Dear Editor:

Thank you very much for giving us this opportunity to revise our manuscript for possible publication in *World Journal of Gastrointestinal Oncology*.

We sincerely thank you and the reviewers for their detailed, constructive, and professional comments on our manuscript (No.79346) entitled "Prevention of malignant digestive system tumors should focus on chronic inflammation".

We have carefully studied the reviewer's comments and revised the manuscript, which is highlighted in red. At the same time, we also carefully read the Editorial Office's comments and suggestions and revised the manuscript. According to the suggestions of the company editor-in-chief, we have supplemented the contents of the manuscript in detail to improve the highlights of the cutting-edge research results.

As we are non-native English users and have poor English writing ability, we have sent the revised manuscript to the professional English editing company (AJE) recommended by BPG publishing group for language polishing. After language polishing, our revised manuscript has met the publishing requirement (Grade A). A new language certificate has been uploaded to the system with the revised manuscript.

We are very grateful to you and the reviewers for reviewing and evaluating our manuscript. Looking forward to hearing from you.

Thanks for all your help. If you have any questions, please feel free to contact me.

Best regards from China,
Corresponding author: Kaijuan Wang
E-mail: kjwang@163.com

79346-Answering Reviewers

Dear reviewers:

The co-authors and I would like to thank you for the time and effort spent reviewing the manuscript. Thank you for your excellent and insightful series of comments, which has raised the quality of the manuscript significantly We have done our best to revise our manuscript with your comments point to point, and modified parts are highlighted in red in the revised manuscript.

We hope that the revision will be acceptable and look forward to your reply.

Best regards,
Corresponding author: Kaijuan Wang
E-mail: kjwang@163.com

Reviewer #1:
We appreciate your time and effort in reviewing this manuscript. Thank you for your encouraging comment!

Reviewer #2:
Q1. In the introductory part, it should have been discussed which mechanisms can be influenced by inflammation in the GI tract to cause cancerous changes. The authors do not even mention the protumor and antitumor effects of the innate immune system, autophagy, inflammasome activation, and the plexin-semaphorin system in relation to inflammation-carcinogenesis. Mentioning these would form the basis of how it is possible to not therapeutically influence chronic inflammation with a pro-tumor effect.

Response: We appreciate your time and effort in reviewing this manuscript. Thanks to the reviewer for your comments. We have supplemented the introduction part (highlighted in **red** on pages **4 to 5** of the revised manuscript), including the mechanism by which inflammation affects gastrointestinal carcinogenesis, and the protumor and antitumor effects of the innate immune system. More mechanisms are described in detail in the other parts of the article. There is a complex interaction and balance between inflammation, immunity, and tumorigenesis. This article focuses on recent advances in gastrointestinal tumor prevention strategies based on chronic inflammation. Interested readers can learn more about the immune mechanisms of inflammation and tumors based on the cited references.

Q2. In acute inflammation, immunosuppression occurs after tissue repair or ends inflammation by eliminating pathogens and necrotic cells. However, in chronic inflammation, due to the lack of normal negative feedback mechanisms, immunosuppression permanently persists." Immunosuppression is not equal to anti-inflammatory immune processes.

Response: Sincerely thank the reviewer for your insightful review. We rewrite the section highlighted in **red** on page **4** of the revised manuscript, as follows:
Inflammation represents the host's immune response to destructive stimuli caused by irritants or pathogens. While most pathogens stir up an acute inflammatory response that completely clears irritants from suitable hosts, insufficient resolution of inflammation and an unrestricted inflammatory response can trigger chronic inflammation, destroy host immunity, and predispose the host to various diseases, including cancer[2].

Q3. Chronic inflammation usually triggers colon cancer through three main

mechanisms, namely chromosome instability [14], microsatellite instability, and CpG island methylation." The tumorigenesis of sporadic and colitis-associated CRCs is different.

