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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics
ESPS manuscript NO: 26964
Title: A20 is critical for inhibition of lipopolysaccharide-induced inflammation in enterocytes
Reviewer's code: 03473336
Reviewer's country: Poland
Science editor: Jing Yu
Date sent for review: 2016-05-02 10:31
Date reviewed: 2016-05-10 16:13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] 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

This paper in interesting and clear way shows the negative regulation of inflammation under the influence of bacterial lipopolysaccharide. The quality of work is in general acceptable but I have some suggestions that might be considered by the authors of the manuscript. I believe they improve the legible of this paper for the potential readers. Major comments: I think that the words in the title: "critical" and "inflammation" are overused, because the paper does not contain sufficient comparative analysis among other cytokines (e.g. IL-10, IL-12, IL-23) or bacterial surface antigens. If we make an assumption that LPS is recognized by TLR-4 receptors, we should be aware that the same receptors TLR-4 recognize viral components, lipoteichoic acids (from Gram-positive bacteria). I realize that the suggested analysis would become time-consuming, so it is easier to adjust the title. Could you please specify what king of therapeutic value has A20? Can you suggest any therapeutic way in which A20 can be used? Authors do not tell anything about the apoptosis of the tested enterocytes, did any experiments were done? It could be interesting. LPS is able to delay the apoptosis or enhance, which manner relates to this paper? Minor comments: Keywords: Why did authors chose

TNF-alpha? in paper you also concentrate on IL-8 and IL-1 Results: page 3, 13, analysis of IL-6 is described in the paper I did not found the results for this interleukin Page 6: please add the word "cells" after "to normal components of the intestinal micro-biota ..." Page 7: There is no the whole name for the shortcut "IEC" Page 7: Escherichia coli should be in italics Page 8: the sentence beginning with "The presence of the 90-kDa bands..." fits to results section Page 10: To clarity, please add B in the brackets (Figure 2B and 3B) Page 10: Section: Overexpression...I suppose there are mistakes in the numbers of Figures: there should be Figure 4 and 5 Page 12: for IBD is always needed, "always" sound not good

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics
ESPS manuscript NO: 26964
Title: A20 is critical for inhibition of lipopolysaccharide-induced inflammation in enterocytes
Reviewer's code: 03519163
Reviewer's country: United States
Science editor: Jing Yu
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this manuscript, Zheng et al. investigated whether overexpression of A20 can prevent LPS-induced inflammation in the intestinal epithelium. At first, the authors examined the dose and time dependent induction of A20 in LPS stimulated HT-29 cells by analyzing its mRNA and protein levels. A20 was induced by LPS in a dose-dependent manner. Expression of A20 mRNA peaked 2 to 4 hrs post LPS stimulation and then gradually decreased. Overexpression of A20 prevented LPS-induced nuclear translocation of the NF-kB p65 subunit in the intestinal epithelium. Likewise, overexpression of A20 suppressed LPS-induced IL-8 expression in the intestinal epithelium. Since A20 was identified as a negative regulator of NF-kB signaling some time ago, the conceptual and experimental designs of this study lack novelty. Induction of A20 by LPS (Fig. 2 and 3) has been reported in previous reports, and, therefore, is not novel. Inhibition of NF-kB activation by A20 overexpression is not surprising since A20 is a known inhibitor of the NF-kB signaling pathway. Likewise, suppression of IL-8 by A20 overexpression is a predictable result. Overall, this reviewer could not find any conceptual and technical advances beyond what has been published previously. As such, the

manuscript can hardly be considered novel or innovative. Specific comments: 1. Since A20 is a well-studied negative regulator of NF-kB signaling, the experiments described in this manuscript are not novel. The approach to inhibit intestinal inflammation by overexpression of A20 is potentially of interest, and may lead to new therapeutic approaches for inflammatory diseases, such as IBD. However, the experiments performed by the authors only used in vitro conditions. Perhaps an experimental approach that utilizes overexpression of A20 in mouse colitis models can address this point. 2. Some Figure legends are poorly written and hard to understand. For example, in Fig. 4, it is not clear what was tested. Did overexpression of A20 decrease nuclear translocation of the p65 subunit? Or phosphorylation of IkBa? Or ubiquitination of IkBa? The authors only wrote NF-kB and this is quite unclear. Likewise, in the Fig. 6 legend, the authors stated that there were no differences among the 3 groups. However, statistical significance (*) was indicated at certain time points. This is quite confusing. 3. In Figure 7, panels were labeled 1 to 4. Letters A to D should be used instead of numbers so that all Figures are consistent.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics
ESPS manuscript NO: 26964
Title: A20 is critical for inhibition of lipopolysaccharide-induced inflammation in enterocytes
Reviewer's code: 03262819
Reviewer's country: Spain
Science editor: Jing Yu
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COMMENTS TO AUTHORS

The authors present a very interesting study to evaluate the role of A20 in the intestinal inflammation. The experiments are well designed and the results demonstrate that A20 is able to limit the intestinal inflammation associated to NF-KB. My only concern is related to the introduction section. At the final of the introduction the aim of the study is not clearly defined. The last paragraph of the introduction presents some conclusions that may be deleted and included at the final of the discussion section.