March 6, 2023

Lian-Sheng Ma

Editorial Office director and Company Editor-in-Chief

World Journal of Stem Cells

Dear Dr. Lian-Sheng Ma:

Thank you for your letter of February 16, 2023, informing that the Manuscript NO: 82012 titled "**How the interplay among the tumor microenvironment and the gut microbiota influence the stemness of colorectal cancer cells**" has been found to be potentially publishable in the journal pending appropriate revision.

We have carefully reviewed the comments of the reviewers, the Science editor and the Company editor-in-chief and have modified the manuscript in response to their suggestions. We appreciate this criticism which has contributed to improving the presentation of our work.

Detailed in the enclosed sheet there is an enumeration of the changes made in our manuscript. We hope that it will be possible for you to find our paper fully acceptable for publication in the World Journal of Stem Cells.

. Yours sincerely,

Dr. Claudia Gentili

Address for correspondence:

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Comments to the Editorial Office

As indicated below, we revised the manuscript according to the Editorial Office's comments and indications.

Comments to the Science Editor

We appreciate the opinion of the Science editor regarding our work. We have carefully checked the entire contribution and we have improved the language.

We have responded to all the Reviewers' concerns and queries. In this regard we have added suggested information in the following the sections:

1) **INFLUENCE OF THE TME ON CCSC FEATURES**
2) **ESTABLISHED DYNAMICS BETWEEN THE GUT MICROBIOTA, THE TME AND CCSC**
3) **THERAPEUTIC TARGETING OF TME AND THE GUT MICROBIOTA: A KEY TOOL TO MODULATE STEMNESS IN CRC**
4) **FUTURE PERSPECTIVES**

We have now included information regarding the effects of the tumor microenvironment (TME) and the colon cancer stem cells (CCSC) on gut microbiota. We also addressed in the revised manuscript the novel implications of fecal microbiome transplantation (FMT) and the impact of the intestinal microbiota on the immune status of tumor patients focusing on how the microbiota affect the expression of PD-L1. Moreover, we have now improved Table 2 and Figure 2 of the final manuscript according with reviewers 'suggestions. We hope that after these modifications you consider our Minireview acceptable for publication.

Comments to the Company editor-in-chief

Thank you for considering that the manuscript is conditionally accepted. We have revised the manuscript according to the Peer-Review Report, the Editorial Office's comments and the Criteria for Manuscript Revision by Authors. We have carefully checked the entire contribution and we have improved the language. We supplement and improve the reviewed information presented in this work with recent publications on the subject by applying the Reference Citation Analysis (RCA) according to the Peer-Review Report.

We also provide decomposable figures that are organized into a single PowerPoint file and we check that the tables meet the requirements of standard three-line tables, with only the top line, bottom line, and column line displayed.

We confirm that all figures are original; so, we add the copyright information on the bottom right-hand side of each picture in PowerPoint (PPT).

Comments to the reviewers:

We appreciate that the Reviewers, the Science Editor and the Company editor-in-chief taking the time to revise our work. We consider your opinion very valuable to improve the quality of our work. We hope that all the changes made meet your expectations. We indicate in this letter the pages and paragraphs of the revised manuscript where we incorporated the modifications according with the suggestions of each reviewer.

Reviewer #1:

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revisión

Novelty of This Manuscript: Grade B (Good)
Creativity or Innovation of This Manuscript: Grade B (Good)
Scientific Significance of the Conclusion in This Manuscript: Grade B (Good)

Specific Comments to Authors:

1.This research focused on How the interplay among the tumor microenvironment and the gut microbiota influence the stemness of colorectal cancer cells, after check the pubmed, there are not similar articles , so was very innovative. 2.The topic of this manuscript fall within the scope of the journal, focus on stem cells.

Author response:

Dear reviewer, thank you for your time reviewing our work. We appreciate your valuable observations. We have arranged and numbered your comments to facilitate the process of analyzing our revised manuscript.

Reviewer's comment 1.

3.There are so many studies identified that gut microbiota and its metabolites on the host immune system and the formation of TME, but how TME effect on gut microbiota? Also the same question how CCSC effect on gut microbiota?

