

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	Single cell/nuclei RNA-Sequencing data was demultiplexed and mapped to a reference transcriptome using Cell Ranger 3.0.2. Spatial transcriptomics sequencing data (Visium, 10X Genomics) was demultiplexed and mapped to reference transcriptome (mm10-1.2.0-premrna), using Space Ranger 1.2.2.
Data analysis	Custom analysis scripts were constructed in R using adaptations of the Seurat 4.1 single cell analysis package. Classification, segmentation, and quantification of images (including) mFISH data was performed using custom scripts written in Matlab 2020a and Fiji (RRID: SCR_002285). Flow cytometry data was analyzed using FlowJo (Tree Star). Statistical analyses were performed using GraphPad Prism software 9.4.1. Custom code is publicly available at Zenodo (DOI: 10.5281/zenodo.7055957)

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](#)

Sequencing data has been uploaded to GEO and is under review and awaiting an Accession number.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender

patients are reported individually

Population characteristics

patients are reported individually

Recruitment

Adult patients undergoing heart transplantation or surgical implantation of a ventricular assist device were recruited from the advanced heart failure service at UCSD.

Ethics oversight

University of California San Diego Medical Center Institutional Review Board (#181206)

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

Sample size was limited by the cost of single cell/nuclei sequencing and spatial transcriptomics. Sample size calculations were not performed

Data exclusions

Samples were only excluded if sequencing libraries exhibited low complexity or low cell counts.

Replication

The results of spatial transcriptomic experiments were replicated on at least 3 separate biological samples and at least 2 separate days. In cases where fewer samples are reported, it was due to technical failures due to low transcriptome quality or complexity or low nuclei counts.

Randomization

Randomization was not performed because the study did not test an intervention.

Blinding

Blinding was not performed because the study did not test an intervention.

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

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

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	Mouse experiments were performed with adult C57BL/6J (Jax stock #000664) mice, 10-14 weeks of age. Neonatal rat ventricular myocytes (NRVM's) were isolated from 1-day old Sprague-Dawley hearts.
Wild animals	No wild animals were used in the study.
Reporting on sex	Only male mice were included in this study because they are preferentially known to undergo extreme ventricular remodeling and rupture after MI.
Field-collected samples	N/A
Ethics oversight	All animal experiments were approved by the Subcommittee on Animal Research Care at UC San Diego. No field collected samples were used in the study.

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

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	Single nuclei were isolated from frozen tissue using a modified version of the protocol described (52). Mouse hearts were weighed and minced before flash freezing with liquid nitrogen. Minced samples were resuspended in 0.5 ml nuclei lysis buffer (Millipore Sigma, Nuclei EZ prep, NUC101), 0.2 U/μl RNase inhibitor (stock 40U/μl, Enzymatics Y9240L) and homogenized with a 2 ml dounce grinder for 10 strokes with A motor and at least 20 strokes with B motor (Sigma-Aldrich D8938). The lysates were resuspended with another 1 mL of nuclei lysis buffer and 2.5 minutes of incubation, and were filtered through 100 μm, 50 μm and 20 μm cell strainers (CellTrics filters 04-004-2318, 04-004-2317, 04-0042-2315). Then, they were centrifuged at 1000 x g for 5 min at 4°C to pellet nuclei. As Cui et al., 2020 described, the nuclear pellet was subsequently washed once in 6 mL of Sucrose buffer and centrifuged the cushioned suspension at 1,000 g for 10 min at 4°C to pellet nuclei. The pellet then was washed with 2ml of Nuclei Storage Buffer with 10 μg/ml 4',6-diamidino-2-phenylindole (DAPI) and centrifuged at 1000 x g for 5 min at 4°C (5mg/ml, Invitrogen D1306). 200 μl of nuclei wash buffer (freshly 2% bovine serum albumin (BSA) in 1xPBS, 0.2 U/μl RNase inhibitor and 1mM of EDTA) were added and nuclei were resuspended. Fluorescence-activated cell sorting (FACS) were used to sort extracted nuclei. Nuclei were collected based on the separation between DAPIhigh and DAPIlow (Extended Data fig. 1c); After sorting using purity mode, DAPIhigh nuclei were pelleted at 1000 x g for 15 min at 4°C, resuspended in 2% BSA and trypan blue stained nuclei suspension were quality controlled and counted using hemocytometer (Hausser Scientific 3110V).
Instrument	SONY MA-900
Software	FlowJo (Tree Star)
Cell population abundance	Post-sorted nuclei suspensions were quality controlled and counted using a hemocytometeer (Hausser Scientific 3110V)

Gating strategy

Fluorescence-activated cell sorting (FACS) were used to sort extracted nuclei. Nuclei was collected based on the separation
The gating strategy for nuclei isolation utilized forward scatter and side scatter followed by DAPIhigh vs DAPIlow discrimination - illustrated in Extended Data fig. 1c.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.