March 4, 2023

Dear Prof. Lian-Sheng Ma,

World Journal of Gastrointestinal Oncology

RE: # NO: 82154, Exosomes in Metastasis of Colorectal Cancers: Friends or Foes?

Dear Prof. Lian-Sheng Ma,

On behalf of my co-authors, we are very grateful to you for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions on our manuscript with title **"Exosomes in Metastasis of Colorectal Cancers: Friends or Foes?" (ID: 82154).** We have studied reviewers' comments carefully and tried our best to revise our manuscript according to the comments. The following are the responses and revisions we have made in response to the reviewers' questions and suggestions on an item-by-item basis. Our Manuscript was also polished by a native English speaker with biological background to make it easy understanding to readers. The revised portions are highlighted in yellow in the paper. Thank you again for the hard work of the editor and reviewers.

With many thanks and best wishes.

Jing Liu

Cancer Hospital of Shantou University Medical College

The main corrections are in the manuscript and the responds to the reviewers' comments are as follows point-to-point (the replies are marked in blue).

To Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. The title of this article is: Exosomes in Metastasis of Colorectal Cancers: Friends or Foes? It vividly reflects the theme of the article.

Responses: Thank you for your positive comments. We really appreciate your efforts in reviewing our manuscript.

2. In this paper, TME plays an important role in the occurrence and metastasis of malignant tumors. As a bridge between cancer cells and different components of TME, exosomes can promote or inhibit the progress and metastasis of CRC. Especially the role and mechanism of miRNAs in exosomes in CRC metastasis, and its application as a novel biomarker in the diagnosis and treatment of metastatic CRC. Abstract summarized and reflected the manuscript.

Responses: Thank you for your positive comments. We really appreciate your efforts in reviewing our manuscript.

3. Introduction should be added to introduce the role of exosomes in cancer and CRC.

Responses: Thank you for your professional suggestion. As suggested by reviewer, we summarized the role of exosomes in cancer and CRC in the Introduction section to emphasize the importance of exosomes in such field, in Page 4-5. All the revision has been highlighted with yellow for tracking.

4. The role of exosomes in the metastasis of CRC should be described more emphatically in the text, and the introduction of exosomes should be reduced appropriately at the same time.

Responses: Thank you for coming up with this deficiency. According to the reviewer's professional suggestion, we revised this section to reduce the introduction of exosomes and emphasize their role in cancer and CRC, with yellow highlight for tracking in Page 10-11.

5. In the discussion part, compared with the current frontier diagnosis and treatment of CRC, the advantages of exosomes and exosomal miRNAs should be elaborated in detail.

Responses: Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. It is useful to compare the different methods of diagnosis and treatment of CRC, which will facilitate the development of novel and promising biomarkers including exosomes and exosomal miRNAs. So according to the reviewer's suggestion, we have added the relevant content in the manuscript in Page 29, with yellow highlight for tracking.

6. A large number of references were included in the manuscript, with appropriate references to newer and important authoritative references.

Responses: Thank you for your positive comments. We really appreciate your efforts in reviewing our manuscript.

7. Quality of manuscript organization and presentation. The manuscript is organized and presented concisely and coherently, and its style, language and grammar are accurate and appropriate.

Responses: Thank you for your positive comments. We really appreciate your

efforts in reviewing our manuscript.

8. This manuscript comprehensively expounds the mechanism of exosome in CRC metastasis and the role of exosome miRNA in the early screening, diagnosis, treatment strategies and prognosis of CRC, providing a promising method for the prevention and treatment of CRC patients with metastasis. It represents the latest review on this topic, but its safety and clinical application in targeted therapy still need to be further explored and studied.

Responses: Thank you for your valuable suggestions. The safety should be considered seriously during the development of targeted therapy, which will restrict the clinical application accordingly. So as the reviewer suggested, we revised our manuscript and described more details related to such aspect in Page 31-33. All the revision was highlight with yellow for tracking.

To Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: As extracellular vesicles carrying biological goods, exosomes play their roles in primary tumors and metastasis, mainly in intercellular communication. This article details the mechanism of exosomes in CRC metastasis, including the formation and influencing factors of TME, the formation, function and role of exosomes in cancer, and the role of exosomes miRNA in CRC metastasis. Due to the heterogeneity of exosomes, the level of miRNA in individuals varies greatly, and even when studying the same cancer type, the results between groups are inconsistent. Another common disadvantage is that the method used to separate exosomes from plasma is different from the method used to extract miRNA from exosomes, and research lacks the common endogenous miRNA control for quantifying

exosomes miRNA. These problems affect the reliability of circulating exocrine miRNA as a cancer biomarker in clinical diagnosis or prognosis. At the same time, the technology of isolating exocrine miRNA from body fluid and the method of quantifying miRNA or protein also need to be further standardized. The author had better make a summary on this, so that readers can learn from it.

Responses: Thank you for your positive comments and valuable suggestions. As biomarkers for cancer diagnosis and prognosis, exosome miRNAs need to be proven reliable due to their heterogeneity and isolation techniques, we revised our manuscript according the reviewer's professional comments and suggestions, and described the overview of existing exosome isolation and purification techniques and explained the advantages of exosomes as biomarkers in Page 31-33. All the revision was highlight with yellow for tracking. We think that the revised manuscript has been improved accordingly and benefit the readers.

To EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Responses: Thank you for the editor's and reviewers' positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to the valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Responses: Thank you for the editor's and reviewers' positive comments and valuable suggestions to improve our manuscript. We have revised the manuscript according to the valuable comments and suggestions. The revised manuscript has been polished by an English-native speaker with biological background. All the revision was highlight with yellow for tracking. The Figure is original and decomposable in PowerPoint file with Copyright ©The Author(s) 2022. The form of citations was followed the style of BPG publications using EndNote software.