Author response to comment 1:

To satisfy the concern of the reviewer, we described the impact of the stroma cells on gut microbiota with focus on: 1- physiological condition and 2- pathological situation.

1- In physiological conditions, stromal and immune cells interact with microorganisms and its products to maintain the intestinal equilibrium (Hooper et al., 2012). Cells from the immune system recognize antigens from foreign cells and generate memory and effector cells, which control or avoid the generation of diseases (Hooper et al., 2012).

2- On the other hand, in a disease as CRC, the local metabolic environment is modified (Garza et al., 2020). In this context, metabolites and factors derived from CRC cells and TME cells such as spermidine, L-valine, L-lysine or stearic acid confer an advantage for the growth and development of certain bacterial species, conditioning changes in the intestinal microbiota. (Garza et al., 2020). Although different factors produce changes in gut microbiota, recently it has been seen that the shift in the metabolome of tumor cells and TME cells is a key aspect in this event (Garza et al., 2020; Seely et al., 2022; Gao et al., 2022).

Appropriate comments regarding the influence of stroma cells in normal and pathological situation (in the last case with updated bibliography) are now added in the Section "**Established dynamics between the gut microbiota, the TME and CCSC**" (page 13 paragraph 4 - page 15 paragraph 2).

It is noted that to satisfy the suggestion of the other reviewers, we have now added information in our manuscript concerning the influence of the intestinal microbiota on the immune status and TME of CRC patients, and how this interaction could affect therapy response in the Section "**Established dynamics between the gut microbiota, the TME and CCSC**" (page 14 and 15).

Regarding whether CCSC affect gut microbiota, today no information is available on the subject at least to our knowledge. However, the findings observed in the area of study support the following idea: since the altered intestinal microbiota acts through the action of their metabolic products triggering the development of CCSC, it is probably that the presence of CCSC in the intestinal mucosa may be favor, by the release of specific factors, the dysbiotic changes of the gut microbiota.

At the present, researchers' efforts have focused on the study of how a dysbiotic condition can influence CCSC development and properties or the TME that promote CRC progression. We have reviewed this information in our manuscript. However, the other point of view is of great interest, so we have incorporated a paragraph referring to this topic in the "**Future perspectives**" section (page 23 paragraph 3)

Reviewer's comment 2.

4.In table 2, totle molecular subtypes (CMS) of CRC>100%

Author response to comment 2:

We appreciate the reviewer's observation. Based on the Reviewer's comment, we have now improved **Table 2** of the revised manuscript (**Table 1** of this letter). We completed this table with the unclassified subtype of colorectal cancer. So, the 5 subtypes of CRC now reaches 100%. An appropriate comment is now added in the Section "**Influence of the TME on CCSC features**" (page 12 paragraph 5) of the revised manuscript.

Table 1. Consensus molecular subtypes (CMS) of CRC.

Consensus Molecular Subtypes					
	CMS1 - Immune (14%)	**CMS2 - Canonical (37%)**	**CMS3 - Metabolic (13%)**	**CMS4 - Mesenchymal (23%)**	**Unclassified (13%)**
General features	Hypermutated, Microsatellite unstable	Epithelial, WNT and MYC signaling activation	Epithelial, Metabolic dysregulation	TGF-β activation, angiogenesis, upregulation of EMT,	Mixed phenotype of multiple CMS
Mutations	BRAF MSH6, RNF43, ATM, TGFBr2, PTEN	APC, KRAS, TP53, PIK3CA	APC, KRAS, TP53, PIK3CA	APC, KRAS, TP53, PIK3CA	
TME	Decrease of CAFs High immune and inflammatory signature	Decrease of CAFs Low immune and inflammatory signature	Decrease of CAFs Low immune and inflammatory signature	Increase of CAFs Immunosuppressive signature	

APC, adenomatous polyposis coli gene; ATM, ataxia telangiectasia mutated gene; BRAF, serine/threonine-protein kinase B-raf gene; CAFs, Cancer associated fibroblasts; CMS, Consensus Molecular Subtype; EMT, Epithelial to mesenchymal transition; *KRAS, ki-ras2 kirsten rat sarcoma viral oncogene homolog gene; MSH6, MutS homolog 6 gene; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PTEN, phosphatase and tensin homolog gene; RNF43, ring finger protein 43 gene*; TGF-β , Transforming growth factor beta; *TGFBr2, transforming growth factor beta receptor 2 gene*; TME, tumor microenvironment; *TP53, transformation-related protein 53 gene.*

Reviewer's comment 3.

