Author's response to reviews

Title: Mitogen Activated Protein Kinase Kinase Kinase 3 (MEKK3) overexpression is an early event in Esophageal Tumorigenesis and is a predictor of poor disease prognosis

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Author's response to reviews: see over
July 24, 2013

To,
The Editor
BMC Cancer

Sub: Submission of manuscript entitled “Mitogen Activated Protein Kinase Kinase Kinase 3 (MAP3K3/MEKK3) overexpression is an early event in Esophageal Tumorigenesis and is a predictor of poor disease prognosis”

Authors: Md. Raghibul Hasan, Rinu Sharma, Anoop Saraya, Tushar K. Chattopadhyay, Siddartha DattaGupta, Paul G. Walfish, Shyam S. Chauhan, Ranju Ralhan

Dear Editor,

We are submitting the revised manuscript entitled “Mitogen Activated Protein Kinase Kinase Kinase 3 (MAP3K3/MEKK3) overexpression is an early event in Esophageal Tumorigenesis and is a predictor of poor disease prognosis” on behalf of all the authors for consideration for publication in BMC Cancer.

The manuscript has been extensively revised taking into consideration all comments from both the reviewers. Answers to reviewer comments are appended along with this letter. The changes made in the revised manuscript have been highlighted. The point wise response to all the reviewers’ comments is also appended for ready reference.

We look forward to a favorable response.

Sincerely yours,

Ranju Ralhan

(Dr. Ranju Ralhan)
Reviewer: Liru He

Reviewer's report:

Major compulsory revision
1. The definition about disease-free survival is not correct.

   Author response: The definition about disease free survival has been revised.

2. Poor quality of figure 4, original picture should be provided.

   Author response: This figure has been deleted.

3. The author discussed a lot about the specific mechanism of MEKK3 in the carcinogenesis and progression of ESCC, however, none of the mechanism study and cell biological study was provided in this article, some speculations seem not well-founded.

   Author response: The discussion has been revised taking this comment into consideration.

Minor essential revision
1. Some of the reference is outdated, e.g. reference 5, 6, 7, and the statement that “the prognosis for ESCC patients still remains poor with an average 5-year survival of less than 10% globally” is not true now.

   Author response: The references 5,6,7 have been replaced by new references and the statement that “the prognosis for ESCC patients still remains poor with an average 5-year survival of less than 10% globally” has been revised.

2. The monitored period of the patients should be reported as a median (and range) pattern.

   Author response: The monitored period of follow up of the patients has been reported as median and range.

3. The last follow-up time is December 2010, the follow-up data should be updated.

   Author response: The follow-up has been updated as of June 2013. The survival analysis has been carried out with the updated follow up.

4. The reason for choosing TE13 but not other ESCC cell lines should be provided.

   Author response: This section has been deleted.
Reviewer: Huan Ren

Reviewer's report:

The study examined MEKK3 expression mainly by immunochemistry in archived formalin fixed and paraffin embedded tissue sections from 93 ESCCs, 47 histologically normal and 61 dysplastic esophageal tissues to evaluate the significance between the MEKK3 expression and clinicopathological parameters, and its prognostic relevance for ESCC patients. Although the patients’ materials and related examinations were of value and significance, the analysis on the work appeared superficial, and the manuscript was poorly organized.

-Major Compulsory Revisions

1. Discrepancies in the manuscript. In the abstract results section, the manuscript stated that, the accumulation of MEKK3 and node positivity emerged as important predictors of reduced disease free survival, where there were only one set of p value, HR and 95% CI; However, in the Results section under the subtitle (MEKK3 overexpression as a prognostic marker for ESCC) of the first paragraph, it stated that, MEKK3 overexpression, or nodal metastasis was an independent parameter of the prognostic relevance for ESCC patients, as each had a set of p value, HR and 95% CI. Whether there was a combination effect between the MEKK3 expression and nodal positivity on the prognostic significance for ESCC patients, such discrepancies in the manuscript were misleading.

Author response: This discrepancy in the results and abstract sections arose because of word limit of the abstract section which could accommodate only one set of p value and HR ratio. However, the abstract has now been revised to rectify this discrepancy. The follow up was updated as of June 2013 and the survival analyses were carried out with updated follow up. The abstract has been revised.

2. Lack of detailed analysis and description on the clinicopathological parameters. Besides the follow up study on collection of relevant patients’ survival data, the manuscript failed to provide relevant description and selection criteria for other important parameters such as nodal positivity or metastasis, etc.

Author response: The details of clinical and pathological parameters were recorded in a predesigned Performa as described in our previous publication (Kausar et al., Cancer Investigations 2010, 5: e11939). The data on TNM staging were collected following the TNM staging based on UICC TNM classification of malignant tumors 2002.

3. The cell culture section was unnecessary and irrelevant to the present manuscript.

Author response: This section has been deleted.
4. Irrelevant paragraphs in the Discussion section. The present study mainly focused on the MEKK3 expression by immunochemistry and its relevance of prognostic significance for ESCC patients, the discussion on the relationship of MEKK3 expression with other factor expression in ESCC samples or cell lines, such as NF-kB, was unnecessary.

Author Response: The section on the discussion of the relationship of MEKK3 expression with other factor expression in ESCC samples or cell lines, such as NF-kB, has been deleted from the revised manuscript.

5. The authors needed to clarify the exact cellular location of MEKK3 expression in the relevant chapters across the manuscript. Most of the staining positivity in the manuscript was shown as nuclear/cytoplasmic on expression of MEKK3, however, some of the description on that was indicated as only nuclear MEKK3 expression (The Results section under the subtitle MEKK3 overexpression as a prognostic marker for ESCC of the 2nd paragraph).

Author response: We regret this error. It has been rectified. The staining has been shown as nuclear/cytoplasmic throughout the revised manuscript.

-Minor Essential Revisions Minor spelling errors. -Discretionary Revisions None.