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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 25000
Title: Dominating expression of negative regulatory factors and downmodulated MHC Class-II expression cause dysfunctional dendritic cells in chronic Hepatitis C infection
Reviewer's code: 00004603
Reviewer's country: United States
Science editor: Ze-Mao Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google 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	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The paper of Shallu Tomer et al. discusses the effects of HCV on dendritic cells isolated from PBMC of IFNα-treated HCV patients. The comparisons in gene expression have been done between the responders and non-responders to treatment vs DC from healthy donors exposed or not to HCV proteins. This is an interesting attempt to elucidate the role of HCV-infection in impairment of DC function and to link this situation to non-responsiveness to IFNα treatment, which provides a promising connection to translational research. Totally understanding all difficulties of the study conducted in a frame of clinical trial, there is no way to avoid addressing several concerns: 1. Quality of figures and figure legends are poor. In certain cases, it is almost impossible to read what is presented. Figure legends also do not shed the light on how experiment has been done. Instead of guessing, the reader should clearly see and understand the results. 2. Using Dendritic Cell Isolation kit, the enrichment of DC was 65% vs 10% in PBMC. It is definitely, DC-enriched population, but we should not forget that 35% of PBMC were not DC, which needs to be taken into account in the results interpretation. 3. There is intensive discussion in the paper regarding HCV in dendritic cells. Even if

some researches showed very low expression of HCV in PBMC or DC, it is not obvious, since hepatocytes are the cells that replicate the virus. If you want to claim the infection in DC, at HCV RNA should be measured in extensively washed DC; otherwise, since usual stimulation of macrophages through TLR2 by HCV core protein takes place, it cannot be named "infection". Furthermore, if these DC are not infected, there is no reason to measure anti-viral interferon-stimulated genes (ISGs) like OAS1, OAS2, etc) in the cells and definitely, there is no sense in the interpretation that authors provided. **4**. Gene array always is a great option when you can then confirm the dysfunction of certain signal transduction pathways. As an example, in the IFN-induced JAK-STAT1 pathway, this dysfunction is not based on the general expression of STAT1, STAT2, PIAS1 or ISG15, but on posttranslational modifications of phosphorylated STAT1, which cannot be addressed by using this gene array. If there is no chance to study it in a proper way, there is no reason to start it at all. 5. It is difficult to judge which changes in gene array are related to response to treatment, since they were not examined before treatment has been started. It is known that overstimulation of ISGs at a baseline may be of a poor prognostic value; however, we do not know whether the changes observed in the paper existed before or are the result of treatment. If PBMC of patients that undergo treatment were examined at a baseline, with further retrospective distribution of them to responders and non-responders, this study would make more sense and really would be able to answer the questions that were asked by the authors. 6. In the Discussion, the authors tried to parallel the changes in gene activation induced by HCV proteins in healthy donors and in what they found studying responders vs non-responders. First, the arrays are not completely the same; second, the interpretation is wrong (they mentioned the things they only want to see), so this comparison proves nothing. Collectively, the attempt to do basic-translational research is certainly appreciated; however, this type of studies should be planned well and allow generating interpretable data.

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COMMENTS TO AUTHORS

Summary The manuscript by Tomer et al. addresses the potential role of dendritic cell (DC) dysfunction in unresponsiveness to interferon-? (IFN-?)/ribavirin treatment in chronic hepatitis C virus (HCV) infection. Myeloid dendritic cells were isolated from the peripheral blood of 10 treatment responders, 10 treatment non-responders and 10 healthy controls, then RNA was extracted for analysis of gene expression related to DC maturation/function and innate immunity. An ex vivo model for the influence of HCV on DC maturation was also used where monocyte derived DC from healthy controls were generated in the presence or absence of HCV proteins. The authors found a number of differentially expressed genes relevant to DC function and general immune responsiveness and suggest that this may have an influence on development of immune responses against HCV in treatment non-responders. General comments Rationale for the study is clearly presented with appropriate selection of study subjects, cellular isolation/differentiation methodology, and set up for microarray analysis of relevant gene expression. Data presented generally support the authors' conclusions and speculation, but some additional discussion and interpretation should

be included. Given that the numbers are relatively low, objective criteria for considering a two fold or some other change in gene expression level significant should be stated and justified. Many of the gene expression changes in the non-responders seem to represent continued exposure to IFN-?? as would be expected with unresolved infection. As stated by the authors, there was not much overlap in the dysregulated DC genes observed in vivo versus ex vivo. This should be discussed in greater length as to an explanation or as to the general validity of the ex vivo model. It's not clear what information is being conveyed in figure 4, which is barely referred to in the text and figure 6 requires considerably more explanation as to the information represented by the individual elements and its overall interpretation. Specific comments The discussion suggests that HLA-DR was down-regulated, but only HLA-DP and DQ are referred to in the results section. Since HLA-DR expression was assessed by flow cytometry for analysis of DC populations, some verification of down regulation of HLA class II genes at the protein level should be possible. In the results section text, HLA-DPB1 is referred to as HLA-DPQ1. In the results section, DC are referred to as "elutriated", but the methods describe a sequential magnetic-bead isolation process based on surface antigen expression, not cell size or density. In the introduction, the authors refer to approximately 180 million persons worldwide "affected" by HCV. I think this should read "infected".