

Peer Review File

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Reviewer A

The paper titled “Identification of key modules and miRNAs associated with colorectal cancer via a WGCNA and ceRNA network analysis” is interesting. The study established a network of the co-expressed ceRNAs associated with CRC and identified the genes and miRNAs related to the prognosis of CRC patients. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1:

1) The analysis content of this study is too simple, and it is recommended to increase the analysis of immune related genes and transcription factors, which may make the study more complete.

Reply 1:

Thanks for your suggestion. We performed an analysis of immune cells in the tumor and added the related content in the page 9, lines 9-18.

Changes in the text: page 9, lines 9-18.

Comment 2:

2) This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.

Reply 2:

We appreciate the reviewer's comment and agree that in vivo and in vitro experimental studies are important to validate the bioinformatics findings. However, due to the limited scope and resources of this study, we focused on the bioinformatics analysis of publicly available data sets to explore the potential role of miRNAs in CRC immune cell infiltration. We acknowledge the limitations of our study and have added a sentence in the discussion section to suggest future directions for experimental validation. We hope that our study can provide some novel insights and hypotheses for further research on CRC immunotherapy.

Comment 3:

3) In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study and the clinical significance of this study.

Reply 3:

Thank you for your comment. We appreciate your suggestion to improve the introduction of our manuscript. We have revised the introduction to address the knowledge gaps and limitations of prior studies and the clinical significance of this study.

Changes in the text: page 5, lines 4-24.

Comment 4:

4) All figures are not clear enough. It is recommended to provide clearer figures again.

Reply 4:

Thank you for your comment. We apologize for the poor quality of the figures in our manuscript. We have revised the figures to make them clearer and more readable. We have also provided high-resolution versions of the figures as supplementary files. We hope that the revised figures can better illustrate our results and findings.

Comment 5:

5) It may be more meaningful to add functional research on key ceRNAs and key genes of key modules.

Reply 5:

Thank you for your comment. We agree that functional research on key ceRNAs and key genes of key modules would be more meaningful and informative. However, due to the limited time and resources, we could not perform such experiments in this study. We have added a sentence in the discussion section to acknowledge this limitation and to suggest future directions for functional research. Here is our revised sentence:

“Although our study identified a novel ceRNA network associated with CRC and revealed the potential roles of some core genes and miRNAs in CRC progression and prognosis, it still has some limitations. One of the main limitations is the lack of experimental validation and functional research on the key ceRNAs and key genes of the key modules. Future studies should perform in vitro and in vivo experiments to confirm the ceRNA interactions and to elucidate the molecular mechanisms and biological functions of the key ceRNAs and key genes in CRC development and progression.”

Changes in the text: page 12, lines 2-9.

Comment 6:

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Construction of a co-expression network and prediction of metastasis markers in colorectal cancer patients with liver metastasis, J Gastrointest Oncol, PMID: 36388701”. It is recommended to quote the articles.

Reply 6:

Thank you. We add the citation.

Comment 7:

7) How to judge the prognostic characteristics of CRC based on the results of this study? How to provide candidate targets for the treatment of CRC? It is recommended to include relevant descriptions in the discussion.

Reply 7:

Thank you for your comment. We appreciate your suggestion to include relevant descriptions in the discussion about the prognostic characteristics of CRC and the candidate targets for the treatment of CRC based on the results of this study. We have revised the discussion section to address these points: Our study also identified some core genes and miRNAs that were significantly associated with the overall survival (OS) of CRC patients. Among them, mir-874 was negatively correlated with OS, suggesting that it may act as a tumor suppressor in CRC. In contrast, IZUMO4, WT1, NPEPL1, TEX22, PPFIA4, SFXN3, LINC00858 and PRR7-AS1

were positively correlated with OS, indicating that they may function as oncogenes in CRC. These genes and miRNAs may serve as potential prognostic biomarkers for CRC patients. Moreover, some of these genes and miRNAs have been reported to be involved in various biological processes and pathways related to CRC development and progression, such as cell cycle, apoptosis, epithelial-mesenchymal transition (EMT), Wnt signaling, and immune response. Therefore, these genes and miRNAs may also provide candidate targets for the treatment of CRC. However, further experimental studies are needed to validate their roles and mechanisms in CRC.

Reviewer B

1. Should it be a reference? Please check your manuscript. Use the reference number to cite the articles.

1 may contribute to the development of cancer. Currently, it has been shown that ceRNA
2 networks play an important role in the onset and progression of several types of cancer
3 {Kouhsar, 2019 #8;Chen, 2019 #9;Lin, 2022 #101}. Several studies have constructed
4 ceRNA networks for CRC based on different datasets and methods. However, these

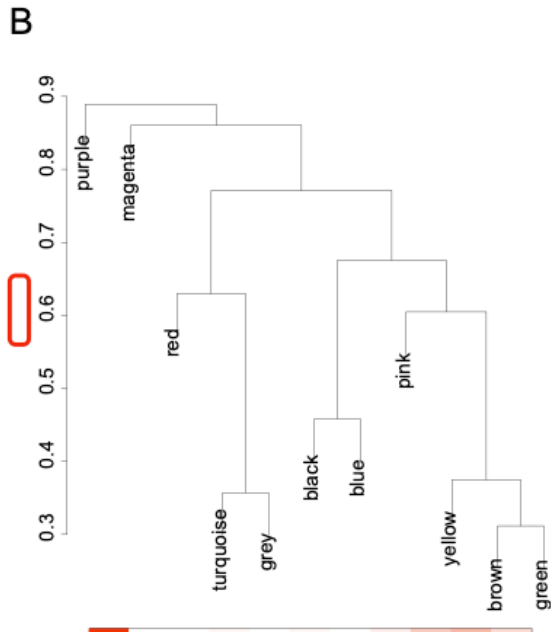
Reply: Yes, we update the number of citation.

2. You've mentioned "studies", while only one reference was cited in this sentence. Please give more than one reference in this sentence.

3 {Kouhsar, 2019 #8;Chen, 2019 #9;Lin, 2022 #101}. Several studies have constructed
4 ceRNA networks for CRC based on different datasets and methods. However, these

Reply: We delete this sentence.

3. Figure 2: Check if description of Y-axis should be supplemented.



Reply: Thank you for your suggestion. We have checked the description of the Y-axis in Figure 2 and found that it was incomplete. We have revised it as follows:
 “Distance between modules” We apologize for this oversight and hope that this revision is satisfactory.

4. Figure 3D was not cited in your paper, please cite it consecutively in text.

Reply: Thank you for your comment. We have cited Figure 3D in the text as follows: