Muscle wasting and aging: Experimental models, fatty infiltrations, and prevention

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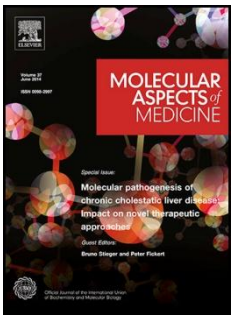

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Title: Muscle wasting and aging: experimental models, fatty infiltrations, and prevention

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Abstract

Identification of cost-effective interventions to maintain muscle mass, muscle strength, and physical performance during muscle wasting and aging is an important public health challenge. It requires understanding of the cellular and molecular mechanisms involved. Muscle-deconditioning processes have been deciphered by means of several experimental models, bringing together the opportunities to devise comprehensive analysis of muscle wasting. Studies have increasingly recognized the importance of fatty infiltrations or intermuscular adipose tissue for the age-mediated loss of skeletal-muscle function and emphasized that this new important factor is closely linked to inactivity. The present review aims to address three main points. We first mainly focus on available experimental models involving cell, animal, or human experiments on muscle wasting. We next point out the role of intermuscular adipose tissue in muscle wasting and aging and try to highlight new findings concerning aging and muscle-resident mesenchymal stem cells called fibro/adipogenic progenitors by linking some cellular players implicated in both FAP fate modulation and advancing age. In the last part, we review the main data on the efficiency and molecular and cellular mechanisms by which exercise, replacement hormone therapies, and β-hydroxy-β-

methylbutyrate prevent muscle wasting and sarcopenia. Finally, we will discuss a potential therapeutic target of sarcopenia: glucose 6-phosphate dehydrogenase.

Keywords: Muscle disuse, Sarcopenia, Microgravity, Intermuscular adipose tissue (IMAT), Exercise, Beta-hydroxy-beta-methylbutyrate (HMB)

Vitae:

Thomas Brioche is currently a postdoctoral researcher on the "muscle remodeling and signaling" team in the UMR 866 DMEM at Montpellier University, with a grant from the French Space Agency (CNES). After receiving his Ph.D. in the laboratories of Prof. José Viña (Spain) and Prof. Arlette Delamarche (France), he has been a Temporary Lecturer and Research Assistant in the Faculty of Sports Sciences (UFR STAPS, Montpellier). His research is focused mainly on muscle mass regulation under physiological (exercise, nutrition, and aging), pathological, or microgravity conditions, with special interest in the development of strategies against muscle deconditioning and studying the involvement of oxidative stress.

Allan F. Pagano is a Ph.D. student at the University of Montpellier (France) on the "muscle remodeling and signaling" team (INRA, UMR 866 DMEM). He received a thesis grant from the Graduate School of Human Movement Sciences (SMH). First, his work was focused, during his Master's program, on autophagy and protein turnover signaling in skeletal muscle during exercise. He is currently studying the development and accumulation of fatty infiltrations in skeletal muscle, especially during regeneration.

Guillaume Py, Ph.D., is a cosupervisor of the "muscle remodeling and signaling" team in the UMR 866 DMEM at Montpellier University. His work is focused on muscle mass regulation under physiological (exercise and nutrition) or pathological conditions, with special interest in muscle regeneration.

Angèle Chopard is a Professor at the University of Montpellier. She teaches physiology and anatomy in the Faculty of Sports Sciences (UFR STAPS, Montpellier). She is a scientific member of the "muscle remodeling and signaling" team in the UMR INRA 866 DMEM. She is a principal investigator in space and microgravity experiments conducted under the aegis of

the European and French space agencies (ESA and CNES). Her research is focused mainly on the study and prevention of skeletal muscle deconditioning after chronic disuse and in relation to the effects of spaceflight and its bed rest analog.

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1. Introduction

Skeletal muscle is the most abundant tissue in the human body representing ~40% of the body weight and ~30% of the basal energy expenditure (Reid and Fielding, 2012). Skeletal muscle plays a central role in locomotion enabling a person to perform activities of daily living, posture maintenance, and balance (Reid and Fielding, 2012). Moreover, skeletal muscle performs a major function in thermogenesis processes, energy supply (this tissue contains the most important glucose and amino acids stocks), and insulin resistance protection (Brook et al., 2015). In order to ensure these essential functions, skeletal muscle must have sufficient mass and quality.

Skeletal muscle plasticity expresses itself at different levels. Substantial muscle adaptations are first observed during childhood and adolescent growth with an increase in muscle mass and strength. The opposite trend appears by the age of 30 and older: a natural decrease in muscle mass defined as sarcopenia (Giresi et al., 2005; Thomas, 2007). Skeletal muscle plasticity can also translate into muscle tissue adaptations to environmental constraints. Thus, an increase in stimulation, exercise, or nutrition can cause a positive protein balance and involve muscle hypertrophy and reinforcement (Cureton et al., 1988; Sartorelli and Fulco, 2004a; Staron et al., 1990). Conversely, a decrease in mechanical constraints will lead to muscle deconditioning and atrophy (Bonaldo and Sandri, 2013; Glass, 2005; Jackman and Kandarian, 2004; Kandarian and Stevenson, 2002; Pagano et al., 2015; Ventadour and Attaix, 2006). Skeletal muscle deconditioning can be defined as primary deconditioning, in case of direct consequences of unfavorable environmental conditions, such as chronic disuse, immobilization, bed rest, a microgravity environment, sedentary lifestyle, and aging, or as secondary deconditioning, in case of indirect consequences of pathological changes like cancer (cachexia), diabetes, or chronic obstructive pulmonary disease (COPD).

Muscle deconditioning occurring with aging is characterized by a decrease in muscle mass, in muscle strength, and in physical performance and is considered a geriatric syndrome called sarcopenia (Cruz-Jentoft et al., 2010; Fielding et al., 2011; Morley et al., 2011; Muscaritoli et al., 2010). Multiple factors contribute to sarcopenia, including diet, chronic diseases, physical inactivity, and the aging process itself (Derbre et al., 2014; Sayer et al., 2008; Thompson, 2007). Due to social, technological, and medical progress, life

expectancy has been increasing since the 19th century in our modern western societies, leading to global aging of the world population. Currently, it is projected that the number of elderly people will double worldwide from 11% of the population to 22% by 2050 (UN, 2007). Inevitably, due to this aging population, prevalence of sarcopenia is growing, and it is currently estimated that one-quarter to one-half of men and women of age 65 and older are likely sarcopenic (Janssen et al., 2004). The increasing prevalence of sarcopenia is considered catastrophic for the public health costs, and, for example, the total cost of sarcopenia to the American healthcare system is approximately $18.4 billion (Janssen et al., 2004). These healthcare costs are linked to general deterioration of the physical condition resulting in an increased risk of falls and fractures, a progressive inability to perform basic activities of daily living, loss of independence for the elderly, and ultimately, death (Cruz-Jentoft, 2012; Delmonico et al., 2007; Goodpaster et al., 2006). Identification of cost-effective interventions to maintain muscle mass, muscle strength, and physical performance in the elderly is a major public health challenge. It requires understanding the cellular, molecular, and systemic mechanisms as well as the underlying pathways involved in sarcopenia onset and development.

To identify these mechanisms, the gold standard of research is comparison of healthy young people with old healthy people. Such a project is hard to undertake due to the high cost, the difficulty with finding healthy old people, and the invasive method used (e.g., muscle biopsies). To overcome these problems, muscle deconditioning processes have been deciphered by means of several experimental models, bringing together the opportunities to devise comprehensive analysis of muscle wasting.

Abundant literature already describes a multitude of muscle adaptations affecting the expression of metabolic, structural, and contractile proteins during muscle deconditioning (Bonaldo and Sandri, 2013; Brioche and Lemoine-Morel, 2016; Chopard et al., 2005; Chopard et al., 2001; Fitts et al., 2000; Schiaffino et al., 2007; Stein et al., 2002), and these data will be presented in the this review only briefly. To date, our understanding of the effects of hypokinesia and hypodynamia on skeletal muscle has mainly been derived from studies focused on elucidating the specific contributions of transcriptional mechanisms, intracellular signaling molecules, and the extent of crosstalk among these various pathways during muscle wasting. The present review is aimed at addressing three main points. First,

we mainly focus on available experimental models involving cell, animal, or human experiments to study muscle wasting. The second part points out the role of fatty infiltrations, also called intermuscular adipose tissue (IMAT), in muscle wasting and aging, keeping in mind that the loss of strength and power mostly exceeds the loss of muscle mass during muscle deconditioning (Berg et al., 1997a; di Prampero and Narici, 2003). The third part presents the main data on the efficiency and molecular and cellular mechanisms by which exercise, replacement hormone therapies, and β-hydroxy-β-methylbutyrate (HMB) prevent muscle wasting and sarcopenia.

2. Translational approaches and experimental models for studies on skeletal muscle wasting and aging

In the past decades, the scientific community validated several selected cell, animal, and human experimental models for studying and deciphering the processes of muscle wasting. Various ground-based models and spaceflight studies contribute at this time to the research into muscle weakness and appear to contribute substantially to studies on the aging process **(Figure 1)**. Musculoskeletal research in the spaceflight context contributes to the research on age-related osteoporosis and sarcopenia (Fitts et al., 2000; Trappe, 2009). Although aging and spaceflight may involve biological changes in the structure and function via different cellular and molecular pathways, they share the common feature of adaptation to changing levels of strain (Lecker et al., 2004a). Thus, the studies on adaptation of the musculoskeletal system, from microgravity to 1 × *g* conditions, mimic the age-related muscle atrophy. Furthermore, the types of countermeasures required to maintain muscle function in altered-gravity environments must take into account preservation of muscle strength, endurance, and postural balance. Similar approaches are relevant to the prevention of falls and fractures in elderly subjects. Moreover, the greatest difficulty with studying the aging process is the long time span, and microgravity experiments appear to involve physiological events mimicking aging-associated changes that take a lifetime to develop (Biolo et al., 2003). Indeed, muscle atrophy and weakness, reduced capacity for exercise, unbalanced immune responses, insulin resistance, and impaired oxidative metabolism contribute to the effects of both aging and space travel.

2.1. Real microgravity experiments

These experiments on skeletal muscle include mainly studies on rodents and humans. In the past decades, life science Spacelab and Spacehab programs included experiments involving human astronauts as well as animals and insects taken along on several missions (Fitts et al., 2010; Miu et al., 1990; Roffino et al., 1998). On-board experiments on rodents have also been conducted on the series of life science satellites called BION, and more recently BION-M. For this program, spacecraft are launched on a Soyuz rocket from the Plesetsk Cosmodrome in northern Russia (Ogneva et al., 2015; Roffino et al., 2006; Ulanova et al., 2015).

The actual orbital International Space Station flies 400 km above the ground at the speed of 28,800 km/h. It takes only 90 min for the weightless laboratory to make a complete circle around the Earth. Astronauts working and living aboard the Station experience 16 sunrises and sunsets each day. The International Space Station has provided the opportunity to study long-term microgravity. A hallmark of spaceflight is considerable variability in the extent of muscle atrophy and functional loss among crewmembers (Fitts et al., 2000; Fitts et al., 2010; Trappe, 2009). The Mice Drawer System program, actually gives an opportunity to accommodate mice aboard the International Space Station, and has been aimed, for example, at research on the consequences of long-term (91-day) exposure to microgravity in mice (Cancedda et al., 2012; Sandona et al., 2012).

2.2. Human ground-based models of muscle disuse

Experimental ground-based models of induced muscle atrophy and weakness contribute for the most part to scientific studies related to muscle disuse and aging. The goal of these types of studies is also to identify appropriate countermeasures for men and women to prevent or suppress disuse-induced muscle atrophy such as that encountered during short- and long-term microgravity and in the clinic (Blottner et al., 2006; Chopard et al., 2005; Chopard et al., 2009a; Rudnick et al., 2004). Studies conducted on human healthy subjects, are mainly focused on bed rest (Pavy-Le Traon et al., 2007), dry immersion (Navasiolava et al., 2011), and unilateral limb suspension (ULLS) experiments (Brocca et al., 2015; Gustafsson et al., 2010; Hackney and Ploutz-Snyder, 2012; Tesch et al., 2008) and allow researchers to distinguish the effects of disuse from those associated with

comorbidities, both in the context of fracture healing and in atrophy due to a prolonged hospital stay.

In ULLS protocols, the treated limb is flexed and suspended above the ground by means of a shoulder harness **(Figure 1)** (Horstman et al., 2012). This model has been successfully used for decades to induce disuse atrophy in one limb (Brocca et al., 2015; Tesch et al., 2008). Moreover, by confining disuse muscle atrophy to the unloaded limb, the model closely resembles joint unloading after muscle and skeletal injuries, a frequent and relevant condition in clinical practice. ULLS globally causes a loss of muscle mass (just as other disuse models) of approximately 0.44% per day in the vastus lateralis, which is among the most affected muscles (Hackney and Ploutz-Snyder, 2012). Like bed rest and spaceflight, ULLS primarily affects the soleus over gastrocnemius fibers. In contrast to the other models, slow soleus fibers obtained after ULLS show a decrease in unloaded shortening velocity and a greater reduction in specific force (Widrick et al., 2002).

Continuous exposure of healthy volunteers to a −6° head-down tilt position while resting in a bed has been shown to be an excellent model of many of the physiological changes that take place in spaceflight. In addition to providing the opportunity to study physiological, cellular, and molecular events, the bed rest studies also allow for testing the effectiveness of countermeasures and related protocols. Bed rest studies have produced and continue to generate a wealth of data on the physiological effects of inactivity on healthy individuals, its clinical implications, and the importance of activity for health. These studies have collectively shown that the antigravity extensors of the knee and ankle are the most affected (Alkner and Tesch, 2004b; LeBlanc et al., 1992; Rittweger et al., 2005). The greater relative decrease in maximal strength than size (as demonstrated in these studies) suggests that atrophy alone cannot account for the strength loss (Alkner and Tesch, 2004a, b). Altered motor control, changes in the properties of the contractile machinery, reduced efficiency of the electromechanical coupling, and fat infiltrations may contribute to the loss of strength (Addison et al., 2014; Berg et al., 1997b; di Prampero and Narici, 2003). In the past 20 years, a more comprehensive understanding emerged regarding the complex nature and variety of ways in which the reduction in z-axis gravitational stimuli affects body sensors and responses when a person is lying continuously in the horizontal position or during head-down bed rest

(Pavy-Le Traon et al., 2007). Removal of both z- and x-axis gravitational stimuli can be achieved only in outer space or possibly reduced in the dry-immersion bed rest model.

