Baishideng Publishing 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: 37377
Title: PAR2 promotes tumor cell proliferation and metastasis by inducing EMT and predicts poor prognosis in hepatocellular carcinoma
Reviewer's code: 02670181
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2017-12-08
Date reviewed: 2017-12-12
Review time: 4 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Comments on " PAR2 promotes tumor cell proliferation and metastasis by inducing EMT and predicts poor prognosis in hepatocellular carcinoma" manuscript number 37377 Conclusion: very minor revision required In this paper, the authors proved the importance of PAR2 in the process of HCC growth and invasion in several situation: (1) the relationship between immunohisological PAR2 expression and HCC patients' prognosis, (2) the effect of PAR2 gene manipulation on cell proliferation, migration, and invasion in in vitro setting using cell lines, (3) the effect of PAR2 gene manipulation on tumor formation or metastases in tumor xenograft nude-mouse model, and (4) the effect of PAR2 gene manipulation on EMT process in in vitro setting using cell lines. These results seem to be very informative to the readers of World Journal of Gastroenterology . I strongly recommend the publication of this paper when the authors appropriately

Baishideng Publishing 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

reply the opinion raised by me. Major points 1) Basically, PAR2 is activated (without its own ligand) via its N-terminal cleavage by several proteases. I agree with PAR2's role in in vivo model (such as xenograft model) since many proteases would exist in transplanted tumors. However, can HCC cell lines produce active form of protease? The authors had better refer the others' paper reporting the protease production by HCC or other cancer cell lines. 2) From this study results, I strongly convince that PAR2 promote HCC cells' EMT. However, what subcellular molecules are responsible for EMT? How about SNAIL or SLUG? Minor points 1) In the abstract part, the sentence "PAR2 could promote proliferation and metastasis of~" is not understandable. The authors performed overexpression or knockdown of PAR2 by lentivirus-mediated RNA interference. Therefore, the authors had better describe the method of PAR2 gene manipulation in the abstract. 2) What cell expresses PAR2 in HCC tissue? The authors had better explain PAR2-expressing cell and the intracellular localization of PAR2.

Baishideng Publishing 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: 37377
Title: PAR2 promotes tumor cell proliferation and metastasis by inducing EMT and predicts poor prognosis in hepatocellular carcinoma
Reviewer's code: 00724887
Reviewer's country: India
Science editor: Ze-Mao Gong
Date sent for review: 2017-12-08
Date reviewed: 2017-12-16
Review time: 8 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS
Well written article

Baishideng Publishing 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: 37377
Title: PAR2 promotes tumor cell proliferation and metastasis by inducing EMT and predicts poor prognosis in hepatocellular carcinoma
Reviewer's code: 00068209
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2017-12-08
Date reviewed: 2017-12-17
Review time: 9 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Comment on the manuscript 37377 by Sun, et al. PAR2 is known is known to play a crucial role in tumor development of numerous caners. The authors investigated the effects of PAR2 for liver cancer cells and shown that PAR2 can predict the patients survival by IHC, promote cell proliferation, invasion in vitro, and migration, and accelerate tumor growth and metastasis in vivo. The study was well designed and provided detailed biochemical mechanism on the role of PAR2 in liver cancer progression. There are several questions and suggestions for corrections: 1) Abstract: Methods is too long, while Results should be written in detail. 2) Introduction: The last paragraph is a conclusion of this study, which should not be written in Introduction. 3) Immunohistochemistry: How many experienced pathologists diagnosed the staining of PAR2? In addition, the antibody used in this study should be demonstrated. 4) Results:

Baishideng Publishing 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

The authors stated that PAR2 could predict the patient prognosis. Then, it should be analyzed whether PAR2 expression level by IHC is an independent factor or not by Cox-hazard model. 5) In IHC study, which part of the cancer cells was stained, nucleus, cytoplasm, or membrane? In addition, the patient distribution of IHC score should be shown (score 0, __ patients; score 1, __ patients, …). 6) In wound healing assay, rate of decrease of the wound breadth should be shown.

Baishideng Publishing 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: 37377
Title: PAR2 promotes tumor cell proliferation and metastasis by inducing EMT and predicts poor prognosis in hepatocellular carcinoma
Reviewer's code: 00255973
Reviewer's country: Canada
Science editor: Ze-Mao Gong
Date sent for review: 2017-12-08
Date reviewed: 2017-12-18
Review time: 10 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

I read the article with great interest. The article is well written. The introduction is perfect to set the context of the research aim. The experiments are well performed, and the results support the conclusions. The findings about the function of PAR2 for EMT in HCC patients described in this article could initiate new research to exploit PAR2 in prognostic and therapeutic approaches to efficiently combat HCC progression. Major Comments: The manuscript implies that PAR2 promotes EMT in HCC cells partly by activating the ERK signaling pathway. It is unclear if this ERK activation is constitutive or occurs in response to growth factors present in the serum. The authors could examine if growth factors such as HGF promotes PAR2-mediated EMT. In this context, the authors could quote a recent page published in WJG on HGF-induced EMT in HCC cells (World J Gastroenterol. 2017 Sep 28;23(36):6639-6649). It has been reported in several

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

previous studies that EMT is modulated by the induction of different transcription factors (SNAI1, SNAI2, ZEB1, ZEB2, TWIST1). Particularly, ERK has been implicated in inducing EGR-1 (EMBO J 2006; 25: 3534-3545). It would be informative if the authors could examine EGR-1 expression is modulated by PAR-2. In the wound healing assay, the increased wound closure caused by overexpressed PAR2 (Fig. 4C) could result from increased cell proliferation. To avoid this complication, it would be necessary to inhibit cell growth (for example using hydroxylurea; Ref: J Hepatol 2011; 55: 1300-1308) and evaluate cell migration alone. However, the increased matrigel invasion caused by PAR2 is supportive of increased EMT. Minor comments: First paragraph of the discussion is redundant as most of the points are already described in the introduction. Instead, it would be nice if the authors could suggest some future line of research based on their findings. The author could indicate the rationale behind the use of HepG2 and SMMC-7721 cell lines in this study.