Author's response to reviews

Title: Overexpression of GOLPH3 is associated with poor prognosis and clinical progression in pancreatic ductal adenocarcinoma

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Version: 3
Date: 27 June 2014

Author's response to reviews:

Dear Editors and Reviewers,

Thank you for reviewing our manuscript entitled “Overexpression of GOLPH3 is associated with poor prognosis and clinical progression in pancreatic ductal adenocarcinoma”. We thank the editor and all reviewers giving us excellent suggestions.

Please see the following detailed response to the referees’ comments. We are now give point-to-point responses to the critiques from editor and reviewers as indicated and re-submitting a revised manuscript. I hope that you will find that the current version of our manuscript is suitable for publication in BMC cancer.

If you have any question regarding the re-submitted manuscript, please do not hesitate to contact us.

Sincerely yours,

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Reply for the reviewer's report
Reviewer 1: Hua Lu
Quality of written English: Needs some language corrections before being Published

Reply: According to the suggestion of Reviewer 1, the paper has been revised by a native English speaker. The editor is employed by ELIXIGEN Co. (Huntington Beach, California, USA).

Reviewer 3: Gregory Lesinski
Reviewer’s report:
The manuscript by Zhang et al. is well written and describes a series of studies using patient-derived material to explore the relationship between GOLPH3 expression and prognosis in pancreatic cancer. The authors provide data suggesting there is a correlation between GOLPH3 expressions being tied to prognosis in this disease. Although this manuscript appears to be novel, there are a number of concerns that need addressing before the data can be interpreted with confidence.

Major Compulsory Revisions:
1. It is unclear why the cutoff values of SI ≥ 6 were chosen to stratify patients for Kaplan-Meier analysis. Would the data be different if the median SI value was chosen? As it stands, the groups are unevenly distributed and unclear whether the optimal cutoff value chosen is biologically relevant in some way. This cut off value is the foundation of much of the paper, which could drastically affect conclusions if it does not hold true at other SI values.

Reply: Yes, this cut off value is very important in current studies. The cutoff values of SI > or = 6 was chosen to stratify patients for Kaplan-Meier analysis as the median SI value was 6 in this unevenly distributed groups data.

Median SI value
N 109
Median 6.00
Minimum 0
Maximum 12
Percentiles 25 4.00
75 9.00

2. For samples where non-cancer adjacent lesions were obtained, what was the degree of fibrosis/stromal desmoplasia in these areas? This could greatly affect interpretation of the data.

Reply: Adjacent non-cancer tissue was dissected at less 2 cm away from lesion parts of this four paired tumor tissues and then precede western blotting and PCR. We add this description in material and methods.
No obviously fibrosis/stromal desmoplasia in non-cancer tissue and no or very low GOLPH3 expression were found in lesion fibrosis/stromal desmoplasia areas (Fig. 1C) which had been observed by frozen section and HE staining before extracting the protein and RNA.

3. Page 5, methods, please specify type of chemotherapy used in the postoperative setting.

Reply: Gemcitabine or 5-FU/leucovorin was used in 24 patients of advanced stage as the postoperative treatment. We have added this data to Material and method. However, we did not analyze the relationship of Golph3 with the chemotherapy regimens in current studies.

Minor compulsory revisions.

4. It is unclear what is responsible for over-expression of GOLPH3 in pancreas cancer. This information should be stated as part of the introduction and/or discussion. Also, if this is a protein expressed at some level in normal tissues, how truly valid as an anticancer target will this be?

Reply: GOLPH3 had been studied as an oncogene which overexpressed in many types of cancer as well as pancreas cancer (ref, 19). GOLPH3 expression level are significantly higher in cancer cell than adjacent normal epithelium (ref, 19). GOLPH3 gene amplification is responsible for overexpression of GOLPH3 (ref, 19).

Farber-Katz, S.E., et al recently find that interference with the GOLPH3/MYO18A pathway significantly impaired cell survival after DNA damage, suggesting that small-molecule inhibitors of the pathway may have therapeutic utility [DNA Damage Triggers Golgi Dispersal via DNA-PK and GOLPH3. Cell, 2014. 156(3): 413-27]. We add this paper in our revised manuscript at the part of discussion (ref 25). Overexpression of GOLPH3 in pancreatic cancer as well, will be explored to find out its function in our further studies.