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Peer Review

Review of: "High-Resolution Imaging Atlas Reveals Context-Dependent Role of Pancreatic Sympathetic Innervation in Diabetic Mice"

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This manuscript examines the distribution and remodeling of pancreatic islet cells (alpha and beta) and the density of sympathetic innervation in wild-type and diabetic mouse models (db/db and diet-induced obesity, DIO). While the topic is of clinical and scientific interest, the study's novelty is not fully convincing because similar work has been published in the past. Several methodological and interpretational issues also limit the impact of the findings.

Major comments:

1. Insufficient evidence of diabetes progression. Quantitative data on blood glucose levels in DIO and db/db mice at 10 and 26 weeks are missing. Since there is an age-dependent effect in the WT regarding the morphological features of alpha/beta cells and TH-beta cells), it is not clear why two different diabetic models have been tested at two separate ages. Demonstrating clear metabolic phenotypes is crucial to validate the progression of diabetes in these models.
2. Unclear extent of sympathetic denervation. A single 6OHDA injection may be inadequate to achieve selective or complete chemical sympathectomy. Classical protocols often require multiple doses. It also remains unclear whether cPSD (chemical pancreatic sympathetic denervation) was effectively targeted only to the pancreas or if there was leakage to adjacent organs (e.g., small intestine). Data confirming the extent of tyrosine hydroxylase (TH)-positive fiber loss in the pancreas versus neighboring tissues would strengthen the conclusions.
3. Statistical and sample size concerns. The manuscript does not clearly state the number of animals used in each experimental group. Instead, "n" appears to refer to numbers of cells/fibers

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rather than biological replicates. In addition, there is no justification for why only parametric statistical analysis has been used; at least normality should be tested and reported. The absence of a robust statistical model and clearly defined group sizes raises concerns about the validity and reliability of the results.

4. Ambiguity in separating age-related vs. diabetes-related effects. The discussion merges changes due to aging (10 vs. 26 weeks) with those induced by hyperglycemia, making it difficult to discern which factors drive specific findings. A more structured approach would enhance clarity.
5. Potential misinterpretation of TH-positive fibers. TH is not exclusive to sympathetic neurons; it may also label other catecholaminergic cells. A rigorous approach or additional markers would be needed to definitively attribute TH signals to sympathetic innervation.
6. Inconsistencies between text and figures. Certain textual descriptions (e.g., alpha cells predominantly in islet cores vs. the "shell") conflict with the accompanying images. Ensuring figures and descriptions align is critical for accurate interpretation.
7. Limited novelty. Given the extensive literature on sympathetic innervation of islets and changes in diabetic models, the manuscript needs to clarify what truly differentiates this work from existing studies. Emphasizing unique experimental approaches, more comprehensive analyses, or mechanistic insights could bolster its originality.

Minor comments:

1. The acronym DIO should be introduced in the abstract.
2. Image quality and clarity. Pancreatic slice images (Figures S1B, S2C) are not sufficiently clear. Insulin and glucagon signals appear to overlap, making it difficult to distinguish alpha and beta cells.
3. Figure and text alignment. The authors should ensure that references to figures accurately reflect what the images depict. For example, re-check the labeling and color coding in figure panels to avoid confusion. Graphical abstract 10 and 26 would be more clearly labeled as 10w and 26w.

While the manuscript explores an important aspect of pancreatic physiology and pathology, its contribution would be stronger if the authors:

1. Provide more rigorous statistical analysis and clarify animal group sizes.
2. Verify effective and selective sympathectomy with robust controls.
3. Distinguish clearly between aging- and diabetes-driven changes.

4. Improve the clarity and consistency of both text and figures.

Declarations

Potential competing interests: No potential competing interests to declare.