ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14160
Title: Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma
Reviewer code: 02936283
Science editor: Su-Xin Gou
Date sent for review: 2014-09-23 21:11
Date reviewed: 2014-09-25 11:48

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

COMMENTS TO AUTHORS

Manuscript ID: 14160 Manuscript Title: Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma   This clinicopathological study showed that low STAT4 expression was associated with poor prognosis in HCC patients and subsequent in vitro study showed that the poor prognosis might be related to high rate of tumor cell proliferation.   However, this study had critical points to be addressed, as follows: < Major Points > 1. The Authors argued that STAT4 expression was an independent prognostic indicator in HCC patients who underwent curative resection.   To support that conclusion, multivariate cox proportional hazard model should have been used.   However, as shown in Table 2, they performed cross sectional comparison using Pearson χ^2 test which compared the variables between alive and dead patients, but not longitudinal survival analysis using multivariate cox proportional hazard model as indicated in the Methods section. 2. The inclusion criteria included curative resection. However, 13 of 90 patients had tumor metastasis, as shown in Table 1.   They should exclude these patients from this study. 3. The in vitro studies showed that STAT4 expression was closely associated with HCC cell proliferation.   Considering that result, it would be better to compare the time-to-recurrence as well as overall survival between high- and low-STAT4 groups.   < Minor Points > 1. An extensive English editing is required. 2. The summary of results in the end of Introduction section should be removed. 3. The unit of AFP must be ng/mL, but not µg/mL. 4. It

should be clarified how the cut-off values of STAT4 and Ki67 intensity score (i.e. 0.53 and 0.48, respectively) were made? Were they median values? 5. The term of 'tumor nodes' needs to be changed to 'tumor numbers in Tables 1 and 2.

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Title: Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma
Reviewer code: 02151769
Science editor: Su-Xin Gou
Date sent for review: 2014-09-23 21:11
Date reviewed: 2014-10-06 16:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for
[Y] Grade C: Good	[ ] Grade C: A great deal of	[ ] No records	publication
[ ] Grade D: Fair	language polishing	BPG Search:	[ ] Rejection
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		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The manuscript describes a study of "Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma ". The topic of this manuscript is very interesting, but I think that the manuscript is not perfect to publish at this version.

The comments as below:

1, The novelty of this manuscript must be revised. A paper titled "High STAT4 Expression is a Better Prognostic Indicator in Patients with Hepatocellular Carcinoma After Hepatectomy." Published in Ann Surg Oncol. 2014 Jun 26 (http://www.ncbi.nlm.nih.gov/pubmed/24965572), The authors must be compare the manuscript to this paper.

2, The western blot assay in Fig4 seems need to re-do. The authors stated that the expression level of stat4 is lower in HCC cell lines in Fig4 a, and the data not support this; also in Fig 4b cyclin D; the stat4 expression level in Fig4a and the cyclin D expression level in Fig 5a.

3, in the abstract, the authors says "However, a detailed involvement of Stat4 in HCC development remains much elusive." So this sentence need to be revised. And the above paper must be involved in introduction and discussion.

4, in discussion, the authors says that "we speculated that HBV infection might reduce the level of hepatocellular STAT4 through posttranscriptional-dependent mechanisms. Alternatively, HBV may

influence the activation of STAT4 through the modulation of STAT4 phosphorylation state." Why do these speculations? There is no data to support these speculations, and these speculation have no connection with the manuscript. Or the authors could do some assay to validate that these speculations.

5, "In addition to HBV infection, we showed that the expression of STAT4 related with the histological degree of HCC as well as the prognosis of HCC subjects." The authors could say "We showed that the expression of STAT4 related……"directly.

6, the discussion must be more clearly. "Indeed, the level of STAT4 expression varies in different types of cancers, and even in the same type of cancer with different genetic backgrounds and in patients from different geographic regions. We are interested in further investigating how these factors modulate the STAT4 expression and activation, contributing to the development and progression of HCC." And the following paragraph is illustrated this sentence, so the authors integrate these sentence to a paragraph, and show the changes in these cancers.

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ESPS manuscript NO: 14160
Title: Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma
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Science editor: Su-Xin Gou
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for
[Y] Grade C: Good	[ ] Grade C: A great deal of	[ ] No records	publication
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COMMENTS TO AUTHORS

Manuscript ID: 14160 Manuscript Title: Decreased STAT4 Expression was associated with Poor Prognosis and enhanced cell proliferation in Hepatocellular Carcinoma An interesting article which examine the expression of STAT4 in HCC using different methods. The give sufficient Information about the Technical part of each method which allows somebody to repeat the experiments. The plan and the whole procedure of this Research is quite attractive, however they need to be more careful in the interpretation of their results. There is a weakness in the statistic part of the Research. Moreover, the photos from immunohistochemistry, although the differences between high and low expression is obvious, they show quite background even in Ki-67 immunostain.