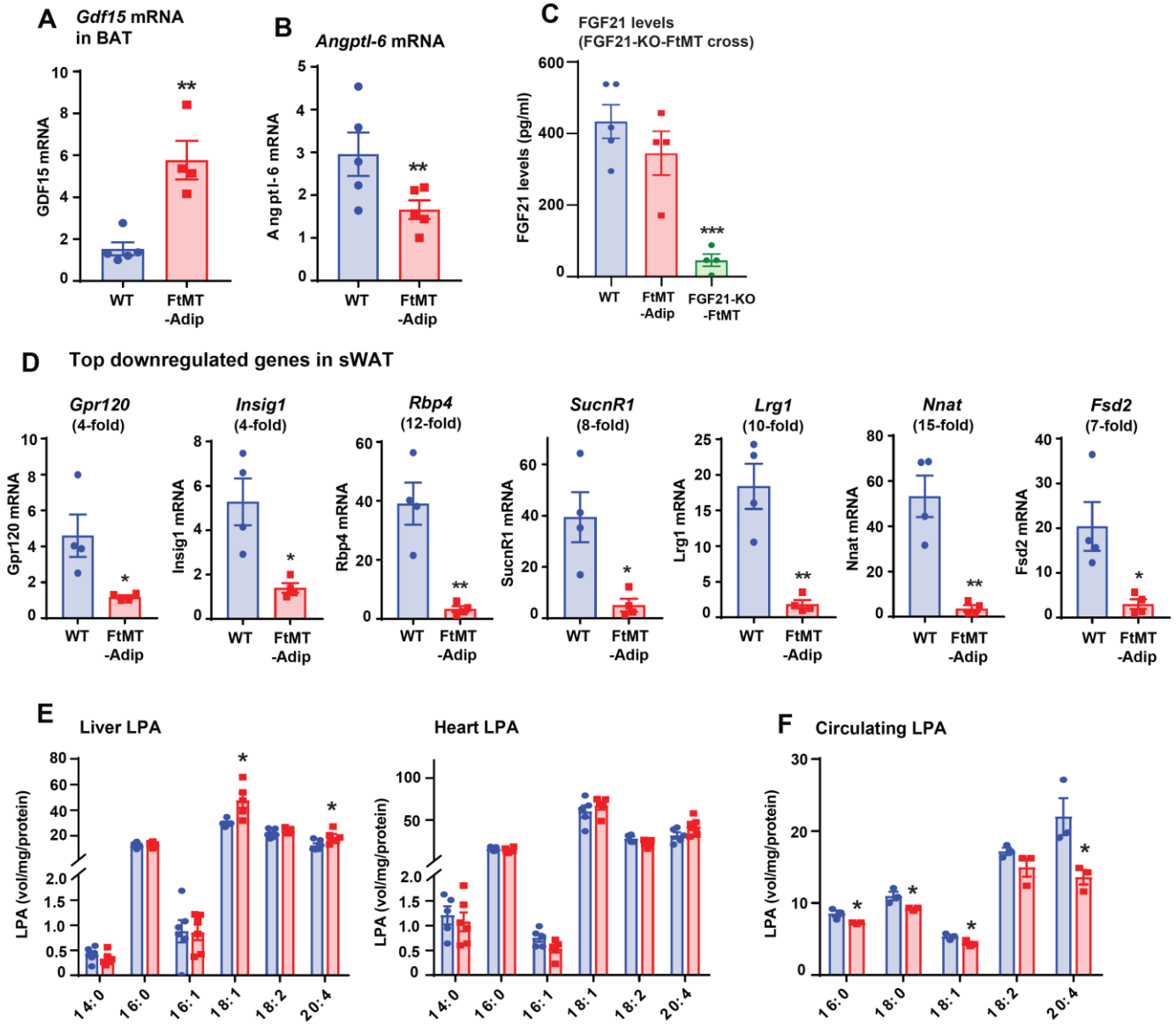
SUPPLEMENTARY DATA

Supplementary Figure 4. ROS damage in tissues following acute 12 h Dox-HFD exposure. **(A)** ROS damage (lipid peroxide adducts) (as measured by bound F2-isoprostane levels) in sWAT, liver and heart tissues from WT and FtMT-Adip mice post 12-h Dox-HFD feeding. n = 3-4.



SUPPLEMENTARY DATA

Supplementary Figure 5. Gene expression and LPA analyses following FtMT induction in fat and circulating levels of FGF21.
(A) *Gdf15* and **(B)** *Angptl-6* expression levels in BAT from WT and FtMT-Adip mice following 3-weeks of Dox-HFD (600 mg/kg) feeding. n = 4-5. **(C)** Circulating FGF21 levels in WT, FtMT-Adip and fat-specific FGF21-KO mice crossed with FtMT-Adip mice (FGF21-KO-FtMT). n = 5-8. **(D)** Real-time qPCR data showing expression levels of the top downregulated genes (as identified by Illumina microarray (*Gpr120*, *Insig1*, *Rbp4*, *SucnR1*, *Lrg1*, *Nnat* and *Fsd2*) in sWAT from WT and FtMT-Adip mice following 3-weeks of Dox-HFD feeding. n = 4. **(E)** LPA levels in WT and FtMT-Adip liver and heart tissues. n = 6. **(F)** Circulating LPA levels in WT and FtMT-Adip mice post 3 weeks Dox-HFD. n = 3. Data are shown as mean ± s.e.m. **P* < 0.05; ***P* < 0.01.