Dry immersion involves immersing a subject (covered with an elastic waterproof fabric) in thermoneutral water. As a result, the immersed subject, who is freely suspended in the water mass, remains dry (Navasiolava et al., 2011). For a relatively short period, the model can faithfully reproduce most of physiological effects of microgravity, including centralization of body fluids, support unloading, and hypokinesia. In the last decades, this model has been useful for the space program as a ground simulation tool. Its application to space research contributed to improvement of this model and development of immersion under dry conditions that allows for longer experiments. Dry immersion induces an obvious decline in postural muscle tone and a decrease in the electromyographic activity of extensor muscles with a simultaneous increase in flexor activity within the first few hours. The intensity and rate of neuromuscular changes that occur during dry immersion are much higher than those during head-down bed rest (Navasiolava et al., 2011). The unique pathophysiological model of dry immersion lately became relevant for basic research, with potential therapeutic applications. Russian scientists at the Institute of Biomedical Problems (Moscow, Russia) developed this model initially to simulate a microgravity environment. The removal of afferent signals from the support zones of the feet has been shown to trigger a dramatic drop in activity of the postural muscle system (Gevlich et al., 1983; Miller et al., 2004). Today, it also appears to be a model relevant to pathophysiological and aging studies.

2.3. Animal ground-based models of muscle disuse

The animals most frequently used for studying intervention strategies against skeletal-muscle aging are rats and mice. Yet even in rodents, life-long interventions still require 18–26 months of follow-up and are therefore costly and time-consuming (Kovanen and Suominen, 1987; Leeuwenburgh et al., 1997; Viidik et al., 1996). Senescence-accelerated mice (SAM) represent rodent models characterized by accelerated senescence and age-related pathologies (Takeda, 1999). Among these murine lineages, SAMP8 mice appear to be a suitable model for studies on skeletal-muscle aging (Derave et al., 2005).

Among rodent models of skeletal muscle disuse and wasting, most of the relevant scientific studies have used experimental models of denervation and hindlimb unloading (Bodine et al., 2001). Denervation has drastic and rapid effects on skeletal muscle, with

accelerated protein degradation (Furuno et al., 1990), and denervation's role in aging muscle has always been difficult to identify. In this context, and because advancing age is associated with increased denervation, the experimental procedures of denervation have been largely used to explore and study the molecular consequences for skeletal muscle. As in several models of muscle deconditioning, investigators usually report a disproportional loss of muscle mass and force. The study by Carlson et al. (1996) revealed a 75% decrease of muscle mass and a 99% reduction in maximum isometric contractile force in the rat extensor digitorum longus (EDL) after 4 months of denervation. Moreover, Carlson et al. (2001) showed a decrease of 49% of muscle mass and a 83% reduction of maximum force in EDL of 32-month-old rats. Thus, the losses of muscle mass and force during aging appear much slower. At the histological level, denervated muscle and old muscles share some common signs: reduced microvasculature and increased amounts of interstitial connective tissue and collagen (Borisov et al., 2000). In parallel, the processes of apoptosis and myonuclear death are observed, both in denervated muscles and during aging, but it remains unclear which pathways lead from nuclear death to cellular death (Borisov et al., 2001). As a general rule, severity and extent of skeletal-muscle damage observed in aging muscles are less than those observed after denervation.

The rodent model of hindlimb unloading (HU) has been developed by the National Aeronautics and Space Administration (NASA) Ames Research Center in the mid-1970s and was validated to simulate weightlessness (Morey, 1979; Morey-Holton and Globus, 2002). Several hundred research articles have been published. The most crucial parameters of this model are the housing unit, the device to which a rat or mouse is attached to allow for mobility, the angle of unloading, and the harness system (Chowdhury et al., 2013; Morey-Holton and Globus, 2002). The skeletal muscle wasting of HU rats is comparable in studies involving tail-HU and pelvic-HU in animals within the same period (usually 2 weeks). Soleus muscle mass, for example, decreases by ~40% after 2 weeks, either in tail-HU or pelvic-HU experiments (Bodine et al., 2001; Chopard et al., 2001; Chowdhury et al., 2013; Cros et al., 1999; Mueller et al., 2005; Picquet and Falempin, 2003). The study by Bodine et al. (2001), which describes a transcript profiling analysis comparing immobilization, denervation, and HU models, emphasized that although most genes perturbed during immobilization are regulated similarly during denervation, most of these genes are unaltered in the HU model,

even though similar rates of atrophy are observed in these models. Nonetheless, this study reported for the first time that the two atrogenes, MuRF1 (Muscle RING finger 1) and MAFbx (muscle atrophy F-box) are upregulated in all three models of atrophy (Bodine et al., 2001).

2.4. Cell models of muscle wasting

It has been proposed that with various types of muscle atrophy, such as those induced by fasting, unloading (Stevenson et al., 2003), immobilization (Pattison et al., 2003), and diseases, there are subsets of genes whose differential expression is common for these types of atrophy (Lecker et al., 2004b), suggesting that these processes share common mechanisms regardless of the triggering event. Indeed, in muscle-wasting conditions cited above, several subsets of genes show differential expression similar to that in disease models (Lecker et al., 2004b) and thus attribute all kinds of atrophy inducers to a common pathway (Sandri et al., 2004; Sartorelli and Fulco, 2004b). To study the molecular details of muscle atrophy, several cell culture models have been developed. Starvation of cultured cells was used as a system for identification of molecular details of whole-muscle atrophy (Sandri et al., 2004). The failure to replenish differentiation media, the simple application of short-term (hours to 2 days) phosphate-buffered saline (PBS) treatment to mature myotube cell lines (C2C12, L6) leads to rapid atrophy (Stevenson et al., 2005). PBS-treated cells showed activation of at least the ubiquitin protein ligase MAFbx (Sandri et al., 2004). These cell culture models have been said to "mimic" atrophy in vivo because they have in common at least a few changes in protein and mRNA expression (Sartorelli and Fulco, 2004b). On the other hand, starvation of myotubes in culture revealed a distinctive phenotype: not a suitable model to study signaling pathways of whole-muscle atrophy conditions, such as those presented below. Yet the above approach indicated that the overt atrophy phenotype reflects a great many differentially expressed genes and is not simply attributable to a particular set of genes.

Glucocorticoids (GCs) are key mediators of muscle proteolysis and atrophy (Britto et al., 2014; Kuo et al., 2013; Schakman et al., 2013a). Metabolic disruptions reported in atrophying skeletal muscle in humans and experimental animal models are also observed in cell experiments involving dexamethasone, and GC-treated cultured myotubes have been used in several studies as an in vitro model of muscle wasting (Klaude et al., 2007; Schakman et al., 2013b; Thissen, 2005; Thompson et al., 1999; Tiao et al., 1997; Wang et al., 1998). In

these experiments, dexamethasone-treated myotubes based on rat (L6) and mouse (C2C12) cell lines have been used to identify the mechanisms of muscle wasting. The concentration of dexamethasone varied among the studies, and the effects of dexamethasone were found to be induced by concentrations ranging from 10–50 nM to 100 µM (Latres et al., 2005; Stitt et al., 2004; Sultan et al., 2006; Thompson et al., 1999). One study revealed, for example, that treatment with dexamethasone or corticosterone resulted in dose-dependent increases in protein degradation rates in both L6 and C2C12 myotubes accompanied by 25-30% reduction of myotube diameter. (Menconi et al., 2008).

Mechanistically, GCs act via activation of the ubiquitin proteasome (UPS) and the lysosomal systems (Schakman et al., 2013b; Thissen, 2005). Stimulation of these proteolytic systems, especially the UPS, is mediated by upregulation of several atrogenes such as FoxO1/3a, MAFbx, and MuRF-1 (Schakman et al., 2013b). Aside from the GC-induced atrophy, inflammation-related atrophy has been extensively used for muscle cell culture (Schakman et al., 2013b; Thissen, 2005). Tumor necrosis factor α (TNF-α), originally called "cachectin" (Mirza et al., 2014a), can induce C2C12 atrophy when added to cell culture. TNF-α is a potent trigger of muscle wasting in vitro and in vivo, through inhibition of myogenesis and induction of apoptosis and proteolysis, via activation of nuclear factor κ B (NF-κB) and various components of the UPS even at a low concentration (1–3 ng/ml) (Bakkar and Guttridge, 2010; Cai et al., 2004; Li et al., 1998; Magee et al., 2008). In addition to the canonical Akt-dependent pathway, the FoxO4 pathway is stimulated by TNF-α treatment and leads to MAFbx mRNA upregulation (Moylan et al., 2008). A cocktail of proinflammatory cytokines such as TNF-α plus interferon (IFN)-γ has also been used to simulate muscle wasting in the C2C12 cell line (Dehoux et al., 2007; Kimura et al., 2014b). Transforming growth factor β1 (TGF-β1) belongs to a family of multifunctional cytokines including bone morphogenic proteins (BMPs) and activins (Massagué, 1990). TGF-β1 plays essential roles in various biological processes, including cell growth, differentiation, apoptosis, tissue development, and inflammation (Massagué, 1990; Shull et al., 1992). Besides the fibrogenic effects, studies showed that TGF-β1 is also a potent inhibitor of growth and differentiation of myoblasts (Allen and Boxhorn, 1987) and can suppress division and block fusion of satellite cells both in vitro and in vivo by suppressing myogenic factors (Allen and Boxhorn, 1987; Zhu et al., 2004). When incubated with C2C12 cells, 1 ng of TGF-β1 reduces myotube

diameter and increases protein expression of MuRF-1 and MAFbx (Abrigo et al., 2016; Mendias et al., 2012). More recently, Nozaki et al. (2015) developed the C2C12 cell line from the BubR1 hypomorphic mouse model of accelerated-aging (Baker et al., 2008); these cells are characterized by a subpopulation of muscle stem cells expressing p16Ink4a (Nozaki et al., 2015). This modified cell line shows increased expression of the muscle-specific ubiquitin ligases MAFbx and MuRF-1, reduced expression of MyoD and myogenin, and a decreased fusion index (Nozaki et al., 2015).

3. Characteristics of sarcopenia-related muscle deconditioning

The three components of sarcopenia are low muscle mass, low muscle strength, and poor physical performance (Cruz-Jentoft et al., 2010; Fielding et al., 2011; Morley et al., 2011; Muscaritoli et al., 2010). **Table 1** presents methodologies used to assess muscle mass, muscle strength, and physical performance in humans and rodents.

Typically, in humans, muscle mass remains stable during early life, but after age ~50 years, muscle mass declines at a rate of ~1% per year in men and ~0.5% in women (Mitchell et al., 2012). Nevertheless, the decline of skeletal-muscle mass may accelerate along with aging, amounting to 6% per decade between 30 and 70 years of age (Fleg and Lakatta, 1988), 1.4% to 2.5% per year after age 60, and can start as early as 35 years of age (Frontera et al., 2000a). In humans, it is accepted that aging is accompanied by a decrease in muscle mass by ~40% from the adulthood to death (Ibebunjo et al., 2013; Kimball et al., 2004; Lexell et al., 1988); this decrease can exceed 50% (Baumgartner et al., 1998). Rodents, especially rats, are experimental animals particularly useful for studying sarcopenia. Depending on the strain, rats are considered elderly between 18 and 30 months (Hopp, 1993). Fischer 344 Brown Norway F1 hybrid and Wistar rats are the most popular rat strains for studies on sarcopenia. Usually, regardless of the strain, at age ~18 months (middle age for rats), the weight of the soleus, EDL, gastrocnemius, quadriceps, tibialis anterior, and plantaris is reduced as compared to animals aged 6 or 12 months (Ibebunjo et al., 2013; Kimball et al., 2004; Paturi et al., 2010). This decrease is relatively slow and small at 18 months of age (~10%) but accelerates thereafter to reach 30% to 40% at age 24 months (old age in rats) (Ibebunjo et al., 2013; Kimball et al., 2004; Paturi et al., 2010). In very old animals (~30 months old), this decrease can reach 60% in some muscles, notably the gastrocnemius (Ibebunjo et al., 2013; Kimball et al., 2004).

In humans, the age-related decrease in muscle mass is mainly due to a loss of muscle fibers affecting both type I fiber and type II fiber (Aniansson et al., 1986; Lexell et al., 1988; Young et al., 1985). Although a decrease by only 5% in the number of fibers occurs between 24 and 50 years of age, a reduction of 30% to 40% is reported between 50 and 80 years (Aniansson et al., 1992). Nonetheless, atrophy of muscle fibers (reduction of their cross-sectional area) is also implicated in the decrease of muscle mass associated with aging (Aniansson et al., 1986; Lexell et al., 1988). Atrophy does not affect all types of muscle fibers similarly. Indeed, fast type II fibers appear to be the most affected by aging, with a decline from 20% to 60% in their size (Hikida et al., 2000; Larsson et al., 1978; Lexell et al., 1988). Among type II muscle fibers, greater reductions are observed in the fiber IIx type compared to type IIa fibers (Aniansson et al., 1986; Coggan et al., 1992).

The decrease in muscle strength is a key diagnostic criterion of sarcopenia, and the functional consequences are important for autonomy of the affected person (Cruz-Jentoft et al., 2010). Muscle strength of the knee extensors should be considered due to its functional importance (Doherty, 2003). On average, the peak strength decreases by 20-40% between 20-30 and 70–80 years (Larsson et al., 1979; Murray et al., 1985; Young et al., 1985). Similar results were observed with other muscle groups such as shoulder and wrist flexors (Bassey and Harries, 1993; McDonagh et al., 1984). Greater reductions (50%) are still reported in subjects aged over 90 years (Murray et al., 1985; Murray et al., 1980). Decreased muscle strength seems to be accelerated especially between 60 and 70 years. Indeed, longitudinal studies revealed a reduction by 30% to 40% in the peak strength of the knee and shoulder extensors between ages 60 and 70 years (Aniansson et al., 1986; Frontera et al., 2000b; Hughes et al., 2001). Similar results were observed in rodents, but the onset of this phenomenon seems to depend on the strain and age of the rodent. Thus, in Fisher 344 Brown Norway F1 hybrid and aged mice, a decrease in maximal force is generally observed between 32 and 36 months in the soleus, gastrocnemius, and EDL (Brooks and Faulkner, 1988; Ryall et al., 2007; Thomas et al., 2010). In Wistar rats, no difference was observed in the EDL, but maximal force decreased after 24 months in the soleus.

