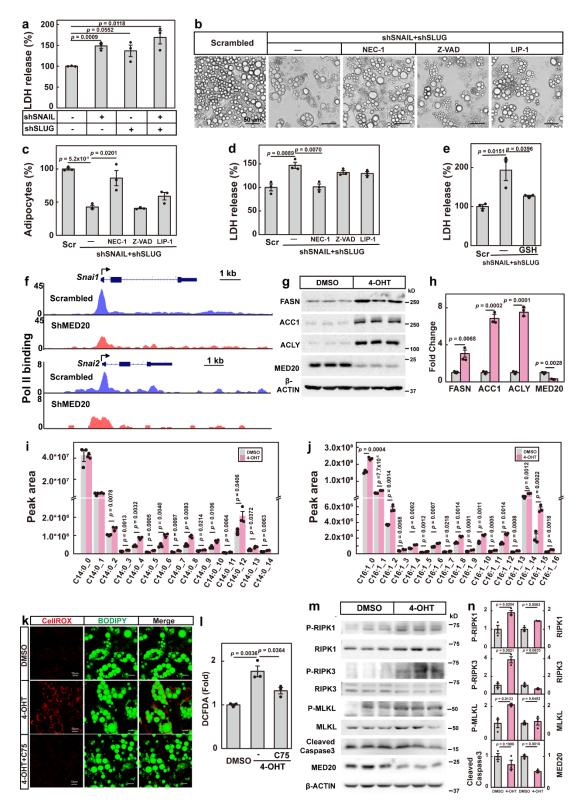
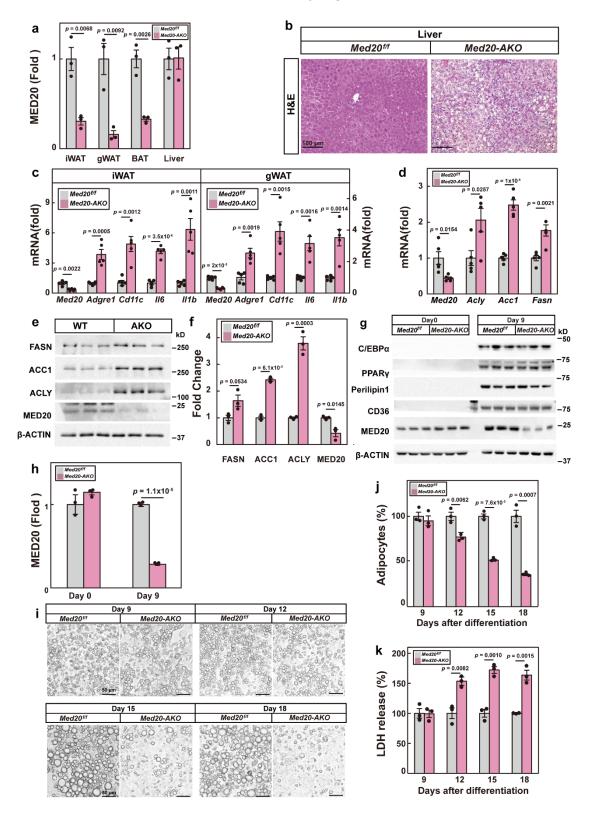


Supplementary Figure 1. Overexpression of FASN leads to necroptosis of the adipocytes. **a**, On day 10, *de novo* fatty acid synthesis was performed as in Fig. 1e. An illustration of the ¹³C incorporation into palmitate (C16:0) was shown. **b-d**, Control and FASN^{oe} 3T3-L1 cells were set up and differentiated into adipocytes as in Fig. 1h. Starting from day 9, cells were treated with C75 (50 μ M). On day 15, cells were harvested for imaging under bright field (b), quantification of the numbers of adipocytes (c) and lipid droplet size (d). **e**, Quantitative analysis of the protein levels in Fig. 1o. For a, c, d and e, each value represents mean ± s.e.m. a triplicate. Statistical analysis was performed using two-sided unpaired Student's t-tests.