SUPPLEMENTARY DATA

Supplementary Table 1. Fed and fasted (24 h) serum parameters in WT *versus* FtMT-Adip mice following 12 weeks Dox-HFD (600 mg/kg) feeding. n = 5. Data are shown as mean ± s.e.m. *p<0.05, **p<0.01, ***p<0.001.

	Fed		Fasted (24 h)	
	WT	**FtMT-Adip**	**WT**	**FtMT-Adip**
Glucose (mg/dL)	179.6 ± 16.3	328.8 ± 15.6***	144.6 ± 5.5	115.0 ± 12.6
Insulin (ng/mL)	39.6 ± 7.3	66.5 ± 7.9*	3.8 ± 0.4	3.5 ± 0.2
Triglycerides (mg/dL)	70.6 ± 8.7	49.9 ± 4.6	68.2 ± 2.9	46.6 ± 3.5**
FFAs (mmol/L)	0.26 ± 0.02	0.19 ± 0.02*	0.27 ± 0.01	0.25 ± 0.02
Glycerol (mmol/L)	0.35 ± 0.07	0.04 ± 0.03**	0.33 ± 0.10	0.05 ± 0.01*

SUPPLEMENTARY DATA

Supplementary Table 2. Fed and fasted (5 h) serum parameters in ob/ob mice versus FtMT-Adip-ob/ob mice following Dox-chow (600 mg/kg) feeding. n = 4-5. Data are shown as mean ± s.e.m. *p<0.05, **p<0.01, ***p<0.001.

	Fed		Fasted (5 h)	
	ob/ob	**FtMT-Adip-*ob/ob***	***ob/ob***	**FtMT-Adip-*ob/ob***
Glucose (mg/dL)	137 ± 9	170 ± 10*	99 ± 6	100 ± 7
Insulin (ng/mL)	20.9 ± 3.4	19.7 ± 3.9	10.5 ± 2.5	7.9 ± 2.0
Triglycerides (mg/dL)	24.2 ± 3.3	28.3 ± 1.1	28.0 ± 2.2	23.8 ± 2.7
FFAs (mmol/L)	0.51 ± 0.05	0.58 ± 0.03	0.61 ± 0.03	0.63 ± 0.09
Glycerol (mmol/L)	0.20 ± 0.04	0.18 ± 0.03	0.30 ± 0.06	0.37 ± 0.07
Adiponectin (µg/mL)	5.1 ± 0.2	5.7 ± 0.0	5.4 ± 0.2	5.7 ± 0.0

SUPPLEMENTARY DATA

Supplementary Table 3. Fed and fasted (5 h) serum parameters in ob/ob mice versus FtMT-Adip-ob/ob mice following Dox-HFD (600 mg/kg) feeding. n = 3-6. Data are shown as mean ± s.e.m. *p<0.05, **p<0.01, ***p<0.001.

	Fed		Fasted (5 h)	
	ob/ob	FtMT-Adip-*ob/ob*	*ob/ob*	FtMT-Adip-*ob/ob*
Glucose (mg/dL)	163 ± 8	318 ± 40*	143 ± 7	304 ± 45*
Insulin (ng/mL)	22.1 ± 1.2	21.2 ± 1.7	12.6 ± 3.5	11.2 ± 2.4
Triglycerides (mg/dL)	46.1 ± 6.8	68.8 ± 12.4	35.2 ± 3.6	42.2 ± 4.1
FFAs (mmol/L)	0.62 ± 0.04	0.67 ± 0.12	0.54 ± 0.04	0.49 ± 0.11
Glycerol (mmol/L)	0.42 ± 0.03	0.25 ± 0.04*	0.26 ± 0.08	0.26 ± 0.05
Adiponectin (µg/mL)	5.6 ± 0.1	5.2 ± 0.1	5.7 ± 0.0	4.8 ± 0.2*

SUPPLEMENTARY DATA

Supplementary Table 4. Top upregulated genes identified using Illumina microarray of WT versus FtMTAdip sWAT following 3 weeks of Dox-HFD feeding (600 mg/kg). n = 9. Data are shown as fold increase. *p<0.05, **p<0.01, ***p<0.001.

