Dear Editor
Please find enclosed the edited manuscript in Word format (file name: 7249-review-revised.doc and 7249-review-clean.doc).

Title: The regulation and function of signal transducer and activator of transcription 3

Author: Qian-Rong Qi, Zeng-Ming Yang

Name of Journal: *World Journal of Biological Chemistry*

ESPS Manuscript NO: 7249

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: Review manuscript need to discuss about STAT3 inhibitors in theraputic aspect to cancer treatment. 2. Authors need to add a figure summarizing regulation and function of STAT3 to better understand and highlight the review manuscript.
Answer: Yes, we agree with you. We have provided the following contents about STAT3 inhibitors in therapeutic aspect to cancer treatment, as well as two figures summarizing the regulation and function of STAT3 in our revised manuscript:

"Targeting the STAT3 pathway should be a promising and novel form of treatment for these human cancers. Blocking STAT3 by siRNAs, antisense oligonucleotides, dominant-negative mutants, and specific inhibitors of STAT3 in combination with chemotherapeutics can synergistically inhibit the growth, invasion and metastasis of carcinoma cells[62-64]. Therefore, inhibiting STAT3 signals are profounding therapeutic target for most types of human cancers with constitutively activated STAT3. "

"**Figure legends**

Figure 1 The domain structure of STAT3 α and STAT3β. The STAT3 α protein is composed of N-terminal, coiled-coil, DNA binding domain, linker, SH2, and transactivation domain. However, the transactivation domain is absent in the alternative splicing variant ofSTAT3 β.

Figure 2 Converging roles of STAT3. Different signals can selectively trigger STAT3

phosphorylation. Tyr-phosphorylated STAT3 translocates into nucleus and regulates gene expression, thus playing an important role in cell proliferation, tumorigenesis, self-renewal and pluripotency. On the other hand, Ser-phosphorylated STAT3 translocates into mitochondria, binds with the complexes in respiratory chain, and ultimately maintains the cellular respiration and mitochondrial protection."

(2) Reviewer 2:

This manuscript summarizes the regulation of STAT3 expression at the level of transcription, post-transcription and post-translational modification. In addition, functional regulation of STAT3 via nucleo-cytoplasmic shuttling, and STAT3 function in physiological and tumorigenic processes are described. The manuscript is well-written. However, I would like to comment minor points as below

Minor points

1. Page 5, line 106: It would be better that the subtitle "Post-transcription regulation of STAT3 expression through alternative splicing" is changed to main title "POST-TRANSCRIPTIONAL REGULATION OF STAT3 EXPRESSION. Because main headline "TRANSCRIPTIONAL REGULATION ON STAT3" (Page 4, line 74) is not matched to "Post-transcription regulation of STAT3 expression through alternative splicing"

Answer: Yes, it is corrected.

2. Subtitle "STAT3 in stem cells" (page 11, line 271), subtitle "STAT3 in proliferation and apoptosis" (page 12, line 298), subtitle "STAT3 in tumorigenesis and cancer inflammation" (page 13, line 331) could be grouped under main title, such as "FUNCTION OF STAT3 IN PATHOPHYSIOLOGY AND DEVELPOMENT".

Answer: Yes, it is changed.

3. Page 13, line 331: The word "cancer inflammation" needs to be corrected (for example, cancer-related inflammation).

Answer: Yes, it is changed.

4. Page 4, line 74: “OF STAT3” is better instead of “ON STAT3”.

Answer: Yes, it is changed.

5. Page 4, line 84: space between STAT3 and executes.

Answer: Yes, it is changed.

6. Page 4, line 98: SCOSmis-spelling.

Answer: Yes, it is corrected.

7. Page 5, line 104: It would be better to change the description “SOCS3 have a negative regulation on STAT3 expression” to “STAT3 expression is negatively regulated by SOCS3”

Answer: Yes, it is changed.

8. Page 5, line 112: Space between of and STAT3.

Answer: Yes, it is changed.

9. Page 5, line 118: Space between that and STAT3.

Answer: Yes, it is changed.