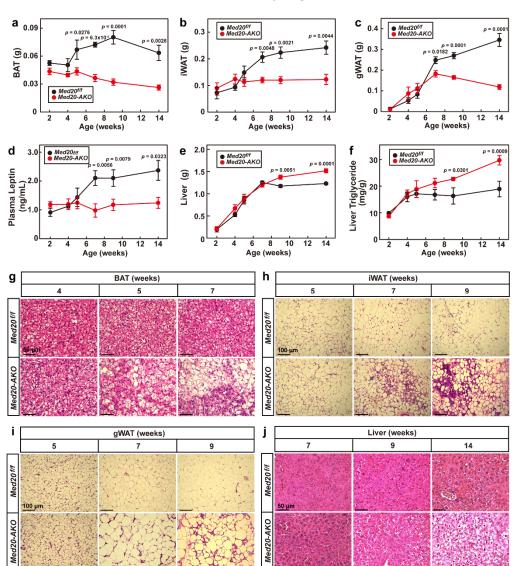
Supplementary Figure 2. MED20 inhibits the transcription of *Fasn* **through SNAIL and SLUG. a**, The experiment was set up as in Figure 3b. The released LDH were

measured. b-d, Starting from day 9 of differentiation, SNAIL and SLUG double knockdown adipocytes were treated with NEC-1 (20 µM), ZVAD (10 µM) or LIP-1 (200 nM). On day 15, cells were harvested and subjected to imaging under bright field (b), quantification of cell numbers (c) and released LDH (d). e, The experiment was set up as in Fig. 3d. The released LDH were measured. f, ChIP-Seq analysis of the binding of Pol II on the promoters of Snai1 and Snai2 in control and MED20 knockdown 3T3-L1 cells. These data were reanalyzed from GEO: GSE163281. g,h, Control and MED20-depleted (4-OHT) adipocytes were harvested on day 9 of differentiation. Cells were subjected to western blot using the indicated antibodies (g) and quantification of the protein levels (h). I,j, An illustration of the incorporation of ¹³C into myristate (C14:0) (h) and palmitoleate (C16:1) (i). The experiment was as performed in Fig. 3i. k, The experiment was set up as in Fig 3j. Representative images were shown. I, On day 12, cells were treated with DCFDA (25 µM) for 45 min and harvested for quantification of the fluorescent intensity. m,n, On day 10 of differentiation, Control and MED20depleted (4-OHT) adjpocytes were harvested and subjected to western blot using indicated antibodies (**m**) and quantification of protein level (**n**). For h and n, β -actin was used as an internal control. For a, c, d, e, h, l, j, l and n, each value represents mean ± s.e.m. a triplicate. Statistical analysis was performed using two-sided unpaired Student's t-tests.



Supplementary Figure 3. Knockout of *Med20* in adipose tissues leads to **lipodystrophy.** The same mice were from Fig. 4b. **a**, The protein level of Fig 4a was

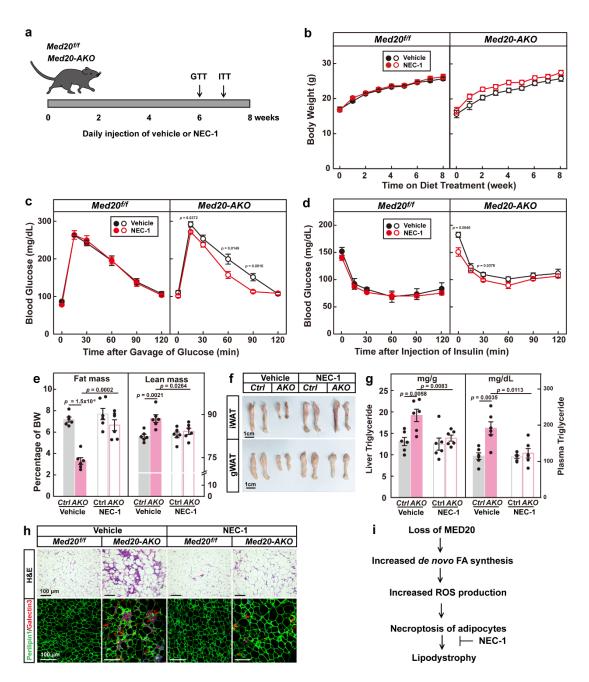
quantified. **b**, H&E analysis of liver samples. **c**, qRT-PCR analysis of the inflammationrelated genes in iWAT and gWAT. 36B4 was used as an internal control. **d-f**, RNA (**d**), protein (**e**) analysis of *de novo* fatty acid synthesis genes in iWAT. The protein level in (e) was quantified and shown in (f). Each value represents mean \pm s.e.m. of 3-4 mice. **g-k**, Primary SVFs were isolated from *Med20^{t/f}* or *Med20-AKO* mice and differentiated into mature adipocytes. On the indicated days, cells were harvested for western blot (g,h), imaging under bright field (i), and quantification of cell number (j) and released LDH (k). For a, f and h, β -actin was used as an internal control. For h, j and k, each value represents mean \pm s.e.m. a triplicate. Statistical analysis was performed using two-sided unpaired Student's t-tests.



