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Reviewer 1:

1. The authors should discuss what is already known and what is new and what is their view points for each point discussed.

Answer: When we draft and revise this manuscript, we keep all these three points in our mind and try our best to summarize valuable information from relevant publications.

What is already known: PAK family is divided into two groups, with different activation mechanisms. PAK1 and PAK4 are the most studied PAK family members in different types of cancer in the past, especially pancreas, colorectal and lung cancer. PAKs are involved in tumor initiation and progression through its interaction and regulation of multiple essential oncogenic pathways, such as NF-κB, STAT3 and Kras-dependent RAF/MEK/ERK and PI3K/PDK1/AKT pathway.

What is new: The role of PAK in chemo-resistance of pancreatic cancer has not been fully elucidated. There are only a few evidences showing that inhibition of PAK is associated with improved gemcitabine sensitivity via different pathways, such as up-regulation of hENT1 or down-regulation of NF-κB. In addition, PAK1 is emerging as a critical mediator within the interaction between tumor and stroma in pancreatic cancer. Our latest study has shown that inhibition of PAK1 can suppress pancreatic stellate cell activation and improve survival of mice with pancreatic cancer. More importantly, immunotherapy is believed to be a promising approach to treat cancer. In this regard, immune re-modulation within the tumor microenvironment has become a hot spot in pancreatic cancer research. The novel role of PAK in tumor-associated immune modulation has been unveiled by showing that inhibition of PAK1 can stimulate tumor-infiltrated T lymphocytes. However, there is little direct evidence linking PAK to anti-tumor immune response, so the underlying mechanisms should be investigated further.

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Author's point of view: As an important down-stream effector of mutated Kras, PAK is not only involved in the intrinsic tumor cell biology, but also is emerging as a potential target in tumor microenvironment re-programming, including tumor-stroma crosstalk and intra-tumoral immune modulation.

2. Introduction should be more succinct. Conclusion should be greatly expand to provide reader author view points in details.

Answer: Introduction has been cut down to be more succinct (page 5-6). More information has been added to Conclusion part (page 29).

Reviewer 2:

1. However, there are still some inappropriate depictions need to be reconsidered before acceptance, for example, page 6 "and the importance of PAKs as a therapeutic target in Kras signalling highlighted"; page 13 "PAK4 expression correlates with pancreatic cancer pathology"; page 24 "Recently, a novel role of PAK1 in up-regulating the immune response to tumours in a genetically modified mouse model of colorectal cancer (the APC14/+ mouse) was revealed."

Answer: The sentences have been corrected in the manuscript.

Corrected "and the importance of PAKs as a therapeutic target in Kras signalling highlighted" on page 7;

Corrected "PAK4 expression correlates with pancreatic cancer pathology" on page 15;

Corrected "Recently, a novel role of PAK1 in up-regulating the immune response to tumours in a genetically modified mouse model of colorectal cancer (the APC14/+ mouse) was revealed." on page 27.

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Reviewer 3:

Major comment:

The manuscript would benefit much from a better structure when adding information on signaling pathways in cancers other than pancreatic cancer. This is especially evident in the paragraph "The role of PAKs in Kras-driven oncogenic pathways". Subheadings could also be useful in the long paragraph on "PAK signaling in pancreatic cancer".

Answer: As discussed in the paragraph "The role of PAKs in Kras-driven oncogenic pathways" (page 9), the important role of PAKs in Kras-driven signalling pathway is summarized from different types of human cancer and cell line, especially pancreatic, colorectal, lung cancer. Subheadings have been used in the long paragraph on "PAK signaling in pancreatic cancer", giving a better structure to differentiate PAK1 (page 13) and PAK4 (page 15) in regulating oncogenic signaling.

Minor comments:

1. The manuscript is generally well-written but some of the wording should be improved. Examples are "combinational" (page 1), "notorious" (page 3) and "a new war" (page 4 – maybe the authors mean campaign?)

Answer: The words mentioned have been corrected or re-word in the paragraph. "combinational" (page 2), "notorious" (page 5), "a new war" (page 6)

2. Several abbreviations are not defined at their first use e.g. PI3K, AKT and MEK in the introduction, EMT (page11), shRNA (page 13) and HIF1a (page 16).

Answer: All the abbreviations have been re-arranged in the "Abbreviations" section.

3. The sentence "Phosphorylation at the Thr423 site is important for maintaining PAK1

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activation" (page 6) lacks transition from the paragraph.

Answer: This sentence has been re-organized to give a more natural and smoothly transition (page 8).

4. For ease of reading, could the authors add the cell type / organ source of NIH3T3 and HeLa cells?

Answer: Cell type/organ source has been added in the manuscript (page 11).

5. Pancreatitis is not widely believed to be an important risk factor for pancreatic cancer (page 14, first paragraph). The authors either need to re-word this sentence if they meant to say something else or should remove it.

Answer: This sentence has been removed in the manuscript (page 16).

6. If gemcitabine induced NF-kB activity in pancreatic cancer cell lines (page 17), then this would imply that gemcitabine could actually enhance cancer growth? Could the authors comment on this, please.

Answer: As discussed in the paragraph (page 19-20), NF-κB is associated with gemcitabine resistance, and gemcitabine induces NF-κB activity in a dose-dependent manner. The potential reason should be: gemcitabine treatment is cytotoxic and induces cell apoptosis. Increased activity of NF-κB could be a compensatory mechanism for the cells to survive. When treated with gemcitabine, part of the cells will be killed, but a certain sub-population of the cells will survive by up-regulating some proliferation and survival-related factors. NF-κB is probably one of them. This mechanism is supported by some other points in the paragraph: (1) resistant cell line shows higher expression of NF-κB than sensitive cell line. This indicates that resistant cell line has more potential and capacity to survive in the gemcitabine treatment via a NF-κB-dependent pathway; (2)

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Inhibition of NF-κB activity leads to increased gemcitabine sensitivity and suppression of cell proliferation and survival.

7. In the first paragraph on stromal remodeling (page 18), it would be enough to just state that PAK1 leads to stromal fibrosis in pancreatic cancer similar to liver fibrogenic pathways. The additional information from other fields is generally a bit to extensive and makes it difficult to focus on the evidence in pancreatic cancer. The same applies e.g. to the sentences on the APC14/+ mouse on page 24.

Answer: The sentences have been re-organized to make it more focus on pancreatic cancer "liver fibrosis" on page 20 and "APC14/+ mouse" on page 27.

8. Is it the absence of stromal TILs or a low CD4:CD8 ratio that is associated with disease-free and overall survival (page 24)? It would help the readers understanding if the authors could be more specific.

Answer: More information has been added to the manuscript, making the readers easier to understand (page 27).

9. Are the figures derived from any previous publications or are they the author's own work? In case of the former, this should be acknowledged.

Answer: The figures are the authors' own work on the bases of the authors' study and previous publications.