

Responses to Editor and Reviewers:

Reviewer #1:

This is a timely review by Crosignani et al., on the contribution of peripheral blood dendritic cells to HCV pathogenesis, and the potential use of this cell population as a non-invasive tool in the follow-up of patients with chronic HCV. The review is well written and adds on a gap on HCV-related literature analysis.

R: We are pleased with the Reviewer's positive comments.

The manuscript would benefit of the addition of at least one figure model that recapitulates the current view on peripheral blood DCs on HCV pathogenesis.

R: According to the Reviewer's suggestion, we added a figure that recapitulates the impairment of peripheral blood DCs in chronic HCV infection. The new figure is named Figure 1 in our revised manuscript; as a consequence, Figure 1 of the original version moved to Figure 2 in the revised manuscript. We thank the Reviewer for his/her helpful suggestion.

Reviewer #2:

The review manuscript written by Crosignani et al. describes the role of DCs in the natural course and treatment of HCV infection. The review is interesting and well summarized the reports on the issue. However, there are some concerns that need to be addressed.

Major pints,

1. The review should focus on the role of DCs in HCV infection. Therefore epidemiology, natural course, and clinical management of HCV infection should be more concise.

R: According to the Reviewer's suggestion, the paragraphs "Epidemiological aspects and natural history" and "Clinical management" were shortened substantially in our revised manuscript. The references relative to the deleted text were removed, and the list of references was renumbered accordingly.

2. In page 13, the statement "multiple viral and non-viral mechanisms may directly and indirectly contribute to the decrease of mDCs and pDCs in the circulation" needs reconsideration, because reduction of the numbers of DCs might be due to the enhanced recruitment of DCs to the inflamed liver.

R: We agree with the Reviewer that an enhanced recruitment of DCs to the inflamed liver may be at least in part responsible for the reduction of pbDCs in HCV-infected patients.

We added this point in the discussion of the mechanisms possibly involved in pbDC reduction. We thank the Reviewer for his/her helpful suggestion.

Is there a negative correlation between HCV viral load and the numbers of DCs in HCV-infected patients?

R: There is no correlation between HCV viral load and the number of pbDCs. This finding, observed in previous studies by us and other Authors, is reported at p. 14.

3. Regarding the alterations in the function of DCs, most studies examined the cytokine production by DCs after in vitro stimulation with high concentrations of cytokines, which is an extremely abnormal condition in vivo. Therefore, the interpretation of those data may be questionable.

R: We agree with the Reviewer that the cytokine production by DCs upon stimulation with high concentrations of cytokines would be poorly relevant to in vivo DC behavior. However, the studies we examined stimulated pbDCs with either TLR ligands [poly(I:C), CpG, R848, LPS] or viruses (HSV), or interaction with T cells (CD40L-transfected T cells, MLR). This very important information was added in our revised manuscript.

Minor points,

1. In page 6, "Both pegIFN and RBV are indirect antiviral agents because they do not target a specific HCV protein or nucleic acid, while they have different immunomodulating actions" needs to be revised. Antiviral action of pegIFN is not specific for HCV, but has direct antiviral activity through induction of various antiviral proteins.

R: According to the Reviewer's suggestion, that inaccurate sentence was modified in our revised manuscript.

2. TIM3, LAG3, and CTLA4 in page 10, and DPP4 in page 11 should be full-spelled.

R: Full-spelling of the above acronyms were provided in the revised manuscript. We apologize for the inadvertence.

3. In page 12, the statement "strongly support a role for DCs in the activation of HCV-specific immune responses in the liver environment." should be reconsidered, because DC activation occurs in the liver but antigen-specific T cell activation by the DCs could mainly occur in the drainage lymph nodes (there is no evidence for antigen-specific T cell activation in the liver).

R: The sentence was modified according to the Reviewer's suggestion.

Administrator:

Please provide language certificate letter by professional English language editing companies

R: One of the Authors of the manuscript, Dr. Antonio Riva, has been living in London since 2006. He revised the manuscript for English language. Moreover, the assessment of Language evaluation by both Reviewers was "Grade A: priority publishing". Therefore, we kindly ask you to exempt us from providing language certificate.

Please rearrange all the authors' affiliations with Department, University or Institute, City, Postcode, Country, etc.

R: We rearranged all the authors' affiliations as required.

You also should add some information here,

1. Conflict-of-Interest Statement

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R: The required information was added.

You also should add some information and files, as follow:

1. Core tip: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

R: We added the Core tip in our revised manuscript.

Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

R: We provided the Audio core tip.

2. Please provide all authors abbreviation names and manuscript title here. World J Gastroenterol 2015; In press

R: We added all the required information.

3. some files [Conflict-of-Interest Statement (COI), Copyright (need signature of all authors) and language Certificate (.pdf)] and Audio core tip (.mp3)

R: We provided all the required files except for language certificate (as explained above).

Abbreviations and acronyms are often defined the first time they are used within the main text and then used throughout the remainder of the manuscript. Please consider adhering to this convention. Search all abbreviations in your manuscript and do like this when they were used firstly.

R: We provided the full-spelling of the acronyms used in the manuscript, when missing.

Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

R: We provided the decomposable figure, that is Figure 2 in the revised manuscript, as ppt file.