

Dear Editor:

We are pleased to receive your email regarding our manuscript (46498) and thank all the reviewers for their thoughtful comments, those advices and suggestions are useful for upgrading our research. We considered each issue carefully and completed our revision accordingly. We believed the revised paper is now much improved. A point-by-point response to Editor's and Reviewers' comments is outlined below.

### Reviewers' Comments to Author

Reviewer 1:

The authors have conducted an interesting review which highlights the role of hepatic stellate cells in the various types of liver failure. The authors have apparently worked and have knowledge on the subject. However, I have the following issues with the manuscript:  
Major issues:

1. The authors don't differentiate the role of HSC in the different kinds of liver failure i.e acute, chronic (cirrhosis) or acute on chronic.

Reply: Thanks, this is quite a good suggestion.

At beginning, we want to talk about the role of HSCs in liver failure, including acute, chronic and acute-on-chronic liver failure. We checked the whole manuscript after your suggestion and found most researches were about acute liver failure. As these three types of liver failure have different pathophysiologic processes, we then focus HSCs on the pathogenesis of acute liver failure.

2. The sentence "firstly, HSCs activation participates in the maintenance of cell attachment and the architecture of liver tissue via ECM production; secondly, HSCs activation assists liver regeneration by producing growth factors; thirdly, HSCs inflammation plays a role in relaying inflammation signaling from sinusoids to parenchyma via secretion of inflammatory cytokines" is repeated as it is in Abstract, Core tip and Conclusions. Please consider revision.

Reply: Thanks, this is quite a good suggestion. We modified as you suggested.

3. Part of the sentences "Liver failure, including acute liver failure, chronic liver failure and acute-on-chronic liver failure, is a rare but dramatic clinical syndrome characterized by massive hepatocyte death and over activation of hepatic inflammation. Liver failure usually results in hepatocellular dysfunction and coagulopathy and carries a high mortality rate" is repeated as it is in Abstract, core tip and Introduction. Please consider revision.

Reply: Thanks, this is quite a good suggestion. We modified as you suggested.

Minor issues:

1. There is not Page numbering.

Reply: Thanks, we modified as you suggested.

2. Introduction "The main causes of liver failure include viral hepatitis, ischemia and drug-induced toxicity" The causes of liver failure vary according to the type. There are different

in acute, in chronic or in ACLF. Please revise.

Reply: Thanks, we modified as you suggested.

3. Abstract "Liver failure, including acute liver failure, chronic liver failure and acute-on-chronic liver failure" The word "failure" is repeated four times in the same phrase!

Reply: Thanks, we modified as you suggested.

4. In many positions the References are missing. For example "Clinical data have revealed that patients with chronic liver disease are not sensitive to the deleterious effects of toxic compounds .....healthy individuals" (any reference?).

Reply: Thanks, we modified as you suggested.

5. "GalN is a hepatotoxic agent, which inhibits protein synthesis, and is usually used together with LPS to create ALF mouse models." (any reference?) Please revise and put references where they are missing.

Reply: Thanks, we modified as you suggested.

6. Abstract: "Hepatic stellate cells (HSCs) are famous for their roles in liver fibrosis, although some recent studies revealed that HSCs may participate in the pathogenesis of liver failure, the accurate mechanism is still not fully understood." **The phrase is not correct.** Please revise

Reply: Thanks, we modified as you suggested.

7. "Moreover, Alexander et al found that ALF is accompanied by active hepatic fibrogenesis, and revealed positive correlations between liver stiffness, degree of hepatocyte death and the intensity of HSCs activation, which suggests that fibrosis is a response to ALF, and an attempt to repair liver damage, and a decrease in liver stiffness in the remission stage of the disease was also found in these ALF patients" **The phrase is not correct.** Please revise.

Reply: Thanks, we modified as you suggested.

8. The abbreviation "ECM" is present in the Abstract without explanation.

Reply: Thanks, we modified as you suggested.

Reviewer 2:

Mini issues:

1. Referring to their previous works, the authors suggest that HSCs inflammation is involved in the pathogenesis of liver failure (which?). HSC inflammation or inflammation in HSCs - what is it? In my opinion, the title of the article is not correct. Probably the correct call it is "Roles of hepatic stellate cells in acute liver failure"...? It is not clear where the authors write about acute, chronic, or acute-on-chronic liver failure.

Reply: Thanks, this is quite a good suggestion.

At beginning, we want to talk about the role of HSCs in liver failure, including acute, chronic and acute-on-chronic liver failure. We checked the whole manuscript after your suggestion and found most researches were about acute liver failure. As these three types

of liver failure have different pathophysiologic processes, we then focus HSCs on the pathogenesis of acute liver failure.

2.The text has a link to the article [28]. Her author is Alexander Dechene. Alexander is a name.

Reply: Thanks, we modified as you suggested.