Jan. 26nd, 2022

Dear WJG Editor:

We want to thank the reviewers for their positive comments and insights after their reviews of our paper entitled "*Inflammation, the microbiome, and colorectal cancer disparity in African-Americans: Are there bugs in the genetics*" by Ahmad et al. We have now revised the manuscript to address the reviewers' concerns as well as followed the guidelines provided to format the manuscript in accordance with *World Journal of Gastroenterology* standards. We have provided a copy of the manuscript as supplemental information and with the revisions underlined.

**A-Reviewer #1:**

"The manuscript raises interesting questions, related to the patient-specific cancer prediction and treatment. However, I have some critical comments"

1. Please, provide figures, relevant to the content of the manuscript […] . figures are not carrying any useful information.

We agree with the reviewer that without text, the figures maybe difficult to follow. We edited the figures especially figure 1 by adding annotations. However, we strongly believe that these three figures are important to illustrate the main points our review aimed to highlight: 1, In figure 1, the selection of immune relevant genetic variants can be beneficial for survival to infection in endemic region, but become a risk factor for Colorectal Cancer when associated with different environmental factors (Rural African versus African Americans); 2, Figure 2 is important to explain how a bacteria or a genetic variant may not be critical risk factors for Colorectal Cancer by themselves, but when combined in a same host may facilitate colon carcinogenesis. Therefore, GWAS or microbiome GWAS (mGWAS) have lower chance to capture this "combined risk". That is the follow up of figure 1, explaining how a genetic variant not associated with Colorectal Cancer in Rural Africans may become a Colorectal Cancer Risk factor in western environment where different bacteria may interact with an immune response which is regulated by the inherited genetic variant; 3, Figure 3 is the final aspect of the review, illustrating that for the reasons depicted in the 2 first figures, population-specific mGWAS are necessary to detect these associations between bacteria (Taxa) and SNP (host genetic) and generally missed by studies not adequately powered for population diversity.

We have revised the legends and modified the graphics, hoping that they will support better the review [**page 45-49**].

2. […] Tables are very hard to read.

We have revised and edited the tables. We apologize to the reviewers because we realized that several headers of the columns were missing and making the reading of these tables indeed difficult.

We have also provided the original Tables as supplemental information since we have some concerns that the formatting guideline proposed by the journal may make the tables difficult to follow (alignment concerns). See below

3. In general, the manuscript is separated into several sections not connected to each other, jumping from one topic to another. Please, organize the manuscript in a logical way, so the reader could follow it step by step.

We have edited the introduction [**page 6**] and several other parts [**pages 6 and 9**] of the text to explain better the choice and organization of the sections. These sections have a logical organization: 1-the first section recalls the links between inflammation and microbiome with CRC pathogenesis. This sets up the choice of the following sections: Ancestry and inflammation then ancestry and microbiome ; 2-the second section looked at the role of genetic ancestry into the regulation of the innate immunity; 3-the third section looked at the role of the genetic ancestry into the nature of the microbiome; 4-The conclusion is proposing the concept that genetic and microbial risks should be integrated in population (African American) specific CRC risk studies to take into account the role of the genetic ancestry in the regulation of the innate immunity and the microbiome.

We strongly believe that this layout makes perfect sense, but we agree with the reviewer that we may not have previously linked appropriately the sections to each other. We have therefore edited the introduction and added transition statements to facilitate the reading [**pages 6 and 9**].

4. Please, provide a clear conclusion (without references) and state clearly the advantages and significance of the suggested "integrated concept", comparison to the current and/or other concepts.

We have reorganized the conclusion statement and explained better the need of integrated genetic/microbial risk factors and the use of the genetic ancestry/admixture as a proxy of population diversity. We compared this approach with the GAME-ON initiative of the NIH and emphasized (using figure 2 and 3) how GWAS or mGWAS and meta-analysis are poised to miss CRC risks at the level of minority populations [**pages 18-20**].

We rewrote the conclusion and eliminated most of the reference except the ones used for comparison purpose.

**B-Reviewer#2 :**

" The authors wrote a quite interesting review on intersections of inflammation, microbiome, genetics, and colorectal cancer (CRC). This is generally of high interest"

We thank the reviewer for the appreciation of our study.

" Following things should be addressed and the authors should improve the paper".

General response from the authors to the reviewer#2 comments: reviewer#2 comments are mainly focused on the environment features, which, we agree, are predominant risk factors to CRC and important for prevention. We have stated several times in the manuscript [**pages 6, 16**] that these aspects of CRC have been extensively reviewed in other journals. Herein, we are specifically focusing on one aspect of CRC that has been, to our opinion, underestimated and which is the modulation of CRC risk by the genetic background of minorities and ethnicities.