Supplementary Figure 4. Med20-AKO mice progressively develop lipodystrophy.

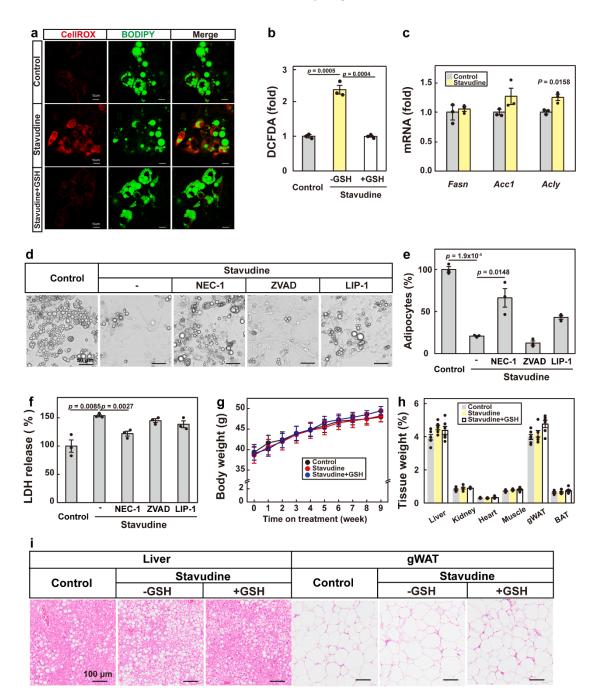
a-j, Chow-fed *Med20^{iif}* and *Med20-AKO* mice (male, 4-6 per group) were examined at different ages. Weights of BAT (a), iWAT (b), gWAT (c) and liver (e), plasma leptin (d) and liver triglyceride (f) were measured. H&E staining of BAT (g), iWAT (h), gWAT (i) and liver (j) were performed as in Fig. 4j. Scale bars were as indicated. Each value represents mean ± s.e.m. of 4-6 mice. Statistical analysis was performed using two-sided unpaired Student's t-tests.





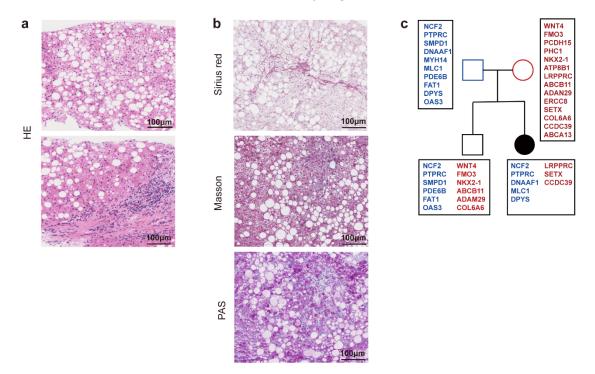
Supplementary Figure 5. Inhibiting necroptosis reverses lipodystrophy in *Med20-AKO* mice. **a-h**, Chow-fed male *Med20^{i/f}* and *Med20-AKO* mice (5-week-old, n=6) were intraperitoneally injected with vehicle (0.2% DMSO in PBS) or NEC-1 (1.65 mg/kg in PBS) every day for 8 weeks. **b**, Body weights were monitored for 8 weeks. **c-d**, Glucose (c) and insulin (d) tolerance tests were performed on week 6 and 7,

respectively. **e**, Body composition was analyzed on week 8. **f-h**, On week 8, mice were euthanized, and tissues were collected. Representative images of iWAT and gWAT were shown (f). Plasma and liver triglyceride levels were measured (g). h, iWAT was subjected to H&E and immunostaining using anti-Perilipin and Galectin3 antibodies. i, A schematic summary of the key findings in this figure. Each value represents mean ± s.e.m. of 6 mice. Statistical analysis was performed using two-sided unpaired Student's t-tests.



