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Review

Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy

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ABSTRACT

Sarcopenia, the age-related loss of skeletal muscle mass, is a significant public health concern that continues to grow in relevance as the population ages. Certain conditions have the strong potential to coincide with sarcopenia to accelerate the progression of muscle atrophy in older adults. Among these conditions are co-morbid diseases common to older individuals such as cancer, kidney disease, diabetes, and peripheral artery disease. Furthermore, behaviors such as poor nutrition and physical inactivity are well-known to contribute to sarcopenia development. However, we argue that these behaviors are not inherent to the development of sarcopenia but rather accelerate its progression. In the present review, we discuss how these factors affect systemic and cellular mechanisms that contribute to skeletal muscle atrophy. In addition, we describe gaps in the literature concerning the role of these factors in accelerating sarcopenia progression. Elucidating biochemical pathways related to accelerated muscle atrophy may allow for improved discovery of therapeutic treatments related to sarcopenia.

1. Introduction

Sarcopenia, the age-related loss of muscle mass and quality, is a major healthcare concern for older adults (Fig. 1). The condition is associated with the development of functional disability (Janssen et al., 2004; Visser et al., 2005) and may lead to the loss of independence for afflicted individuals. Because of the costs associated with caring for an individual with compromised function, sarcopenia has been linked to elevated healthcare costs (Janssen et al., 2004). Moreover, the absolute costs associated with sarcopenia are likely to rise sharply in the coming decades considering that the total number of persons over 65 years is expected to double over the next 25 years (Federal Interagency Forum on Aging-Related Statistics, 2009). Hence, additional knowledge of mechanisms underlying sarcopenia development is necessary to advance prevention and treatment efforts that will improve the quality of life for millions of older adults.

1.1. Need for a standardized definition

Currently, clinical awareness of the signs and consequences of sarcopenia is lacking. This problem stems, at least partially, from the absence of an established clinical definition of sarcopenia (Visser, 2009) which precludes medical diagnosis of the condition. Without a definition, the ability of physicians to recognize and appropriately treat sarcopenia will remain poor. Previously, this same challenge faced clinicians treating patients with cachexia (Evans et al., 2008). In addition to these clinical difficulties, the absence of a universally-accepted definition of sarcopenia creates challenges for investigators studying the underlying causes of the condition. Presently, scientists disagree on whether sarcopenia refers only to age-related muscle atrophy as it was originally proposed (Roubenoff and Hughes, 2000), or whether muscle function – i.e. strength and endurance – should be included as part of the definition (Clark and Manini, 2008; Visser, 2009). Muscle function is clearly the critical step that links sarcopenia to func-

Abbreviations: 4EBP1, eukaryotic translation initiation factor 4E binding protein 1; atrogin1/MAFbx, muscle atrophy F box; AIF, apoptosis inducing factor; CI, caloric insufficiency; CKD, chronic kidney disease; CNF, ciliary neurotrophic factor; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eIF4G, eukaryotic translation initiation factor 4G; FoxO, Forkhead Box O; GC, glucocorticoid; HAART, highly active antiretroviral therapy; HF, heart failure; IGF1, insulin like growth factor 1; IL, interleukin; MHC, major histocompatability complex; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; MuRF1, muscle-specific RING finger 1; NFkB, nuclear factor kappa B; NPY, neuropeptide Y; p70S6K, 70-kDa ribosomal protein S6 kinase; PAD, peripheral artery disease; PEM, protein energy malnutrition; PI3K, phosphotidyl-inositol-3-kinase; POMC, pro-opiomelanocortin; PMC, peripheral mononuclear cell; ROS, reactive oxygen species; RPS6, ribosomal protein S6; S6K1, ribosomal protein S6 kinase; SC, satellite cell; TNFα, tumor necrosis factor alpha; UCP, uncoupling protein; UPS, ubiquitin-proteasome system.

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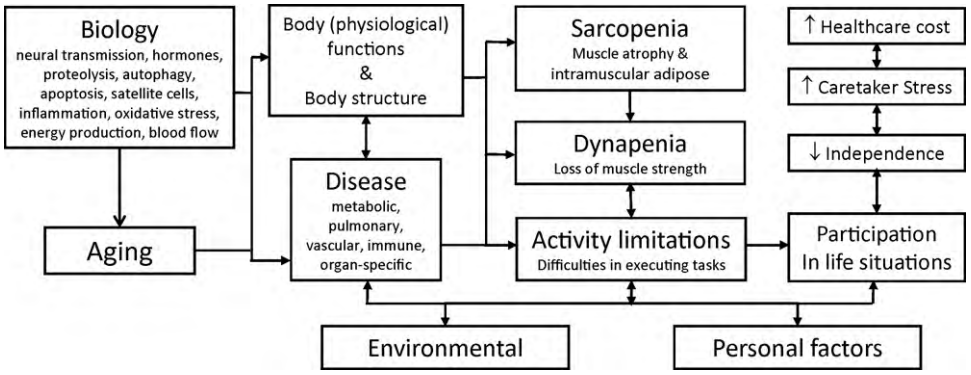

