Author's response to reviews

Title: Upregulation of Wnt5a promotes epithelial-to-mesenchymal transition and metastasis of pancreatic cancer cells

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Author's response to reviews: see over
Responses to the comments on our manuscript (MS: 1734429067959864)

We thank reviewers for critical review of our manuscript, and highly appreciate their comments and suggestions that greatly contributed to improving the quality of the manuscript. Our point-by-point responses to the reviewers’ comments are provided below. The major changes to the manuscript have been highlighted in red.

Reviewer: Amir Avan

Reviewer's report: Authors adequately addressed my concerns. No additional concerns noted.

Response: Thank you very much for your work.
Reviewer: Francesco Fabbri

Reviewer's report:

1: Although authors affirmed their data validate and extend in vitro studies, and make known that Wnt5a expression facilitates cancer invasion and metastasis in an orthotopic mouse MODEL of pancreatic cancer, I still don’t see their point: they must not state “Up-regulation of Wnt5a promotes EMT and metastasis in pancreatic cancer”, generalizing a preclinical concept, because they saw it only in a preclinical models and not in the clinical setting. They cannot extend the meaning of their preclinical results to the general situation because their “data indicate that the median cancer-specific survival was comparable between patients with positive versus negative expression of Wnt5a [and] this result suggests that tumor Wnt5a expression alone may NOT be suitable for predicting survival in patients with operable pancreatic cancer.”. So, at present, Wnt5a will retain only a base research value without a clear clinical meaning. In other words, if a preclinical result, even outstanding, is not confirmed by the clinical setting, its meaning is severely limited. Therefore, their research is important, but still clinically quite irrelevant.

Response: Agree. The conclusion statement has been improved as “upregulation of Wnt5a promotes EMT and metastasis in pancreatic cancer models, which involves activation of β-catenin-dependent canonical Wnt signaling. These findings warrant further investigation of the clinical relevance of Wnt5 upregulation in pancreatic cancer”. Thank you very much for your constructive comments on our manuscript.
2: Authors did not upload the complete / final version of this answer. I can read only “As you suggested, morphological changes of pancreatic cancer cells transfected with Wnt5a-expressing plasmid were examined. The results demonstrate that …” … What? I know that the final text has been changed in agreement to my previous suggestion, ok, but, please, be accurate when responding directly to the reviewer also.

**Response:** As shown in Fig. 6b, overexpression of Wnt5a induced a mesenchymal spindle-like morphology in PANC-1 cells under a phase-contrast microscope. Western blot analysis further confirmed that Wnt5a-overexpressing pancreatic cancer cells undergo an EMT, as evidenced by an increase in the expression of vimentin and snail and a concomitant reduction in the E-cadherin expression. These results have been given in the end of page 17.

4/5: Again on the subject of the inconsistency between the biological and clinical findings, I think that the authors did not furnish sufficient evidences / hypothesis on this matter. They affirmed only that, in patients, #-catenin signaling can be regulated by “multiple factors other than Wnt5a”, strengthening in my mind the idea that in the clinical setting Wnt5a may not be a relevant marker. If “multiple factors other than Wnt5a” is the answer, why should I investigate Wnt5a? Please, clarify.

**Response:** Although the in vitro evidence indicated a master role of Wnt5a in inducing aggressive tumor phenotypes, the prognostic impact of Wnt5a expression in pancreatic cancer appears not to be of significance. We found that there was no significant difference in the cancer-specific survival of patients with Wnt5a positive
vs. negative pancreatic tumors. Such inconsistency between the biological and clinical findings remains to be further clarified. The possibility can not be excluded that tumoral Wnt5 expression may have significant prognostic implications in a subgroup of pancreatic cancer patients. The above comments have been added to the 2nd paragraph, page 22.

In conclusion, authors have to be very careful when extending the meaning of their preclinical results to the general situation and they must clearly stress it. For example, when the state “Up-regulation of Wnt5a promotes EMT and metastasis in pancreatic cancer”, in the last sentence of the abstract, and they must change it at least adding the word/s “model/cells” (“Up-regulation of Wnt5a promotes EMT and metastasis in pancreatic cancer models”). Notwithstanding the significant pre-clinical data showed by authors, they have to state strongly that further studies are certainly needed to clarify the real clinical value of Wnt5a.

**Response:** Agree. The conclusion statement has been improved as “upregulation of Wnt5a promotes EMT and metastasis in pancreatic cancer models, which involves activation of β-catenin-dependent canonical Wnt signaling. These findings warrant further investigation of the clinical relevance of Wnt5 upregulation in pancreatic cancer”.