

Name of journal: *World Journal of Diabetes*

Manuscript NO: 67981

Dear Editor and Reviewers,

Thank you for your kind letter and for the Reviewers' comments concerning our manuscript entitled "Inhibitory Effect of Maspin on Neovascularization in Diabetic Retinopathy". Those comments are all valuable and very helpful for revising and improving our paper. We have studied the comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responses to Reviewers' comments are as the following:

1. Responses to comments of Reviewer 1:

Specific Comments to Authors: I found the manuscript entitled "Inhibitory Effect of Maspin on Neovascularization in Diabetic Retinopathy" original, very interesting, well-structured and with huge impact on clinical treatments. Diabetic retinopathy is a complication of diabetes, caused by high blood sugar levels damaging the back of the eye (retina). It can cause blindness if left undiagnosed and untreated. Retinal neovascularization is one of the main pathological features of PDR, and inhibiting retinal neovascularization is a research focus. In this study, Mouse OIR model was used to simulate neovascularization in diabetic retinopathy and maspin was injected into the vitreous cavity. The protein and mRNA expression of VEGF, HIF-1 α in retina was measured. The number of vascular cell nuclei that broke through the ILM was counted in HE stained retinal sections. Conclusion was that maspin can inhibit neovascularization of DR by modulating the HIF-1 α /VEGF pathway, which provides a potential and effective strategy for the treatment of DR. Comments/suggestions: 1. Title and key words - well chosen. 2-The abstract summarized and reflect the described in the manuscript. I suggest that it could be revised to structure: aim, methods, results and the conclusions need to be described separately. 3. Introduction contains the most important data to support the importance of the study. 4. Material and methods - the paragraphs are generally well structured and explained. 5. Results section is well and clearly presented with pertinent statistics. 6. Discussion paragraph could be expanded to underline the clinical application of this study and the potential limitations. Also, directions for future research could be discussed. 7. Good quality of

the Figures. I suggest that arrows could be used in Figure1, e.g., it could indicate pathologic neovascular tufts. 8. References –appropriate, latest and important.

Response:

Thank you very much for your kind comment. The comments is very helpful for us to revise and improve our paper.

We have revised the structure of the abstract; the abstract has been revised to structure: aim, methods, results and the conclusions need to be described separately. Discussion paragraph have been expanded The corresponding part has been changed according to your suggestion (page 11). The arrows have been used in Figure1, it could indicate pathologic neovascular tufts. .

2. Responses to comments of Reviewer 2:

Specific Comments to Authors: The manuscript used animal experiments to find more effective strategy for the treatment of DR. The topic has a clinical relevance since the mouse OIR model has much in common with human ischemic retinopathy and can effectively simulate the occurrence of retinal neovascularization in vivo. The manuscript is well written: the title reflects the main subject of the article, abstract and keywords well summarize the arguments. The methodology is described in detail and is well structured. Newborn C57BL/6J mice were randomly divided into three groups: the normal control group, the Maspin injection OIR group and the OIR group. The protein and mRNA expression of VEGF, HIF-1 α in retina was measured and the number of vascular cell nuclei that broke through the ILM was counted in HE stained retinal sections. The discussion is well articulated according to results and the authors have clearly underlined the limitations and drawbacks of the manuscript. A point of strength of the article in my opinion is also that it provides a potential and effective strategy for DR clinical treatments. The manuscript cites appropriately the latest and authoritative references. Reading the manuscript some minor concerns have emerged:

- Page6Line17, “neovascularizar tufts” should be modified to “neovascularizar tufts”.
- Fig. 1 is not clear. What is the magnification power used, it should be noted on the figure. Thank you for giving opportunity to review your study.

Response:

Thank you very much for your kind comment. The comments is very helpful for us to revise and improve our paper.

The minor concern in Page6Line17 has been revised. The magnification power is, $\times 200$, it has been noted.

3. Responses to comments of Reviewer 3:

Specific Comments to Authors: Diabetic retinopathy (DR) is a serious and potentially blinding complication of diabetes mellitus. Authors used a mouse oxygen-induced retinopathy (OIR) model to simulate neovascularization in DR and aimed to evaluate the effect of intravitreal injection of recombinant human maspin on neovascularization in DR. The article is well written, and the idea of the study is novel. The text is strictly logical. The results are interesting and they found potential agents to inhibit neovascularization in DR. The manuscript provided a theoretical basis for clinical treatments and could be useful for other studies in this field. I recommend that the manuscript can be published.

Response:

Thank you very much for your kind comment.

4. LANGUAGE QUALITY

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A). Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Response:

Thank you very much for your suggestion. A native English-speaking expert has polished the manuscript. The detailed information has been in revised manuscript.

5. EDITORIAL OFFICE'S COMMENTS

Science editor: (1) The “Author Contributions” section is missing. Please provide the author contributions; (2) 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); (3) The authors did not provide original pictures. 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; (4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (5) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text. 6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.

(1) Comment

The “Author Contributions” section is missing. Please provide the author contributions;

Response:

We are sorry for our negligence of missing author contributions.

Author contributions:

Author contributions: Feng Qiu was involved in the data curation and writing of the original draft; Huijuan Tong performed the data curation and formal analysis, and participated in the writing and editing of the manuscript. The Author Contributions section has been added at the end of the revised manuscript.

(2) Comment

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);

Response:

We are sorry for our negligence of missing grant application form(s). We will upload the approved grant application form(s) or funding agency copy of any approval document(s);

(3) Comment

The authors did not provide original pictures. 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;

Response:

We will provide the original figure documents using PowerPoint.

(4) Comment

PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Response:

The comment is very helpful for us to revise and improve our paper. The references in revised manuscript have been revised, where PMID and DOI numbers have been added and all authors of the reference have been listed.

(5) Comment

The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

response

We have completed the supplement of the “Article Highlights” according to the specified format. The “Article Highlights” section has been added at the end of the revised manuscript.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We hope that the corrections will meet with approval. Once again, thank you very much for your kindly letter and for the Reviewer’ comments.

Look forward to your reply.

Sincerely yours,
Feng Qiu