Gene	Gene definition	Fold	Alteration	P-value
Gdf15	Growth differentiation factor-15	22-fold	↑	0.0173*
Trib3	Tribbles pseudokinase 3	5.8-fold	↑	0.0055**
Gadd45A	Growth arrest and DNA-damage-inducible 45 alpha	5.4-fold	↑	0.00004***
Atf3	Activating transcription factor 3	4.9-fold	↑	0.0048**
Fgf21	Fibroblast growth factor 21	4.9-fold	↑	0.0055**
Cbr3	RAP1B, member of RAS oncogene family	4.4-fold	↑	0.0285*
Ddit3/Chop10	DNA-damage inducible transcript 3	3.9-fold	↑	0.0186*
Irf7	Interferon regulatory factor 7	3.8-fold	↑	0.0081**
Adam8	A disintegrin and metallopeptidase domain 8	3.5-fold	↑	0.0035**
Ark1b8	Aldo-keto reductase 1B8	3.4-fold	↑	0.0411*
Chac1	Cation transport regulator 1	3.4-fold	↑	0.0017**
Usp18	Ubiquitin specific peptidase 18	3.3-fold	↑	0.0321*
Mmp13	Matrix metallopeptidase 13	3.3-fold	↑	0.0041**
C1qb	Complement component 1q	3.2-fold	↑	0.0294*
Cd180	CD180 antigen	3.1-fold	↑	0.0043**
Gpr105/P2ry14	Purinergic receptor P2Y, G-protein coupled 14	3.1-fold	↑	0.0218*
Tgif1	TGFB-induced factor homeobox 1	2.8-fold	↑	0.0197*
S1pl	Sphingosine phosphate lyase 1	2.7-fold	↑	0.0074**
Ftl1	Ferritin light polypeptide 1	2.1-fold	↑	0.0035**
Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	1.7-fold	↑	0.0085**
Aco2	Aconitase 2, mitochondrial	1.5-fold	↑	0.0154*
Ndufs6	NADH dehydrogenase (ubiquinone) Fe-S protein 6	1.4-fold	↑	0.0219*
Rpl15	Ribosomal protein L15	1.4-fold	↑	0.0486*
Rps2	Ribosomal protein S2	1.4-fold	↑	0.0265*

SUPPLEMENTARY DATA

Supplementary Table 5. Top downregulated genes identified using Illumina microarray of WT versus FtMTAdip sWAT following 3 weeks of Dox-HFD feeding (600 mg/kg). n = 9. Data are shown fold decrease. *p<0.05, **p<0.01, ***p<0.001.

Gene	Gene definition	Fold	Alteration	P-value
Nnat	Neuronatin	8.6-fold	↓	0.0110*
Mest	Mesoderm specific transcript	6.1-fold	↓	0.0179*
Lrg1	Leucine-rich alpha-2-glycoprotein	6.0-fold	↓	0.0169*
HP/Trf	Transferrin	4.9-fold	↓	0.0088**
Adpn	Adiponectin	4.7-fold	↓	0.0401*
Gpr43/Frar2	Free fatty acid receptor 2	4.5-fold	↓	0.0082**
Smoc1	SPARC related modular calcium binding 1	3.8-fold	↓	0.0078**
Fsd2	Fibronectin type III and SPRY domain containing 2	3.8-fold	↓	0.0091**
SucnR1/Gpr91	Succinate receptor 1	3.7-fold	↓	0.0231*
Rbp4	Retinol binding protein 4	3.5-fold	↓	0.0009***
Gpr120/Ffar4	Free fatty acid receptor 4	3.3-fold	↓	0.0017**
Lox	Lysyl oxidase	2.9-fold	↓	0.0139*
Sparc	Secreted acidic cysteine rich glycoprotein	2.3-fold	↓	0.0138*
Acsl1	Acyl-CoA synthease long-chain family member 1	2.3-fold	↓	0.0130*
Lipe/Hsl	Lipase, hormone sensitive	2.0-fold	↓	0.0193*
Lpin1	Lipin 1	1.9-fold	↓	0.0378*
Igf1	Insulin-like growth factor 1	1.8-fold	↓	0.0288*
Fabp4	Fatty acid binding protein 4, adipocyte	1.8-fold	↓	0.0198*
Mfn1	Mitofusin 1	1.7-fold	↓	0.0025**
Atf1	Activating transcription factor 1	1.7-fold	↓	0.0425*
Flot1	Flotillin 1	1.6-fold	↓	0.0451*
Flot2	Flotillin 2	1.4-fold	↓	0.0437*
Cpt2	Carnitine palmitoyltransferase 2	1.5-fold	↓	0.0319*

SUPPLEMENTARY DATA

Supplementary Table 6. Primer sequences that were utilized for real-time qPCR analyses.

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
Ucp1	TCTCAGCCGGCTTAATGACTG	GGCTTGCATTCTGACCTTCAC
Cidea	TCATCACAACTGGCCTGGTTAC	CATGAAAATGCGTGTTGTCCCTT
Otop1	TCCAAATCCAAGAGCGAGTC	ACCCTGTAAATCCAGCTTCC
Dio2	CAGTGTGGTGCACGTCTCCAATC	TGAACCAAAGTTGACCACCAG
Cox7a1	CTCATCTACCAGAAGCCACTTAG	TACAGGACGTTGTCCATTCC
β-actin	TACCACAGGCATTGTGATGG	TTTGATGTCACGCACGATTT
Gdf15	CCTGAGTCCCAACTCAACG	CTTGGTTCTGAGTTCGAGTCC
Fgf21	ATGGAATGGATGAGATCTAGAGTTGG	TCTTGGTGGTCATCTGTGTAGAGG
Trib3	GCCAAGTGTCCAGTCCTAAA	ACAGCAGGTGACAAGTCTG
Atf3	TGCTAACCTGACACCCTTTG	GTTGACGGTAACTGACTCCAG
C1qb	AGAACTATGAGCCACGCAAC	CCACGAACGAGATTCACACA
Gpr120	CTTCCCTTTCTTCTCGGATGTC	CAGCAGTGAGACGACAAAGA
Insig1	CGACAGTTAGCTATGGGTGTTC	CCAGGACCAGTGTCTCTACAT
Rbp4	GTTTCTCTGGGCTCTGGTATG	GCGCTCATATGACCCTTCTC
SucnR1	GCCACAAGGATGTACACAGAAG	GGTCTCCCATGAGGAAGTAGAA
Lrg1	GTCCTGTTCCTGAATGACAACC	CGTGCTGGACAGAGAGTTATTG
Nnat	TGGACCAAGTCGGAACAGTA	CAGCTGGTGATGTCAGAATGTC
Fsd2	GAATGCTTAGTCATGGGTGGAG	GCGGTAGTGGAGAGGTTTATTC