5.Figure 2 I think not very clear and cannot represent the relationship between each other clearly.

Author response to comment 3:

Thank you for your comment. Based on the Reviewer's observation, we have now improved the **Figure 2** and its legend of the revised manuscript (**Figure 1** of this letter). We have described more precisely each step presented on this of the figure and also complete it with the known effects that have the components of the CCSC-TME-microbiota triad on each other, in CRC.

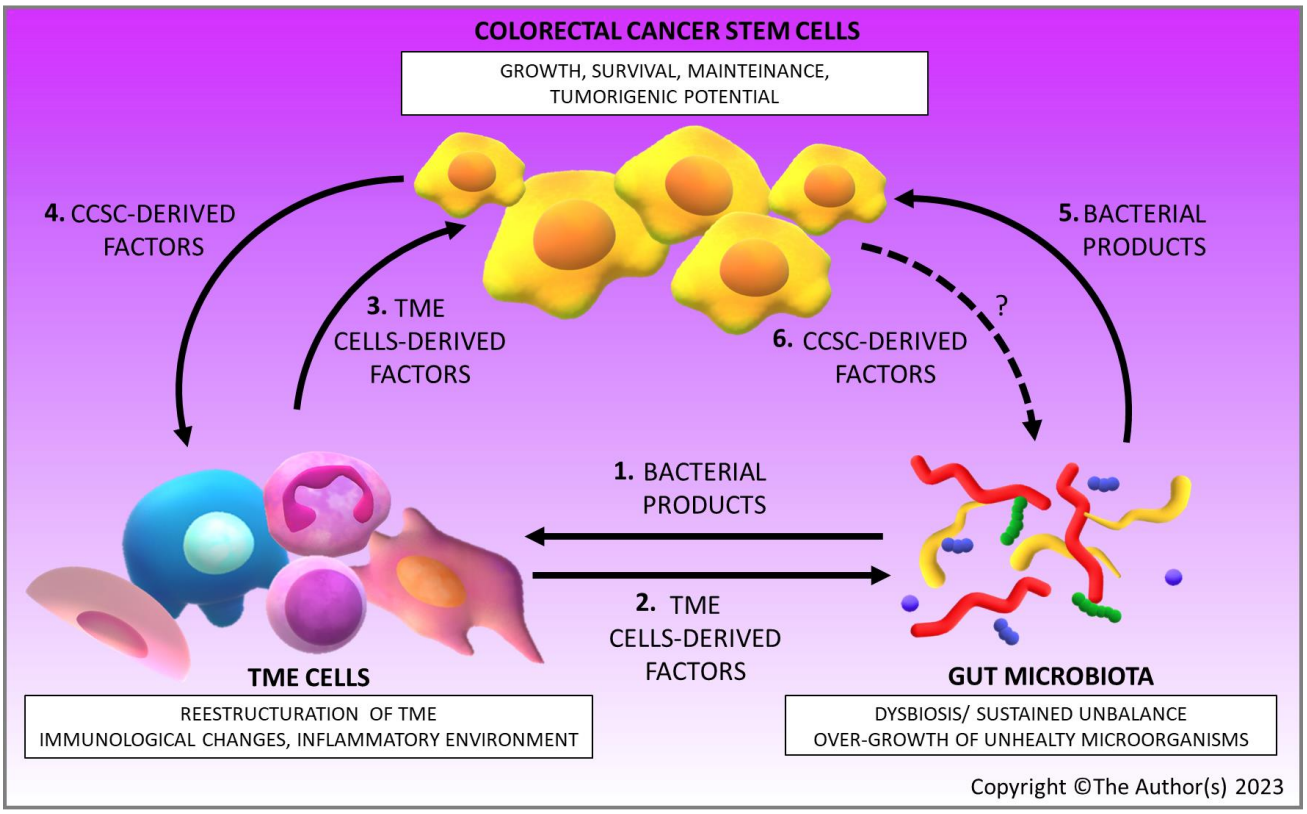

Figure 1. The interplay among the tumor microenvironment and the gut microbiota influences the stemness of colorectal cancer cells

