genes

Opinion

Secreted Protein Acidic and Rich in Cysteine as an Exercise-Induced Gene: Towards Novel Molecular Therapies for Immobilization-Related Muscle Atrophy in Elderly Patients

Abdelaziz Ghanemi [1,2], Mayumi Yoshioka [2] and Jonny St-Amand [1,2,*]

[1] Department of Molecular Medicine, Faculty of Medicine, Laval University, Quebec, QC G1V 0A6, Canada; abdelaziz.ghanemi@crchudequebec.ulaval.ca
[2] Functional Genomics Laboratory, Endocrinology and Nephrology Axis, CHU de Québec-Université Laval Research Center, Quebec, QC G1V 4G2, Canada; mayumi.yoshioka@crchudequebec.ulaval.ca
* Correspondence: jonny.st-amand@crchudequebec.ulaval.ca; Tel.: +1-(418)-654-2296

Abstract: Long periods of immobilization, among other etiologies, would result is muscle atrophy. Exercise is the best approach to reverse this atrophy. However, the limited or the non-ability to perform the required physical activity for such patients and the limited pharmacological options make developing novel therapeutic approaches a necessity. Within this context, secreted protein acidic and rich in cysteine (*SPARC*) has been characterized as an exercise-induced gene. Whereas the knock-out of this gene leads to a phenotype that mimics number of the ageing-induced and sarcopenia-related changes including muscle atrophy, overexpressing SPARC in mice or adding it to muscular cell culture produces similar effects as exercise including enhanced muscle mass, strength and metabolism. Therefore, this piece of writing aims to provide evidence supporting the potential use of *SPARC*/SPARC as a molecular therapy for muscle atrophy in the context of immobilization especially for elderly patients.

Keywords: SPARC; muscle atrophy; immobilization; ageing

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The increased number of hospitalized individuals lead to the development of various fields aiming to improve and optimize the healthcare within hospitals [1–5]. Patients admitted to hospitals have, beside treating the reasons of their admission, also to face other challenges such as possible nosocomial infections [6], bedsores [7,8] and musculoskeletal atrophy. Furthermore, post-hospitalization recovery of the mobility remains a challenge due to the immobilization (bed rest)-induced muscle atrophy. Such bed resting (immobilization) does not only lead to muscle atrophy, but also reduces both muscle strength as well as key regulators of mitochondrial biogenesis/remodeling and activity; it also alters genes expression and leads to metabolic decline including insulin resistance [9–12]. Bed resting also impacts bones and reduces their mineral density [13]. Cardiovascular complications and cardiac atrophy have also been reported following bed rest [14,15]. The consequences on the locomotor system impact the mass, the strength and the metabolism. Thus, patients, especially elderly people, have a difficulty to return to normal life after a certain period of bed rest caused by hospitalization or immobilization mainly because of muscle atrophy. In addition, ageing reduces both myogenesis [16] and skeletal muscle stem cells regenerative capacity [17]. Ageing also has specific genes expression signature [18,19] and shares numerous patterns with obesity such as epigenetic changes, inflammation and metabolic impairments [20]. These elements show the seriousness of the clinical outcomes of combining immobilization and ageing. The increased hospitalization rate represents one of the features of the current ongoing COVID-19 pandemic especially among the elderly patients who are already vulnerable. Intensive care unit patients (also increased with COVID-19) have more muscle loss especially with long hospitalization periods [21]. Furthermore, the

elderly population has a limited physical activity within their lifestyle. Indeed, many of them spend long periods of immobilization due to some diseases or accidents requiring bed rest or hospitalizations. Ageing is another factor which, either independently or combined to immobilization, significantly contributes to the muscle and bone loss. Sarcopenia is an age-related decline in muscles mass and strength [22]. Age-related comorbidities such as chronic heart failure [23] and chronic obstructive pulmonary diseases [24] accelerate sarcopenia [25]. Clinically, sarcopenia epidemiological profile is increasing and enhances mortality [26] especially with the increasing number of elderly people who develop a poor lifestyle (reduced activity, unhealthy diet, etc.).

