



BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 15264

Title: Hepatocyte Nuclear Factor 4 α Induces Differentiation and Activation of Rat Hepatic Stellate Cells

Reviewer's code: 01807328

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2014-11-19 08:54

Date reviewed: 2014-12-08 10:31

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed 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"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input checked="" 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

The authors indicate that HNF-4 α induces transdifferentiation form rat stem like HSCs into hepatocyte like cells but not the activation. Furthermore, the readers can not believe the phenomenon in the present study. Major comments: 1. Title: Please should change it. In the activated HSCs, upregulation of collagen I, alpha-SMA and TIMP-1 are observed. However, HNF-4 α inhibited them in the present study. 2. Abstract: Please should rewrite it like as title and delete the last sentence. 3. Introduction: Please add the more information of stem like HSCs. 4. Figure 1: Please add the clear phase contrast images of HSC-T6 and HSC-T6/HNF-4 α and write the state of cell phape. 5. Figure 4 and 5: Please should indicate the images of E-cadherin and vimention. 6. Discussion: The authors should discuss about the mechanisms of transdifferentiation form rat stem like HSCs into hepatocyte like cells via HNF-4 α .



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 15264

Title: Hepatocyte Nuclear Factor 4 α Induces Differentiation and Activation of Rat Hepatic Stellate Cells

Reviewer's code: 00053659

Reviewer's country: Japan

Science editor: Ya-Juan Ma

Date sent for review: 2014-11-19 08:54

Date reviewed: 2014-11-19 20:29

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed 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		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Liu, Lou, and Li, et al. reported that HNF4 α can induce the differentiation of HSCs into mature hepatocytes by transient expression of HNF4a and the phenomenon was inhibited by HNF4a shRNA. Although the form of the manuscript does not follow the instruction at all, the finding is interesting. Their conclusion of the finding is to provide novel donor cell for cell transplantation. However, it is jumping too high in conclusion. First of all, you should add several immunofluorescence studies such as ALB-HNF4a, CK8-HNF4a, CK18-HNF4a and CEBPa-HNF4a. Second, you should re-running PCR data in Fig.2. Because actin product is small and others are large. So, you could present all data with actin product like multiplex PCR. Third, the conclusion was overstated, so it should be changed. Otherwise, overall writing is interesting if it is true.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 15264

Title: Hepatocyte Nuclear Factor 4 α Induces Differentiation and Activation of Rat Hepatic Stellate Cells

Reviewer's code: 00003519

Reviewer's country: United States

Science editor: Ya-Juan Ma

Date sent for review: 2014-11-19 08:54

Date reviewed: 2014-12-12 03:41

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed 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
<input checked="" 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 type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input checked="" 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

The authors present interesting results suggesting that a mesenchymal to epithelial transition occurs in stellate cells following forced expression of HNF4 after infection with an adenovirus vector. The authors state that the infection forced expression of albumin and alfa fetoprotein, but no data are giben in any of the figures in that regard. While the overall findings are interesting, it would take more information to validate the assertion made by the authors in their abstract, which states "HNF4 α can induce the differentiation of HSCs into mature hepatocytes". The following additional information would be required to validate that assertion: 1. Provide data to demonstrate that expression of HNF4 in stellate cells is also associated with expression of albuminand alpha-fetoprotein, as claimed but not demonstrated in the manuscript. 2. Provide gene expression data by gene array or RNAseq to demonstrate that expression of HNF4 is associated with a broad spectrum of gene expression changes. This approach, even if it does not provide evidence for a complete hepatocyte transdifferentiation, it will at least document the extent of the mesenchymal to epithelial transition of the stellate cells after HNF4 expression. 3. Provide electron-microscopy



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evidence about morphologic changes associated with formation of hepatocytes after expression of HNF4. A cell expressing albumin is not necessarily a hepatocyte. Hepatocytes have characteristic structural features.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 15264

Title: Hepatocyte Nuclear Factor 4 α Induces Differentiation and Activation of Rat Hepatic Stellate Cells

Reviewer's code: 01047169

Reviewer's country: South Korea

Science editor: Ya-Juan Ma

Date sent for review: 2014-11-19 08:54

Date reviewed: 2014-12-03 09:30

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This manuscript describes the function of HHNF-4a in the regulation of the differentiation and activation of hepatic stellate cells. The authors provided a reasonable hypothesis and clear results to support their notion. However, there are several points to be revised. 1. In Figure 1, the resolution of Fig. 1D is not so good to support your notion. Please replace the figure with another clear one. 2. In Figure 2, please indicate the method to analyze the image intensity (ie. name of used software). 3. In Figure 3, the description of method is not clear. In the case of AFP, ALB, G-6-P, and PEPCK, the authors performed RT-PCR and Western blot analyses (3A and 3B). However, In Fig. 3C, they performed only RT-PCR. Therefore, it will be clearer to describe the two sets of experiment separately. Did you perform Western blot analysis for the genes in Fig. 3C? It will be nice if you include the data set, too. 4. In Figure 4, I can't find Western blotting data. Please check the legend and figure to make them be consistent. 5. In the abstract, please check the first sentence. “~ liver repair and regeneration of after liver injury.”