nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

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

No custom software was central to this study. Following software were used for data collection:
Metabolomics: Xcalibur 4.1
OCR and ECAR measurements: Wave v2.4.3.3 (Agilent Technologies)
Immunoblot: Compass for SW v4.0.0 and v6.1.0 (ProteinSimple, Bio-Techne)
Absorbance and luminescence measurement: SoftMax Pro v6.4.0.2 (Molecular Devices)
RT-qPCR: CFX Maestro 2.3 v5.3.022.1030 (Bio-Rad)
Cell counting: Cellometer K2 v2.1.7.6 (Revvity)
Histology: TissueFAXS 7.1, TissueFAXS 8.0

Data analysis	Graphs and statistics: GraphPad Prism v10 and v11 Metabolomics: Tracefinder 4.1, El-MAVEN Proteomics: Monocle, Perseus, Comet Histology: TissueFaxsViewer v7.1.6245.135, Fiji/ImageJ v1.54r NGS data analysis: Scripts utilized R (v4.2.1, v4.2.3, and v4.4.0; including standard packages, DESeq2, and ChIPpeakAnno) and Python (v3.8.8). The following pipelines, packages, and tools were also used: nf-core/rnaseq v3.12.0 pipeline, bcl2fastq v2.19.1, BCL Convert (v3.10.4 and v4.2.7), fgsea v1.24.2, pheatmap v1.0.12, cutadapt (v4.1 and v4.2), FastQC v0.11.2, Bowtie v1.1.2, bowtie2 (v2.4.1, v 2.4.5, and v2.5.4) , deepTools (v3.5.1 and v3.5.6), Trimmomatic v0.39, samtools v1.15.1, bcftools v1.15.1, bedtools (v2.29.3 and v2.30.0), MACS2 v2.2.9.1, UMI-tools v1.1.5, CAGEfightR, seqMiner, SeqMonk v1.48.1, IGV v2.19.1, nf-core/scrnaseq v4.0.0 pipeline, Seurat v5.3.0, scvi-tools v1.2.2.post1, and sctransform v0.4.2. Custom scripts used for bulk RNA-seq and scRNA-seq are available in the NUPulmonary/utils GitHub repository.

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 MS data have been deposited into the ProteomeXchange Consortium with the dataset identifier PXD054020. GEO accession codes for bulk RNA-seq, mRRBS, ATAC–seq, m6A sequencing, ChIP–seq, PRO-seq, scRNA-seq, and CUT&RUN are GSE326291, GSE326292, GSE326293, GSE326294, GSE273473, GSE273474, GSE326782, and GSE309886, respectively. Human MDH2, rat L2hgdh, and L2hgdh-cyto insert sequences are provided in the Supplementary Methods. Supplementary Table 3 contains peak areas of different proteins analyzed by Simple Western technology (automated capillary western analysis). Source data are provided with this paper.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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

Life sciences study design

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

Sample size	No statistical tests were used to predetermine sample sizes. We made every effort to avoid excessive or needless use of animals. We used sample sizes commonly used in literature in the field. We used statistical analysis consistent with the sample size for each experiment.
Data exclusions	No animal data were excluded from analyses.
Replication	All experiments involved biological replicates (if not mentioned otherwise) as indicated in the figure legends.
Randomization	Experiments were not randomized. Transgenic mice were predetermined by mouse genotype and therefore could not be randomized. All

Randomization	mice were sex- and age-matched, and littermates when possible.
Blinding	Investigators were not blinded. Blinding was not relevant in this study, as groups consisted of previously genotyped mice or treated cell lines in order to have correct experimental and control groups.