Muscle atrophy includes protein degradation, mitochondrial dysregulation and inflammation among its key biological features [27–29]. Biological markers suggested for sarcopenia [25,30] would represent significant diagnosis tools for muscle atrophy as well. Both muscle atrophy and bone loss (key tissues of the locomotor system) can be reversed by physical activity [31,32]. Exercise is known for its benefits in respect to muscle function and metabolism including as sarcopenia treatment [33–36]. The effects of exercise, including pre-training, on muscle atrophy and recovery has also been highlighted [37–39]. Indeed, muscle atrophy could be prevented by exercise [40], including a pretraining as suggested by electrical stimulation studies [41,42]. Exercise represents the main treatment approach and electrical stimulation and "cytoprotective" dietary interventions are also used against muscle atrophy [43,44]. Other therapeutic options represent potential approaches such as gene therapy and epigenetic drugs [45–47]. Pharmacological therapies, however, remain limited to some growth factors among which we cite insulin, ghrelin/IGF-1 analogues, testosterone and growth hormone [45,47]. The limitation in therapeutic options is in part due to the limited knowledge on the underlying molecular pathways and physiopathological processes.

To reveal such mechanism and deepen our understating of these immobilization-induced atrophy, animal models of immobilization-induced muscle atrophy (rats, mice, rabbit) [26,48–50] have been developed. Mice remain the best choice due to their affordable cost, genetic manipulation possibilities and short lifespan; in addition to the ageing process similarities, they share with humans [51–55]. Cast immobilization is the most used because it mimics prolonged immobilization in terms of muscle atrophy [56,57]. The immobilization also induces bone loss in both growing and adult mice [58]. Thus, such immobilization alters the two main parts of the locomotor system, muscles and bones. Bone and muscle mass are reduced with immobilization in which various biological changes such as inflammation, increased muscle RING finger 1 and mRNA contents of polyubiquitin and the ubiquitin ligases muscle atrophy F-box along with reduced rapamycin complex 1 signaling and reducing the myofiber size were reported [49,57,59–61]. Immobilization-induced muscle loss depends on factors such as age and sex. For instance, unilateral hindlimb immobilization in rats of different ages leads to a muscle mass loss inversely proportional to age [61]. The difference between male and female in muscle atrophy depends on whether it is aging-induced or inflammation-based [21]. In addition, hindlimb unloading induced more muscle loss in female rats than in males [62]. This could indicate that females would be more impacted by bed resting. Such age and sex differences suggest the need to adapt the treatment (nature and intensity) based on these two factors as well.

Functional genomics and genes expression patterns can lead to the identification of potential novel therapies for the atrophy resulting from the immobilization including during bed rest. Herein, we focus on the gene secreted protein acidic and rich in cysteine (*SPARC/Sparc*). SPARC is a non-collagenous protein that is abundant in mineralized tissues [63]. It is expressed in various situations in which tissues renewal and cell remodeling occur (exercise, regeneration, obesity, cancer, inflammation, etc.) [64]. It is also associated with cell turnover, remodeling and tissue repair [65]. Based on this expression pattern, we and others previously suggested using SPARC as a molecular physiological and pathological biomarker [64,66]. SPARC, also known as osteonectin or basement membrane-40 (BM-40) [67], has a calcium and collagen binding property [68]. It is a secreted protein that comprises three distinct structural domains [69] and its biosynthesis is regulated by various

growth factors and cytokines [70–72]. As exemplified below, SPARC plays important roles in muscles biology. This gene was initially characterized as induced by exercise [73,74], potentially mediating exercise-induced muscle phenotype changes [75] and as up-regulated during skeletal muscle regeneration [76]. *Sparc* overexpression mimics exercise, including enhancing muscle mass, strength, metabolism as well as ameliorating glycemia [77]. SPARC is expressed both in fetal and neonatal muscle and following muscle damage as well [78]. Adding SPARC to muscle C2C12 (myoblast cell) culture increased myoblasts differentiation in addition to myogenic and mitochondrial proteins expression [79]. Moreover, SPARC plays roles in muscle stiffness maintenance [80], muscle morphological change [81] and promotes muscle progenitor cells myogenic differentiation in vitro [80]. On the other hand, *Sparc* expression [82] and muscle mass [83] decline with ageing. Such age-related decline in SPARC expression would explain why SPARC downregulation using siRNA reduced myogenesis in young rats skeletal muscle progenitor cells (SMPCs) but had little effect in SMPCs from old rats [84] since old rats would already have low SPARC levels. A resistance to SPARC with age is suggested by the fact that exogenous SPARC improved differentiation in young SMPCs, but exogenous SPARC did not affect old SMPCs [84]. This indicate that SPARC would be combined to other therapies which require further investigation especially with the other effects SPARC has on muscles as we detail below.

