

## Responses to Reviewer's Comments

We thank the reviewers for their constructive comments, which we feel have helped to improve our manuscript. All comments concerning the manuscript were taken into consideration. Below are our point-by-point responses to the reviewer's comments and of the changes that we made in the manuscript. All changes are marked in red color throughout the manuscript.

### **Reviewer #1:**

***Q1. The manuscript needs careful editing by an English-native speaker paying particular attention to English grammar, spelling, and sentence structure. For instance, the following sentences need modifications: "Previous studies showed alterations in the gene expression profile between the individuals with family history of T2D and those without family history of the disease" and "STUDYING THE MECHANISMS UNDERLYING THE DEVELOPMENT OF INSULIN RESISTANCE".***

Following the reviewer's comment, we have corrected the grammatical errors and the spelling throughout the manuscript, including the two sentences mentioned in the reviewer's comment.

***Q2. In the Introduction section, the description of iPSC was insufficient and should be supplemented.***

We have added some sentences in the 2<sup>nd</sup> paragraph of the "Introduction" (marked in red).

***Q3. Although the logic of this manuscript is clear and unobstructed, the content was a bit broad and the focus was not prominent enough. The iPSC section should be highlighted.***

Following the reviewer's suggestion, we have added more details about the iPSCs models used to study insulin resistance under the section titled "USING INDUCED PLURIPOTENT STEM CELLS (iPSCs) TO STUDY INSULIN RESISTANCE". Also, we have added a new table to summarize all the human iPSC models used to study IR (Table 1).

### **Reviewer #2:**

***Q1. Some typos and acronyms should be corrected thorough the text.***

Following the reviewer's comments, we have corrected the typos and acronyms throughout the manuscript.

**Q2. Please add a sentence in the abstract about iPSC.**

Following the reviewer's comment, we have added a sentence in the "Abstract" about iPSCs as follows:

*"Human induced PSCs (hiPSCs) can be generated from the somatic cells of the patients without the need to destroy a human embryo. Therefore, patient-specific hiPSCs can generate cells genetically identical to IR individuals, which can help in distinguishing between genetic and acquired defects in insulin sensitivity".*

**Q2. Moreover the authors overview the use of iPSC technology to understand and treatment of IR and explain the challenges and limitations of using the human iPSC-based model. In this view, will be useful for the readers to add a representative table of the recent literature findings on this topic.**

Following the reviewer's suggestion, we have added a table (Table 1) to summarize all the human iPSC models used to study the insulin resistance.

**Reviewer #3:**

**Q1. There is a conflict of using abbreviations in the figure legends, the authors should make a difference between insulin receptor (INRS)/ insulin receptor (INS) and insulin resistance (IR) abbreviations.**

Following the reviewer's comment, we have corrected the abbreviations in the Figure legends and throughout the manuscript. INSR refers to insulin receptor and IR refers to insulin resistance (IR).

**Q2. In writing, I prefer for the authors to focus on hiPSCs not on hPSCs (ethical problems) as this make some sort of confusion.**

In this review we summarize all the available options of human pluripotent stem cells (hPSCs), which include human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs). The commercially available hESC lines can be used to understand insulin

resistance without any ethical concerns. For examples, the genes involved in insulin resistance can be overexpressed, silenced or knocked out in hESCs without the need to generate patient-specific iPSCs. In this review, we described all the iPSC models that have been used to study insulin resistance and summarized them in [Table 1](#).

***Q3. What was written in the figure legends should be deleted from the text as example downstream signaling pathways of figure 1.***

Following the reviewer's comment, we have deleted the duplicated details from the text.

### **EDITORIAL OFFICE'S COMMENTS**

***(1) Science editor: 1 Scientific quality: The manuscript describes a minireview of the modeling of insulin resistance using iPSCs. The topic is within the scope of the WJSC. (1) Classification: Grade B, Grade B and Grade C; (2) Summary of the Peer-Review Report: The manuscript described the mechanisms of IR and the advantages and limitations of iPSC as an in-vitro model for study of IR. Some typos and acronyms should be corrected thorough the text. Please add a sentence in the abstract about iPSC. Moreover, the authors overview the use of iPSC technology to understand and treatment of IR and explain the challenges and limitations of using the human iPSC-based model. The questions raised by the reviewers should be answered; and (3) Format: There are 3 figures. A total of 89 references are cited, including 10 references published in the last 3 years. There are 5 self-citations. 2 Language evaluation: Classification: Grade B, Grade B and Grade B. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Qatar National Research Fund. The topic has not previously been published in the WJSC. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found 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); (2) I found the authors did not provide the original figures. 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; and (3) There are 5 self-citations. The manuscript could only have 3 self-citations according to the editorial policy of BPG. Please check and revise. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.***

We have responded to the most of the editor's comments in our response to the three reviewers. Furthermore, we did the followings in response to the editor's comments:

- We deleted two from our references and now we have only three references from our work.
- We provide the original Figures with high quality. We do not have ppt figures, because they were prepared on photoshop.
- We corrected some typos and acronyms thorough the text.
- We provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.