Gait speed is now the recommended parameter for assessment of physical performance for diagnosis of sarcopenia (Cruz-Jentoft et al., 2010; Fielding et al., 2011; Morley et al., 2011); however, there is still no consensus on the cutoff value for diagnosis of

sarcopenia. Gait speed is usually evaluated by the 6-meter test (Fielding et al., 2011; Morley et al., 2011) or the 4-meter test (Cruz-Jentoft et al., 2010). Cutoff levels for sarcopenia are defined as a speed less than 1 m/s in the first case and less than 0.8 m/s in the second (Cesari et al., 2009). Gait speed can be easily used in clinical practice and research. Other tests designed specifically for elderly people are also acceptable. The most popular are the Short Physical Performance Battery (SPPB) (standardized battery of short physical tests), the timed get-up-and-go (TUG), or the stair climb power test (SCPT). The SPPB evaluates balance, gait speed, strength, and endurance by examining an individual's ability to stand with the feet together in side-by-side, semitandem, and tandem positions, time to walk 8 feet, and time to rise from a chair and return to the seated position five times (Guralnik et al., 1994). Each event yields a performance score, and the sum of the scores on all the subtests characterizes overall performance. A score below 8/12 points to probable sarcopenia (Guralnik et al., 2000). SPPB is a standard measure for research and for clinical practice. The TUG is a test of the time required to perform a series of basic motor tasks. The subject must stand up from a chair, walk a short distance, turn around, and come back to sit. This method allows for estimation of the dynamic balance that is assessed on a scale of 1 to 5 (Mathias et al., 1986). A score below 3 means probable sarcopenia (Mathias et al., 1986). Finally, the SCPT when used clinically estimates power of the lower limbs (Bean et al., 2007). The subject must climb 10 steps as soon as possible. The power of the lower limbs is then calculated in relation to the height of the steps and the rate of climbing and is normalized to the weight of the subject (Bean et al., 2007). This test may be useful in some research settings but the cutoff point for sarcopenia needs to be defined. Poor physical performance is also revealed by a decrease in both resting and maximal oxygen consumption with advancing age in humans (Short et al., 2004). In rodents, there is no consensus on how to evaluate the decrease in physical performance in old animals, but numerous tests are available **(Table 1)**. Very few data are available on old rodents. Nevertheless, alterations in the balance and coordination in old rodents (23–24 months) have been reported by Altun et al. (2007) and Emerich et al. (2008), who measured the time that a rodent can stay on a narrow beam (Beam Balance Test) or a tightrope (tightrope test). Decreased physical performance in old rodents is also shown by decreased endurance capacity in old rats compared to young rats (Derbre et al., 2012).

Sarcopenic (and more generally deconditioned) muscle is also characterized by an increase in IMAT infiltrations (Addison et al., 2014; Goodpaster et al., 2000). This point will be discussed in part 5.

4. Cellular and molecular alterations of skeletal muscle

The development of effective treatments or prophylactic measures against sarcopenia requires understanding the cellular and systemic mechanisms as well as the pathways involved in sarcopenia onset and development.

Maintaining muscle mass is mostly a balancing act between protein synthesis and protein degradation systems. It is well established that sarcopenia involves negative protein turnover (Combaret et al., 2009) characterized by the reduction of myofibrillar (especially myosin heavy chain: MyHC) and mitochondrial proteins synthesis (Balagopal et al., 1997; Cuthbertson et al., 2005; Haddad and Adams, 2006) and their increased proteolysis via the UPS and calcium-dependent activation of proteases (i.e., calpains and caspases) (Gumucio and Mendias, 2013; Konopka and Sreekumaran Nair, 2013). The decrease in MyHC synthesis is at least due to a decrease in its transcription because the amounts of mRNA of different isoforms decrease during aging, e.g., MyHC IIa and MyHC IIx isoforms (Balagopal et al., 2001; Short et al., 2005). This may explain in part why MyHC protein content in the muscle of old animals is reduced as compared to young animals (Haddad and Adams, 2006; Thompson et al., 2006) and why MyHC IIa and IIx protein levels decline by 3% and 1% per decade, respectively, in humans (Short et al., 2005). This decrease in the synthesis of myofibrillar proteins appears to be specific because actin synthesis is not affected by aging in humans (Hasten et al., 2000) and its protein expression in muscle is unchanged in aged animals (Haddad and Adams, 2006; Thompson et al., 2006).

Given the vital functions carried out by mitochondria in the context of energy provision, redox homeostasis, and regulation of several catabolic and cell death pathways, it is not surprising that age-related alterations of mitochondrial functions are viewed as the central cause of sarcopenia by numerous authors (Calvani et al., 2013; Konopka and Sreekumaran Nair, 2013; Marzetti et al., 2013). One major consequence of age-associated mitochondrial dysfunction is a decline in bioenergetics, judging by a decrease in both resting and maximal oxygen consumption ($\dot{V}O_2max$) with advancing age in humans (Short et al., 2004) and mice (Lee et al., 2010) and by decreased endurance capacity in old rats compared

to young rats (Derbre et al., 2012). Moreover, perturbations in mitochondrial energetics of skeletal muscle have been shown to correlate with reduced $\dot{V}O_2max$ (Short et al., 2005), walking capacity (Coen et al., 2013), and maximal isometric strength (Safdar et al., 2010) in older adults and are associated with an increase in muscle fatigability in old rats (Chabi et al., 2008). The bioenergetic failure of the sarcopenic muscle is related to a reduction in mitochondrial numbers and functions (Calvani et al., 2013; Vina et al., 2009), which is the result of a vicious cycle involving production of reactive oxygen and nitrogen species and damage to (and/or depletion of) mitochondrial DNA (mtDNA), and defective quality control of mitochondria (Marzetti et al., 2013).

The equilibrium between apoptosis and regeneration processes is also involved in the maintenance of muscle mass (Hikida, 2011; Marzetti et al., 2012a; Snijders et al., 2009). Decreased capacity for muscle regeneration (Hikida, 2011; Snijders et al., 2009) and exacerbation of apoptosis (Marzetti et al., 2012a) are believed to be involved in sarcopenia-associated muscle deconditioning. This notion is supported by the observation that apoptotic signaling correlates with slow walking speed and reduced muscle volume in older persons (Marzetti et al., 2012b). Moreover, numerous studies have revealed that the extent of apoptotic DNA fragmentation increases in skeletal muscle in the course of aging, thus paralleling the development of sarcopenia (Braga et al., 2008; Kovacheva et al., 2010; Marzetti et al., 2012b; Siu et al., 2006; Wohlgemuth et al., 2010); this fragmentation is likely involved in the decrease in transcriptional efficiency observed during sarcopenia (Cuthbertson et al., 2005; Roberts et al., 2010). This phenomenon is probably worsened by alterations in muscle regeneration capacity limiting incorporation of new nuclei into aging muscle fibers by satellite cells (SCs). This point will be addressed in part 5.2.

Although skeletal muscle atrophy contributes substantially to the loss of muscle strength during aging, it is not considered the only factor involved in this phenomenon. Indeed, data from animal studies have shown that specific strength of isolated muscle fibers (i.e., force normalized to the cross-sectional area of the fiber) also decreases with age (Gonzalez et al., 2000; Renganathan et al., 1998; Thompson, 2009; Thompson and Brown, 1999), but contradictory results have been reported too (Claflin et al., 2011). Several mechanisms are proposed to explain these results, e.g., posttranslational modifications of contractile proteins (Lowe et al., 2001), decoupling of complex excitation-contraction (Wang et al., 2000), and decreased myosin ATPase activity (Lowe et al., 2004). Studies focused on

permeabilized muscle fibers have shown that the decrease in specific strength is also explained by a reduction in the fraction of myosin heads that bind to actin filaments (Lowe et al., 2001; Lowe et al., 2004). The research on isolated intact muscle fibers revealed the involvement of excitation-contraction coupling in age-associated changes of muscle contractile properties. Thus, the maximal release of calcium from the sarcoplasmic reticulum is decreased in aged rodent muscle tissue (Jimenez-Moreno et al., 2008). Neuromuscular impairments such as a loss of motor units and loss of motor neurons are also involved in muscle strength reduction during aging as reviewed well by Piasecki et al. (2015).

These mechanisms contribute to the onset of sarcopenia and are affected by numerous upstream factors including a decrease in the release of anabolic hormones (e.g., growth hormone [GH], insulin like growth factor 1 [IGF-1], or testosterone) (La Colla et al., 2015; Morley and Malmstrom, 2013), increased production of proinflammatory cytokines (e.g., interleukin 6 and TNF-α) (Lee et al., 2007), insulin resistance (Walrand et al., 2011), neuromuscular aberrations (Edstrom et al., 2007; Piasecki et al., 2015), dysregulation of microRNAs (McGregor et al., 2014; Rivas et al., 2014; Zampieri et al., 2015), and an increase in muscle oxidative stress (Brioche and Lemoine-Morel, 2016; Derbre et al., 2014; Jackson, 2009; Jackson and McArdle, 2011; Ji, 2007).

5. IMAT: an important factor of sarcopenia

There is now a growing body of evidence that the loss of strength and power mostly exceeds the loss of muscle mass observed after inactivity (Berg et al., 1997a; di Prampero and Narici, 2003). Fatty infiltrations or IMAT may be an additional independent variable explaining the loss of muscle strength. IMAT can be first defined as adipocyte deposition located between the muscle fibers and between muscle groups; IMAT should not be confused with intramyocellular triglyceride accumulation (Addison et al., 2014; Karampinos et al., 2012; Vettor et al., 2009). Although IMAT may be a variable part of healthy human skeletal muscle, its increase and accumulation are linked to muscle dysfunction, deconditioning, and even perturbed regeneration (Addison et al., 2014; Marcus et al., 2010; Sciorati et al., 2015; Uezumi et al., 2014b). These fatty infiltrations are well known to be associated with many conditions: myopathies, diabetes, COPD, cachexia, or even sarcopenia, among many others. To our knowledge, Aherne (1965) was the first to describe fat

infiltration in various tissues, including skeletal muscle, in a newborn infant, and this report was followed by other studies (Birkbeck, 1970; Kannan et al., 1976; Kelley et al., 1991; Nordal et al., 1988). Recognition of the role of IMAT in muscle function seems to increase year after year, and scientific knowledge will certainly continue to expand around this subject. This part of the review is focused on IMAT accumulation with aging, its impact on muscle function, and the major role of increasing physical activity as a countermeasure. We will also try to highlight some cellular players possibly responsible for IMAT development with advancing age, in particular, one specific skeletal-muscle mesenchymal-stem-cell population called fibroadipogenic progenitors (FAPs).

5.1. The fight against inactivity: the real purpose

The literature highlights a correlation between IMAT levels and muscle function. Indeed, numerous studies have demonstrated that an increase in IMAT accumulation matches a decrease in muscle mass, muscle strength, and insulin-sensitivity (Delmonico et al., 2009; Goodpaster et al., 2000; Miljkovic-Gacic et al., 2008; Visser et al., 2005). First, it has long been well known that IMAT levels increase strongly with age (Addison et al., 2014; Goodpaster et al., 2000; Kirkland et al., 2002) and some relatively old papers have already showed larger fatty infiltrations in old men (Borkan et al., 1983; Rice et al., 1989) and women (Ryan and Nicklas, 1999; Song et al., 2004) using computed tomography, or more recently, magnetic resonance imaging. Two studies, Borkan et al. (1983) and Rice et al. (1989), were the first to demonstrate fatty infiltrations with aging accompanied by a decrease in muscle mass (Gallagher et al., 2000) and in muscle strength (Jubrias et al., 1997). Subsequent studies evaluated the relation between levels of IMAT and muscle function. Two studies, performed on the same elderly cohort, demonstrated a correlation between the degree of IMAT accumulation and the loss of both muscle strength and performance (Goodpaster et al., 2001; Visser et al., 2002). In fact, a study by Visser et al. (2002) showed decreased performance on the 6-meter walk and repeated chair stands tests, with a correlation between IMAT levels and performance on both tests. Later, a study by Delmonico et al. (2009) confirmed that the loss of muscle strength with aging matches IMAT development. Altogether, these studies have helped to identify a new important component of sarcopenia: IMAT accumulation. In the specific context of sarcopenia, other studies have shown that IMAT infiltration into the mid-thigh muscle remains an independent risk factor of

mobility limitations (Beavers et al., 2013; Tuttle et al., 2012; Visser et al., 2005). The level of fatty infiltrations was also found to be a good predictor of clinical fracture in older adults (Schafer et al., 2010). Finally, a study by Marcus et al. (2012) demonstrated again the IMAT contribution to the impaired mobility of older adults and showed once again that IMAT is an essential component of sarcopenia.

Although IMAT is widely known to be strongly linked to sarcopenia, the following studies suggest that IMAT accumulation may also be a result of global muscle inactivity rather than aging *per se* (Leskinen et al., 2009; Manini et al., 2007; Tuttle et al., 2011). Indeed, a study by Manini et al. (2007) demonstrated that only 4 weeks of unilateral limb suspension can increase IMAT accumulation in healthy young adults. Moreover, a longitudinal study based on twin populations showed that physically inactive cotwins have greater IMAT accumulation as compared with the active cotwins (Leskinen et al., 2009). A study by Tuttle et al. (2011) also revealed a correlation between physical activity levels, measured by the average daily step count, and IMAT accumulation in people with diabetes and peripheral neuropathy. One research group also found an increase in IMAT area 6 weeks after incomplete spinal cord injury (Gorgey and Dudley, 2007), and another study showed IMAT accumulation to be associated with mobility limitations in older adults (Murphy et al., 2014). Although these studies were performed on different populations, they contribute to the knowledge on IMAT accumulation and highlight the highly plausible role of physical activity interventions in aging.

A study by Goodpaster et al. (2008) was the first to detail precisely 1 year of increased physical activity among older adults. They demonstrated a clear protective effect of physical activity against the aging-associated IMAT increase and against the decrease in knee extensor strength. Another study, published almost at the same time, by Marcus et al. (2008), revealed similar data on IMAT accumulation during both combined aerobic and eccentric resistance training or only aerobic training in a type 2 diabetes population. Two years later, the same group investigated the effect of 12 weeks of eccentric exercise training in the elderly (Marcus et al., 2010) and found an 11% decrease in thigh IMAT area. Under almost the same conditions, Ryan et al. (2011) also found a decrease in the IMAT area in old stroke survivors. Another study examined the effect of 8 months of endurance exercise on sedentary subjects with dyslipidemia and showed a decrease in IMAT accumulation

(Durheim et al., 2008). Two studies also prevented an increase in IMAT with aging by a 1-year diet-and-moderate-exercise intervention in overweight and obese patients with type 2 diabetes (Gallagher et al., 2014) or by a more intensive but shorter exercise intervention in older people prone to falls (Jacobs et al., 2014). A recent study has shown a decrease in the IMAT area after 5 months of moderate resistance training in overweight and obese older adults (Nicklas et al., 2015). Taaffe et al. (2009) also observed an increase in IMAT content among the elderly after a detraining session followed by a decrease in IMAT levels after a retraining resistance exercise session. Lastly, an interesting study by Wroblewski et al. (2011) on old elite athletes, trained for fitness and sports competitions at least four or five times per week, showed that they do not exhibit any loss of lean muscle mass or any increase in IMAT amount with aging. The last two studies strengthen the notion that some muscular alterations observed in sarcopenia are a direct consequence of a gradual decrease in physical activity among older adults.

