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Peer Review

Review of: "Endurance Training Restores Ageing-Impaired Lysosomal Biogenesis Factors in Rest and Response to Acute Exercise in Rat Skeletal Muscle"

Elena Monti[1]

1. Stanford University, United States

Rajabi and colleagues investigate the effects of aging, long-term, and acute (1-bout) aerobic exercise on rats' soleus muscle fibers' diameter/number, "activity" of the lysosomal biogenesis-promoting protein TFE3, mRNA expression of mTORC1, and calcineurin. While conceptually the idea behind the work is interesting, there are several criticisms faced by this work, highlighted below:

Major:

1. The authors use the words "aging" and "sarcopenia" interchangeably. Sarcopenia is not equal to "aging." Sarcopenia is a clinical syndrome, diagnosed in humans following strict guidelines that entail measuring muscle mass and muscle strength/function. In rodents, a recent paper proposed a method to "assess" sarcopenia. Given that no functional measure was performed in this paper, the authors cannot talk about "sarcopenia." They can only speak to the "age-related muscle atrophy." This is a conceptually very important issue that should be addressed before the paper gets published.
2. The authors use the soleus muscle for their analyses but don't provide any justification for it. The soleus is a slow-twitch muscle, which has been consistently shown to be the least affected by aging. Some of the aging-related changes observed by the authors may be either blunted or completely different from those in other major muscles (fast or mixed), which comprise much bigger proportions of the lower limbs' muscle mass and function (such as TA, GA). The authors should provide a strong rationale for not performing any experiments with these muscles.

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3. mRNA of mTORC1 and Calcineurin: why did the authors only measure mRNA? A lot of the function of these proteins may not correspond to their mRNA production - so basing all the conclusions of the paper on 2 genes' expression seems a bit limiting and should be acknowledged by the authors.
4. Graphing: the 5 conditions should be graphed on the same graph chart, which would make the comparison much easier and more reader-friendly.
5. Conclusions/discussion of the data: the authors employ very strong statements that are not supported by the data provided in the paper. Aging is an extremely complex phenomenon, and claiming that one gene changing in one muscle is responsible for explaining muscle atrophy in aging seems to me an overstatement. In particular, the authors conclude: "It could be assumed that the decrease in TFE3 activity (Figure **3**) by aging leads to lysosome dysfunction and subsequently causes the cellular processes related to this organelle to function inefficiently, all of which explain the developed sarcopenia in the aged sedentary group (Figure **2**)". I think the maximum that could be derived from the present data is that the decreased TFE3 activity, inferred from western blot analyses, suggests a contribution of this protein to the lysosome dysfunction observed in aging. Lysosome dysfunction has been suggested to play a role in aging-related muscle atrophy (cite relevant literature here).

Minor:

1. Abstract: please explain the abbreviation "BS" - since it's not a statistical approach most readers are familiar with, it's essential to spell the abbreviation and provide the reader with a range of what is considered "a big effect size," "small," "trivial," "anecdotal," etc.
2. The introduction is long and filled with many details about pathways that can be shortened.
3. The names of the 5 groups are a bit confusing; it is worth trying to define clearer names.
4. Deducing that Ca2+ is not dysregulated because the mRNA of one gene related to its handling (calcineurin) is not changing seems an overstatement to me.
5. The explanation about why the authors observed a strong hyperplasia following endurance training is not clear - in particular, the soleus has a small pennation angle, so it seems unlikely to me that the fiber length on such a small muscle and pennation angle would explain the "artifact" of the strong increase in fiber number observed in the soleus?

Declarations

Potential competing interests: No potential competing interests to declare.