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Journal Club

Aging of skeletal muscle - myofiber reinnervation as a protective determinant of age-related loss of physical function

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Title:

Aging of human skeletal muscle - myofiber reinnervation as a protective determinant of age-related loss of physical function

During the last decades mayor strides have been made in our knowledge of the regulation of human skeletal muscle mass with aging (Wilkinson *et al.*, 2018), while age-induced changes in human myocellular neuromotor plasticity remain less well-documented. Overall considered, however, it is well-described that human aging results in neuromotor degradation manifested as a loss of spinal motoneurons and a reduced number of functioning motor units (Manini *et al.*, 2013; Hepple & Rice, 2016), which serve as a problem, as well preserved neuromotor function may be an essential prerequisite for the maintenance of neuromuscular and locomotor capacity (Manini *et al.*, 2013). Notably, cross-sectional data obtained in elderly human individuals suggest that motor unit number may be better preserved in active highly functioning compared to sedentary lower functioning

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individuals (Hepple & Rice, 2016). However, currently it remains unknown whether there exists a link between the capacity of physical function and myofiber innervation/denervation in aging human adults. Consequently, gaining increased insight into factors regulating neuromotor integrity at the myocellular level appears very important, with an overall aim of reducing the degree of dynapenia (i.e. age-related loss of muscle function), in turn serving to preserve physical function and quality of life at old age.

In a recent issue of *The Journal of Physiology*, Sonjak and colleagues (2019) investigated skeletal muscle fibre denervation and innervation related to aging and level of physical function. Muscle biopsies from m. vastus lateralis were collected from 17 frail elderly sedentary women (77.9 ± 1.5 yrs.) and 12 sedentary young women (24.0 ± 1.0 yrs.) to investigate the effect of aging, while tissue samples from 7 highly active female world-class master athletes (80.9 ± 2.2 yrs.) were used to differentiate between elderly individuals with low (frail elderly) and high levels (master athletes) of physical function. Through extensive immuno-histochemical analyses, the authors gathered data on myofiber cross-sectional area (CSA), myofiber type distribution (I, IIa and IIx) and myofiber grouping as well as indicators of myofiber denervation (NCAM positive myofibers) and long-term neurogenic atrophy (pyknotic nuclei, identified as deeply basophilic nuclear clumps). In addition, gene expression analyses were performed to quantify mRNA transcripts of targets related to myocellular denervation (AChRα, AChR*γ*, AChR*ε*, MuSK, TGF-*β*2, FGFBP-1 and TBP).

The authors hypothesized that the frail elderly inactive women would show clear signs of myocellular denervation compared to the young inactive women, whereas aging master athletes were expected to demonstrate less myocellular signs of denervation compared to their age-matched sedentary counterparts.

Overall the frail elderly women performed worse in tests of physical function (chair stands, 4-meter gait speed and timed up-and-go) compared to age-matched female master athletes and young inactive women, thus demonstrating a marked age-related loss of physical function in the frail/prefrail elderly women and the prevention hereof in master athletes.

At the myocellular level, both groups of aging women showed a morphological pattern typical of aging skeletal muscle, i.e. smaller myofiber CSA and more atrophic myofibers (≤ 1450 μm^2) compared to their young counterparts. While surprisingly few clear differences in these parameters were noted between master athletes and frail elderly women, a higher type IIa/I myofiber CSA ratio was observed in master athletes compared to their age-matched counterparts, suggesting type II myofiber area to be preserved in older adults with preserved high ability of physical function. Myofiber type grouping classically recognized as a myocellular sign of recurrent denervation/innervation cycles was evident in both groups of elderly individuals compared to young, but overall more pronounced in master athletes compared to frail age-matched women, suggesting myofiber reinnervation to be more pronounced in the group of master athletes. NCAM positive myofibers suggestive of fibre denervation did not differ between groups, whereas pyknotic nuclei content indicating long-term denervation-induced myofiber atrophy was specifically elevated in frail elderly individuals. The lack of clear differences in the investigated mRNA transcripts (AChRα, AChRγ, AChRε, MuSK, TGF-β2, and TBP) might reflect a lack of well-documented age-related biomarkers of non-acute myocellular neural degeneration/regeneration. Interestingly, however, the gene expression of fibroblast-growth factor-binding protein-1 (FGFBP-1), a cytokine associated with myofiber re-innervation, was reported to be upregulated in elderly master athletes compared to frail elderly and young adults.

