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Reporting Summary

Nature Research 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 Research 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 software code was used
Data analysis	Graphs and statistical analysis were done using GraphPad, Prism versions 7-9. Western blot images were quantified using Adobe Photoshop SC6 and ImageJ version 1.51. Tuxedo Suite software package was used for alignment, differential expression analysis, and post-analysis diagnostics. The RNA sequencing reads were aligned to the reference using TopHat (version 2.0.13) and Bowtie2 (version 2.2.1.).

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Figures 2 and 6, and Extended Data Figures 1, 2, and 6-10 have associated raw data provided as source data files. All raw data is also available upon request. 5edu.pdb was used for the docking reported in Fig. 8.

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	Experimental sample sizes used are noted in the figure legends. Cohort sizes for animal studies and other experiments (e.g., immunoblots) were determined based on the experience of the co-authors (IC, RDC, MGL, and TAM) as well as the published literature of similar experimental protocols. Number of animals used in the metabolic cage measurements were determined based on the available animal housing chambers of the unit in our facilities.
Data exclusions	In the metabolic cage studies described in Fig. 3k and 3l, the data collected during the time frame the metabolic cages were opened for mouse injections were excluded from analysis. This criteria was pre-established to avoid the potential misleading readings by oxygen and carbondioxide sensors due to free gas exchange, and due to the animals being removed out of the chambers due to injections. For the studies that involve stereotaxic surgeries into the lateral ventricle, the animals that tested negative during the water intake test (Angiotensin II test) were excluded from the study.
Replication	Majority of the animal experiments in the study were conducted at least in two separate cohorts. There is no data presented that is known to be irreproducible. The RNA sequencing analyses were conducted once. Experiments reported in Figures 1-6 were conducted at least twice. The effect of tubastatin in DIO female mice reported in Extended Data Fig. 1g, h, results in Extended Data Fig. 3, Extended Data Fig.6 e-g, and the effect of SE-7552 in db/db mice presented in Fig. 8f were conducted once. The effect of liver specific ablation of HDAC6 presented in Extended Data Fig. 8 were analyzed in one cohort. Fat and neuronal HDAC6 KO cohorts were analyzed in at least two independent cohorts.
Randomization	Allocation of samples/animals were random.
Blinding	In most experiments, the investigators were not blinded to the experiment except for the experiments presented in Fig. 6h-j. Most experiments were conducted and analyzed by the same investigator except the results presented in Fig. 6h-j.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	mouse IL-6 antibody from Bio X Cell (Cat# BE0046), Rabbit monoclonal anti-HDAC6 (Cat# 7612), Rabbit monoclonal anti-Acetyl-α-Tubulin (Cat# 5335), Rabbit polyclonal anti-α-Tubulin (Cat# 2144), Rabbit monoclonal anti-GAPDH HRP conjugate (Cat# 8884) were from Cell Signaling (Danvers, MA). HDAC6 antibody from Novus Biologicals Cat#: NB100-61065) was used for immonoprecipitation. anti-p-STAT3 was used for IHF staining (Cell Signaling catalog #: 9145S) and western blots. HRP-conjugated secondary antibodies (Cell Signaling, Cat# 7074 and 7076) were used for western blotting.
Validation	Rabbit monoclonal anti-HDAC6 (Cat# 7612), Rabbit monoclonal anti-Acetyl-α-Tubulin (Cat# 5335) antibodies were validated using wild-type and HDAC6 KO mouse tissues as in Extended Data Fig. 2b, c, and also by Cell Signaling using western blots ("Western blot analysis of extracts from HeLa and Jurkat cells using HDAC6 (D21B10) Rabbit mAb.; Western blot analysis of extracts from C2C12 cells, wild-type mouse embryonic fibroblasts (MEFs), and HDAC6 (-/-) MEFs using HDAC6 (D21B10) Rabbit mAb (upper) or β-Actin (13E5) Rabbit mAb #4970 (lower); "Western blot analysis of extracts from HeLa cells, untreated or TSA-treated (400 nM for 16 hours), using Acetyl-α-Tubulin (Lys40) (D20G3) XP® Rabbit mAb (upper) and α-Tubulin (11H10) Rabbit mAb #2125 (lower). The acetyl-

specificity of the antibody was verified by blocking with an acetyl- or non-acetylpeptide."). The other antibodies from Cell Signaling (anti-GAPDH HRP conjugate-Cat# 8884, anti-p-STAT3 Cat#: 9145) have been validated through various protocols including western blotting, immunoprecipitation and/or IHC/IF as stated on the vendor's web site ("Western blot analysis of extracts from NIH/3T3 and HeLa cells using GAPDH (D16H11) XP® Rabbit mAb (HRP Conjugate)."; "Western blot analysis of extracts from IFN-alpha treated Jurkat cells and HeLa cells (left), as well as EGF treated A431 cells (right), using Phospho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb..; Immunohistochemical analysis of paraffin-embedded human neuroendocrine lung carcinoma using Phospho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb performed on the Leica® BOND™ Rx.; mmunohistochemical analysis of paraffin-embedded human prostate adenocarcinoma using Phospho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb performed on the Leica® BOND™ Rx.; Immunohistochemical analysis of paraffin-embedded Apc (min/+) mouse intestine, using Phosho-Stat3 (Tyr705) (D3A7) XP® Rabbit mAb.";). IL-6 neutralizing antibody have been used and validated by several laboratories listed on the suppliers (BioXCell) website: https://bxcell.com/product/m-il-6/#references

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Human embryonic kidney (HEK-293) cells and 293T cells were from ATCC, and Embryonic Mouse Hypothalamus Cell Line N1 (mHypoE-N1, catalog #: CLU101) from Cellutions Biosystems Inc.
Authentication	Cell lines were not independently authenticated.
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	000664 - C57BL/6J - The Jackson Laboratory age; 000632 - B6.Cg-Lep<ob>/J - The Jackson Laboratory; 000697 - B6.BKS(D)-Lepr db /J - The Jackson Laboratory; 003245 - B6.129S7-Il1r1<tm1Imx>/J - The Jackson Laboratory; 006414 - B6;129S4-Mc4r<tm1Lowl>/J - The Jackson Laboratory; 028020 - B6.FVB-Tg(Adipoq-cre)1Evdr/J - The Jackson Laboratory; 003966 - B6.Cg-Tg(Syn1-cre)671Jxm/J - The Jackson Laboratory. HDACflox mice were donated by Dr. Venetia Zachariou, Icahn School of Medicine at Mount Sinai). HDAC6 KO mice were described in Gao et.al., Mol Cell Biol. 2007 Dec;27(24):8637-47.) and were maintanined by crossing mice to wild type C57BL/6J mice. Male and female mice were used at the age range 8-30 week.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve field-collected samples
Ethics oversight	The Institutional Animal Care and Use Committees (IACUC) at the University of Michigan, Vanderbilt University , and University of Colorado Anschutz Medical Campus approved the experimental protocols and euthanasia procedures used in this study.

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