Peer Review File
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Answers to Reviewer A

Comment 1: Lines 155 - 159: "In this review, we integrate the knowledge of both well-established and recent discoveries using genetically modified organisms and in vitro models elucidating how miRNAs affect islet function in the context of insulin resistance and T2D (and also, to a lesser extent, T1D) with a focus on functional roles in beta-cell proliferation, differentiation, apoptosis, insulin biosynthesis and secretion (Figure 1)." The authors should explain how similar or different islet functions are among different species, especially compared to humans.

We thank the reviewer for his comments. Following his advice, we have added a paragraph in the conclusion section mentioning the limitations of working with rodent models given the species specific differences in the macro/microarchitecture of the pancreas in the cellular transcriptome and function. We have added several references that elaborate and provide critical information on this subject.

Comment 2: The organisms or species of target studies must be clearly written. For example, Lines 194 - 196: "On the other hand, the knockout of miR-223 shows impaired beta-cell proliferation and insulin secretion in vitro and glucose intolerance, but interestingly also insulin resistance in vivo." Also, Figure 1.

Following the reviewer's advice, we have added the organism of study whenever appropriate.

Comment 3: Although figures are well designed, the authors should provide tables listing miRNAs, model organisms used, phenotypes, and mechanisms of actions for each miRNA as it is difficult to follow the storyline with so many miRNAs being listed.

Following Reviewers' suggestion, we have added a table summarizing the list of different miRNAs, their described mechanism(s) of action and the overall metabolic phenotype whenever possible. Figure 1 has been removed to avoid redundancy to this new table (now Table 1) and following Reviewer C's comments.

Answers to Reviewer B

Comment 1: Add more detail in Abstract.
Following the Reviewer's suggestion and the Editor's guidance, we rewrote the abstract.

Comment 2: The address for the first author (Du RQ) is not clear.
The affiliation and address of the first author have been added accordingly.

Comment 3: Cite recent publications in related miRNAs, such as miR-21 (Nat Commun. 2022), miR-30d (Sci Rep. 2022), miR-125b (Diabetes. 2022).

We thank the reviewer for providing these three recently published manuscripts. We have added them to the respective relevant sections.

Comment 4: Include miR-409-3p in T1D section (Diabetologia. 2020)?

We thank the reviewer for providing this manuscript. We have added it to the T1D section.

Comment 5: Write streptozotocin (STZ) in the first place (pg 10). Change streptozotocin (pg 20) to STZ.
We have made changes in the text according to the reviewers' comments.

Comment 6: n Fig.1, any difference between bold and regular font miRNA names? The text size in Fig. 3 is too small?
Following Reviewer C comments, we have removed Figure 1 and substituted it with a table to make the information provided more comprehensive.

Answers to Reviewer C

Comment 1: title could be more precise:

"The potential impact of microRNAs on beta-cell homeostasis and function – a narrative review"

Following the Reviewers advice and editorial comments, we now have changed the title to **miRNAs PROVIDE MECHANISMS FOR INTEGRATED CONTROL OF ENDOCRINE PANCREAS HOMEOSTASIS AND METABOLIC DISEASE PATHOGENESIS: A NARRATIVE REVIEW.**

Comment 2: Section 8

microRNAs regulate glucagon

I suggest to skip this paragraph, which is not the focus of the review.

Following the reviewer's suggestion, we have removed this section from the review, given the limited information regarding the role of miRNA controlling glucagon.

Comment 3: Section 9

microRNA mediates cell to cell organ to organ crosstalk

It is not microRNA but exosome- and/or EV-derived microRNAs that maintain interorgan crosstalk.

We thank the reviewer and agree with this comment. We have corrected this on the manuscript.

Comment 4: There is increasing literature evidence for the importance of exosomal microRNA exchanges.

We thank the reviewer for his comments and for providing a list of relevant manuscripts on the subject that were initially overlooked. We have read them and included the ones we consider more appropriate for the aim of our review. These additions will make our review more comprehensive.

Comment 5: Figure 1 provides no useful information. What are "pancreatic diseases"? The information is meaningless. Cancel Fig. 1 or present a table.

Following the Reviewers suggestion, we have removed Figure 1 and added a comprehensive table summarizing the relevant information.

Comment 6: Figure 2

This figure needs to be restructured into 4 subfigures:

a) microRNA interactions promoting beta-cell proliferation

b) microRNAs reported inducing beta-cell apoptosis

c) microRNAs related to beta-cell differentiation

d) microRNA involved in the regulation of insulin biosynthesis and secretion.

We acknowledge the reviewer's comments, but we anticipate these changes will make the figures a bit cumbersome and redundant given the number of miRNAs involved in the control of different

processes. The purpose of this figure is to provide a graphical snapshot of some details in the main text.

Comment 7: Figure 3

This figure needs improvements as well. It should show exosomes or EVs as transporters of microRNA cargo.

Following the Reviewers' comments, we have added exosomes in the figure to reinforce the role of exosomes/EV as the carriers of the miRNA.

Comment 8: Throughout the manuscript and even in the same sentence the authors use alternatively the abbreviation "microRNA" or "miRNA". Please, select one abbreviation.

We thank the reviewer for pointing this out. We have made changes accordingly and used a consistent nomenclature throughout the manuscript.