The data presented by Sonjak and colleagues overall suggest that although the recruited elderly participants generally appeared to be similarly affected by denervation at the myocellular level, physically active well-functioning individuals (master athletes) may possess a superior capacity for reinnervation (i.e. less pyknotic nuclei, more widespread myofiber type grouping, higher FGFBP-1 mRNA) compared to their age-matched frail/prefrail individuals. Thus, the greater level of physical function and less pronounced atrophy (i.e. retained type IIa myofiber area) in the master athletes may be related to the apparent better myocellular denervation/reinnervation, which might provide protection against non-reversible peripheral neuromotor denervation. Important also, several additional factors including age- and exercise-mediated myocellular post-translational and transcriptional modulators of myocellular protein synthesis and degradation may play a role as well.

Contrary to previous reports of selective type II loss and atrophy in aging skeletal muscle, Sonjak et al. observed similar fibre type distribution and CSA for all fibre types across their two groups of elderly participants, although a higher ratio of type IIa/I myofiber area was noted in the group of master athletes. In parallel with an apparent higher fat free mass to body weight ratio (FFM/BW) and elevated appendicular muscle mass index (AMMI) in master athletes (FFM/BW: 0.76) compared to young and frail elderly women (FFM/BW: 0.61-0.65) (Sonjak *et al.*, 2019), these data indicate that the master athletes may maintain muscle mass and functional capacity partly as a result of myofiber survival (cf. higher re-innervation) and less atrophy of type IIa myofibers. Interestingly, Sonjak and co-workers (2019) were able to establish a link between the myocellular observations and the physical capacity of the involved women, by demonstrating moderate-to-strong associations between physical functional performance (TUG, gait speed) and FGFBP-1 mRNA expression

(r=-0.501, r=0.719). Although mRNA transcript levels are only suggestive of translation-induced increases in given target proteins, the observed relationships emphasize the potential of FGFBP-1 as an important adaptive molecular regulator of neuromotor remodelling with increasing age.

At the whole-body scale, the higher FFM/BW ratio and AMMI, as well as the greater ratio of type IIa/I myofiber CSA observed in the master athletes are highly interesting from a functional perspective. These data indicate a basis for a higher relative (maximal strength per kg body mass) and enhanced rapid force capacity (maximal muscle power, rate of force development), which at least partly would explain the superior locomotor capacity observed in the octogenarian master athletes (Sonjak et al. 2019). We speculate that the apparent better preservation of the type IIa/I myofiber CSA ratio may be a result of the master athletes' weekly engagement in physical training comprising intensive/maximal muscle actions, due to a higher degree of high threshold motor unit recruitment and in turn favourable fibre-type II specific post-translational regulation of myocellular protein synthesis/degradation.

Importantly, the study by Sonjak et al. (2019) along with previous reports (Wilkinson *et al.*, 2018) suggest that myofiber innervation can be preserved at least partly in well-functioning master athletes. On the other hand, it should be acknowledged that the negative effect of aging on neuromuscular function remains to dominate, as signs of myofiber denervation and decline in motor unit numbers are present even in high-level master athletes (Hepple & Rice, 2016; Sonjak *et al.*, 2019). Moreover, the specific mechanisms governing degradation of the neuromuscular junction and the potential preventive role of physical exercise have not yet been fully established (Nishimune *et al.*, 2014) and such knowledge appears highly relevant for reducing the negative consequences of dynapenia and sarcopenia.