Furthermore, *Sparc* KO leads to a phenotype that mimics number of the ageing-induced and sarcopenia-related changes including muscle atrophy with a decrease in muscle mass, strength and metabolism [77]. Small interfering RNA (siRNA)-mediated transient suppression of SPARC leads to muscle atrophy [59] and myofibers atrophic changes [80]. Anti-SPARC antibodies reduced C2C12 differentiation and decreased myogenin expression [79,81]. These suggest that the muscle atrophy could have the decline of SPARC expression as one of its key underlying pathways. Thus, SPARC decline would be implicated within both sarcopenia as well as ageing process that impacts muscles as well.

Such similarities between SPARC impacts on muscles (enhanced functional, structural and metabolic properties) and the exercise-induced muscle changes hypothesize that exercise effects are mediated, at least in part, by SPARC. Therefore, increasing *SPARC* expression (gene therapy) or administering SPARC protein would possibly lead to exercise-like effects similarly to those seen in mice overexpressing *Sparc* [77]. This would result in increasing muscles mass, strength and metabolism and counteract the atrophy resulting from hospitalization (immobilization), ageing, or more importantly hospitalization of elderly patients (combines ageing and immobilization). Indeed, hospitalized patients have long periods of immobilization during which they are not able to perform physical activity. Similarly, elderly individuals usually have a limited ability to perform high amounts of exercise. Therefore, administering SPARC or inducing its expression could be an option to overcome these struggles by generating some of the exercise-induced effects without in fact performing exercise. As muscle atrophy is among the most important health problems for these patients (immobilized and/or aged), SPARC comes as a potential therapy as its specific impacts on muscles are well documents. Importantly, the literature also shows the divers beneficial properties and implications of SPARC including metabolic properties [85,86], anticancer [87], anti-inflammatory [88], collagen regulation in the heart [89], tissue repair and regeneration [90,91]. These SPARC properties allowed us to classify it as a regeneration factor [90] that would create a biological environment with optimum conditions for regeneration, muscle differentiation and growth properties.

The importance of SPARC in bones increases the potential of SPARC in managing the bed rest-induced atrophy since immobilization also leads to bone loss. Indeed, SPARC is important for bone formation, remodeling and regeneration [90]. *Sparc* KO mice develop osteopenia [92], decreased bone formation [93]. SPARC deficiency also affects bone marrow stromal function [94]. In addition, SPARC also plays roles in bone remodeling [95] and osteoblast maturation [67]. It also regulates hydroxyapatite crystals formation and growth [96] and influence osteogenic differentiation [97]. Furthermore, the implication of SPARC in other locomotor system constituents (such as ligaments [98,99] and ten-

dons [100,101]) would make that treating with SPARC would not only improve muscle phenotype but could also have positive effects on the whole locomotion system. Therefore, SPARC administration might contribute to the maintenance of the musculoskeletal system responsible for the individual mobility during hospitalization and recovery periods. It is worth highlighting that increased SPARC expression has been reported in negative biological status such as metabolic disorders [102], rheumatoid arthritis [70], cancer [103], coronary artery disease [104] and intracranial aneurysms [105]. We have hypothesized that such expression would not indicate the involvement of SPARC in the pathogenesis or prognosis but rather represents an attempt to counteract the effects generated by such pathologies or disorders via the beneficial SPARC-mediated effects. Examples of SPARC counteracting inflammation [88] and cancer [87,106] would be two illustrations of such "regulatory feedback".

