

Manuscript NO.: 88375, Basic Study

Title: Single-Cell Analysis Reveals Activation of Endothelial Cell and Identifies Phospholysine Phosphohistidine Inorganic Pyrophosphate Phosphatase as a Target in Ulcerative Colitis

Dear editor,

We thank all the editors and reviewers for their valuable comments and suggestions, which have significantly contributed to the enhancement of our manuscript. We are very grateful for the valuable suggestions and for the opportunity to revise and improve our paper. Below is a point-to-point response embedded in the comments (blue text).

Therefore, the new manuscript has been reorganized based on insightful comments and helpful suggestions from the editors and reviewers. Altogether, we believe that the reviewers' concerns have been fully addressed and hope that the revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*.

Thank you for allowing us to resubmit our manuscript for your consideration. We look forward to hearing from you.

Yours sincerely,

Dr. Yanfei Cao

The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou Zhejiang, 310012, China

SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report, and highlighted the revised/added contents with yellow color in the revised manuscript. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this manuscript, you are reporting interesting original research data relevant to understanding the immunopathogenesis leading to inflammatory bowel disease. However, in its present form, your manuscript is too large and difficult to understand by an average reader. In my view, the impact of your manuscript should significantly benefit by condensing the text by about 50%. Alternatively, you may consider presenting your data in two separate manuscript.

Thank you for your careful evaluation of our manuscript and for providing valuable

feedback. We appreciate your positive remarks about the relevance of our original research data to understanding the immunopathogenesis of inflammatory bowel disease.

We have taken your comments on board and have made substantial modifications to enhance the manuscript's clarity and readability. Our focus has been on simplifying the language and improving overall comprehension. We believe that the current modifications strike a balance between conciseness and completeness. Furthermore, the study's narrative and logical flow are intricately interwoven, making it difficult to separate without compromising the integrity of the research. We hope for your understanding in this matter. We hope you find the revised version more accessible and aligned with the scientific objectives. We genuinely value your expertise and would be grateful for any further specific recommendations you may have to improve the manuscript.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The role of Single-Cell Analysis on Activation of Endothelial Cell and LHPP hasvbeen proposed as a new Target for treartment of Ulcerative Colitis. Some midifications shoud be done.

1. Please write the full name of LHPP in the title and abstract section.

Thank you for your kind suggestion. We apologize for our oversight in using the abbreviation "LHPP" in the title and abstract without providing its full name at the first appearance. We have made the corrections in the revised manuscript according to your suggestion.

2. Please write the first letter of each all keyword with capital letter.

Thank you for your kind suggestion. We have made the corrections in the revised manuscript according to your suggestion.

3. All references numbers cited in the text should be move before punctuation.

Thank you for your kind suggestion. We have made the corrections in the revised manuscript according to your suggestion.

4. Please cite to new references about experimental UC induction and pathophysiology in the introduction section. (doi: 10.1016/j.jep.2022.115595).

Thank you for your valuable feedback. We appreciate your suggestion to include new references regarding experimental ulcerative colitis (UC) induction and pathophysiology in the introduction section. We have now incorporated relevant information from the suggested reference to enhance the comprehensiveness of our manuscript.

5. Why the authors have used the serum for assessing IL-6 and LHPP?

Thank you for your meticulous review of our manuscript. The decision to utilize serum as the biological matrix for assessing IL-6 and LHPP levels was based on several considerations. Firstly, ulcerative colitis (UC) is a chronic intestinal condition characterized by inflammation and ulceration. By interrogating the single-cell landscape of UC-affected colonic tissues, we identified sustained upregulation of inflammatory response pathways during the progression of UC and characterized the features of damaged endothelial cells in colitis (Figures 1F & G). Concurrently, we observed a progressive increase in the proportion of endothelial cells within the colon microenvironment (Figures 1F & G). This phenomenon underscored the significant role of angiogenesis in the ulcerative colitis's progression. A robust vascular network can facilitate the intravasation and extravasation of inflammation factors, enabling metastasis to distant sites within the body (Figures 3C to G).

Additionally, serum samples are not only relatively easily accessible, which enhances their practicality for biomarker analysis in both clinical and research settings, but they also offer a comprehensive reflection of the organism's overall physiological state. Moreover, the use of serum allows for non-invasive or minimally invasive sample collection, facilitating longitudinal studies and greatly enhancing the translational potential of our findings.

We trust that the rationale for selecting serum as the matrix for our IL-6 and LHPP assessments is in accordance with the scientific objectives of our study.

6. Please move the figure captions after the references section.

Thank you for your kind suggestion. We have made the corrections in the revised manuscript according to your suggestion.

