Dear Editors and reviewers,

Thank you very much for your positive suggestion to our manuscript (No. 67394) . We have studied the comments from editors and reviewers carefully and have made revisions, The amendments are highlighted in yellow scene in the revised manuscript. In the following pages are our point-by-point responses.

Responses to the comments of Company editor-in-chief: The manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in official language of the authors' country to the system.

A: We have revised the manuscript carefully according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. In addition, the primary version (PDF) of the Institutional Review Board's official approval in Chinese has been uploaded in the system.

Responses to the comments of Science editor:

(1) The title is too long, and it should be no more than 18 words;

A: We have shorten the title to 15 words.

(2) The "Author Contributions" section is missing. Please provide the author contributions;

A: We have added the Author Contributions section.

(3) 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);

A: The funding agency copy of approval documents have been uploaded.

(4) 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;

A: Original pictures and figure documents have been arranged in PowerPoint. All graphs or arrows or text portions can be reprocessed follow your suggestion.

(5) 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;

A: PubMed numbers and DOI citation numbers were both added in references. All authors are listed in references throughout.

(6) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;

A: The "Article Highlights" section has been added at the end of the main text.

Responses to the comments of Reviewer #1

There are a few typos in the manuscript that need to be corrected before publication.

1、line 51: "Almost recently, studies indicated patients who suffered coronavirus disease 2019 (COVID-19) associated with intestinal hypoperfusion which may further deteriorate barrier dysfunction and acute lung injury by a positive feedback mechanism". Change to: Almost recently, studies indicated patients who suffered coronavirus disease 2019 (COVID-19) associated with intestinal hypoperfusion which may further deteriorate barrier dysfunction and acute lung injury by a positive feedback mechanism

A: We have corrected this sentence in manuscript following your suggestion.

2、Line 269: "intestinal mucusal", change to: intestinal mucosal

A: Line 269: "intestinal mucusal" have been change to: intestinal mucosal.

3、Line 351: "lessons the autophagy" change to: lessens the autophagy

A: Line 351: "lessons the autophagy" have been change to: lessens the autophagy

4、Line 357: "oxidatation" change to: oxidation.

A: Line 357: "oxidatation" have been change to: oxidation.

5、Line 432: "induction of autpophagy" change to: induction of autophagy

A: Line 432: "induction of autpophagy" have been change: induction of autophagy.

6、Line 495: "rhANGPTL4 can lesson I/R injury", change to: rhANGPTL4 can lessen I/R injury.I recommend this manuscript for publication.

A: We have corrected "rhANGPTL4 can lesson I/R injury" to: "rhANGPTL4

can lessen I/R injury" follow your suggestion.

Responses to the comments of Reviewer #2

1) Recombinant human ANGPTL4 was used in a rat model of intestinal I/R in the study. How about the similarity compared to rat ANGPTL4? The authors used 28 mg/kg body of rhANGPTL4. Is this concentration based on the previous study? The authors should discuss the issue.

A: We have compared the similarity using " Multialin Multiple sequence alignment by Florence Corpet" (http://multalin.toulouse.inra.fr/multalin/multalin.html) and the result indicates 78%. The dose was referred previous studies [1,2] and our preliminary experiments.

2) Intestinal mucosal barrier function was assessed by mucosal-to-serosal clearance of FITC-conjugated dextran (FD-4) in everted intestinal ileal sacs incubated ex vivo. How long incubated? What is the concentration of FD-4? The intestinal I/R model (60 minutes of ischemia followed by 240 minutes of reperfusion) appears to be severe. Is the assessment of intestinal permeability appropriate for the intestinal I/R model? The authors should explain/discuss the issue.

A: 30 minutes were incubated and 15mg/kg FD4 was employed. The intestinal I/R model (60 minutes of ischemia followed by 240 minutes of reperfusion) was achievable in our labs. In addition, we also find intestinal permeability evaluated in rats suffered I/R ranging from 1-24 hours reperfusion in independent labs[3-5].

3) Figure 2A needs scale bar. Intestinal scores were also shown in Figure 2. Each score should be shown as a dot spot in different groups. Also, different statistical analysis should be considered.

A: We have added scale bar follow your suggestion. Each score have be shown as a dot spot in different groups and A one-way analysis of variance (ANOVA) has been performed.

4) The authors have assessed the effects of rhANGPTL4 on the apoptosis and autophagy induced by intestinal I/R. After all, which effect is much important? The authors should discuss the issue.

A: We didn't evaluate which effect is much more important in this process. However, like oxidative stress and inflammatory cascade, both of them are exert essential effects and interplay with each other in this pathogenesis. We will be give a special investigation in future.

5) Figure 7A needs scale bar. The effects of si Angptl4 and rh Angptl4 were shown in Figure 7 and Figure 8, respectively. How about the effect of rh Angtl4 on H/R-induced si-ANGPTL4 cells? The authors should discuss the issue.

A: We have added scale bar in Figure 7A, the effect of rh Angtl4 on H/R-induced si-ANGPTL4 cells exhibits in Figure 8

Figure 9 showed that rhAngptl4 restored the VE-cadherin in HUVECs after H/R and VE-cadherins level. Is there any reason for the experiment? How about the role of VE-cadherin in the rat study? The authors should explain the issue.

A: The vascular permeability is another key factor contribute to the maintenance of intestinal barrier in intestinal I/R and microvascular endothelial cell layer including VE-cadherin (VE-cad) formed a semi-permeable barrier between blood and tissue [6]. In present study, HUVECs with RNA interfere of ANGPTL4 suffering H/R exhibit a significant loss of the key regulator VE-cad.

6) In abstract, line 7: radio-induced? In abstract, line 13: VE-cad were significantly increased after intestinal I/R. No data of VE-cad in vivo study? In manuscript and figure, si Angptl4 or siANGPTL4 and rhANGPTL4 or rhAngptl4 were used.

A: We have correct the mistake-spelling "radio" to "radiation" and amending the missing words “or cells H/R" in the sentence end following "intestinal I/R” in manuscript. Moreover, we have uniformed the spelling of "angptl4" to"ANGPTL4" follow your suggestion.

REFERENCE

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5. Tyvold SS, Solligård E, Gunnes S, Lyng O, Johannisson A, Grønbech JE, Aadahl P. Bronchial microdialysis of cytokines in the epithelial lining fluid in experimental intestinal ischemia and reperfusion before onset of manifest lung injury. Shock. 2010 Nov;34(5):517-24. doi: 10.1097/SHK.0b013e3181dfc430. PMID: 20354465.
6. Kannan L, Kis-Toth K, Yoshiya K, Thai TH, Sehrawat S, Mayadas TN, Dalle Lucca JJ, Tsokos GC. R-spondin3 prevents mesenteric ischemia/reperfusion-induced tissue damage by tightening endothelium and preventing vascular leakage. Proc Natl Acad Sci U S A. 2013 Aug 27;110(35): 14348-53. doi: 10.1073/pnas.1309393110. PMID: 23942120.

Thank you for pointing out the limitations of our study.

We have tried our best to improve the manuscript. We sincerely appreciate the Editors'/Reviewers' helpful work and hope that the revised manuscript will meet your expectations.

Once again, thank you for your comments and suggestions.

Best regards.

Yours sincerely,

Huirong Jing