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

☐ 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. mean), 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 was used.

Data analysis

The data were analyzed using GraphPad Prism 9, Software MaxQuant version 1.6.2.10, R statistical computing software version 4.1.0, Workstation Software version B.06.00, XCMS package version 3.18.0, SIMCA-P 14.0, ImageJ software version 1.5.

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 authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information Files, or are available from the corresponding authors on reasonable request.
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.

- [x] 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 these points even when the disclosure is negative.

| Sample size | Sample sizes were based on previous experiments, therefore no statistical method was used to predetermine sample size (Nat Commun. 2019 Sep 20;10(1):4303.). |
|-------------|----------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | No data was excluded.                                                                                                           |
| Replication | For all experiments, 6-10 mice were included for each group. For cell experiments, independent experimental repeats were performed at least three times to ensure reproducibility of the results. |
| Randomization | All the cells and mice were randomly allocated into different groups. We performed a retrospective analysis rather than a clinical trial. So, samples from human were collected from CKD patients or healthy subjects and these samples were all analysed, which did not involve in allocation. |
| Blinding | Blinding was not performed in most of the experiments of this study, as experimental observations would be consistent irrespective of blinding. Investigators who performed animal experiments were not blinded because they needed to prepare the drug or cells freshly. But the Investigators were blinded during the sample collection and data analysis. |

### Behavioural & social sciences study design

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

| Study description | Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study). |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Research sample | State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source. |
| Sampling strategy | Describe the sampling procedure (e.g. random, snowball, stratified, convenience). 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. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed. |
| Data collection | Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection. |
| Timing | Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort. |
| Data exclusions | If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established. |
| Non-participation | State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation. |
| Randomization | If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled. |

### Ecological, evolutionary & environmental sciences study design

All studies must disclose 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. |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------|

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf
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

Field work, collection and transport

Field conditions
Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).

Location
State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).

Access & import/export
Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).

Disturbance
Describe any disturbance caused by the study and how it was minimized.

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

Methods

| n/a | Involved in the study |
|-----|-----------------------|
| ☑   | Antibodies            |
| ☑   | Eukaryotic cell lines |
| ☑   | Palaeontology and archaeology |
| ☑   | Animals and other organisms |
| ☑   | Human research participants |
| ☑   | Clinical data         |

| n/a | Involved in the study |
|-----|-----------------------|
| ☑   | ChIP-seq              |
| ☑   | Flow cytometry        |
| ☑   | MRI-based neuroimaging |

Antibodies

Antibodies used
anti-collagen I (ab260043, Abcam, rabbit, dilution 1:1000 for WB), anti-fibronectin (ab2413, Abcam, rabbit, dilution 1:2000 for WB), anti-a-SMA (ab124964, Abcam, rabbit, dilution 1:5000 for WB), anti-GAPDH (HRP-60004, Proteintech, dilution 1:4000 for WB), anti-TGF-β1 (21898-1-AP, Proteintech, rabbit, dilution 1:1000 for WB), anti-Smad2 (#5339, CST, rabbit, dilution 1:1000 for WB), anti-Smad3 (#9523, CST, rabbit, dilution 1:1000 for WB), anti-12-LO (C-5) (sc-365194, Santa Cruz Biotechnology, mouse, dilution 1:100 for WB), anti-Rac1 (66122-1-Ig, Proteintech, mouse, dilution 1:1000 for WB), anti-Keap1 (10503-2-AP, Proteintech, mouse, dilution 1:1000 for WB), anti-HO-1 (66743-1-Ig, Proteintech, mouse, dilution 1:1000 for WB), anti-SGLT2 (ab37296, Abcam, rabbit, dilution 1:1000 for WB), ZO-1(21773-1-AP, Proteintech, rabbit, dilution 1:2000 for WB), Occludin (66378-1-Ig, Proteintech, mouse, dilution 1:5000 for WB), anti-TGR5 (ab72608, Abcam, rabbit, dilution 1:1000 for WB and 1:100 for IHC), anti-IL-1β (ab254360, Abcam, rabbit, dilution 1:1000 for WB), anti-TNF-α (ab215188, Abcam, rabbit, dilution 1:1000 for WB)
Validation

