nature portfolio

Corresponding author(s): Zong Wei

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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	qPCR were collected using Bio-rad CFX Opus and Bio-Rad CFX Maestro 2.3 (5.3.022.1030). Multiomic Sequencing data were collected using Illumina NovaSeq6000 platform
Data analysis	GraphPad Prism 10 - for data plotting and statistic analysis Softwere used in bioinformatic analysis: Seurat v4.3.0, ArchR v1.0.1, R v4.1.2, MACS2 v2.2.71, Signac v1.10.0, ComplexHeatmap v2.10.0, STAR v2.7.9a, ChIPseeker v1.30.3, Scanpy v1.4.3, SAMtools v1.13, scVelo v1.0, CellRank v1.5.1, Nebulosa v1.11.0, NicheNet v2.0.1, Paired-tag(https://github.com/cxzhu/Paired-Tag), deepTools v3.3.2, featureCounts v2.0.1, Bedtools v2.27.1, Bowtie2 v2.3.3.1, HOMER v4.11, FigR v1.0.1

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 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 sequencing data obtained in this study have been deposited at the NCBI Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo/) under accession number GSE241639. This paper also analyses existing, publicly available data. FoxA2 ChIP-seq data was obtained from the GEO (GSM1306337). H3K4me1 ChIP-seq data was obtained from the NCBI SRA (SRR9840908, SRR9840909). H3K27ac ChIP-seq data of mouse pancreatic islets was obtained from the NCBI SRA (SRR9840900, SRR9840901). H3K27me3 ChIP-seq data was obtained from the NCBI SRA (SRR6728238). H3K27ac ChIP-seq data in EndoC-βH1 cells was obtained from the NCBI SRA (SRR9336435, SRR9336436, SRR9336437, SRR9336438, SRR9336439, SRR9336440, SRR9336441, SRR9336442). RNA-seq data from mouse islets and PP2 cells was obtained from the NCBI SRA (SRR6159442, SRR6159443, SRR6159444, SRR6159445, SRR6159446, SRR10708482). Ntrk1 RNA-seq data was obtained from the GEO (GSE80673).

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 methods were used to predetermine sample size. C57BL/6J mice were from Jackson laboratory (cat. no. 000664). For Paired-tag, ten female or male mice (n=10) on postnatal week 12 were used for islet isolation. For high-fat diet treatment, mice were fed with 60% fat diet paste (BioServ, S1850) for 8 weeks and 16 weeks before tissue was collected. For RT-qPCR, the number of samples in each experiment was determined based on standards practice in the field (N=3). Therefore, we did N = or > 3 independent experiments unless state otherwise, which was sufficient to calculate standard error. The number of independent experiments are indicated in the legend of each Figure. For NGF administration in Akita mice: n = 5 (control) or 5 (NGF) animals per group.
Data exclusions	Low quality single nuclei (low number of reads, low number of genes captured) were excluded from downstream analysis as outlined in the Methods section. We retained cells with total RNA counts >200 and total single-cell DNA profiles bin counts >500.
Replication	All RT-qPCR assays were repeated at least 3 times (biological replicates) and the results were reproduced each time. All WB assays were repeated at least 2 times and the results were reproduced each time.
Randomization	For HFD treatment and NGF administration, mice were randomized into treatment conditions. Randomization was not applicable for in vitro experiments.
Blinding	Blinding was not applied in this study.

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

Rabbit monoclonal anti-H3K4me1 (Cell Signaling Technology, Cat#5326S)
Rabbit monoclonal anti-H3K27ac (Cell Signaling Technology, Cat#8173S)
Mouse monoclonal anti-CHOP (Cell Signaling Technology, Cat#L63F7)
Rabbit monoclonal anti-α/β-Tubulin (Cell Signaling Technology, Cat#2148)
HRP-linked anti-rabbit IgG (Cell Signaling Technology, Cat#7074S)
HRP-linked anti-mouse IgG (Cell Signaling Technology, Cat#7076S)
Mouse monoclonal anti-TrkA antibody (Sigma-Aldrich, MABN2308)
Rabbit monoclonal anti-TrkA antibody (ThermoFisher MA5-32123)
Mouse CD63 monoclonal antibody, APC (eBioscience, 17-0631-82)
Insulin Polyclonal Antibody (ThermoFisher PA1-26938)

Validation

Rabbit monoclonal anti-H3K4me1 (Cell Signaling Technology, Cat#5326S) previously validated in HeLa cells by ChIP assay as stated by manufacturers on their website (https://www.cellsignal.com/products/primary-antibodies/mono-methyl-histone-h3-lys4-d1a9-xp-rabbit-mab/5326)
Rabbit monoclonal anti-H3K27ac (Cell Signaling Technology, Cat#8173S) previously validated in HeLa cells by ChIP assay as stated by manufacturers on their website (https://www.cellsignal.com/products/primary-antibodies/acetyl-histone-h3-lys27-d5e4-xp-rabbit-mab/8173)
Mouse monoclonal anti-CHOP (Cell Signaling Technology, Cat#L63F7) previously validated in C6 cells by WB as stated by manufacturers on their website (https://www.cellsignal.com/products/primary-antibodies/chop-l63f7-mouse-mab/2895)
Rabbit monoclonal anti-α/β-Tubulin (Cell Signaling Technology, Cat#2148) previously validated in HeLa cells by WB as stated by manufacturers on their website (https://www.cellsignal.com/products/primary-antibodies/a-b-tubulin-antibody/2148)
Mouse monoclonal anti-TrkA antibody (Sigma-Aldrich, MABN2308) previously validated by ELISA as stated by manufacturers on their website (https://www.sigmaaldrich.com/US/en/product/mm/mabn2308)
Rabbit monoclonal anti-TrkA antibody previously validated by immunostaining by manufacturers on their website(https://www.thermofisher.com/antibody/product/TrkA-Antibody-clone-SU0354-Recombinant-Monoclonal/MA5-32123)
Mouse CD63 monoclonal antibody previously validated by FACS by manufacturers on their website (https://www.thermofisher.com/antibody/product/CD63-Antibody-clone-NVG-2-Monoclonal/17-0631-82)
Insulin Polyclonal Antibody previously validated by immunostaining by manufacturers on their website (https://www.thermofisher.com/antibody/product/Insulin-Antibody-Polyclonal/PA1-26938)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	MIN6 cells were purchased from AddexBio
Authentication	Cell lines were authenticated by the manufacturer and no further authentification was performed
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	N/A

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	C57BL/6J mice were purchased from Jackson laboratory (Cat. No. 000664). C57BL/6-Ins2 Akita/J mice were purchased from Jackson Laboratory (Cat .No. 003548).
Wild animals	No wild animals were used in this study.
Reporting on sex	We used both male and female C57BL/6J mice for paired-tag experiments. We used male Akita/J mice in the NGF experiments.
Field-collected samples	N/A
Ethics oversight	All animal experiments and procedures were peformed according to protocols approved by the IACUC Committee at Mayo Clinic.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A