7. Please make the figure captions self-sufficient. They are confusing.

Thank you for your constructive feedback of the figure captions. We appreciate your input and understand the importance of clear and effective figure captions in scientific communication. We have carefully revised the captions to ensure that they are more standalone and provide clearer information regarding the key findings of each figure.

8. Please use arrows in H&E figure for showing damages and alterations.

Thank you for your insightful feedback. We appreciate your suggestion to enhance the clarity of the H&E figure by using arrows to indicate damages and alterations. We will incorporate this valuable suggestion into the revised manuscript to provide a more explicit representation of the observed changes.

9. Please mention to P value in the results section. The quality and discipline of figures are excellent.

Thank you for your positive feedback on the quality and discipline of the figures. We are pleased to hear that they meet the expected standards.

Regarding your suggestion, we appreciate your attention to detail. We have ensured the

inclusion of *P* values in the results section of the revised manuscript. This adjustment provides a more comprehensive presentation of the statistical significance associated with our findings.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

- 1 Conflict of interest statement: Academic Editor has no conflict of interest.
- 2 Academic misconduct: No academic misconduct was found.
- 3 Scientific quality: The authors submitted a study of single-cell analysis reveals activation of endothelial cell and identifies LHPP as a target in ulcerative colitis. The manuscript is overall qualified.
(1) Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. Classification: Grade A and Grade B; Language Quality: Grade B and Grade B. This manuscript reports interesting original research data related to understanding the immune pathogenesis of inflammatory bowel disease. Some mitigating measures should be taken.

(1) Please modify the title and abstract sections;

Thank you for your feedback. We have revised both the title and abstract sections of the manuscript, as per your suggestion. The modifications aim to ensure that both sections accurately reflect the content of the research

(2) All reference numbers cited in the text should be moved before the punctuation mark;

Thank you for your kind suggestion. We have made the corrections in the revised manuscript according to your suggestion.

(3) Please cite new references on experimental UC induction and pathophysiology in the introduction section; and

Thank you for your valuable feedback. We appreciate your suggestion to include new references regarding experimental ulcerative colitis (UC) induction and pathophysiology in the introduction section. We have now incorporated relevant information from the suggested reference to enhance the comprehensiveness of our manuscript.

(4) Modify images, etc.

We appreciate the reviewer's kind suggestion. We have made refinements to the font in our figures. Additionally, we have incorporated arrows into the stained images. We believe that these adjustments will contribute to a more nuanced and comprehensible presentation of our research findings. Your expertise has been instrumental in refining the visual elements

of our work.

(2) Main manuscript content: The author clearly stated the purpose of the study and the research structure is complete. However, the manuscript still require a further revision according to the detailed comments listed below.

Thank you for your valuable feedback. We have taken your comments on board and have made substantial modifications to enhance the manuscript's clarity and readability.

(3) Table(s) and figure(s): There are 6 Figures and no Table should be improved. Detailed suggestions for each are listed in the specific comments section.

Thank you for your constructive feedback of the figure captions. We appreciate your input and understand the importance of clear and effective figure captions in scientific communication.

(4) References: A total of 27 references are cited, including 8 published in the last 3 years. The author does not have self-cited references. The reviewer didn't request the authors to cite improper references published by him/herself. 4 Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend:

<https://www.wjnet.com/bpg/gerinfo/240>.

We sincerely appreciate your generous feedback and recognition of our research. We have made revisions to the manuscript to ensure clarity for the readers of the journal. Additionally, understanding your concerns regarding the language, we have enlisted the services of a professional manuscript editing company to refine the language (the relevant editing certificate is included in the uploaded files). We believe that these modifications will align the language of the manuscript more closely with the expectations of the journal's readership.

5 Specific comments:

(1) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A,B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

Thank you for your kind suggestion. We have uploaded two file formats, Adobe Illustrator and PPT, in the attachments as per your request to facilitate the processing of our images. Additionally, we would like to emphasize that all the images in the manuscript are original creations.

(2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the

figure to be re-published, and correctly indicate the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Thank you for your kind suggestion. We would like to emphasize that all the images in the manuscript are original creations.

Thank you for your kind suggestion. We have made the corrections in the revised manuscript according to your suggestion.

(4) Please add the Core tip section. The number of words should be controlled between 50-100 words.

Thank you for your kind suggestion. We have added the core tip section in the revised manuscript.

(5) Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

Thank you very much for your suggestion. We have adjusted the reference format according to the journal's requirements, and all the information you mentioned has been incorporated.

(6) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text (and directly before the References).

Thank you for your kind suggestion. We have added the “Article Highlights” section at the end of the revised manuscript.

(7) Please provide the Informed consent statement.

