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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43267

Title: Ubiquitin-specific protease 22 enhances intestinal cell proliferation and tissue regeneration after intestinal ischemia reperfusion injury

Reviewer's code: 00053419

Reviewer's country: Spain

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-12

Date reviewed: 2018-11-17

Review time: 8 Hours, 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript provides evidences of USP22 contributing to repair the intestinal IR-induced damage through promoting cell proliferation. The manuscript describes the results comprehensively, the experimental strategy has been well designed and the

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overall study has been well conducted. However, some of the conclusions seem speculative without further experiments: correlation of USP22 levels and changes on cell proliferation are clear while its role in intestinal damage recovery needs further studies, some of which are mentioned in the manuscript (using USP22 deficient mice, for instance). There are additional specific issues for the authors' consideration: - The main concern is that USP22 has been shown to be associated with progression and chemoresisitance of colorectal cancer and therefore its therapeutic interest is at least dubious. Further discussion is needed. - In addition to cell proliferation there might be additional effects triggered by up-regulation of USP22 that should be analyzed to to define better the mechanisms involved in its postulated postulated protective effect after I/R (PPAR gamma, ER stress....) - For non-specialized readers it is worth mentioning that IEC-6 cells are normal rat small intestinal epithelial cells. - Antibody dilutions should be indicated. - The first paragraph on page 11 (discussion section) is a repetitive description of the results, it should be removed.

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43267

Title: Ubiquitin-specific protease 22 enhances intestinal cell proliferation and tissue regeneration after intestinal ischemia reperfusion injury

Reviewer's code: 01115220

Reviewer's country: United Kingdom

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-12

Date reviewed: 2018-11-21

Review time: 13 Hours, 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have explored the role of USP22 in intestinal reperfusion injury. The experiments are generally appropriately designed, although the methodology is often not presented fully enough. Overall the data do support the conslusions, although in

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several places the papers structure and presentation could be improve. Major points: 1. I feel that the continued use of the abbreviations I/R and H/R in the paper are unhelpful and actually reduce readability. I suggest these are written out in full throughout. 2. The abstract needs to be rewritten with more information in the methods. For instance nothing is mentioned at all about under- or over-expression of USP22 until this suddenly appears in the results section. 3. Both in the abstract and the main text, the authors have clearly shown a tendancy to over-interpret the in vivo studies. These data certainly show a change in expression of USP22 which correlates with other phenomena described. This however does not imply causation. The IEC cell studies are more convincing of a direct link but the authors must ensure that they do not imply causation and biological linkage just from the in vivo experiments. 4. Some of the English ca be improved. In particular the use of "in the clinic" in the Introduction. The standard idiomatic meaning of this would the ambulatory outpatient clinic rather than the intensive care unit, where these patients usually are. 5. Overall the experiments seem appropriate but they are curiously under-described. Several experiments are reported in the results (including but not limited to western blotting of mouse intestine, FACS with the over-expression plasmid) and a lot of important experimental details are not included. The authors need to rewrite the methods to make sure all experiments are included and must provide sufficient methodology. Important inclusions would be the type and titre of antibodies used, the nature of the expression plasmid and control plasmid. I am not sure why forward and reverse primer sequences for siRNA are given? It is only necessary to have one strand to silence mRNA, is one actually meant to be the control sequence? What exactly does the cell counting assay measure? The inference is that this measures viable cells? In which case the authors should refrain from calling this a proliferation assay? For the immunohistochemistry the authors performed cell counting - but what size microscopic field was used? 6. The figure legends are rather inadequate and in all cases

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should be expanded, so that the figures can be understoons in complete isolation without and recourse to the text. Additonally the authors have included some histology: I suggest that the figure legends actually report what is being seen in each image, which indicators on the histology images if helpful. Most readers will not be pathologists by training and will need some assistance in interpreting the histology. Hence please tell the readers what they are seeing here. 7. The authors have performed some nice over and under expression studies with USP22, which obviously does support their hypothesis that USP22 directly influences cyclin D1 and proliferation. However, it is disappointing they have limited their experiments in this way so much. Surely the appropriate experiments with the over and under USP22 expression are to essentially repeat the experiments in figure 2 with the under and over expression and provide a time course for the changes in proliferation and cyclin D1 in relation to altered USP22? This is a very important point as the time course of the changes in USP22, proliferation and cyclinD1 appear to be mostly synchronous, it might be reasonable to expect the changes in USP22 to precede the others? A fuller time course would help clarify this? 8. In the discussion section the authors mention the results of the FACS analysis in the USP22 overexpression system, but no data about this are included in the results section 9. The discussion is rather long and could be shortened and focused more on the data actualu in the paper. Much of the first paragraph of the discussion is redundant and repetition of previously included information and could be removed. However the authors do stress the importance of de novo proliferation in recovery from reperfusion injury, they do not mention other potential methods of recovery such as cell motility and wound closure? These are important in other GI tract pathologies but are they important in this system? 10. In the methods section, the authors mention a power calculation and sample size estimate. However they have not included the figures on this. These data should be included.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43267

