

Dear Editor,

We are submitting a revised version of our manuscript (#39247) "Role of complement in alcoholic liver disease". We are appreciative of the comments from the reviewers and have attempted to respond to their comments and suggestions in the revised manuscript.

We have attached a detailed description of how we have dealt with the reviewers' and the Associate Editor's comments for your consideration. A statement including point-by-point changes/additions.

We hope that the inclusion of requested materials and the responses to the reviewers' comments would be satisfactory. We look forward to working with your editorial staff.

Sincerely,
Songqing He

Response to comments of the reviewers

Reviewer #1

This is an interesting review on a novel topic. However, review is short (like a mini review) and must include new published studies (2017 and 2018). The table and figure are not satisfactory.

Response: The review have been renewed, and new published studies (2017 and 2018) have been included.

Reviewer #2:

Review on the manuscript “The Role of Complement in Alcoholic Liver Disease” The authors of this manuscript summarize the role of complement activation in the development of alcoholic liver disease. The topic is interesting and novel. There have been a few new animal studies published recently, and studies in humans are rare. Therefore, summarizing the current knowledge in this field is justified. However, the manuscript needs major revision in several points:

1. This review would benefit if the authors include a table summarizing the most important publications on complement in alcoholic liver disease, with information on the specific complement factors involved in the development of alcoholic liver disease and of the species/model studies have been performed (mouse/rat/human) in.
2. The manuscript lacks detailed information on findings of the involvement of complement activation in humans with ALD (e.g. Shen H. et al “Increased activity of the complement system in the liver of patients with alcoholic hepatitis”; Wlazlo N. et al “Activated complement factor 3 is associated with liver fat and liver enzymes: the CODAM study”; Jia Q. et al “Association between complement C3 and prevalence of fatty liver disease in an adult population: a cross-sectional study from the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIHealth) cohort study”)
3. I suggest including a recently published study on the role of Factor D in alcoholic liver disease “McCullough et al., Complement Factor D protects mice from ethanol-induced inflammation and liver injury.
4. The abstract states that “most scholar believed ...”. Please be more careful with the wording – that the complement activation might be involved in the development of alcoholic liver disease does not exclude other important factors.
5. Introduction, last paragraph: Please include citations for the statements made (e.g. liver becomes the main target of damage by complement activation)
6. Complement activation pathway: this paragraph is too long and is missing several citations. It is solely a repetition of the already known facts on the complement system Please concentrate more on the factors important in the development of alcoholic liver disease. Furthermore, the figure legend of Figure 1 should include a better description; this could shorten the text of this paragraph.
7. 3.1., 2nd paragraph: Please correct English grammar.
8. 3.2. 1st paragraph: Authors should describe the animal model used in more detail.

Response:

1. This is indeed a very good advice. As there're a lot of researches on it, and some researches of the current literature are still controversial, we intend to do a next system review or meta-analysis for this problem.
2. Detailed information on findings of the involvement of complement activation in humans with ALD were included in the manuscript.
3. We ignored the studies of D factor in alcoholic liver which were very important in the regulation of complement in our review. As the reviewer 2's comment: McCullough. et al. found FD-dependent amplification of complement is an adaptive response that promotes hepatic healing and recovery in response to chronic ethanol.
4. We have revised "most scholar believed ..." to "many scholar believed" in the abstract.
5. We have included citations for the statements made (e.g. liver becomes the main target of damage by complement activation) .
6. We have revised the paragraph of complement activation pathway. And the Figure 1 legend have been revised.
7. We have corrected the English grammar in the manuscript.
8. We have added the animal model description in 1st paragraph.

Reviewer #3:

The authors have performed an interesting review about a usually overlooked topic. However, I think that some improvements may be made:

1. We recommend authors include some figures (e.g., regarding activation of complement or explaining how different parts of the complement system are activated in ALD) and tables.
2. "Alcoholic hepatic fibrosis" maybe should be termed "alcoholic liver cirrhosis". Subheading 3.4. should include some word regarding Kupffer cells (e.g., "Complement induced Kupffer-cell activation or modulation... " Authors should also talk about gut permeability and/or gut-liver axis since this is a key concept in alcoholic liver disease. For instance, please see: Prosteatotic and Protective Components in a Unique Model of Fatty Liver: Gut Microbiota and Suppressed Complement System. Long Liu, Xing Zhao, Qian Wang, Xiaoxian Sun, Lili Xia, Qianqian Wang, Biao Yang, Yihui Zhang, Sean Montgomery, He Meng, Tuoyu Geng & Daoqing Gong. Scientific Reports volume 6, Article number: 31763
3. No references are listed from 2017 or 2018. There have been some interesting publications (e.g. <https://www.ncbi.nlm.nih.gov/pubmed/28982257>), so authors should update their reference list.
4. This article is also an example of potential clinical implications of complement system modulation in alcoholic liver disease. We recommend authors include another subheading (Clinical implications) regarding diagnosis and therapeutic aspects of complement system in alcoholic liver disease

Response:

1. The activation and regulation of complement have been indicated in the figure 1 and table 1. So we didn't summarize them further.

2. We have revised Subheading 3.4 to “Complement induced Kupffer-cell activation in alcoholic liver disease”. And gut permeability and/or gut-liver axis have been talked in the review.

3. we also updated the references about the complement system modulation in alcoholic liver disease.

4. The study of the relationship between complement and alcoholic liver is mostly researched in animal experiments, and there is little research on clinical application. Therefore, this review did not elaborate on the clinical implications of complement. This part of research needs further study by scholars before making a summary.

Reviewer #4:

The topic is very interesting. But the review is very short. Only one table and one figure. You can expand the information. Thank you

Response: To Reviewer: 4

We have updated the information about the regulation of complement in the manuscript.