SUPPLEMENTARY DATA

Supplementary Table 6 (cont).

Sod1	ACCAGTGCAGGACCTCATTTTAA	TCTCCAACATGCCTCTCTTCATC
Sod2	CACATTAACGCGCAGATCATG	CCAGAGCCTCGTGGTACTTCTC
Sod3	CTCTGTCACCATGTCAAATCCA	CGTGTCGCCTATCTTCTCAAC
Catalase	ACCAGGGCATCAAAAACTTG	GCCCTGAAGCTTTTTGTCAG
Gpx3	TGAGTGGTACCATCTACGAGT	GGCTACGTTGACAAAGAGGATA
Gpx7	CCTGCCTTCAAGTACCTAACC	CATGCTCCCACCACCTTT
Gpx8	CCAACAGCTTCTACTCCTTTGA	GCAGTCACTAGCCACGTTTA
Gsta4	CCCTTGGTTGAAATCGATGG	GAGGATGGCCCTGGTCTGT
Gstm1	CCTACATGAAGAGTAGCCGCTACAT	TAGTGAGTGCCCGTGTAGCAA
Gstp1	CCTTGGCCGCTCTTTGG	GGCCTTCACGTAGTCATTCTTACC
mGst1	GCTTTGGCAAGGGAGAGAATG	CCTTCTCGTCAGTGCGAACA
mGst2	TGCAGCCTGTCTGGGTCTC	CAGAAATACTTGTGACGGGCG
mGst3	GGAGGTGTACCCTCCCTTCC	TGGTAAACACCTCCCACCGT
Gstk1	CGCATCCTGGAACTCTTCTAC	CCGCAACTGCAGCTTTATATTC

SUPPLEMENTARY DATA

Supplementary Table 7. All statistical information.

SUPPLEMENTARY DATA

Figure	N (sample size)	Statistical test method	*p*-value
Figure 1E	WT: 4, FtMT-Adip: 3	Unpaired *Student's t* test	$p=0.0300$ (mito iron)
Figure 1F	WT: 4, FtMT-Adip: 6	Unpaired *Student's t* test	$p<0.0001$ (circulation) $p=0.0049$ (adipose tissue)
Figure 1H	WT: 4, FtMT-Adip: 5	Unpaired *Student's t* test	Basal: $p<0.0001$ Succinate: $p<0.0001$ Ascorbate: $p<0.0001$
Figure 2A	WT: 5, FtMT-Adip: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Week 6: $p=0.0097$ Week 7: $p=0.0032$ Week 8: $p=0.0009$ Week 9: $p<0.0001$ Week 10: $p<0.0001$ Week 11: $p<0.0001$ Week 12: $p<0.0001$ Week 13: $p<0.0001$ Week 14: $p<0.0001$ Week 15: $p<0.0001$ Week 16: $p<0.0001$
Figure 2B	WT: 3, FtMT-Adip: 4	Unpaired *Student's t* test	$p=0.0010$
Figure 2C	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	sWAT: $p=0.0002$ gWAT: $p<0.0007$
Figure 2D (1-wk Dox-HFD)	WT: 5, FtMT-Adip: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	1-wk Glc time 15': $p<0.0001$ 1-wk Glc time 30': $p<0.0001$ 1-wk Glc time 60': $p=0.0392$ 1-wk Ins time 15': $p<0.0001$ 1-wk Ins time 30': $p<0.0001$
Figure 2D (3-wk Dox-HFD)	WT: 5, FtMT-Adip: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	3-wk Glc time 15': $p=0.0187$ 3-wk Glc time 30': $p=0.0007$ 3-wk Glc time 60': $p=0.0251$ 3-wk Ins time 0: $p=0.0004$ 3-wk Ins time 120': $p=0.0289$
Figure 2E	WT: 9, FtMT-Adip: 9 Insulin: WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	Basal glucose: $p=0.0362$ Basal insulin: $p=0.0047$ Glc infusion rate: $p<0.0001$ Hepatic glc output: $p=0.0067$
Figure 2G	WT: 9, FtMT-Adip: 9 sWAT: WT: 4, FtMT-	Unpaired *Student's t* test	Glc disposal rate: $p=0.0127$ sWAT 2-DG: $p=0.0457$

