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Group**

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39865

Title: PAK signalling in pancreatic cancer: new insights into tumour biology and immune modulation

Reviewer's code: 02615988

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-05-23

Date reviewed: 2018-05-23

Review time: 8 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review article needs a lot of improvements. More specifically, the authors should discuss what is already known and what is new and what is their view points for each points discussed. Introduction should be more succinct. Conclusion should be greatly



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expand to provide reader author view points in details.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39865

Title: PAK signalling in pancreatic cancer: new insights into tumour biology and immune modulation

Reviewer's code: 03552346

Reviewer's country: China

Science editor: Xue-Jiao Wang

Date sent for review: 2018-05-23

Date reviewed: 2018-05-27

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review comprehensively summarized the relationship between the initiation/progression of pancreatic cancer and Kras/PAKs signaling pathway in terms of oncogenesis, gemcitabine chemoresistance and tumor immune microenvironment



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modelling. This review depicted a landscape thoroughly to facilitate investigators to have a new insight into the important function which PAKs had in pancreatic cancer. In addition, this review also brought out some new hypothesis based on the past investigations which may trigger more and more investigations to make a comprehensive understanding of the functions that PAKs had in pancreatic cancer. This review is of great importance because PAK signaling pathway may harbor great therapeutic breakthroughs in pancreatic cancer in the future. This manuscript is well organized and style, language and grammar errors are seldom found. 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.”.

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39865

Title: PAK signalling in pancreatic cancer: new insights into tumour biology and immune modulation

Reviewer's code: 02445558

Reviewer's country: United Kingdom

Science editor: Xue-Jiao Wang

Date sent for review: 2018-05-23

Date reviewed: 2018-05-31

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The author present a review on the existing evidence on hallmark molecular pathways of pancreatic cancer including tumour biology, chemoresistance and immune evasion. It therefore highlights an important topic as pancreatic cancer is highly prevalent and



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continues to be associated with one of the highest cancer-related mortalities. I have one major comment and a couple of minor comments that should help the authors to improve the quality of the manuscript. 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”. 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?) 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). 3. The sentence “Phosphorylation at the Thr423 site is important for maintaining PAK1 activation” (page 6) lacks transition from the paragraph. 4. For ease of reading, could the authors add the cell type / organ source of NIH3T3 and HeLa cells? 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. 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. 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 too 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. 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. 9. Are the



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

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