World Journal of Gastrointestinal Oncology. Manuscript # **NO: 65261**

Title: **The role of exosomal long non-coding RNAs in colorectal cancer**

Dear *World Journal of Gastrointestinal Oncology.*,

We appreciate the constructive criticisms/suggestions from the Editor and the Reviewers regarding our manuscript entitled "The role of exosomal long non-coding RNAs in colorectal cancer", which we are resubmitting for consideration of publication in *World Journal of Gastrointestinal Oncology.* We have addressed the issues and comments presented by the reviewers and believe these changes significantly enhanced our study.

Response to Reviewer 1:

In this study, the authors review relevant literatures, and describe function and mechanism of exosomal lncRNAs in CRC tumorigenesis. The topic is current hotspots in the field of life science and this paper is publishable. A few tips for the manuscript as below. 1. When quoting the studies of other researcher, we should add our own judgment with critical analysis by discussing the pros and cons. 2. In the manuscript, the author did cite a lot of newly-published references, but did not make logical combination, but simply listed and piled up.

Reply: Thank you for this suggestion. We have made the appropriate changes in the revised manuscript (Page 8 line 167-178; Page 9 line 191-201; Page 10 line 212-225; Page 11 line 245-252).

Response to Reviewer 2:

Dear authors, I've read your job regarding the role of lncRNAs in colon cancer with great interest, excellent done, congratulations. However I was wondering if you can add some clinical data (if available) for example if there is any evidence about the sidedness or the metastatic sites with the detection of a particular lncRNAs, thus meaning that specific disease behavours could be follow thoroughtt specific lncRNAs. Moreover it could be of interest if you can add something more regarding the role of lncRNAs and acquired mechanism of resistance against some drugs, for example antiEGFR.

Reply: Thanks for your suggestion. We have added the corresponding description in the revised manuscript (Page 13 line 265-283; Page 10 line 212-225), and included the following text (the red marks are representative of the newly revised text):

Many clinical studies have indicated a close association between exosomal lncRNAs and various clinical symptoms. Li et al.[74] found that elevated expression of exosomal lncRNA-SPINT1-AS1 was associated with regional lymph node metastasis, distant metastasis, and short recurrence-free survival (RFS) of CRC patients. Liu et al.[43] showed that elevated

expression of exosomal lncRNA-GAS5 was correlated with CRC tumor TNM stage, Dukes stage, local recurrence rate, and distant metastasis. In addition, elevated expression of CCAT2 was associated with local invasion and lymph node metastasis in CRC [79].

Exosomal lncRNAs serve as novel potential diagnostic and prognostic biomarkers of CRC. Using exosomal lncRNA-CRNDE-h as a diagnostic biomarker [76], receiver operating characteristic (ROC) curve analysis showed that lncRNA-CRNDE-h expression was a good candidate for distinguishing CRC patients from healthy control participants providing serum samples (sensitivity 70.3%, specificity 94.4%). The area under the curve (AUC) of the ROC was 0.892 (95% confidence interval [CI]: 0.860–0.918, $p<0.05$). Moreover, exosomal miRNAs act as prognostic biomarkers, and Oehme et al.[78] found that low expression of exosomal lncRNA-HOTTIP was positively correlated with poor overall survival (OS) in CRC patients ($p = 0.0009$), and further found that low expression of lncRNA-HOTTIP was an independent prognostic marker for OS (HR: 4.5, CI: 1.69–11.98, $p = 0.0027$) within a multivariate analysis. With the widespread use and development of new technologies, the detection of exosomal lncRNAs may provide a novel strategy for the screening, early diagnosis, and therapy of CRC.

Recent studies have demonstrated the important role of exosomal lncRNAs in CRC chemoresistance. These chemotherapy drugs of CRC contain cetuximab, mitomycin and oxaliplatin, et al. Yang et al.[61] reported that cetuximab-resistant CRC cells secrete the exosomal lncRNA-UCA1, which can transmit cetuximab resistance to sensitive cells, and that the expression of exosomal lncRNA-UCA1 is closely related to the clinical outcome of cetuximab therapy in CRC patients. Interestingly, Chen et al.[41] revealed that lncRNA-HOTTIP is highly expressed in mitomycin-resistant CRC cells and can be encapsulated into exosomes, transferring lncRNAs from mitomycin-resistant cells to sensitive cells; after entering the sensitive cells, lncRNA-HOTTIP can upregulate the expression of karyopherin subunit alpha 3 (KPNA3) by binding to miR-214, thereby promoting drug resistance in sensitive cells. Moreover, Deng et al.[46] found that carcinoma-associated fibroblasts (CAFs) can secrete exosomal lncRNA-CCAL to promote oxaliplatin resistance in CRC cells. Functional studies revealed that lncRNA-CCAL can interact directly with the mRNA stabilizing protein HuR (human antigen R) to increase the expression of β-catenin, thereby inducing chemoresistance in CRC. Targeting exosomal lncRNAs might thus be a promising strategy for overcoming drug resistance in CRC.

Response to Science Editor:

1 Scientific quality: The manuscript describes a minireviews of the role of exosomal long non-coding RNAs in colorectal cancer. The topic is within the scope of the WJGO. (1) Classification: Grade B and Grade B; (2) Summary of the Peer-Review Report: The authors review relevant literatures, and describe function and mechanism of exosomal lncRNAs in CRC tumorigenesis. The topic is current hotspots in the field of life science. However, some clinical data (if available) for example should be added. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 2 figures. (4) References: A total of 86 references are cited, including 37 references published in the last 3 years; (5) Self-cited references: There

are 13 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B and Grade A. A language editing certificate issued by Editage was provided. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by 4 grants. The topic has not previously been published in the WJGO. 5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (4) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

Reply: Thank you for this suggestion. We made the appropriate changes in the revised manuscript.

Thank you so much for your input into helping us improving this paper.

Sincerely,
Chunlin Ou