UNIVERSIDADE ESTADUAL PAULISTA
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Response to Reviewers

28.MAY. 2021

To World Journal of Gastrointestinal Oncology

Article Type: REVIEW

Manuscript Title: MicroRNA expression in inflammatory bowel disease-associated colorectal cancer

Manuscript NO.: 64642

Dear Editor

Thank you for the opportunity to revise our manuscript. We are delighted that the journal has welcomed a revision. Based on the suggestions of reviewers, we have modified the original manuscript. Our responses to the reviewer' concerns, and the subsequent modifications made to the manuscript are listed below on a point-by-point basis.

The authors would like to thank the reviewers for their careful and constructive comments.

Sincerely Yours,

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Comments from the Reviewer:

#Reviewer 1

1. The authors should better emphasize the interest of the figure 1.

Response: First of all, thank you for reviewing the submitted manuscript and making such important considerations aiming a greater clarity about some key points of the study. Figure 1 was modified and aimed to clarify the numbers of miRNAs differentially expressed in patients with ulcerative colitis, Crohn´s disease and colorectal cancer, and the correlations between the diseases. This phrase was added in the manuscript (page 12).

2. The manuscript could be strengthened by a section/figure/table highlighting the possible targets of the identified miRNAs, especially for IBD-related CRC group, using appropriate tools (mirtarbase, diana, …).

Response: Thank you for the suggestion. Table 5 was added showing the analysis of the target genes of the altered microRNAs in inflammatory bowel disease-associated colorectal cancer.

3. Some very interesting articles have not been discussed and deserve some explanations. Please see below.

Response: Thank you for your suggestions that greatly improved the quality of the article. Most of the suggested articles were included, as well as other important articles in the field, as shown below.

30. Thorlacius-Ussing G, Schnack Nielsen B, Andersen V, Holmstrøm K, Pedersen AE. Expression and Localization of miR-21 and miR-126 in Mucosal Tissue from Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23: 739-752 [PMID: 28426456 DOI: 10.1097/MIB.0000000000001086]

44. Tian Y, Xu J, Li Y, Zhao R, Du S, Lv C, Wu W, Liu R, Sheng X, Song Y, Bi X, Li G, Li M, Wu X, Lou P, You H, Cui W, Sun J, Shuai J, Ren F, Zhang B, Guo M, Hou X, Wu K, Xue L, Zhang H, Plikus MV, Cong Y, Lengner CJ, Liu Z, Yu Z. MicroRNA-31 Reduces Inflammatory Signaling and Promotes Regeneration in Colon Epithelium, and Delivery of Mimics in Microspheres Reduces Colitis in Mice. Gastroenterology 2019; 156:2281-2296.e6 [PMID: 30779922 DOI: 10.1053/j.gastro.2019.02.023]

72. James JP, Riis LB, Malham M, Høgdall E, Langholz E, Nielsen BS. MicroRNA Biomarkers in IBD-Differential Diagnosis and Prediction of Colitis-Associated Cancer. Int J Mol Sci 2020;21: 7893 [PMID: 33114313 DOI: 10.3390/ijms21217893]

95. Tsukamoto M, Iinuma H, Yagi T, Matsuda K, Hashiguchi Y. Circulating Exosomal MicroRNA-21 as a Biomarker in Each Tumor Stage of Colorectal Cancer. Oncology 2017;92: 360-370 [PMID: 28376502 DOI: 10.1159/000463387]

96. Asangani IA, Rasheed SA, Nikolova DA, Leupold JH, Colburn NH, Post S, Allgayer H. MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene 2008; 27: 2128-2136 [PMID: 17968323 DOI: 10.1038/sj.onc.1210856]

97. Giráldez MD, Lozano JJ, Ramírez G, Hijona E, Bujanda L, Castells A, Gironella M. Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study. Clin Gastroenterol Hepatol 2013;11:681-688 [PMID: 23267864 DOI: 10.1016/j.cgh.2012.12.009].

98. Wang LG, Gu J. Serum microRNA-29a is a promising novel marker for early detection of colorectal liver metastasis. Cancer Epidemiol 2012; 36: e61-7 [PMID: 22018950 DOI: 10.1016/j.canep.2011.05.002]

99. Sun Y, Liu Y, Cogdell D, Calin GA, Sun B, Kopetz S, Hamilton SR, Zhang W. Examining plasma microRNA markers for colorectal cancer at different stages. Oncotarget 2016; 7:11434-11449 [PMID: 26863633 DOI:10.18632/oncotarget.7196]

100. Hu J, Cai G, Xu Y, Cai S. The Plasma microRNA miR-1914* and -1915 Suppresses Chemoresistant in Colorectal Cancer Patients by Down-regulating NFIX. Curr Mol Med 2016; 16:70-82 [PMID: 26695693 DOI: 10.2174/1566524016666151222144656]

101. Lee SL, Rouhi P, Dahl Jensen L, Zhang D, Ji H, Hauptmann G, Ingham P, Cao Y. Hypoxia-induced pathological angiogenesis mediates tumor cell dissemination, invasion, and metastasis in a zebrafish tumor model. Proc Natl Acad Sci U S A 2009; 106:19485-19490 [PMID: 19887629 DOI: 10.1073/pnas.0909228106]

102. Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. Angiogenesis 2017; 20: 409-426 [PMID: 28660302 DOI: 10.1007/s10456-017-9562-9]

103. Goradel NH, Mohammadi N, Haghi-Aminjan H, Farhood B, Negahdari B, Sahebkar A. Regulation of tumor angiogenesis by microRNAs: State of the art. J Cell Physiol 2019; 234:1099-1110 [PMID: 30070704 DOI: 10.1002/jcp.27051].

