

Dear Dr. Dou,

We have now revised our manuscript according to editorial and reviewer comments, as detailed below. We believe that we addressed entirely all raised concerns and that the current version of our manuscript meets all necessary requirements to be published in its present form.

We are looking forward hearing your opinion,

Jovica Ninkovic

Detailed responses to Editorial comments:

Please provide the manuscript documents in word version so that we can edit.

[We uploaded the manuscript file as word version to be edited.](#)

Running title : A short running title of no more than 6 words should be provided. It should state the topic of the paper. For example, Losurdo G et al. Two-year follow-up of duodenal lymphocytosis. (no more than 6 words)

[We added a running title to the revised manuscript.](#)

The author "Jovica Ninkovic" ORCID number is incorrect. Please check

[The ORCID number for Jovica Ninkovic has been corrected.](#)

Please check and confirm that there are no repeated references! Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI. PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) (Please begin with PMID:) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**)

[We carefully checked that no repeated references are present in the text. Reference list has been formatted according to the requirements.](#)

Coding system: The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces. For example, "Crohn's disease (CD) is associated with increased intestinal permeability [1,2]." If references are cited directly in the text, they should be included with the direct citation content within the text; for example, "From references [19,22-24], we know that...". Before submitting your manuscript, please ensure that the order of citations in the text is the same as in the references section, and also ensure the spelling accuracy of the authors' names. Do not list the same citation twice (i.e., with two different numbers)

[Reference order is based on their order of appearance in the text. Reference numbers have been formatted according to the requirements.](#)

All references do not provide PMID number, please check and add.

All references now contain PMID and DOI numbers.

Did you draw this figure yourself? If figure is not drawn by the author, proof of copyright is required. If you made this figure yourself, please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - image files.ppt" on the system. Make sure that the layers in the PPT file are fully editable.

All the figures were drawn by us. For this reason, we provided the decomposable files for all the figures. However, since we had problems to export them in Powerpoint due to a drastic resolution loss, we uploaded the fully editable files in the Illustrator format (.ai) for all figures.

For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast.

We changed colors and avoided the use of both green and red in the same figure.

Detailed responses to Reviewer's comments:

In this manuscript, the authors introduced the cellular environment of different brain regions of zebrafish under physiological conditions and the injury models used to study the regeneration response of zebrafish. In addition, the authors also summarized the cellular and molecular mechanisms of zebrafish in repairing the tissue and function of the central nervous system and expounded the critical role of inflammation in the process of nerve repair. However, the potential applicability and challenges of zebrafish central nervous system to reveal the repair mechanism for mammal central nervous system have not been well described, which is the main problem of this manuscript.

1. The nerve repair therapy mentioned by the authors in the Abstract section is not reflected in the text.

Thanks to the reviewer's comment, we realized that our sentence could be misunderstood. We did not intend to describe new therapeutic interventions but rather suggest that new cellular and molecular programs identified in the adult zebrafish regenerating brain could be used to improve the existing therapeutic approaches for human brain repair. For this reason, we modified the Abstract text to make our point clearer (Page 3, Lines 9,10).

2. In this manuscript, the authors did not elaborate on the significance of the zebrafish central nervous system repair mechanism to the study of mammal nerve repair, which is very necessary.

Throughout the text, there are several comparisons between zebrafish and mouse to highlight the significance of zebrafish CNS repair mechanisms for the study of mammalian CNS repair. However, we agree with the reviewer that a deeper elaboration would be useful and for this reason we added it to the final paragraph “Conclusions and Perspectives”.

3. The authors should analyze in detail the potential risks and challenges of the current research on the mechanism of central nervous system repair in zebrafish.

We agree with the reviewer and for this reason potential risks and challenges of studying regeneration in the adult zebrafish CNS were added to the final paragraph “Conclusions and Perspectives”.

4. In the section of “Progenitor lineages in the adult zebrafish brain”, the authors compared neural progenitor cells in the brains of zebrafish and mammals instead of describing the “progenitor lineages in the adult zebrafish brain”.

The title of the paragraph was changed into “Introduction and comparison of progenitor lineages in the adult zebrafish and mouse brains” (Page 5, Line 3) to make it more coherent with the content of the paragraph.

5. P14L10: “Moreover, Notch1b is not present during heart embryogenesis...”. The heart-related mechanism of zebrafish is not the focus of this manuscript.

We agree with the reviewer and we deleted the part of Notch in the heart.

6. P15L30: “Different kinetics of the inflammatory response between...”. This point deserves further discussion.

With “different kinetics” we referred to the quick resolution of the inflammatory response in the zebrafish brain in comparison with the more prolonged inflammatory response observed in the mouse brain after injury. For this reason, we slightly modified the sentence (Page 16, Lines 16,17) and added more information about this to support our statement (Page 16, Lines 18-20).

7. A summary of the text is necessary for the manuscript.

The paragraph “Conclusions and Perspectives” has now been added.

8.1. The resolution of all figures is too low.

All the figures have been now exported from Illustrator as PNG with 600 ppi. Additionally, we uploaded the original Illustrator files for all the figures that can be edited or used to export the figures in other formats or with lower/higher resolution.

8.2. The references should be updated. It would be better to be replaced by more references of the latest three years, such as Cells 2019, 8 (8), 886.

Some references were added to support statements in the last paragraph “Conclusions and Perspectives”.

The reviewer suggested to use more recent references, proposing “Mesenchymal Stem Cells for Regenerative Medicine”, Cells 2019, 8 (8), 886 as an example. However, we do not see how the review proposed by the reviewer would be more relevant than the current references to support the data mentioned in the text and our main points for the review. We strongly believe that the data that we mentioned is well supported by the references that we used and, to our knowledge, no more recent publications would be more significant. For this reason, we would like to keep the reference list as it is, or we kindly ask the reviewer to provide more specific and recent articles and not reviews that could replace the ones that we used.

8.3. Some spelling and grammatical errors should be corrected, such as "divide" should be replaced with "divides" (P5L14).

The review has now been proofread and edited by professional English editor and the proof for editing is also submitted along with revised manuscript. All additions and corrections to the revised manuscript have been highlighted in yellow.