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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

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.

For single cell RNA-seq, the Fluidigm C1 system has a maximum capturing capacity of 96 cells per plate. Depending on the capture efficiency in that plate, we generally had 60-90 healthy single cells per plate. For bulk RNA-seq, sample size were two (biological replicates). For cell culture experiments such as immunostaining, flow cytometry, and qRT-PCR, sample size were usually three. For imaging analysis, 10 - 40 fields were counted.

2. Data exclusions

Describe any data exclusions.

Multimers and empty capture sites on the C1 plate were excluded for downstream cDNA library construction. After gene counting, each cells' % reads mapped to spikein and % reads mapped to mouse mRNA were plotted and outliers are removed. After Combat normalization, the last few outliers were removed using the default "outlier removal" function in the SinGuLAR analysis package from Fluidigm, which was based on median gene expression level in each cell.

3. Replication

Describe whether the experimental findings were reliably reproduced.

The number of replication plates for scRNA-seq were: five plates for M+G+T-transduced cells (three full plates and two half plates), four plates for DsRed retroviral transduction control cells (four half plates), and two half plates for untransduced control cells. Experimental findings from the scRNA-seq data were reproducible. All other cell culture experiments were also repeated for usually three or more times. Conclusions were only made when results were consistent among replicate experiments.

4. Randomization

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

For scRNA-seq data, we intentionally mixed differently-treated samples in the sample plate (plate M4, M5, C1, and C2) for the purpose of randomization. For most cell culture experiments, at least one other postdoc repeated the experiment and verified the results. For important findings such as the role of Ptbp1 knocking-down on iCM reprogramming, all four participating postdocs have repeated the experiment and confirmed the finding.

5. Blinding

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

Blinding was widely used in the study. Data collection and analysis, such as immunostaining, image counting, RNA extraction, and qRT-PCR, were frequently performed by participants other than the experiment designer. During these data collection and analysis steps, the participants were routinely blinded to group allocation.

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.	fastqc/0.11.4, tophat/2.1.0, samtools/0.1.19, bedtools/2.24.0, bamtools/1.0.2, bowtie2/2.2.6, pico/5.04, htseq-count/0.6.1p1, Combat, R, DESeq, DESeq2, SINGuLAR/3.5.2, Rtsne, prcomp, SLICER, LLE, rMATS/3.2.5, rMAPS/1.0.5, VGAM, FlowJo 7.6.1, Prism5

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.	No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	rabbit anti-GFP (Invitrogen, A11122, 1:500), chicken anti-GFP (Abcam, ab13970, 1:1500), anti-αSMA (Sigma, A2547, 1:200), anti-SM22α (Abcam, ab14106, 1:200), anti-αActinin (Sigma, A7811, 1:500), anti-Cx43 (Sigma, C6219, 1:200), APC-Thy1.2 (ebioscience, 17-0902-81, 1:100), APC-Cd200 (Biolegend, 123809, 1:200), cy3-αSMA (Sigma, C6198, 1:500), APC-Thy1.1 (ebioscience, 17-0900-82, 1:100), PE-CD31 (Biolegend, 102408, 1:200), and anti-Ptbp1 (Cell Signaling 8776, 1:500).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	platE cells (Cell Biolabs), 293T cells (ATCC)
b. Describe the method of cell line authentication used.	Virus packaging and transgene expression were successful.
c. Report whether the cell lines were tested for mycoplasma contamination.	All cell lines were tested negative for mycoplasma contamination.
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.	No commonly misidentified cell lines were used.

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.	Transgenic mice of CD1 background that contain αMHC promoter driven-GFP were used. Breeders of 2-6 months old were set up and P1.5 pups were collected for cardiac fibroblast or tail-tip fibroblast cell isolation. Mouse embryonic fibroblasts were isolated from E13.5 embryos.

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.	This study does not involve human research participants.