Often the distinctions between populations in the context of CRC is limited to difference in diet, SES, and exposures (antibiotics, chemical, smoking, and alcohol). We of course did not contest this aspect of CRC disparities and which is fundamental to CRC pathogenesis. But we pointed out that the genetic regulation of the innate immunity, which can be impacted by the level of African admixture may also differently modulate the risk between African Americans and European Americans. The consequences in term of prevention are highlighted in our conclusion by the consideration of a risk calculation that would integrate genetic variants and microbiome in population-specific studies (Figure 3). Comments have been added **pages 6 and 19**

Specific comments:

1-"The authors should discuss more prevention and early detection as main topics since they are important in reducing the cancer burden much more effectively than treatment"

The scope of the review is more focused on evidence of interaction between host genetics and bacteria into CRC risk. However, we added general comments in the conclusion remark

2-"The authors touch on environment only little. There are many environmental, dietary, and lifestyle factors that influence the microbiome (in both intestine and other tissue), inflammation, immune system, pathogenic mechanisms. The authors should emphasize factors other than diet too, eg, smoking, alcohol, obesity, diabetes, bowel habits, etc".

We mentioned these factors **page 16**. However, we believe that these important factors for CRC pathogenesis and prevention are beyond our primary scope (genetic ancestry and microbiome into CRC risk).

3-"The authors touch on genetics. There are also influences of germline genetic variations on both immune system and microbiota".

We believe that genetic variants are part of the germline genetics. We limited the host genetics to the genetic ancestry-associated variants which could explain population-specific regulation of inflammatory pathways. But we also briefly mentioned the impact of somatic mutations on the microbiome [**pages 16-18**].

4-"Gene-by-environment interactions should be emphasized. In these lines, research on dietary / lifestyle factors, microbiome, immunity, and personalized molecular biomarkers in tumor is needed for prevention and treatment research".

See comment below.

5-"The authors should discuss molecular pathological epidemiology research that can investigate those factors in relation to microbiome, molecular pathologies, immunity, inflammation, and clinical outcomes. Molecular pathological epidemiology research can be a promising direction. Strengths and challenges of molecular pathological epidemiology (Ann Rev Pathol 2019, Curr Colorectal Cancer Rep 2017, etc.) should be discussed".

Thanks to the reviewer for this comment which is indeed relevant to our review. We have added two references by Ogino's group including "Integration of Molecular Pathology, Epidemiology,

and Social Science for Global Precision Medicine" in 2017 Expert Rev Mol Diagn which discuss the benefit of MPE for addressing CRC disparities [**pages 17 and 19; ref 127 and 128**]

Since the scope of our review which focused on the host genetics, we pointed out the necessity to incorporate the genetic ancestry and admixtures to this model of integrative science [**page 19**].

6-"Tables must have HUGO-designated official gene symbols for all genes. The authors used proper standardized SNP IDs. The same principle holds for gene names. Some names (eg, TGFb and many others) are not official symbols. Please check every gene at www.genenames.org".

We have corrected gene and protein names according to their official HUGO-designated official symbols.

**C- Science editor:**

The manuscript describes a review of " INFLAMMATION, MICROBIOME AND COLORECTAL CANCER DISPARITY IN AFRICAN AMERICANS: Are there bugs in the genetics? "The topic is within the scope of World Journal of Gastroenterology. The authors wrote a quite interesting review on intersections of inflammation, microbiome, genetics, and colorectal cancer (CRC).The authorsconcluded that multi-ancestry microbiome GWAS is needed to study colorectal cancer disparities.and it could be acceptable for publication after a minor revision. The questions raised by the reviewers should be answered. Recommendation : Minor revision.

Thank you for the comments. We have answered and addressed the comments of the reviewers to the best of our knowledge.

**D-Company editor-in-chief**

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Figure 1 has been done using Biorender and can't be decomposed in Power-Point file. The decomposable figure is accessible by sharing the Biorender document and we will be happy to share the access to the figure. The two other figures are now provided in their ppt format.

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Tables have been reformatted following the journal guidelines.

*To the attention of the editor*: we have nevertheless added as a supplemental document the original tables since the formatting recommended by your journal is interfering with the alignement of SNP, corresponding genes and comment that may make the tables difficult to follow. We are willing to work with the editing office to improve the table format.

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

The manuscript (text and tables) has now been edited and formatted using Filipodia services. A locked version and a copy of the certificate have been submitted as revised manuscript.