Numerous studies also failed to detect any decrease in IMAT content after an exercise program (Christiansen et al., 2009; Jung et al., 2012; Ku et al., 2010; Prior et al., 2007; Santanasto et al., 2011; Walts et al., 2008), even though studies demonstrating no increase in IMAT content after an exercise intervention among the elderly may also be a good result. These discrepancies can be explained from a methodological point of view in relation to the age of participants, their race, and the associated diseases or even the type of exercise used, its intensity, and duration. Altogether, these studies appear to reveal an important role of increasing physical activity in stabilization of (or even a decrease in) IMAT development and accumulation during aging. Further studies are needed to precisely define the most effective way to train the elderly in order to combat the progressive sedentary lifestyle leading to sarcopenia and IMAT accumulation, both affecting muscle function and overall health of older adults.

5.2. How does fat infiltration occur in sarcopenia?

Even if IMAT development and accumulation will be studied more, the mechanisms leading to fatty infiltrations during sarcopenia or a sedentary lifestyle are poorly understood. To our knowledge, a review by Kirkland et al. (2002) was the first to give some clues to IMAT accumulation during aging. They highlighted a possible role of disruption of the leptin pathway in a decreased ability to metabolize fatty acids with aging (Koteish and Diehl, 2001;

Wang et al., 2001) and also pointed to potential involvement of SCs and mesenchymal stem cells (MSCs).

Concerning SCs, it appears that the SC pool is maintained until ~70 years of age (Dreyer et al., 2006; Roth et al., 2000) and then declines (Kadi et al., 2004; Renault et al., 2002; Sajko et al., 2004; Verdijk et al., 2014). There is a specific decline in SC content located under the basal lamina of type II muscle fibers (Verdijk et al., 2012; Verdijk et al., 2007; Verdijk et al., 2014), which coincides exactly with the preferential development of sarcopenia in the fast-twitch type of muscle. It is also important to note that advancing age is associated with impaired proliferation capacity of SCs (Conboy et al., 2003; Schultz and Lipton, 1982; Suetta et al., 2013) concomitant with the expected decrease in regenerative capacity (Collins-Hooper et al., 2012; Gallegly et al., 2004; Marsh et al., 1997; Renault et al., 2002; Sadeh, 1988). Numerous studies based on parabiosis and whole-muscle grafting experiments have demonstrated that the decline in muscle SC function with aging may be largely attributed to extrinsic/microenvironmental factors (Brack et al., 2007; Carlson and Faulkner, 1989; Conboy et al., 2005; Harrison, 1983; Villeda et al., 2011). However, newer studies, involving more powerful SC isolation/purification tools, have also confirmed SC-specific alterations in sarcopenia (Bernet et al., 2014; Chakkalakal et al., 2012; Cosgrove et al., 2014; Price et al., 2014; Sousa-Victor et al., 2014). A large number of reviews have already discussed the recent research on this subject (Blau et al., 2015; Brack and Munoz-Canoves, 2015; La Colla et al., 2015; Sousa-Victor et al., 2015) and precisely detail both extrinsic and intrinsic factors that influence SC function during aging. The review by Brack and Munoz-Canoves (2015) also highlights the importance of SC heterogeneity as the main source of discrepancies among studies on SC function with advancing age, and those authors argue that distinct SC subsets are differentially sensitive to extrinsic and intrinsic factors probed in these studies. Our review will not elaborate on SC function in sarcopenia or on transdifferentiation as already discussed in other reviews (Sciorati et al., 2015; Vettor et al., 2009) but will instead discuss the potential role of FAPs in IMAT accumulation in conjunction with advancing age.

The muscular environment contains various populations of tissue-resident progenitors, including the MSCs called FAPs. These FAPs, which are positive for the cell surface marker platelet-derived growth factor receptor α (PDGFRα or CD140a), are a widely

studied stem cell population in skeletal muscle. FAPs are able to proliferate quickly after injury, participate in phagocytosis of necrotic muscle fibers, and support SC-mediated efficient muscle regeneration without differentiating into adipocytes (Heredia et al., 2013; Joe et al., 2010; Lemos et al., 2015). In muscle disuse or pathological conditions, such as Duchenne muscular dystrophy, FAPs proliferate and differentiate into adipose and/or fibrous tissue (Uezumi et al., 2014a; Uezumi et al., 2011). Simultaneously with the decrease in SC content (Blau et al., 1983; Heslop et al., 2000), in this case, FAPs lead to accumulation of IMAT. In order to investigate IMAT development and accumulation in an experimental mouse model, the glycerol model of regeneration is commonly used (Joe et al., 2010; Lukjanenko et al., 2013; Pagano et al., 2015; Pisani et al., 2010; Uezumi et al., 2010) and allows for better characterization of muscle-resident adipocyte precursors **(Figure 2)**. Even though no study has been conducted to characterize the role of FAPs in sarcopenia, the literature highlights a possible important function of FAPs in age-related development of IMAT (Blau et al., 2015; Farup et al., 2015). Moreover, two *in vitro* studies have demonstrated that skeletal-muscle-FAP-derived adipocytes are insulin resistant (Arrighi et al., 2015; Laurens et al., 2015). These studies support, on the one hand, the correlations between IMAT accumulation and the decrease in insulin sensitivity observed during aging and obesity (Goodpaster et al., 1999; Goodpaster et al., 2000; Goodpaster et al., 1997; Ryan and Nicklas, 1999; Simoneau et al., 1995), and on the other hand, the fact that FAPs can be the main stem cell population implicated in sarcopenia-related IMAT development.

The recent literature underscores the critical role of the immune and inflammatory systems in efficient muscle regeneration, and various reviews excellently summarized recent advances in this field (Aurora and Olson, 2014; Madaro and Bouche, 2014; Maffioletti et al., 2014; Sciorati et al., 2015). A study by Lemos et al. (2015) also showed the crucial effect of the balance between TNF-α and TGF-β1 on FAPs. This study demonstrated that TNF-α that is released by M1 macrophages provokes FAP apoptosis, whereas TGF-β1 (released by M2 macrophages) promotes their survival. Interestingly, regeneration and aging are associated with deregulation of numerous systems including inflammation. Indeed, Butcher et al. (2001) showed alteration of neutrophil function with aging, and these results, in light of those of Heredia et al. (2013), may indicate a defective neutrophil-induced IL-4/IL-13 release and further signaling toward FAPs, promoting their adipocytic differentiation.

A study by Lemos et al. (2015) also elegantly demonstrated the precise and crucial temporal transition of TNF-α (proinflammatory) to TGF-β1 (proregenerative) cytokine production during muscle regeneration. Przybyla et al. (2006) demonstrated defective regulation of muscle macrophage function with advancing age, and some studies also showed an increase in both TNF-α and TGF-β levels (Carlson et al., 2008; Carlson et al., 2009; Fagiolo et al., 1993; Merritt et al., 2013). Therefore, the inflammatory deregulation and the possible overlap between TNF-α and TGF-β1 signaling may promote survival of FAPs and adipocytic differentiation leading to IMAT development and accumulation during sarcopenia. The upregulation of TGF-β observed during aging can also explain the increase in the muscle levels of FAPs discussed in a review by Shadrach and Wagers (2011) although these are unpublished observations. Nevertheless, some other molecular pathways can also modulate the fate of FAPs during aging and will be discussed below.

Numerous studies by the same group evaluated the effect of histone deacetylase inhibitors (HDACi) on dystrophin-deficient mdx mice (characterized by permanent muscle lesion-regeneration cycles). These researchers first showed that HDACi treatment of mdx mice promotes a functional and morphological recovery of skeletal muscle, certainly mediated in part by an increase in follistatin expression (Minetti et al., 2006). They next showed that in young mdx mice, FAPs are sensitive to adipogenesis inhibition mediated by HDACi and thus still support SC differentiation (Mozzetta et al., 2013). However, they also demonstrated in old mdx mice the inability of HDACi treatment to be as effective as in young mdx mice. Another study showed that an epigenetic intervention, again with HDACi, not only suppresses the adipogenic potential of FAPs from young mdx mice but also unexpectedly promotes FAPs' myogenic lineage (Faralli and Dilworth, 2014; Saccone et al., 2014). In contrast, FAPs from old mdx mice fail to adopt a myogenic phenotype, and altogether these studies reveal that FAPs are highly influenced by environmental changes during aging. It is important to note, however, that the population isolated in that study was not only purified FAPs: it may contain other populations such as PW1 interstitial cells (PICs), side population cells (SP), or even type 1 pericytes (Boppart et al., 2013; Judson et al., 2013); this methodological point may explain the unexpected development along the myogenic lineage.

The Notch signaling pathway may also be involved in FAP-driven IMAT development during aging. This pathway is a major one implicated in the maintenance of SC quiescence as well as promotion of their proliferation after injury (Bjornson et al., 2012; Conboy et al., 2003; Mourikis et al., 2012; Pellegrinet et al., 2011; Wen et al., 2012). During aging, an attenuated Notch signaling response results in impaired proliferation of SCs and a regeneration failure (Conboy et al., 2003; Conboy et al., 2005). Interestingly, TGF-β is a Notch inhibitor upregulated during aging (Buas and Kadesch, 2010; Carlson et al., 2008; Carlson et al., 2009) and may explain the spontaneous entry of SCs into the cell cycle during aging. In addition, research has demonstrated that altered Notch signaling in the adult heart leads to abnormal development of fibrosis (Croquelois et al., 2008; Nemir et al., 2014). Notch signaling thereby regulates key mechanisms in mesenchymal cardiac progenitors and controls the balance between fibrosis development and cardiac repair in the adult heart. Nevertheless, there are no studies concerning the function of the Notch signaling pathway in FAPs, and further research is clearly needed to identify a highly possible role of this pathway in aged skeletal muscle.

Plenty of studies have already shown a major role of Wnt signaling in the inhibition of MSC differentiation into adipocytes accompanied by promotion of their myogenic fate (Bennett et al., 2002; Brunt et al., 2012; Chung et al., 2012; Moldes et al., 2003; Ross et al., 2000; Shang et al., 2007; Zaragosi et al., 2008). A study by Vertino et al. (2005) was focused particularly on Wnt10b, and they concluded that during aging, altered Wnt10b signaling increases expression of key adipogenic genes promoting IMAT accumulation. The Wnt signaling pathway appears to be particularly complex, especially when related to aging because expression levels of Wnt proteins will not all vary in the same direction. Further studies are needed to elucidate the mechanisms underlying age-related deregulation of Wnt signaling and IMAT development during sarcopenia.

Aging is also linked to altered synthesis of nitric oxide (NO) in skeletal muscle (Nyberg et al., 2012; Samengo et al., 2012). A study by Cordani et al. (2014) demonstrated *in vitro* that NO regulates FAP fate through inhibition of their differentiation into adipocytes. This mechanism was already reviewed by the same group recently (Sciorati et al., 2015), and these findings reveal another potential mechanism behind FAPs' driving adipogenesis with advancing age.

Comment citer ce document :
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Finally, the fibroblast growth factor 2 protein (FGF-2) seems to also play an important role in age-related impairment of skeletal muscle regeneration. FGF-2 expression increases with age, due to decreased expression of its inhibitor Sprouty 1. This mechanism induces a loss of stem cell quiescence, driving SCs to enter the cell cycle, and then most likely contributes to the loss of SCs observed during aging (Chakkalakal et al., 2012). No studies have been conducted on the effect of FGF-2 on FAPs even though this growth factor seems to also perform significant functions in differentiation of MSCs (Bae et al., 2015; Cai et al., 2013; Lee et al., 2013).

In conclusion, this part of the review highlighted the increasing recognition of the role of IMAT in the age-mediated loss of skeletal-muscle function. We first described the now well-known IMAT accumulation during sarcopenia and emphasized that this new important factor is closely linked to inactivity. We next reviewed various studies demonstrating the major role of increasing physical activity in stabilization of (or even a decrease in) IMAT accumulation in the elderly depending on the training characteristics. After that, we tried to emphasize new clues concerning FAPs and aging by linking them to some cellular players. We showed that many signaling pathways including HDAC, Notch, Wnt, NO, and FGF-2 may be implicated in aging-induced IMAT development and accumulation. We are confident that new studies will strengthen the links among FAPs, aging, and the influence of the stem cell niche regulating IMAT development.

6. Strategies against sarcopenia

Identification of cost-effective interventions to maintain muscle mass, muscle strength, and physical performance in the elderly is an important public health challenge. The perfect strategy would act on the three components of sarcopenia and would have the fewest possible side effects. Exercise appears to be the perfect strategy against sarcopenia (Montero-Fernandez and Serra-Rexach, 2013; Pillard et al., 2011; Wang and Bai, 2012). However, large-scale implementation of such an intervention is hampered by the lack of motivation among most persons. In addition, many senior citizens are nonambulatory or have comorbidities such as moderate to severe osteoarthritis (Bennell and Hinman, 2011) or certain forms of unstable cardiovascular disease that can preclude participation in resistance

training exercises (Williams et al., 2007). To overcome such barriers, development of alternative methods for prevention and treatment of sarcopenia is very important.

Here, we will focus on exercise, hormone replacement therapies, and HMB. In the last part, we will discuss the possibility of targeting the glucose 6-phosphate dehydrogenase (G6PDH) as a new effective strategy against sarcopenia. Other strategies such as pharmacological treatments (angiotensin-converting-enzyme inhibitors, statins, myostatin inhibitors, or anti-inflammatory drugs), nutritional strategies (e.g., whey proteins, branched amino acids, and vitamin D) and antioxidant strategies (e.g., supplementation with antioxidants or pharmacological inhibitors of pro-oxidant enzymes such as allopurinol) have been reviewed well elsewhere (Brioche and Lemoine-Morel, 2016; Brook et al., 2015; Cruz-Jentoft and Landi, 2014; Gomez-Cabrera et al., 2013; Maggio et al., 2013; Morley and Malmstrom, 2013; Sanchis-Gomar et al., 2011). For each strategy, we will present data on the efficiency and the mechanisms of action on sarcopenia.