Such approach can also be extended to those chronically bedridden, with physical disability or even space missions (microgravity environment) [107] as summarized in Figure 1. Evidence suggests that *Sparc* decline contributes to the muscle atrophy, ageing and the resulting phenotypes, whereas its overexpression induced by exercise would be a mechanism via which exercise corrects and improves muscle atrophy and ageing. Therefore, we suggested measuring exercise-induced SPARC/*SPARC*/*Sparc* expression as a molecular tool to optimize exercise therapy towards a personalized medicine [108] and also using SPARC as a potential "exercise substitute" [109]. Such measure could be applied to immobilized patients during a potential pre-training session aiming to counteract muscle atrophy. We believe that further animal and clinical studies could lead to a new generation of molecular therapies for muscle atrophy based on *SPARC* and permit the overcoming of this challenging atrophy resulting from hospitalization, immobility and ageing. The best option, when available, is to rather focus on exercise-induced SPARC as a possible treatment and we emphasize that further studies are needed to further map the mechanistic links between exercise, the exercise-induced myokines (including SPARC) and the exercise induced effects.

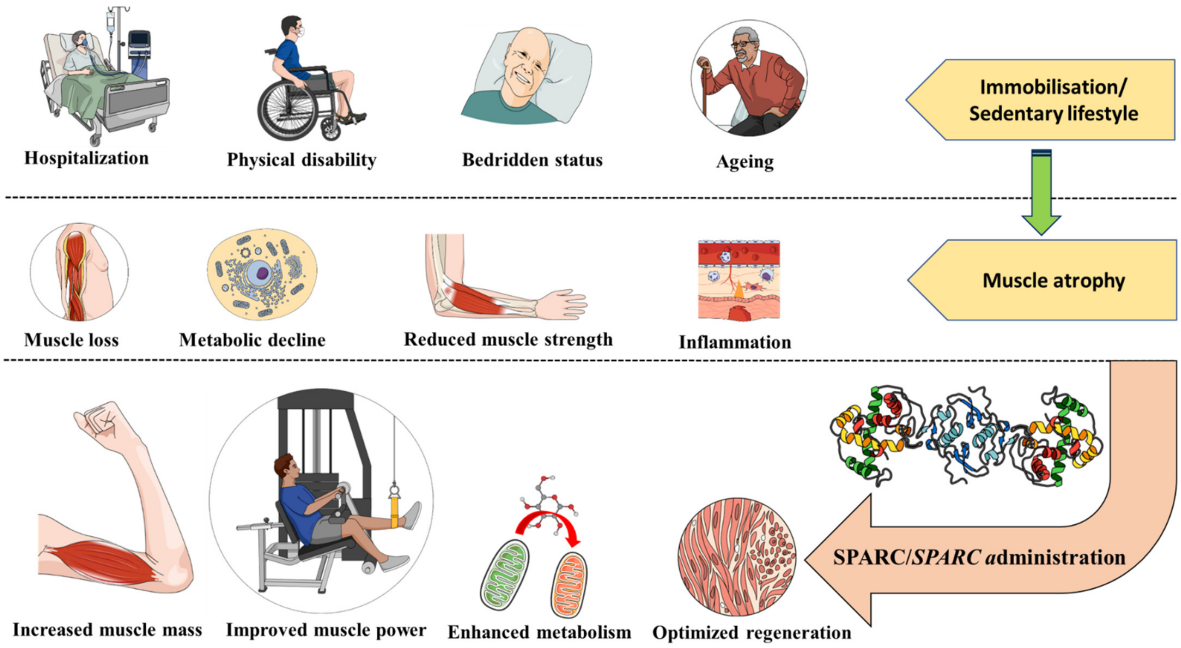

Figure 1. Secreted Protein Acidic and Rich in Cysteine (SPARC/*SPARC*) as a muscle atrophy therapy. Situations such as hospitalization, physical disability or being bedridden represent an immobilization that might lead to muscle atrophy. Ageing (usually accompanied with a sedentary lifestyle) is another risk factor for the muscle atrophy. SPARC properties of enhancing muscles mass, strength and metabolism are towards counteracting muscle atrophy and highlight SPARC/*SPARC* (protein administration or gene therapy) as a molecular therapy for muscle atrophy.

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