Dear Professor,

Re: Resubmission of manuscript reference no. 61279

Thank you very much for your letter and the reviewer's assessment. These comments are very valuable and provided us with guidance to improve our work. Based on your comments and requests, we have made extensive modifications to the original manuscript. A document answering every question from the reviewer and editors is also summarized and enclosed. All the modified parts have been marked blue in the manuscript, which has uploaded to the system as required.

Should you have any questions, please contact us without hesitation.

Responds to the reviewer's comments:

Reviewer 1

Comment 1: Some English revision would be beneficial.

Response: Thank you for pointing out this issue. Our revised article has been professionally edited again by a native English speaker for grammar. In accordance with the requirements of language quality, we have once again contracted a language editing service for the revised manuscript and have attached the language editing certificate.

Comment 2: Briefly explain in the abstract background why the VEGF pathway (specifically VEGF-B) is important in the context of beta-cell function.

Response: Thank you for pointing out the question about the importance of VEGF-B. A paragraph has been added to the background section of the abstract to briefly explain the importance of VEGF-B in the context of β-cell function. The supplementary text is as follows:

The level of vascular endothelial growth factor B (VEGF-B) is significantly increased in T2D patients. The inactivation of VEGF-B could restore insulin

sensitivity in db/db mice by reducing fatty acid (FA) accumulation. It is speculated that VEGF-B is related to pancreatic β-cell dysfunction and is an important factor affecting β-cell secretion of insulin.

Comment 3: In the abstract/introduction it would be maybe worth mentioning the pro-proliferative effect that VEGF-B had on these cells.

Response: Thank you for the valuable recommendation. The proliferative effect of VEGF-B on cells has been supplemented in the introduction of the manuscript. The supplementary text is as follows:
Compared with VEGF-A, VEGF-B does not regulate the growth of blood vessels but can regulate the uptake of endothelial FAs and promote the survival of cardiomyocytes, retinal neurons and other cells, showing a proliferative effect on cells.

Comment 4: It would be important to verify the specificity of VEGF-B signaling in promoting the observed effects by selective KD of VEGFR1 versus VEGFR2, for example. Also, it could be interesting to see whether stimulation with VEGF-A might have, or have not, similar activity.

Response: Thank you for this valuable recommendation. This opinion is very valuable and points out a future direction for our follow-up studies. VEGF-A and VEGF-B belong to the same VEGF family, and studies have shown that they both can bind to VEGFR1; furthermore, VEGF-A can also bind to VEGFR2. In 2016, studies by Marius R. Robciuc et al. revealed that VEGF-B can compete with VEGF-A to bind VEGFR1, thus promoting the combination of VEGF-A and VEGFR2 to further induce angiogenesis in fat tissues.
We detected changes in VEGFR1 expression and found that VEGF-B binding to VEGFR1 affected insulin secretion in MIN6 cells. This part of the results has been presented in the manuscript.

Thank you again to the reviewer for these suggestions, which have provided us ideas for our follow-up research. We will continue to investigate the effect of VEGF-A stimulation on insulin secretion in MIN6 cells and detect the phosphorylation and expression levels of VEGFR1 and VEGFR2. At the same time, we will further explore the relationship and mechanism of VEGF-A and VEGF-B in insulin secretion in MIN6 cells.

Comment 5: The authors should check the phosphorylation status of VEGFR1, along with the expression levels.

Response: We deeply appreciate the reviewer's suggestion. The phosphorylation status and expression level of VEGFR1 are very important factors that we will explore in future experiments. In the manuscript, we reported changes in VEGFR1 expression. In the next experiment, we will monitor the level of phosphorylated VEGFR1 and the phosphorylation state and expression level of VEGFR2.
Thank you very much for the comments, which provided great help for the further improving our manuscript and framing future directions.

Comment 6: It would be better to use non-saturated WB images to appreciate the differences between samples and control (e.g. Fig 2A and Fig 3D).

Response: Thank you for reminding us about the presentation of WB images. Nonsaturated WB images were used to better highlight the differences between the treated samples and the control.

Comment 7: In all figures, authors should indicate p value significance by asterisk above the graph bars (in comparison to the control) instead of letters. In the figure legend, they should also mention what statistical test was used.

Response: Thank you for the detailed recommendation. In all the figures, we have indicated the significance of p value by asterisks above the graph bars (in comparison to the control). In the figure legends, we have supplemented the statistical tests used.

Comment 8: In figure 1 it is not clear that 5.5 and 25 mmol/L refer to glucose treatment.

Response: Thank you for the detailed recommendation. In Figures 1 and 4, we have added the word “glucose” after the 5.5 and 25 mmol/L values to indicate glucose treatment.

Responds to editorial office’s comments:

1. Academic norms and rules:

We have provided the ARRIVE Guidelines with page number, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. The Institutional Animal Care and Use Committee Approval Form or Document has been changed to Chinese format, and we have uploaded the Chinese version of the MIN6 cell manual.

2. Issues raised:

(1) The “Author Contributions” section has been provided.

(2) Approved grant application forms or funding agency copies have been provided.

(3) Documents containing the original images and PowerPoint files have been provided and uploaded to the system as required.

(4) The “Article Highlights” section has been added at the end of the main text.

We thank the reviewer and editors for their insightful and constructive

analyses of this work. In this revised manuscript, we believe we have addressed all the concerns thoroughly and hope that the revisions in the updated manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in the World Journal of Diabetes.