1) Gut microorganisms and/or their derived products in a dysbiosis context influence the restructuration of TME, favoring the release of several factors (growth factors, cytokines, non-coding RNAs and enzymes), immunological changes and an inflammatory environment. 2) The factors released by TME cells impact on intestinal microbiota promoting the growth of unhealthy microorganisms and their sustained unbalance. 3) Moreover, these TME factors can modulate the properties and behavior of CCSC promoting effects such as their growth, survival, maintenance and tumorigenic potential. 4) In this context, CCSC response expressing factors that enable them to communicate with stromal cells and also influence a TME restructuration. 5) Microorganisms and/or their derived products can directly

modulate the features and properties of CCSC, which in response 6) probably affect the intestinal microbiota. All these associated events contribute to CRC progression.

CCSC, colorectal cancer stem cells; CRC, colorectal cancer; TME, tumor microenvironment.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Novelty of This Manuscript: Grade B (Good)

Creativity or Innovation of This Manuscript: Grade B (Good)

Scientific Significance of the Conclusion in This Manuscript: Grade B (Good)Specific

Specific Comments to Authors:

The well established fecal microbiome transplantation (FMT) have been applied in CRC research and treatment. Please kindly search with term "fmt tme crc" for additional literature about it and add them.

Author response*:*

Dear reviewer, thank you for your valuable time reviewing our work. Your comments and suggestions have been considered so the manuscript has been modified accordingly. We agreed with your comment, since microorganisms play a key role in the development of CRC, and fecal microbiota transplantation (FMT) may have a great impact on future treatments for this type of cancer. We are grateful for this suggestion and we have added information on this subject in the final manuscript. These changes can be seen in Section "T**herapeutic targeting of TME and the gut microbiota: a key tool to modulate stemness in CRC"** (page 22 paragraph 3 - page 23 paragraph 1) where this approach was mentioned.

Reviewer #3:

Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Novelty of This Manuscript: Grade B (Good)
Creativity or Innovation of This Manuscript: Grade B (Good)
Scientific Significance of the Conclusion in This Manuscript: Grade B (Good)

Specific Comments to Authors:

Colorectal cancer (CRC) represents one of the most prevalent tumors worldwide. The tumor microenvironment (TME) through its proinflammatory role, among others, actively participates in CRC progression and the disturbance of gut microbiota (dysbiosis)Colorectal cancer stem cells (CCSC) are a tumor cell subpopulation that drives CRC initiation, progression and treatment failure. The paper is well arranged and the logic is clear, and. The cited literature is comprehensive and modern. The provided figure and tables are well composed and understandable. The quality of language of the manuscript is acceptable for me. So, I recommend to you that this manuscript may be accepted. There are some advices for autor.

Author response:

We appreciate the valuable observation of the reviewer. We have arranged and numbered your comments to facilitate the process of analyzing our revised manuscript.

Reviewer's comment 1.

In addition to the impact on tumor microenvironment, does intestinal microbiota have an impact on the immune status of tumor patients?

Reviewer's comment 2.

Does intestinal microbiota affect the expression of PD-L1 in tumor?

Author response to comment 1 and 2:

We appreciate the valuable observation of the reviewer. As we mentioned in Section "**Established dynamics between the gut microbiota, the TME and CCSC**" in response to intestinal dysbiosis, cells from gut mucosa give rise to a pro-inflammatory environment and promote an adaptive immune response that contributes to CRC development. However, we agree with the reviewer that it is crucial to further expand the knowledge regarding the relevance of the microbiota impact on the immune status of CRC patients in the manuscript. For this reason, and since concerns 1 and 2 are related, we proceeded to response both with

new information which was added in Section "**Established dynamics between the gut microbiota, the TME and CCSC"** (page 14 paragraph - page 15 paragraph 1) of the revised manuscript.

