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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	Vevo® 3100 high resolution Preclinical Imaging System (FUJIFILM VisualSonics, Toronto, Canada), DP74 fluorescence microscope (OLYMPUS, Tokyo, Japan), ChemiDoc™ XRS+ System (Bio-Rad Laboratories, Inc.), Roche LightCycler 480 system, BioTek microplate reader (Winooski, Vermont, USA), ADVIA® 2400 automatic biochemical analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), Illumina Novaseq 6000 platform (San Diego, CA, USA)
Data analysis	Image-Pro Plus 6.0 software (Media Cybernetics, Bethesda, MD, USA), Image Lab Software (version 6.0, Bio-Rad Laboratories, Inc.), GraphPad Prism (version 7.0), Excel

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 data that support the findings of this study are available within the main text and its Supplementary Information file and Source data. Source data are provided

with this paper. Additional data that support the findings in this study are available from the corresponding author upon reasonable request. The datasets generated for the transcriptome analysis are available through the Gene Expression Omnibus under accession code GSE277729.

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	Human heart samples were collected from men and women depending on the availability of the heart explants, independently of the sex. Difference between male and female participants were not compared due to small group sizes. 9 men (5 for IHD patients) and 3 women (1 for IHD patients) were included in this study. Human plasma samples were collected from men and women depending on the availability of the plasma samples, independently of the sex. Difference between male and female participants were not significant. 40 men (25 for AMI patients) and 28 women (17 for AMI patients) were included in this study.
Reporting on race, ethnicity, or other socially relevant groupings	We did not use the socially constructed or socially relevant categorization variables in this study.
Population characteristics	All the patient's characteristics of heart samples were described in our previous studies (PMID: 37291168, 30407523). To measure the level of FNDC4 protein in human hearts, 9 men (5 for IHD patients) and 3 women (1 for IHD patients) were included in this study. Age of the patients is between 28 and 74. To measure the level of FNDC4 protein in human plasma, 40 men (25 for AMI patients) and 28 women (17 for AMI patients) were included in this study. Age of the patients is between 25 and 85.
Recruitment	Patients were recruited according to the etiology and the severity of heart disease. Sex and age were random.
Ethics oversight	Written informed consent was obtained from all donors or their legal guardians. All experimental procedures involving human samples in this study were in accordance with the Declaration of Helsinki, and also approved by the Review Board of Renmin Hospital of Wuhan University.

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	The sample size was determined based upon similar studies in this field by us and other groups (PMID: 24630721, 34536344, 35166002, 31209361, 38637328, 37291168), as being sufficient for quantification purposes, and upon variability observed in past experiments of similar nature.
Data exclusions	No data were excluded.
Replication	The detailed replication of each experiments has been provided in the Figure Legend, and all attempts at replication were successful yielding similar results.
Randomization	Mice were fully randomized to treatments throughout the study.
Blinding	The investigators were blinded to the animal genotype and grouping information.

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

FNDC4 , OriGene , CF505459, WB (1:500); GAPDH, CST, 2118, WB (1:1000); CD31, Abcam, ab24590, IF (1:100); α-SMA, Abcam, ab5694, IF (1:100); BAX, CST, 2772, WB (1:1000); BCL-2, Abcam, ab196495, WB (1:1000); HIF1α, CST , 36169, WB (1:1000), IF (1:100), IP (1:50); Hydroxy-HIF-1α (Pro564) , CST, 3434, WB (1:1000); Ubiquitin, CST, 3936, WB (1:1000); α-actinin, CST, 69758, IF (1:100)

Validation

All antibodies in this study were used and validated according to the provided data sheets and references for the specific technique (western blot, immunostaining or immunoprecipitation) found directly on the manufacturer's website.