Title: Ubiquitin-specific protease 22 enhances intestinal cell proliferation and tissue regeneration after intestinal ischemia reperfusion injury

Reviewer's code: 02495872

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-20

Date reviewed: 2018-11-21

Review time: 7 Hours, 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript is interesting and potentially clinically important. The experimental design, results and their interpretation is fine. There are, however, some minor problems which need to be addressed: 1) English needs some polishing, as in some cases the

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sentences are confusing - e.g., the first sentence in the Abstract - "the mechanism of action?" 2) First part of Introduction deals with general knowledge and importance of I/R, but there is very little references supporting the statements. 3) The background on USP22 is good, but it is still not clear how the authors got into the hypothesis that it might participate in intestinal regeneration. Please improve.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 43267

Title: Ubiquitin-specific protease 22 enhances intestinal cell proliferation and tissue regeneration after intestinal ischemia reperfusion injury

Reviewer's code: 00503516

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-11-20

Date reviewed: 2018-11-27

Review time: 2 Hours, 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

An-Long Ji et al explore the effect and mechanism of the ubiquitin-specific protease 22 (USP22) in intestinal cell proliferation and regeneration after intestinal ischemia/reperfusion (I/R) injury. The authors show that USP22 can promote intestinal

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cell proliferation and has the potential to accelerate intestinal tissue regeneration after intestinal I/R. The work I clearly presented and of potential practical interest. However, the authors should address some issues. -It is necessary to indicate the concentration of the siRNA used as well as the ratio siRNA/transfectant agent; it is also necessary to show the sequence of the control siRNA. - In the result section the authors write:" Therefore, our results demonstrated that USP22 played a vital role during intestinal regeneration…" this sentence is not correct as since this point of the manuscript the authors just showed observational data about USP22 and no functional data are provided. Therefore, I suggest to modify the sentence as it follows: "Therefore, our results demonstrated that USP22 is associated to intestinal regeneration…." - In the result section the authors write:" Thus, our results demonstrated that USP22 can improve proliferative and regenerative activity…." Again this sentence is not correct as the authors just showed that USP22 levels just parallel cell vitality and no evidence of its functional role are provided. Thus, I suggest to modify the sentence as it follows: "Thus, our results demonstrated that USP22 directly correlates to the proliferative and regenerative activity….". Similarly the tile of Fig 2 legend should be modified as it follows: " USP22 correlates with….." - In the result section the authors write:" …..siRNA (si-USP22) dramatically decreased cell proliferation (Fig. 3B).." this sentence is not correct as fib 3B just show the correlation with the levels of Cyclin D and not with cell proliferation. I suggest to modify the sentence :" …..siRNA (si-USP22) dramatically decreased USP22 level and in parallel the levels of cyclin D and of cell vitality (Fig. 3B)..". -In figure 3 D and E the authors show the increase of G1 phase cells. Data about S and G2-M phase cells should be also reported. In the presence of a G1 block, one would expect a reduction of S and probably also G2-M phase cells. In this regard, the authors write in the discussion: "….in the G1 phase of the cell cycle and stopped them from entering S phase…" however, no data about S phase cells are shown. - In the result

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section the authors write:"… USP22 overexpression weakens I/R-induced injury and promotes cell proliferation and viability in this process" however, no data about the effects of USP22 overexpression on I/R-induced injury are shown; the authors jus show the effect of in vitro cell proliferation. Thus, the words : …..weakens I/R-induced injury" should be deleted. - Lines 1-17 (Intestinal-monolayer), 32-42 (USP22-repair) and 55-61 (Cyclin D-phase) of the discussion should be condensed in the introduction and removed from the discussion. Lines 42-55 (Since- hypothesis) should be condensed as they just repeat the results obtained. In the discussion, the authors should better discuss their data in relation to previously published papers.

INITIAL REVIEW OF THE MANUSCRIPT

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