Author’s response to reviews

Title: M1 Macrophage Infiltrations Exacerbate Muscle and Bone Atrophy after Peripheral Nerve Injury

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Atul K.Taneja,
Editor
BMC Musculoskeletal Disorders

Dear Editor,

We are submitting a revised version of our manuscript entitled "M1 Macrophage Infiltrations Exacerbate Muscle and Bone Atrophy after Peripheral Nerve Injury" by N. Shimada, A. Sakata, T. Igarashi, M. Takeuchi and S. Nishimura which was originally submitted on October 17, 2019. The manuscript number is BMSD-D-19-01573.

We would like to appreciate the comments and suggestions given by editor and reviewers which we believe have resulted in a much improved manuscript. We corrected the manuscript according to reviewer’s comments. The revised manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose native language is not English again. We attach a certificate stating that the English text has been properly proofread. We included a cover letter responding individually reviewer and detailing all changes and corrections we’ve done and copy of the manuscript with changes shown in red.

We hope that the revised manuscript will be suitable for publication in BMC Musculoskeletal Disorders.
Sincerely yours,

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Comments to reviewer #1

We would like to appreciate your review.

Comments to reviewer #2

We would like to appreciate your careful review, your keen and scrupulous comments, and giving us the opportunity for revision. In particular, the attachments you provided about the proper representation of the English sentence were very helpful in improving manuscript. We revised the manuscript as follows.

1) Improve on language and grammar in text. Some sentenced were difficult follow as highlighted in the attachment.

Answer) Thank you for pointing out the appropriate English language expression. We have corrected all English sentences to proper expressions according to your suggestions. The revised manuscript has been carefully reviewed by an experienced editor whose first language is English and who specializes in editing papers written by scientists whose native language is not English again. We attach a certificate stating that the English text has been properly proofread. In abstract, we address the gap in knowledge before presenting our hypothesis. We also corrected the labeling in Figure 3 to clear.

2) The manuscript does not highlight the relance to chronic pain. It would be of great interest if the authors also showed improvement in the chronic-pain like behaviour upon suppression of M1 macrophages at the site of peripheral injury. A link between inhibition of bone/muscle atrophy to that of pain-like behaviour would further stengthen the manuscript.

Answer) We completely agree with you. This study should be linked to pain studies, especially chronic pain studies. However, in this study, we did not perform the experiment of the pain such as behavior test. Because, in this study, we focused on muscle/bone atrophy due to peripheral nerve injury. Furthermore, there is a behavioral approach to evaluating pain in animal models only for neuropathic pain. Evaluation of pain due to muscle/bone atrophy has not been established, and it is unclear whether conventional pain evaluation can be applied. In the future,
we will also investigate the pain based on the methods in this study. We described in the revised manuscript that we did not perform the experiment of the pain, and this study should be linked to pain studies (P15 L353).

3) It would be interesting to know whether suppression of peripheral inflammation has any impact on inflammation in the spinal cord?

Answer) As you pointed out, central sensitization include the dorsal horn of the spinal cord is reportedly involved in neurogenic inflammation. Suppression of peripheral inflammation may any impact on inflammation in the spinal cord. However, contrary to our expectations, from this study, central nervous system involvement in muscle/bone atrophy was considered small since the drugs, whose analgesic pathway is mediated mainly by central nervous system, are ineffective. This study alone cannot rule out the effects of the central nervous system on muscle/bone atrophy following peripheral nerve injury, the relationship between central sensitization in the dorsal horn of the spinal cord and muscle/bone atrophy should be considered further in the future. We described them in the manuscript (P16 L385).