Feature Review

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Muscle stem cell aging: regulation and rejuvenation

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Aging is characterized by a progressive decline of physiological integrity leading to the loss of tissue function and vulnerability to disease, but its causes remain poorly understood. Skeletal muscle has an outstanding regenerative capacity that relies on its resident stem cells (satellite cells). This capacity declines with aging, and recent discoveries have redefined our view of why this occurs. Here, we discuss how an interconnection of extrinsic changes in the systemic and local environment and cell-intrinsic mechanisms might provoke failure of normal muscle stem cell functions with aging. We focus particularly on the emergent biology of rejuvenation of old satellite cells, including cells of geriatric age, by restoring traits of youthfulness, with the final goal of improving human health during aging.

Skeletal muscle as a paradigmatic model system for tissue aging

Aging is a universal complex process affecting all tissues of an organism. Although the rate of aging varies among species, it inexorably leads to a decline in health and an increased susceptibility to disease. In fact, aging is the greatest risk factor for most chronic diseases and mechanistic links between aging and disease are starting to emerge (Box 1) [1]. However, what makes us age remains a mystery. Nevertheless, common hallmarks of aging across different species have been proposed [2,3] and the aging community has recently put forward an integrated view of the basic mechanisms of aging [1,2]. These include cell autonomous alterations linked to epigenetic changes, macromolecular damage leading to genomic instability, and impaired proteostasis [2,3]. In multicellular organisms, cell intrinsic changes result in the impairment of cell–cell interactions that govern tissue damage responses and stress adaption [4] and in systemic dysregulation affecting metabolic function and inflammation [5]. Although the nexus between the different aging factors remains largely unknown, it is increasingly evident that the interplay between environmental and cell intrinsic factors is itself an aging determinant in mammalian tissues, including those of humans. Importantly, a nodal point where several of these aging factors converge is the decline in regenerative capacity associated with loss of adult stem cell function and number.

Adult stem cells are major regulators of organismal homeostasis, mediating the growth and regeneration of adult tissues after damage. Given their fundamental role, a causal link between stem cell loss-of-function and aging has been postulated [6]. Although long-term tissue homeostasis requires stem cells to remain in a quiescent and undifferentiated state and retain their self-renewal ability, efficient regeneration depends on the ready activation of stem cells in response to damage, and the engagement of their appropriate differentiation program. Proper stem cell function is supported and regulated by growth factors,

Glossary

Apoptosis: process characterized by alterations to cellular architecture leading to cell death. It is a tightly regulated process that prepares cells for removal by phagocytes, thereby enabling the elimination of damaged cells without undesirable immune responses. It is also referred to as programed cell death.
Biogerontology: a subfield of gerontology. It studies the aging process in an effort to understand why and how we age, and how to slow down aging.
DNA damage: alterations in the chemical structure of DNA (such as a break in a strand of DNA, a base missing from the DNA backbone, or a chemically changed base) caused by endogenous and/or environmental agents.
Dynapenia: the age-associated loss of muscle strength.
Heterochronic parabiosis: experimental procedure in which two living animals of different ages are joined surgically and develop a shared circulatory system.
Macroautophagy: inducible type of autophagy (self-digestion of cellular components) responsible for the degradation of both long-lived soluble cellular proteins and complete organelles under stress conditions, such as starvation. A portion of the cytosol is surrounded by a *de novo* formed membrane (limiting membrane) that seals to generate a double-membrane organelle called an autophagosome. Fusion with lysosomes provides the enzymes required for degradation of the sequestered material.
Reactive oxygen species (ROS): chemically reactive oxygen-containing molecules (including oxygen ions and peroxide) that are constantly produced in aerobic organisms as a by-product of oxygen metabolism. Uncontrolled increase in ROS production may result in a significant damage to cellular components and important signaling pathway alterations.
Sarcopenia: the age-associated loss of muscle mass. It is estimated that humans over 50 years of age lose 0.5–1% muscle mass per year.
Satellite cells: skeletal muscle stem cells. They can proliferate, differentiate, and fuse into myofibers, and also self-renew to make more satellite cells.
Senescence: cellular state of irreversible cell cycle arrest induced by damage or stress. Senescent cells secrete a set of cytokines, growth factors, and proteases, usually referred to as the senescent-associated secretory phenotype (SASP).

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Box 1. Understanding the aging process to prevent age-related disease

Biological understanding of aging mechanisms has serious implications for defining interventions aimed at preventing and/or treating human diseases. However, the approach towards intervention depends on whether aging is considered a disease or a process that increases the chances of disease onset. Modern biogerontology research supports the idea that aging is not a disease, because it is an evolutionary conserved process that happens to every individual within a population that survives to adulthood [92]. Nevertheless, it is now clear that aging increases the risk of disease, leading to the emerging concept of age-related diseases when referring to conditions such as metabolic, cardiovascular, and neurodegenerative diseases and cancer [93]. However, what drives the aging process and how the different aspects of aging biology affect health decline and disease risk are only beginning to be understood.

