

Dear Editor and Reviewers:

Thank you for your kind letter of “**Metastasis-associated long noncoding RNAs in gastrointestinal cancer: implications for novel biomarkers and therapeutic targets**” on 20 Jun 2016. We revised the manuscript in accordance with the reviewers’ comments, and carefully proof-read the manuscript to minimize typographical, grammatical, and bibliographical errors. According to editor’s suggestion, text has been altered and highlighted to help speed up assessment of the revised version.

Here below is our description on revision according to the reviewers’ comments.

To reviewer #1:

The reviewer’s comment: This manuscript is about a very interesting and timely subject. The only criticism I make is the English language, which should be improved throughout the paper.

The authors’ Answer: Thanks for the reviewer’s suggestion. Many grammatical or typographical errors have been revised by Dr. Rui Zhou (The Chinese University of Hong Kong, Hong Kong SAR, China). Text has been altered and highlighted to help speed up assessment of the revised version.

To reviewer #2:

The reviewer’s comment: The best illustration of lack of organization is the table provided, which is very comprehensive (8 pages) but lacks any attempt to categorize and digest the information for the reader. I suggest that the authors re-organize the table according to individual lncRNAs and according to different sites of cancers. In the gene locus column the chromosome and arm location should be added in all occasions instead of the actual number of nucleotides and wherever known the gene where the lncRNA is located (e.g. IGF2 for H19) should be added for completeness. In the size column both nt number and MW should be presented for every lncRNA when known. If not known this should be clearly stated.

The authors’ Answer: Many thanks for the reviewer’s suggestion. We have re-organized the table according to individual lncRNAs and according to different

sites of cancers. We also added the chromosome, arm location, the known genes and nt number for every lncRNA.

The reviewer's comment: In the discussion on pathways and EMT, authors should attempt to analyze the information instead of just mention the title of the study they review.

The authors' Answer: We are sorry for our poor writing skill. We have digested and analyzed the related information in the discussion on pathways and EMT.

The reviewer's comment: There is a lot of redundant information repeated in the article. For example the HOTAIR and Wnt connection at the second paragraph of page 17 is repeated in the 1st paragraph of page 21 and towards the end of page 23. Similarly the HOTAIR – PRC2 connection is mentioned in page 19, paragraph 2 and again in the end of page 20. Authors should review and re-write.

The authors' Answer: We are sorry for our carelessness. Indeed, some information is repeated in the manuscript. We have simplified the redundant contents and re-write the HOTAIR – PRC2 connection.

The reviewer's comment: An important issue to be emphasized is the distinction between lncRNAs promoting metastases versus antimetastatic and the fact that the same lncRNA may have both actions depending on the specific pathway that they regulate in various occasions. Authors should include a section on this subject with examples.

The authors' Answer: Many thanks for the reviewer's suggestion. Indeed, lncRNA 91H played the distinct role in gastroenterological cancer, such as ESCC and CRC, via the specific pathway. We have added the discussion in page 19 of revised manuscript.

The reviewer's comment: Overall this review needs major re-organization of the significant amount of data it presents as well as major language editing.

The authors' Answer: Thanks for the reviewer's suggestion. Many grammatical or typographical errors have been revised by Dr. Rui Zhou (The Chinese University of Hong Kong, Hong Kong SAR, China). Text has been altered and highlighted to help speed up assessment of the revised version.

To reviewer #3:

The reviewer's comment: 1. This manuscript is too long for readers. I suggest that authors need to summarize succinctly.

The authors' Answer: Many thanks for the reviewer's suggestion. We have simplified the manuscript and deleted a lot of redundant information.

The reviewer's comment: 2. Authors showed a plenty of results from references. Not only readers, also reduce the pages of the journal, I suggest that authors need to reduce the number of cited references.

The authors' Answer: Many thanks for the reviewer's suggestion. We have re-organized and simplified the manuscript. We have deleted 29 references in revised manuscript.

The reviewer's comment: 3. Authors introduce a plenty of results from cited references in this manuscript, but it is not clear the importance of lnc RNA on gastroenterological area. I suggest that authors need to describe the speculations from cited reference.

The authors' Answer: We are sorry for our poor presentation. We have further digested and analyzed the related information in the discussion on pathways and EMT. We have greatly improved the manuscript to describe the speculations.

The reviewer's comment: There are some spelling and spacing mistakes in this manuscript.

The authors' Answer: Thanks for the reviewer's suggestion. Many grammatical or typographical errors have been revised by Dr. Rui Zhou (The Chinese University of

Hong Kong, Hong Kong SAR, China). Text has been altered and highlighted to help speed up assessment of the revised version.

All the markers and pages indicated above are in the revised manuscript.

Thank you and all the reviewers for the kind advice.

Sincerely yours,

Liang Zhao