

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	Metabolomics data of biological samples were acquired using a Vanquish UHPLC coupled to an Orbitrap Exploris 480 (ThermoFisher Scientific, United States) using Xcalibur (version 4.4.16.14, Thermo Fisher Scientific, USA). The structures of new metabolites discovered in this study were confirmed with nuclear magnetic resonance (NMR) spectroscopy.
Data analysis	The source code of IsoNet is provided on GitHub [https://github.com/ZhuMetLab/IsoNet] (version 0.2.13). Other software tools: R (version 4.0.3); Xcalibur (version 4.4.16.14); ProteoWizard (version 3.0.20360); R package "xcms" (version 3.12.0); MetDNA2 (version 1.4.4); MetaboAnalyst 6.0; CAMERA (version 1.46.0); Genform (download on June 28th, 2020); MetTracer (version 2.0.1); Skyline (version 21.1.0.278); R package "Accucor" (version 0.3.0); Cytoscape (version 3.9.1); R package "igraph" (version 1.2.9); CFM-ID (version 4.4.10); mzCloud (version 1.1.5.50160); SIRIUS (version 5.5.5); KEGG database (download on March 7th, 2017); R package "base" (version 4.0.3).

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](#)

Unless otherwise stated, all data supporting the results of this study can be found in the article, supplementary, and source data files. The raw LC-MS data files generated in this study have been deposited in the MassIVE database under accession code MSV000097764 [<https://massive.ucsd.edu/ProteoSAFe/dataset.jsp?accession=MSV000097764>]. 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	No human participant is involved in this study.
Reporting on race, ethnicity, or other socially relevant groupings	No human participant is involved in this study.
Population characteristics	No human participant is involved in this study.
Recruitment	No human participant is involved in this study.
Ethics oversight	No human participant is involved in this study.

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	Datasets acquired in this study were performed on 3-7 biological replicates per group to demonstrate replication of biological results. These replicates were chosen because they are the commonly used number for most biological studies.
Data exclusions	No samples were excluded from analysis in this study.
Replication	The cell samples labeled with ¹³ C-tracers (n=6 biologically independent samples for each group) were used for data analysis in Figure 1, 2 and 4. The mouse tissue samples (n=3-4 biologically independent samples for each group) was used for data analysis in Figure 3. The cell samples (n=4-7 biologically independent samples for each group) was used for metabolite treatment experiments in Figure 5. Each sample was analyzed once by LC-MS.
Randomization	For all datasets, samples were assigned randomly to acquire LC-MS data.
Blinding	The investigators were blinded to group allocation during data collection. At the time of sample acquisition and processing, scientists were completely unaware of the sample group. The data analyses were blinded.

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	Involvement 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	Involvement in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

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

Cell line source(s)	HEK293T (CRL-3216, ATCC)
Authentication	Authentication was done using STR (Short Tandem Repeat) analysis.
Mycoplasma contamination	The cell lines were routinely tested for mycoplasma contamination. The cell lines used are free of mycoplasma but not described in text.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cells were used.

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	Wild type C57BL/6j male mice; 12-week-old.
Wild animals	The study did not involve animals collected from the field.
Reporting on sex	The findings apply to only male mice. Sex is not considered in study design.
Field-collected samples	The study did not involve animals collected from the field.
Ethics oversight	The animal experiments were compliant with the ethical guidelines of the Institutional Animal Care and Use Committees of Interdisciplinary Research Center on Biology and Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (approval research project number: ECSIOC_2023-23)

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

Plants

Seed stocks	No plant is involved in this study.
Novel plant genotypes	No plant is involved in this study.
Authentication	No plant is involved in this study.