Author’s response to reviews

Title: Genome-wide discovery and characterization of long noncoding RNAs in patients with multiple myeloma

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Version: 2 Date: 15 Jul 2019

Author’s response to reviews:

Dear Editor,

Thank you for carefully reviewing our manuscript previously titled “Genome-wide discovery and characterization of long noncoding RNAs in patients with multiple myeloma” for possible publication in the BMC Medical Genomics. We are grateful to you and two reviewers for their expert critique. We have revised the manuscript, highlighting our revisions, and have attached point-by-point responses detailing how we have revised the manuscript in response to your comments below.

James J. Driscoll, MD, PhD (Reviewer 1)

1 Page 9, line 1 - indicate where is Chao Yang Hospital located?

In the section of Methods , “Beijing Chao Yang Hospital”, modified to “Beijing Chao Yang Hospital (Beijing, China)”.

2 How were CD138+ cells purified and sorted?
The method of purification and classification of CD138 + cells, we completed and added to the methods of manuscript.

3. What criteria was used for the diagnosis of MM.

The criteria of International Myeloma Working Group updated criteria was used for the diagnosis of multiple myeloma. This diagnostic criterion has been supplemented and added to the section of the patients and cell samples.

4. Since these patients were not treated, a greater number of newly-diagnosed patient samples should be included to increase the power of the study.

Thank you very much for this beneficial advise. At present, this research is a preliminary exploration. Based on this work, we intend to expand the NDMM sample size to verify these DE lncRNA to further strengthens the evidence linking lncRNAs with the etiology and mechanism of MM. Now samples are being collected. In addition, experiments in vivo and in vitro will be carried out in the subsequent experiments.

5. A greater number of MM patient samples could also help identify lncRNAs that are associated with the different subtypes of MM.

This suggestion will help us to better understand the mechanism of pathogenesis of lncRNA on the development and progression of MM. We will do further studies, to further strengthens the evidence linking lncRNAs with MM.

6. Comparison to the lncRNA profile in bone marrow plasma cells from healthy Asian adults would be valuable.

Thanks a lot for this suggestion for revision, profile in bone marrow plasma cells from healthy Asian adults would be further strengthen the lncRNA research. We plan to add healthy adults as controls in consequent research.

7. Are the findings consistent with those previously detected in other populations diagnosed with MM?

In the discussion, we quoted relevant literature of lncRNA on multiple myeloma to illustrate whether the results are consistent with previous studies.

8. The legends for figures 6 through 12 require more details.

We revised the text description. More explanations of the legends for figures 6 through
12 were added to the article,

9 The text in figures 2, 6, 10 and 12 is not legible.
We replaced the legible chart and removed the unclear picture.

10 The discussion is brief and could include some information on the potential of lncRNAs to diagnose MM (using bone marrow, peripheral blood, etc.).
We expanded the discussion by illustrates the point of view in detail. The information were added on the potential of lncRNAs to diagnose MM by using peripheral blood.

11 The association of the lncRNAs identified here with other cancer types is missing. CCAT1 and CCDC2 are only discussed briefly.
We expanded the discussion with supplementary information by citing relevant literature of previous studies on lncRNA of the other malignant tumors. CCAT1 and CCDC2 are discussed in more detail.

Jie Sun (Reviewer 2):

1 In the introduction, recently several publications about lncRNAs biomarkers and multiple myeloma are missing, these related efforts should be introduced and commented, for example: PMID: 26362431, PMID: 26895470, PMID: 29700321.

In the revised manuscript, these missing content of related lncRNAs biomarkers on multiple myeloma has been supplemented in the introduction, by introduction of new research, including PMID: 26362431, PMID: 26895470, PMID: 29700321.

2 There is unclear in method section. For example, how lncRNA and mRNA expression were obtained from RNA sequencing data. When the authors identified the differentially expressed lncRNAs, how many lncRNAs were measured in RNA sequencing data? There is a lack of results from the DE analysis, eg. methods, adjusted p-value, mean expression in groups, log fold changes. How the ceRNA network was constructed?

The unclear section in method, including the construction of ceRNA network, were illustrated and replenished in the method, and the results from the DE analysis are supplied and shown in tables.
3 The samples used in study is very small, is not enough for get some conclusion.

We are very grateful to Professor Sun for this comments, and revised our conclusions cautiously. More research is needed to confirm the findings with larger sample sizes in more NDMM patients and different stages of MM.

4 Although the authors checked the enriched GO and kegg annotations for lncRNAs, there was no further study on the involved biological pathways or molecular mechanism about the individual lncRNAs.

In this study, we found that CCDC26 may be identified as a novel oncogene in MM, which had not reported in previous MM studies. C-KIT is the pathway of CCDC26, we will do follow-up research. There are known miRNA aim at CCDC26 and MEG3, targeted to CCDC26, hsa-mir-30c-1-3p constitutes ceRNA, this conclusion will be validated in subsequent research.

5 There are many grammar errors all through the text. The English needs significant improvement to increase the quality and clarity of the article.

I'm very sorry for the grammar errors, we exert oneself to checked the manuscript and revised the grammar errors to meet your requirements.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Wenming Chen