Author’s response to reviews

Title: Major vault protein suppresses lung cancer cell proliferation by inhibiting STAT3 signaling pathway

Authors:
Hui Bai (huibai@njmu.edu.cn)
Chenchen Wang (wcc0113@sina.com)
Yu Qi (qiyu7272@gmail.com)
Jin Xu (jinxu@njmu.edu.cn)
Nan Li (2397648344@qq.com)
Lili Chen (514468494@qq.com)
Bin Jiang (jiangbin@njmu.edu.cn)
Xudong Zhu (zhuxudong@njmu.edu.cn)
Hanwen Zhang (hanwenzhang@njmu.edu.cn)
Xiaoyu Li (xyli@njmu.edu.cn)
Qing Yang (qyang@njmu.edu.cn)
Junqing Ma (1289366375@qq.com)
Yong Xu (yxu@njmu.edu.cn)
Jingjing Ben (bijj@njmu.edu.cn)
Qi Chen (qichen@njmu.edu.cn)

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Please address the following concerns and request of a BMC Cancer Editorial Board Member:
Upon reading the manuscript and the comments I feel that the authors have not justified their results properly. There are a number of publications on STAT proteins and NSCLC which should have been referenced. The figures also need good statistical analysis and hence the authors should be asked to revise the discussion and justify their findings.

1) Authors described in detail about the how they performed this analysis in the Method section to address reviewer’s comment about explaining their calculations for figure 1E. However, authors didn’t fully address reviewer comment on “the authors have not described what was included in this analysis or highlighted the fact that some of these patients received treatment which could affect the results”. Authors have pointed out that in their own cohort (data used to generate figure S1C, S1D and S1E), patients didn’t receive chemotherapy nor radiotherapy. But the published data used to generate Figure 1E, S1A and S1B have NOT been restricted for treatment conditions. I have personally performed the analysis authors did for figure 1E. And if I select to restrict for patients not received chemotherapy nor radiotherapy, the database performed analysis for 227 patients and the results showed HR=0.69 (0.45-1.04) and logrank P=0.075, which is comparable to authors own cohort, but is NOT significantly different. This database wasn’t be able to filter only adenocarcinoma or squamous cell carcinoma without chemotherapy and radiotherapy. Therefore, the analysis from published data cannot address whether there is treatment bias, but the authors own cohort could.

A : We agree with the reviewer. We re-calculated the survival data of lung cancer patients received chemotherapy/radiotherapy or not in the online database. As the reviewer indicated, Figure S1C showed that patients not received chemotherapy or radiotherapy but with higher MVP expression had a trend of better outcome though the difference is not statistical (P = 0.075). While, higher MVP expression indicates better prognosis in patients received both chemotherapy and radiotherapy (P = 0.0065) (Figure S1D). These results suggest that MVP be related to the sensitivity of treatment in lung cancer. Combining with the results from our own cohort, our population investigation reveal that MVP might be associated with the pathogenesis of lung cancer, especially with adenocarcinoma. Figure S1C and D have been added to the results (line 208, page 9).

Additionally, authors didn’t provide sufficient discussion about why adenocarcinoma and squamous cell carcinoma showed such a difference in survival curve.

A : Yes, we added this important issue in the discussion (line 332, page 15).

I also would like to point out that the authors should check their “array quality control” method for figure 1E in the revised manuscript (line 185 in Methods) because I recapitulated the results of Figure 1E in the revise2 version by using “exclude biased arrays”, not “exclude outlier arrays”.

A : We have re-analyzed all the data by using “exclude biased arrays” (Figure S1) and re-edited the methods as the reviewer suggested (line 186, page 8).

2) Authors have included more discussion about published findings about MVP expression in NSCLC and its role in other diseases. The discussion about the possibly mechanism of MVP represses lung cancer growth by suppressing STAT3 signal pathway. But there’s missing discussion about published work on the role of STAT3 signaling pathway in lung cancer, particularly adenocarcinoma.

A : Yes, we added this important issue in the discussion (line 341, page 15).

3) Authors’ conclusion should be more precise and specific about the key findings and significance – authors should conclude the finding that MVP is associated with pathogenesis of adenocarcinoma, MVP suppresses tumor cell growth in vivo and in vitro, and is playing an role in lung cancer cell apoptosis, finally, the mechanism of its tumor suppression role is through inhibition of STAT3 signaling pathway.
A: We appreciate the reviewer’s indication and re-edited the conclusion as the reviewer suggested (line 381, page 17).

Reviewer 2 (Reviewer 2): REVISION ASSESSMENT FROM THE ACADEMIC PEER REVIEWER: Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? Yes.
Reviewer comments: I thank the authors for addressing my concerns. Re-analysis of human samples, as reported now, definitely supports the hypothesis. Also, use of human cells increases the confidence in research conclusions. A: Thanks for the reviewer’s efforts.