List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Metabolomic profiling and relevant pathway of taurine in hepatic stellate cells (HSCs) by using HPLC-ESI/Q-TOF-MS" (Manuscript NO: 33840). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. **Response to comment:** In the abstract all terms should be spelled out the first time, ie HPLC ESI/Q-TOF MS

Response: Thank you very much for the reviewer's comments. We have made correction according to the Reviewer's comments.

2. **Response to comment:** Have the authors considered using inhibitors to verify pathway involvement?

Response: We have considered using inhibitors to verify pathway involvement. However, our study involved with several limitations. Validation of the pathway using inhibitors need to further study in the future. In another study (submitted and un-published), We used the gene microarray chip and bioinformatics to identity and annotated the differential expression genes. As a result, nineteen significantly enriched pathway with differential expression genes were identified, including sphingolipid pathway, glutathione pathway and glycerophospholipid pathway. The result verify indirectly the pathway in the present study.

3. **Response to comment:** What do the authors see as potential clinical application, ie inhibition of which pathway or combination thereof and at what level?

Response: As mentioned in the paper, sphingolipid metabolism pathway, glutathione metabolism pathway and thiamine metabolism pathway were found to be the most important metabolic pathways for taurine in HSCs. Moreover, amino-dodecanoic acid, 2-Oxo-4-methylthiobutanoic acid, oxo-dodecenoic acid, valine, citric acid, thiamine, N-acetylaspartate were found in the current study, and it proposed that taurine may intervene HSCs through the way of Valine, leucine and isoleucine biosynthesis pathway, cysteine and methionine metabolism pathway, citrate cycle (TCA cycle) pathway, alanine, aspartate and glutamate metabolism pathway, lysine degradation pathway, glyoxylate and dicarboxylate metabolism pathway, arginine and proline metabolism pathway and aminoacyl-tRNA biosynthesis pathway. The above findings, We think it can be seen as potential application.

Responds to the editor's comments:

1. **Response to comment:** Please add these content, which must be provided, otherwise the manuscript will be unaccepted finally.

   Response: We have added the "Institutional review board statement: All patients involved in this study gave their informed consent. Institutional review board approval of our hospital was obtained for this study."

2. **Response to comment:** Please add these content, which must be provided, otherwise the

manuscript will be unaccepted finally.

Response: We have added the "Institutional animal care and use committee statement: The animal protocol was designed to minimize pain or discomfort to the animals. The animals were acclimatized to the laboratory conditions (23℃, 12h/12h light/dark, 50% humidity, ad libitum access to food and water) for two weeks prior to experimentation. Intragastric gavage administration was carried out with conscious animals, using straight gavage needles appropriate for the animal size (15-17g body weight: 22 gauge, 1 inch length, 1.25mm ball diameter). All animals were enthanized by barbiturate overdose (intravenous injection, 150mg/kg pentobarbital sodium) for tissue collection."

3. **Response to comment:** Please add these content, which must be provided, otherwise the manuscript will be unaccepted finally.

   Response: We have added the "Data sharing statement: No additional data are available."
4. **Response to comment:** The email address should be your institutional email of yourself.

   Response: Sorry, our institution don't have institutional email, so I can only provide this email address: **Dr_JianLiang@163.com**.
5. **Response to comment:** Ref. 22 as well as Ref. 24, please revise it.

   Response: We have deleted the Ref 24.

Special thanks to you for your good comments.

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. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

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