Peer Review File
Article Information: https://dx.doi.org/10.21037/apm-21-3286

Reviewers #A:

"1- First part of the manuscript corresponding to the presentation of the PI3K/Akt pathway would benefit from a figure describing the different actors and isoform of the pathway. Importantly a scheme or a table giving a comprehensive view of the cell specific expression and function of the pathway would help."

Response: Thank you for this suggestion. In view of your suggestion, we have drawn two tables for the composition, tissue distribution and function of PI3K and Akt, as shown in table 1 and table 2.

"2- Part 2 is more a listing of cellular processes that have been linked to LIRI and to the PI3K/Akt pathway than a comprehensive analysis of the role of the pathway in LIRI."

Response: We are very grateful for this comment, which is very helpful in improving the quality of this article.We have carefully reviewed the related literature, and according to the sequence of events during LIRI, the role of PI3K/Akt signaling pathway was analyzed as comprehensively as possible, see Part 3 for details.

"3- An authors' critical view of the pathophysiological importance and the therapeutic potential of the PI3K/Akt pathway in LIRI is lacking."

Response: Thank you for your helpful comments. We performed a thorough literature review to identify that PI3K/Akt signaling pathway plays an important role in LIRI, and activation of this pathway can help reduce LIRI. However, the current research on PI3K/Akt signaling pathway is only at the basic experimental stage and only carried out in small animals. There is still a long way to go for clinical application. Nevertheless, the study of this pathway provides the possibility to reduce LIRI and is expected to be one of the potential targets for prevention and treatment of LIRI in the future. We added

the above views at the end of the article, as shown in part 4.

"4- Future directions and unmet needs would be of interest for the readers."

Response: Thank you for this suggestion.Based on your suggestion, we reviewed the relevant literature and found that there are indeed some problems to be solved regarding the application of PI3K/Akt in LIRI. In the fourth part of the article, we listed several directions that need to be worked on in the future, hoping to be of some help to the subsequent research.

"5- To integrate the cell-specific role of the PI3K/Akt pathway into its pathophysiological role in LIRI will add to the impact of this manuscript."

Response:Thank you very much for this comment. Through literature review, we found that the activation of PI3K/Akt signaling pathway can promote the occurrence and development of a variety of tumors, indicating that the activation of this signaling pathway may have different effects in different diseases and different cells. Therefore, interventions targeting the PI3K/Akt signaling pathway need to be treated in specific circumstances.We appropriately added the above in Part 4 of the article.

Reviewer #B:

"1. For a better understanding, the authors should also summarize what happens during ischemia and subsequent reperfusion in the liver at the molecular level."

Response: Special thanks to you for your good comments. According to your suggestion, We added a summary of the LIRI mechanism in Part 2 of the article.

"2. The authors devoted many pages to explain the details of PI3K and AKT, especially about their isoforms (lines 63-137). However, this information has little or nothing to do with the following contents. The authors should reconsider the structure of the text."

Response: Thank you for your comment. We have appropriately simplified the

overview of PI3K and Akt, and attached two tables to get a better sense of them, as described in the first part of the article. In addition, we have reorganized the structure of the whole paper.

"3. How does LIRI activate the PI3K/AKT signaling pathway? The authors referenced a few literatures (ex. lane 162-164, 280-283), however, are these mechanisms enough to explain the PI3K/AKT pathway activation by LIRI?"

Response: Thank you very much for this comment. We have reviewed a large number of relevant literatures, but have not found any literatures that further elaborate the specific mechanism of LIRI activation of PI3K/Akt signaling pathway. Most of the current studies can only partially clarify the activation of PI3K/Akt signaling pathway by LIRI, which is not enough to fully explain, and this is also one of the directions we need to continue to explore in the future.

"4. Many biological phenomena including oxidative stress, inflammatory, immune cells regulation, autophagy, and apoptosis that are explained by the authors in the text, are mutually related. Although the authors explained each contribution to LIRI, I could not grasp the overview of how these phenomena are coordinately related and affect LIRI. Also, I did not get what we should do to uncover this complicated issue in the future, therefore, it would be better to know the author's idea on that."

Response: Thank you for your comment. As shown in the second part of the article, we added an overview of the related mechanisms and pathological processes in the process of LIRI to better understand the mechanism of LIRI. Through Part 3, we hope to show that PI3K/Akt signaling pathway can affect the whole stage of ischemia and reperfusion of LIRI in a relatively comprehensive way, and it is very important for LIRI. Activation of PI3K/Akt signaling pathway can alleviate LIRI in many aspects.

"5. The figure should be changed to easily understand the relationships between LIRI and other biological phenomena for the reader's better understanding."

Response: Thank you very much for this comment. Following your suggestion, We

modified the figure to better understand the LIRI process and the role of PI3K/Akt signaling pathway in LIRI, as shown in Figure 1.