Supplementary Figure 6. Glutathione reverses stavudine-induced partial lipodystrophy in mice. **a**, Representative images of Fig. 6c were shown. **b**, cells were differentiated into mature adipocytes. On day 0, cells were treated with stavudine (1 mM) with or without GSH (1 mM). On day 4, cells were treated with DCFDA (25 μ M) for 45 min and harvested for quantification of the fluorescent intensity. **c**, On day 0,

cells were treated with stavudine (1 mM). On day 4, cells were harvested for qRT-PCR analysis of *de novo* fatty acid synthesis genes. 36B4 was used as an invariant control. **d-f**, 3T3-L1 cells were differentiated into mature adipocytes. On day 0, cells were treated with stavudine (1 mM) in the presence or absence of NEC-1 (20 μ M), ZVAD (10 μ M) or LIP-1 (200 nM). On day 6, cells were harvested for imaging under bright field (d) and quantification of cell numbers (e) and released LDH (f). For b, c, e and f, each value represents mean ± s.e.m. of 3 samples. **g-i**, Mice were the same as in Fig. 6d. Body weights were monitored (g). After the experiment, each organ was collected and the percentage of each tissue to body weight was plotted (h). H&E analysis was performed in liver and gWAT (i). Each value represents mean ± s.e.m. of 6 mice. Statistical analysis was performed using two-sided unpaired Student's t-tests.



Supplementary Figure 7. Diagnosis of the patient with acquired lipodystrophy.

a-b, Liver biopsy was performed and subjected to H&E analysis (a), or Sirius red, Masson or PAS staining (b). Scale bar, 100 μ m. **c**, Whole-exon sequencing of the patient and her family members. The mutations inherited from her father and her mother were colored in blue and red, respectively.