Comment to the Editor:

Based on the suggestions of all the referees, we now added new information in the revised manuscript with the new following references:

[96] L. V. **Hooper,** D. R. Littman, and A. J. Macpherson, "Interactions Between the Microbiota and the Immune System," *Science (80-.).*, **vol. 336**, no. 6086, pp. 1268–1273, Jun. 2012, [PMID: 22674334 doi: 10.1126/science.1223490].

[98] M. **Avril** and R. W. DePaolo, "'Driver-passenger' bacteria and their metabolites in the pathogenesis of colorectal cancer," *Gut Microbes*, **vol. 13**, no. 1, Jan. 2021, [PMID: 34225577 doi: 10.1080/19490976.2021.1941710].

[99] M. **Hanus** *et al.*, "Immune System, Microbiota, and Microbial Metabolites: The Unresolved Triad in Colorectal Cancer Microenvironment," *Front. Immunol.*, **vol. 12**, Mar. 2021, [PMID: 33841394 doi: 10.3389/fimmu.2021.612826].

[100] K. D. **Seely**, A. D. Morgan, L. D. Hagenstein, G. M. Florey, and J. M. Small, "Bacterial Involvement in Progression and Metastasis of Colorectal Neoplasia," *Cancers (Basel).*, **vol. 14**, no. 4, p. 1019, Feb. 2022, [PMID: 35205767 doi: 10.3390/cancers14041019].

[101] M. P. **Roberti** *et al.*, "Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer," *Nat. Med.*, **vol. 26**, no. 6, pp. 919–931, Jun. 2020, [PMID: 32451498 doi: 10.1038/s41591-020-0882-8].

[102] Y. **Lin**, D.-X. Kong, and Y.-N. Zhang, "Does the Microbiota Composition Influence the Efficacy of Colorectal Cancer Immunotherapy?," *Front. Oncol.*, **vol. 12**, Apr. 2022, [PMID: 35463305 doi: 10.3389/fonc.2022.852194].

[103] S. **Rezasoltani,** A. Yadegar, H. Asadzadeh Aghdaei, and M. Reza Zali, "Modulatory effects of gut microbiome in cancer immunotherapy: A novel paradigm for blockade of immune checkpoint inhibitors," *Cancer Med.*, **vol. 10**, no. 3, pp. 1141–1154, Feb. 2021, [PMID: 33369247 doi: 10.1002/cam4.3694].

[104] Q. **Qiu** *et al.*, "Exploring the Emerging Role of the Gut Microbiota and Tumor Microenvironment in Cancer Immunotherapy," *Front. Immunol.*, **vol. 11**, Jan. 2021, [PMID: 33488618 doi: 10.3389/fimmu.2020.612202].

[105] A. **Aghamajidi** and S. Maleki Vareki, "The Effect of the Gut Microbiota on Systemic and Anti-Tumor Immunity and Response to Systemic Therapy against Cancer," *Cancers (Basel).*, **vol. 14**, no. 15, p. 3563, Jul. 2022, [PMID: 35892821 doi: 10.3390/cancers14153563].

[107] Y. **Lu** *et al.*, "Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies," *J. Hematol. Oncol.*, **vol. 15**, no. 1, p. 47, Dec. 2022,

[PMID: 35488243 doi: 10.1186/s13045-022-01273-9].

[108] Y. **Ren** *et al.*, "TRAPPC4 regulates the intracellular trafficking of PD-L1 and antitumor immunity," *Nat. Commun.*, **vol. 12**, no. 1, p. 5405, Sep. 2021, [PMID: 34518538 doi: 10.1038/s41467-021-25662-9].

[109] C. **Li** *et al.*, "THADA drives Golgi residency and upregulation of PD-L1 in cancer cells and provides promising target for immunotherapy," *J. Immunother. Cancer*, **vol. 9**, no. 8, p. e002443, Aug. 2021, [PMID: 34341130 doi: 10.1136/jitc-2021-002443].