	Adip: 4 Gastro-muscle: WT: 4, FtMT-Adip: 4		Soleus-muscle 2-DG: p=0.0063 Gastro-muscle 2-DG: p=0.0030 Heart 2-DG: p=0.0056
Figure 2H	WT: 7, FtMT-Adip: 5	Unpaired *Student's t* test	Lean body mass: p=0.0127 RER: p=0.0032
Figure 2I	WT: 5, FtMT-Adip: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 0 min: p=0.0194 Time 15': p=0.0005 Time 30': p=0.0356
Figure 2J	WT: 3, FtMT-Adip: 4 WT: 4, FtMT-Adip: 3	Unpaired *Student's t* test	*Angptl-3*: p=0.0127 *Angptl-4*: p=0.0127
Figure 2K (ELISA)	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	Fed: p=0.0001 Fasted: p=0.0013
Figure 2K (Western)	WT: 4, FtMT-Adip: 4	Unpaired *Student's t* test	p=0.0030
Figure 2L	WT: 9, FtMT-Adip: 9	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 3: p<0.0001 Day 6: p<0.0001 Day 9: p<0.0001 Day 12: p<0.0001
Figure 2M (FFAs)	WT: 6, FtMT-Adip: 7	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 15': p<0.0001 Time 30': p<0.0001 Time 60': p<0.0001 Time 120': p<0.0001
Figure 2M (Glycerol)	WT: 7, FtMT-Adip: 7	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 15': p<0.0001 Time 30': p<0.0001 Time 60': p<0.0001 Time 120': p<0.0001
Figure 2N	WT: 7, FtMT-Adip: 7	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 60': p<0.0001 Time 120': p=0.0255
Figure 2P	WT: 5, FtMT-Adip: 4	Unpaired *Student's t* test	p=0.0002
Figure 3A	*ob/ob*: 3, FtMT-Adip-*ob/ob*: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Week 8: p=0.0121 Week 9: p=0.0053 Week 10: p=0.0011 Week 11: p=0.0004 Week 12: p<0.0001

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Figure 3B (Glucose)	*ob/ob*: 3, FtMT-Adip-*ob/ob*: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 0: p=0.0009 Time 120': p<0.0001
Figure 3B (Insulin)	*ob/ob*: 3, FtMT-Adip-*ob/ob*: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 30': p=0.0445 Time 60': p=0.0047
Figure 4A	WT: 7, FtMT-Adip: 7 mCAT-FtMT: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	WT vs FtMT 30': p=0.0020 WT vs FtMT 60': p<0.0001 WT vs mCAT-FtMT 60': p<0.0001 WT vs FtMT 90': p<0.0001 WT vs mCAT-FtMT 90': p<0.0001 WT vs FtMT 120': p<0.0001 WT vs mCAT-FtMT120': p<0.0001
Figure 4B	WT: 8, FtMT-Adip: 8	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 2 hr: p=0.0398 Time 3 hr: p=0.0341 Time 6 hr: p=0.0001 Time 12 hr: p<0.0001
Figure 4C (Glucose)	WT: 7, FtMT-Adip: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 15': p<0.0001 Time 30': p=0.0002 Time 60': p=0.0270
Figure 4C (Insulin)	WT: 7, FtMT-Adip: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Time 15': p=0.0430
Figure 4D	WT: 6, FtMT-Adip: 5	Unpaired *Student's t* test	sWAT: p=0.0018
Figure 4E (Superoxide dismutases)	WT: 4, FtMT-Adip: 4	Unpaired *Student's t* test	*Sod1*: p=0.0076 *Sod2*: p=0.0203 *Catalase*: p=0.0418
Figure 4E (Glutathione peroxidases)	WT: 7, FtMT-Adip: 4	Unpaired *Student's t* test	*Gpx3*: p=0.0001 *Gpx7*: p=0.0185
Figure 4E (Glutathione peroxidases)	WT: 7, FtMT-Adip: 4	Unpaired *Student's t* test	*Gsta4*: p=0.0051 *Gstp1*: p=0.0001 *mGst2*: p=0.0476 *Gstk1*: p=0.0012
Figure 5A	WT: 3, FtMT-Adip: 3	Unpaired *Student's t* test	p=0.0155
Figure 5B	WT: 3, FtMT-Adip: 3	Two-way analysis of variance (ANOVA)	Time -15': p<0.0001

