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ESPS manuscript NO: 12026

Title: Hyperhomocysteinemia as a potential contributor of colorectal cancer development in inflammatory bowel diseases: A review

Dear Editor-in-Chief,

Thanks a lot for giving us the opportunity to revise our manuscript titled "Hyperhomocysteinemia as a potential contributor of colorectal cancer development in inflammatory bowel diseases: A review" that has been submitted to your prestigious journal. This is our point-by-point response to the comments raised by the 4th reviewer (#01441415) in the second round of review. Please notice that the comments from the first three reviewers have been answered by us in the first round of the peer-review process. All required changes have been highlighted in green in the revised manuscript. Please feel free to contact me if you require further information.

Sincerely yours,

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Reviewer code: 01441415

1) This review manuscript by Keshteli et al. summarized current knowledge regarding the role of hyperhomocysteinemia and colorectal cancer in IBD patients in a comprehensive fashion. Although, the evidence for the direct mechanism for cancer development is sparse, the topic itself is quite attractive and promising. Thanks for your feedback. We are glad to hear that!

The authors mentioned about MTHFR C677T polymorphisms in this manuscript. This polymorphism seems to predominantly contribute to hyperhomocysteinemia. It is also known that the polymorphism is functional, relatively common mutation (the T allele frequency is reported to be 0.33). Reported genetic studies suggested the association between the polymorphism and cardiovascular diseases. If studies investigating the association between the

polymorphism and colon cancer (and/or IBD) exist, please mention it. We appreciate your excellent suggestion. Yes, there are some studies regarding the association between the polymorphism and risk of colorectal cancer/IBD. We have added them to relevant sections in the manuscript. Please see page 11 for MTHFR C677T and IBD (reference # 39 and 40) and page 12-13 for MTHFR C677T and colorectal cancer associations (reference #26, 45-47).

Reviewer #00068723

This review is a rare theme on hyperhomocysteinemia and carciongenesis. “4. Homocysteine metabolism and pathogenesis of hyperhomocysteinemia” illustrates background information synergistic with Figure 1. Interesting point is a potential application of hyperhomocysteinemia as a tumor marker of colorectal cancer. Thanks for showing interest in the review!

The relation between hyperhomocysteinemia and colorectal cancer was not clear. Does hyperhomocysteinemia promote carcinogenesis of colorectal cancer? Are there any experimental evidence on this? How do serum levels of homocysteinema change during progression from IBD to colorectal cancer? Do the authors have any speculation on role of hyperhomocysteinemia in carcinogenesis of colorectal cancer? Thanks for your comments. Unfortunately, we were unable to find relevant experimental studies. In the revised manuscript we have highlighted the importance of performing such studies. More information regarding the role of homocysteine in the cancer and colorectal cancer development has been added to the revised manuscript (please see section 5-7 of the revised manuscript)

Reviewer #02438768

I have some comments regarding the manuscript. 1. No cirtical supportive data are intended for demonstrating that hyperhomocysteinemia can promote colorectal carcinogenesis. More supportive data has been added to sections 5, 6 and 7 of the revised manuscript.

2. There is little evidence for a mechanistic relation between hyperhomocysteinemia and increased risk of colorectal cancer in IBD patients, though the authors claimed that they would review the mechanisms between them. The aim of the present review is to highlight the potential role of hyperhomocysteinemia in colorectal cancer development in IBD patients. Current epidemiological data, although limited, support such association. In the revised manuscript taking into account such limitations in the number of such studies in IBD patients, after providing more documents on how

homocysteine level can be related to colorectal cancer development we have suggested performing more well-designed experimental and clinical studies. We hope such modifications can satisfy you.

**** PLEASE notice that the comments from this reviewer in the format of a word document file, is NOT related to our manuscript at all!**

Reviewer #00068278

This is a well written review. As already stated, the relation between hyperhomocysteinemia-folate deficiency and colorectal cancer is still open to question. Thanks a lot for showing interest in our manuscript!

A minor correction: Page 9, line 8, must be .. dysplasia-associated lesions or messes, or colorectal CARCINOMA in 114 IBD patients. Thanks a lot for your comment. It has been corrected in the revised manuscript.

Comments from Wen Lingling

Author contributions: This section has been added to the revised manuscript.

Core tip: This section has been added to the revised manuscript.

Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. PMID and DOI was added for each citation.

Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily. The revised figure was added. Please kindly let us know if the current format is satisfactory.