

Nov 16, 2020

Dear Na Ma and reviewers,

Thank you very much for considering and reviewing our manuscript entitled "Pancreatic β cell regeneration induced by clinical and preclinical agents" with manuscript number 57914. We have carefully evaluated the reviewers' comments and thoughtful suggestions and made the following amendments as you requested. We hope that the amendments will be helpful for the acceptance for publication of the revised manuscript.

Here are our point-by-point answers.

To reviewer 1:

Q1: In this review, Wang et al. summarizes the clinical and preclinical agents used in different approaches for β cell regeneration and highlighted the challenges and future perspectives. There are some major points need to be addressed: 1) The authors should differentiate between beta cell regeneration in T1D and T2D. Therefore, it is better to have two new sections focusing on "beta cell regeneration in T1D" and "beta cell regeneration in T2D".

A1: Thank you very much for your kind advice. Both in T1D and T2D, beta cell regeneration could be achieved with the similar mechanism: correction of metabolic disorder and inhibition of apoptosis, inhibition of β cell dedifferentiation, stimulation of β cell proliferation, promotion of stem cell differentiation, induction of cell transdifferentiation and transdetermination. In this article, we focus on the regeneration mechanism and related agents. We would like to keep the current structure. Your suggestion is wonderful; maybe your suggested structure can be used in our next paper.

Q2: In the "PROMOTION OF STEM CELL DIFFERENTIATION" section, the authors only cited old protocol for beta cell differentiation, which produce non-functional beta cells (D'Amour et al. 2006). However, there are several recent protocols published in 2019 and 2020. The new protocols generate functional beta cells.

A2: We cited the old protocol because it is a classical protocol in which stem cells can be induced into beta cells by mimicking embryonic development. At present, most differentiation protocols were based on the step-wise protocol, and even the most recent review cited the protocol [*Nat Rev Endocrinol*, 2020, 16(9):506-518.].

Of course, your opinion is totally right. In 2014, functional beta cells could be obtained [*Cell*. 2014;159:428-439.][*Nat Biotechnol*. 2014;32:1121-1133.]. They are

the landmark protocols. Besides, as you suggested, we added the recently published articles in the revised version [*Nat Biotechnol*, 2020, 38(4):460-470.] [*Stem Cell Reports*. 2019;12:351-365.]. Thank you very much.

Q3: The authors neglected the progenitors derived from hPSCs, which are currently in clinical trials to treat T1D patients. Also, it has been recently reported generation of hPSC-derived pancreatic progenitors lacking PDX1 and have mesenchymal phenotypes. They should add this article and comment on it (Memon et al. 2020; PMID: 32857429).

A3: We totally agree with you. The progenitors derived from hPSCs are important cell source for beta cell replacement. We added the article as you suggested. Thank you.

Q4: The authors should add a Table with citations to summarize the types pancreatic progenitors that can generate beta cells in vivo or in vitro (ductal, acinar, hPSCs,...etc).

A4: Thanks for your useful advice. We added Table 1 in the revised version, as you suggested.

Q5: Another table to summarize the factors that are used in the clinical or the pre-clinical studies should be provided.

A6: Thanks for your constructive advice. We added Table 1 in the revised version, as you suggested.

Q6: The manuscript needs a grammar correction.

A6: Thanks for your advice. We used Willy language editing service to ensure a native-English speaker edit the manuscript.

To reviewer 2:

The paper submitted by Wei et al., is very well written, clear and easy to understand. The manuscript can be accepted with minor revisions. The authors need to incorporate a table for molecules/ clinical agents that are reported in this manuscript.

A: Thanks for your high evaluations to our manuscript, and thanks for your constructive advice. We added Table 1 in the revised version, as you suggested.

To editorial office

Q1: Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

A1: We used Willy language editing service to ensure the language quality. Thank you.

Q2: Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

A2: We have uploaded the grant approval documents and the original picture documents. Thank you very much.

We believe that the revisions have improved the manuscript significantly according to reviewer's kind suggestions and editor's advice. Many thanks to all the editors and reviewers for the time and efforts devoted to our manuscript. We are looking forward to your final decision.

Yours sincerely,

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