		followed by a Bonferroni post-test to compare replicate means in each time point	Time 0 min: $p<0.0001$ Time 2': $p<0.0001$ Time 4': $p<0.0001$ Time 8': $p<0.0001$ Time 12': $p<0.0001$ Time 20': $p<0.0001$ Time 30': $p<0.0001$ Time 45': $p<0.0001$ Time 60': $p<0.0001$ Time 90': $p<0.0001$ Time 120': $p<0.0001$
Figure 5C	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	$p=0.0020$
Figure 5D	WT: 5, FtMT-Adip: 4	Unpaired *Student's t* test	$p=0.0199$
Figure 5F	WT: 5, FtMT-Adip: 4	Unpaired *Student's t* test	$p=0.0002$
Figure 5G	WT: 5, FtMT-Adip: 3	Unpaired *Student's t* test	$p=0.0003$
Figure 5H	WT: 5, FtMT-Adip: 6	Unpaired *Student's t* test	$p=0.0002$
Figure 5J (BAT markers)	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	*Ucp1*: $p=0.0045$ *Cidea*: $p=0.0002$ *Otop1*: $p=0.0034$ *Dio2*: $p=0.0007$ *Cox7a1*: $p=0.0060$
Figure 5K	WT: 4, FtMT-Adip: 6 WT: 4, FtMT-Adip: 5	Unpaired *Student's t* test	Lipid-uptake: $p<0.0001$ Lipid-oxidation: $p=0.0002$
Figure 6A	WT: 4, FtMT-Adip: 4	Unpaired *Student's t* test	*Gdf15*: $p=0.0045$ *Fgf21*: $p=0.0222$ *Trib3*: $p=0.0045$ *Atf3*: $p=0.0001$ *S1pl*: $p=0.0014$
Figure 6B	WT: 5, FtMT-Adip: 5 WT: 9, FtMT-Adip: 9	Unpaired *Student's t* test Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	GDF15, 3 hr fast: $p=0.0001$ GDF15 Dox-HFD timecourse: Day 6: $p=0.0199$ Day 9: $p=0.0002$ Day 12: $p=0.0069$
Figure 6C	WT: 6, FtMT-Adip: 4	Unpaired *Student's t* test	$p=0.0163$
Figure 6D	WT: 3, FtMT-Adip: 4	Unpaired *Student's t* test	$p=0.0495$
Figure 6E (Adiponectin)	WT: 8, FtMT-Adip: 6 YY1-FtMT: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 6, WT vs FtMT: $p<0.0001$ Day 6, WT vs YY1: $p=0.0038$ Day 9, WT vs FtMT: $p<0.0001$

Figure 6E (GDF15)	WT: 8, FtMT-Adip: 6 YY1-FtMT: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 9, WT vs YY1: $p<0.0001$ Day 12, WT vs FtMT: $p<0.0001$ Day 12, WT vs YY1: $p<0.0001$ Day 3, WT vs YY1: $p<0.0001$ Day 3, FtMT vs YY1: $p<0.0001$ Day 6, WT vs YY1: $p<0.0001$ Day 6, FtMT vs YY1: $p=0.0021$ Day 9, WT vs FtMT: $p=0.0003$ Day 9, WT vs YY1: $p<0.0001$ Day 12, WT vs FtMT: $p=0.0004$ Day 12, WT vs YY1: $p<0.0001$
Figure 6F (Adiponectin)	WT: 8, FtMT-Adip: 6 GDF15-KO-FtMT: 8	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 3, WT vs FtMT: $p=0.0026$ Day 3, WT vs KO: $p=0.0006$ Day 6, WT vs FtMT: $p=0.0002$ Day 6, WT vs KO: $p<0.0001$ Day 9, WT vs FtMT: $p<0.0001$ Day 9, WT vs KO: $p<0.0001$ Day 12, WT vs FtMT: $p<0.0001$ Day 12, WT vs KO: $p<0.0001$
Figure 6F (GDF15)	WT: 8, FtMT-Adip: 6 GDF15-KO-FtMT: 8	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 0, WT vs KO: $p=0.0001$ Day 0, FtMT vs KO: $p<0.0001$ Day 3, WT vs FtMT: $p=0.0057$ Day 3, WT vs KO: $p<0.0001$ Day 3, FtMT vs KO: $p<0.0001$ Day 6, WT vs KO: $p<0.0001$ Day 6, FtMT vs KO: $p<0.0001$ Day 9, WT vs FtMT: $p=0.0046$ Day 9, WT vs KO: $p<0.0001$ Day 9, FtMT vs KO: $p<0.0001$ Day 12, WT vs FtMT: $p=0.0008$ Day 12, WT vs KO: $p<0.0001$ Day 12, FtMT vs KO: $p<0.0001$
Figure 6G (Adiponectin)	WT: 5, FtMT-Adip: 8 FGF21-KO-FtMT: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 6, WT vs FtMT: $p<0.0001$ Day 6, WT vs KO: $p<0.0001$ Day 9, WT vs FtMT: $p<0.0001$ Day 9, WT vs KO: $p<0.0001$ Day 12, WT vs FtMT: $p<0.0001$ Day 12, WT vs KO: $p<0.0001$
Figure 6G (GDF15)	WT: 5, FtMT-Adip: 8 FGF21-KO-FtMT: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 9, WT vs FtMT: $p=0.0008$ Day 12, WT vs FtMT: $p=0.0014$ Day 12, WT vs KO: $p=0.0068$

