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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.

All sample sizes were determined on the basis of previously established literature standards. Results from initial experiments were used to inform the need for subsequent samples on the basis of the effect sizes observed.

2. Data exclusions

Describe any data exclusions.

No data were excluded.

3. Replication

Describe whether the experimental findings were reliably reproduced.

No replication attempts were unsuccessful.

4. Randomization

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

In animal studies, animals were randomly allocated into groups such that as animals were added to the experiment, the numbers of animals in each group did not significantly differ. Exosome miRNA samples were randomized prior to sequencing. Samples in all other experiments were randomly allocated when possible.

5. Blinding

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

In animal studies, the surgeon was blinded to the contents of the applied patch. In subsequent analysis of echocardiography, histology and arrhythmia, the investigators were blinded to the animal group.

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.	General data were analysed using Microsoft Excel (2016) and MATLAB(R2015a). Custom code was used to measure cardiomyocyte contractility as well as endothelial networks. miRNA sequence data were analysed using Python(3.6), miRSearch(3.0), and PANTHER(11.1).

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).	Antibodies were used at the following concentrations: anti-TSG101 rabbit polyclonal antibody (1:1,000, abcam, Cambridge, UK), anti-Alix polyclonal antibody (1:8,000, Covalab, Villeurbanne, France), anti-GM130 mouse monoclonal antibody (1:500, BD Transduction Laboratories, Franklin Lakes, NJ), anti-Rab5 mouse monoclonal antibody (1:1,000, Synaptic Systems, Goettingen, Germany), polyclonal rabbit anti-active caspase 3 (1:40, Abcam, Cambridge, MA), monoclonal mouse anti-cardiac troponin T (4 µg/mL, Developmental Studies Hybridoma Bank, Iowa City, IA, Alexa Fluor 488 goat anti-mouse IgG (1:500, ThermoFisher Scientific, Waltham, MA), Alexa Fluor 488 goat anti-rabbit IgG (1:500, ThermoFisher Scientific, Waltham, MA), Alexa Fluor 594 goat anti-mouse IgG (1:500, ThermoFisher Scientific, Waltham, MA). TUNEL staining was conducted with the in situ cell death detection kit (Sigma-Aldrich, St. Louis, MO). Cells and sections were counterstained with DAPI (ThermoFisher Scientific, Waltham, MA) or Alexa Fluor 594 conjugated Wheat Germ Agglutinin (ThermoFisher Scientific, Waltham, MA) per manufacturer protocol. Sections were mounted using ProLong Gold Antifade Mountant with DAPI (ThermoFisher Scientific, Waltham, MA).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	Human iPS cell line C2A was provided through a collaboration with Stephen A. Duncan.
b. Describe the method of cell line authentication used.	The C2A cell line has been extensively characterized in a previously published article: Si-Tayeb et al., Hepatology, 2010
c. Report whether the cell lines were tested for mycoplasma contamination.	Cell lines were tested for mycoplasma contamination regularly.
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.	Male athymic nude (Hsd:RH-Foxn1rnu) Sprague Dawley Rats (Harlan, Indianapolis, IN) age 15-19 weeks were used in this study.

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.	The study did not involve human research participants.