Peer Review File

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Reviewer A

Comment 1: The title is not focused and detailed.
Reply 1: The title has been changed (page 1; lines 1-2)

Comment 2: Lack of in vivo data and other published papers to support the hypothesis. Excluding basics knowledge of PSC, phosphatidylcholine transport story in intestine, there are few information about interplay between PSC and phosphatidylcholine, which more like a discussion section rather than a review article.
Reply 2: We describe a hypothesis based on data obtained in ulcerative colitis patients and ulcerative colitis mouse models. Beside these in vivo data we review the experimental evidence for a tight junction mediated apical transport of phosphatidylcholine in a cholangiocyte derived tumor cell line. More in vivo data of our proposed PSC mouse model are not available. There are also no other papers published to this issue.
However, findings fitting to our hypothesis are reviewed. These are basic mechanisms, correlation to findings in intestine and clinical observations.
We included all relevant literature dealing with this issue. Accordingly we draw conclusions. It is still only a theory. However, it could be a first step to open a new perspective in the darkness of pathogenesis of PSC. We are confident, that this is worth to be communicated. To follow the suggestion of the reviewer, we removed details and speculations about future in vivo experiments.
Accordingly we rewrote the manuscript in the respective paragraphs (page 8).

Comment 3: Since Mz-ChA-1 is a biliary tumor cell line. It is important have supporting data from primary cholangiocytes.
Reply 3: We refer to published data on transport of phosphatidylcholine across a confluent, polarized layer of the biliary tumor cell line Mz-ChA-1. It is considered the best model for biliary epithelium and it is used in numerous publications around the world. Primary cholangiocytes are not available for tissue culture experiments (page 12, first paragraph).

Comment 4: The authors put a lot of their published figures in this manuscript, which is inappropriate. The authors may reference the paper but not put the same figures.

Reply 4: We reduced the figures dealing with the experimental evidence down to one combined figure (now: new figure 3). The former figure 6A was skipped. The arrangement of the figure is different to the ones published. We think it is now more comprehensive. Its presentation is important for comprehensiveness of our hypothesis presented in this review article.
This can be seen in the new figure 3.

Comment 5: Did the authors summarize the PC concentration in bile/serum in different animal models of PSC or human PSC?
Reply 5: There are papers which describe the PC concentration in bile. We cited one representative publication. The PC concentration in serum is available in textbooks. We did not refer to PC in serum because it was not directly part of our argumentation in this review.
(page 10, 11).

Comment 6: As the authors mentioned "tamoxifen inducible intestinal deletion of kindlin-1 or -2 is an animal model of ulcerative colitis", "patients with ulcerative colitis develop PSC", did the authors see any phenotype changes in liver of this model?
Reply 6: We now mention that we did not see any changes in the liver of the genetic ulcerative colitis mouse models. It indicates that the induced colitis does not secondarily cause PSC due to bacterial translocation from intestine. (page 8)

Reviewer B
Comment 1: In this review manuscript, authors described and discuss various aspects of PSC including clinical features, diagnosis, treatment and their hypothesis towards pathogenesis of PSC. As result, this manuscript seems to be redundant. Authors may rewrite this article putting focus on their hypothesis. The latter part of this manuscript contains a lot of findings on various experiments. Authors may re-write this manuscript as an original article using these findings.
Reply 1: This manuscript was meant as a review and not as an original article. About 30% of the paper describes common knowledge regarding clinical presentation, natural course, diagnosis and therapy. It should point to the dilemma of the disease and the need for discovery of new avenues in pathophysiology and therapy.
It is not meant to be "only" an original article for the PSC scientific community. It is a bridge between ulcerative colitis and PSC which is the clue of the hypothesis.

Indeed 70% of the manuscript deals with our new hypothesis which is most likely not known to the readership.
For better communication of our theory we expanded on the proposed pathogenesis. Accordingly, we reduced the part on description of expected in vivo experiments.
Therefore it seemed appropriate for us to provide experimental evidence to support our theory. These already have been published as original articles.
We basically rewrote the entire article and structured the manuscript as a review article. Redundancies were avoided.