10. Page 6, line 129: remove space between epithelium- and derived.

Answer: Yes, it is changed.

11. Page 6, line 137: Space between phosphorylates and STAT3.

Answer: Yes, it is changed.

12. Page 6, line 140: Spaces between Dimerized, STAT3 and translocates.

Answer: Yes, it is changed.

13. Page 6, lines 142 and 143: Src instead of Scr.

Answer: Yes, it is corrected.

14. Page 6, lines 149-150: It would be better to change the sentence as follow. “Recently, several articles reported that un-phosphorylated STAT3 can interact with nuclear factor- B (NF- B)”.

Answer: Yes, it is changed.

15. Page 6, line 155: “post-translational” instead of “posttranslational”, which is consistent with Page 6, line 134.

Answer: Yes, it is changed.

16. Page 7, line 64: delete “as”--- CD44, a transmembrane glycoprotein,

Answer: Yes, it is deleted.

17. Page 7, line 166: Space between cyclin and D1.

Answer: Yes, it is changed.

18. Page 7, line 170: remove space between Ac-STAT3/ and DNMT1

Answer: Yes, it is changed.

19. Page 7, line 172: STAT3 acetylation instead of Ac-STAT3.

Answer: Yes, it is changed.

20. Page 7, line 181: It is better to change the sentence as follow. “STAT1 and STAT3 are also subjected to SUMOylation-----.

Answer: Yes, it is changed.

21. Page 7, line 183: Space between STAT3 and SUMOylation.

Answer: Yes, it is changed.

22. Page 8, line 186: STAT3 LOCALIZATION instead of STAT3 LOCATION

Answer: Yes, it is changed.

23. Page 8, line 193: NLS- and NES-containing proteins instead of NLS and NES proteins.
Answer: Yes, it is changed.

24. Page 8, line 201: delete “way”
Answer: Yes, it is deleted.

25. Page 8, line 210: Space between unphosphorylated and STAT3
Answer: Yes, it is changed.

26. Page 9, line 212: Space between U-STAT3 and can
Answer: Yes, it is changed.

27. Page 9, line 216: delete (2f-FCS), because 2f-FCS is not mentioned further in the manuscript.
Answer: Yes, it is deleted.

28. Page 9, line 218: delete (STAT3-NT), because STAT3-NT is not mentioned further in the manuscript.
Answer: Yes, it is deleted.

29. Page 9, line 226: phosphorylated STAT3 instead of STAT3 mono-phosphorylation
Answer: Yes, it is changed.

30. Page 9, line 227: localized to the mitochondria of hepatocytes
Answer: Yes, it is changed.

31. Page 10, line 258: HIF-1 -dependent and HIF-1 -independent.
Answer: Yes, it is changed.

32. Page 11, line 261-262: The meaning of “or DNA binding domain” is not clear.

Answer: Yes, this sentence is rephrased as "Mitochondrial STAT3 displays Serine 727 phosphorylation, while tyrosine phosphorylation or DNA binding activity is not detected, unlike canonical transcriptional activation."

33. Page 12, line 304: STAT3 knockout mice exhibit complete embryonic lethality.
Answer: Yes, it is changed.

34. Page 13, line 350: activates a lot of inflammatory-related genes
Answer: Yes, it is changed.

35. Page 15, lines 380-382: It is better to modify this sentence.
Answer: Yes, this sentence is rephrased as "STAT3 phosphorylation in uterine luminal epithelium activated by LIF and some LIF targeted genes, such as Irg1, is significantly inhibited by STAT3 inhibitor both in vivo and in vitro[69]."

36. Page 15, line 386: Conditional ablation of STAT3 only in PR-positive cells
Answer: Yes, it is changed.

37. Page 15, line 388: Conditional ablation of STAT3 in the uterus (Stat3d/d) results in embryo implantation failure.
Answer: Yes, it is changed.

38. Page 15, line 396: Space between alternative and splicing. post-translational
Answer: Yes, it is changed.

39. Page 15, line 397: STAT3 , a novel isoform of STAT3
Answer: Yes, it is changed.

3 References and typesetting were corrected

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

Sincerely yours,

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