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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28397
Title: MicroRNA-155 promotes the pathogenesis of experimental colitis by repressing SHIP-1 expression
Reviewer's code: 00058419
Reviewer's country: Canada
Science editor: Yuan Qi
Date sent for review: 2016-07-01 17:05
Date reviewed: 2016-08-03 21:44

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] 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 their manuscript, Dr. Lu and colleagues reported their studies on the potential mechanisms of miR-155 in the immunopathogenesis of inflammatory bowel diseases (IBD) using the mouse model of DSS-induced colitis. Previous studies by others have demonstrated the multiple physiological and immunological functions of miR-155 and have also implicated the involvement of this miRNA in the development of IBD both in patients and in mice. Therefore, further studies on the potential role and particularly the mechanisms of miR-155 in IBD are important for the clinical management of the disease and the development of novel therapeutic modalities. Since SHIP-1 is a well-established target of miR-155 and the suppression of SHIP-1 expression and function by miR-155 has been documented in several in vitro and in vivo studies (such as refs. 16-19), the real value of the experiments presented in Figs. 1 and 2 is arguable. Nevertheless, the reported study has convincingly and systematically demonstrated the beneficial effect of miR-155 inhibition on the development of DSS-induced colitis in this model. Similar results have also been reported or implicated in other mouse models (such as T cell mediated or TNBS) of IBD. Moreover, the current study demonstrated

the involvement of Akt as a downstream signaling pathway in the SHIP-1-mediated inflammatory responses. The experiments were overall well designed with the appropriated controls included and statistical methods employed for data analysis. However, the significance of the study is somewhat diminished because the treatment of antagomiR-155 was initiated during the colitis-inducing phase (day 2 and 5 of DSS treatment), not after the completion of DSS treatment. To promote such approach as a potential novel therapeutic alternative, additional studies with the antogomiR-155 starting at day 7 or thereafter will be needed. At the minimal, the authors should discuss the limitation of their study in the manuscript. In addition, the manuscript will be benefited by some language editing.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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Reviewer's country: China
Science editor: Yuan Qi
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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
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COMMENTS TO AUTHORS

This work put focus on the role of SHIP-1 on the way how miR-155 associates with IBD. Following the recent findings (one of miR-155's targets is SHIP-1, and SHIP-1 is associated with IBD), in this study, using DSS-induced IBD biological models, this work added evidences to clarify that the drop of SHIP-1, which is resulted from the increase in miR-155, is the reason why IBD patients have high level of miR-155. I would like to say this work offers new insight into the understanding of the inflammatory mechanisms in IBD. However, some conclusions in this manuscript are not fully supported and discussed, also, there are some typos and grammar errors in writing. After these issues get solved, I suggest this work would be considered to publish in World Journal of Gastroenterology. 1. In figure 2A, why PTEN did not balance out the effect of the suppressed SHIP-1 on Raw264.7 cell proliferation? In PI3K/Akt pathway, PTEN acts as a gatekeeper, converting PIP3 to PIP2, in this regard, in your experiment, should the PTEN have consumed the extra PIP3 resulted from the less SHIP-1? And as a result, could the cell proliferation result from the other causes? I suggest an experiment on the expression of p-Akt should be added, so that we can have a

closer look at the effect of miR-155 suppressed SHIP-1 on cell proliferation. Also, it was reported that macrophages produce IL-4 (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0046989, http://europepmc.org/abstract/med/15969673), and IL-4 contributes to macrophage proliferation (http://science.sciencemag.org/content/332/6035/1284.long), in this regard, is there any possibility that miR-155 would affect Raw264.7 proliferation through IL-4? Besides, what does it look like in BMDM in terms of cell proliferation? As primary macrophage cell, the result could be interesting. 2. In figure 2B, have you normalized the concentration data based on the same cell number? From Fig 1A, the cell number was different in different groups in the end, as a result, the concentration of cytokines would vary with the cell number other than different treatments. And, what would be the possible explanations on the result that no significant difference was observed between group 'miR-155' and group 'miR-155+SHIP-1' in IL-6? 3. In figure 5D, the expression of IL-10 should be included to fully support the effect of anti-miR-155, this is because, unlike pro-inflammatory cytokines, IL-10 is the anti-inflammatory cytokine that has been identified as being involved in IBD. 4. Other than the above, the writing should be checked carefully, especially in the discussion section. The following are some examples: On p13, in line 20, "restoration of SHIP-1 could effectively inhibited or reversed them" should be "restoration of SHIP-1 could effectively inhibit or reverse them". On p24, in the description of Fig. 5, "lower than that of in mice from other colitis groups" should be "lower than that in mice from other colitis groups".

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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COMMENTS TO AUTHORS

major concerns: 1.The logic of result section seems to be confused. Author should rearrange the presentation. eg, Fig3 and Fig 5 could be combined; 2.Gene name should be italics. eg, SHIP-1 mRNA should be SHIP-1 mRNA 3.Authors should add a luciferase reporters to confirm that SHIP-1 is one of targets of miR-155; 4.The results seem not to be obvious in BMDM groups in Fig1b; 5.It lacks one group that SHIP-1 inhibited the proliferation of raw264.7 cells in Fig 2. Authors should also use SHIP-1 inhibitors to assess the secretion capacity of IL-6, TNF-α, and IL-1β; 6.Author claimed that antagomiR-155 reduced disease active index (DAI) of experimental mice, whether this effect of antagomiR-155 was dose-dependant? 7.Phosphorylated Akt was detected in Fig 5b, and which phosphorylated site(s) of Akt were analyzed? 8.Authors claimed that Akt was obviously activated in Fig5b due to SHIP-1 up-regulation, however, the results of Akt were inconsistent with SHIP-1; Inhibition of Akt activation has better treatment effect compared to antagomiR-155? 9.Authors found that SHIP-1 was slightly reduced after overexpression of miR-155 in Fig 1, and miR-155 was up-regulated about 2 folds in DSS or DSS+NC in Fig 3a, however, SHIP-1 showed more obvious

change in Fig5a. Authors should try to explain this inconsistent; 10.The quality of Fig5c was so poor. Negative control is needed; 11.Just as Fig 5d, IFN-gamma and IL-17 should also be determined in Fig 2; The protein level of cytokines should also determined in Fig 5d.