

ROUND 1

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: First, this manuscript revealed that PRMT1 interacted with PRMT6 in vitro and in vivo. Second, the author showed that the R106 of PRMT6 was the major methylation site induced by PRMT1, and PRMT1-mediated methylation suppressed the activity of PRMT6 on H3 methylation. Altogether, this work illustrates the dynamic interplay between PRMT1 and PRMT6. However, as shown by Kang et al (Skeletal muscle-specific Prmt1 deletion causes muscle atrophy via deregulation of the PRMT6-FOXO3 axis, DOI:

10.1080/15548627.2019.1569931), muscle-specific PRMT1 deficiency led to PRMT6 upregulating FOXO3 and muscle atrophy, meaning that PRMT1 suppresses PRMT6.

Response: We think this study is well in line with our result. We added the result of the study by Kang et al (Skeletal muscle-specific Prmt1 deletion causes muscle atrophy via deregulation of the PRMT6-FOXO3 axis, DOI: 10.1080/15548627.2019.1569931) in the discussion part.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1. The English need improvement since there are some grammatical and syntax errors in the manuscript. For example, the words “RNA splicing” may be as “and RNA splicing”; “Type I” as “the Type I”; “6-well” as “a 6-well”; “to cells” as “to the cells”; “knock down” as “the knock down”; “stored 16” as “stored for 16”; “phosphor” as “a phosphor”; “varied” as “the varied”; “in presence” as “in the presence”; “washed by” as “washed with”; “PBS for 3” as “PBS 3”; “PBS for 5” as “PBS 5”; “western” as “a western”; “as template” as “as a template”; “stored in” as “stored at”; “mutants was” as “mutants were”; “of P81” as “of the P81”; “of other” as “of the other”; “cell lysate” as “and cell lysate”; “Anti-Myc” as “The anti-Myc”; “down PRMT1” as “down the PRMT1”; “in presence” as “in the presence”; “clearly was” as “clearly”; “as PRMT1” as “as the PRMT1”; “, PRMT6” as “, the PRMT6”; “SAM-binding” as “the SAM-binding”; “2-fold” as “a 2-fold”; “The past” as “Past”; “finding of” as “findings about”; “samples were” as “and samples were”; “Michaelis-Menten” as “the Michaelis-Menten”; “highlighted on” as “are highlighted on”. The grammar mistakes which are not mentioned here are also to be checked and corrected properly.

Response: Edit has been made as requested. Grammar mistakes have been checked and corrected.

2. There are some typing mistakes as well, and authors are advised to carefully proof-read the text. For example, the words “steady state” may be as “steady-state”; “therapeutic effect” as “therapeutic effects”; “process require” as “processes require”; “time dependent” as “time-dependent”; “pulled down” as “pulled-down”; “in gel” as “in-gel”; “Site directed” as “Site-directed”; “Then single” as “The single”; “high pressure” as “high-pressure”; “beads firstly” as

“beads first”; “clearing showing” as “clearly showing”; “knock down” as “knockdown”; “PRMT6 concentration” as “PRMT6 concentrations”; “wild type” as “wild-type”; “varying concentration” as “varying concentrations”; “wellg” as “well”; “concentration were” as “concentrations were”; “PRMT1 mediated” as “PRMT1-mediated”; “impact in” as “impact on”; “cancer relevant” as “cancer-relevant”; “bind to” as “binds to”; “pulled down” as “pulled-down”; “concentration dependent” as “concentration-dependent”; “the corresponded” as “the corresponding”. The typos not mentioned here are also to be checked and corrected properly.

Response: Edit has been made as requested. Typing mistakes have been checked and corrected.

3. Check the abbreviations throughout the manuscript and introduce the abbreviation when the full word appears the first time in the abstract and the remaining for the text and then use only the abbreviation (For example, LC-MS/MS, asymmetric dimethylarginine (ADMA), etc.,). Make a word abbreviated in the article that is repeated at least three times in the text, not all words to be abbreviated. The authors should avoid the usage for abbreviations in the keywords.

