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Responses to the reviewer's comments

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53626

Title: Dysregulation of microRNA in cholangiocarcinoma identified through a meta-analysis of microRNA profiling

Dear Editor,

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We edited the paper according to the reviewer's comments. Please find enclosed the revised manuscript in Word format (file name " 53626-Manuscript File"). Each comment has been answered accordingly in the manuscript and each text that has been altered was highlighted yellow in the revised manuscript.

We hope that the revised version will fulfill the requirements for publication in the World Journal of Gastroenterology.

Thank you for your consideration. We look forward to hearing from you.

Sincerely yours,

Tavan Janvilisri, Ph.D.

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THAILAND



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Responses to the reviewer's comments

The present manuscript is a meta-analysis that aims to identify the miRNAs and the most significant pathways involved in the tumorigenesis of CCA. The selection of miRNA microarray datasets and data processing are accurate. I believe that the following paper might be considered for the publication in world journal of gastroenterology after minor revision.

Our response: We would like to thank the reviewer for his/her valuable comments. I made our best efforts to revise the manuscript accordingly.

1. The manuscript is well written in English but some language polishing is needed.

- Line 17: "A miRNA" instead of "An miRNA"
- Line 21: "have been discovered/were" instead of "are discovered"
- Line 29: "to be associated" instead of "to associate"

Our response: Thank you for your suggestion. The texts have been adjusted accordingly.

2. It is not clearly reported the choice of the most representative miRNAs in miRNA up-regulated and down-regulated groups.

Our response: We apologize for the confusion. The lists of up-regulated and down-regulated miRNA are shown in Tables 2 and 3, respectively. These represent a total differentially expressed (DE) miRNA between CCA and normal groups. We stated in 'Materials and Methods' under 'Statistical analysis' that DE miRNA which showed statistical significance among test sets and validation sets from all 10-fold cross validation were collected as validated DE miRNAs.



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3. A weakness of this analysis could be the different origin of miRNAs in the different datasets. Please emphasize it.

Our response: We thank the reviewer for his/her comments. In our revised manuscript, we added in the conclusion that as the analyses reported herein were based on the different origin of miRNAs, validations of such findings are warranted.

4. Another limit is the absence of distinction between different primary tumor sites. Please clarify it.

Our response: In our study 8 miRNA microarray datasets from independent research studies were employed. Based on the information in GEO, all datasets were retrieved from CCA tissues/cells. However, we included the statement in the discussion in our revised manuscript that 'The lack information on whether the samples were from primary or metastatic sites would pose as one of the limitations of this study.'

5. In the discussion, authors should make their manuscript more appealing for clinician's readers highlighting the translational relevance of the detection of miRNA. In example given the conflicting results in adjuvant setting (please add in the reference of the manuscript Messina C et al. Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials. Crit RevOncol Hematol. 2019 Nov;143:124-129.), the detection of a specific miRNA may be associated with an increased risk of recurrence after surgery. Therefore the expression of a miRNA may predict the risk of recurrence and drive clinician's decision making to prescribe adjuvant chemotherapy. Similar emerging data are reported for several solid tumours. I.e. see Nappi L, et al. Developing a Highly Specific Biomarker for Germ Cell Malignancies:



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Plasma miR371 Expression Across the Germ Cell Malignancy Spectrum. *J Clin Oncol.* 2019 Nov 20;37(33):3090-3098.

Our response: We thank the reviewer for his/her comments. In our revised manuscript, we added the statements on clinical relevance of our findings in the discussion and included both references as the reviewer suggested.

Email: tavan.jan@mahidol.ac.th

Responses to the editor's comments

1 Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Our response: We have uploaded the approved grant application form (grant no. DBG5980006; as indicated in the top right on the first page).

2 Please re-provide the original figure documents. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes; For line drawings that were automatically generated with software, please provide the labels/values of the ordinate and abscissa in text boxes; Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Our response: We uploaded the PowerPoint file containing all the figures with editable text with our revision.

3 Please write the "article highlights" section at the end of the main text. Detailed writing requirements for "article highlights" can be found in the Guidelines and Requirements for Manuscript Revision which can be downloaded at



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<https://www.wjgnet.com/bpg/GerInfo/291>.

Our response: We included the 'article highlights' section at the end of the main text as required.

4 Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. The author should provide the first page of the paper without PMID and DOI numbers. NOTE: The PMID is required, and NOT the PMCID; the PMID number can be found at <https://pubmed.ncbi.nlm.nih.gov>. (Please begin with PMID:) The DOI number can be found at <http://www.crossref.org/SimpleTextQuery/>. (Please begin with DOI: 10.**). Please verify that the references are cited by Arabic numerals in square brackets and superscripted in the text, and that the numbering order is correct. There should be no space between the bracket and the preceding word or the following punctuation. When references in the text and tables are cited with author name(s), it is necessary to manually verify that the name(s) is consistent with the first author's surname in the corresponding reference list.

Our response: The reference format has been corrected accordingly.