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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 39153
Title: Effects of hepatitis E virus infection on interferon production via ISG15
Reviewer's code: 00068723
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-30
Date reviewed: 2018-03-30
Review time: 1 Hour

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] 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 authors investigated interferon production with HEV infection to hepatoma cells C3A. They found that ORF3 suppressed the interferon production. The infection model of HEV to C3A was useful. C3A is a derivative of HepG2. Brief introduction of C3A would be necessary for readers to understand the rationality of C3A. Did the authors analyzed cell lines other than C3A? Titration of the HEV was not clear. How did the authors determine the titer of HEV? This information is necessary for the other researchers to perform experiments with HEV. It was not clear how the authors avoid infection of HEV. How did the authors achieve biological safety to them? Plasmid construction of OR3 was absent. How the plasmid was constructed should be clearly presented so that the other researchers could follow the experiments. Construct of HEV infectious cDNA was absent. The virus production procedure was followed the manufactures instruction. But this procedure should be clearly stated. Western blot

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analysis. Dilution or concentration of antibodies were not clear. Real-time PCR. PCR machine was not described. Primer sequences were absent. What internal control did the authors use? What did the authors have in mind regarding the application of this experiments?

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 39153
Title: Effects of hepatitis E virus infection on interferon production via ISG15
Reviewer's code: 02860897
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-30
Date reviewed: 2018-04-01
Review time: 1 Day

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	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Acute hepatitis E is caused by infection of hepatitis E virus (HEV) that likes the hepatitis A virus, it is orally transmitted, the clinical symptoms are similar to hepatitis A, and transient infection without chronicity except in special cases such as immunodeficiency. Hepatitis E is a constantly sporadic disease occurring in developing countries, but it is sometimes known to cause a large-scale epidemic via drinking water. Hepatitis E has been considered as a disease in areas where hygienic environments are not well established. In this paper, using HEV 's infectious clone, it was revealed that HEV replication causes interferon production and at the same time induces ISG 15 that brakes interferon production. Major point 1. What is the role of ORF3 in HEV replication? 2. Previous studies revealed that the ORF 3 protein plays an important role in releasing HEV particles from infected cells as a result of analysis using ORF 3 deficient mutant clones. In this paper, why does ORF 3 deficient mutant clone not induce interferon?

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 39153
Title: Effects of hepatitis E virus infection on interferon production via ISG15
Reviewer's code: 03537043
Reviewer's country: Poland
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-30
Date reviewed: 2018-04-05
Review time: 5 Days

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

Wang M et al. submitted the manuscript entitled "Effects of hepatitis E virus infection on interferon production via ISG15" for peer review. The Authors study the potential effects of hepatitis E virus (HEV) on the production of Type I interferons (IFNs) and its associations with production of ISG15, one of many interferon stimulated genes. The manuscript is well written , seems accurate and well organized. My major comments mainly concern the descriptions of the techniques used by authors. 1) Why did the authors use the C3A cells. A study conducted on other liver cell lines would have greater cognitive value. 2) Whether in the transfection processes different concentrations of HEV construct and plasmids for ORF3 and ISG15 were used. What concentrations were used for the results presented in manuscript. 3) The authors should describe in more detail or place references on the construction of constructs. 4) Real time PCR; What housekeeping gene was used in the study. Please put the primer sequences for the test gene and

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E-mail: bpgoffice@wjgnet.com
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housekeeping normalization gene in the manuscript. How authors removed residual genomic DNA in RNA samples obtained by TRIzol extraction. 5) Legends for figures should be described in more detail - developing Con, GFP or NC abbreviations.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 39153
Title: Effects of hepatitis E virus infection on interferon production via ISG15
Reviewer's code: 02535507
Reviewer's country: Italy
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-30
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Review time: 6 Days

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
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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this experimental study, entitled "Effects of hepatitis E virus infection on interferon production via ISG15", Min Wang et al demonstrated that HEV leads to over-production of interferon (IFN) alpha and beta in a liver cell line. Moreover, they showed that this process could be mediated by ISG15, an interferon-induced protein. The article is well written and easy to read. Moreover, the design of the study is clear and results have been illustrated effectively in the text as well as in the figures. Only few minor criticisms could be moved. 1) Authors designed 3 different siRNA to silence ISG15. They should report more details about them, for example their sequence in a supplementary table. 2) Authors did not report the concentration of plasmids, siRNA and ISG15 in their experiments. This detail is of major importance for ISG15 since, as Authors themselves hypothesized (page 11 lines 1-3), it could act through a negative feedback mechanism. In this case, it would be interesting to assess which ISG15 concentration may elicit this

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feedback. 3) An aspect that was not investigated was cell replication. Indeed, it would be remarkable to evaluate whether HEV could induce cell apoptosis or replication and if those events could be mediated by IFN or ISG15.