Response: Edit has been made as requested.

4. The full form of the species should be given when the first time appears in both the abstract and in the remaining part of the manuscript and it should be followed by only the first letter of the genus (For example, *Escherichia coli* when the first time appear and followed by *E. coli*).

Response: Edit has been made as requested. Full form of the species has been added.

5. In the materials and methods, the authors may cite references for standard protocol, instead of mentioning kit or manufacture instructions, if reference is given with it and the same should be added in the reference section.

Response: Edit has been made as requested.

6. The table and figure legends should be improved and a proper footnote should be given. All legends should have enough description for a reader to understand the table and figures without having to refer back to the main text of the manuscript. For example, the necessary abbreviations should be given.

Response: Edit has been made as requested.

7. The limitation of the present research and future direction may be given along with conclusion or under separate heading for understanding the concepts clearly.

Response: Edit has been made as requested. The future direction has been given along with conclusion.

ROUND 2

1. There are some grammatical, alignments and typographical errors are noted in the manuscript and it should be thoroughly checked and corrected throughout the manuscript. For example, the words “emerges” may be as “emerged”; “methyltranferase” as “methyltransferase”; “study we” as “study, we”; “shows PRMT6” as “shows that PRMT6”; “knock down” as “knockdown”; “by high-pressure” as “by a high-pressure”; “observed PRMT6” as “observed that PRMT6”; “, the cell lysate” as “, and the cell lysate”; “PRMT6 was decreased” as “PRMT6 were decreased”; “1A was resulted” as “1A has resulted or 1A resulted”; “data were fit” as “data fit”; “for detecting” as “to detect”; “possible is” as “possible”; “radioactive gel” as “a radioactive gel”; “histone H3” as “the histone H3”; “that H3R2me2a” as “that the H3R2me2a”; “As showed” as “As shown”; “member in the” as “member of the”; “fine tune” as “fine-tune”; “hint at” as “hints”; “KmoF” as “Km of”; “PRMT6R106Kstill” as “PRMT6R106K still”; “retains similar” as “retains a similar”; “exhibited similar” as “exhibited a similar”; “The previous” as “Previous”; “HOXAgenes” as “HOXA genes”; “given on” as “given to”.

Response: The grammatical, alignment and typographical errors were corrected as requested. However, some of the issues that you mentioned are correct in the original text. Such as the words “emerges” as “emerged”; “methyltranferase” as “methyltransferase”; “study we” as “study, we”; “shows PRMT6” as “shows that PRMT6”; “KmoF” as “Km of”; “PRMT6R106Kstill” as “PRMT6R106K still”; “HOXAgenes” as “HOXA genes”.

2. This suggestion is not carried out properly (Check the abbreviations throughout the manuscript and introduce the abbreviation when the full word appears the first time in the abstract and the remaining for the text and then use only the abbreviation). For example, the expansion for LC-MS/MS is not given in both abstract and the remaining part of the manuscript and it should be rectified.

Response: The full word of LC-MS/MS was given in abstract. “Through Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) analysis and site-directed mutagenesis studies”. The full word of LC-MS/MS was added when it first appears in the text.

3. The technical terms (Latin Phrase) “in vivo” should be italic and it should be checked all over the manuscript.

Response: Edit has been made as requested.

4. This suggestion is not carried out properly and it should be rectified. In the materials and methods, the authors may cite references for standard protocol, instead of mentioning kid or manufacture instructions, if reference is given with it and the same should be added in the reference section.

Response: Done.

5. The figure legends should be improved and a proper footnote should be given. All legends should have enough description for a reader to understand the figures without having to refer back to the main text of the manuscript. For example, the necessary abbreviations should be given (PRMT1-PRMT6).

Response: The abbreviations were given in the footnote, last response letter mentioned that for the title of the figures we should not use abbreviations so that is the reason why we are using

“Protein arginine methyltransferase 1” for “PRMT1” or “Protein arginine methyltransferase 6” for “PRMT6.