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☐	☒ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	anti-L2HGDH (Abcam, catalog no. ab230230); anti-COFILIN (Cell Signaling Technology (CST), catalog no. 5175, clone: D3F9); anti-VINCULIN (CST, catalog no. 13901, clone: E1E9V); anti-MDH2 (Abcam, catalog no. ab181873, clone: EPR14882(B)); anti-TOM20 (CST, catalog no. 42406, clone: D8T4N); anti-eIF2α (CST, catalog no. 9722); anti- p-eIF2α (Ser51) (CST, catalog no. 9721); m6A antibody (Synaptic Systems, catalog no. 202-003); anti-H3K9me3 (CST, catalog no. 13969; clone: D4W1U); anti-H3K27me3 (CST, catalog no. 9733; clone: C36B11); Drosophila spike-in antibody (ActiveMotif, catalog no. 61686); anti-H3K9me3 (Abcam; catalog no. ab176916; clone: EPR16601); anti-RPB1-S2P/S5P (CST, catalog no. 13546; clone: D1G3K).
Validation	anti-L2HGDH (Abcam, catalog no. ab230230) antibody has been tested for WB and IHC-P by the manufacturer. anti-COFILIN (CST, catalog no. 5175, clone: D3F9) antibody has been tested by the manufacturer for WB and IF. It has been cited in 292 publications. anti-VINCULIN (CST, catalog no. 13901, clone: E1E9V) antibody has been tested for WB, IHC and F by the manufacturer. It has been cited in 504 publications. anti-MDH2 (Abcam, catalog no. ab181873, clone: EPR14882(B)) antibody has been tested for IHC-P and WB and KO validated by the manufacturer. It has been cited in 3 publications. anti-TOM20 (CST, catalog no. 42406, clone: D8T4N) antibody has been tested for WB, IP, IHC, and IF by the manufacturer. It has been cited in 319 publications. anti-eIF2α (CST, catalog no. 9722) antibody has been tested for WB by the manufacturer. It has been cited in 1062 publications. anti-p-eIF2α (Ser51) (CST, catalog no. 9721) antibody has been tested for WB by the manufacturer. It has been cited in 1142 publications. m6A antibody (Synaptic Systems, catalog no. 202-003) has been tested for Dot blot and ELISA by the manufacturer. I t has been cited in 4 publications for WB, 168 publications for Dot blot, 359 publications for IP, 27 publications for ICC, 12 publications for IHC, 8 publications for IHC-P, and 114 publications for MeRIP. anti-H3K9me3 (CST, catalog no. 13969; clone: D4W1U) antibody has been tested for WB, IP, IF, F, and ChIP by the manufacturer. It has been cited in 152 publications. anti-H3K27me3 (CST, catalog no. 9733; clone: C36B11) antibody has been tested for WB, IHC, IP, IF, F, ChIP, C&R, and C&T by the manufacturer. It has been cited in 1517 publications. Drosophila spike-in antibody (ActiveMotif, catalog no. 61686) has been tested for ChIP normalization by the manufacturer. It has been cited in 42 publications. anti-H3K9me3 (Abcam; catalog no. ab176916; clone: EPR16601) antibody has been tested for WB, Dot, PepArr, IHC-P, ICC/IF, ChIP, C&R, and C&T by the manufacturer. It has been cited in 106 publications. anti-RPB1-S2P/S5P (CST, catalog no. 13546; clone: D1G3K) antibody has been tested for WB, IP, ChIP, C&R, and C&T by the manufacturer. It has been cited in 9 publications.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	293T cell line purchased from ATCC. 143B-WT, 143B-dCYTB, 143B-dCYTB-EV, 143B-dCYTB-LbNOX-Mito, 143B-dCYTB-LbNOX-Cyto, and 143B-dCYTB-AOX cell lines were described previously (PMID:32641834). 143B-WT and 143B-dCYTB were originally provided by Dr. I.F.M. de Coo, University Medical Center, Rotterdam, Netherlands. mESC line was received from the Ingenious Targeting Laboratory.
Authentication	Neither of the cell lines used were authenticated.

Mycoplasma contamination	All cell lines tested negative for Mycoplasma contamination. Cells were checked periodically.
Commonly misidentified lines (See ICLAC register)	These cell lines are not listed in the database of commonly misidentified cell lines maintained by ICLAC.

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	L2HGDH knock-in mice (C57Bl/6 background) were generated at the Ingenious Targeting Laboratory. Ndufs2 floxed mice and SFTPC-Cre mice used in this study were described previously (PMID: 37558881). NOD scid gamma (NSG) mice (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ, The Jackson Laboratory, stock #005557) and b-actin Cre mice (B6N.FVB-Tmem163Tg(ACTB-cre)2Mrt/CjDswJ, The Jackson Laboratory, stock #019099) were obtained from the Jackson Laboratory. Mice of different ages (E17.5 to 2 years of old) were used, which are specified in the figure legends and methods. Only male NSG mice were used for teratoma formation assay. Both males and females were used in all other experiments. All animals were housed at Northwestern University animal facility with a standard dark/light cycle, temperature of 72+/-2 °F, and approximate humidity of 30-70%.
Wild animals	This study did not involve wild animals.
Reporting on sex	Only male NSG mice were used for teratoma formation assay. Both males and females were used in all other experiments. We did not observe any differences in phenotypes based on sex among the experimental and control mice; therefore, mice of both sexes were analyzed together for these experiments.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All animal procedures were reviewed and approved by Northwestern University's Institutional Animal Care and Use Committee (IACUC).

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE273473
Files in database submission	fastq and bigwig files.
Genome browser session (e.g. UCSC)	No longer applicable

Methodology

Replicates	Two biological replicates per treatment group.
Sequencing depth	All samples were sequenced as paired-end and are above a QC threshold of 20M mapped reads per sample.
Antibodies	H3K9me3 (CST, catalog no. 13969; clone: D4W1U); H3K27me3 (CST, catalog no. 9733; clone: C36B11)

Peak calling parameters	Broad regions were called using macs2 "callpeak" function with parameters:-q 0.05 --broad --broad-cutoff 0.01 --keep-dup auto --nomodel --extsize.
Data quality	Data quality was assessed with FastQC v.0.11.2.
Software	ChIP-seq data was analyzed and visualized using deepTools v3.5.1., MACS2 v2.2.9.1 for peak calling.