nature research

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Last updated by author(s): Mar 24, 2022

Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	Software used include: Sony FACS software (Version 2.1.5),Vevo 3100 (Version 5.5.1.) NIS-Elements AR 5.11.03, Bio-Rad CFX96 Real Time System (Bio-Rad), Chromium Controller Firmware version XYZ, NanoZoomer HT (Hamamatsu Photonics, Hamamatsu, Japan), Graphpad (Version 8.4.3), FlowJo (10.6.1.), Adobe Photoshop (21.2.4.), Adobe Illustrator (24.3), ImageJ (1.53)
Data analysis	All software/scripts used in data analysis is described here: https://github.com/saezlab/visium_heart. Software used include: python (v3.7.8), R (v4.0.2, v4.1.0), CellRanger software (v6.0.2), CellRanger ATAC pipeline (v2.2.0), SpaceRanger software (v1.3.2), Seurat (v4.0.1), scDblFinder (v1.4.0), edgeR (v3.32.1), scanpy's (v1.7.0), ArchR (v1.0.1), MACS2 (v2.2.7), HINT-ATAC (v0.13.2), decoupleR (v1.1.0), Plink (v1.9), gchromVAR (v0.3.2), chromVAR (v1.16), cell2location (v0.05), PROGENy (v1.12.0), SPARKX (v1.1.1), mistyR (v1.2.1), scran (v1.18.5), Mesmer (v0.3.0), RS-FISH (v2.3.1)

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The data is made available through the Human Cell Atlas (HCA) Data Coordination Platform (DCP) and can be accessed here: https://data.humancellatlas.org/explore/projects/e9f36305-d857-44a3-93f0-df4e6007dc97 . Additionally, the data can be explored through the interactive data explorer cellxgene (cziscienceee) here: https://cellxgene.cziscience.com/collections/8191c283-0816-424b-9b61-c3e1d6258a77/private.

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	For an overview on sample please see supplementary table 1. No statistical methods were used to predetermine sample size. The patients were selected to give an equal representation of cells from healthy and myocardial infarction tissue from different zones. RT-qPCR and histological analysis were performed on multiple independent replicates with a minimum of 3 (n=shown in the figure and described in legends).
Data exclusions	For full details see description in Methods. For snRNA-Seq experiments, low-quality droplets were excluded based on standard, pre-established approaches: (1) transcript count, (2) doublet score, (3) mitochondrial transcript content and (4) gene recovery. For spatial transcriptomics experiments, spots were excluded based on their (1) transcript count and (2) gene recovery. For snATAC-Seq experiments, low-quality droplets were excluded based on : (1) number of unique fragments; (2) transcription start site (TSS) enrichment.
Replication	The reported findings were replicated across multiple biological samples (n reported in each figure or Methods). Immunofluorescenct imaging was performed on 3 heart samples minimum.
Randomization	Randomisation was not relevant due to the study design where human control and acute myocardial infarction tissues were used on availability.
Blinding	Blinding of the tissue was not possible. All analyses were performed in an automated manner across conditions.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

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

Antibodies

Antibodies used	Antibody, Company, Catalog number, Clone, Dilution: anti-ACTA2(aSMA)-Cy3 (Sigma-Aldrich, C6198, 1:250) anti-SEMA3G (Sigma Aldrich, HPA001761, 1:100) anti-PDGFRb, R&D, MAB1263, PR7212, BQF0715061, 1:100 AF647 anti-rabbit Jackson ImmunoResearch, 711-605-152, 1:200 anti-mouse IgG1-MicroBeads solution, Miltinyi, 130-047-102
Validation	All antibodies used in this study are commercially available. They are validated by the vendors for the specific assay and species used. The validation is available on the vendors website. Primary antibodies for immunostaining were validated by performing comparisons to species-matched isotype antibodies and unstained controls. For the primary flow antibodies the specificity was validated by staining directly against species-matched isotype and unstained controls.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The immortalized human PDGFRb+ heart cell line from heart failure patients was generated as described in the methods.
Authentication	None of the cell lines used were authenticated.
Mycoplasma contamination	Mycoplasma tests showed no evidende of contamination by PCR.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	This study involved trangenic mice (Mus musculus). Used strains were PDGFRßCreERt2 (i.e. B6-Cg-Gt(Pdgfrß-cre/ERT2)6096Rha/J, JAX Stock #029684), Rosa26tdTomato (i.e. B6-Cg-Gt(ROSA)26Sorttm(CAG-tdTomato)Hze/J JAX Stock # 007909). PDGFRbCreER;tdTomato mice were males and females with an age of 8 weeks. Mice were housed two to five animals per cage with a 12-h light–dark cycle (lights on from 0700 to 1900 h) at sustained temperature (20 °C±0.5°C) and humidity (~50%±10%) with ad libitum access to food and water.
Wild animals	This study did not involve any wild animals.
Field-collected samples	This study did not involve any samples collected from the field.
Ethics oversight	LANUV (Landesamt für Natur, Umwelt und Verbraucherschutz) North Rhine-Westphalia (Germany) approved the study protocol with reference No. 81-02.04.2017.A410.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Please see Extended Data table 1 for the clinical characteristics of the patients used in this study for snRNA, snATAC and spatial transcriptomics. Extended Data table 5 described cohort of patients used for in-situ studies. Ethnicity was caucasian.
Recruitment	Patients were recruited as described in the Methods. All tissue samples used for this study were obtained with written informed consent from all patients in accordance with the guidelines of The Declaration of Helsinki 2000.
Ethics oversight	The local ethics committee of the Ruhr University Bochum in Bad Oeynhausen, the RWTH Aachen University, Utrecht University and WUSTL approved all human tissue protocols (No. 220-640, EK151/09, 12/387, No. 201104172 respectively).

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	n/a
Data collection	n/a
Outcomes	n/a

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	FACS protocol and flow cytometry and detailed sample preparation are described in the Methods.
Instrument	SH800 Sorter (SONY)
Software	SONY Sorter software.
Cell population abundance	Post-Sort purity was confirmed over 95%.
Gating strategy	Please see Methods and Fig. 1b. for gating on DAPI+ nuclei.

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