

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
<input type="checkbox"/>	<input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
<input type="checkbox"/>	<input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input type="checkbox"/>	<input checked="" type="checkbox"/> A description of all covariates tested
<input type="checkbox"/>	<input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input type="checkbox"/>	<input checked="" type="checkbox"/> A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
<input type="checkbox"/>	<input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input checked="" type="checkbox"/>	<input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
<input type="checkbox"/>	<input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	RNA-seq and m6A-seq: Sequence reads were trimmed for adaptor sequence/low-quality sequence using Cutadapt (4.2). Trimmed sequence reads were mapped to mm10 (GRCm38.102) or hg38 (GRCh38.107) using HISAT2 (2.2.1).
Data analysis	RNA-seq and m6A-seq analysis: Read count extraction and differential expression levels of exons and genes were analyzed using RADAR (0.2.4) followed by DEseq2 (1.36.0). For differential m6A regions of mRNA, RADAR software (0.2.4) was used as well. Pathway analysis for Ensembl Gene IDs extracted from RNA-seq was performed using ConsensusPathDB (http://cpdb.molgen.mpg.de/) For the analysis of immunoblot results, band intensities were quantitatively assessed utilizing the ImageJ software (1.53a). Prism software version 9 (GraphPad, USA) was used for statistical analyses.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The RNA-sequencing (RNA-seq) and N6-methyladenosine sequencing (m6A-seq) datasets have been submitted and are publicly available in the Gene Expression Omnibus (GEO) repository. These can be accessed using the assigned accession number: GSE250137. Additionally, all raw data, including uncropped immunoblots, are made available for further examination and validation.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

In this study sex was defined based on the biological attribute. We have reported the sex of the subjects in the human cohort. A cohort consisted of 40 women and 32 men with obesity, exhibiting a range of body mass index (BMI) spanning from 20.5 to 54.5 kg/m² was purposefully recruited.

The immortalized human brown and white preadipocytes are derived from SVF from female donor.

Reporting on race, ethnicity, or other socially relevant groupings

We have not reported on ethnicity in this manuscript.

Population characteristics

The human cohort consisted of lean and individuals with obesity, exhibiting a range of BMI spanning from 20.5 to 54.5 kg/m². Based on BMI and homeostatic model assessment of insulin resistance (HOMA-IR > 2.9) scores, the cohort was categorized into four subgroups: lean-insulin sensitive, lean-insulin resistant, individuals with obesity who are insulin-sensitive, and individuals with obesity who are insulin-resistant. Notably, patients with type 2 diabetes were newly diagnosed and had not yet received anti-diabetic medication. Detailed patient information can be found in Supplementary Table 1.

Recruitment

Klötting et al. 2010: We studied 60 individuals with a BMI of 45 ± 1.3 kg/m² who were scheduled to undergo elective cholecystectomy, explorative laparotomy, or gastric sleeve resection. Three hundred fifty-eight previously described patients were recruited at the Departments of Medicine and Surgery (University of Leipzig) and the Clinic of Visceral Surgery (Karlsruhe Hospital) between May 2005 and October 2008 (Klötting N, JCI, 2006). For the purpose of this study, we selected 72 donors with a wide range of BMI and insulin sensitivity.

Ethics oversight

The acquisition of human biomaterial, serum analyses, and phenotypic assessments was approved by University of Leipzig's ethics committee (approval numbers: 159-12-21052012 and 017-12-23012012), and informed written consent was obtained from all participants.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

No statistical method was used to predetermine sample size. The sample size was chosen based on our pilot study and previous experience with similar in vivo experiments (Dario de F Jesus, Nat Metab, 2019; Ling Xiao, BioRxiv, 2023).

Data exclusions

All mice were included in this study.

Replication

Most animal experiments were replicated at least twice, and most in vitro experiments were repeated at least three times, with replicate values reported throughout the manuscript. All the attempts got similar trend.

Randomization

The experiments were not randomized since all the genotyped mice were used for this study. Animals with same genotype were randomly assigned to different groups, to have the same average body weight in each group with different diets feeding.

Blinding

Although the primary investigators were not blinded for most of the studies, some of the sample analyses were performed in different labs or facilities where the researchers were not informed of the grouping during the analyses.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used

Primary antibodies for Western blotting:
 Anti-METTL14, NBP1-81392, Novus
 β -Actin Antibody, #4967, CST
 Anti-UCP1 antibody, #ab155117, abcam
 GAPDH (D16H11) Rabbit mAb #5174, CST
 Akt (pan) (11E7) Rabbit mAb, #4685, CST
 Phospho-Akt (Ser473) (D9E) XP® Rabbit mAb, #4060, CST
 Phospho-IGF-I Receptor β (Tyr1135/1136)/Insulin Receptor β (Tyr1150/1151) (19H7) Rabbit mAb, #3024, CST
 Insulin Receptor β (4B8) Rabbit mAb, #3025, CST
 Anti-TRAIL antibody, ab231265, abcam
 Vinculin Antibody (7F9), sc-73614, santa-cruz
 Adiponectin (C45B10) Rabbit mAb, #2789, CST
 DR5-Specific Polyclonal antibody, 15497-1-AP, Proteintech
 Recombinant Anti-TNF alpha antibody [EPR19147], ab183218, abcam
 RIP (D94C12) XP® Rabbit mAb, #3493T, CST
 Caspase 3/p17/p19 Polyclonal antibody, 19677-1-AP, Proteintech
 Recombinant Anti-Cleaved Caspase-7 antibody [EPR22840-25], ab256469, abcam
 α -Tubulin (11H10) Rabbit mAb, #2125a, CST
 YTHDF1 Polyclonal antibody, 17479-1-AP, proteintech
 YTHDF2 Polyclonal antibody, 24744-1-AP, proteintech
 YTHDF3-specific Polyclonal antibody, 25537-1-AP, proteintech
 Anti-TNF alpha antibody [EPR19147], AB183218, Abcam
 Anti-TNF Receptor I antibody, AB19132, Abcam
 Anti-TRAIL antibody, AB231265, Abcam