[110] Y. **Gao** *et al.*, "Fusobacterium nucleatum stimulates cell proliferation and promotes PD-L1 expression via IFIT1-related signal in colorectal cancer," *Neoplasia*, **vol. 35**, p. 100850, Jan. 2023, [PMID: 36371909 doi: 10.1016/j.neo.2022.100850].

[111] A. **Sivan** *et al.*, "Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy," *Science (80-.).*, **vol. 350**, no. 6264, pp. 1084–1089, Nov. 2015, [PMID: 26541606 doi: 10.1126/science.aac4255].

[112] F. P. **Canale** *et al.*, "Metabolic modulation of tumours with engineered bacteria for immunotherapy," *Nature*, **vol. 598**, no. 7882, pp. 662–666, Oct. 2021, [PMID: 34616044 doi: 10.1038/s41586-021-04003-2].

[113] D. R. **Garza** *et al.*, "Metabolic models predict bacterial passengers in colorectal cancer," *Cancer Metab.*, **vol. 8**, no. 1, p. 3, Dec. 2020, [PMID: 32055399 doi: 10.1186/s40170-020-0208-9].

[114] R. **Gao** *et al.*, "Integrated Analysis of Colorectal Cancer Reveals Cros Cohort Gut Microbial Signatures and Associated Serum Metabolites," *Gastroenterology*, **vol. 163**, no. 4, pp. 1024-1037.e9, Oct. 2022, [PMID: 35788345 doi: 10.1053/j.gastro.2022.06.069].

[160] P. C. **Konturek** *et al.*, "Successful therapy of Clostridium difficile infection with fecal microbiota transplantation.," *J. Physiol. Pharmacol.*, **vol. 67**, no. 6, pp. 859–866, Dec. 2016, [PMID: 28195066].

[161] K. **Myneedu**, A. Deoker, M. J. Schmulson, and M. Bashashati, "Fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis," *United Eur. Gastroenterol. J.*, **vol. 7**, no. 8, pp. 1033–1041, Oct. 2019, [PMID: 31662860 doi: 10.1177/2050640619866990].

[162] H. **Sokol** *et al.*, "Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study," *Microbiome*, **vol. 8,** no. 1, p. 12, Dec. 2020, [PMID: 32014035 doi: 10.1186/s40168-020-0792-5].

[163] **W. Fong**, Q. Li, and J. Yu, "Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer," *Oncogene*, **vol. 39**, no. 26, pp. 4925–4943, Jun. 2020, [PMID: 32514151 doi: 10.1038/s41388-020-1341-1].

[164] **S. P. Rosshart** *et al.*, "Wild Mouse Gut Microbiota Promotes Host Fitness and Improves Disease Resistance," *Cell*, **vol. 171**, no. 5, pp. 1015-1028.e13, Nov. 2017, [PMID: 29056339 doi: 10.1016/j.cell.2017.09.016].

[165] **C.-W. Chang** *et al.*, "Fecal Microbiota Transplantation Prevents Intestinal Injury, Upregulation of Toll-Like Receptors, and 5-Fluorouracil/Oxaliplatin-Induced Toxicity in Colorectal Cancer," *Int. J. Mol. Sci.*, **vol. 21**, no. 2, p. 386, Jan. 2020, [PMID: 31936237 doi: 10.3390/ijms21020386].

[166] **P. Y. Min Ho** *et al.*, "Health-related quality of life of patients with inflammatory bowel disease in Singapore," *Intest. Res.*, **vol. 17**, no. 1, pp. 107–118, Jan. 2019, [PMID: 30419638 doi: 10.5217/ir.2018.00099].

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R. **Gao** *et al.*, "Integrated Analysis of Colorectal Cancer Reveals Cros Cohort Gut Microbial Signatures and Associated Serum Metabolites," *Gastroenterology*, **vol. 163**, no. 4, pp. 1024-1037.e9, Oct. 2022, [PMID: 35788345 doi: 10.1053/j.gastro.2022.06.069].

