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Dear editor

We would like to thank the reviewers for their valuable suggestions. Our manuscript has been revised based on every comment from the reviewers (see the next pages for details). We have also asked Editage colleagues of native English speakers to proof read the manuscript and they have already gave us the certification of English editing. We sincerely hope that the paper is now suitable for publication on *World Journal of Gastrointestinal Surgery*. If you have any questions, do not hesitate to contact me.

Regards,

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Review Comments

(1) Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Various studies show that mir-125b-5p plays an important role in various processes of carcinogenesis and inflammation. Its role in acute pancreatitis has not been studied. Zheng et al. investigated the role of mir-125b-5p in acute pancreatitis in vitro and in vivo in a complex experimental approach. The results are very interesting and form the basis for further investigations.

Reply 1: Thank you for the reviewer's recognition of the article. The reviewer think that the results are very interesting and form the basis for further investigations.

Changes in the text: No need to revised.

(2) Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Your essay has clear ideas, good language expression, acceptable innovation, and rigorous experimental design. It would be better if the language of the introduction part of the article could be streamlined.

Reply 2: Thank you for the reviewer's valuable suggestion. We have streamlined the introduction of article.

Changes in the text:

Acute pancreatitis (AP) is a common clinical inflammatory disease of the digestive system, with an increasing trend worldwide， which is a pathophysiological process with complex etiology. At present, there are no consistent and effective therapies for treatment of AP, resulting in a high mortality rate. The fundamental reason is that the underlying mechanism of AP pathogenesis is not been fully understood. During severe acute pancreatitis (SAP), inflammatory mediators released from the pancreas enter the liver. Then, inflammatory mediators produced by the liver spread to

the lungs, activate alveolar macrophages, release MCP-1, platelet-activating factor (PAF), and reactive oxygen species (ROS), causing lung parenchyma injury. However, previous research has mainly focused on the influence of macrophages on remote organ injury of AP. Few studies have been conducted on the intrinsic macrophages of the pancreas, and a majority of them have focused on the changes of the AP phenotype. Furthermore, there is lack of research on the potential molecular biological mechanisms causing the phenotypic changes.

Previous studies have established that exosomes, as a form of extracellular vesicles, are involved in the pathophysiological process of various diseases and playing a biological regulatory role. Bonjoch et al demonstrated that in the rat model of AP, plasma exosomes can effectively activate alveolar macrophages, promote M1 polarization, and secrete a large number of proinflammatory factors such as IL-1βand IL-6 that participate in AP-related acute lung injury (ALI). In addition, studies by Jimenez-Alesanco et al also found that upregulation of miR-155 and decreased expression of miR-21 and miR-122 in plasma-derived exosomes can activate M1-type polarization and promote the release of inflammatory factors, thereby aggravating the progression of AP. This suggests that in the course of the pathogenesis of AP, exosomes derived from acinar cells may participate in the regulation of local pancreatic inflammatory injury, macrophage activation, and extra-pancreatic organ injury via their intrinsic proinflammatory miRNAs.

Additionally, miR-125b-5p is a bidirectional regulatory miRNA, which has been found to have low expression in bladder cancer and high expression in stage I lung cancer. Therefore, researchers speculate that it can be used as a potential means of diagnosis and treatment in the future. At present, miR-125b-5p inhibits the proliferation and migration of bladder tumor cells by inhibiting the HK2 gene, suggesting that it can exhibit anti-tumor activity. Additionally, miR-125b-5p can promote cardiomyocyte self-remodeling after ischemia by improving cardiomyocyte apoptosis. Previous studies have shown that miR-125b-5p is highly expressed in exosomes secreted by acinar cells, proposing that it might play a role in the pathogenesis of AP. Therefore, miRNAs may play a biological regulatory role in local pancreatic inflammatory injury, macrophage activation, and extra-pancreatic organ injury in the course of AP through a certain mechanism. However, exosome-derived miR-125b-5p in AP has not been reported.

Therefore, we aimed to elucidate the molecular mechanism of exosome-derived miR-125b-5p promoting AP exacerbation from the perspective of the interaction between immune cells and acinar cells.

(3) Certification of English editing: We have asked Editage colleagues of native English speakers to proof read the manuscript and they have gave us the certification of English editing.

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Editing Certificate

This document certifies that the manuscript listed below has been edited to ensure language and grammar accuracy and is error free in these aspects. The logical presentation of ideas and the structure of the paper were also checked during the editing process. The edit was performed by professional editors at Editage, a division of Cactus Communications. The sections titled references were not edited by Editage upon the author's request.

The author's core research ideas were not altered during the editing process. Editage guarantees the quality of editing with the assumption that our suggested changes have been accepted and the edited text has not been altered without the knowledge of our editors.

MANUSCRIPT TITLE

Acinous cell AR42J-derived exosome miR125b-5p promotes exacerbation of acute pancreatitis by inhibiting M2 macrophage polarization via PI3K/AKT signaling pathway

AUTHORS

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JOB CODE

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THE EDITAGE Promise QUALITY GUARANTEE

Vikas Narang

Vikas Narang
Chief Operating Officer - Editage

(4) **EDITORIAL OFFICE'S COMMENTS**

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
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, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of

Gastrointestinal Surgery, 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. 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. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. 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)

Reply 4: I have prepared and arranged the figures using PowerPoint.