Thank you for your kind suggestion. We have added the “Informed consent statement” in

the revised manuscript.

(8) Please provide the Institutional review board statement.

Thank you for your kind suggestion. We have added the “Institutional review board statement” in the revised manuscript.

(9) Please provide the Biostatistics statement.

Thank you for your kind suggestion. We have provided details of our “Statistical analysis” in the Methods section of the manuscript.

6 Recommendation: Conditional acceptance.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and 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. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, it is recommended that the author(s) provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>, or visit PubMed at: <https://pubmed.ncbi.nlm.nih.gov/>.

We sincerely appreciate your generous feedback and recognition of our research. We have made revisions to the manuscript to ensure clarity for the readers of the journal. Additionally, understanding your concerns regarding the language, we have enlisted the services of a professional manuscript editing company to refine the language (the relevant editing certificate is included in the uploaded files). We believe that these modifications will align the language of the manuscript more closely with the expectations of the journal's readership.

Lastly, we express our heartfelt gratitude for recommending the RCA paper retrieval system.

Through this efficient system, we have incorporated some of the latest research findings into our revised manuscript. We believe that your recommendation has facilitated scientific exchange and added fresh perspectives to our paper.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

Step 1: Author Information

Please click and download the Format for authorship, institution, and corresponding author guidelines, and further check if the authors names and institutions meet the requirements of the journal.

Step 2: Manuscript Information

Please check if the manuscript information is correct.

Step 3: Abstract, Main Text, and Acknowledgements

(1) Guidelines for revising the content: Please download the guidelines for Original articles, Review articles, or Case Report articles for your specific manuscript type (Basic Study) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise the content your manuscript according to the Guidelines and Requirements for Manuscript Revision.

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(4) Common issues in revised manuscript. Please click and download the List of common issues in revised manuscripts by authors and comments (PDF), and revise the manuscript accordingly.

Step 4: References

Please revise the references according to the Format for References Guidelines, and be sure to edit the reference using the reference auto-analyser.

Step 5: Footnotes and Figure Legends

(1) Requirements for Figures: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, and submit as "88375-Figures.pptx" on the system. The figures should be uploaded to the file destination of "Image File". Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s). Please click to download the sample document: Download.

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Reminder: Please click and download the Guidelines for preparation of bitmaps, vector graphics, and tables in revised manuscripts (PDF), and prepare the figures and tables of your manuscript accordingly.

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Authors cannot replace and upload the "Manuscript File" separately. Since we only accept a manuscript file that is automatically generated, please download the "Full Text File" or click "Preview" to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal. If you find that there is content that needs to be modified in the Full-Text File, please return to the corresponding step(s), modify and update the content, and save. At this point, you then have to click the "Save & Continue" button in Step 5 and the F6Publishing system will automatically regenerate the Full-Text File, and it will be automatically stored.

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For all required accompanying documents (listed below), you can begin the uploading process via the F6Publishing system. Then, please download all the uploaded documents to ensure all of them are correct.

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- (3) 88375-Biostatistics Review Certificate
- (4) 88375-Conflict-of-Interest Disclosure Form
- (5) 88375-Copyright License Agreement
- (6) 88375-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)

- (7) 88375-Institutional Animal Care and Use Committee Approval Form or Document
- (8) 88375-Institutional Review Board Approval Form or Document
- (9) 88375-Non-Native Speakers of English Editing Certificate
- (10) 88375-Video
- (11) 88375-Image File
- (12) 88375-Table File
- (13) 88375-The ARRIVE Guidelines
- (14) 88375-Supplementary Material

For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. This is mandatory and is one of the determining factors for whether or not the manuscript will be finally accepted. If human and animal studies received waiver of the approval requirement from the ethics committee, the author(s) must provide an official statement to this effect made by the ethics committee. The guidelines for manuscript type and related ethics and relevant documents/statements can be found at: <https://www.wjgnet.com/bpg/GerInfo/287>.

If your manuscript has supportive foundations, the approved grant application form(s) or funding agency copy of any approval document(s) must be provided. Otherwise, we will delete the supportive foundations.

If your manuscript has no “Video” or “Supplementary Material”, you do not need to submit those two types of documents.

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Reminder: If any of the authors do not receive the email of CLA, please check the spam folder. If the author still can't find the email, please contact us via email at: submission@wjgnet.com.

9 CONFLICT-OF-INTEREST DISCLOSURE FORM

Please click and download the fillable ICMJE Form for Disclosure of Potential Conflicts of Interest (PDF), and fill it in. The Corresponding Author is responsible for filling out this form. Once filled out completely, the Conflict-of-Interest Disclosure Form should be uploaded to the file destination of ‘Conflict-of-Interest Disclosure Form’.