6.1. Exercise as the most effective strategy against sarcopenia

Exercise appears to be the perfect strategy against sarcopenia because it can increase muscle mass, strength, and physical performance (Brook et al., 2015; Montero-Fernandez and Serra-Rexach, 2013; Pillard et al., 2011; Wang and Bai, 2012). In this work, when not specified, the word "exercise" will refer to repetition of different exercise sessions (i.e., training). Exercise also has positive effects on the metabolic, cardiovascular, and reproductive systems (Montero-Fernandez and Serra-Rexach, 2013; Pillard et al., 2011; Wang and Bai, 2012). In addition, exercise is known to improve quality of life and psychological well-being and is associated with better mental health and social integration: it alleviates anxiety and depression and improves self-efficacy in older adults (Mather et al., 2002). Usually, four types of exercise are recommended for older adults to prevent sarcopenia: aerobic (endurance), resistance (strength), flexibility (stretching), and balance (proprioception) training. Recommendations regarding the prescription of exercise to the elderly are not the objective of this review, but this topic has already been reviewed well elsewhere (Montero-Fernandez and Serra-Rexach, 2013; Phu et al., 2015; Pillard et al., 2011; Wang and Bai, 2012). Here, we will focus on the main mechanisms by which exercise (essentially resistance and endurance exercise) helps to fight sarcopenia.

6.1.1. Exercise during aging improves protein balance

Although whole-body protein synthesis appears to be unchanged by resistance exercise in older people (Hasten et al., 2000; Welle et al., 1995; Yarasheski et al., 1993), numerous studies showed that exercise can specifically increase mixed muscle protein synthesis (Balagopal et al., 2001; Hasten et al., 2000; Short et al., 2004; Welle et al., 1995; Yarasheski et al., 1999; Yarasheski et al., 1993), in particular, the synthesis of myofibrillar proteins such as MyHC (Balagopal et al., 2001; Hasten et al., 2000; Welle et al., 1995). In response to resistance exercise, these increases are always associated with improvement of muscle mass and muscle strength (Balagopal et al., 2001; Hasten et al., 2000; Welle et al., 1995; Yarasheski et al., 1999; Yarasheski et al., 1993). Typically, resistance training programs used in the cited studies lasted 3–4 months, with three sessions per week (separated by a rest day) with two to three sets of multiple exercises alternating between the upper and lower body, at gradually increasing intensity from 50–60% to 75–80% of the maximal repetition (1RM). Moreover, 1 week of resistance exercise is sufficient to obtain these results, and with only 2 weeks, the beneficial effect will persist for as long as 3 months (Hasten et al., 2000). Interestingly, although resistance training is typically associated with the most profound gains in strength, elderly subjects who completed a 3-month moderate-intensity aerobic program (3–5 days per week, with sessions of 20–45 min at 60–80% of the heart rate reserve) also demonstrated a marked increase in whole-muscle size and strength associated with increased mixed muscle protein synthesis and MyHC synthesis (Konopka et al., 2011; Short et al., 2004). Although many studies have shown an increase in muscle protein synthesis after resistance and aerobic training in the elderly, few studies have investigated the signaling pathways involved in this phenomenon. Nevertheless, it seems that activation of the PI3K/Akt/mTOR pathway is involved. Indeed, Mayhew et al. (2009) and Williamson et al. (2010) showed in elderly people that resistance exercise (12–16 weeks, 3 days per week, 80% of 1RM) leads to muscle hypertrophy (cross sectional area increase), an increase in muscle strength, and substantial muscle protein accretion associated with increased Akt, p70S6K, and rpS6 phosphorylation (activation). Data obtained from hypertrophied skeletal muscle of old rats indicated similar mechanisms. Indeed, chronic muscle overload induced by bilateral ablation of the gastrocnemius for 28 days increases plantaris weight in aged animals in conjunction with an increase in mTOR and rpS6 phosphorylation (Chale-Rush et al., 2009). On the other hand, it has been shown that

aerobic exercise (lifelong running wheel exercise or treadmill training) in old rats increases IGF-1 and IRS-1 protein content in skeletal muscle and Akt and mTOR activation associated with hypertrophied muscles (Kim et al., 2008; Pagano et al., 2014; Pasini et al., 2012). Finally, there are very few studies on older people or old animals that have explored the protein synthesis signaling pathways in response to training. Further research is needed to test various types and combinations of training and to explore responses in the functions of different muscle types (slow or fast) and evolution of these responses over the decades.

To date, various studies have shown that exercise (resistance and aerobic) in elderly subjects has no effect on proteolysis (Hasten et al., 2000; Welle et al., 1995; Yarasheski et al., 1993). This phenomenon may be explained in several ways: a lack of sensitivity of the techniques used to measure proteolysis; amino acids from proteolysis may be recycled during protein synthesis; exercise increases the activity of several proteolysis systems, while others are downregulated at the same time.

Data on the effects of exercise on the UPS systems in elderly people and old rodents are scarce. Moreover, to the best of our knowledge, proteasome activity has never been measured in older people and rodents in response to physical training. Nevertheless, some available data on the expression of the widely studied ubiquitin ligase E3 (i.e., MuRF1 and MAFbx) and muscle ubiquitinated protein (marker of E3 ligase activity) seem consistent with decreased activity of UPS after training. Indeed, it has been shown that 4 weeks of supervised endurance training in patients with chronic heart failure and muscle atrophy (mean age 72 years) is associated with a decrease in muscle content of ubiquitinated protein along with a marked decrease in muscle MuRF1 mRNA and protein content. In the same way, in old mice subjected to short and low-intensity treadmill training (4 weeks, 5 days per week, 20 min per session at 10 m/min), LeBrasseur et al. (2009) showed a marked decrease in muscle content of MuRF1 protein. Other studies after resistance training (12 weeks, 3 days per week, 70–75% 1RM) or a moderate-intensity aerobic program (12 weeks, 3–5 days per week, 20–45 min per session, 60–80% heart rate reserve) did not detect any change in the expression of MuRF1 or MAFbx (Konopka et al., 2010; Williamson et al., 2010). Finally, more studies are needed to definitively determine the effect of exercise on the UPS in sarcopenic people.

The most pronounced effect of exercise on proteolysis in the elderly and older animals is related to autophagy regulation. In humans and rodents, sarcopenia is associated

with decreased autophagy (Carnio et al., 2014; Fry et al., 2013; Kim et al., 2008; McMullen et al., 2009; O'Leary et al., 2013; Wohlgemuth et al., 2010; Zampieri et al., 2015), whereas exercise (endurance as well as resistance training) may reverse this impairment and cause muscle hypertrophy (independently of muscle type), decrease muscle fatigue, and increase strength (Carnio et al., 2014; Kim et al., 2013; Luo et al., 2013; Wohlgemuth et al., 2010; Zampieri et al., 2015). Indeed, in response to 8 weeks of treadmill training (5 days per week, 40 min per session at 16.4 m/min), there was an increase in muscle content of Beclin-1, LC3, and Lamp-2 proteins in old mice along with an increase in EDL and gastrocnemius weight (Kim et al., 2013). Earlier, Wohlgemuth et al. (2010) showed that rats subjected to lifelong exercise show upregulation of Lamp-2 RNA, Atg7, and Atg9 proteins along with increased plantaris weight. On the other hand, similar results were obtained in response to a resistance training protocol (climbing of a 1-m ladder inclined at 85° with weight attached to the tail) in old rats (Luo et al., 2013). Moreover, these authors showed an increase in lysosomal content of protease proteins (e.g., cathepsin L). Recently, similar results were published about old athletes compared to sarcopenic elderly people (Carnio et al., 2014; Zampieri et al., 2015). Indeed, these two studies on the same subjects showed that exercise completely reverses age-associated impairment in muscle content of autophagy markers such as ATG7, LC3II, and Bnip3. Finally, upregulation of these different markers suggests that aerobic exercise as well as resistance exercise during aging should stimulate autophagy induction, autophagosome formation, and fusion with lysosomes. Indeed, because no studies have directly measured the number of autophagy vesicles, the upregulation of various molecules regulating autophagy points only to enhancement of the latter. Because deregulation of the autophagic system is associated with accumulation of dysfunctional mitochondria and unfolded proteins (Carnio et al., 2014; Kim et al., 2013), Kim et al. (2013) speculated that an exercise training-induced autophagic response can be considered one of the mechanisms of cellular "clearance" that may be related to protection against accumulation of dysfunctional mitochondria and unfolded proteins.

6.1.2. Exercise during aging decreases myonuclear apoptosis

Several studies showed that aerobic exercise and resistance training during aging decrease myonuclear apoptosis and increase muscle mass and strength in old animals (Luo

et al., 2013; Marzetti et al., 2008; Song et al., 2006; Wohlgemuth et al., 2010). It seems that no data are available on older humans.

Regarding the effects of exercise training on myonuclear apoptotic signaling, Song et al. (2006) showed that 12-week treadmill exercise (5 days per week, 60 min per session) reduces the expression of Bax in gastrocnemius extracts of old rats. Conversely, levels of Bcl-2 are increased in trained rodents, resulting in a dramatic decrease in the Bax-to-Bcl2 ratio, reaching youth-related values. In addition, cleavage of caspase 3 is lowered by 95% in old exercising rats. As a consequence, the extent of apoptotic DNA fragmentation in the gastrocnemius is significantly attenuated by the exercise intervention, such that old trained rats show the levels of apoptosis similar to those observed in young control animals. It is noteworthy that the reduced severity of apoptosis is accompanied by an increased fiber cross sectional area along with increased muscle weight (soleus and gastrocnemius). Similarly, Marzetti et al. (2008) found that 4-week treadmill exercise training downregulates the death receptor pathway of apoptosis in the EDL of old rats. Indeed, exercise reversed the age-related upregulation of TNF-R1, activated caspase 8, and cleaved caspase 3, resulting in reduced levels of apoptotic DNA fragmentation. These adaptations were accompanied by improvements in exercise tolerance and forelimb grip strength. Furthermore, the same group published similar data on rats subjected to lifelong exercise with free access to a running wheel (Wohlgemuth et al., 2010). In addition, they showed that exercise reverses the age-related increase in caspase 9 activity. Recently, Luo et al. (2013) found that 9 weeks of resistance training prevent the loss of muscle mass and improve muscle strength, accompanied by reduced cytosolic concentration of cytochrome c in the gastrocnemius and inhibition of cleaved caspase 3 production, thus resulting in a reduced apoptotic index.

The decreased number of apoptotic myonuclei or decreased DNA fragmentation may be explained by a renewal of the latter thanks to SC activation.

6.1.3. Exercise during aging stimulates SCs

This topic was reviewed well by Snijders et al. (2009). Although some studies failed to demonstrate any effect of exercise on SCs in older people (Leiter et al., 2011; Petrella et al., 2006), most of them showed exercise-related activation of the latter in elderly people and older rodents along with improvement in muscle mass and strength (Leenders et al., 2013; Mackey et al., 2007; Shefer et al., 2010; Verdijk et al., 2009; Verney et al., 2008). For

instance, Verdijk et al. (2009) found that 3 months of resistance training (3 days per week, 80% 1RM) increase muscle mass, reduce fat mass, and increase muscle strength in healthy elderly men. The observed skeletal muscle hypertrophy was specific for type II muscle fibers and was accompanied by a specific increase in SC numbers. These data were recently confirmed by Leenders et al. (2013), who showed that 6 months of resistance-type exercise training (3 days per week, 80% 1RM) lead to increased lean mass of legs and quadriceps CSA, resulting in increased strength of one-repetition maximum leg extension and decreased sit-to-stand time. These results were accompanied by a type II muscle fiber-specific increase in myonuclear and SC content. On the other hand, Verney et al. (2008) and Shefer et al. (2010) reported similar results on the response to endurance training in the elderly (13 weeks of combined lower-body endurance and upper-body resistance training) and old rats (14 weeks of treadmill training, 6 days per week, 20 min per session): an increased size of type II muscle fiber accompanied by an increase in SC numbers.

6.1.4. Exercise during aging improves mitochondrial function and dynamics

Aerobic exercise of sufficient intensity (at least 60% $\dot{V}O_2$max) and duration (at least 3 weeks with 3 sessions of 1 h per week) can significantly increase $\dot{V}O_2$max and endurance capacity in older adults and rodents (Hammeren et al., 1992; Huang et al., 2005; Koltai et al., 2012; Lambertucci et al., 2007; Lanza et al., 2008; Malbut et al., 2002; Radak et al., 2002; Safdar et al., 2010; Short et al., 2004; Short et al., 2003). An increase in mitochondrial function and number, in the expression of mitochondrial proteins, and/or in the expression of transcription factors involved in mitochondrial biogenesis are mechanisms that explain the above improvements. Short et al. (2003) were among the first to show in humans that endurance training (16 weeks, four sessions per week at 80% of maximal heart rate for 40 min) increases $\dot{V}O_2$max associated with an increase in activities of mitochondrial enzymes (citrate synthase and cytochrome c oxidase), in mRNA levels of mitochondrial genes (e.g., COX4), and in mRNA of genes involved in mitochondrial biogenesis in skeletal muscle (PGC-1α, NRF-1, and TFAM). These results suggested that aerobic exercise could induce de novo mitochondrial biogenesis and improve mitochondrial function during aging. Indeed, Lanza et al. (2008) demonstrated in older trained people (performing at least 1 h of cycling or running 6 days per week during the past 4 years) an increase in mitochondrial ATP production rate; in citrate synthase activity; in muscle content of PGC1-α, NRF-1 and TFAM proteins; and in

mtDNA abundance. Moreover, an increased protein level of Sirt 3 (known to stimulate PGC-1α) was also observed. Moreover, Safdar et al. (2010) confirmed such results and showed that they are associated with functional improvements (an increase in maximal isometric strength and a decrease in time to perform the 30-feet walk test and stair climb tests). Furthermore, they found that physical activity in older people increases complex IV activity and protein levels of COX subunits I and II in skeletal muscle. More recently, Koltai et al. (2012) showed in old trained rats (6 weeks of treadmill training at 60% $\dot{V}O_2$max, 1 h/day) that increased mitochondrial biogenesis (according to increased protein levels of PGC-1α, succinate dehydrogenase, and COX4 in muscle and increased mtDNA abundance) is driven by an increase in Sirt 1 activity and AMPK phosphorylation. Moreover, these authors found that aerobic exercise can restore mitochondrial dynamics (fusion and fission) to levels similar to those observed in young rats (according to quantitative data on protein levels of mitofusin 1, fission protein 1, and Lon protease); this finding may reflect a reduction in the number of impaired mitochondria. Konopka and Sreekumaran Nair (2013) confirmed these results in older people after aerobic training (four sessions of 45 min per week at 80% heart rate reserve). Indeed, trained elderly people showed increased protein levels of mitofusins 1 and 2, fission protein 1, PGC-1α, and citrate synthase in muscle and increased $\dot{V}O_2$max and CSA. Because resistance training is usually not associated with improvement of mitochondrial function, very few studies are available on this topic. However, in older people after 12 weeks of whole-body resistance training (three sessions per week, 80% of 1RM), Parise et al. (2005) found an increase in complex IV activity, reflecting improvement of the electron transport chain. Moreover, in older rats, Luo et al. (2013) found increased AMPK phosphorylation associated with an increased mitochondrial concentration of cytochrome C in skeletal muscle after 9 weeks of resistance training. In both studies, however, physical parameters were not measured.

