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Review

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.

Contents

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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, 2004; 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., 2001, 2005; Fitts et al., 2000; Schiaffino et al., 2007; Stein et al., 2002), and these data will be presented only briefly in this review. To date, our understanding of the effects of