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Regenerative decline of stem cells in sarcopenia

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ABSTRACT

Skeletal muscle mass and function decline with aging, a process known as sarcopenia, which restrains posture maintenance, mobility and quality of life in the elderly. Sarcopenia is also linked to a progressive reduction in the regenerative capacity of the skeletal muscle stem cells (satellite cells), which are critical for myofiber formation in early life stages and for sustaining repair in response to muscle damage or trauma. Here we will review the most recent findings on the causes underlying satellite cell functional decline with aging, and will discuss the prevalent view whereby age-associated extrinsic factor alterations impact negatively on satellite cell-intrinsic mechanisms, resulting in deficient muscle regeneration with aging. Further understanding of the interplay between satellite cell extrinsic and intrinsic factors in sarcopenia will facilitate therapies aimed at improving muscle repair in the increasing aging population.

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Contents

1. Introduction

1.1. Background on sarcopenia and muscle stem cells

Clinically, sarcopenia is defined as a geriatric syndrome characterized by loss of skeletal muscle mass and decline in muscle strength that compromise health span (Delmonico et al., 2007). The sarcopenic muscles exhibit distinct features that include atrophy of type 2 (fast-twitch)

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myofibers and heterogeneity in fiber size, accumulation of intramuscular connective tissue and fat as well as decreased oxidative capacity. These cellular features are associated with defective mitochondrial energy metabolism, denervation, increased inflammation and protein catabolism, which distinguish the sarcopenic muscle from other features of normal aging (Barns et al., 2014; Ibebunjo et al., 2013). Motor neurons and mature myofibers are, thus, the major targets for clinical intervention to ameliorate sarcopenia (Grounds, 2014). Sarcopenia is also accompanied by a significant decline in satellite cell function and numbers, which strongly compromise regenerative capacity of the skeletal muscle (Sousa-Victor et al., 2014a). Satellite cell loss might not contribute to age-associated loss of muscle mass, as suggested by recent studies in which satellite cells were ablated in young animals, without affecting skeletal muscle myofiber size or composition (Fry et al., 2015); at variance, other studies proposed that satellite cells do contribute to myofibers in all adult muscles in sedentary mice, although the extent and timing differs (Keefe et al., 2015). Nevertheless, satellite cell loss contributes to age-dependent muscle fibrosis (Fry et al., 2015) and age-related decline in satellite cell function compromises the recovery capacity of sarcopenic muscles in response to injury (Sousa-Victor et al., 2014a).

In this review we will discuss the state of the art on the age-associated decline of satellite cell function in the sarcopenic muscle, focusing on the consequences for muscle function and regenerative capacity. We will focus on the current knowledge on aging of murine satellite cells and will provide perspectives on the potential implications for human satellite cells. Further we will discuss recent findings on satellite cell rejuvenation strategies and their potential impact in counteracting age-related decline of regenerative capacity of the skeletal muscle in the elderly.

2. Stem cells and aging

Age is the major risk factor for chronic diseases (Kennedy et al., 2014), suggesting the existence of a mechanistic link between aging and disease. However, modern biogerontology supports the notion that aging itself is not a disease but a process that increases the chances of disease onset, leading to the emerging concept of age-related diseases when referring to conditions such as sarcopenia (Partridge, 2014). Although the consequences of aging on human health and tissue homeostasis are broadly apparent, the causes and drivers of the aging process are just beginning to be understood. Aging is a complex process that, in multicellular organisms, results from the interplay among cell intrinsic, inter-cellular communication and systemic dysregulations which coordinately compromise the homeostatic capacity of the organism. The aging community has now identified several hallmarks or pillars of aging and is starting to elucidate an integrated view of the basic mechanisms of the aging process (Kennedy et al., 2014; Lopez-Otin et al., 2013). Understanding the molecular mechanisms that underlie and link the different causes of aging is thus crucial to develop strategies that will impact the development and progression of age-related diseases.

Adult stem cells are specialized cell types responsible for sustaining homeostatic renewal and regenerative capacity in different tissues. Importantly, stem cells are a major target of the aging process where several of the aging pillars converge. Aging compromises stem cell maintenance and function which, in turn, contributes to a decline in regenerative capacity and tissue homeostasis throughout life. This causal link is the basis for the postulation of a stem-cell centered theory of aging (Sharpless and DePinho, 2007).

Stem cells can exist in two different states – quiescent and activated. Quiescent stem cells are in a state of reversible cell cycle arrest and can become activated upon proliferative pressure imposed by homeostatic demand of a renewing tissue, or regenerative demand following an injury or damage. Upon activation, stem cells re-enter the cell cycle and proliferate. Activated stem cells need to coordinate two basic functions: self-renew a new stem cell by re-instating quiescence and thus ensuring the maintenance of the stem cell pool; and differentiate to give rise to a specialized mature progeny that can replenish the lost cells with specialized functions in the renewing or regenerating tissue. Stem cell quiescence, activation, self-renewal and differentiation are coordinated by the interplay between intrinsic programs and signals from the surrounding milieu, referred to as 'niche'. These include growth factors, trophic factors and cytokines derived from the somatic and stromal cells in the niche as well as from the systemic environment that regulate stem cell function. Thus it is not surprising that the process of stem cell aging is a consequence of the combined effects of age-dependent alterations in the environment and age-associated intrinsic dysregulations of the stem cell itself (Dumont et al., 2015).

The relative impact of different aging stressors on a particular stem cell population depends on the proliferative pressure imposed by their host tissue. While genomic instability associated with repeated DNA replication is an aging hallmark of stem cells from high turnover tissues (e.g., intestine, hematopoietic system), genotoxic stress driven chronological aging contributes to stem cell dysfunction in quiescent stem cell populations of low turnover tissues (e.g., skeletal muscle and brain). These aging stressors can impact stem cell function at multiple levels, compromising self-renewal capacity, activation and/or differentiation. Depending of the stem cell function(s) that are affected, aging can result in different outcomes that range from stem cell depletion to hyperplastic conditions that irrespectively compromise tissue maintenance and regenerative capacity (Adams et al., 2015; Burkhalter et al., 2015).

3. Satellite cells in the sarcopenic muscle

3.1. Regenerative functions of adult satellite cells

The stem cells of the skeletal muscle are usually referred to as satellite cells due to their anatomical location peripheral to the myofiber and underneath the basal lamina. Muscle stem cells were first identified in the 1960s by electron microscopy (Mauro, 1961) and their chromatin and organelle characteristics suggested that they were mitotically and metabolically quiescent cells. Following studies showed that satellite cells are established early during

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