Here, we presented the main molecular mechanisms of prevention of sarcopenia by exercise, but other mechanisms, which are beyond the scope of this review, are also involved, such as better regulation of microRNAs controlling muscle mass (McGregor et al., 2014; Rivas et al., 2014; Zampieri et al., 2015). Finally, exercise appears to be the best countermeasure against sarcopenia because it can act on all the deleterious effects of aging, and at the same time, improve muscle mass, strength, and physical performance. As discussed here, resistance training leads to the most profound gains in strength and muscle

mass, whereas aerobic training enhances $\dot{V}O_2$max and endurance capacity. Performing the resistance training cycles and endurance training separately appears to be the best solution to combat sarcopenia.

6.2. Hormone replacement therapies as a possible strategy

There is evidence that hormones, in particular testosterone and GH (whose levels decrease with age) play a key role in the age-related onset of sarcopenia (Giannoulis et al., 2012; Maggio et al., 2013; Sakuma and Yamaguchi, 2012). Consequently, numerous researchers have tried to reverse sarcopenia using hormone replacement therapies.

6.2.1. Testosterone replacement therapy

In 2006, the findings from 11 randomized controlled trials were examined using the methods of meta-analysis to determine whether androgen treatment (testosterone or its more potent derivative 5α-dihydrotestosterone) increases strength in men aged 65 years and older (Ottenbacher et al., 2006). This meta-analysis was recently completed by Maggio et al. (2013), who reviewed the most recent randomized controlled trials. Those authors concluded that testosterone or 5α-dihydrotestosterone treatment can effectively increase muscle mass, strength, and physical performance (Ottenbacher et al., 2006; Maggio et al. 2013). The most convincing and complete data come from the Testosterone in Older Men with Mobility Limitations (TOM) trial conducted by Travison et al. (2011). The aim of this placebo-controlled randomized trial was to determine whether testosterone therapy (10 g of testosterone gel daily for 6 months) in community-dwelling men (age 74 years; with severe limitation in mobility) improves muscle strength and physical function. Muscle strength was assessed by means of leg press and chest press strength. Physical function was evaluated using a 12-step stair climb and 40-meter walk tests. Muscle fatigue was also assessed, by tests involving lifting and lowering a basket of a weight equivalent to 15% of body weight. Finally, lean body mass was determined by dual energy X-ray absorptiometry (DXA) . All these parameters were enhanced by this treatment and were associated with upregulation of serum total and free testosterone. Nevertheless, adverse cardiovascular events occurred in more men receiving testosterone as compared to men receiving placebo, thus causing the organizers to stop the study. This study showed that despite numerous significant beneficial effects of testosterone treatment on elderly men, more studies are needed to find the the optimal regimen of administration. Currently, intermittent

treatments and/or treatments associated with 5α-reductase inhibitors (to avoid adverse effects on prostate), injections instead of oral or transdermal treatments, are new approaches being tested to decrease adverse effects of testosterone (Borst and Yarrow, 2015).

Different mechanisms can explain the beneficial effects of testosterone. Testosterone is known to stimulate muscle protein synthesis, to improve recycling of intracellular amino acids, to decrease the protein breakdown rate, and to enhance neuromuscular function (to increase activity of motoneurons) (Dubois et al., 2012). Testosterone also promotes SC activation and may inhibit their differentiation into adipocytes via an androgen receptor-mediated pathway (Grossmann, 2011). Testosterone treatment is also associated with upregulation of hemoglobin; this effect can be considered an additional mechanism by which this hormone improves muscle oxygenation and function (Fernandez-Balsells et al., 2010). Moreover, testosterone seems to have anti-inflammatory effects because it can reduce the plasma concentration of TNF-α and several interleukins (Malkin et al., 2004). More recently, it was shown that testosterone is effective at reversing sarcopenia in rodents (Kovacheva et al., 2010). Those authors showed that testosterone decreases lipid oxidative damage and apoptosis and explained this result by the concomitant increase in muscle content of the glucose 6-phosphate dehydrogenase (G6PDH) protein. Moreover, testosterone treatment led to SC activation though the Notch signaling pathway due to myostatin inhibition and Akt activation (Kovacheva et al., 2010).

6.2.2. GH replacement therapy

GH is a single-chain peptide of 191 amino acid residues; it is produced and secreted mainly by the somatotopic cells of the anterior pituitary gland. GH coordinates postnatal growth of multiple target tissues, including skeletal muscle (Florini et al., 1996). GH secretion occurs in a pulsatile manner with a major surge at the onset of slow-wave sleep and less conspicuous secretory episodes a few hours after meals (Ho et al., 1988). GH secretion is controlled by the actions of two hypothalamic factors: GH-releasing hormone (GHRH), which stimulates GH secretion, and somatostatin, which inhibits GH secretion (Giannoulis et al., 2012). The secretion of GH is maximal at puberty, accompanied by very high circulating IGF-I levels (Moran et al., 2002), with a gradual decline during adulthood. Indeed, circulating GH levels decline progressively after 30 years of age at a rate of ~1% per year. In aged men, daily

GH secretion is 5- to 20-fold lower than that in young adults (Ryall et al., 2008). Moreover, Veldhuis et al. (1995) found a decrease in GH secretory burst amplitude with age (maximal rate of GH secretion attained within a release episode). The age-dependent decline in GH secretion is secondary to downregulation of GHRH and to an increase in somatostatin secretion (Kelijman, 1991).

The effects of GH administration in elderly people on muscle mass, strength, and physical performance are still debated (Giannoulis et al., 2012). Some researchers demonstrated an improvement in strength after short- and long-term administration (3–11 months) of GH (Blackman et al., 2002; Brill et al., 2002; Welle et al., 1996). For instance, in healthy subjects over 60 years old, Welle et al. (1996) found that GH treatment for 3 months (0.03 mg per kg of body weight subcutaneously, three times per week) increases lean body mass, muscle mass, and thigh strength. Similar data were published by Blackman et al. (2002) on a 26-week randomized, double-blind, placebo-controlled parallel-group trial in healthy, ambulatory, community-dwelling US men aged 65 to 88 years, who received GH at 20 µg/(kg body weight) subcutaneously three times per week. Treated men showed a fat mass decrease along with an increase in lean mass, which was higher as compared to another group (receiving testosterone). Furthermore, men's $\dot{V}O_2$max increased under the influence of GH and was directly related to changes in lean body mass. Unfortunately, some adverse effects such as arthralgia were more common with GH treatment. Interestingly, in older men, it has been shown that GH therapy leads to substantial upregulation of the MyHC 2X isoform (Lange et al., 2002). In contrast, other researchers did not find any improvement of muscle strength or muscle mass after GH treatment in the elderly (Giannoulis et al., 2012). There may be several reasons for the lack of effectiveness of GH treatment, for example: failure of exogenous GH treatment to mimic the pulsatile pattern of natural GH secretion (Sakuma and Yamaguchi, 2012). In animal models, beneficial effects were also observed when recombinant human GH was used. Indeed, in old rats treated with GH (2.7 mg per kg per day during 12 weeks), (Andersen et al., 2000) observed an increase in maximal tetanic tension of calf musculature (soleus, plantaris, gastrocnemius, tibialis anterior, EDL) associated with muscle hypertrophy (assessed by muscle weight and volume) likely due to the concomitantly increased protein synthesis. Similarly, using a treatment mimicking the pulsatile pattern of natural GH secretion (2 mg/kg per day, diluted in saline, divided into two subcutaneous injections: at 10:00 and 17:00 h), with doses resulting in hepatic and plasma

IGF-1 levels of young rats, Castillo et al. (2005) and Brioche et al. (2014) showed that GH treatment during 4 or 8 weeks increases lean mass and gastrocnemius mass and decreases fat mass. Nevertheless, others did not detect such beneficial effects, may be because of shorter treatment duration or a different dose or source of GH (e.g., recombinant porcine GH) (Marzetti et al., 2008).

Molecular mechanisms by which GH may increase muscle mass, strength, and maximal oxygen consumption in the elderly and in older animals have not been studied well in skeletal muscle. It is clearly established that effects of GH are driven by IGF-1, which can be produced in either the liver or skeletal muscle. Different isoforms of IGF-1 have diverse effects. Liver-derived IGF-1 appears to predominantly increase muscle mass by improving protein synthesis, whereas muscle-derived IGF-1 has effects on the development of SCs and on maintenance of neuromuscular function (Perrini et al., 2010). Recently, Brioche et al. (2014) showed that GH treatment prevents the muscle mass decrease observed in old rats. These beneficial effects are driven by an increase in protein synthesis concomitant with a decrease in proteolysis, as expected after activation of p70S6K and weaker MuRF1 expression. The downregulation of myostatin observed in the old treated rats could explain these results. Indeed, in the absence of myostatin, mice show increased protein synthesis owing to increased activation of the PI3K/Akt/mTOR pathway (Guo et al., 2009). Moreover, inhibition of myostatin with a specific inhibitor has been shown to decrease MuRF1 expression in the skeletal muscle of mice (LeBrasseur et al., 2009). In the same study, rats treated with GH showed downregulation of the cell cycle inhibitor p21 and upregulation of the myogenic factor Myf-5 implying activation of SCs. These different results may explain how GH treatment prevents a decrease in muscle mass in the elderly. An increase in mitochondrial biogenesis is usually associated with increased maximal oxygen consumption and/or increased endurance capacity in the elderly and older rats (Derbre et al., 2012; Koltai et al., 2012; Short et al., 2003). Interestingly, GH treatment used in the study by Brioche et al. (2014) led to improved mitochondriogenesis in the treated rats. Indeed, GH treatment was associated with increased muscle content of cytochrome c protein and citrate synthase activity, likely because of the concomitant activation of the PGC-1α/NRF-1 pathway. Earlier, Vescovo et al. (2005) working on the rat soleus muscle, reported that GH activates PGC-1α via IGF-1 and calcineurin pathways. Similarly, Short et al. (2008) demonstrated in healthy young humans that acute GH action promotes an increase in mitochondrial oxidative

capacity and expression of several mitochondrial genes (e.g., COX3, TFAM). However, mitochondrial protein synthesis was not increased likely because of the unique dose of GH. As reviewed well by Derbre et al. (2014), oxidative stress is involved in protein balance impairment and mitochondrial dysfunction in sarcopenia. Interestingly, GH treatment in old rats improves the redox status according to a decrease in oxidative damage to protein and DNA and the upregulation of key intracellular antioxidant enzymes, such as catalase, glutathione peroxidase, and G6PDH. Although the exact mechanisms by which GH activates the expression of antioxidant enzymes are still unknown, the better redox status observed in old rats treated with GH is likely involved in the improvement of protein balance and mitochondriogenesis. These results and those of Kovacheva et al. (2010) suggest that in general, growth factors (at least GH and testosterone) can alleviate oxidative stress. GH treatment may also improve muscle mass and physical performance via a reduction in apoptosis (Forman et al., 2010; Vescovo et al., 2005); however, to our knowledge, this effect has never been demonstrated in aged muscle.

Hormone replacement therapies, notably testosterone and GH, are useful for improving muscle mass in the elderly. Nevertheless, the doses currently used are often associated with side effects. More studies are needed to continue exploration of other parameters of various treatments such as dose (physiological doses), duration, and periodicity (intermittent versus continuous) to prevent adverse effects. With respect to GH, pilot treatments mimicking its pulsatile secretion in humans could be a new way. Moreover, by elucidating which mechanisms mediate the action of hormones in older animals, it is possible to find new molecules to target in sarcopenia and more generally to combat muscle disuse in various situations.

6.3. Nutritional interventions: the case of HMB

Nutritional interventions seem effective at improving muscle strength and physical performance with or without increasing muscle mass (Cruz-Jentoft and Landi, 2014). Nissen et al. (1996) first demonstrated that dietary supplementation with HMB lowers muscle proteolysis after resistance training and augments gains in lean body mass and strength in a dose-dependent manner in young people. A few years later, Vukovich et al. (2001) reported a similar result in the elderly, whereas May et al. (2002) showed that the mixture HMB/Arginine/Glutamine is effective in increasing fat-free mass of aged patients with

advanced cancer (May et al., 2002; Vukovich et al., 2001). Since then, HMB has been studied under a variety of anaerobic and aerobic training and wasting conditions (Wilson et al., 2008; Wu et al., 2015). As explained in this section, among nutritional strategies, HMB (a metabolite of the branched-chain amino acid leucine) may be considered an effective strategy against sarcopenia—and other wasting conditions—when taken alone or combined with exercise or other nutritional supplements.