Secondary antibodies for Western blotting:
 Anti-rabbit IgG, HRP-linked Antibody, #7074, CST
 Anti-mouse IgG, HRP-linked Antibody, #7076, CST

Validation

The manufactures have shown the validation of each antibody by using to perform western blotting on relevant cells. Most of the m6A related antibodies were validated before in (Dario de F Jesus, Nat Metab, 2019). We have further validated all the other antibodies used in this study in our own hands using primary mouse tissues, pre- or differentiated human brown/white adipocytes, or human adipose tissues.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Immortalized human brown (A41 hBAT-SVF) and white preadipocytes (A41 hWAT-SVF) were derived from the SVF of deep neck fat collected from a human subject.
 Primary SVF cells isolated from human (Subject 5 (A41): Female (sex was defined based on the biological attribute), Age = 56 y, BMI = 30.8) neck fat were expanded in culture and split a few times before immortalization. For immortalization, primary hBAT-SVF cells were infected with retroviruses expressing the plasmid pBABE-Hygro-hTERT (Addgene Plasmid #1773, Cambridge, MA) and primary hWAT-SVF cells were infected with retroviruses expressing the plasmid, pBABE-Neo-hTERT (Addgene Plasmid #1774, Cambridge, MA). Following retrovirus infection, cells were selected with 200ug/ml Hygromycin (for hBAT-SVF) or 700 ug/ml G418 (for hWAT-SVF) for two weeks. Once drug selection was finished, immortalized cells were

grown and maintained in DMEM/H medium containing 10% FBS.

The differentiation capacity of the cells has been tested using the differentiation protocol described in Xue et al (Nature Medicine 2015). Oil Red O staining showed that the majority of cells were differentiated into lipid-laden adipocytes. Gene expression analysis demonstrated that both differentiated A41 hBA (human brown adipocytes) and hWA (human white adipocytes) expressed high level of adipocyte markers such as PPAR γ and FABP4. Additionally, the differentiated A41 hBA cells expressed very high level of brown fat-specific marker UCP1, while differentiated A41 hWA cells expressed high level of leptin.

Authentication

Both Immortalized human brown (A41 hBAT-SVF) and human white preadipocytes (A41 hWAT-SVF) were authenticated by Dr. Yu-Hua Tseng.

Mycoplasma contamination

The cells have been tested negative for mycoplasma.

Commonly misidentified lines (See [ICLAC](#) register)

No commonly misidentified cell line was used in this study

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

Mettl14fl/fl mice on a C57BL/6N background (De Jesus et al. 2019) were crossed with Ucp1cre strain (stock no.024670, the Jackson Laboratory) or Adipoqcre strain (stock no.028020, the Jackson Laboratory) mice, which do not harbor the nicotinamide nucleotide transhydrogenase (Nnt) mutation, to generate the knockouts. M14fl/fl, M14fl/fl-Ucp1cre, and M14fl/fl-Adipoqcre mice were fed with chow diet (cat. no. 5020, LabDiet). For studies on diet-induced obesity and long-term insulin resistance, M14fl/fl, M14fl/fl-Ucp1cre, and M14fl/fl-Adipoqcre mice were fed either 10% fat LFD or a conventional 60% fat HFD for 14 weeks, starting at 6 weeks of age. To examine tissue-specific insulin sensitivity, mice were fasted for 16 hours. After being anesthetized, 1 U of insulin was injected directly into the vena cava as described previously (Xiao et al. 2023). Tissues were harvested at the indicated time points as shown in Figure 3a.

6-week-old ob/+ and ob/ob (B6.Cg-Lepob/J) male mice were purchased from The Jackson Laboratory and maintained on a CD for 6 weeks. ITT and GTT were performed for phenotyping at either 11 weeks or 12 weeks of age. Adipose tissues were collected for the assessment of m6A regulator protein abundance by Western blot analysis. Additionally, serum samples were collected at 12 weeks of age for insulin measurement.

db/+ and db/db (BKS.Cg-Dock7^{m>+/+}Lepr^{db>/J}) mice were purchased from The Jackson Laboratory (Strain 000642). Adipose tissues were collected for the assessment of m6A regulator protein abundance by Western blot analysis. Additionally, serum samples were collected at 10 weeks of age for insulin measurement.

Wild animals

No wild animals were used

Reporting on sex

This study incorporated both female and male mice. Given the absence of sexual dimorphism in the phenotypic outcomes, and in the interest of conciseness, we have chosen to present only the data derived from male mice in the manuscript.

Field-collected samples

No field samples were collected

Ethics oversight

All animal protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of the Joslin Diabetes Center following National Institutes of Health (NIH) guidelines.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks

Not applicable

Novel plant genotypes

Not applicable

Authentication

Not applicable