D. R. **Garza** *et al.*, "Metabolic models predict bacterial passengers in colorectal cancer," *Cancer Metab.*, **vol. 8**, no. 1, p. 3, Dec. 2020, [PMID: 32055399 doi: 10.1186/s40170-020-0208-9].

L. V. **Hooper,** D. R. Littman, and A. J. Macpherson, "Interactions Between the Microbiota and the Immune System," *Science (80-.).*, **vol. 336**, no. 6086, pp. 1268–1273, Jun. 2012, [PMID: 22674334 doi: 10.1126/science.1223490].

K. D. **Seely**, A. D. Morgan, L. D. Hagenstein, G. M. Florey, and J. M. Small, "Bacterial Involvement in Progression and Metastasis of Colorectal Neoplasia," *Cancers (Basel).*, **vol. 14**, no. 4, p. 1019, Feb. 2022, [PMID: 35205767 doi: 10.3390/cancers14041019].

Editor-in-Chief review comments

This is an interesting and comprehensive review article, with a good balance between a general view and a detailed dissection of the covered issues. Moreover, the Authors have satisfactorily addressed the criticisms and suggestions raised by the Reviewers who had previously the opportunity to assess their work. Nevertheless, in carefully reading the manuscript I have noticed a number of grammar errors (as those related to the use of singular/plural in some verbs), plus the needs for some rephrasing. To make the reviewing process easier and faster, I'm therefore enclosing below some of the needed corrections. - In the manuscript title "influence" must be changed into "influences" - Page 5: "In all these cases, the synergy among genetic mutations…….promotes instead of promote. - Page 7: "a key CCSC biomarker that decreases in advanced (instead of advances) stages of CRC[20,29] …… - Page 8: "related to tumorigenesis and progression….", should be changed into "related to tumorigenesis and malignant progression…" - Page 12: This CRC staging contains four consensus molecular subtypes (CMS) plus an unclassified group which are summarized in Table 2 (add"which") - Page 12 (bottom): and the interactions arising…. (instead of "that arose") - Page 13: Please, change into "This imbalance of the local microbiota promotes the restructuring of the intestinal environment and alters (verbs were in the plural form). - Page 14: Change "Although different factors produces changes in gut microbiota" into "Although different factors produce changes in gut microbiota" - Page 23: Please, use the following rephrasing or similar: "These features result in the use of microorganisms with potential preventive or palliative action in CRC currently receiving special attention. In fact, microbe-based therapies, and bacteria-mediated modulatory strategies are studied to be used for the delivery…." - Page 24: The following rephrasing should be preferred: "In the near future, the challenge will be the development of selective and combined therapies to promote: (1) CSC eradication; (2) eradication of cancer cells, owing to their phenotypic plasticity, even in the absence of CSC features; and (3) reduction of….." - Page 24, Conclusions Section: Please, rephrase as it follows or similar: "The knowledge described in the present review provides data that may promote future research aimed at addressing the complexity of the components in the CRC-associated microenvironment and microbiota. Compounding such complexity, CRC is not an isolated neoplasm, but it's rather emerging as a dynamic pathology …." In addition, I have noticed an error within the body of Figure 1, bottom right part, where "Intermediateph enotypes" must be changed into "Intermediate phenotypes". Similarly, within the body of Figure 2, in bottom left part "Reestructuration" must be corrected. Indeed "Restructuration" is not really a proper English term, and should be changed into "Restructuring" in this Figure, as well as throughout the text and in figure legends. In Table 1, please use the following changes in singular/plural verbs I : maintains their properties and evades the immune system miR-135 a/b and miR-17: Promote stemness….. miR-34 and miR-93: Inhibit stemness… miR-20a and miR-106 a/b: Repress TGF-β activity… Affect stem cell fate or…. miR-221/222 and miR-21: Induce the development and maintenance of CCSC On the whole, the above highlighted corrections are solely an indication for the needs of additional English polishing and rephrasing, which leads to my request for minor revision.

Response:

Dear Lian-Sheng Ma, Founder and CEO Baishideng Publishing Group Inc We attach the document with the requested changes. We attach the file with the modified figures.