Supplementary Table 1

A. Primers to generate different constructs mFASN-sgRNA TGGGGTAATGGCCCGGGAGT mMED20-shRNA1 GCTGATGTACGTGATGCATAA mMED20-shRNA2 GTACATGGAACTCTTCAACAA mSNAIL-shRNA1 ATGTGTCCCAGAACTATTT mSNAL-shRNA2 CCACTCGGATGTAAGAGAAA mSLUG-shRNA2 CTCTATGAAAGTTACCCTATA Quantitative real-time PCR Primers CTTTGCAGGGGCACACTC mAcly GCCAGCGGGAACCTCAGGAAAT AGAGACGTGTCACTCAGGAAAT AGAGACGTGTCACTCCTGGACTT mAcly GCTGCGGAAACTTCAGGAAAT mAcly GCTGCGGAACCTACCCACACAC mAcc1 TGGACAGCGTCACTCAGGACAAC mAdgre1 CACTTCCAAGATGGGTTAACATCC cTGCCATCAACTGCTGCGAACTC CTGGCATCACCCTGGTGCGAACTC mIl1b TAGTCCTTCCTACCCCAACTC mIl1b TAGTCCTTCCTACCCCAATTTCC mSnai1 CACCCGTGCTGTTGTCCCAAAT mSnai2 TGGTCAAGAAACATTTCAACGCC GGTGAGGAATCTCGGTAGACACT GGTGAGGAACTTCCGTTATTGGT mSnai2 TGGTCAAGAAACATTTCAACGCC mSnai2 TGGTCAAGAAACCTTGTGTGTGTCGAAGATC MED20-flox-F GGGCAGCCAAGGTATGCACATA MED20-flox-F GG	Primers	Source of Primer sequences
mFASN-sgRNATGGGGTAATGGCCCGGGAGTmMED20-shRNA1GCTGATGTACGTGATGCATAAmMED20-shRNA2GTACATGGAACTCTTCAACAAmSNAIL-shRNA1ATGTGTCTCCCAGAACTATTTmSNAIL-shRNA2CCACTCGGATGTGAAGAGATAmSLUG-shRNA2CCCACTCGGATGTGAAAQuantitative real-timePCR PrimersPCR PrimersGCCAGCGGGAGCACATCmAclyGCCAGCGGGAGCCACTCATCAmAclyGCCAGCGGGAGCCACTCATCAmAcl1TGGACAGCTGATCAGGAAATAGGACGTGCACTCCTGGACTTMACC1mAcc1TGGACAGCTGATCCCGGAAACTmAdgre1CACTTCCAAGATGGGTTAACATCCCTGCCATCAAGTGGGTTAACATCCCTGCCATCAACTCATGAAACTmIl1bTAGTCCTTCCTACCCAACTCmil1bTAGTCCTTCCTACCCCAATTTCCmMed20AGGTGGAGTATGGCCCTTGTmMed20AGGTGGAGTATGGCCCTTGTTCTmSnai1CACACGCTGCTTGTTCCCAAATmSnai2TGGTCAAGAAAACATTTCAACGCCmSnai2TGGTCAAGAAAACATTCCAACTGGTTGTGTmSnai2TGGTCAAGAAACATTTCCAACGCCMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAAGCA	A. Primers to generate of	
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CTTTGCAGGTGCCACTTCATCmFasnGCTGCGGAAACTTCAGGAAAT AGAGACGTGTCACTCCTGGACTTmAcc1TGGACAGACTGATCGCAGAGAAAG TGGAGAGCCCCACACACAmAdgre1CACTTCCAAGATGGGTTAACATCC CTGCCATCAACTCATGATACCCTmCd11cCTGGATAGCCTTTCTTCTGCTG GCACACTGTGTCCGAACTCmll1bTAGTCCTTCCTACCCAATTTCC TTGGTCCTTAGCCACTCCTTCmll6TAGTCCTTCCTACCCCAATTTCC TTGGTCCTTAGCCACTCCTTCmMed20AGGTGGAGTATGGCCTTGTTC GCACACTGTGTCTGTCCCAAATmSnai1CACACGCTGCCTTGTGTCC GGTCAGCAAAAGCACGGTTmSnai2TGGTCAAGAAACATTTCAACGCC GGTGAGGATCTCTGGTTCCGATAGACACCGCTmSnai2GGGCAGCCAAGGTCAGTA MED20-flox-FMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGT AdipoQ-WT-FAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTCAGCATCATCCAdipoQ-TG-FTGAAACAGGGGCAATGGTGGGERT2-TG-FTGAAACAGGGGCAATGGTGCG	mAcly	GCCAGCGGGAGCACATC
AGAGACGTGTCACTCCTGGACTTmAcc1TGGACAGACTGATCGCAGAGAAAG TGGAGAGCCCCACACACAmAdgre1CACTTCCAAGATGGGTTAACATCC CTGCCATCAACTCATGATACCCTmCd11cCTGGATAGCCTTTCTTCTGCTG GCACACTGTGTCCGAACTCmll1bTAGTCCTTCCTACCCAATTTCC TTGGTCCTTAGCCACTCCTTCmll6TAGTCCTTCCTACCCCAATTTCC TTGGTCCTTAGCCACTCCTTCmMed20AGGTGGAGTATGGCCTTGTGTCCAAAT GCACACGTGCTGTTCCCAAATmSnai1CACACGCTGCCTTGTGTCCCAAAT GGTCAGCAAAAGCACGGTTmSnai2TGGTCAAGAAACATTTCAACGCC GGTGAGGATCTCTGGTTCCCAAATmSnai2GGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGT AdipoQ-WT-FAGTGGTGGAGAATTCAAGAACATTCAACGACC GTAGGTGAGAAATTCAACGCACATCTAdipoQ-WT-RGTAGGTGGAAATTCAAGAATCT AdipoQ-TG-FAdipoQ-TG-FGGATGTGCCATGTGAGTCTG GGATGTGCCATGTGAGTCTG GGATGTGCCATGTGAGTCTG ERT2-TG-F		CTTTGCAGGTGCCACTTCATC
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GGTCAGCAAAAGCACGGTTmSnai2TGGTCAAGAAACATTTCAACGCC GGTGAGGATCTCTGGTTTTGGTAGenotyping PrimersGGGCAGCCAAGGTCAGTAMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-FGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG		GCATCGTGTCTGTTCCCAAAT
mSnai2TGGTCAAGAAACATTTCAACGCC GGTGAGGATCTCTGGTTTTGGTAGenotyping PrimersMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-FGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	mSnai1	CACACGCTGCCTTGTGTCT
GGTGAGGATCTCTGGTTTTGGTAGenotyping PrimersMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG		GGTCAGCAAAAGCACGGTT
Genotyping PrimersMED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	mSnai2	TGGTCAAGAAACATTTCAACGCC
MED20-flox-FGGGCAGCCAAGGTCAGTAMED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG		GGTGAGGATCTCTGGTTTTGGTA
MED20-flox-RAAGTGCTTCCCGTTATTGTGTAdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	Genotyping Primers	
AdipoQ-WT-FCTAGGCCACAGAATTGAAAGATCTAdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	MED20-flox-F	GGGCAGCCAAGGTCAGTA
AdipoQ-WT-RGTAGGTGGAAATTCTAGCATCATCCAdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	MED20-flox-R	AAGTGCTTCCCGTTATTGTGT
AdipoQ-TG-FACGGACAGAAGCATTTTCCAAdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	AdipoQ-WT-F	CTAGGCCACAGAATTGAAAGATCT
AdipoQ-TG-RGGATGTGCCATGTGAGTCTGERT2-TG-FTGAAACAGGGGCAATGGTGCG	AdipoQ-WT-R	GTAGGTGGAAATTCTAGCATCATCC
ERT2-TG-F TGAAACAGGGGCAATGGTGCG	AdipoQ-TG-F	ACGGACAGAAGCATTTTCCA
	AdipoQ-TG-R	GGATGTGCCATGTGAGTCTG
ERT2-TG-R CGGAATAGAGTATGGGGGGGCTCAG	ERT2-TG-F	TGAAACAGGGGCAATGGTGCG
	ERT2-TG-R	CGGAATAGAGTATGGGGGGGCTCAG

