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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5285
Title: Role of innate immunity in the development of hepatocellular carcinoma
Reviewer code: 00054993
Science editor: Cui, Xue-Mei
Date sent for review: 2013-08-28 14:05
Date reviewed: 2013-08-29 17:14

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	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
This is an excellent up to date review of the highly complex issue of hepatocarcinogenesis with focus on the role of innate immunity, toll-like receptors and inflammation.The wisdom to caution researchers from interventions with miRNA mimics and TLR inhibitors in clinical trials seems very apprpriate. The addition of a glossary explaining the many abbreviations might improve the readability.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Role of innate immunity in the development of hepatocellular carcinoma
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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	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Innate immunity acts as the first barrier of defense against exogenous pathogens including HBV and HCV. The pattern-recognition receptors (PRRs) play an important role in pathogen recognition in the innate immune response. Toll like receptors (TLRs) are PRRs that recognize invading pathogens and behave as a vital link between inflammation and hepatocarcinogenesis. This review article precisely summarized current advances concerning the roles of TLRs, related signaling pathways, and other innate immunity components that are indispensable for innate immunity in the development of HCC. Based on the current proceedings, the author also suggested the promising immunological therapies based on the TLR signaling pathways and microRNAs. Generally, this review article covers a wide range of current knowledge about innate immunity and HCC, which should be very instructive for readers. This review article can be greatly improved if some concerns below can be properly addressed. 1. Epidemiologically, chronic infection with hepatitis viruses, especially the infection with hepatitis B virus (HBV), is a leading risk factor of HCC worldwide. Chronic HBV infection results in approximately greater than three-quarters of all the HCC patients. One of the reasons of dramatic rise in the incidence of HCC in Western countries is the immigration of HBV-carriers from the endemic areas in recent years. Even though, this is not an initial motivity of generating "intense efforts to understand the mechanisms of HCC" because the mechanism of hepatocarcinogenesis has been extensively studied in some HCC-endemic countries. Diet should not be a risk factor of HCC unless author point out what kind of diet increase the prevalence of HCC. Coffee consumption is not a risk factor of HCC, it is a protective one according to recent published meta-analyses (Clin Gastroenterol Hepatol. 2013 May 6. doi:pii:S1542-3565(13)00609-5.10.1016/j.cgh.2013.04.039; Hepatology. 2007;46(2): 430-5.). This reviewer suggests that corresponding alterations should be made at the first paragraph

of the introduction section. 2. In the Abstract section, the order of HCC risk factors should be re-organized 3. The relationships between TLR signaling pathways and HBV infection should be enforced. Some contents about HBV should be added, such as TLR-mediated immune responses down-regulate HBV replication, and the interactions between HBV and key molecules on the TLR signaling pathways, etc. Compared to HBV/HCV, bacterial infections and LPS have much less importance in hepatocarcinogenesis, which should not be overstated in this review. 4. It is arbitrary to state that "chronic inflammation is mediated by TLR activation" (page 15). I like to believe that chronic infection with HBV and/or HCV and imbalanced immunity contribute to chronic inflammation, while TLR activation might be one of the intermediate steps of the infection-caused chronic inflammation. 5. page 10, "Co-infection with one or more viruses is also a major threat". Co-infection with HBV and HCV contributes to a higher risk of HCC than the infection with HBV or HCV alone, however the co-infection is generally rare. The most HCC worldwide is caused by single infection. 6. The section about microRNAs in this paper should be simplified, and author should present his or her own idea based on the summarization/integration of the findings of current studies, instead of enumerating these findings. 7. There are too many abbreviations in this manuscript, which make this manuscript difficult to read. Uncommon abbreviations such as KC (Kupffer cell), LSEC (liver sinusoidal endothelial cell), CAF (cancer-associated fibroblast), ALD (alcoholic liver disease), ASH (alcoholic steatohepatitis), NEMO (NF-κB-B essential modulator), TAK1 (TGF-β-activated protein kinase 1), and PDCD4 (programmed cell death 4), as well as those used only once such as SOCS1 (suppressor of cytokine signaling 1) should be spelled in full names because this jou

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] 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)	[ ] 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 following points should be clarified. 1. Correlation between TLR expression and tumor staging/grading 2. TLR polymorphisms and HCC susceptibility

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] 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	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

There are detailed review of the role of innate immunity in chronic liver diseases and the development of HCC in this paper. However, thinking of the title "Role of innate immunity in the development of hepatocellular carcinoma", the volume of discussion for the development of HCC is too small. Also, the development and progression of HCC should be different steps which involve different mechanisms. There is no discussion for this matter. Although the author mentioned about sorafenib (this drug is usually thought to work on the step of progression), he does not discuss about the role of innate immunity in progression of HCC. This paper should be re-submitted after the revision of these points.