

January 10, 2014

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World Journal of Biological Chemistry, MS ID00289695

Dear Drs. Ma and Mo, Editor-in-Chief of the World Journal of Biological Chemistry (WJBC),

Thank you very much for positive comments on our review article.
Please find enclosed the edited manuscript in Word format (file name:
Dai_WJBC_7770_rev.docx).

Title: *Deubiquitinating enzyme regulation of the p53 pathway: A lesson from Otub1*

Author: Xiao-Xin Sun, Mu-Shui Dai

Name of Journal: World Journal of Biological Chemistry

ESPS Manuscript NO: 7770

The manuscript has been improved according to the suggestions of reviewers:

(1) Format has been updated.

(2) Revision has been made according to the suggestions of the reviewers and my response to the reviewers' comments, point-by-point, is listed below:

Reviewer 1#:

1. ***"Ring domain" should be changed to "RING domain" throughout the entire article.***

My response: The "ring domain" has been all replaced with "RING Domain".

2. ***A more detailed legend should be provided for Fig. 1.***

My response: A detailed legend has been added in the revised manuscript.

3. ***Conclusion and Perspectives: it would be nice to recap what we know about p53 regulation by various DUBs, and perhaps to discuss how regulations of p53 by these DUBs are coordinated.***

My response: It has been done as suggested in the last paragraph.

Reviewer 2#:

The authors have written an excellent review of a topic on which that they have been working for a number of years, which is the regulation of p53 activity and stability by MDM2/MDMX complex. This manuscript will no doubt serve a good introductory review for readers interested in the field of ubiquitination and deubiquitination in general, and the p53-MDM2-MDMX pathway, DNA-damage repair, and Otub1 in particular.

The only advice about the manuscript is that it should go through a thorough check of the English and the reference list. There are minor errors or omissions in the use of English, such as the addition of apostrophe s after Otub1, the omission of “with” after “associated” in line 4 of page 3, and an assortment of errors at multiple other places in the manuscript. Omissions of publication year and inconsistent use of letter case and abbreviations for journal names are also present in the reference list.

My response: Thanks for the positive comments and pointing out the typos. We have now added “with” in page 3 and the missed years in the literatures. We have also carefully proofread the manuscript and made corresponding corrections in the text.

Reviewer 3#:

Overall, this is a very nice review to summarize the current findings in the ubiquitin regulation of P53. The authors further focused the deubiquitination regulation of P53 by USP7, USP10, USP29, USP42, USP2 and USP4. Finally they also discussed their recent identified DUBs-OTUB1. Among the identified P53's DUBs, OTUB1 is unique because it does not require its enzymatic function. The most of available references regarding p53 deubiquitination is well included. Therefore, this manuscript will provide basic summary of current knowledge of p53 ubiquitination regulation.

My response: Thanks for the positive comments.

Reviewer 4#:

The manuscript is well written, but minor changes should be made before publication.

1, On page 6, the authors described “95 DUBs” and cited some of the literatures. However, in a more recent paper by Clague et al., JCS 2012, it was speculated that the human genome encodes ~80 DUBS. These numbers should be clarified.

My response: Thanks for the positive comments. In the 2012 JCS paper, the authors cited the same two papers as we cited in this manuscript (Nijiman 2005; Komander 2009). Nijiman et al used the ENSEMBL human genome database to search putative Dubs and found there are 95 putative Dub members. Later in the Kmoander’s review in 2009, it was predicted that there are 79 active Dubs. Actually, in the 2012 JCS review, the putative Dub was also mentioned to be ~90, roughly, but active Dub numbers are probably ~80. Therefore, in the revised manuscript, we changed the “95 Dub” to “95 predicted Dubs”, trying to cover all possible Dubs in human genome.

2, The authors used much space to discuss the regulation of P53 by the MDM2-MDMX complex. However, none of the very interesting inhibitors, such as nutlin, were discussed. In addition, the



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authors should have expanded a little bit more in describing the strategies that targeting Otub1 complexes for cancer therapy ideas.

My response: I mentioned some inhibitors in the “Conclusion and Perspective” section, and also directed the readers to refer our recently published review article for detailed discussion of targeting the UPS to reactivate p53 in cancer therapy (2013).

3, page 9, reference(s) are needed after “ARF-1 is thought to antagonize the function of Otub1 in cells.” 4, Page 12, reference(s) are needed for “T134E, but not T134A, failed to rescue the DNA damage.....”

My response: Thanks. The references have been added.

(3) References and typesetting were corrected.

We hope that with these modifications our manuscript can now be accepted by the *WJBC*.

Thank you very much for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Mushui Dai".

Mu-Shui Dai