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Last updated by author(s): Apr 22, 2025

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	Applied Biosystem 7900HT Real-Time PCR System (qPCR), OLYMPUS CX41-32RFL microscope system and Leica SP8 confocal microscope system(immunofluorescence), DEXA (GE Medical Systems, Madison, WI), Bio-Rad VARIANT II Hemoglobin Testing System, the Comprehensive Lab Animal Monitoring System (CLAMS, USA), a Fluke TiX1000 Infrared Camera, Western Blot images were captured by Image Lab version 4.1(Bio-Rad).
Data analysis	GraphPad Prism (v.9.5.0),R (v.4.3.2) and QIIME2 (v.2018.6)., ImageJ 1.44 (imaging analysis), The “clusterProfiler” package (v3.16.1) in R2, SmartView software,SPSS software version 19.0 (SPSS Inc.),.

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

Provide your data availability statement here.

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	We have reported the gender of the subjects in all of the human studies in Supplementary Table1 and Table2.
Reporting on race, ethnicity, or other socially relevant groupings	We have not reported on race, ethnicity, or other socially relevant groupings in this manuscript.
Population characteristics	Distal ileum mucosa biopsies were collected from two distinct cohorts (n = 6 and 6, respectively) as part of this study. The participants in both cohorts were undergoing routine colonoscopy and had not been diagnosed with type 2 diabetes. Baseline demographic characteristics, including gender and age, were similar between the nonobese cohort and the cohort with obesity, as indicated in Supplementary Table 1. All participants met the following inclusion criteria: (i) absence of significant acute or chronic viral hepatitis; (ii) no substantial alcohol consumption; (iii) no evidence of thyroid dysfunction; (iv) no history of inflammatory bowel disease; (v) non-pregnant status; and (vi) suitability for biopsy as determined by the attending clinician. The biopsies obtained from cohort 1 (n = 12) were utilized for immuno-histochemical staining and western blot analysis, while the sample collected from cohort 2 (n = 84) were dedicated to fecal analysis (Supplementary Table 2).
Recruitment	The participants were randomly recruited at The Second Xiangya Hospital of Central South University. There is no potential self-selection bias or other biases. All participants recruited in the study signed informed consent. The obese patients were recruited from out-patient department who were diagnosed as obesity. The non-obese controls were recruited from healthy people.
Ethics oversight	The Ethics Committee of The Second Xiangya Hospital at Central South University(Approval No.ID:LYG20250003). And the protocols followed were compliant with the ethical principles of the Helsinki Declaration. Written informed consents were 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

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. Sample size was decided based on previous studies of similar experiments in the metabolism field. For animal experiments, n≥4 was chosen based on the previous publications (Meilian Liu et al, 2014, Cell Metabolism; Haiyan Zhou et al, 2021, Nature Communications). For in vitro experiments, n≥3 was chosen based on the previous publications (Tuo Deng et al.,2013, Cell metabolism) and this size is necessary to calculate statistical significances.For selected in vivo experiments with limited sample sizes, exploratory post hoc power analyses were conducted and are provided for transparency (https://doi.org/10.6084/m9.figshare.30277207).
Data exclusions	Mice that did not respond to glucose/insulin in GTT/ITT experiments were excluded
Replication	All experiments were, at least, twice repeated and the results were successful in replication.
Randomization	Age and gender matched mice were randomly allocated to experimental groups. For cell culture experiments, cells were randomly assigned to experimental groups. The participants were randomly recruited at The Second Xiangya Hospital of Central South University.

Blinding	Animal experiments were performed blindly by investigators. For cell culture experiments, investigators were not blinded to treatments, because the investigators who performed the experiments was the person making the analysis. However, no subjective assessments were made. Human data were analyzed blindly.