Figure 6H (GDF15)	WT: 7, FtMT-Adip: 7 mCAT-FtMT: 6	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	Day 6, WT vs FtMT: p=0.0206 Day 6, WT vs mCAT: p=0.0024 Day 9, WT vs FtMT: p<0.0001 Day 9, WT vs mCAT: p=0.0003 Day 12, WT vs FtMT: p=0.0007 Day 12, WT vs mCAT: p=0.0045
Figure 6I (LPA)	WT: 6, FtMT-Adip: 6	Unpaired *Student's t* test	LPA 18:1: p=0.0007 LPA 20:4: p=0.0250 LPA 16:0: p=0.0055 LPA 18:2: p=0.0499
Figure 6J (Phosphatidic acid (PA))	WT: 6, FtMT-Adip: 5	Unpaired *Student's t* test	PA 32: p=0.0002 PA 34:1: p<0.0001 PA 36:1: p=0.0004 PA 36:2: p=0.0006 PA 36:4: p=0.0001 PA 38:2: p<0.0001 PA 38:4: p=0.0001 PA 38:5: p=0.0025 PA 38:6: p<0.0001 PA 40:6: p=0.0006
Figure 6K (Sphinolipids) (Lactosyl-ceramides) (Dihydro-ceramides) (Hexosyl-ceramides)	WT: 5, FtMT-Adip: 3	Unpaired *Student's t* test	Sphingosine: p=0.0002 Sphinganine: p=0.0431 Deoxy-sphinganine: p=0.0081 Lactosyl 16: p=0.0355 Lactosyl 18: p=0.0047 Lactosyl 20: p=0.0002 Lactosyl 22: p=0.0015 Lactosyl 24:1: p=0.0072 Lactosyl C24: p=0.0080 Dihydro 16: p=0.0009 Dihydro 20: p=0.0260 Dihydro 22: p=0.0003 Dihydro 24:1: p=0.0164 Dihydro 24: p=0.0003 Hexosyl 16: p=0.0055 Hexosyl 18: p=0.0097 Hexosyl 20: p=0.0207 Hexosyl 22: p=0.0180 Hexosyl 24:1: p=0.0185 Hexosyl 24: p=0.0356

(Ceramides)			Ceramide 16: p=0.0027 Ceramide 18:1: p=0.0113 Ceramide 22: p=0.0356 Ceramide 24:1: p=0.0026 Ceramide 24: p=0.0018
Suppl. Figure 1A	WT: 5, FtMT-Adip: 5	Two-way analysis of variance (ANOVA) followed by a Bonferroni post-test to compare replicate means in each time point	2-wk Glc time 15': p<0.0001 2-wk Glc time 30': p<0.0001 2-wk Glc time 60': p=0.0001 2-wk Insulin time 15': p=0.0001 2-wk Insulin time 30': p=0.0023 6-wk Glc time 30': p=0.0120 6-wk Glc time 60': p=0.0016
Suppl. Figure 1D	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	Sphingosine: p=0.0037
Suppl. Figure 1D	WT: 4, FtMT-Adip: 6	Unpaired *Student's t* test	p=0.0144
Suppl. Figure 3E	WT: 4, FtMT-Adip: 4	Unpaired *Student's t* test	p=0.0151
Suppl. Figure 4A	WT: 3, FtMT-Adip: 4	Unpaired *Student's t* test	sWAT: p=0.0338
Suppl. Figure 5A	WT: 5, FtMT-Adip: 4	Unpaired *Student's t* test	p=0.0020
Suppl. Figure 5B	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	p=0.0473
Suppl. Figure 5C	WT: 5, FtMT-Adip: 4 FGF21-KO-FtMT: 4	Unpaired *Student's t* test	p=0.0002
Suppl. Figure 5D	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	*Gpr120*: p=0.0276 *Insig1*: p=0.0111 *Rbp4*: p=0.0026 *SucnR1*: p=0.0144 *Lrg1*: p=0.0021 *Nnat*: p=0.0017 *Fsd2*: p=0.0204
Suppl. Figure 5E (Liver LPA)	WT: 6, FtMT-Adip: 6	Unpaired *Student's t* test	LPA 18:1: p=0.0182 LPA 20:4: p=0.0431
Suppl. Figure 5F	WT: 6, FtMT-Adip: 6	Unpaired *Student's t* test	LPA 18:0: p=0.0473 LPA 18:1: p=0.0499 LPA 20:4: p=0.0381

(Circulating LPA)			LPA 16:0: p=0.0413
Suppl. Table 1	WT: 5, FtMT-Adip: 5	Unpaired *Student's t* test	Fed glucose: p=0.0003 Fed insulin: p=0.0421 Fed FFAs: p=0.0135 Fed glycerol: p=0.0039 Fasted TG: p=0.0015 Fasted glycerol: p=0.0497
Suppl. Table 2	*ob/ob*: 5, FtMT-Adip-*ob/ob*: 4	Unpaired *Student's t* test	Fed glucose: p=0.0428
Suppl. Table 3	*ob/ob*: 3, FtMT-Adip-*ob/ob*: 6	Unpaired *Student's t* test	Fed glucose: p=0.0334 Fed glycerol: p=0.0391 Fasted glucose: p=0.0442 Fasted adiponectin: p=0.0283

