Dear Dr/Pofessor

We thank you very much for giving us an opportunity to revise our manuscript. We appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled " Role of Estrogen Receptor β Selective Agonist in Ameliorating Intrahepatic Resistance and Portal Hypertension in Rats with CCl4-induced Liver Cirrhosis " (WJG, NO: 23607).

We have studied reviewers' comments carefully and have made revision which marked in red in the revised manuscript. We have tried our best to revise our manuscript according to the comments. Please find the revised version in the attached file, which we would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Cheng-gang Zhang

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List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled " Role of Estrogen Receptor β Selective Agonist in Ameliorating Intrahepatic Resistance and Portal Hypertension in Rats with CCl4-induced Liver Cirrhosis " (WJG, NO: 23607). 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 manuscript. The main corrections in the paper and the responds to the reviewers' comments are as following.

Responds to the reviewers' comments:

Reviewer #1:

COMMENTS FOR THE AUTHOR:

This is a well done experimental study. Practical benefits from this study in clinical practice will not occur too soon. But being done, the study should be published and know. The authors should discuss the hyperestrogenism observed sometimes in cirrhosis in the context of the therapeutic potential of estrogen in therapy of fibrosis. Given the authors result, the inactivation of estrogen encountered in cirrhosis should have a favorable effect for the progression of disease. Authors should comment this issue. Many language errors and typos.

Response:

This comment is very valuable and helpful for revising and improving our paper. The relationship between estrogen and cirrhosis is very interesting and profound. There does exist the hyperestrogenism sometimes in clinical practice, which leads to a range

of symptoms including liver palm, spider angioma, changes in sexual function, and so on[1]. There are many reasons accounting for this phenomenon, such as the decrease of liver function to inactivate hormone, the portal venous shunt and so on. However, Epidemiological studies have reported the male to female ratio among patients with cirrhosis is in the range of 2.3:1–2.6:1 [2, 3], moreover, many animal experiments and clinical trials have provided consistent evidence for the protective effect of endogenous and exogenous estrogen on liver fibrosis[2-6]. Therefore, the increase of estrogen in fibrosis maybe is the processes of self-modulation and self-protection. But symptoms of the liver palm, spider angioma, changes in sexual function could be considered as the side effects of hyperestrogenism because of hypercorrection.

Using multivariate analysis with patients with chronic hepatics C, Poynard et al.[7] reported that the hypoestrogenism of male people was associated with advanced fibrosis. Furthermore, menopause increases the susceptibility to cirrhosis[8]. In addition, treatment with a neutralizing antibody against rat E2 in males or an ovariectomy in females led to enhanced fibrogenesis[9].

Hence ERβ selective agonists hold the promise of providing the protection actions of estrogens against liver cirrhosis and PHT, while reducing classic side effects of estrogens side effects.

Reviewer #2:

COMMENTS FOR THE AUTHOR:

This is a fine experimental study concerning efficacy of ER agonist against cirrhosis-related portal hypertension. I congratulate the authors of this excellent work. However, I have one concern in the morphometric analysis. Their theoretical basis consists of the decline of activated HSCs by ER agonist. Figure 2 shows the comparative method of SMA-positive cell amounts. Importantly, Figure 2a demonstrates that SMA-positive cells in this investigation are mostly vascular smooth muscle cells. Hence, the data don't reflect changing of the number of activated HSCs. The authors should have done a more specific analysis for activated HSCs. The methodology should be reconsidered.

Response:

Thank you for the reviewers' comments. α-SMA expression is a marker for activated HSCs, which play a critical role in liver fibrogenesis [10]. In fact, the data reflect changing of the number of activated HSCs. It is our carelessness leading to the leakage of symbols (* & #) in figure 2d, and we will revise in the updated version of the manuscript.

1. Foutch PG, Sullivan JA, Gaines JA, Sanowski RA. Cutaneous vascular spiders in cirrhotic patients: correlation with hemorrhage from esophageal varices. Am J Gastroenterol 1988;83:723-726.

2. Shimizu I. Impact of oestrogens on the progression of liver disease. Liver Int 2003;23:63-69.

3. Shimizu I, Ito S. Protection of estrogens against the progression of chronic liver disease. Hepatol Res 2007;37:239-247.

4. Shimizu I, Kohno N, Tamaki K, Shono M, Huang HW, He JH, Yao DF. Female hepatology: favorable role of estrogen in chronic liver disease with hepatitis B virus infection. World J Gastroenterol

2007;13:4295-4305.
5. Campbell M, Yang YX, Reddy KR. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2005;41:939; author reply 939-940.
6. Shah V. Molecular mechanisms of increased intrahepatic resistance in portal hypertension. J Clin Gastroenterol 2007;41 Suppl 3:S259-261.
7. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001;34:730-739.
8. Kage M, Shimamatu K, Nakashima E, Kojiro M, Inoue O, Yano M. Long-term evolution of fibrosis from chronic hepatitis to cirrhosis in patients with hepatitis C: morphometric analysis of repeated biopsies. Hepatology 1997;25:1028-1031.
9. Yasuda M, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. Hepatology 1999;29:719-727.
10. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134:1655-1669.