The concept behind the idea of aging as a disease risk factor developed from the basic understanding that the survival of an organism is a dynamic balance between the consequences of exposure to damage and its capacity to repair and reinstate homeostasis. Increased probability for the onset of age-related and chronic diseases arise when the tissue repair and homeostatic capacity starts to decline, resulting in a reduced ability for stress tolerance, damage control, and remodeling [94,95]. Based on this perspective, recent studies support the idea that aging interventions should be focused on methods of maintaining and strengthening health mechanisms, rather than on disease management and treatment. Prospective studies focused on the economic and social impact of aging also support the notion that aging interventions focused on improving healthspan are economically and socially more sustainable than disease-treatment approaches [96].

Anchored on these views, studies have focused on identifying interventions capable of improving health during aging and/or increasing lifespan in multiple model organisms, including mammals. Dietary restriction has proved to be a powerful intervention to increase both healthspan and lifespan in nearly all organisms [39]. Interventions using drugs acting to reduce the activity of insulin/insulin-like growth factor signaling (IIS) and the connected target of rapamycin (TOR) pathway were also able to extend the lifespan in several organisms [97]. The next big challenge is to understand the mechanisms behind their mode of action to remove any adverse effects on health. Given that basic research has made significant advances in defining basic molecular and cellular determinants of the aging process [2], biogerontologists can now start focusing on understanding the mechanisms behind health- and lifespan extension interventions.

trophic factors, and cytokines from the surrounding microenvironment, usually referred to as the 'niche' [7,8]. Aging impacts stem cell function in terms of the capacity to self-renew, which in some cases results in an age-dependent decline of the stem cell pool, and the capacity for proper activation and/or proliferation; it may also lead to skewed or altered lineage commitment. There are multiple ways in which aging stressors can impact stem cell function, and the relative weight of each on a particular type of stem cell depends on the homeostatic and regenerative requirements of the host tissue [9,10]. Sustaining high-turnover tissues, such as the hematopoietic system or the intestine, renders stem cells susceptible to the genomic instability derived from high rates of DNA replication. By contrast, quiescent stem cell populations residing in low-turnover tissues, such as skeletal muscle and brain, are subjected to endogenous and exogenous genotoxic stressors that cause a progressive decline in function with chronological aging, independently of proliferation-induced damages [11–13].

Box 2. Sarcopenia

The term 'sarcopenia', literally meaning poverty of flesh, was first proposed in 1989 to describe the dramatic decline in lean body mass in humans experienced with aging [98]. Despite the increasing attention given to this process, the lack of a clear definition of sarcopenia has hampered the use of consensus diagnostic criteria suitable for clinical practice and research, limiting the understanding of its etiology and the development of therapeutic interventions [99]. The current view is that, clinically, sarcopenia should be considered as a geriatric syndrome involving progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life, and death [100]. Thus, besides reduced muscle mass, sarcopenia requires the presence of 'dynapenia' or the age-related loss of muscle strength and function, because muscle strength does not exclusively depend on muscle mass, and the relation between strength and mass is not linear [99].

Factors contributing to sarcopenia have been related to nutritional, hormonal, metabolic, and immunologic alterations that affect the neuromuscular system and lead to the loss of motor neurons and myofiber atrophy [101]. At the cellular level, sarcopenic muscles show increased heterogeneity in fiber size, predominant atrophy of type 2 (fast-twitch) fibers, decreased oxidative capacity, and increased presence of intramuscular connective and fat tissues. Integration of muscle genomic and proteomic data has recently allowed the identification of a specific molecular signature of sarcopenia versus aging itself [102,103]. Multiple perturbations in sarcopenic muscle include a strong deficit of mitochondrial energy metabolism, neuromuscular remodeling processes related to denervation, and increased protein degradation and inflammation, setting the basis for designing strategies to counteract sarcopenia [102].

Motor neurons and mature myofibers are the major targets of sarcopenia [104] and, in the absence of stress imposed to the muscle, experimental loss of satellite cells does not accelerate this process, but instead increases age-dependent muscle fibrosis [20]. However, aged muscles show a clear decline in satellite cell number and function [19]; therefore, upon stress situations or injuries, in which the participation of muscle stem cells is required, the recovery capacity of sarcopenic muscles is compromised by the limited regenerative capacity of satellite cells.

The adult skeletal muscle is a postmitotic tissue comprising multinucleated myofibers with a remarkable regenerative capacity, providing an attractive model to study tissue regeneration. Muscle stem cells, also referred to as satellite cells (see Glossary), due to their anatomical location between the myofibers and the basal lamina, are responsible for sustaining muscle regeneration and, therefore, have been widely used as a model to study adult stem cell function. Characterized by the expression of the paired box protein 7 (Pax7), a transcription factor involved in muscle precursor cells proliferation, satellite cells are mostly quiescent through life and are activated by environmental signals (e.g., injury or stress) or in pathological environments (e.g., in degenerative muscle diseases) [14–16]. Upon activation, satellite cells give rise to committed myogenic progenitors, which engage the myogenic program to generate new myofibers to sustain regeneration and/or muscle growth [17]. Studies to date support the idea that aging affects both the myofiber and satellite cell function. Aged skeletal muscle is characterized by a significant decline in tissue mass and function, generally referred to as 'sarcopenia' (Box 2). This is accompanied by a decline in regenerative potential, derived from age-associated satellite cell loss of function, which is particularly pronounced in the sarcopenic muscle of both humans and mice [18,19]. Although myofiber aging significantly