Furthermore, it must be underlined that a large part of the current literature investigating the effect of human aging on myocellular and neuromuscular properties is based on observational study designs. One explanation of the data of Sonjak et al. (2019) is that the potential protective effect of the neuromuscular junction in high-functioning older adults may be related to these individuals' high weekly engagement in physical training. However, additional factors including genetics (i.e. 'physical survival of the fittest'), macro/micro nutritional intake and exposure/absence to various stressors may also play a significant role, and consequently, there remains a need to investigate the relative importance of these factors using longitudinal study designs.

In conclusion, Sonjak *et al.* (2019) have offered valuable insight into the role of aging and the capacity for physical function on myocellular denervation/innervation in human skeletal muscle. Moreover, their data suggest a potentially important role of FGFBP-1 as a factor protecting peripheral neuromuscular function and suggest that further investigations of FGFBP-1 and related molecular candidates with the potential to reduce neuromotor denervation and/or improve re-innervation should be conducted.

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Competing interests

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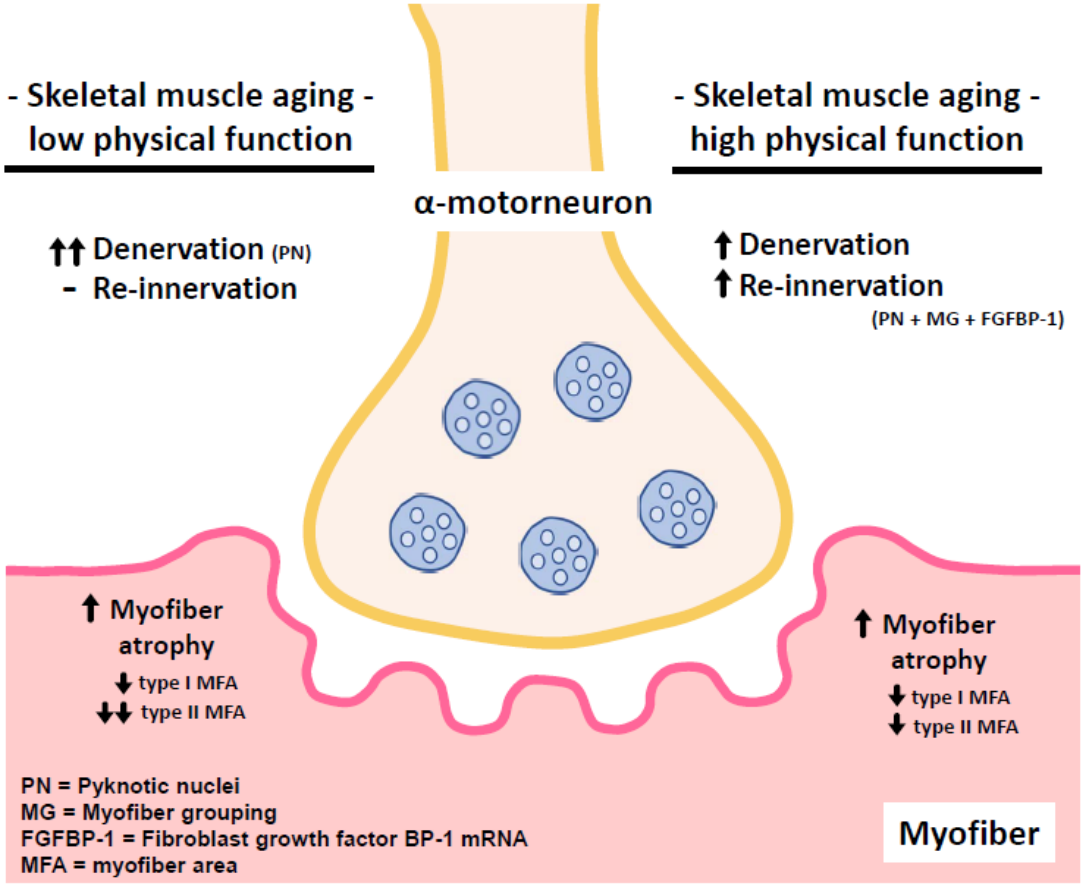

Fig. 1 – Summary representation of the key findings reported by Sonjak *et al.* (2019)