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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39989

Title: DL in HCC intrinsically promotes tumour growth and suppresses HBV replication

Reviewer’s code: 02445571

Reviewer’s country: China

Science editor: Ze-Mao Gong

Date sent for review: 2018-06-03

Date reviewed: 2018-06-04

Review time: 1 Day

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 type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input 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 type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript, the authors examined the DLL4 signal on HCC tumor growth and VEGF/VEGFR2 expression on HCC tumor by employing HCC xenograft of mouse models made by HepG2.2.15 or shDLL4 HepG2.2.15 cell line subcutaneous injection. The



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overall experimental design and performance are well conducted. The results from the studies are convincing and interesting. The data are properly presented.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39989

Title: DL in HCC intrinsically promotes tumour growth and suppresses HBV replication

Reviewer’s code: 03730829

Reviewer’s country: Egypt

Science editor: Ze-Mao Gong

Date sent for review: 2018-06-16

Date reviewed: 2018-06-17

Review time: 1 Day

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 type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" 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 type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input checked="" 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

The study by Kunanopparat et al. investigated the role of DLL4 on tumour growth in HCC associated with HBV in a xenograft model and detailed the molecular mechanism of HCC. They demonstrated that DLL4 is important for tumor growth of HBV-associated



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HCC in a xenograft model. They found that the level of angiogenesis regulators, VEGF-A and VEGF-R2, was significantly decreased in HCC xenograft tumors with silencing of Dll4 compared with the control group. They concluded the suppression of DLL4 expression in the tumor cells reduced cell proliferation and the formation of new blood vessels in tumor. The subject is interesting. However, the results and discussion are not clearly presented: Major comments: 1] Some studies stated that high level of dll4 may inhibit the growth and metastasis of HCC; which may be different than your findings. So; you should give clear explanation to the readers and add this in discussion. a) Liu X, et al. SYNJ2BP inhibits tumor growth and metastasis by activating DLL4 pathway in hepatocellular carcinoma. Journal of Experimental & Clinical Cancer Research 2016;35:115. b) Chen H et al. High level of Delta-like ligand 4 suppresses the metastasis of hepatocellular carcinoma. Int J Clin Exp Pathol 2016;9(3):2989-2997 2] Do you think these results could be applied to other etiologies of HCC? : This should be clarified in discussion. With warm regards,

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39989

Title: DL in HCC intrinsically promotes tumour growth and suppresses HBV replication

Reviewer's code: 00054255

Reviewer's country: South Korea

Science editor: Ze-Mao Gong

Date sent for review: 2018-06-03

Date reviewed: 2018-06-17

Review time: 14 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 type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" 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

DLL is one of the Notch pathway that have pancancer signaling pathway of cell fate decision, cell proliferation and apoptosis. DLL4 is one of the Notch ligand. Many genes except well revealed genes, k-ras, p53 etc, have chimeric faces, promotor effect in some



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cancers and suppressor genes in others. Authors hypothesized that the DLL4 has a promoter in HCC in particularly for the hepB related. Authors performed experiments two modalities, in vitro and in vivo, one in DLL4 silenced HCC cell line another with cancer xenograt in nude mouse. And in analysis, the result of western blot, immunohistochemical stain using anti-ki67 and ant-CD31 antibodies to the tumor tissues obtained from the xenografted tumor, tumor vascular imaging, and VEGF expression and quantitative RNA expression shows consistent finding of tumor suppression by silencing of the DLL4. Additionally authors found that DLL4 HBV DNA and RNA expression was significantly decreased and suppressed in the DLL4 silenced culture of cell line and tumor xenograft. Authors' investigation is informative for uncover one of the pathway of HCC carcinogenesis Criticism: 1. The authors investigated the tumor suppressing effect of DLL4 silenced HCC cell line using HepB expressing cell line in vitro and increased HBV viral production that is not consistent previous result of authors'. Is it applicable to another cellines, non-hepB expressing cell line? Virus can intervene for the promotion or inhibition of the carcinoma. 2. Recently a lot of result of gene set affecting on the cancer cells were reported, like TCGA data published last year(Cell, July 2017). That is very intensive result using HCC tumor tissues that is collected globally. There are strong gene characteristics, copy number, RNA expression, microRNAs, methylation etc. genomic characterization related HCC. Notch or DLL is not enlisted in the significant genes in that study. Reviewer would recommend the result is to be validated or compared by the result of other investigators including TCGA data, and put the authors' view in the discussion.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39989

Title: DL in HCC intrinsically promotes tumour growth and suppresses HBV replication

Reviewer's code: 00031629

Reviewer's country: Pakistan

Science editor: Ze-Mao Gong

Date sent for review: 2018-06-16

Date reviewed: 2018-06-18

Review time: 2 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 type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" 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 is an interesting study. However the effect of DLL4 silencing is not clearly elucidated requiring further explanation. Moreover the conclusion in this regard is confusing "intrinsically suppresses HBV replication" as mentioned in the abstract



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conclusion. while in results and discussion it is mentioned "Unexpectedly, increased viral replication was observed in HepG2.2.15 upon DLL4 silencing in vivo"

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