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Jin-Zhou Tang  
Science Editor, Editorial Office  
Baishideng Publishing Group, Inc.  
WORLD JOURNAL OF GASTROENTEROLOGY  
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**RE: Point-by-point responses to the comments of the reviewers of the invited Review article (MS number, 52439), entitled "Examining pathogenic concepts of autoimmune hepatitis for cues to future investigations and interventions," by Albert J. Czaja, MD (author ID: 02396550).**

**Author ID: 02396550**

**Manuscript type: REVIEW**

**Manuscript number: 52439**

**Journal: WORLD JOURNAL OF GASTROENTEROLOGY**

Dear Jin-ZhouTang:

My invited original Review article (manuscript number, 52439) entitled, "Examining pathogenic concepts of autoimmune hepatitis for cues to future investigations and interventions," has been revised in accordance with the suggestions of the reviewers. These suggestions have now been incorporated into the revised version, and they have been strengthened the article.

The revised manuscript (MS number, 52439) has been submitted electronically as instructed for further consideration of publication in the WORLD JOURNAL OF GASTROENTEROLOGY.

My point-by-point responses to the comments of the reviewers and the nature of the revisions are provided below. As requested, the changes in the revised manuscript have been highlighted to facilitate the review process.

Reviewer: 02540329

1. No specific comments were made.

Reviewer: 02708103

1. General comments: The female bias for autoimmune hepatitis is now addressed on page 21 in the first 6 lines of the first paragraph in the subsection entitled, “*Intestinal microbiome and gender bias*”.
2. Genetic Predisposition: The references to De Boer YS, Gastroenterology 2014;147:443-452 and Webb GJ, J Autoimmunity 2016;66:25-39 had been included in the subsection entitled “Genetic predisposition” (pages 6-7), and they are now highlighted on page 7 as references 65 (De Boer) and 23 (Webb). The reference to Qiu F, Nat Commun 2017;8:14828 was excluded because it relates to GWAS results in primary biliary cholangitis (PBC).
3. Epigenetic changes: The controversy regarding the heritability of epigenetic changes is acknowledged, and its mention has been deleted from the text (page 7, first paragraph, subsection on “Epigenetic changes”).
4. Microbial infection: The subsection on “Microbial infection” has been revised to indicate that a single viral agent that causes autoimmune hepatitis is unlikely (after decades of observation and pursuit) and that viruses mainly have role (like other environmental factors) in exposing individuals to epitopes that can help overcome immune tolerance of self-antigens (last two sentences, 1<sup>st</sup> paragraph, page 12)
5. Superantigens: This subsection has been shortened as indicated in the first paragraph on page 13.
6. Neo-antigens and Bystander Activation: The subsections on pages 18 and 19 have been shortened, but their core components have been retained since their role in autoimmune hepatitis has not been assessed and they may constitute areas of future investigation.
7. Intestinal dysbiosis: The justification for retaining the subsection on “Intestinal microbiome and gender bias” has been strengthened by the revisions made at the top of the first paragraph of the subsection entitled “Intestinal microbiome and gender bias” (page 21, first two sentences). It is in this paragraph that the importance of female bias for autoimmune hepatitis is addressed (as requested in comment 1 above). It is also an avenue of investigation that may help explain (and possibly manipulate) the gender bias. Similarly the subsection on the “Intestinal microbiome and the hygiene hypothesis” has been retained to indicate another uninvestigated area in autoimmune hepatitis that may explain the risk for its occurrence.
8. Former reference 50 has been deleted.

Reviewer: 00681914

1. The organization of the headings and subheadings of the manuscript was made in accordance with the author instructions provided by the journal. The proposed numbering of the headings and subheadings has merit, but I have been reluctant to incorporate these changes without instruction from the editors.
2. The diagnosis of autoimmune hepatitis is now discussed in the first paragraph of the Introduction (page 4), and the various autoantibodies that have been most commonly used (and available) for the diagnosis are provided. The table provided by the reviewer on the serological markers in autoimmune liver diseases is comprehensive and valuable, and I have incorporated key components relevant to autoimmune hepatitis in the first paragraph of the Introduction (page 4). I agree that the diagnostic aspects of autoimmune hepatitis should be addressed in another paper.

Editors

1. The manuscript has been formatted in accordance with the example provided by the journal, and it now includes a “core tip” (see highlighted paragraph).
2. The files labelled “52439-Manuscript File”, “52439-Answering Reviewers”, “52439-Audio Core Tip”, “52439-Conflict of Interest Disclosure Form”, and “52439-Copy License Agreement”, “52439-Image File. Figure 1”, and “52439-Image File. Figure 2” have been submitted as requested.
3. The 4 files (“52439-Approved Grant Application Form”, “52439-Non-Native Speakers of English Editing Certificate”, “52439-Video”, and “52439-Supplementary Material” are not pertinent to this manuscript and not submitted.

Please do not hesitate to contact me if there are questions or concerns. Thank you for considering this revised original review for publication.

Sincerely,

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