SUPPLEMENTARY DATA

Mice

mCAT mice (mitochondrial-targeted human catalase recombineered into a GAPDH BAC and inserted into transgenic mice) were kindly provided by the P. Rabinovitch lab, and genotyped using the primer set: 5'-CTGAGGATCCTGTTAAACAATGC and 5'-CTATCTGTTCAACCTCAGCAAAG. GDF15-KO sperm was obtained from the MRC Harwell Institute (Oxfordshire, UK) and mice generated were genotyped using the PCR primer set: (GDF15-KO-F) 5'- TGAAGCAGAATTGCCTTG AGT, (GDF15-KO-R1) 5'-GAACTTCGGAATAGGAACTTGG and (GDF15-KO-R2) 5'-AGCATGGATCTCTCCAACCTT. Floxed-FGF21-KO mice were kindly provided by the D. Mangelsdorf and S. Kliewer lab and were genotyped using the primer set: 5'-AAGCATTCCTGGTACCACGG and 5'-CAGCACTAAGGGAGGCAGAGGCAAGTGATT. We generated TRE-YY1 mice and the genotypes were confirmed using the primer set: 5'-TACCGG AGACAGGCCCTATG and 5'-GAAAACTTTGCCCCCTCCAT. All overexpression experiments were performed in a pure C57/BL6 background.

Transmission Electron Microscopy (TEM)

Fresh sWAT was fixed by perfusion with 4% paraformaldehyde and 1% glutaraldehyde in 0.1 M sodium cacodylate buffer. Fixed tissues were then transferred to 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, post-fixed in buffered 1% osmium tetroxide, *en bloc* stained in 4% uranyl acetate in 50% ethanol, dehydrated with a graded series of ethanol, then embedded in EMbed-812 resin. Thin sections were cut on a Leica Ultracut UCT ultramicrotome and post-stained with 2% uranyl acetate and lead citrate. Images were acquired on a FEI Tecnai G2 Spirit TEM equipped with a LaB6 source and operating at 120 kV.

Isolation of Mitochondria and Oxygen-Consumption Experiments

To isolate mitochondria, BAT was homogenized using a motorized Dounce homogenizer in ice-cold MSHE buffer (70 mM sucrose, 210 mM mannitol, 5 mM HEPES, 1 mM EDTA) containing 0.5% FA-free BSA. Homogenates then underwent low centrifugation (800 g for 10 min) to remove nuclei and cell debris, followed by high centrifugation (8,000 g for 10 min) to obtain the mitochondrial pellet, which was washed once in icecold MSHE buffer and re-suspended in a minimal amount of MSHE buffer prior to determination of protein concentrations. Oxygen consumption rates (OCRs) were determined using the XF24 Extracellular Flux Analyzer (Seahorse Bioscience, MA), following the manufacturers' protocols. For the electron-flow (EF) experiments, isolated BAT mitochondria were seeded at 10 μg of protein per well in XF24 V7 cell-culture microplates (Seahorse Bioscience), then pelleted by centrifugation (2,000 g for 20 min at 4°C) in 1X MAS buffer (70 mM sucrose, 220 mM mannitol, 10 mM KH_2PO_4, 5 mM $MgCl_2$, 2 mM HEPES, 1 mM EGTA in 0.2% FA-free BSA; pH 7.2), supplemented with 10 mM pyruvate, 10 mM malate and 4 μM carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP), with a final volume of 500 μl per well. The XF24 plate was then transferred to a temperature-controlled (37°C) Seahorse analyzer and subjected to a 10-min equilibration period and 2 assay cycles to measure the basal rate, comprising of a 30-sec mix, and a 3-min measure period each; and compounds were added by automatic pneumatic injection followed by a single assay cycle after each; comprising of a 30-sec mix and 3-min measure period. OCR measurements were obtained following sequential additions of rotenone (2 μM final concentration), succinate (10 mM), antimycin A (4 μM) and ascorbate (10 mM) (the latter containing 1 mM N,N,N',N'-tetramethyl-p-phenylenediamine [TMPD]). OCR measurements were recorded at set interval time-points. All compounds and materials above were obtained from Sigma-Aldrich.

^{3}H-triolein Uptake and β-oxidation

For assessment of tissue-specific triolein lipid-uptake and lipid-oxidation rates, protocols were adapted from previously documented protocols (1, 2). In brief, 3H-triolein was tail-vein injected (2 μCi/mouse in 100 μl of 5% Intra-lipid) into mice following a 16 h fast. Blood samples (20 μl) were then collected at 1, 2, 5, 10 and 15 min post injection. Following 20 min post injection, mice were sacrificed, blood samples were obtained and tissues were immediately excised, weighed and frozen at -80oC until further

processing. Lipids were then extracted using a chloroform-to-methanol based extraction protocols (3). The radioactivity content of tissues, including blood samples, was then quantified, as previously documented (2).

Bomb Calorimetry

Feces were weighed before and after drying. The weight difference was considered as sample water content. Samples were dried for 72 hr using a LABCONCO Centrivap concentrator equipped with a LABCONCO Centrivap cold trap (-50 C) (Labconco Corporation, Kansas City, MO). Dried feces then were pulverized using a multiplex bead tissue disruptor (TissueLyserII, Qiagen, Germantown, MD). Heat of combustion was determined in a 6200 Isoperibol Calorimeter Equipped with a semi-micro oxygen combustion vessel. Benzoic acid was utilized as standard (Parr Instrument Company, Moline IL).

SUPPLEMENTARY REFERENCES

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