Response: Many thanks to the reviewer for your comments. As the reviewers said, the tumorigenesis of sporadic CRC and CAC is different, and we carefully and repeatedly read the relevant sentences and modified the relevant descriptions to make them clearer and more professional **on page 12** in the revised manuscript, as follows:

The genetic mechanisms of tumorigenesis in CAC are similar to that in sporadic CRC, including chromosomal instability, microsatellite instability, mutations in pivotal tumor suppressor genes, and aneuploidy. But the timing and frequency of these conditions are different between CAC and sporadic CRC [62]; TP53 variants and aneuploidy were detected earlier in CAC, than sporadic CRCs, while KRAS and APC variants showed a lower prevalence at later stages of tumorigenesis [60].

Q4. Upon the time point when inflammation affects DSMT pathogenesis, three types can be distinguished: chronic inflammation before tumorigenesis, inflammation caused by tumor and inflammation induced by treatment." These sentences are not professionally written. Instead of these classifications, one can distinguish between inflammation-associated tumorigenesis and tumor-associated inflammation. Treatment-induced inflammation is not the correct phrase.

Response: Thanks to the reviewer for your professional advice. According to the reviewer's prompt, we carefully examined, read, and considered the expression of the sentence. Due to our limited language level, this sentence is somewhat inappropriate, and we are very sorry for that. By reading professional literature and consulting native speakers, rewrite the sentence **on page 7** in the revised manuscript as follows:

Chronic inflammation caused by exposure to long-term environmental irritants or associated with infection or autoimmune disease precedes tumor development and can promote it through oncogene mutations, genomic instability, early tumor promotion, and heighten angiogenesis[25]. Tumor-associated inflammation develops with tumor development. These inflammatory responses can heighten neoangiogenesis [26], promote tumor development and metastasis, cause local immunosuppression[25], and further increase genomic instability[27]. By causing necrosis and tissue injury, tumor therapy can also trigger an inflammatory response that promotes tumor reemergence and resistance to therapy.

Reviewer #3:

Q5. The section on MECHANISM OF CHRONIC INFLAMMATION IN THE OCCURRENCE OF DIGESTIVE SYSTEM MALIGNANT TUMOR lacks a more extensive and detailed overview of the mechanistic insights on how chronic inflammation triggers relevant phenotypical changes toward the malignant transformation. It is not enough to mention a couple of enzymes and transcription factors, chronic inflammation is much more complex than what is stated in this section.

Response: Thanks to the reviewer for this question. After being reminded by the reviewers, we read this section repeatedly. As the reviewers point out, the pathogenesis of chronic inflammation-triggered malignancies is very complex and diverse. We have supplemented this section **on pages 6 to 9** in the revised manuscript, but due to space constraints and the focus of the article on prevention strategies through the life course, the overly detailed mechanisms by which chronic inflammation triggers tumorigenesis are not described in detail. The mechanism of chronic inflammation carcinogenesis is also described in the sub-thesis section of colorectal cancer, liver cancer, and gastric cancer. Interested readers can read the cited references in detail.

Q6. This reviewer missed a section about the contributions of gut microbiota. Compelling evidence are supporting that alteration of gut microbiota, particularly the dysbiosis condition might produce enrichment in pro-inflammatory opportunistic pathogens and a decrease in butyrate-producing bacteria, which may lead to an imbalance in intestinal homeostasis that could ultimately lead to tumor formation.

Response: We thank the reviewer for pointing out this issue. In the highlighted **red** section on **pages 7 to 9** of the revised manuscript, we have added the contribution of relevant gut microbes to tumorigenesis.

Q7. Nothing is mentioned about the contribution of Salmonella typhi, which is now considered an oncogenic bacteria that alter the human immune system and thus contributes to gallbladder cancer.

Response: Thanks for the suggestion above. Following your suggestion, we have added a description about the contribution of *Salmonella typhi* of gallbladder cancer in the highlighted **red** sections on pages **8 to 9** of the revised manuscript.

Q8. Helicobacter pylori must be written in italics. appears as H. pylori and sometimes as helicobacter pylori. Please abbreviations must be defined in

the first use.

Response: Thank you for pointing out this problem in manuscript. In accordance with the magazine's requirements for punctuation, abbreviations, and italics, we re-read the manuscript carefully and revised them.