Reviewer’s report

Title: Secretion of fibronectin by human pancreatic stellate cells promotes chemoresistance to gemcitabine in pancreatic cancer cells

Version: 1 Date: 19 Apr 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The authors' rationale, reasoning and presentation is straightforward and easy to understand and follow. Indeed, PDAC is a deadly disease and resistance to gemcitabine a clinical nightmare. Under these circumstances, the work is timely and very important.

In my opinion, the last paragraph of Introduction reveals a lot about the results which is not needed. Introduction needs to just lay the foundation for the study and perhaps provide a logic to the necessity
and importance of study. I suggest that the authors do not describe major results rights here (i.e. modify the last sentence to tone down on results).

Why do I see 'tumor' and several other words/phrases highlighted in green in the manuscript?

Why did the authors evaluate the effect of a single dose of gemcitabine against PSC cultures in Fig 1A? Why was this dose chosen? Is it possible to use increasing doses of gemcitabine and report IC-50 values for PSCs, similar to IC-50s for cell cultures in Fig 1C to get a general idea of the cytotoxicity of gemcitabine against PSCs.

I suggest that Fig 1C be presented as a stand-alone Table.

Are FN effects and MEK/ERK pathways mutually exclusive? Their inter-dependence / hierarchy has not been evaluated?

Looks like FN inhibition has profound effects on ERK signaling but not to the same extent on gemcitabine sensitivity?

Considering the effects in BxPC3 cells, is there a possibility of cell line-specific effects?

Finally, I highly recommend providing a cartoon figure summarizing the explored mechanism.

Note: This reviewer report can be downloaded - see attached pdf file.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

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

Yes

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

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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