Author's response to reviews

Title: Co-expression of nuclear and cytoplasmic HMGB1 is inversely associated with infiltration of CD45RO+ T cells and prognosis in patients with stage IIIB colon cancer

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Author's response to reviews: see over
Dear Editor-in Chief:

Thank you for the review on our manuscript (MS: 1625007225303036).
Now I answer the comments as follow:

For comment from Editor:

1. There is one point that should be accounted for prior to publication.

   The study design is purely descriptive; therefore, the conclusions made by the authors are not justified (e.g. ?these observations indicated that the spontaneous chronic release of HMGB1 contributes to the progression of colon cancer, and inhibiting the spontaneous release of HMGB1 is a promise therapeutic strategy?) because they suggest a functional relationship, which is entirely speculative. Accordingly, the authors should go through the whole manuscript (particularly abstract, discussion, and conclusions) and tone down all statements that are not compatible with the descriptive nature of the study.

Answer: Thank you for your suggestion. Since this study design was descriptive, I modified the conclusions to ‘These observations indicated that the distribution patterns of HMGB1 contribute to the progression of colon cancer. The co-expression of nuclear and cytoplasmic HMGB1 might be used as a marker for poor survival in
patients with local advanced colon cancer.’ and toned down all
statements that were not compatible with the descriptive nature of the
study.

2. Methods ? Please add a statement to the Methods section indicating
that the study received approval by the institutional ethics committee,
as well as the details of this committee.
Answer: I had added a statement to the Methods section indicating
that the study received approval by the institutional ethics committee,
as well as the details of this committee.

3. Figure title - The image file should not include the title (e.g. Figure 1...
etc.) or figure number. The legend and title should be part of the
manuscript file after the reference list. The figures are numbered
automatically in the order in which they are uploaded.
Answer: I had deleted the title in the image files.

4. Figures - It is important for the final layout of the manuscript that the
figures are cropped as closely as possible to minimise white space
around the image. Our online figure cropping guide may be of some
help, and can be viewed here:

http://www.biomedcentral.com/info/ifora/cropping.
Answer: I had cropped the figures as closely as possible to minimise white space around the image according to the online figure cropping guide.

For comment from reviewer1:

1. Is the question posed by the authors well defined? NO
   Answer: I had checked the questions and answers one by one and made some changes. I hope that would satisfy you.

2. Are the methods appropriate and well described? No, see my previous comments. Additionally, the answer to previous comment 1 is not satisfactory. Specifically, I do not understand what is the "stroma of cancer center". By such an unclear approach, it would be easy to reach unsafe conclusion using methods that might overestimate differences, like the minimum p-value.

   Answer: I had introduced the method to count the immune cells in Methods. The immune cells in the tumor stroma were counted. I’m sorry to give a misleading concept of “stroma of cancer center” to you, which would be “the tumor stroma”.

3. Are the data sound? No. Statements concerning intra-sample heterogeneity are vague, and no measure is provided. Stating that fields were added to measurements doesn't make measure better, if experimental data are not provided.
Answer: As I mentioned previously that in the immunohistochemical assay the staining was usually heterogeneous. So we chose 10 areas of the highest density in the cancer as “hot-spot”, which would be a representative for the whole section.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Not really, in my opinion.

Answer: This manuscript did adhere to the relevant standards for reporting and data deposition. The example could be seen in *J Clin Oncol*, 2008, 27: 186-192.

5. Are the discussion and conclusions well balanced and adequately supported by the data? No

Answer: Since this study design was descriptive, I had made some changes in the discussion and conclusions.

6. Are limitations of the work clearly stated? No

Answer: I had added some limitations of the work in the Discussion part.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes

8. Do the title and abstract accurately convey what has been found? I believe the title is an overstatement

Answer: In this study, we really found that the co-expression of HMGB1 in the nuclear and cytoplasmic of colon cancer tissues was inversely associated with the density of CD45RO+ T cells in the tumor stroma via
immunohistochemistry. Moreover the co-expression pattern of HMGB1 was associated with poor survival in patients with stage IIIB colon cancer. So we thought the title was suitable for this study.

9. Is the writing acceptable? Somehow

Answer: I had chose American Journal Expert to edited the writing for me. I hope that the writing will be acceptable.

Since I could not open the comments from reviewer2 (http://www.biomedcentral.com/imedia/8824857435760932_comment.pdf), I had no idea what I had to answer for reviewer2.

With best wishes

Xiao-Shi Zhang