Reviewer's report

Title: Proteasome Inhibition Alleviates Prolonged Moderate Compression-induced Muscle Pathology

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Reviewer: Zhaoyong Hu

Reviewer's report:

In this study, authors investigated the involvement of ubiquitin proteasome system (UPS) in pressure-induced skeletal muscle injury. They concluded that UPS plays critical role in the pathogenesis of pressure-induced muscle injury. The evidences to support this conclusion are: 1) Ubiquitin and muscle E3 ligase MAFbx/atrogin-1 were up-regulated in damaged muscle. 2) Muscle proteasome (20S) activity was increased with deep muscle injury. 3) Administration of proteasome inhibitor ameliorated pathologic changes in pressure-injured muscle.

The results also demonstrated an association between MG132's effect on injured muscles versus on inflammation. It is an interesting study using a well established animal model. The data however appear accidental and preliminary. There are few issues that need to be addressed

Major Compulsory Revisions:

1. MG132 suppresses ubiquitin and Atrogin1 expression (Fig 4,5). Are these transcriptional suppressions? As hydrophobic peptide aldehydes, MG132 blocks the peptidase sites on the 20 S proteasome (Rock K. L. et al, 1994 Cell). It is very interesting to know how MG132 regulates the expression of ubiquitin and Atrogin-1.

2. Base on the Fig1 and Fig 2, compression causes inflammatory cells infiltration into injury site; however, MG132 inhibits this response, what is the mechanism? Authors should discuss it.

3. The induction of Atrogin-1 was only evidenced by immunostaining (Fig1 and Fig 5). To support this finding, it would be better to add convincing data either by western blot or real-time qPCR. Could authors examine Atrogin1 mRNA expression at early time point? For example, at 6 h after second time injury.

Minor points:

1. Which skeletal muscle was used in this study, EDL, Soleus or TA? Because the fiber type of these muscles is deferent, the response to injury may be different.

2. Fig2, low right panel, looks like there are a lot of “central nuclei” in uninjured myofibers. It would better to change to new one.

3. Please change “ubiquitin proteasome pathway” to “ubiquitin proteasome system”
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.