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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42334

Title: Dbx2 performs a tumor-promoting function in HCC cell lines via regulating the Shh-Gli1 pathway

Reviewer's code: 03742333

Reviewer's country: United Kingdom

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-28

Date reviewed: 2018-10-04

Review time: 6 Days

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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced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

SPECIFIC COMMENTS TO AUTHORS

I have read with great interest the manuscript entitled "Dbx2 performs a tumor-promoting function in HCC via regulating the Shh-Gli1 pathway", submitted to the World Journal of Gastroenterology. In this basic study the authors investigate the

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role of Dbx2 in regulating the HCC cell proliferation, apoptosis and cell migration. Additionally, they correlated the immunohistochemical expression of this marker in 76 surgically resected HCC with clinical and pathological features of the tumour. First of all, I would like to congratulate the authors for the extensive work performed and also for the investigating the expression of Dbx2 in human tissue, apart from HCC cell lines. The methodology employed for the experiments is scientifically sound and meaningful, and the manuscript well written and reads well. However, I have some concerns mainly regarding over-interpretation of the data. Major comments: 1. Major concern is over-interpretation of the data. Many statements throughout the manuscript are based on the finding that overexpression of Dbx2 is associated with tumour growth/ large tumour size on the surgically resected HCC. For example, this affirmation can be found: - At the introduction, in the results section, “resected HCC tissues compared to that in matched adjacent non-tumorous tissues and clinically correlated with large tumour size” - At the result, “We speculate that Dbx2 may participate in the development of HCC.” - At the discussion, “the first evidence of aberrant upregulation of Dbx2 in HCC tissues and indicate the clinical significance of Dbx2 in HCC pathogenesis” The data provided to support those statements are presented in table 2. Examining carefully the results, it can be seen that the occurrence of male sex was higher in Dbx2 high group. However, the whole cohort of patients were predominantly constituted of men, thus attributing this difference to Dbx2 may be at least debatable. This should be addressed or discussed. More worryingly, the interpretation of the second significant difference between groups, regarding tumour size, should be re-considered. The “Dbx2 Low group” had the majority of patients with a tumour <5cm, however in “Dbx2 High” group the number of patients with a tumour greater or smaller than 5cm was basically equal. Therefore, higher expression of Dbx2 was not really associated with large tumour size and this data does not support those statements above. Additionally, Dbx2 was positive in 40.79%

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of the cases in adjacent NON-tumour tissues. Although this rate was higher in tumours, this figure is relevant, and in accordance, it should be at least discussed in the manuscript. From figure 1E, approximately 38% of the tumour tissue had a similar or lower expression of Dbx2 than the adjacent non-tumour tissue. 2. The response to ectopic expression of Dbx2 varies between different HCC cell lines, as seen in Figure 5A. Please comment on this. Minor comments: 1. In accordance with the previous comments, please clarify along the manuscript that whereas the mechanistical findings observed suggest that Dbx2 works in HCC lines, further studies should look how it would actually affect an in vivo human tumour. For example, the first phrase of the second paragraph in the discussion says "knockdown of Dbx2 inhibited HCC proliferation". Please consider discussing that there may differences in response between HCC cell lines and the human tumours in situ, as suggested by the expression of the staining also in non-tumour adjacent tissue. 2. The title should be amended accordingly, as "Dbx2 performs a tumor-promoting function in HCC CELL LINES via regulating the Shh-Gli1 pathway"

INITIAL REVIEW OF THE MANUSCRIPT

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[ ] Plagiarism

[ ] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42334

Title: Dbx2 performs a tumor-promoting function in HCC cell lines via regulating the Shh-Gli1 pathway

Reviewer's code: 03017782

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-29

Date reviewed: 2018-10-11

Review time: 12 Days

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

SPECIFIC COMMENTS TO AUTHORS

Congratulate the authors. Very interesting study about the Dbx2 performs a tumor-promoting function in HCC via regulating the Shh-Gli1 pathway. The study was well designed and the manuscript is well organized. Only some very minor languge

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polishing should take attention. Thank you.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42334

Title: Dbx2 performs a tumor-promoting function in HCC cell lines via regulating the Shh-Gli1 pathway

Reviewer's code: 03017792

Reviewer's country: Japan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-29

Date reviewed: 2018-10-15

Review time: 15 Days

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

SPECIFIC COMMENTS TO AUTHORS

Very interesting study. After a minor revision, it can be accepted for publication. The discussion should be revised, there may differences in response between HCC cell lines and the human tumours in situ, as suggested by the expression of the staining also in

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non-tumour adjacent tissue.

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No

BPG Search:

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[Y] No