Fig. 1. Mechanisms and consequences of sarcopenia placed within the context of the International Classification of Function (ICF) model developed by the World Health Organization. Sarcopenia is influenced by a host of diseases, cell biology and aging, that manifest through direct or indirect physiological consequences. Subsequently the condition contributes to a number of personal, familial, and societal consequences. Sarcopenia mediates activity limitations (i.e. physical limitation & disability) through influences on muscle strength (dynapenia). Dynapenia: the loss in muscle strength and function that partially results from muscle atrophy (Clark and Manini, 2008). Participation in life situations is the ICF language used to describe the ability of individuals to participate in daily societal activities such as going to the grocery store, attending family events, or traveling.

tional disability (Clark and Manini, 2010), but the degree to which remains unclear. Not intending to disregard the importance of muscle function, the aim of the current article is to describe age-related changes in skeletal muscle size and the role of co-morbid conditions.

1.2. Consequences of sarcopenia

Individuals tend to lose muscle mass at a rate of 1–2% per year after the age of 50 years (Lauretani et al., 2003; Hiona and Leeuwenburgh, 2008; Marcell, 2003). This decline is primarily due to the progressive atrophy and loss of type II muscle fibers and motor neurons (Larsson et al., 1978; Tomlinson et al., 1973). However, other morphological changes occur during the atrophy process including increased variability in fiber size, accumulation of non-grouping, scattered and angulated fibers, expansion of extracellular space, and deposition of protein aggregates within the interstitial matrix (Kim et al., 2008). These morphological changes occur in conjunction with increased infiltration of non-contractile material such as adipose and connective tissues (Brooks and Faulkner, 1994; Goldspink et al., 1994; Goodpaster et al., 2008; McNeil et al., 2005; Petersen et al., 2003). These changes contribute to declines in functional capacity of the muscle that contribute to functional disability (Evans, 1997; Janssen et al., 2002; Muhlberg and Sieber, 2004; Rolland et al., 2008; Visser et al., 2005).

While impaired locomotion is certainly the hallmark concern of sarcopenia, muscle atrophy may impair other physiological functions including glucose regulation, hormone production, and cellular communication. Moreover, muscle tissue provides the body's only major "reserve" of readily available amino acids. Thus, inadequate muscle mass prior to the onset of a disease condition may be dangerous in patients who need a large protein reservoir to recover. As a result, patients with sarcopenia prior to disease diagnosis may face impaired recovery from surgery (Rutan and Herndon, 1990; Watters et al., 1993) or increased risk of mortality (Prado et al., 2009). Still, while contributions of sarcopenia to functional impairments are well-documented, data regarding the importance of skeletal muscle in the recovery from life-threatening situations, such as severe burns or traumatic surgeries, are few. Like a standardized definition, further study of the clinical impact of sarcopenia in these stressful situations could improve physician awareness of the problem.

2. Potential mechanistic triggers of sarcopenia

Developing treatments for sarcopenia is also complicated by the large number of contributing mechanistic factors. Age-related changes in both systemic and cellular properties contribute to loss of organelles, cytoplasmic contents, and protein from skeletal muscle. The loss of these critical myocyte components results in either atrophy or complete fiber loss. Age-related changes in these contributing factors are numerous and include, among others, increases in oxidative stress and pro-inflammatory cytokine production and decreases in production of anabolic hormones such as testosterone. These changes ultimately trigger cellular changes to the myocyte. Among the cellular mechanisms commonly proposed to be involved in the onset and progression of sarcopenia are myocyte apoptotic signaling (Marzetti et al., 2008b), altered protein synthesis and/or turnover (Combaret et al., 2009), and impaired satellite cell (SC) function (Hepple, 2006) Further complexity is added to this discussion by the number of upstream factors that may affect each of these specific mechanisms. For example, proteolytic signaling may be stimulated by a number of factors including catabolic hormones (Ma et al., 2003), pro-inflammatory cytokines (Li and Reid, 2000; Tsujinaka et al., 1996), or denervation (Sacheck et al., 2007). Moreover, ubiquitin-proteasome system (UPS) upstream factors can modulate multiple regulatory pathways. For example, tumor necrosis factor alpha (TNFα) can either stimulate proteolysis through the UPS or induce apoptosis via the death-receptor pathway. A comprehensive review of all of these systemic factors is beyond the scope of the present review. Here we briefly describe three cellular mechanisms commonly implicated in the development of sarcopenia.

2.1. Myonuclear apoptosis

Several reports indicate that enhanced activation of apoptosis takes place in aged skeletal muscle, likely contributing to the development of sarcopenia (reviewed in Marzetti and Leeuwenburgh, 2006). Apoptosis is an evolutionary conserved process of programmed cell death, which is performed via a systematic set of morphological and biochemical events, resulting in cellular self-destruction without inflammation or damage to the surrounding tissue (Kerr et al., 1972). Execution of apoptosis in skeletal muscle displays unique features due to the multinucleated nature of myofibers. Therefore, apoptosis in myocytes may result in the elimination of individual myonuclei and the surrounding portion of sarcoplasm, without the dismantling of the entire fiber (reviewed