Behavioural & social sciences study design

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

Study description	Intestinal epithelial cell-specific cGAS knockout mice were constructed,High-fat diet induction,metabolic index were monitored
Research sample	Male C57BL/6J wild-type mice were procured from Slac Laboratory Animal Inc. (Shanghai, China) when they were seven weeks old. Intestine-specific cGAS knockout mice (cGAS-IKO mice) were generated by crossing cGAS floxed mice (cGAS fl/fl) with Villi-Cre mice (Jackson Laboratory; Cat No. 004586).
Sampling strategy	Mouse body weight was assessed on a weekly basis.
Data collection	Mouse fat mass, lean mass, fluid mass, and percentage of fat were determined using DEXA (GE Medical Systems, Madison, WI).
Timing	mice were divided by gene type when 4 weeks old,high-fat diet induction in 8 weeks old,sample collection in 20th week
Data exclusions	Mice that did not respond to glucose/insulin in GTT/ITT experiments were excluded.
Non-participation	n/a
Randomization	Age and gender matched mice were randomly allocated to experimental groups. For cell culture experiments, cells were randomly assigned to experimental groups. The participants were randomly recruited at The Second Xiangya Hospital of Central South University.

Ecological, evolutionary & environmental sciences study design

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

Study description	*Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.*
Research sample	*Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocereus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.*
Sampling strategy	*Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.*
Data collection	*Describe the data collection procedure, including who recorded the data and how.*
Timing and spatial scale	*Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Reproducibility	*Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.*
Randomization	*Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.*
Blinding	*Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

Did the study involve field work? ☐ Yes ☒ No

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

cGAS(H) Cell Signaling Cat #79978(Dilution ratio,1:100)
cGAS(m) Cell Signaling Cat #31659(Dilution ratio,1:1000)
UCP1 Sigma Cat#U6382(Dilution ratio,1:1000)
Actin Sigma Cat#A3854(Dilution ratio,1:40000)
α/β-Tubulin Cell Signaling Cat#2148(Dilution ratio,1:1000)
GAPDH Cell Signaling Cat#5174(Dilution ratio,1:1000)
PGC1α Abcam Cat#ab54481(Dilution ratio,1:1000)
CREB Cell Signaling Cat #9197(Dilution ratio,1:1000)
Phospho CREB Cell Signaling Cat #9198(Dilution ratio,1:1000)
Phospho PKA substrate Cell Signaling Cat#9624(Dilution ratio,1:1000)
STING Cell Signaling Cat#50494(Dilution ratio,1:1000)
IRF-3 Cell Signaling Cat#4302(Dilution ratio,1:1000)
Phospho-IRF-3 Cell Signaling Cat#4947(Dilution ratio,1:1000)
TBK1 Cell Signaling Cat#38066(Dilution ratio,1:1000)
Phospho-TBK1 Cell Signaling Cat#5483(Dilution ratio,1:1000)

Validation

See the product's official website, for example
cGAS(H) Cat #79978
https://www.cellsignal.cn/products/primary-antibodies/cgas-e5v3w-rabbit-mab/79978
UCP1 Sigma Cat#U6382
https://www.sigmaaldrich.cn/CN/zh/search/u6382?focus=products&page=1&perpage=30&sort=relevance&term=U6382&type=product

Palaeontology and Archaeology

Specimen provenance

Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.

Specimen deposition

Indicate where the specimens have been deposited to permit free access by other researchers.

Dating methods

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

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

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

Male C57BL/6J wild-type mice were procured from Slac Laboratory Animal Inc. (Shanghai, China) when they were seven weeks old. Intestine-specific cGAS knockout mice (cGASIKO mice) were generated by crossing cGAS floxed mice (cGAS fl/fl) with Villi-Cre mice (Jackson Laboratory; Cat No. 004586).All in vivo experiments in this study were mainly conducted using male mice, as stated in the

	title, abstract, and Methods. This choice was made a priori to reduce variability related to sex-specific metabolic and hormonal differences.
Wild animals	No wild animals were used in the study.
Reporting on sex	Sex was not considered in the study design and male mice were used except that female mice were used in fig.2b-m, male mice and female mice showed consistent metabolic phenotypes.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All animal studies were performed in accordance with procedures approved by the Central South University Animal Care and Use Committee.

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks: n/a

Novel plant genotypes: n/a

Authentication: n/a

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.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session
(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.

Instrument

Identify the instrument used for data collection, specifying make and model number.

Software

Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.

Cell population abundance

Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy

Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Indicate task or resting state; event-related or block design.

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☐	☒ Graph analysis
☐	☒ Multivariate modeling or predictive analysis

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.