Author's response to reviews

Title: The role of the REG4 gene and its encoding product in ovarian epithelial carcinoma

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Version: 4
Date: 17 April 2015

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Responses to Reviewer:

Chen and colleagues provide a revised manuscript that addresses most of my concerns. It is disappointing though that a large proportion of these answers is not included in the revised version of the manuscript but only written out in the comments. Overall the manuscript is improved although some of the figures are still of low quality and hard (impossible) to read.

The numbers below refers to my original comments.

1. The numbers of fresh-frozen/paraffin are still missing from the manuscript. And perhaps my initial question was not completely clear, but I would like to see all these questions answered in the manuscript and an analysis (like in table 2) of whether or not this affects REG4 expression.

Response: Dear reviewer, thank you for your important suggestions for the improvement of our manuscript. We apologize for misunderstanding your question previously. We have added the numbers of fresh-frozen/paraffin samples in the Materials and methods section. The fresh-frozen tissues were used only for RT-PCR analysis (mRNA expression), while paraffin tissues were used for IHC analysis (protein expression); details of the proportion of the tumor types in these categories can be found in Supplemental Table 1. The relationship between REG4 mRNA expression and the clinicopathological features of ovarian carcinomas are also given in Supplemental Table 2, according to your suggestion and the related text has also been revised in the manuscript. Besides, we also had copyedited the manuscript by an English Editing Company to improve the style of written English.

2. OK.

3. I find no description of this in the manuscript and I think this is important information to convey to the readers. This should be mentioned and the detailed results could be given in supplementary.

Response: Spearman’s rank correlation coefficient showed that there was no correlation between REG4 protein expression and different years (r = 0.0061; P = 0.355; Supplemental Table 3). We have added this information in the Results section. Further details are also included in the Supplementary section.

4. OK.

5. Again, this should be clearly written out in the manuscript (e.g. in section 2.12).

Response: Thank you for your advice. This has been included in the revised manuscript in section 2.12.

6-8. OK.

9. If you really mean that the REG-4 expression stratification in figure 6 D/E was done taking “Age, Pathological classification, FIGO staging, Differentiation and Ki-67 expression” into account. Please specify this in the figure legend or in the methods section.

Response: Thank you so much for your advice. We may have misunderstood your question, in which we thought that you were referring to the COX model. The REG4 protein expression was stratified by IHC results; we had specified this in the figure legend and in the results section in the revised manuscript.
10-12. OK.

13. Overall, the texts (e.g. axis labels etc) are still blurry and very hard to make out unless the figure is really big. The legend in figure 2 (example: upper right in panel 1, above G1:63.06%) is still impossible to read regardless of magnification. If this information is not needed, please remove from the panels.
Response: We have revised the Figures according to your suggestion; thank you so much.

14-15. OK.

16. The reference was intended to help you strengthen your arguments on REG4 expression in cancers. As you only copied my informative text on it, the formatting (e.g REG-4 vs REG4) and wording doesn’t follow the flow of your writing. Please rephrase into something like “and in hepatocellular carcinoma cell lines by stimulation with TGFb” or something along those lines. Or remove the reference/sentence if you don’t feel that it contribute to your argumentation.
Response: We have revised the sentence according to your suggestion, which help us better clarify REG4’s function. Thank you again for all your kind efforts help us improving our manuscript.

17-21. OK.