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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34639
Title: Prostaglandin E1 Protects Hepatocytes against Endoplasmic Reticulum Stress-induced Apoptosis via PKA-Dependent Induction of GRP78 Expression
Reviewer's code: 02822428
Reviewer's country: Spain
Science editor: Ze-Mao Gong
Date sent for review: 2017-05-13
Date reviewed: 2017-05-24

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

The authors investigated the effect of prostaglandin E1 (PGE1) against endoplasmic reticulum (ER) stress-induced hepatocyte apoptosis by challenging human hepatic cell lines L02 and HepG2 with Thapsigargin (TG). Interestingy, pretreatment with PGE1 protected against TG-induced apoptosis. The paper is interesting and sound. The authors need to fix the WBs in terms of size and position since some of them are larger than the others. Do the cells change morphologically after TG treatment or they keep the same phenotype when treated with PGE1? Some representative images would help. Moreover, a graphic abstract with a summary of the results would be also valuable. Last, but not least, what happens to JNK activation in presence/absence of PGE1 upon TG-induced ER stress?

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Title: Prostaglandin E1 Protects Hepatocytes against Endoplasmic Reticulum Stress-induced Apoptosis via PKA-Dependent Induction of GRP78 Expression
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Reviewer's country: United States
Science editor: Ze-Mao Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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[ ] Grade E: Poor		[Y] No	[Y] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript by Yang et al. describes that ER stress-induced apoptosis via TG induces GRP78 expression and hepatocyte apoptosis. The authors use pharmacological and genetic approaches in L02 and HepG2 cells to show that PGE1 can inhibit the effects of TG. The strengths of this study lie in the experimental design, methodology and that the authors describe the caveats and potential pitfalls in great detail. Overall, the study was well-designed though there are areas that could be improved to increase its quality, which are outlined below: Major Concerns 1) Due to H89 targeting multiple kinases, the authors should use a more specific antagonist (such as KT5720) or genetic approach to ensure the effects of PGE1 are PKA-dependent. 2) For the apoptosis studies, were the concentration of necrotic cells increased/decreased by any of the treatments? If there was no change, and thus it did not warrant reporting in the manuscript, this technique (line 181) should be removed from the methods. 3) Cell viability was only reported on a small subset of experiments performed. The authors should perform MTS assays in all

of the groups from experiments 5B, 6D and 6E. 4) Intracellular calcium should be assessed in both cell lines including all study groups to give a better idea of the specific signaling effects of PGE1 in these in vitro studies. Minor Concerns 1) Wording and grammar errors exist in the text. An example of this is on line 259 where the text reads, "As showed in Figure 2a…". This should read "As shown….". Please carefully proofread entire manuscript and make appropriate corrections. 2) Many of the figures are missing labels or cannot be read. Specific figures that need to be addressed are figure 2C (bars missing/covered), figure 5B (legend only contains 3 of the 5 groups). 3) Line 166, 2820 microM should be converted to 2.82 mM 4) The fold change values reported for the western blots seem to be scaled incorrectly based on the representative images. For example, in figure 1 GRP78 is essentially absent (with a more intense beta actin band) yet the difference between 0 and 6 hours is only 1.6 fold. sXBP has a much higher fold change though it looks like the change should be equivalent to GRP78. To help explain this better, the authors need to report the fold change +/- standard deviation or standard error of the mean so that variability between the three gels can be determined. 5) In sections 1 and 2 of the results, the authors report on figures 2a, 2b and 2c (lines 259 through 265) but then come back to them in the next section and report additional data in those figures (lines 268 through 274). These should be combined and not be in different sections (all in section 2 of the results would be best).