6.3.1. HMB, who are you?

HMB is a metabolite of the essential amino acid leucine, which is generated after after a transamination reaction producing α-ketoisocaproate (KIC; an intermediate of the Krebs cycle) and subsequent conversion to HMB by KIC-dioxygenase in the cytosol (Nissen and Abumrad, 1997; Van Koevering and Nissen, 1992). The liver is the major site of production of HMB; muscle and other tissues produce HMB but in low amounts (Nissen and Abumrad, 1997). Under normal conditions, approximately 2–10% of the dietary leucine (~6.1 g per day) is converted to HMB corresponding to ~0.3–0.6 g for a subject weighing 70 kg (Van Koevering and Nissen, 1992). HMB is present in such foods as citrus fruits, some fish, and breast milk (Nissen and Abumrad, 1997). Nonetheless, it may be impractical to provide via diet the quantities of HMB used in human studies that demonstrate efficiency of HMB (3 g/day) (Wilson et al., 2013; Wu et al., 2015). For example, 3 g of HMB would represent 60 g of leucine, which would be supplied by 600 g of high-quality protein and a very large amount of food. Currently, HMB can be used as monohydrated calcium salt [formula: $Ca(HMB)_2 \cdot H_2O$] or a free acid form of HMB (FaHMB) (Fuller et al., 2011). Although currently, the calcic HMB (CaHMB) form is more widely used in humans and in rodent studies, Fuller et al. (2011) found that FaHMB improves HMB availability in human subjects as compared with the CaHMB. Surprisingly, it seems that the opposite occurs in rodents (Shreeram et al., 2014). Whatever the HMB form, HMB half-life is ~2–3 h, with a return to normal values ~9 h postabsorption (Wilson et al., 2013). Nowadays in humans, 3 g of CaHMB taken three times a day (1 g each time) is the optimal posology, which allows for continual bioavailability of HMB in the body (Wilson et al., 2013). In rodents, the optimal dose seems to be 0.250 mg/(kg·day) in mice and 320 mg/(kg·day) in rats (Szczesniak et al., 2014). In rodent studies, HMB is often administered via unique intragastric gavage to better control the treatment; however, this approach may minimize the effect of treatment because plasma will be free of

HMB for ~15 h/day. CaHMB is completely safe, and its safety in humans and animals has been well studied and reviewed (Szczesniak et al., 2014; Wilson et al., 2013). However, a possible decrease in insulin sensitivity and higher glucose intolerance have been reported in young healthy rats treated for 4 weeks with CaHMB (320 mg/[kg·day]) in the first case (Yonamine et al., 2014), or in rats treated with glucocorticoids combined with HMB, as compared to rats treated only with glucocorticoids (Nunes et al., 2013). These findings have not been reported in any previous human study but have to be studied in the future along with the safety of FaHMB, which has been studied only in rodents and showed no side effects (Fuller et al., 2014). Moreover, safety of very long treatments can be studied because the longest study lasted for 1 year (Baier et al., 2009), whereas treatment of sarcopenia or other wasting conditions such as cachexia can last longer.

6.3.2. HMB: a very potent strategy against various muscle-wasting conditions

Beneficial effects of HMB in human subjects have been reported in several muscle-deconditioning conditions characterized by a loss of muscle mass and a decrease in muscle strength and physical performance, for example, cancer cachexia (May et al., 2002), AIDS (Clark et al., 2000), chronic obstructive pulmonary disease (Hsieh et al., 2006) and aging (Baier et al., 2009; Deutz et al., 2013; Flakoll et al., 2004; Hsieh et al., 2010; May et al., 2002; Stout et al., 2013; Vukovich et al., 2001). Efficiency of HMB in various muscle-deconditioning conditions in rodents and cell lines has also been reported, e.g., experimental models of cachexia (Aversa et al., 2011; Caperuto et al., 2007; Eley et al., 2007; Mirza et al., 2014b; Nunes et al., 2008; Smith et al., 2005), glucocorticoid treatments (Aversa et al., 2012; Baptista et al., 2013; Giron et al., 2015; Nunes et al., 2013), and experimental models of sepsis and endotoxemia (Eley et al., 2008a; Kovarik et al., 2010; Supinski and Callahan, 2014) in response to muscle-wasting treatments such as TNF-α and angiotensin II (Eley et al., 2008a, b), a mouse model of Duchenne muscular dystrophy (Payne et al., 2006), and hypokinesia and hypodynamia models (HU or immobilization) (Alway et al., 2013; Baptista et al., 2013; Hao et al., 2011; Mirza et al., 2014b). In animals, effects of HMB during aging have been studied only in combination with other muscle-deconditioning circumstances (Alway et al., 2013; Hao et al., 2011), and specific studies are needed.

6.3.3. Efficiency of HMB in various muscle-wasting conditions in the elderly

Now, we will specifically focus on the studies showing HMB efficiency in the elderly and discuss the underlying molecular and cellular mechanisms. Very recently, Wu et al. (2015) published a meta-analysis of the effect of HMB supplementation on muscle in older adults. Currently, only seven studies have been conducted on the elderly receiving HMB alone (Deutz et al., 2013; Hsieh et al., 2010; Stout et al., 2013) or in combination with exercise (Stout et al., 2013; Vukovich et al., 2001) or with arginine and lysine or glutamine supplementation (Baier et al., 2009; Flakoll et al., 2004; May et al., 2002). Among these studies, four were devoted specifically to the protective effect of HMB on muscle deconditioning related to aging (Flakoll et al., 2004; Stout et al., 2013; Vukovich et al., 2001), whereas two of them dealt with the protective effect of HMB during bed rest (Deutz et al., 2013; Hsieh et al., 2010), and one study involved older cachexic patients (May et al., 2002). According to all these studies, supplementation with HMB alone or in combination with other compounds or exercise has a beneficial effect on body composition (especially, in terms of greater muscle mass) in the groups receiving HMB, without an obvious effect on fat mass in elderly people despite the wasting condition. Effects on muscle strength and physical performance are more controversial. Among these studies, five measured muscle strength by different methods (handgrip strength, leg strength, or knee extensor and flexor strength), whereas only four evaluated the effect of HMB on physical performance (e.g., SPPB, TUG). Deutz et al. (2013) did not report any effect of HMB on muscle strength after 10 days of bed rest in the elderly (men and women) but showed a clear tendency to limit the decrease observed; the latter result did not reach statistical significance probably due to the small sample size. Baier et al. (2009) observed similar results after 1 year of HMB treatment in aged subjects. After 8 weeks of resistance training with or without HMB supplementation, Vukovich et al. (2001) observed a similar increase in both upper-body strength and lower-body strength in different groups. Stout et al. (2013) reported similar results on elderly people after 24 weeks of resistance training, combined or not combined with HMB supplementation. However, the same authors showed that when used alone for 24 weeks, HMB increases muscle strength as compared to a placebo group. Flakoll et al. (2004) observed similar results in elderly females receiving HMB supplementation for 12 weeks, which significantly improved their muscle strength (measured by leg extensor force and handgrip strength) and physical function.

6.3.4. Molecular and cellular mechanisms by which HMB prevents muscle wasting

Mechanisms by which HMB prevents a loss of muscle mass or muscle strength or deterioration of physical performance have not been studied well in humans, but studies on animals and cell cultures provided a lot of data. As demonstrated above, in section 4, negative protein turnover and an imbalance between apoptosis and regenerative processes may largely explain the decrease in muscle mass and muscle strength during sarcopenia, while impairment of mitochondrial dynamics and functions may mostly be involved in the deterioration of physical performance.

In elderly subjects, HMB increases muscle mass or prevents a muscle mass decrease by improving protein turnover (Baier et al., 2009; Deutz et al., 2013; Flakoll et al., 2004; Hsieh et al., 2010). Protein balance improvement seems to be caused by an increase in muscle protein synthesis (Baier et al., 2009; Deutz et al., 2013; Flakoll et al., 2004) and a decrease in protein breakdown (Hsieh et al., 2010). Similar data have been published about animals and cellular muscle-wasting models (Aversa et al., 2012; Eley et al., 2007; Eley et al., 2008a, b; Giron et al., 2015; Kovarik et al., 2010; Smith et al., 2005). The increase in protein synthesis after HMB supplementation may be explained by activation of the PI3K/Akt/mTOR pathway and its targets. Indeed, prevention of gastrocnemius mass loss in cachexic rats by HMB is associated with increased activation of mTOR and p70S6K phosphorylation (Aversa et al., 2011). Similar results were reported in numerous studies on culture of muscle cells exposed to different muscle-wasting treatments such as TNF-α, INF-γ, GCs (dexamethasone), and angiotensin II (Aversa et al., 2012; Eley et al., 2007; Eley et al., 2008a, b; Kimura et al., 2014a). The stronger activation of the PI3K/Akt/mTOR pathway and its targets in response to HMB treatment may be explained by an increased activity of the GH/IGF-1 axis, which is known to improve protein synthesis through mTOR activation (Schiaffino et al., 2013). Indeed, healthy young rats treated with GH show higher GH mRNA and protein content in the pituitary gland, along with higher IGF-1 serum and hepatic levels as compared to rats receiving a placebo (Gerlinger-Romero et al., 2011). Similar results were observed in cultured human SCs (Kornasio et al., 2009). The mechanistic link between HMB and the GH-IGF-1 axis is completely unknown.

Decreased protein breakdown observed in the elderly receiving a supplement of HMB may be explained by lesser proteasomal activity and expression of subunits associated

with lesser expression of MAFbx and MuRF1 (two important E3 ubiquitin ligases involved in muscle wasting). Indeed, in cachexic mice receiving HMB, Smith et al. (2005) showed a decreased proteasomal activity along with a decrease in protein content of proteasome subunits in hindlimb muscles, as compared to cachexic control mice. In line with these results, Noh et al. (2014) found decreased mRNA and protein content of MuRF1 and MAFbx associated with less ubiquitinated MyHC and higher total MyHC protein content in the soleus of rats treated with GCs and receiving HMB, as compared to a placebo group. Similarly, Russ et al. (2015) showed recently that HMB treatment combined with β-alanine in sedentary aged male rats (20 months) reduces muscle MuRF1 expression as compared to control rats. Similar data have been obtained in muscle cell cultures exposed to wasting treatments such as TNF-α, IFN-γ, and GCs (dexamethasone) (Aversa et al., 2012; Giron et al., 2015; Kimura et al., 2014a). Inhibition of proteasome and E3 ubiquitin ligases by HMB could be due to its anti-inflammatory and antioxidant effects (Eley et al., 2008b; Hsieh et al., 2006) mediated by decreased expression of TNF-α and activation of the redox-sensible p38 MAPK (Aversa et al., 2012; Townsend et al., 2013), which are known to activate the UPS system (Schiaffino et al., 2013). Nonetheless, these mechanisms need to be confirmed.

HMB's effect on autophagy may be involved in the improvement of the protein balance observed in aged subjects receiving a supplement of HMB. Nonetheless, only data obtained in response to glucocorticoid treatments are available; although autophagy increases in response to GCs (Giron et al., 2015), it decreases during sarcopenia (McMullen et al. 2009; Wohlgemuth et al. 2010; O'Leary et al. 2013; Fry et al. 2013; Kim et al. 2013). However, HMB treatment of muscle cells normalizes the dexamethasone-induced autophagy pathway through the increased ratio phosphorylated-FoxO3/total-FoxO3 and via Akt activation (Giron et al., 2015). More data are needed to explore the effects of HMB under sarcopenic and more generally under muscle-wasting conditions.

The decrease in apoptosis in response to HMB supplementation may be involved in HMB's protective effect on muscle mass in the elderly. Indeed, HMB can decrease apoptosis, judging by a dramatic decrease in the number of TUNEL-positive nuclei in the soleus and plantaris of hindlimb-unloaded old rats treated with HMB, as compared to a placebo group. This effect of HMB was due to downregulation of cleaved caspases 3 and 9 in the soleus and

plantaris (Hao et al., 2011). Similar data were obtained in muscle cell cultures (Kornasio et al., 2009).

Finally, HMB may participate in prevention of muscle mass loss in the elderly by acting on SC proliferation and differentiation. This way, data have been obtained in old rats during muscle recovery after hindlimb unloading. Indeed, those authors showed increased numbers of bromodeoxyuridine-positive, PAX7- and PAX7/Ki67-positive nuclei (markers of SC proliferative state) in the plantaris of HMB-treated rats compared to control rats (Alway et al., 2013). As a result, there was a greater number of differentiated stem cells judging by a greater number of MyoD/myogenin-positive myonuclei relative to all myonuclei, in HMB-reloaded plantaris muscles as compared to reloaded muscles from vehicle-treated animals. Furthermore, HMB increased the nuclear protein levels of proliferation markers—inhibitor of differentiation 2 and cyclin A—as compared to vehicle treatment of reloaded muscles. Enhanced SC proliferation leading to an increased number of differentiated myonuclei should promote the transcriptional potential to support hypertrophic changes in muscle and functional changes in sarcopenic muscles; and this effect may partly explain the reduced apoptosis in HMB-treated muscles (Alway et al., 2013).

Increased physical performance in aged subjects treated with HMB may also involve better mitochondrial functions and dynamics (mitochondrial biogenesis and fusion/fission). Indeed, Pinheiro et al. (2012) found that HMB supplementation increases ATP and glycogen content and citrate synthase activity in the skeletal muscle of young healthy rats and raises specific force generation and resistance to acute fatigue (without changes in contraction) as well as relaxation velocities in electrostimulated hindlimb muscles. It has been demonstrated that leucine stimulates mitochondrial biogenesis genes *Sirt1*, *PGC-1α*, and *NRF-1* through AMPK activation and increases mitochondrial mass (by 30%) and oxygen consumption in C2C12 myotubes (Liang et al., 2014). Moreover, HMB has been reported to activate AMPK synergistically with resveratrol in C2C12 myotubes (Bruckbauer and Zemel, 2013). Consequently, it can be hypothesized that HMB activates mitochondrial biogenesis through AMPK activation, leading to increased citrate synthase activity thus eventually resulting in better physical performance in HMB-treated elderly people. Nevertheless, all of this has to be confirmed.

In conclusion, HMB treatment clearly appears to be a safe potent strategy against sarcopenia, and more generally against muscle wasting, because HMB improves muscle mass, muscle strength, and physical performance. It seems that HMB is able to act on three of the four major mechanisms involved in muscle deconditioning (protein turnover, apoptosis, and the regenerative process), whereas it is hypothesized to strongly affect the fourth (mitochondrial dynamics and functions). Moreover, HMB is cheap (~30–50 US dollars per month at 3 g per day) and may prevent osteopenia (Bruckbauer and Zemel, 2013; Tatara, 2009; Tatara et al., 2012; Tatara et al., 2007; Tatara et al., 2008) and decrease cardiovascular risks (Nissen et al., 2000). For all these reasons, HMB should be routinely used in muscle-wasting conditions especially in aged people.

