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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4125
Title: Up-regulation of IGF-I receptor expression in hepatocarcinogenesis as a pertinent biomarker for hepatocytes malignant transformation.
Reviewer code: 00051373
Science editor: Gou, Su-Xin
Date sent for review: 2013-06-18 08:56
Date reviewed: 2013-06-19 16:53

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

COMMENTS TO AUTHORS
Comments to the author 1. In the Ethics statement, more detail of the approval number of the reviewed and approved by the Institutional Animal Care and Use Committee is need. Not only has the guideline in the Guide for the Care but also the Use of Laboratory Animals as promulgated by the Institute of Laboratory Animal Resources, National Research Council, USA needed to descript detail. 2. Chemical induced hepatoma in animal model is much difference not only what happens in the human beings but also the complication of the viral induced hepatocellular carcinoma. Therefore, the author needs to mention in the conclusion section. 3. According to the Ref. 13, there was a human HCC xenograft model. (Tovar V, Alsinet C, Villanueva A, Hoshida Y, Chiang DY, Solé M, Thung S, Moyano S, Toffanin S, Mínguez B, Cabellos L, Peix J, Schwartz M, Mazzaferro V, Bruix J, Llovet JM. IGF activation in a molecular subclass of hepatocellular carcinoma and pre-clinical efficacy of IGF-1R blockage. J Hepatol. 2010; 52: 550- 559. The author described that this study was rat hepatoma models. Please describe more detail over there. 4. The process of the control, degeneration, precancerosis and HCC seems to be a progressive alteration in dynamic change in the histopathological picture, total RNA, IGF-IR mRNA and liver IGF-IR, linear regression analysis with error bar parameter description may be easy to understand for the readers. 5. Where the figure 4 was came from? A signature is found in the figure 4 right hand side middle part. It needs to describe carefully. 6. In the figure 4 left hand side, it is a pathway talking about the chronicity mechanism of the chronic hepatitis/cirrhosis/hepatocellular carcinoma. It may not be suitable to use to describe in this animal model.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4125
Title: Up-regulation of IGF-I receptor expression in hepatocarcinogenesis as a pertinent biomarker for hepatocytes malignant transformation.
Reviewer code: 00503526
Science editor: Gou, Su-Xin
Date sent for review: 2013-06-18 08:56
Date reviewed: 2013-06-20 22:17

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

COMMENTS TO AUTHORS
It is useful data in HCC. It is acceptable.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4125
Title: Up-regulation of IGF-I receptor expression in hepatocarcinogenesis as a pertinent biomarker for hepatocytes malignant transformation.
Reviewer code: 00053417
Science editor: Gou, Su-Xin
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[Y]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The roles of the insulin-like growth factor-I (IGF) axis in hepatocarcinogenesis have been documented. In this manuscript, the authors investigated the mRNA expression (by RT-PCR) and protein levels (by ELISA) of IGF-1 receptor (IGF-IR) in the liver and serum in a rat hepatoma model. The related work has been published. The study may help accumulation of the knowledge in this field. The design of the study is good, but writing skill and English needs improvement.

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ESPS Peer-review Report
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Reviewer code: 00004520
Science editor: Gou, Su-Xin
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[Y]Rejection
[ ] Grade D (Fair)	[Y] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

This paper was aimed at investigating the expression of insulin-like growth factor-I receptor (IGF-IR) during hepatocarcinogenesis induced by 2-fluorenylacetamide in Sprague-Dawley rats. Increase in IGF-IR mRNA and protein incidence and expression are reported in preneoplastic and neoplastic tissue. On this basis it is concluded that "IGF-1R expression may participate in hepatocarcinogenesis and its abnormality should be an early marker for hepatocytes malignant transformation." This paper contains a number of drawbacks, lacks originality and adds nothing to current knowledge. The results are questionable and do not support the conclusions. 1. The changes in IGF-IR expression in different steps of rat liver carcinogenesis have been elegantly demonstrated by Aleem et al. (Reference n.18). Therefore the statement that "the features of IGF-IR expression during hepatocytes malignant transformation have not yet been reported" (in the Introduction section) is wrong. 2. The experimental system to induce hepatocarcinogenesis has not correctly been used in the present paper. In this system, foci of altered hepatocytes, early nodules, late (dysplastic) nodules, early hepatocellular carcinomas (HCC) and aggressive HCC may be induced. The authors identified only three stages that they denominate: degeneration, precancerous and (early) HCC, without indicating the time of appearance of the different lesions. Moreover, the morphological documentation of the different stages is really poor. 3. It is not clear to me what the authors mean by "dynamic alterations" of the expression of IGF-IR. It would probably be preferable to study the dynamics of the appearance of alterations of the expression of IGF-IR during the different stages of hepatocarcinogenesis. 4. The method used to evaluate IGF-IR mRNA expression is extremely imprecise and poorly sensitive. In addition, the analyses have been performed on whole liver. Thus,

the differences among degeneration, precancerous and HCC could merely reflect differences in the relative extent of the lesions and surrounding tissue at different stages of hepatocarcinogenesis. Quantitative Real-Time Reverse Transcription (qPCR) analysis of isolated precancerous and cancerous lesions must be done in order to obtain reliable results. 5. The determination of the sequence of IGF-IR, to demonstrate the presence of the gene in different tissues is useless. 6. It is not clear if the quantitative immunohistochemical analysis of IGF-IR has been performed blindly by different pathologists as well as the extension of the examined tissue.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4125
Title: Up-regulation of IGF-I receptor expression in hepatocarcinogenesis as a pertinent biomarker for hepatocytes malignant transformation.
Reviewer code: 00053419
Science editor: Gou, Su-Xin
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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	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[Y]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
Xiao-Di Yan et al performed a study to investigate variations in IGF-I receptor in the liver during the progression of HCC induced in rats with 2-fluorenylacetmide. The findings reported do not represent a significant contribution in the field as previous studies have already documented the up-regulation of IGF-IR in a rat model of hepatocarcinogenesis (ref 18 in the manuscript) and also the reduction of tumor growth associated with inhibition of IGF-IR (ref 28 and Yue L et al Oncol Rep 2012). Moreover, studies are also available (Sobrevals L Hepatology 2010) suggesting a beneficial effect of IGF-I in cirrhosis that is widely consider as a preneoplastic condition. In light of these reports, the potentially dual effect of IGF-1 signaling in the liver and its implications in chronic liver injury and HCC must be discussed. There are additional issues for the authors' consideration. 1. The quantification of IGF-IR should be done by qPCR in liver sections representing specifically the different disease stages. 2. The sequencing of PCR fragments do not provide valuable information. 3. References 13 and 29 are the same.