Cover letter

Dear editor,

We are resubmitting our manuscript entitled "**1439-For revision (Hepatic regeneration and the epithelial to mesenchymal transition)**". In this revision, we have addressed the questions raised by two reviewers. We greatly appreciate the insightful and important comments from you and the reviewers, which have greatly improved the manuscript.

The point-by-point responses to the reviewers' questions are indicated below and we have incorporated the responses into the revised manuscript. With these modifications and improvements, we hope the quality of our manuscript would meet the publication standard of World Journal of Gastroenterology

Yours Sincerely,

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Reply to reviewer #1:

Question 1:

I think separating one time insult and continuous damages should consider hepatic regeneration process. The latter is more complex, and the early regeneration process in chronic insults may be different with the late stage of regeneration. The author can discuss these points more clearly.

Answer:

We agree with the point of the reviewer about difference of one time insult and continuous

damages. We add "After partial hepatectomy or CCl_4-induced injury, liver regeneration is replicated by remanent hepatocytes. However, the regeneration of the liver that injures induced by other toxins, such as galactosamine, activation of a progenitor cell compartment to replicate and differentiate [4] " in page 3, paragraph 2.

Question 2:

Another point is whether EMT originated from hepatocytes or bile duct epithelia can be myofibroblasts that are originated from activated HSC.

Answer:

Thank you for your detailed suggestions. It is important whether EMT originated from hepatocytes or bile duct and epithelia can be myofibroblasts that are originated from activated HSC. Mostly, fibroblasts transited to epithelia are considered as MET (Mesenchymal to epithelial transition). However, there are few evidences to support the MET idea in liver fibrosis and regeneration. MET occurs in tumor metastasis and embryonic development. We add "The primary HSCs expressed stable mRNA levels of epithelial markers: Mpk, Ck-19, Ecad, Hnf-4, Afp, and Mpk, which also expressed by liver epithelial cells, including OV, bipotent progenitors that differentiate into mature hepatocytes or cholangiocytes[38]" in page 8, paragraph 1.

Question 3:

Does fibrotic tissue observed in liver cirrhosis derived from different origins such as HSC or EMT from hepatocytes or bile ducts? The author can prove this point.

Answer:

We have discussed the different firbrogenesis origins from resident fibroblasts (hepatocyte stellate cells, HSCs and portal fibroblasts), circulating fibrocytes, bone marrow stem or progenitor cells and EMT cells. The relationship between the transition of HSC or EMT and hepatocytes or bile ducts was discussed in section 'HEPATOCYTE EMT AND FIBROSIS'.

Reply to reviewer #2:

Question 1:

Abstract: the authors wrote: The epithelial to mesenchymal transition (EMT), a newly discovered mechanism, plays an important role in liver fibrosis and tumor metastasis. EMT is not

a newly discovered mechanism. It is known since more than a decade. “Previously” is a better choice here.

Answer:

Thank for your suggestion, we have followed your suggestion.

Question 2:

Introduction: the authors wrote: Additionally, epidermal cells can be regenerated by remnant stem cells in hair follicles, and hepatocytes can be regenerated by cells in the canals of Hering, such as oval stem cells or other progenitors. Where is the reference for this, or is the whole introduction from references 1 and 2?

Answer:

We apologize for not describing the details with sufficient clarity. The reference is 1.

Question 3:

the authors wrote: Recently , the EMT have been proven to play an important role in fibrosis，which may be reversed or attenuated by antagonizing essential cytokines and growth factors [31]. The EMT refers to the loss apicobasal polarity in epithelial cells, and intercellular adhesion complexes undergo dramatic phenotypic changes to become nonpolar, lose intercellular junctions and easily move through the extracellular matrix as mesenchymal cells [32-34]

“Recently” is again not so recent, see comments above. Proven is a hard word for a scientific manuscript. Science yields evidence, not proofs. The last sentence is missing some words or has a bad sentence structure since it is very hard to read and understand at first.

Answer:

We have modified this sentence. “The EMT is believed to play an important role in fibrosis, which may be reversed or attenuated by antagonizing essential cytokines and growth factors [31]. Undergoing an EMT refers to the loss of apicobasal polarity in epithelial cells; intercellular adhesion complexes undergo dramatic phenotypic changes, causing them to become nonpolar and thus allowing these cells to move through the ECM like mesenchymal cells [32-34].”

Question 4:

the authors wrote: A type 2 EMT can continue to respond to ongoing inflammation and lead to the expression of mesenchymal markers on cells, which can advance to various extents through an EMT, namely, a partial EMT . References and examples for the partial EMT e.g. differences in E-cadherin expression levels would be fruitful.

Answer:

Thank you for your detailed suggestions. In the revised manuscript, we added references and the definition.

Question 5: the authors wrote: Using collagen Ⅰ and transferrin costaining demonstrated that half the resident hepatocytes had undergone an EMT phenotype in a TGF-β transgenic mouse model and in samples from patients with hepatitis B virus, and the key transition factor Snail was also found in the damaged regions [43].

Do you mean transition or transcription factor. If transition, transition from what and why is it a key?

Answer:

It should be “transcription”.

Question 6:

The authors wrote: TGF-β exerts its effects by binding to the TGF-β type II receptor and subsequently recruiting Smad2⁄3 and Smad4, which are known intracellular mediators of TGF-β.

It might be worth mentioning the TGF-β type I receptor recruitment and phosphorylation prior to Smad recruitment and phosphorylation.

Answer:

Thank you for your detailed and rigorous suggestions. We add “TGF-β exerts its effects by binding to the TGF-β type II receptor, which causes recruitment and phosphorylation of receptor type I and formation of a complex. The activated receptor type I subsequently recruiting Smad2⁄3 and Smad4, which are known intracellular mediators of TGF-β”.

Question 7:

The authors wrote: In renal tubular epithelial cells and mammary ductal epithelial cells, BMP7

reverses the TGF-beta1 -induced epithelial-to-mesenchymal transition (EMT) by reinduction of E-cadherin by using recombinant human BMP to treat NTN mice (nephrotoxic serum nephritis, a chronic nephritis model) [59]. The style how to write TGF-β should stay the same in the manuscript.

Answer:

We apologize for the mistake and we correct all of them. I have rewritten this sentence so it will be more readily understood: “In renal tubular epithelial cells and mammary ductal epithelial cells, BMP7 has been shown to reverse the TGF-β1 -induced EMT, given that NTN mice (nephrotoxic serum nephritis; a chronic nephritis model) treated with recombinant human BMP can re-induce E-cadherin [59].”