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October 6, 2016

Yuan Qi
Science Editor, Editorial Office
Baishideng Publishing Group, Inc.
WORLD JOURNAL OF GASTROENTEROLOGY
8226 Regency Drive
Pleasanton, CA 94588 USA

RE: Point-by-point responses to the comments of the two reviewers of the invited Frontier article (MS number, 29424), entitled "Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis," by Albert J. Czaja, MD (author ID: 00001621). This article is being considered for publication in the WORLD JOURNAL OF GASTROENTEROLOGY.

Author ID: 00001621
Manuscript type: Frontier
Manuscript number: 29424

Dear Yuan Qi:

My invited original Frontier article (manuscript number, 29424) entitled, "Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis," 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 29424 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 1 (Reviewer's code: 00055095)

1. The ability of butyrate to modulate the beta-catenin-dependent Wnt signaling pathway within specific cells is now presented (last two lines, page 23 to first 18 lines, page 24; see highlighted text). The articles cited by the reviewer have been

examined, incorporated in the text, and included in the references. The key molecular target of butyrate has been provided (PPAR gamma), and the effects of butyrate on caspase activation, apoptosis, and autophagy are now included. The role of butyrate and other short chain fatty acids as moderators of intestinal mucosal cell proliferation and function has been discussed, and the possible impact of these actions on the prevention of systemic autoimmune responses and progressive colorectal cancer has been included.

2. The misspelling of propionate has been corrected.

Reviewer 2 (Reviewer's code: 02441737)

1. The Abstract (now 191 words) has been revised to include the aims of the study and a conclusion (page 4; see highlighted text)..

2. The Introduction has been revised to indicate the incidence and prevalence of autoimmune hepatitis in different geographical regions and ethnic groups, including the USA (1st paragraph, page 8; see highlighted text).

3. The criteria used to select the articles cited, and the number of articles chosen are now provided in a METHODS section (page 11; see highlighted text).

4. The microbiome does vary between ethnic groups within the same country and between different countries. The key factors that shape the microbiome in different ethnic groups are now provided, emphasizing associations mainly with socioeconomic status and long-term dietary habits. There is not an ethnic-specific microbiome, but there are functional and phylogenetic core components of the microbiome that are shared across ethnic groups. These core components are probably preserved because they are important in maintaining well-being by producing short chain fatty acids, synthesizing vitamins, mounting protective immune responses, and modulating digestion and nutrition. These aspects are now included in the section, Intestinal Microbiome and Immune Responses (last paragraph, page 12 and 1st paragraph, page 13; see highlighted paragraphs).

5. The effects of changing levels of estrogen and progesterone on the composition of the intestinal microbiome and the immune response has been expanded to indicate possible direct (promotion of the type 1 cytokine pathway of lymphocyte differentiation) and indirect (alterations in composition of the microbiome) estrogenic effects on the immune response (page 21, 1st 12 lines; see highlighted text). The relationship between sex hormone levels and the intestinal microbiome during pregnancy, menses, and menopause remains uncertain and important to clarify.

6. The role of psychological stress on the intestinal immune response and the intestinal microbiome is speculative and not included.

Editors

1. A conflict of interest statement has been fashioned in accordance with the template provided by the editor and included on page 2 (see highlighted text). A signed and dated TIF of this same statement by the corresponding author has been inserted on page 2.
2. A core tip of 81 words has been provided on page 5 (see highlighted paragraph).
3. An Audio core tip has been pasted as an mp3 file on page 5.
4. A biography of Albert J. Czaja, MD has been provided on pages 5-7 in accordance with the example provided by the journal for Frontier Articles.
5. The sole author abbreviation name and title on the manuscript have been provided on page 7. It is the same as on the copyright.
6. The text has been modified to include pertinent new information not included in the original submission (last sentence, page 9; last two sentences, 2nd paragraph, page 10; see highlighted text).
7. Minor grammatical and spelling corrections have been performed throughout the text.
8. A decomposable Figure 1 has been inserted in the text (page 91) as a color ppt. file.
9. I require additional instruction regarding the use of Google Scholar and CrossCheck. I have searched for the final title on Google Scholar, and I found no matches. I am unclear of the screenshots that are required to document this negative search. The CrossCheck website requires membership and seems to be used mainly by Publishers and Libraries. I could not log in to use this site, and I require instruction as how to use this program. I suspect that it is best applied by the Publisher and not the Author. Accordingly, I was unable to complete the checklist for items 6 and 7 requested for submission of the revised manuscript.

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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