Response to specific comments by the Editor

We thank Editors for providing us with extensive comments. We have revised the manuscript according to the editor's comments. Please note that sentences highlighted in yellow are the comments made by Editors. The revised descriptions from the manuscript are marked using red fonts.

Editor's comments

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response:

Thank you for the comments. I searched the literature using RCA database according to the editor's suggestion and found the following additional articles that demonstrate the clinical prevalence of *PKP2* variants in arrhythmogenic cardiomyopathy patients. I added these articles as references. The other listed latest articles were referenced in the original manuscript.

Page 8

Previous:

Among the desmosomal genes, mutations in *PKP2* are most frequently identified in patients with AC[11,37]

↓

Corrected:

Among the desmosomal genes, mutations in *PKP2* are most frequently identified in patients with AC[11,37-39]

38 Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. Circ Cardiovasc Genet 2015; 8: 437-446 [PMID: 25820315 DOI: 10.1161/CIRCGENETICS.114.001003]

39 Pleiotropic Phenotypes Associated With PKP2 Variants. Front Cardiovasc Med 2018; 5: 184 [PMID: 30619891 DOI: 10.3389/fcvm.2018.00184]

Uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response:
Thank you for the comments. I prepare the figures in PowerPoint file.

LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Response:
I submitted the revised manuscript again to English language editing and obtained an Editing Certificate.

Response to specific comments by Reviewer #1

We thank Reviewer#1 for providing us with extensive comments. Please note that sentences highlighted in yellow are the comments made by Reviewer #1. The revised descriptions from the manuscript are marked using red fonts.

Reviewers' Comments:

Reviewer #1:
This manuscript reviewed the recent advances in disease modeling of desmosome-related cardiomyopathy caused by gene mutations using induced pluripotent stem cell-derived cardiomyocytes. And the authors try to establish a human disease model that recapitulates reduced contractility and impaired desmosome assembly and provided a convenient cellular platform for therapeutic screening to examine upstream molecular targets of desmosome-related cardiomyopathy. However, desmosome protein is a kind of myocardial structure protein, although the experiments achieved gene repair at the cellular level, and promote cardiac cell function recovery, but compared with myocardial secretory proteins, in vivo experiment, myocardial structural protein modification is difficult to reach effective structural and functional recovery. Whether the author can do further elaboration on this issue.

Response:

Thank you for the comments. I agree with the reviewer's comments that myocardial structural protein modification is difficult to reach effective structural and functional recovery in *in vivo* experiment and that the experimental studied using *in vivo* models are required for clinical application. We added the following description.

Page 13

Previous:

No effective therapies are available for these patients who require a novel therapeutic approach for desmosome-related cardiomyopathy.

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Corrected:

No effective therapies are available for these patients who require a novel therapeutic approach for desmosome-related cardiomyopathy. Proof-of-concept studies for structural and functional recovery using both human iPSC-CM models and *in vivo* models are required for future clinical application.

Response to specific comments by Reviewer #2

We thank Reviewer #2 for providing us with extensive comments. We have revised the manuscript as per the comments. Please note that sentences highlighted in yellow are the comments made by Reviewer #2. The revised descriptions from the manuscript are marked using red fonts.

Reviewers' Comments:

Reviewer #2:

Authors wrote a revision focused on iPSc models for desmosome-related cardiomyopathies. Some points should be clarified:

1.- please could clarify if manuscript is focused on ARVD, ARVC or ACM, or all them.

Response:

Thank you for the comments. The terms ARVD and ARVC are still used in the clinical guidelines (*Circ J 2021; 85: 1590-1689, PMID: 34305070 DOI: 10.1253/circj.CJ-20-0910*). However, recent clinical studies have reported left ventricular or biventricular involvement in patients with ARVC, and the use of a broad phrase (Arrhythmogenic Cardiomyopathy (AC)) is recommended. Therefore, I would like to focus on the term "Arrhythmogenic Cardiomyopathy (ACM)" that include both ARVC and ALVC. Please refer to the following description.

Page 6

However, recent studies have reported left ventricular or biventricular involvement in patients with ARVC, resulting in the use of a broad phrase (arrhythmogenic cardiomyopathy (AC))[9,11].

2.- authors focused manuscript on PKP2, main desmosomal gene associated with ACM. What about other desmosomal genes related to ACM (at least DSG2, DSP, and DSC2).

Response:

Thank you for the comments. We carefully searched the previous literatures and added the description and references of the experimental studies using iPSC-CMs generated from the patients with *DSG2*, *DSP*, and *DSC2* variants.

Page 8

Previous:

Among the desmosomal genes, mutations in *PKP2* are most frequently identified in patients with AC[11,37]

↓

Corrected:

Among the desmosomal genes, mutations in *PKP2* are most frequently identified in patients with AC[11,37-39], and have been extensively studied using patient-derived iPSC-CMs compared to other desmosomal genes (DSG2[30,40,41], DSP[42,43], and DSC2[44,45]).

30 Hum Mol Genet 2021 [PMID: 33949662 DOI: 10.1093/hmg/ddab127]

40 Europace 2018; 20: f46-f56 [PMID: 29566126 DOI: 10.1093/europace/euy042]

41 J Clin Med 2020; 9 [PMID: 32050722 DOI: 10.3390/jcm9020486]

42 JCI Insight 2019; 5 [PMID: 31194698 DOI: 10.1172/jci.insight.128643]

43 Stem Cell Res 2020; 48: 101977 [PMID: 32942234 DOI: 10.1016/j.scr.2020.101977]

44 Clin Transl Med 2021; 11: e319 [PMID: 33784018 DOI: 10.1002/ctm2.319]

45 Clin Transl Med 2022; 12: e748 [PMID: 35297182 DOI: 10.1002/ctm2.748]

3.- Please include data or opinion about potential clinical translation of advances achieved using these models.

Response:

Thank you for the suggestive comments. Experimental study using PKP2-deficient isogenic iPSCs demonstrate the proof-of-concept for *PKP2* replacement therapy in human cells and suggest that the isogenic set of the iPSCs is the useful model for providing distinct readouts for therapeutic development. These descriptions were added at the following section.

Page 12

Previous:

Furthermore, time-lapse imaging using NHEJ-iPSC-CMs captured the recovery of desmosomes, which gradually assembled at the cell periphery after AAV-mediated *PKP2* replacement (Figure 2).

↓

Corrected:

Furthermore, time-lapse imaging using NHEJ-iPSC-CMs captured the recovery of desmosomes,

which gradually assembled at the cell periphery after AAV-mediated *PKP2* replacement (Figure 2). The established isogenic iPSCs harboring knocked-in tdTomato alleles allowed desmosome-imaging in living cells and provided distinct readouts for therapeutic development.