

Format for ANSWERING REVIEWERS

May 2, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 16502-Review.doc).

Title: STAT3 regulation by novel binding partners

Author: Tadashi Matsuda, Ryuta Muromoto, Yuichi Sekine, Sumihito Togi, Yuichi Kitai, Shigeyuki Kon, Kenji Oritani

Name of Journal: *World Journal of Biological Chemistry*

ESPS Manuscript NO: 16502

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 reviewer:

(1) Reviewer #1 (No. 3002173)

This reviewer found our manuscript of significance and suitable for the *WJBC* audience. The reviewer had, however, a few points that he/she asked to be addressed.

Our responses are listed as follows:

1) The reviewer asked a table summarizing the proteins discussed their potential mechanism of action and effect on Stat3 activity would provide a useful adjunct to the text. We agree with the reviewer. According to the reviewer's suggestion, we created a table for the binding sites and functions of novel STAT3-interacting proteins we addressed in the manuscript. We thank the reviewer for bringing this important point to our attention.

2) The reviewer asked whether there is some clinical data to support the pre-clinical data described in the review and these proteins have yielded any potential therapeutic targets. We agree with the reviewer. Although this is a very important point, at the present time, we do not have any pre-clinical data about proteins we addressed in this review. However, STAT3 binding proteins described here are likely to have a potential to regulate STAT3 activity under some malignant or inflammatory circumstance; therefore, further experiments, including the establishment of low molecular compounds to inhibit their interaction with STAT3 could help for us to gather information about their clinical utility as well as physiological and/or pathological significance. We described this issue on line 28, p. 12 to 6, p. 13. We thank the reviewer for bringing this important point to our attention.

(2) Reviewer #2 (No. 289387)

This reviewer found our manuscript of some significance and suitable for the *WJBC* audience. The reviewer had, however, several points that he/she asked to be addressed.

Our responses are listed as follows:

1) The reviewer #2 noted that the description of their physical interaction with STAT3 in the absence of strong evidence of their physiological and/or pathological significance, and if it provides evidence for

individual STAT3 and its partners in some pathophysiological conditions such as cancer, other diseases, or animal models, it would be much helpful. We agree with the reviewer. Although this is a very important point, at the present time, we do not have any pathophysiological data about proteins we addressed in this review. Therefore, as information for the *WJBC* audience, we cited some publications (Table 1) concerning knockout mice phenotypes of novel STAT3-interacting protein we addressed in the text. We thank the reviewer for bringing this important point to our attention.

2) The reviewer #2 noted that authors' opinion on some limited information should be added and potential problems should be discussed as well. We agree with the reviewer. We think that STAT3 binding proteins described here are likely to have a potential to regulate STAT3 activity under some malignant or inflammatory circumstance; therefore, further experiments, including the establishment of low molecular compounds to inhibit their interaction with STAT3 could help for us to gather information about their clinical utility as well as physiological and/or pathological significance. We described this issue on line 28, p. 12 to 6, p. 13. We thank the reviewer for bringing this important point to our attention.

3) The reviewer #2 asked whether there are some publications demonstrating agents that can specifically block these binding proteins, If so, please add them because this part may hold promise for disease treatment. We agree with the reviewer. We think that this is the similar question with the reviewer#1. Although this is a very important point, at the present time, we do not have any such data about proteins we addressed in this review.

However, STAT3 binding proteins described here are likely to have a potential to regulate STAT3 activity under some malignant or inflammatory circumstance; therefore, further experiments, including the establishment of low molecular compounds to inhibit their interaction with STAT3 could help for us to gather information about their clinical utility as well as physiological and/or pathological significance. We described this issue on line 28, p. 12 to 6, p. 13. We thank the reviewer for bringing this important point to our attention.

4) The reviewer #2 noted that Core tip should be re-written as it appears to be same as abstract. We agree with the reviewer. We re-wrote Core tip differently of abstract. We thank the reviewer for bringing this important point to our attention.

5) The reviewer #2 noted that NF- κ B signaling and association with STAT3 in the conclusion must be moved to the main text, since conclusion should summarize the main information described in the text, rather than new discussion. We agree with the reviewer. According to the reviewer's suggestion, we omitted some description about NF- κ B signaling and association with STAT3 in the conclusion and move it to in "Possible clinical utility of targeting STAT3-related molecules in future" of the main text. We thank the reviewer for bringing this important point to our attention.

6) The reviewer #2 noted that Figure 2 regarding the disease association was not fully mentioned in the text and it should be omitted. We agree with the reviewer. According to the reviewer's suggestion, we omitted Figure 2. We thank the reviewer for bringing this important point to our attention.

7) The reviewer #2 noted that Figure 1 and 2 legends must be opposite, because they do not match each figure. We think that Figure 1 legend matched for Figure 1, although we omitted Figure 2 as described the above.

We thank the reviewer for their careful thoughts and constructive suggestion to improve our paper.

(3) Reviewer #3 (No. 202869)

This reviewer found our manuscript of significance and suitable for the *WJBC* audience. We thank this reviewer for reading our manuscript.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Biological Chemistry*.

Sincerely yours,

A handwritten signature in black ink, consisting of a large, stylized 'M' followed by a horizontal line.

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