Reviewer’s report

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

Version: 1 Date: 10 Jul 2018

Reviewer: Kathy Gately

Reviewer's report:

The manuscript entitled "Major vault protein suppresses lung cancer cell proliferation by inhibiting STAT3 signaling pathway" has the potential to add some novel data to the literature on the role of MVP/LRP in NSCLC. There is relatively few papers investigating the role of MVP/LRP in NSCLC and very few recent publications. However considerable amendments and additions need to be made to the current draft of the paper as follows:

Introduction:

1) The authors should begin by stating that LRP and MVP are the same protein.

2) In the introduction the authors have not discussed previous published papers documenting the role of MVP/LRP in NSCLC. They do mention instead renal adeno, glioblastoma and colon cancer. The conflicting data on MVP/LRP's role in drug resistance should be discussed including the paper by Huffman K and Corey D 2005 Biochemistry where they dispute role of MVP in drug resistance to doxorubicin in NSCLC. LRP expression correlated to cisplatin resistance but not doxo Int J Cancer 2000. Also need to discuss findings by Janikova et al Neoplasma 2016 where they show LRP/MVP exp alone is not prognostic in NSCLC however there was a correlation when examined in combination with miR-23b, P-gp & MRP.

Materials & Methods:

3) There should be an entire section outlining the Patient Cohort and Tissue collection and the TMA/Immunohistochemistry should also be described in a separate section. Both these sections need more details as follows:

a) Histology of patients - numbers of adenocarcinoma and squamous cell carcinomas. Treatment Regimen - what numbers of patients received treatment prior to surgery and what treatment?

b) What size cores were used in the TMA? How many replicates? What control tissue was used?

c) What dilutions of antibodies were used in the IHC? What controls were used? What cut-off was used for the IHC analysis or was median value used?
4) The authors state that 2 cell lines were used in knockdown experiment pg 8 line 167, what are the two cell lines used? They only mention LLC cells in the methods section?

5) How many mice were used in the in-vivo study?

6) What statistical analysis package was used?

Results:

7) The quality of the images are poor, v blurred in Figure 1A, it is difficult to review the quality of the staining and localisation

8) A Table detailing the patient clinicopathological parameters should be included

9) A Table detailing with a breakdown of the IHC results (</> median or cut-off) and any correlation to clinicopathological parameters should be included

10) The authors need to explain how the following result was calculated "The hazard ratio (HR) was 0.68 (95% CI: 0.59-0.79) with 163 adjusted p value = 7.3e-07" - running this software for the 1926 patients gives a p=values of 0.34. Interestingly if the cohort is broken into adenos and squamous cell histologies the p-value is significant for adenos only. 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...

11) The authors randomly selected 15 matched normal/tumour tissues - what histology were these and did patients receive neo-adjuvant treatment?

12) The authors have not included a K-M plot of PFS and OS for their own 142 cases from this study? it is important that this is included.

13) Overall all figure legends lack detail

14) In Figure 5 why was serum added in this experiment, this is not explained?

15) No p-value given on Pg 9 line 186 although authors state tumour weigths are "significantly" heavier. Also no p-value given on page 11 line 230

Discussion

16) Overall the discussion is very general and does not discuss the results of this study thoroughly

Conclusion:

17) the conclusion section is only one sentence and does not highlight the significance of the results of this study. Also can the authors clearly define the potential of MVP as a therapeutic target given that it's overexpression may suppress tumor cell proliferation?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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