	Before GSH	After GSH	Reference range
Body weight (kg)	52.4	53.3	N/A
BMI (kg/m²)	21.0	21.3	18.5-24.0
ALT (U/L)	70.4	34.3	9.0-50.0
AST (U/L)	43.0	29.5	15.0-40.0
TG (mmol/L)	1.76	2.14	0.00-2.25
TC (mmol/L)	3.81	3.68	3.00-5.70
HDL-C (mmol/L)	0.67	0.63	1.03-1.55
LDL-C (mmol/L)	2.72	2.59	2.60-4.10
Fibroscan			
CAP (dB/m)	263 (S2)	240 (S1)	N/A
LSM (kPa)	6.3 (F0F1)	6.0 (F0F1)	N/A
DXA			
Total body fat (kg)	6.53	6.75	N/A
FMI (kg/ m²)	2.62	2.71	5.00-9.00
ALM (kg)	17.59	17.26	N/A
ALM/height ²	7.05	6.91	≥5.40
Fat monitor			
VAT (cm²)	5	5	10-100
SAT (cm ²)	78	88	N/A

Supplementary Table 2. Medical index before and after GSH treatment

On top of LANTUS insulin glargine injection (20 u, qn), the patient was treated with GSH (0.4 g, tid) from Nov. 2021 to May 2022. Different parameters were monitored before and after GSH treatment. BMI, body mass index; ALT, alanine transaminase; AST, aspartate aminotransferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; DXA, dual-energy x-ray absorptiometry; FMI, fat mass index; ALM, appendicular lean mass, also known as the lean mass of the upper and lower limbs; VAT, visceral fat; SAT, subcutaneous fat. S1 and S2 in CAP indicate steatosis grade 1 and steatosis grade 2, respectively.

Supplementary Table 3

Abbreviation	Meaning
FASN	Fatty Acid Synthase
ROS	Reactive Oxygen Species
LDH	Lactate Dehydrogenase
NEC-1	Necrostatin-1
Lip-1	Liproxstatin-1
ВНА	Butyhydroxyanisole
GSH	L-Glutathione Reduced
SVFs	Stromal Vascular Fractions
Acly	ATP-Citrate Lyase
Acc1	Acetyl-CoA Carboxylase
iWAT	Inguinal White Adipose Tissue
gWAT	Gonadal White Adipose Tissue
BAT	Brown Adipose Tissue
NRTI	Nucleoside Analog Reverse Transcriptase Inhibitors
BMI	Body Mass Index
FMI	Fat Mass Index
NASH	Nonalcoholic Steatohepatitis
САР	Controlled Attenuation parameter
MRI-PDF	Magnetic Resonance Imaging-derived Proton Density Fat Fraction