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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	Bound antibody was visualized using Pierce ECL plus western blotting substrate (Advansta, K-12045-D50). The protein bands were visualized by exposure machine (GE, Amersham ImageQuant 800). Transthoracic echocardiography was performed using a VisualSonics Vevo 3100 Ultrasound system (Visual Sonics). Histological analysis images were captured using a light microscope (Olympus, BX53F2O). Partial cell images were captured using an inverted fluorescence microscope (Nikon, TI-S). Cell mitochondria morphology images were captured with a confocal laser scanning microscope (Nikon, AIR-SIM-STORM). Electron microscope images were captured with a transmission electron microscope (JEOL, JEM-F200). qRT-PCR analysis was performed with a Real-Time PCR System with specific primers (Bio-Rad, CFX96). The oxygen consumption rates were measured with a Seahorse XFe96 Extracellular Flux Analyzer (Agilent Technologies).
Data analysis	The protein bands were quantified using the ImageJ v1.51 software (NIH). Echocardiogram analysis was performed using Vevo Lab v5.6.1 software (Visual Sonics). Microscopy images were analyzed using the ImageJ v1.51 software (NIH). qPCR were quantitated using the 2−ΔΔCT method and normalized to the amount of endogenous Glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Statistical analysis was performed using SPSS version 26.0 (IBM Corporation) and GraphPad Prism (version 8). The oxygen consumption data were analyzed using the Wave v2.6.3 package (Agilent Technologies).

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 mass spectrometry proteomics data have been deposited to the Integrated Proteome Resources repository with the dataset identifier PXD051242. All data generated or analyzed in this study are available within the article and its supplementary information files. 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 sex specific-analyses were perfomed. Both sexes were included in the analyses.
Reporting on race, ethnicity, or other socially relevant groupings	No race, ethnicity and other socially relevant specific-analyses were perfomed.
Population characteristics	Baseline characteristics of patients were shown in Supplementary Table 1
Recruitment	Patients with heart failure with preserved ejection fraction (HFpEF) were admitted to Anzhen Hospital of Capital Medical University (Beijing, China). We enrolled patients with HFpEF following a particular set of inclusion criteria. The inclusion criteria were as follows: Adult patients with typical heart failure symptoms (breathlessness, coughing up pink frothy sputum, lower limb swelling, or jugular venous distension) following a left ventricular ejection fraction (LVEF) over 50% or relevant structural heart changes assessed by echocardiography were included. Subjects with acute heart failure, acute coronary syndrome, congenital heart disease, pericarditis, pulmonary heart disease, valvular heart disease, abnormal liver function, severe renal dysfunction, severe endocrine disorders, tumor, and acute infection in the near future were excluded.
Ethics oversight	The written informed consent was obtained from all participants. This study was approved by the Human Ethics Committees of Beijing Anzhen Hospital and the Third Affiliated Hospital of Wenzhou Medical University in concordance with the ethical guidelines of the 1975 Declaration of Helsinki.

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	Sample size calculation was not performed. The sample size for animals experiments was determined based on common practice of the described experiments in the literature and our previous work (PMID: 29706566). The sample size for cohort was chosen based upon availability of patients meeting our study criteria for inclusion.
Data exclusions	Exclusion criteria were pre-established, so there was no data were excluded from the analyses.
Replication	Each sample is a biological replicate. All attempts at replication were successful. There was no replication in cohort, because these were clinical observations.
Randomization	Animals of the same age, sex and genotype were randomly assigned to treatment groups. For in vitro and ex vivo experiments, cells and treatments were randomly assigned. For the cohort, there was no allocation to experimental or control groups in this study and so no randomization.
Blinding	The investigators were blinded to HFpEF/Control operation of each animal and group allocation during data collection and analyses.

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	GAPDH (Proteintech, HRP-60004, 1:10000), VDAC1 (ABclonal, A19707, 1:1000), FGF21 (Abcam, ab171941, 1:1000), Fibronection (Abcam, ab45688, 1:1000), Collagen I (Abcam, ab260043, 1:1000), α-SMA (Abcam, ab124964, 1:10000), PDK4 (Proteintech, 12949-1-AP, 1:2000), phosphorylated (p)-PDH (Abcam, ab177461, 1:1000), PDH (Proteintech, 18068-1-AP, 1:10000), PI3K (Abmart, T40064, 1:1000), p-PI3K (Abmart, T40065, 1:1000), AKT (CST, 9272S, 1:1000), p-AKT (CST, 12694S, 1:1000), total OXPHOS rodent (Abcam, ab110413, 1:1000) and CPT1b (Proteintech, 22170-1-AP, 1:2000)
Validation	GAPDH: validated by Cell. 2019. PMID: 31230714 VDAC1: validated by Cell Res. 2021. PMID: 34341487 FGF21: validated by Cell Rep Med. 2022. PMID: 35106510 Fibronection: validated by Cell Death Dis. 2022. PMID: 36566325 Collagen I: validated by Cell Death Discov. 2022. PMID: 36581638 α-SMA: validated by Sci Rep. 2022. PMID: 37872392 PDK4: validated by Nutrients. 2020. PMID: 33916004 (p)-PDH: validated by Sci Rep. 2022. PMID: 34996938 PDH: validated by Cell Metab. 2016. PMID: 26853747 PI3K: validated by J Extracell Vesicles. 2023. PMID: 37165987 p-PI3K: validated by BMC Med. 2022. PMID: 36482460 AKT: validated by Nat Commun. 2024. PMID: 39627211 p-AKT: validated by Cell Chem Biol. 2020. PMID: 32668203 Total OXPHOS rodent: validated by Aging Cell. 2022. PMID: 35088525 CPT1b: validated by Adv Sci. 2023. PMID: 37821382

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	All mouse strains used in this study are of C57BL/6 origin and are described in the Materials and Methods sections. All animal experiments and methods performed in this study follow ethical guidelines for animal studies and were approved by the Institutional Animal Care and Use Committee of Wenzhou Medical University, China. Apn KO mice and WT controls with the same genetic background were generated by Shanghai Model Organisms Center. Fgf21 KO mice and WT controls with the same genetic background were generated by Beijing Viewsolid Biotech Ltd. Fgf21-floxed mice and Adipoq-Cre mice were generated by Cyagen Biosciences. Eight- to ten-week-old male mice were used to establish the experimental animal model. The Sprague Dawley (SD) rats were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. The mice were housed at 23 ± 1℃, a humidity of 55% ± 5%, and a 12-hour dark/light cycle.
Wild animals	No wild animals were used in this study.
Reporting on sex	Male mice were used in this study, and the findings are applicable to males.
Field-collected samples	No field-collected samples were used in this study
Ethics oversight	All animal experiments and methods performed in this study followed ethical guidelines for animal studies and were approved by the Institutional Animal Care and Use Committee of Wenzhou Medical University, China

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	N/A
Study protocol	The full trail protocol can be accessed at "Human study" in the manuscript
Data collection	Information on demographic characteristics, history, clinical presentation, physical examination, imaging information, and management was obtained from the medical records. Blood samples were collected at the time of hospital admission, and they were drawn into coagulation-promoting tubes and centrifuged for 1 h at 2000 x g for 10 min.
Outcomes	The primary outcomes were the serum levels of FGF21 and BNP, and cardiac function. Baseline characteristics including clinical history, patients with chronic heart failure (CHF) NYHA class NYHA class, hemodynamics, and laboratory data were also compared.

Plants

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