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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 7074
Title: Role of HBV DNA integration in human hepatocarcinogenesis
Reviewer code: 00504885
Science editor: Qi, Yuan
Date sent for review: 2013-11-04 20:04
Date reviewed: 2013-11-07 23:10

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

COMMENTS TO AUTHORS

Major concerns: 1. The main issue with the manuscript is that it is poorly written, the authors stated that they had some native English persons to edit the MS. However, it contains many typos, grammar problems and many redundant sentences. For examples, the sentences from the abstract are repeated later in the text without changing a word. Even in the text, there are many redundant sentences. The authors need to work on this carefully. 2. I suggest the authors to make a table to list the genes affected by HBV DNA integration. By doing so, it will make reader to easily understand the possible mechanism that HBV uses to cause HCC.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Role of HBV DNA integration in human hepatocarcinogenesis
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Science editor: Qi, Yuan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] 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	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The manuscript by Hai, Tamori and Kawada is a very interesting and well written review on the association of HBV in the development of hepatocarcinoma, which seems to be a multistep event. Minor comments: Page 7 line 5 from bottom: " ...including: hTERT, the PDGF receptor, MLL, calcium signaling-related genes, and ribosomal protein genes...." signaling should be corrected by signalling. In Page 9 Line 10 to 13 from bottom, authors report that the locus of HBV integration was localized in... : " ... within or upstream of the TERT gene in 4 of the 11 HBV-related HCC. These findings are consistent with previous reports of recurrent HBV integration at the TERT gene locus[55]..." However, in page 10 line 4 from top, and in the same sentence, authors claim: "Currently, the most common integration site has not been identified." Both sentences seem contradictory. It should be clarified. Authors discuss about accumulation of genetic and epigenetic changes and instability caused by HBV integration. However, authors do not cite the work by Fernández-Fernandez A., et al The DNA Methylomes of Double-Stranded DNA Viruses Associated with Human Cancer. GENOME RESEARCH 2009; 19(3):438-451. In this paper, authors performed a study of methylation of viruses associated with human cancer. They studied de metilation of HBV genome in different stages of cacinogenesis and found that the HBV genome was almost completely unmethylated in the early stages of carcinogenesis, such as hepatitis and cirrhosis, while it became more methylated in the established liver tumors, both in patients and in cultured cancer cell lines. Most importantly, the presence of DNA methylation at the HBVgp4 and HBVgp2 genes, which, respectively, code for the C and S viral proteins, was associated with their lack of expression, while HBx gene was in an unmethylated state in the malignant lesions. It is recommended to add the contribution of this paper to the manuscript.

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ESPS Peer-review Report
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[Y] 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	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
HBV infection is one of the major causes of human hepatocarcinogenesis, however, the mechanisms are still to be clarified. Recently, there are many progresses published with vary technologies in clinic, especially with NGS technology and GWAS. The authors review in detail the role of HBV DNA integration in human hepatocarcinogenesis mainly from the two potential consequences of integration: 'cis' effect and 'trans' effect. This review is very useful for basic and clinical researchers to understand the mechanisms of hepatocarcinogenesis and to prevent patients from developing HCC in the future, though the role of integrated HBV DNA in hepatocarcinogenesis remains controversial. The text is also present very well.