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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 13633
Title: The chemokines and their receptors play important roles in the development of hepatocellular carcinoma
Reviewer's code: 02860775
Reviewer's country: Italy
Science editor: Yue-Li Tian
Date sent for review: 2014-08-28 19:16
Date reviewed: 2014-10-09 20:55

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	PubMed Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this manuscript, LIANG et al. pinpoint the multifaceted role of the chemokine system in the development and progression of hepatocellular carcinoma (HCC). The authors highlight chemokines and cognate receptors that are relevant in HCC as emerging mechanism mediating tumor-stroma interactions. The authors provide a thorough analysis of the different functions, either pro- or anti-tumorigenic, played by chemokines, including immune cell recruitment, growth, survival, migration and invasion of HCC cells, angiogenesis and inflammation. Finally, promising therapeutic strategies aimed at targeting some critical chemokines (CCL2, CCL21/CCL19) are discussed. This is an intriguing and still evolving topic, carefully unraveled in this review. However, there are some general issues worth being addressed to improve the quality of the review: - Chemokine effects on HCC cells, including migration, invasion, growth and survival, should be all incorporated in one, single chapter. - The table proposed by the authors is quite generic in the current shape, and should be more focused on the topic covered by the review. My suggestion is to include a table summarizing for each chemokine of interest, the pro and anti-tumorigenic effects in HCC as they relate to the

different functional effects (homing of immune cells, inflammation, angiogenesis, cancer cell activities, …) and then, highlighting those amenable of therapeutic interference. - Iconography is absent at all and at least a figure should be included to facilitate the understanding of the general reader. I suggest a micrograph showing histological chemokine expression in HCC, or a cartoon addressing the most relevant paracrine and autocrine mechanisms regulated by chemokines in HCC. - Writing presents some errors (typos, spelling) throughout the text; a fluency improvement by a native English speaker is recommended. In addition, the following specific concerns need to be clarified: 1. The role of macrophages in HCC and their characterization as M1 and M2 phenotypes should be better outlined, for instance in the paragraph dealing with "effects on immune cells", since this issue is then recalled as target of the chemokine-based combination therapy. A recent review on this topic (Sica A, Hepatology 2014) may be of help. 2. Reference #87 is unclearly stated. It is also incorrect to consider NAFLD as a model of liver disease progressing to HCC, as instead, it is the case for NASH. 3. The relevance of CD133+ cells secreting CXCL8 as tumor-initiating cells in HCC should be better addressed (see ref. #96). 4. In page 14, the sentence "the oval cell response is partially ameliorated ..." is quite vague and ambiguous: it must be clarified.

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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

#A):-This review is interesting, and reflects the commitment of the Authors in this field. However, the Authors should take into account that it is addressed to a general audience of clinicians. And clinicians risk to be lost in the conundrum of the different chemokine axes. I would add several tables (see the cartoon in Balkwill FR J Pathol 2012) aimed at summarizing the chemokine systems which are implicated in HCC oncogenesis , tumor progression, and immune escape. This comment applies in particular to the first section of the review (pages 3 and 4) where the Authors enlist the chemokines of relevance in HCC. All these molecules have been associated with the clinical outcome. However, the role played by each axis in cell survival, angiogenesis and leucocyte recruitment are different . For the sake of clarity, this issue should be summarized in a table and should represent the introduction to the "special" sections of the review. #B) Why the sequence of the section is EFFECT ON IMMUNE FUNCTION, MIGRATION AND INVASION OF HCC, GROWTH AND SURVIVAL OF HCC, ANGIOGENESIS, INFLAMMATION? As the natural history of HCC is characterized by the transition from normal liver to chronic hepatitis, cirrhosis,

hepatocellular carcinoma and tumor progression, I would follow this sequence. #C):-Is there a relationship between the genetic and epigenetic alterations which lead to HCC and the expression of distinct chemokine axes? Is there any relationship between the recently published molecular signatures of HCC outcome and intra-tumoral expression of chemokines? In this regard, it is of interest that Hoshida et al (NEJM 2008) found, among the significant survival genes defined in non-tumoral tissue, CCL21, CXCR4 and CCL19. #D):- The text needs some minor language polishing.