Peer Review File

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Reviewer A

The paper titled "Comprehensive analysis of potential cellular communication networks in non-alcoholic steatohepatitis and colorectal adenoma using scRNA-seq and bulk-seq" is interesting. These findings may help formulate early diagnosis and treatment strategies for CRA in NAFLD/NASH patients, and further explore corresponding prognostic markers and potential approaches. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) In the introduction of the manuscript, it is necessary to clearly indicate the prevalence of colorectal neoplasm in NAFLD patients and the risk of colorectal neoplasm in relation to the severity of NAFLD histology.

Reply: Thank you for your valuable comments. The incidence rate of colorectal neoplasm in NAFLD/NASH patients and their correlation have been described. We have made the necessary modifications as requested.

2) This study lacks a description of the results of Figures 10,11,15. Please provide complete information.

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

3) It is suggested to add further experimental studies to clarify the specific role and molecular mechanism of core genes in this study.

Reply: Thank you for your valuable comments. Due to the main focus of this study on the comorbidity relationship and related mechanisms between non-alcoholic steatohepatitis and colorectal adenoma, it is difficult to find suitable clinical samples. If basic research is conducted to verify, there may be difficulties in modeling simultaneously. Therefore, this study is mainly based on data analysis of online database datasets.

4) What is the value of scRNA-seq technology in exploring tumor heterogeneity? What is the biggest challenge facing? It is suggested to add relevant contents.

Reply: Thank you for your valuable comments. The significance of scRNA seq in exploring tumor heterogeneity lies in promoting our understanding of the expression program of tumor related genes in tumor development patterns. However, it must be acknowledged that the

biggest challenge it currently faces is that this analysis may miss out on some biologically significant gene expression programs, such as those that only involve a few genes or exist in rare cells, which requires further exploration by other research methods. We have made the necessary modifications as requested.

5) Some fonts need to be enlarged, as shown in Figures 1,3,7,15.

Reply: Thank you for your valuable comments. Perhaps due to the automatic compression of the image inserted into the manuscript, the clarity of the image is slightly poor. The original image has been supplemented in **Images uploaded one by one**, please check it.

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Identification of novel prognostic biomarkers for osteosarcoma: a bioinformatics analysis of differentially expressed genes in the mesenchymal stem cells from single-cell sequencing data set, Transl Cancer Res, PMID: 36388032","Ultrasonographic index for the diagnosis of non-alcoholic steatohepatitis in patients with non-alcoholic fatty liver disease, Quant Imaging Med Surg, PMID: 35284276". It is recommended to quote the articles.

Reply: Thank you for your valuable comments. We have cited and supplemented the literature as suggested. We have made the necessary modifications as requested.

7) What type of patients benefit most from the results of this study? What is the author's next research plan? It is recommended to add relevant content to the discussion.

Reply: Thank you for your valuable comments. Due to the main focus of this study being on the comorbidity relationship and related mechanisms between non-alcoholic steatohepatitis and colorectal adenoma, NAFLD/NASH patients benefit the most. As they are relatively prone to colorectal adenoma, developing corresponding drugs from the pathogenesis and genetic association is beneficial for early intervention of the disease. Our next research plan is to develop an appropriate basic research protocol to validate the results of this study. We have made the necessary modifications as requested.

Reviewer B

1) **First, in the title the term "Comprehensive analysis" is arbitrary since the current study is not comprehensive and it did not validation experiment for the current findings. The authors need to accurately describe the research focuses and the research design of this study, i.e., a bioinformatics analysis.**

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

2) **Second, the abstract needs some revisions. The background did not describe the potential clinical significance of this research focus. The methods did not specify which research procedures described answer the questions of biomarkers, therapeutic targets, and related effect pathways of CRA-NASH. Further, what biomarkers are, i.e., diagnostic or prognostic biomarkers. The results need to quantify the findings by using detailed data such as the expression levels. The conclusion needs comments for the clinical implications of the findings.**

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

3) **Third, the introduction of the main text needs to review what has been known on the biological mechanisms underlying CRA and have comments on the potential clinical significance of the focus on NASH and what the unique contribution of NASH on CRA. The last paragraph of this part should have a hypothesis on the proposed relationship and mechanisms. The authors need to explain why the bioinformatics analysis can answer the questions on potential biomarkers, therapeutic targets, and related effect pathways.**

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

4) **Fourth, in the methodology of the main text, please describe the research design, the clinical factors and biomarkers in the databases used, and have an overview of the research procedures and their corresponding questions to be answered.**

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

Reviewer C

1. Figure 2

Please explain KEGG in the legend.

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

2. Figure 4

Please explain MCODE in the legend.

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

3. Figure 16

Please explain WNT in the legend.

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.

4. Table 2

Please explain MCODE in the table footnote.

Reply: Thank you for your valuable comments. We have made the necessary modifications as requested.