WJG Editorial Office

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Dear Editors:

We are very grateful for the reviewer's detailed comments on our manuscript (Manuscript NO. 20693). The comments have been helpful in allowing us to revise and improve our manuscript. Below, we have attempted to answer the comments and questions raised by the reviewers.

Response to Reviewer 00068153

Comments To Authors

Hepatic I/R injury is a major problem in liver transplantation and liver resection and a critical event during hepatic I/R injury is the death of liver sinusoidal endothelial cells (LSECs). In this study, the authors developed a new drug delivery system for targeting the LSEC by combining S1P with HA to make a formula of HA-S1P. They found HA-S1P exhibited cytoprotective effect on the liver by protecting LSECs, which demonstrated that HA-S1P might be a promising new agent for hepatic I/R injury.

Answer to Reviewer 00068153

Thank you very much for your constructive comments. We expect that the HA-S1P formulation lead to the development of useful new drugs of hepatic I/R injury.

Response to Reviewer 00053419

Comments To Authors

The manuscript by Sano et al reported the design of a HA-S1P conjugate that is able to prevent liver damage resulting from ischemia/reperfusion more efficiently than S1P. The basis of the reported finding is that HA-S1P target more efficiently sinusoidal epithelial cells and prevent apoptosis. The experiments are well designed and conducted but there are some issues for the author's consideration:

1. According to the reported results, HA-S1P is an efficient way to deliver S1P in liver sinusoidal endothelial cells but it is also important to show if S1P also increases in other cell types/tissues upon treatment since it might induce non-desired side effects.

Answer to Reviewer 00053419

1. With regard to side effects of HA-S1P formulation, in this experiment, it has resulted in hepatic I/R injury after administration of the HA-S1P formulation to rats, respiratory and circulation dynamics in rats was stable, and conspicuous abnormalities were not observed. Moreover, rats did not die after drug administration.

We have added the comments about this point at surgical procedure in the materials and methods (page 7, from line 9 to line 11). Specifically, during the period from drug administration until sacrificed, respiratory and circulatory dynamics of rats was stable. Moreover, all of rats did not die after drug administration.

2. Redox imbalance and mitochondrial injury play central roles in I/R induced liver injury, in fact most of the molecular markers measured in the study are manifestations of these alterations. However, no attention is paid

to these principal drivers of I/R injury in this study. It would be worth to show if HA-S1P prevents mitochondrial damage and redox imbalance.

Answer to Reviewer 00053419

2. Redox imbalance and mitochondrial injury play central roles in I/R induced liver injury. We have confirmed by using transmission electron microscopy that the mitochondria upon administration of HA-S1P was not impaired.

We have added the comments about this point at transmission electron microscopy in the results (page 9, line 29). Specifically, it was no obvious mitochondrial disorders in the HA-S1P group.

3.Some figures are very small and texts (axes titles…) can be hardly read.

Answer to Reviewer 00053419

3. According to the reviewer's comment, we have replaced the figures and texts.

Thank you for your consideration.

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