6.4. A potential therapeutic target in sarcopenia: Glucose 6-phosphate dehydrogenase

G6PDH was first described in 1931 (Kornberg, 1955). Most studies were focused on G6PDH deficiency and lipid metabolism until a few years ago. G6PDH deficiency is the most common gene mutation in the world (Nkhoma et al., 2009). During the last decade, studies have started to explore its involvement in diabetes (Park et al., 2005), heart failure (Assad et al., 2011), and cancer (Kuo et al., 2000). It is now clear, however, that G6PDH is a critical metabolic enzyme under complex control and is at the center of an essential metabolic nexus that affects many physiological processes. Surprisingly, its function in skeletal muscle is poorly studied, whereas several clinical cases of rhabdomyolysis due to G6PDH deficiency were reported more than 15 years ago (Kimmick and Owen, 1996). Moreover, numerous studies have shown since the 1980s that deregulation of its activity is associated with myopathies (Elias and Meijer, 1983; Meijer and Elias, 1984). Finally, G6PDH should be studied more because its upregulation in transgenic flies extends their life span (Legan et al., 2008) and mice overexpressing G6PDH have better protection from aging-associated functional decline, for example, an extended median lifespan, higher levels of NADPH, lower levels of reactive oxygen species-associated damage, and better neuromuscular fitness in females compared to their control littermates (Nobrega-Pereira et al., 2016).

G6PDH controls the entry of glucose 6-phosphate (G6P) into the pentose phosphate pathway also known as the hexose monophosphate shunt. The major products of the pentose phosphate pathway are ribose 5-phosphate (R5P) and nicotinamide adenine dinucleotide phosphate (NADPH) generated from NADP by G6PDH and the next enzyme in

the pathway, 6-phosphogluconate dehydrogenase (PGD). In the following paragraphs, it will be explained why via NADPH and R5P, G6PDH may be involved in sarcopenia and why enhancing their production by G6PDH should help to combat sarcopenia.

Not long ago, G6PDH was described only as the principal source of NADPH in the cytosol. It was recently shown, however, that G6PDH is present in the mitochondria of skeletal muscle cells and provides NADPH as do isocitrate dehydrogenase (ICDH), malic enzyme (ME), and glutamate dehydrogenase (GDH), which were originally described as the principal sources of NADPH in mitochondria. Thus, NADPH is mainly produced by five enzymes in mammalian cells: G6PDH, 6-PGD, ICDH, ME, and GDH. All have been studied extensively and play crucial cellular roles. G6PDH, however, appears to be of unique importance to many cellular processes that use NADPH because inhibition of G6PDH lowers NADPH levels, which are not maintained at normal levels by the other enzymes producing NADPH (Hecker et al., 2013; Stanton, 2012).

It has been traditionally thought that G6PDH is regulated by the NADPH/NADP ratio so that as the ratio decreases, activity increases to provide more NADPH. Indeed, G6PDH is activated after exposure of cells to various extracellular oxidants (Kletzien et al., 1994) that lead to a decrease in the level of NADPH. Regulation by the NADPH/NADP ratio has been clearly demonstrated in vitro (Holten et al., 1976) but not in vivo. G6PDH is tightly regulated at the transcriptional, translational, and post-translational levels and by the intracellular location. G6PDH is the downstream target of many molecules **(Table 2)**, in particular growth factors and their downstream effectors. In the skeletal muscle of old rodents, it has been shown that testosterone and GH treatments (known to activate the PI3K/Akt/mTOR pathway) can increase G6PDH activity and protein content associated with muscle hypertrophy (Brioche et al., 2014; Kovacheva et al., 2010; Max, 1984). Aerobic training was also found to increase G6PDH activity in rat skeletal muscle (Barakat et al., 1989). Other factors also regulate G6PDH and are summarized in **Table 2**. Interestingly, G6PDH is mainly activated by growth factors; this finding is suggestive of a role in cell growth, as discussed below.

Several antioxidant systems depend on the production of NADPH for proper function. The first is the glutathione system dependent on the production of reduced glutathione by glutathione reductase, which depends on NADPH (Scott et al., 1993). Catalase does not need

NADPH to convert hydrogen peroxide to water but has an allosteric binding site for NADPH that can keep catalase in its active conformation (Scott et al., 1993). Superoxide dismutase does not use NADPH to convert superoxide to hydrogen peroxide; however, if this compound is not adequately reduced chemically by catalase or glutathione, the increased hydrogen peroxide levels will quantitatively increase and inhibit the SOD activity (Stanton, 2012). It has been shown in various studies that during sarcopenia and aging, decreased G6PDH activity and/or muscle protein content are associated with depletion of GSH, an increase in the GSSG/GSH ratio associated with decreased activity or protein content of glutathione reductase (GR), glutathione peroxidase (Gpx), catalase, and SOD (Brioche et al., 2014; Kovacheva et al., 2010; Kumaran et al., 2004; Sinha-Hikim et al., 2013). These observations may explain the observed concomitant increase in lipid peroxidation and DNA and protein oxidation (Brioche et al., 2014; Kovacheva et al., 2010; Kumaran et al., 2004; Sinha-Hikim et al., 2013). On the other hand, in response to different antioxidant strategies or testosterone or GH treatment of rats, G6PDH protein content or activity is increased in skeletal muscle; a concomitant increase in GSH, GR, Gpx, Cat, and SOD activities was observed, leading to alleviation of oxidative damage (Brioche et al., 2014; Kovacheva et al., 2010; Kumaran et al., 2004; Sinha-Hikim et al., 2013). These results provided evidence that targeting G6PDH would be a good strategy to combat sarcopenia by restoring youth-associated redox status, which is very important to reestablish protein synthesis and the muscle regenerative potential (Derbre et al., 2014). As mentioned above, Kovacheva et al. (2010) published data on this topic. Indeed, testosterone treatment of old mice is able to increase G6PDH muscle content associated with decreased lipid peroxidation and increased Akt activation and SC activation. Eventually, these mice develop muscle hypertrophy. Similar results were published by Sinha-Hikim et al. (2013) regarding old mice in response to treatment with a GSH precursor. In young animals, it has been shown that aerobic exercise can increase G6PDH activity in the liver and skeletal muscle (Askeq et al., 1975). Moreover, Braga et al. (2008) detected a dramatic decrease in G6PDH protein content in sarcopenic mice. Similarly, G6PDH overexpression in endothelial cells results in decreased reactive oxygen and nitrogen species production as compared to wild-type cells (Leopold et al., 2003).

Various studies in cell culture have shown a direct negative relation between G6PDH activity and/or protein content and apoptosis (Fico et al., 2004; Nutt et al., 2005; Salvemini

et al., 1999; Tian et al., 1999). For instance, G6PDH-null embryonic stem cells are more sensitive to hydrogen peroxide-induced apoptosis associated with GSH depletion and high caspase 3 and 9 protein levels (Fico et al. 2004). On the other hand, Nutt et al. (2005) showed that inhibition of G6PDH by didehydroepiandrosterone (DHEA) activates caspase 2 and promotes oocyte apoptosis. In old rodents, decreased activity and/or protein content of G6PDH in skeletal muscle is associated with increased apoptosis and atrophy (Braga et al., 2008; Kovacheva et al., 2010; Sinha-Hikim et al., 2013). Moreover, Braga et al. (2008) confirmed in old mice that depletion of G6PDH protein is associated with upregulation of caspases 2 and 9 in skeletal muscle. On the other hand, in response to different strategies against sarcopenia, increased G6PDH activity or protein content is associated with decreased apoptosis and with muscle hypertrophy (Brioche et al., 2014; Kovacheva et al., 2010; Sinha-Hikim et al., 2013). This beneficial effect may be mediated by a link between Akt and G6PDH. Indeed, Akt is also known to have antiapoptotic effects (Robey and Hay, 2006). Moreover, in the aforementioned studies, in old muscle, Akt activation and G6PDH protein are both downregulated and associated with muscle atrophy (Brioche et al., 2014; Kovacheva et al., 2010; Sinha-Hikim et al., 2013).

G6PDH activity may play an important role in muscle hypertrophy and regeneration by acting on possible proliferation of SCs, on RNA, and protein synthesis. Indeed, in various old studies on the muscle degeneration-regeneration cycle, it has been shown that during regeneration (known to involve SCs), G6PDH activity is dramatically increased (Wagner et al., 1977; Wagner et al., 1978), while protein synthesis and RNA synthesis are also increased (Wagner et al., 1978). Furthermore, inhibition of mRNA and protein synthesis is associated with G6PDH inhibition (Wagner et al., 1978). Thus, it was argued that G6PDH may perform a major function in mRNA and DNA synthesis because it is the rate-limiting enzyme of the pentose phosphate pathway, which is the main pathway synthetizing R5P, an essential component of nucleic acids. Because of this function, G6PDH may indirectly affect protein synthesis. These various hypotheses were confirmed in in vitro studies, which have shown that overexpression of G6PDH in various cell lines increases DNA and protein synthesis (Tian et al., 1998; Kuo et al., 2000). On the other hand, G6PDH-deficient cells show a lower growth rate (Ho et al., 2000). Furthermore, inhibition of G6PDH makes cells more susceptible to the growth-inhibitory effects of H_2O_2 owing to NADPH downregulation leading to decreased GSH content (Tian et al., 1998). Inhibition of G6PDH in cultured cells decreases their proliferation

because of decreased protein and DNA synthesis associated with impaired redox status. Therefore, it can be hypothesized that G6PDH downregulation (activity and protein content)—observed in skeletal muscle during aging—may contribute to a decrease in the regenerative capacity of skeletal muscle. On the other hand, increased G6PDH activity should improve this mechanism. Data in this regard have been published by Kovacheva et al. (2010) and Brioche et al. (2014), who showed impaired SC proliferation along with a decrease in skeletal-muscle content of G6PDH protein and an increase in oxidative damage in old sarcopenic mice. Conversely, mice or rats treated with testosterone or GH show increased muscle content of G6PDH protein along with SC proliferation and decreased oxidative damage (Brioche et al., 2014; Kovacheva et al., 2010). G6PDH downregulation during aging should contribute to decreased protein synthesis. Until now, only downregulation of Akt and activation of p70S6K associated with decreased G6PDH activity and atrophy have supported this hypothesis in skeletal muscle (Brioche et al., 2014; Kovacheva et al., 2010; Sinha-Hikim et al., 2013).

Finally, decreased G6PDH activity and/or protein content in skeletal muscle observed during aging may be involved in sarcopenia by decreasing the antioxidant capacity; this change can impair the PI3K/Akt/mTOR pathway, thereby decreasing protein synthesis. There are no published data on G6PDH and proteolysis; however, by decreasing antioxidant defense, reactive oxygen and nitrogen species should promote their own accumulation and activation of several proteolysis pathways (Derbre et al., 2014). On the other hand, the parallel decrease in Akt phosphorylation and in G6PDH activity lead to apoptosis through activation of caspases. A decrease in G6PDH activity may reduce the regenerative potential of skeletal muscle by limiting SC proliferation. Activated G6PDH should restore the optimal redox status and reverse these adverse effects. All these mechanisms are summarized in **Figure 3**.

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Figure 1. Experimental models used to study skeletal muscle wasting. **(A)** Microgravity devices: the life sciences BION satellite launched on a Soyuz rocket, and the actual orbital International Space Station (ISS) including the Mice Drawer System (MDS). **(B)** Models of cell line experiments with induction of muscle wasting. **(C)** Ground-based animal models of muscle wasting and aging including transgenic mice, denervated, and hindlimb-unloaded rodents. **(D)** Human experimental protocols for studies on muscle deconditioning: bed rest with a −6° head-down tilt position, dry immersion, and a model of unilateral lower-limb suspension, with a left shoe with a thick sole and the shoulder strap running around the foot and ankle to unload the right foot.

Figure 2. Histological analysis of IMAT accumulation induced in the glycerol model of skeletal-muscle regeneration in mice. (A) A histological longitudinal paraffin-embedded muscle section, stained with hematoxylin-eosin-saffron, 21 days after intramuscular injection of glycerol into the murine tibialis anterior muscle. **(B)** A histological transversal paraffin-embedded muscle section, 21 days after intramuscular injection of glycerol into the tibialis anterior (labeling with an anti-PDGFRα antibody).

Figure 3. G6PDH-linked mechanisms possibly involved in sarcopenia. Aging is associated with a decrease in G6PDH activity and/or protein content in skeletal muscle; this change may lead to less active synthesis of NADPH and ribose 5-phosphate. The decrease in NADPH levels should impair the redox status, and this event may exacerbate apoptosis and proteolysis and impede muscle regeneration and protein synthesis. The downregulation of ribose 5-phosphate may impair DNA and mRNA synthesis, thus decreasing protein synthesis. All these mechanisms may lead to sarcopenia.

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Table 1. A summary of methods for assessment of muscle mass, muscle strength, and physical performance in humans and rodents.

Measured parameter	Humans	Rodents
Muscle Mass	- Computed Tomography (CT) - Magnetic resonance imaging (MRI) - Dual energy X-ray absorptiometry (DXA) - Bioelectrical impedance (BIA)	- Weighing muscle after euthanasia - Postmortem cross-sectional area - Methods used in humans
Muscle Strength	- Handgrip strength - Knee flexion/extension (e.g., Cybex)	- Auto grip strength meter (noninvasive) - Electrostimulation (very invasive)
Physical Performance	- Short Physical Performance Battery (SPPB) - Gait Speed - "Timed get-up-and-go" test (TUG) - Stair climb power test (SCPT)	- Wire Grip test and Mesh Grip tests - Beam balance test, tightrope test, and rotarod test - Maximal aerobic speed test - Maximal oxygen consumption test

Table 2. Positive and negative regulators of G6PDH [adapted from Stanton (2012)].

Positive regulators	Negative regulators
PDGF, EGF, VEGF, HGF	TNF-α
Insulin	P38 MAPK
Benfotiamine (vitamin B1 analog)	P53
Vitamin D	AMPK
Testosterone, Estrogens	Aldosterone
Growth Hormone	Angiotensin II
Exercise	Arachidonic acid
PI3K, Akt, mTOR, p70S6K	cAMP
Nrf2	cAMP-dependent PKA
Src	
TIGAR	
Hsp27	
SREBP	
ATM	
Phospholipase C	
cGMP-dependent PKG	
Ras-GTPase	

Abbreviations: PDGF, platelet-derived growth factor; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; PI-3K, phosphatidylinositol-3-kinase; PKG, protein kinase G; mTOR, mammalian target of rapamycin; TIGAR, TP53-induced glycolysis and apoptosis regulator; Hsp27, heat-shock protein 27; ATM, ataxia telangiectasia mutated; SREBP, sterol-responsive-element–binding protein; PKA, protein kinase A; CREM, cyclic AMP response element modulator; Nrf2,

nuclear-factor-E2–related factor; TNF-α, tumor necrosis factor α; AMPK, adenosine monophosphate-activated protein kinase