Antibodies used are commercially available and have been validated by the respective suppliers. Their validation data are available on the manufacturers websites, as listed below:

WB antibodies verified by supplier:

- anti-collagen I (Abcam, ab260043)
  https://www.abcam.cn/collagen-i-antibody-epr22894-89-ab260043.html
- anti-fibronectin (Abcam, ab2413)
  https://www.abcam.cn/fibronectin-antibody-ab2413.html
- anti α-SMA (Abcam, ab124964)
  https://www.abcam.cn/alpha-smooth-muscle-actin-antibody-epr5368-ab124964.html
- anti-GAPDH (Proteintech, HRP-60004)
  https://www.ptgcn.com/products/GAPDH-Antibody-HRP-60004.htm
- anti-TGF-β1 (Proteintech, 21898-1-AP)
  https://www.ptgcn.com/products/TGF-beta-1-Antibody-21898-1-AP.htm
- anti-Smad (CST, #5339)
  https://www.cellsignal.cn/products/primary-antibodies/smad2-d43b4-xp-rabbit-mab/5339
- anti-Smad3 (CST, #9523)
  https://www.cellsignal.cn/products/primary-antibodies/smad3-c67h9-rabbit-mab/9523?
- anti-12-LO (Santa Cruz Biotechnology, sc-365194)
  https://www.scbt.com/p/12-lo-antibody-c-5?requestFrom=search
- anti-E-cadherin (CST, #14472)
  https://www.cellsignal.cn/products/primary-antibodies/e-cadherin-4a2-mouse-mab/14472

HEK293 cell line was obtained from Stem Cell Bank, Chinese Academy of Sciences. The HK2 cell line was obtained from the Cell Resource Center, Peking Union Medical College (which is the headquarter of National Infrastructure of Cell Line Resource, NSTI). HMC cell line was obtained from FuHeng Biology, Shanghai, China.
Authentication

Cell lines were authenticated by short tandem repeat (STR) analysis.

Mycoplasma contamination

HEK293 cell line was negative for mycoplasma. HK2 and HMC cell lines used tested negative for mycoplasma contamination prior to this study.

Commonly misidentified lines

No commonly misidentified lines were used in this study.

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.

Animals and other organisms

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

Laboratory animals

Mice were housed in pathogen-free and ventilated cages in a 12h light/dark cycle, with room temperature at 25±2°C and humidity between 40 and 60%. All mice used in this work were male. Eight-week-old ICR male mice (18 to 22g) were allowed free access to water and regular chow and their body weights taken every week.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

All animal treatments were approved by Animal Ethics Committee of China Pharmaceutical University (Nanjing, China). Animal testing and research conformed to all relevant ethical regulations.

Human research participants

Policy information about studies involving human research participants

Population characteristics

The human research participants include CKD patients and healthy subjects. The age of participants are around 60 years old. The males are around 60%.

Recruitment

CKD patients with glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m2, or a marker of kidney damage, or both, for a duration of at least 3 months were recruited. Patients with acute kidney injury, liver disease, active vasculitis, gastrointestinal pathology or cancer were excluded from the study. Age- and sex-matched healthy subjects were also recruited. Patients were recruited at admission to the Affiliated Hospital of Nanjing University of Chinese Medicine, Renmin Hospital of Wuhan University, the Putuo People’s Hospital, the Ningbo Hospital of Zhejiang University. Most eligible patients agreed to participation. As a consequence, self-selection bias is low.

Ethics oversight

All procedures were approved by the medical ethics committee of the Affiliated Hospital of Nanjing University of Chinese Medicine and followed the tenets of the Declaration of Helsinki (2019NL-109-02). All subjects were informed of the use of their feces and blood, and written informed consent was obtained.

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

Describe the settings and locales of data collection, noting the time periods of recruitment and 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

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

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

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.
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:**
- [ ] Wholebrain
- [ ] ROI-based
- [ ] Both

**Statistic type for inference**
(See Eklund et al. 2019)

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

**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

**Functional and/or effective connectivity**
Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

**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.