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Wan Chai, Hong Kong, China

ESPS Peer-review Report

Name of Journal: World Journal of Biological Chemistry

ESPS Manuscript NO: 7770

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

Reviewer code: 00338280

Science editor: Wen, Ling-Ling

Date sent for review: 2013-12-02 10:22

Date reviewed: 2013-12-07 23:18

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

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



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ESPS Peer-review Report

Name of Journal: World Journal of Biological Chemistry

ESPS Manuscript NO: 7770

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

Reviewer code: 00289733

Science editor: Wen, Ling-Ling

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

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.



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ESPS Peer-review Report

Name of Journal: World Journal of Biological Chemistry

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

Reviewer code: 00698952

Science editor: Wen, Ling-Ling

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

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. The first part of the manuscript covers a comprehensive and updated overview of mainly the roles of MDM2 and MDMX on the ubiquitination and transcriptional suppression of p53, as well as the regulation of the complex itself by other proteins leading to p53 activation in various cellular stress situations. Given the importance of ubiquitination in regulating p53 by the MDM2/MDMA complex, the authors proceed in the second part of the manuscript to elucidate the crucial roles played by enzymes that do the opposite job, that is, deubiquitination, on the regulation of the p53-MDM2-MDMX pathway. The authors develop further their discussion into their more recent findings of the regulation of MDM2-mediated p53 ubiquitination by an OTU family deubiquitinase (DUB), Otub1. Through their efforts and others', Otub1 has been identified as a DUB that plays a broad range of cellular functions, including the regulation of T cell anergy, DNA damage response, pathogen infection, estrogen signaling and p53 ubiquitination. In addition, it has been found that Otub1 can unusually mediate its deubiquitination-promoting activity by mechanisms other than its DUB catalytic activity, which include the direct inhibition of cognate ubiquitin-conjugating enzymes (E2). The authors not only summarize the important findings about Otub1 in the literature and of their own, but also lucidly delineate what is known so far about the non-canonical activities of this protein in the settings of p53 regulation and K-63 polyubiquitination of histones in DNA-damage repair response. What is more, the authors have not failed to put forth their unpublished observations, perspectives and insights regarding the further mechanism and possible role of Otub1 in cancer development, which is scientifically stimulating. This manuscript will no doubt serve a



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good introductory review for readers interested in the field of ubiquitination and deubiquitination in general, and p53-MDM2-MDMX pathway, DNA-damage repair, 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.



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ESPS Peer-review Report

Name of Journal: World Journal of Biological Chemistry

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Reviewer code: 01299180

Science editor: Wen, Ling-Ling

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<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This is a very nice review on an important topic. I have only a few minor suggestions. 1. "Ring domain" should be changed to "RING domain" throughout the entire article. 2. A more detailed legend should be provided for Fig. 1 (the only figure). 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.