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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**ESPS manuscript NO:** 32302
**Title:** Bone marrow-derived monocyte infusion improves hepatic fibrosis by decreasing osteopontin, TGF-β1, IL-13 and oxidative stress
**Reviewer's code:** 01852132
**Reviewer's country:** Hungary
**Science editor:** Jing Yu
**Date sent for review:** 2017-01-04 10:20
**Date reviewed:** 2017-01-19 22:49

| 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

Comment 1. The authors addressed an interesting, clinically relevant and important issue aiming to modify the state of chronic liver disease. To approach this goal the authors purified bone-marrow derived CD11bhigh monocytes, which were transfused to mice prior the administration of the provoking agents i.e. ethanol and CCl4. Using a C57BL/6 mice model system they showed that the transfusion of monocytes was more effective to decrease IL-13 levels in the liver as compared to the infusion of bone marrow derived mononuclear cells (BMMCs). The authors also demonstrated that monocyte transfusion could reduce the size of the fibrotic area, the amount of hydroxyproline and the concentration of pro-inflammatory cytokines, while the levels of IL-10 and TGF-?1 cytokines and the number of Kupffer cells in the liver were increased as compared to saline transfusion. Due to the limited information of cell based therapies in chronic inflammatory diseases, the identification of immunostimulatory and regulatory pathways in a preclinical setting and in the context of liver metabolism is of high importance. Comment 2. To demonstrate the biological significance of monocytes in the treatment of liver fibrosis, mice suffering from liver fibrosis were transfused with

106 BMMC or with BMMC-derived from CD11bhi monocytes. Statistically significant differences in fibrosis could be detected in group 1 and 3, but the changes in cytokine levels was detected exclusively in case of IL-13. This result raises the possibility that the limited effect of BMMC on hepatic fibrosis (group 2) may be due to the lower ratio of monocytes as compared to the enriched monocyte population (group 3). Thus, to determine the real impact of monocytes in the treatment of liver fibrosis, further control experiments and additional treatment samples should be involved in the study. For example, it would important to determine the baseline levels of the analyzed parameters in healthy mice followed by measuring the effects of monocyte-depleted BMMC transfusion in mice with chronic liver fibrosis. The results of such control experiments could significantly increase the impact and significance of this study. Comment 3. As described in the Material and Methods sections CD11bhiCD14hi monocytes could be isolated from BMMC. However, dot plots or flow cytometry histograms showing the distribution of the purified cell populations are not presented. Moreover, the number of mice involved in these studies is not clearly indicated. It is also not clear, whether the transfused monocytes in groups 1, 2, 3 derived from one or more donors? Comment 4. To analyze statistically significant differences between the groups of mice the authors used both parametric and non-parametric tests. Considering the relatively low number of mice (n=5 /group, which factors have been involved for selecting the most relevant statistical analysis? Comment 5. What was the reason to select exclusively male mice for testing the effects of the selected parameters? Comment 6. The figure showing IL-1? concentration is duplicated in Figure 5 (B and C). The figure showing IL-6 concentrations is missing, while IL-6 is mentioned in the Results. Comment 7. Why exclusively male mice were selected for testing the effects of the selected parameters? Comment 8. It should be noted that proteins, such as cytokines can be present intracellularly upon translation, and also can secrete it by exocytosis. The terms referring to protein expression and production should be clarified throughout the manuscript. Comment 9. In the Title and in the Result section of the Abstract the word ‘interleucin’ should be corrected to interleukin. In the Methods section it was described that the mice were kept at ± 23oC. This text needs revision. On Page 13, the sentence ‘A trend was also observed decreased IL-23 cytokine levels (Figure 6D)’ the text needs revision. On Page 14, the sentence ‘In this regard, some

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**Reviewer's country:** Germany
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| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

Manuscript #: 32302 "Bone marrow-derived monocyte infusion improves hepatic fibrosis by decreasing osteopontin, TGF-β1, interleucin-13 and oxidative stress" General comments: The manuscript provides an analysis of anti-fibrotic effects of monocyte infusion in a murine model of chronic hepatic injury. The authors describe that infusion of monocytes and (to a lesser extent) bone marrow-derived mononuclear cells (BMMC) significantly reduced liver fibrosis and signs of chronic inflammation in the applied mouse model (CCl4/ethanol treatment for 6 months). In particular, the expression of factors supporting fibrosis and/or inflammation was reduced (collagen, TNF, TGF-β, IL-1β, IL-6, IL-13, IL-17, osteopontin, TIMP1), whereas the expression of anti-fibrotic and anti-inflammatory factors was increased (IL-10, GSH, MMP-9). Moreover, monocyte-/BMMC-treated animals were characterized by decreased numbers of activated hepatic stellate cells, but increased numbers of Kupffer cells. The authors conclude that monocyte-based cell therapy may represent a promising approach for the treatment of liver fibrosis. The study is well designed, carried out properly, and technically sound. The results are conclusive and clear. However, there are a few

points requiring the authors' consideration. Specific comments for revision: Major comments (experimental annotations): - Please provide histological sections of normal mice (i.e., not treated with CCl4/ethanol) and the corresponding subsequent analyses for the experiments presented in Fig. 2, 3, and 4 (as a comparative control esp. for the monocyte-treated hepatic injury model mice). - To further assess the impact of GSH amounts on oxidative stress in the different groups, the levels of ROS in the livers of the respective mice have to be determined (e.g., by dihydroethidium staining). Minor comments: - The text of the manuscript has to be revised considerably (typos, missing/redundant spaces, introduction of abbreviations, wording and style, …). - Please revise Figure 5C. According to the Figure Legend, levels of IL-6 in the liver are shown, but the bar diagram appears to be identical to Figure 5B (showing levels of IL-1β).