104. Wang Y, Wang L, Chen C, Chu X. New insights into the regulatory role of microRNA in tumor angiogenesis and clinical implications. Mol Cancer 2018; 17: 22 [DOI 10.1186/s12943-018-0766-4]

105. Leone P, Buonavoglia A, Fasano R, Solimando AG, De Re V, Cicco S, Vacca A, Racanelli V. Insights into the Regulation of Tumor Angiogenesis by Micro-RNAs. J Clin Med 2019; 8:2030 [PMID: 31757094 DOI: 10.3390/jcm8122030]

106. Hansen TF, Carlsen AL, Heegaard NH, Sørensen FB, Jakobsen A. Changes in circulating microRNA-126 during treatment with chemotherapy and bevacizumab predicts treatment response in

patients with metastatic colorectal cancer. Br J Cancer 2015; 112: 624-629 [PMID: 25584492 DOI: 10.1038/bjc.2014.652]

107. Zhang W, Zou C, Pan L, Xu Y, Qi W, Ma G, Hou Y, Jiang P. MicroRNA-140-5p inhibits the progression of colorectal cancer by targeting VEGFA. Cell Physiol Biochem 2015; 37:1123-1133 [PMID: 26402430 DOI: 10.1159/000430237]

108. Qiu Y, Yu H, Shi X, Xu K, Tang Q, Liang B, Hu S, Bao Y, Xu J, Cai J, Peng W, Cao Q, Yin P. microRNA-497 inhibits invasion and metastasis of colorectal cancer cells by targeting vascular endothelial growth factor-A. Cell Prolif 2016; 49:69-78 [PMID: 26840372 DOI: 10.1111/cpr.12237]

109. Casanovas O. Limitations of therapies exposed. Nature 2012; 484: 44-46 [DOI 10.1038/484044a]

110. Jászai J, Schmidt MHH. Trends and Challenges in Tumor Anti-Angiogenic Therapies. Cells 2019;8:1102 [PMID: 31540455 DOI: 10.3390/cells8091102]

111. Romano G, Kwong LN. Diagnostic and therapeutic applications of miRNA-based strategies to cancer immunotherapy. Cancer Metastasis Ver 2018; 37:45-53 [PMID: 29270700 DOI: 10.1007/s10555-017-9716-7]

112. Ma R, Jiang T, Kang X. Circulating microRNAs in cancer: origin, function and application. J Exp Clin Cancer Res 2012; 31: 38 [DOI 10.1186/1756-9966-31-38]

131. Motoyama K, Inoue H, Takatsuno Y, Tanaka F, Mimori K, Uetake H, Sugihara K, Mori M. Over- and under-expressed microRNAs in human colorectal cancer. Int J Oncol 2009;34:1069-1075 [PMID: 19287964 DOI: 10.3892/ijo_00000233]

155. Al-Mustanjid M, Mahmud SMH, Royel MRI, Rahman MH, Islam T, Rahman MR, Moni MA. Detection of molecular signatures and pathways shared in inflammatory bowel disease and colorectal cancer: A bioinformatics and systems biology approach. Genomics 2020; 112: 3416-3426 [PMID: 32535071 DOI: 10.1016/j.ygeno.2020.06.001] PMID: 32535071

160. Huang HY, Lin YC, Li J, Huang KY, Shrestha S, Hong HC, Tang Y, Chen YG, Jin CN, Yu Y, Xu JT, Li YM, Cai XX, Zhou ZY, Chen XH, Pei YY, Hu L, Su JJ, Cui SD, Wang F, Xie YY, Ding SY, Luo MF, Chou CH, Chang NW, Chen KW, Cheng YH, Wan XH, Hsu WL, Lee TY, Wei FX, Huang HD*. miRTarBase 2020: updates to the experimentally validated microRNA-target interaction database. Nucleic Acids Research 2020; 48: D148-D154. [PMID: 31647101 DOI: 10.1093/nar/gkz896]

161. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV, Clark NR, Ma'ayan A. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics 2013; 14:128. [PMID: 23586463 DOI: 10.1186/1471-2105-14-128]

162. Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z, Koplev S, Jenkins SL, Jagodnik KM, Lachmann A, McDermott MG, Monteiro CD, Gundersen GW, Ma'ayan A. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Research 2016; 8; 44: W90- W97 [PMID: 27141961 DOI: 10.1093/nar/gkw377 PMID: 27141961]

163. Xie Z, Bailey A, Kuleshov MV, Clarke DJB, Evangelista JE, Jenkins SL, Lachmann A, Wojciechowicz ML, Kropiwnicki E, Jagodnik KM, Jeon M, Ma'ayan A. Gene Set Knowledge Discovery with Enrichr. Curr Protoc 2021;1:e90 [PMID: 33780170 DOI: 10.1002/cpz1.90]

4. A schematic diagram showing miRNA linked to the progression of IBD-related CRC would be a plus.

Response: A diagram was added (Figure 2. A schematic diagram showing the pathways modulated by miRNAs in IBD-related CRC progression).

5. The authors should add some keywords (diagnosis, prognosis, targets).

Response: The suggested Keywords were added.

We hope the explanations mentioned above can clear some doubts you had while analyzing the manuscript and, yet again, thank for the important considerations. If there is still something to be made clear, we are available for further elucidations.

5 EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

5 Issues raised: (1) 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.

Response: Two original pictures in Power point were provided.

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