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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

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For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

   Describe how sample size was determined.

   Sample sizes were based on the experience of the authors with RNA-seq and physiological studies as published in many studies.

2. Data exclusions

   Describe any data exclusions.

   Outlier tests were performed to remove outliers: First fit a robust nonlinear regression curve, then analyse residuals of the robust fit to identify outliers similar to FDR approach. (ROUT methods - Graphpad Prism)

3. Replication

   Describe whether the experimental findings were reliably reproduced.

   Findings are repeatedly reproduced throughout the manuscript: RNA-seq with RT-qPCR and public data, Protein levels with ELISA, Western Blot, Colorimetric Assays and immuno staining, cellular assays with primary cells from numerous genotypes, in vitro studies with complementary in vivo studies.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   For in vivo GOF studies, the animal were allocated to experimental groups to ensur e equal litter/sex/age across groups. Randomization was not applicable to LOF animal studies due to genotype-dependent analyses.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   For GOF in vivo studies, treatment was not disclosed to investgators generating qu antitative readouts after treatment . For LOF studies, genotypes were not disclosed to investigators treating the animals, or generating quantitative readouts.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.

The quantification of ACTA2 and EdU positive cells were measured using Harmony software version 3.5.2 (PerkinElmer). The measurement of collagen I and POSTN fluorescence intensity per area were performed with Columbus 2.7.1 (PerkinElmer).
Raw sequencing data (.bcl files) were demultiplexed into FastQ files with Illumina's bcl2fastq (version 1.8.4) based on unique index pairs.
The adaptor sequences and low quality reads/bases were trimmed using Trimmomatic v0.3635 and the read quality was assessed using FastQC v0.11.536.
TopHat (version 2.0.12) was used for mapping the reads to the human genome (GRCh38.78).
Gene level counts were computed by using HTSeq (version 0.6.1) with the same human genome reference used for mapping (Ensembl v78).
Differential expression between the stimulated and non-stimulated samples was computed at the gene level from gene counts using DESeq211 R package (version 1.10.1).
Gene Ontology (GO) functional enrichment of the differential expression results was performed with Gene Set Enrichment Analysis (GSEA) software (version 2.2.2).
removeBatchEffect function from limma R package (version 3.26.9) was used to remove technical batch effects.
Spearman's rank correlation coefficient and the corresponding student p-value was computed between the stimulated/non-stimulated delta of each gene and the delta ACTA2 by using the function corAndPvalue from WGCNA R package (version 1.51).
Single cell seq:
Alignment of reads to the genome and generation of gene counts per cell was performed by Cell Ranger 1.2 software (Genomics 10x). Cells of sufficient complexity were clustered using t-distributed stochastic neighbor embedding (t-SNE) and plots were generated using the Seurat R package.
Immunoblotting and Masson Trichrome image analysis were performed by imageJ software (version 1.48).
Statistical analysis was performed by GraphPad Prism (version 6.07)

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	All materials used in this studies are available to the public from well known vendors.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Antibodies used in this study: p-AKT (4060, CST), AKT (4691, CST), p-EIF4E (9741, CST), EIF4E (2067, CST), p-ERK1/2 (4370, CST), ERK1/2 (4695, CST), GAPDH (2118, CST), IL11 (MAB218, R&D Systems), IgG2A (MAB003, R&D Systems), p-MEK1/2 (9154, CST), MEK1/2 (4694, CST), p-mTOR (2971, CST), mTOR (2972, CST), p-p38MAPK (4511, CST), p38MAPK (8690, CST), p-RSK1 (11989, CST), RSK (9355, CST), p-SMAD2 (5339, CST), SMAD2 (3108, CST), p-STAT3 (4113, CST), STAT3 (4904, CST), ACTA2-Operetta (ab7817, abcam), collagen I (AB292, abcam), periostin (POSTN; AB14041, abcam). anti-Ms Alexa Fluor 488 (ab150113, abcam), anti-Rb Alexa Fluor 488 (ab150077, abcam), Rhodamine Phalloidin (R415, Invitrogen), DAPI (D1306, Invitrogen), ACTA2-Mouse IHC (ab5694, abcam), anti rabbit HRP (7074, CST), anti mouse HRP (7076, CST) ELISA kits: Human IL-11 Quantikine ELISA kit (D1100, R&D Systems), Human IL11RA ELISA kit (LSF8919, Lifespan Biosciences), Total MMP-2 Quantikine ELISA kit (MMP200, R&D Systems), Human TIMP-1 Quantikine ELISA kit (DTM100, R&D Systems). Mouse plasma level of CRP, IFNɣ, TGFB, and TNFα were measured using the following kits: CRP Quantikine ELISA Kit (AB157712, Abcam), Mouse IFNɣ ELISA Kit (AB100689, Abcam), Mouse TNFα ELISA Kit (AB208348, Abcam), Mouse TGFB1 ELISA Kit (AB119557, Abcam). All antibodies and ELISA kits used in this study were validated by the manufacturers.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	only primary cells were used in this study, see methods Page 1
b. Describe the method of cell line authentication used.	N/A
c. Report whether the cell lines were tested for mycoplasma contamination.	N/A
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

Animal models
All animal procedures were approved and conducted in accordance with the SingHealth Institutional Animal Care and Use Committee (IACUC). All mice were on C57BL/6 genetic background and they were bred and housed in the same room and provided food and water ad libitum.
Il11ra (-/-) mice
Mice lacking functional alleles for Il11rα (Il11ra-/-) and their wildtype counterparts Il11ra(+/+) were of 10-12 weeks of age and the weight of animal did not differ significantly. Il11ra(+/+) and Il11ra(-/-) male mice were subcutaneously (SC) implanted with an osmotic minipump (Alzet model 1004, Durect) containing either angiotensin II (AngII, 2mg/kg/day) in saline (0.9%w/v) to stimulate cardiac fibrosis or identical volume of saline. Animals were post-operatively treated with enrofloxacin (15 mg/kg, SC) and buprenorphine (0.1 mg/kg, SC) for three consecutive days. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (180mg/kg) in vehicle (0.3M NaHCO3) to Il11ra(+/+) and Il11ra(-/-) female mice; control mice were administered vehicle alone. Animals were sacrificed 28 days post-implantation and post-injection, respectively. Transaortic constriction (TAC) was performed in Il11ra (+/+) and Il11ra (-/-) male mice as described previously. Post-operative treatment was performed as described above. Age-matched sham animals underwent the same procedure without constriction of the ascending aorta. Trans-thoracic two-dimensional Doppler echocardiography was used to confirm increased pressure gradients (>40 mmHg) indicative of successful TAC. Animals were sacrificed at 2 weeks post-TAC for histological and molecular assessments.
Il11 transgenic (Il11-Tg) model
In this model, the mouse Il11 cDNA was expressed under the control of the ubiquitous cytomegalovirus immediate early enhancer and the chicken β-actin promoter. A loxP-flanked STOP cassette was introduced in between the promoter and the transgene so that overexpression could be conditionally induced by Cre recombinase. The conditional transgene was introduced into the Rosa26 gene locus of ES cells and this transgenic mouse line is referred to here as Rosa26-Il11 mice. To direct transgene expression in fibroblasts, heterozygous Rosa26-Il11 mice were crossed with Col1a2-CreER mice to create double heterozygous Col1a2-CreER:Rosa26-Il11 progenies (referred to here as Il11-Tg mice). Il11-Tg mice were injected with 1mg Tamoxifen (T5648, Sigma) (IP) at 6 weeks of age for 10 consecutive days to induce Cre-mediated recombination. Likewise, wildtype littermates were injected with 1mg Tamoxifen for 10 consecutive days as controls. The animals were euthanized 14 days following cessation of tamoxifen administration.
In vivo IL11 administration model
RmIl11 was reconstituted to a concentration of 50 µg/ml in saline. 10 weeks old male mice and transgenic Col1a1-GFP reporter mice25 were subjected to daily SC injection with either 100 µg/kg of rmIl11 or identical volume of saline for 21 days.
Myocardial infarction model
Wildtype male mice (10-12 weeks) underwent MI surgery as described previously. Age-matched sham controls underwent the same procedure without chronic ligation of the coronary artery. In a subset of MI animals, rmIl11 or an identical volume of PBS were administered daily via SC injection for 6 successive days.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Patients (n=84, age >=21 and <=81) undergoing coronary artery bypass grafting (CABG) at the National Heart Centre Singapore were recruited to the study entitled "The National Heart Centre Singapore prospective CABG cohort: multi-level and integrated analysis of mechanisms underlying atrial dysfunction" that was approved by the SingHealth Centralized Institutional Review Board panel C (CIRB ref: 2013/103/C). Patients with valvular heart disease or previous atrial intervention were excluded. Atrial biopsies (94.6mg ± 59.5mg) were harvested from the right atrium and samples used to outgrow primary atrial fibroblasts. Summary patient data are provided in Extended Data Table 1 and detailed patient data are presented in Supplementary Table 1.