Author's response to reviews

Title: Estrogen receptor alpha-coupled Bmi1 regulation pathway in breast cancer and its clinical implications

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Author's response to reviews: see over
Dear editor:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Estrogen receptor α-coupled Bmi1 regulation pathway in breast cancer and its clinical implications” (MS:2087415787104846).

We have studied the reviewer’s comments carefully and tried our best to revise our manuscript according to the comments. And if you have any queries, please don’t hesitate to contact me.

Here a point-by-point response to the comments is listed as follows:

1. In the abstract – results. “In vivo” is not the correct term since this was not performed in animal rather than in cell lines.
   Response: It has been corrected as “the interaction”.

2. Page 4, Background – “basal like breast cancer” should be used instead of triple-negative breast cancer for molecular subtypes rather than IHC subtype.
   Response: It has been corrected as “basal like”.

3. Page 4, Background – For reference 5, please clarify that approximately half patients “in the adjuvant setting” who initially respond well… Since all of the patients in metastatic setting will inevitably develop endocrine resistance at some point in their treatment.
   Response: We have corrected the sentence as “Nevertheless, many patients with ERα positive cancer are unresponsive to endocrine therapy, and all patients with advanced
disease eventually develop resistance to the therapy” and have corrected the cited references.

4. Page 5 Line 18– Please change “ki-67” to “Ki-67”
Response: It has been corrected as “Ki-67”.

5. Page 6 Line 2 – this sentence should be ERα-coupled Bmi1…may be “one of the” main regulatory…
Response: It has been corrected as “ERα-coupled Bmi1 regulatory pathway may be one of the main regulatory mechanisms in breast cancer”.

6. Page 7 Staining evaluation – Clarification of how luminal A and B are determined should be described.
Response: We have added the cited reference to the definition of breast cancer subtypes in Staining evaluation.

7. Page 12 Results – Please also analyze the Bmi1 expression according to luminal A and B rather than only ER + or –.
Response: We have analyzed Bmi1 expression in luminal A and B in Results “The expression of Bmi1 strongly correlated with ERα status in breast cancer” and summarized Bmi1 expression in different subtypes in Table 2.

8. Page 13 Line 3 – …in the view of the fact “that” Bmi1
Response: It has been corrected as “…in view of the fact that Bmi1 is a transcription repressor…”.

9. Figure 2A – Poor quality western blot. Please change or explain. ERα expression seems to be higher in pcD-Bmi1 compared to the control and not at the same level as described in the text.
Response: We have changed the image of ERα expression in Figure 2A according to suggestion of the reviewer.
10. Figure 2B - Please clarify whether it is p-ER or ERα expression in the first row. If it is truly ERα, it appears that the baseline expression is extremely low for MCF7 which is very unusual.
Response: It is truly ERα expression in the first row in Figure 2B. Because of its abundance in MCF7, we reduced the amount of loaded extracts. So it appears that the baseline expression is extremely low.

11. Figure 2B - Please rearrange all of the figure B in the same row instead of using B’
Response: The images in Figure 2 have been rearranged according to the two previous reviewers. And if B’ is deleted, Figure 2 would seem confusing and poor-arranged.

12. All of figure 5 C, D, and E need statistical analysis
Response: We have added statistical analysis in Figure 5C, D and E and added simple declaration in the legend to Figure 5.

13. Page 15 Line 18 – Please correct the term “in vivo” as described.
Response: It has been deleted.

14. Table 2 - Please clarify the definition of luminal A, B and HER2 enriched whether this is by IHC using Ki67? Which cutoff? Or gene expression profiling was performed in these samples?
Response: We have added the cited reference to the definition of breast cancer subtypes in Staining evaluation. And the cutoff of Ki67 is 14%. Gene expression profiling was not performed in these samples.

Looking forward to hearing from you.

Thank you and best regards.

Sincerely yours,

Huali Wang, ph.D