



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 38348

**Title:** Prognostic Value of HIF-1 $\alpha$  and P4HB Overexpression in Gastric Cancer

**Reviewer's code:** 03478635

**Reviewer's country:** Japan

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-02-12

**Date reviewed:** 2018-02-13

**Review time:** 23 Hours

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

**COMMENTS TO AUTHORS**

1. In overexpression of P4HB is associated with hypoxia-associate biomarkers in GC in result section in page 6, Figure 1 should be re-checked. Explanations for clinical pathological characteristics should be added in the correlations between the expression of HIF-1 $\alpha$ , P4HB and clinicopathologic factors. 2. In univariate and multivariate analysis in the cohort of GC patients in page 7, the clinical outcomes and the clinicopathological factors were evaluated by Kaplan-Meier method and log-rank test. Some explanations for Table 3 may be added in the results. The title of Table 3 may be revised. 3. In discussion in page 9, reference 39 is cited to explain that GC cell with ERp19 knockdown dramatically suppressed cell growth and inhibited cellular migration. Please re-check the reference 39. The last paragraph in the result section should be revised.



**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

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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 38348

**Title:** Prognostic Value of HIF-1 $\alpha$  and P4HB Overexpression in Gastric Cancer

**Reviewer's code:** 00505440

**Reviewer's country:** India

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-02-12

**Date reviewed:** 2018-02-15

**Review time:** 2 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

### COMMENTS TO AUTHORS

Very well written manuscript. Minor comments 1) Please remove the copy edit markers when submitting a manuscript in the future 2) In the Kaplan Meier curves, please add the number of patients that followed up at each time point on the X axis



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**Manuscript NO:** 38348

**Title:** Prognostic Value of HIF-1 $\alpha$  and P4HB Overexpression in Gastric Cancer

**Reviewer's code:** 02544209

**Reviewer's country:** Turkey

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-02-12

**Date reviewed:** 2018-02-15

**Review time:** 3 Days

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

**COMMENTS TO AUTHORS**

The authors investigated the prognostic significance of tumor tissue expression levels of HIF-1 alpha and P4HB in resected gastric adenocarcinoma. They found that both markers have a prognostic importance in this setting. The relationship between HIF-1 $\alpha$  expression and poor prognosis and aggressive behaviour in resected gastric cancer patients has been documented with clinical studies and meta-analyses. However, there is no enough information about the effect of P4HB on clinical course of gastric cancer. This condition might increase the value of the manuscript. In introduction and discussion sections authors wrote that they had previously demonstrated P4HB was a potential target of HIF, but they did not give any references. In malignancies, HER2 was shown to increase HIF-1 $\alpha$  synthesis. Therefore assessment of HER2 status of their patients might add new data to their study. Abstract section of the manuscript could be revised: For instance, survival times can be given in detail.



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**Manuscript NO:** 38348

**Title:** Prognostic Value of HIF-1 $\alpha$  and P4HB Overexpression in Gastric Cancer

**Reviewer's code:** 00071054

**Reviewer's country:** Japan

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-02-12

**Date reviewed:** 2018-02-16

**Review time:** 4 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

**COMMENTS TO AUTHORS**

The authors sought to investigate the correlation between HIF-1a, P4HB expression and the related clinicopathological parameters in gastric cancer patients and evaluate whether the prognosis and hepatic/peritoneal metastasis are associated with these expressions. They concluded that both of these proteins over-expression was correlated to TNM stage and peritoneal metastasis. In addition, HIF-1a over-expression was an independent prognostic factor predicting disease-free survival (DFS) and overall survival (OS); however, P4HB was only the independent prognostic factor in predicting DFS but not OS. I have some comments as follows. 1. The authors demonstrated that P4HB was a downstream gene of HIF-1a in the previous research; however, citation of the research was not found. 2. Please explain the significance of the correlation between P4HB and hypoxia-associated biomarkers other than HIF-1a in Figure 1. Hypoxia-associated biomarkers other than HIF-1a were not mentioned in this study



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

thereafter at all. 3. Please describe the median score used as the cutoff point in the evaluation of immunohistochemistry stain. In addition, the number of patients with over-expression of both proteins, over-expression of either protein, and weak-expression of both proteins should be described. 4. Please discuss the differences in the clinicopathological factors and survival between HIF-1a and P4HB expression, if P4HB was a downstream gene of HIF-1a. 5. Finally, images of Figure 2 were hard to see because of low resolution; therefore, it should be replaced by the high-resolution images.