

November 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5337 revised).

Title: The Roles and Mechanisms of Cyclic-ADP Ribose (cADPR)/CD38/Ca²⁺ Signaling Pathway

Author: Wenjie Wei and Jianbo Yue

Name of Journal: *World Journal of biological chemistry*

ESPS Manuscript NO: 5337

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

1 Format has been updated accordingly.

2 Revision has been made according to the suggestions of the reviewers

(1) *p3, spell out IP3 the very first time it appears in the text.*

Inositol 1,4,5-trisphosphate (IP₃) are now spelled out as suggested.

(2) *p3, define and spell out CICR the first time it appears in the text.*

CICR is abbreviation of Calcium-induced Calcium release, which is now spelled out.

(3) *p3, define and spell out RyRs. 4, p4, define and spell out TRPM.*

Ryanodine receptors (RyRs) and transient receptor potential cation channel M2 (TRPM2) are now spelled out.

(4) Page 3, "that homogenates desensitized to IP3 were still..." Please re-phrase, as homogenates cannot be desensitized.

It is now changed to homogenates which have already been desensitized to IP₃

(5) "which is a spliced variant", change to: which is a splice variant

Changed it suggested.

(6) "preincubating with an cADPR antagonist" change to: preincubating with the cADPR antagonist

Changed it suggested.

- (7) Page 4, After the sentence „Nevertheless, further researches are needed to elucidate the direct receptor of cADPR“ it would be nice when the reviewers would suggest own experiments or point to future directions to solve open questions/issues.

It is rephrased to : Nevertheless, further researches such as genome-wide RNAi screen is needed to elucidate the direct receptor of cADPR.

- (8) “was actually ubiquitously existed in a wide variety“, change to: ubiquitously exists in a wide variety....

Changed it suggested.

- (9) “Aplsia“, do you mean Aplysia?

Changed it suggested.

- (10) change “showes“ to shows

Changed it suggested.

- (11) Page 5, “and converted most of NAD to ADP-ribose, thus possesses both cyclase and NADase activities“ I do not understand this sentence, please re-phrase.

It is now rephrased to: When incubating with NAD in vitro, CD38 only cyclized small portion of NAD into cADPR, while converted most of NAD to ADP-ribose, thus it possesses both cyclase and NADase activities.

- (12) “sties“ change to sites

Changed it suggested.

- (13) “in the form of homodimer“, change to in the form of a homodimer

Changed it suggested.

- (14) I do not understand the sentence “as the active site, with a TLEDTL conserved segment“, do you mean that the active site contains the amino acid sequence TLEDTL?

It is now rephrased to: with a TLEDTL conserved sequence sitting in the bottom of the pocket

- (15) “are protonated thereby facilitating“ please insert a comma before the word thereby

Changed it suggested.

- (16) “produced cADPR need to be transported“ change to needs to be transported.

Changed it suggested.

(17) Page 6, "this directly transport" please change to this direct transport

Changed it suggested.

(18) "is a critical for the internalization", do you mean a critical event for....?

It is now changed into:

(19) "43 hemichannels is opened" please change to 43 hemichannels are opened

Changed it suggested.

(20) "coworkers had showed that treatment " change to coworkers had shown that treatment

Changed it suggested.

(21) "Although the exactly location of " change to Although the exact location of

Changed it suggested.

(22) "that containing multiple serine " change to that contains multiple serine

Changed it suggested.

In addition, the grammatical and typographical errors have been checked throughout and revised. All abbreviations have been defined when they first appeared as well. Format of references were changed as required.

Thank you again for publishing our manuscript in the *World Journal of biological chemistry*.

Thank you for your consideration.

Sincerely,



Jianbo Yue, PhD