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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14908
Title: Activated rat hepatic stellate cells influence the Th1/Th2 profile in vitro
Reviewer's code: 00225294
Reviewer's country: Spain
Science editor: Ya-Juan Ma
Date sent for review: 2014-10-30 16:14
Date reviewed: 2014-11-25 03:31

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

COMMENTS TO AUTHORS

The authors address a very important aspect of immune regulation in liver diseases, in particular focusing on the role of T cell differentiation. Indeed, a relatively recent paper (Hepatology. 2012 Oct;56(4):1342-51) also documents this polarization in a very provocative way. The present paper, although of interest, is preliminary and uses a too simplistic model to provide important answers on the mechanisms T cells are modulated by hepatic immunocompetent cells. A few comments follow on the approach and results obtained. 1. Considering that clonal expansion is characteristic of the T cell subsets, it is difficult to give relevance to the data given in Fig. 1 showing the proliferation in the absence and presence of HSCs. Very important, what means the changes in OD (the Y-title is illegible)? Also, why CD4 T cells are dying under these conditions? 2. In Fig 2 the Y axis is also illegible. In addition to this, I am not able to understand the values given in the Y axis, if compared to Fig. 1. 3. The effects/actions of galectin 9 need a more in-depth study, at least as indicated in the above mentioned HEPATOLOGY work. How is this galectin 9 acting? Are the authors able to interfere (and therefore, reprogram) T cell polarization? This is essential to provide new views in the field and to support their working hypothesis. Minor: The text needs a profound English revision

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[Y] No	

COMMENTS TO AUTHORS

The study by Xing et al is a preliminar study with very interesting results. Using an in vitro approach with co-cultures, these authors showed that the Th1/Th2 when the cells were co-cultured with HSC. The proportion of Th1 decreased by 1.73% and the production of Th1 was inhibited. This suggests that HSC may enhance Th2 responses which would favor fibrosis. The authors suggest that this may be an eventual novel pathway for liver fibrogenesis. My general comment is that the paper is well presented, although the English needs to be polished. Authors should criticize their approach or recognize the limits of an in vitro research. This is particularly important in this case, since a co-culture does not reflects the in vivo environment where lymphocytes are separated by the sinusoids from the HSC. In this reviewer opinion, a much more appealing approach would be the use of co-culture separated by a membrane, so that direct contacts would not take place. Please note that a previous study, Muhanna et al (2008) used a in vitro and in vivo approach, demonstrating that lymphocytes were in proximity to HSCs primarily within the periportal regions, and some were directly attached or engulfed. Such a possible mechanism was not addressed in the discussion. This should be discussed and this reference included. Minor points: Introduction, last line:

"anti-fibrogenic role" and TGF-beta. This cytokine is unanimously recognized as fibrogenic. For instance, see Dooley and Dijke, Cell and Tissue Res (2012) 347:245-256. This should be deleted. Materals and Methods: 5th line from the end The sub-cultured cells were positive for GFAP, desmin and ASMA…How can the cells be positive for both ASMA and GFAP? When HSC are activated, usually after 1week culture they loose GFAP expression. Please check this. The reference given [15] refers to renal fibroblasts. Please review this reference. Co-culture HSC:CD4 lymphocytes. Why was the ratio 1 HSC:20 CD4 chosen? Does this reflects the in-vivo reality? This should be discussed or a reference should be given. It should be noted that HSC are ten times less abundant than hepatocytes in the liver, but are they 20 times more rare than CD4 lymphocytes? How many animals were used? The authors state that for each experiment, cells from the same animal were used, but the number of animals is not presented. The authors state that the proportion of Th1 cells decreased 1.73+/- 0.71% and that this difference was significant. Such a small difference may not be significant (it all depends on the n of experiments). Please include a graph to support this claim.

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[Y] No	

COMMENTS TO AUTHORS

The manuscript is interesting, experiments are well designed. However: 1-authors should revise the editing of all the figures. In particular, the blots presented in Fig. 4 seems inverted (bar, apparently do not correspond to the blots shown (inversion of 48 h with 24 h?) 2-The statistical analysis behind to calculate the p value corresponding to letter d in Fig. 3 needs further details. Was it given by a factorial design? Please, give more details.