1. FNDC4: https://www.origene.com/search?q=CF505459
2. GAPDH: https://www.cellsignal.cn/products/primary-antibodies/gapdh-14c10-rabbit-mab/2118
3. CD31: https://www.abcam.cn/products/primary-antibodies/cd31-antibody-p2b1-ab24590.html
4. α-SMA: https://www.abcam.cn/products/primary-antibodies/alpha-smooth-muscle-actin-antibody-ab5694.html
5. BAX: https://www.cellsignal.cn/products/primary-antibodies/bax-antibody/2772
6. BCL-2: https://www.abcam.cn/products/primary-antibodies/bcl-2-antibody-ab196495.html
7. HIF1α: https://www.cellsignal.cn/products/primary-antibodies/hif-1a-d1s7w-xp-rabbit-mab/36169
8. Hydroxy-HIF-1α: https://www.cellsignal.cn/products/primary-antibodies/hydroxy-hif-1a-pro564-d43b5-xp-rabbit-mab/3434
9. Ubiquitin: https://www.cellsignal.cn/products/primary-antibodies/ubiquitin-p4d1-mouse-mab/3936
10. α-actinin: https://www.cellsignal.cn/products/primary-antibodies/a-actinin-e7u1o-mouse-mab/69758
11. Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: https://www.thermofisher.cn/cn/zh/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11001
12. Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: https://www.thermofisher.cn/cn/zh/antibody/product/Goat-anti-Rabbit-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11008
13. Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568: https://www.thermofisher.cn/cn/zh/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11004

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Human umbilical vein endothelial cells (HUVECs) were obtained from YRGene (NC006).
Authentication	Before the experiments, all cell lines were verified through short tandem repeat DNA profiling.
Mycoplasma contamination	Mycoplasma contamination was checked, and the test results were negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cells were used in this study.

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/6 mice were bred in a temperature- and humidity-controlled SPF condition under 12/12 h light/dark cycles with free access to food and water as we previously described. Mice were acclimated at least for one week, and then those at 10-12 weeks of age received a single intravenous injection of AAV9-hFNDC4 or AAV9-shFndc4 at a dose of 1 × 1011 viral genome per mouse to specifically overexpress or knock down FNDC4 in the myocardium 4 weeks, and then exposed to cardiac I/R injury.
Vhl floxed (Vhlfl/fl) mice (#004081) were provided by Jackson Laboratories (Bar Harbor, ME, USA), and backcrossed to C57BL/6 strain over ten generations before used. Cardiac-specific VHL knockout (cKO) mice were generated by mating Vhlfl/fl mice with α-myosin heavy chain (Mhc)-MerCreMer transgenic mice (#005657, Jackson Laboratories).

	To isolate neonatal rat cardiomyocytes (NRCMs), 1-3-day-old Sprague-Dawley rats were used as we previously described. These mice were kept in Individually Ventilated Cages with the density of 4-6 mice per cage at the Cardiovascular Research Institute of Wuhan University. All mice were fed with a irradiated chow diet (#1035 for reproductive feeding and #1025 for maintenance feeding, Beijing HFK Bioscience Co., Ltd, Beijing, China), with free access to drinking water.
Wild animals	No wild animals were used in the study.
Reporting on sex	Several studies showed that risk factors and adaptations of ischemic cardiac injury and heart failure in men and women are different. Pre-menopausal women are better protected against ischemic cardiac injury and exhibit better outcome compared with men. Moreover, maladaptive left ventricular remodelling occurs more frequently in men and is associated with greater activation of profibrotic and inflammatory markers. Collectively, we focused more attention on ischemic cardiac injury in male mice. In addition, it has been extensively reported that male mice are more susceptible to develop ischemic cardiac injury than females (PMID: 24630721, 34536344). Neonatal Sprague-Dawley rats with 1-3 days old were used for the isolation of NRCMs regardless of the sex, as it is difficult to distinguish the sex of these neonatal rats
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All animal studies were approved by the Animal Care and Use Committee of Renmin Hospital of Wuhan University, and were performed in strict accordance with the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health. All experimental procedures involving human samples in this study were approved by the Review Board of Renmin Hospital of Wuhan University, and were also in accordance with the Declaration of Helsinki. Written informed consent was obtained from all donors or their legal guardians.

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*