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Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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Dear editors,

Thank you very much for your valuable comments to our work. We significantly agree with you and consider our work to be meaningful and reasonable. Now we are glad to show you our revised manuscript and make some explanation for you about some major modifications in this revised version.

1 Details of our submission

Journal Title: World Journal of Gastroenterology

Manuscript NO: 35478

Title: Pathological process of liver sinusoidal endothelial cells in liver diseases

Authors: Yao Ni, Juan-Mei Li, Ming-Kun Liu, Ting-Ting Zhang, Dong-Ping Wang, Wen-Hui Zhou, Ling-Zi Hu, Wen-Liang Lv

Received Date: 2017-07-22

Correspondence To: Wen-Liang Lv, Ph.D, Professor, Department of Infection, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5, Bei Xian-ge Road, Beijing 100053, China. lvwenliang@sohu.com

2 Peer-review report

Reviewer #1: The manuscript reviews the role of LSECs in liver fibrosis and liver cirrhosis, the inhibition of LSECs angiogenesis which provide the possibility for future targeted therapy and clinical diagnosis. It is well written. If authors have their study of LSECs and liver fibrosis, it will improve this excellent written manuscript.

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Reviewer #2: Dear Editor, This manuscript is an editorial/mini review on "liver sinisoidal endothelial cells" and their role on viral hepatitis, liver fibrosis and cirrhosis. It is scientifically well written. The most recent findings about LSECs is discussed. However I could not notice citation of the authors' own data on the LSECs or liver fibrosis. I think adding authors' own data will further improve this well written manuscript.

Reviewer #3: The authors presented an excellent overview on the role of LSECs in various pathological conditions of the liver. However, their importance in the pathogenesis of portal hypertension is not sufficiently described. At the same time, it is known that endothelial dysfunction and impaired paracrine interaction between activated HSCs and LSECs, as well as sinusoidal remodeling and capillarization play an important role in improving the hepatic vascular resistance to portal blood flow, adding structural changes associated with diffuse fibrosis and regenerative nodules in liver cirrhosis. This information was presented in a recent publication in World Journal of Hepatology (Garbuzenko D.V., Arefyev N.O., Belov D.V. Mechanisms of adaptation of the hepatic vasculature to the deteriorating conditions of blood circulation in liver cirrhosis. World J. Hepatol. 2016; 8 (16): 665-672).

3 Comments and explanations

Q1: The manuscript reviews the role of LSECs in liver fibrosis and liver cirrhosis, the inhibition of LSECs angiogenesis which provide the possibility for future targeted therapy and clinical diagnosis. It is well written. If authors have their study of LSECs and liver fibrosis, it will improve this excellent written manuscript.

R1: *Thank you very much for this valuable comment.*

We added our own study of LSECs and liver fibrosis to the fifty-second references:

To study the effects of Astragalus polysaccharide (APS), which is the primary effective component of the Chinese herbal medicine Astragalus membranaceus, on nanoscale mechanical properties of LSECs in rats, we found that as APS concentration increased, the value of Young's modulus presented an increasing trend, and the surface topography demonstrated that APS was capable of increasing the total area of fenestrae. The observed changes in mechanical properties of LSECs

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may provide a new therapeutic strategy for mechanistic research of anti-hepatic fibrosis treatments in Chinese medicine[52].

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R2: *Thank you very much for this suggestion.*

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To study the effects of Astragalus polysaccharide (APS), which is the primary effective component of the Chinese herbal medicine Astragalus membranaceus, on nanoscale mechanical properties of LSECs in rats, we found that as APS concentration increased, the value of Young's modulus presented an increasing trend, and the surface topography demonstrated that APS was capable of increasing the total area of fenestrae. The observed changes in mechanical properties of LSECs may provide a new therapeutic strategy for mechanistic research of anti-hepatic fibrosis treatments in Chinese medicine[52].

Q3: The authors presented an excellent overview on the role of LSECs in various pathological conditions of the liver. However, their importance in the pathogenesis of portal hypertension is not sufficiently described. At the same time, it is known that endothelial dysfunction and impaired paracrine interaction between activated HSCs and LSECs, as well as sinusoidal remodeling and capillarization play an important role in improving the hepatic vascular resistance to portal blood flow, adding structural changes associated with diffuse fibrosis and regenerative nodules in liver cirrhosis. This information was presented in a recent publication in World Journal of Hepatology (Garbuzenko D.V., Arefyev N.O., Belov D.V. Mechanisms of adaptation of the hepatic vasculature to the deteriorating conditions of blood circulation in liver cirrhosis. World J. Hepatol. 2016; 8 (16): 665-672).

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R3: *Thank you very much for this suggestion.*

We found the information in the recent publication in World Journal of Hepatology (Garbuzenko D.V., Arefyev N.O., Belov D.V. Mechanisms of adaptation of the hepatic vasculature to the deteriorating conditions of blood circulation in liver cirrhosis. World J. Hepatol. 2016; 8 (16): 665-672). And we added portal hypertension in cirrhosis to the sixty-second references:

Gross hepatic structural disorders also associate with portal hypertension. The modified sinusoids is main place of resistance to portal blood. The damaged LESCs became more sensitivity to endogenous vasoconstrictors, which resulted in less expression of endothelial nitric oxide synthase (eNOS) and less production of nitric oxide (NO). Thus increased resistance for blood supply and oxygen delivery. And the hypoxia leads more production of proangiogenic and profibrogenic factors. Moreover, impaired paracrine interaction between activated HSCs and LSECs and capillarization play the key role in improving the hepatic vascular resistance to portal blood flow. Meanwhile, they also add structural changes associated with diffuse fibrosis and regenerative nodules in liver cirrhosis[62].

Thank you again for your check.

Best wishes!

Authors

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