

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 64921

Title: Direct modulation of hepatocyte hepcidin signaling by iron

Reviewer's code: 03576894

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Postdoc

Reviewer's Country/Territory: Czech Republic

Author's Country/Territory: Germany

Manuscript submission date: 2021-02-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-03-02 21:45

Reviewer performed review: 2021-03-12 22:39

Review time: 10 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear Authors, the manuscript Direct modulation of hepatocyte hepcidin signalling by iron submitted by your team is generally worth reaching audience of World Journal of Gastroenterology. The aims and experimental methods were appropriate and the study brings advancement in the field of hepatology research. Nevertheless, I find several problematic aspects of the manuscript and those deserve improvement before the article gets approval for publication. Some of these issues are formal, some relate to the content and message of the manuscript. First, a declaration was submitted along with the manuscript file, that the text was written by a native English speaker. Contrary to that, author contributions paragraph states it was Sebastian Mueller affiliated with University of Heidelberg who wrote and revised the manuscript. This raises doubts about fair presentation of your work. Some language weaknesses throughout the text reveal, that the manuscript was at least written in haste. Examples include: Why repetitive blood transfusions have been... instead of While...(page 6); ... FAC had no significant effect ... in the presence or absence instead of FAC had significant effect neither in the presence nor in the absence... (page 11); Notable instead of Notably (page 11); Both FAC and LDN had no significant effect instead of Neither FAC nor LDN had significant effect (page 12). Besides that some sentences are too long or have unusual and confusing word order rather suggesting the text was not written by a native speaker. Also some facts are handled inaccurately. Alcoholic liver disease is claimed to be the most common human liver disease (page 6) without referencing any data source. This is not true. In fact, it is the non-alcoholic fatty liver disease (NAFLD) holding the position of the most prevalent chronic liver disease worldwide (see e.g. Wessels DH, Rosenberg Z. Awareness of non-alcoholic steatohepatitis and treatment guidelines: What are physicians telling us? World J Hepatol 2021; 13(2): 233-241 URL: <https://www.wjgnet.com/1948-5182/full/v13/i2/233.htm>). Sometimes the text needs

providing more details to ease readers' experience. Example of that is on page 4: By binding to and degrading the iron exporter ferroportin 1 (Fpn1) which is localized at the plasma membrane of duodenal enterocytes, macrophages and hepatocytes, hepcidin efficiently blocks iron absorption, iron recycling and iron storage. Clarifying the localisation of Fpn1 to either luminal (apical) or basolateral portion of enterocyte membrane would be very useful. Introduction or discussion section would definitely benefit from adding a picture or a scheme of hepcidin interactions. A frequent inaccuracy in the manuscript is the missing specification whether hepcidin transcription, translation or activity is matter of debate. With SMAD6 mRNA and p-SMAD1/5/8 protein expression you succeeded not to omit it. On the other hand, regarding hepcidin - the main factor of interest - the text lacks needed clarity multiple time. The last formal remark is on using adjectives dramatically and drastic to describe the results. It feels inappropriate in the academic style and I would strongly prefer replacing it by profoundly, markedly or another synonyms. Regarding the scientific content I also suggest several improvements. Calling hydrogen peroxide central oxygen metabolite (page 5) is rather weird. Did the Huh7 and THP-1 cell lines reflect mammalian physiological conditions when cultured at 25 mM glucose concentration? (page 6 and 7) What is Ferlecit (page 7)? It is mentioned without any explanation. Hypoxic experiments deserve better description. How readers shall understand 3 minute gas mixture treatment followed by 24 h incubation? Also note on pathophysiological cell ratio (1:4) of macrophage/hepatocyte to mimic the liver microenvironment (page 12) is not sufficiently clear. The discussion and conclusion sections show many sentences deserving rephrasing or language polishing to contribute to clear message of the study. For example (page 14): These patients show pronounced hemolytic anemia and require a continuous (rather repeated) blood transfusion. Patients with severe disease typically show progressive liver disease (rather damage) and cirrhosis due to heavy (rather

serious) iron toxicity. In the figure legends, I strongly recommend adding a space between letters indicating a statistical significance and the P values. In its current wording this looks strange.