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Aging, metabolism and stem cells: Spotlight on muscle stem cells

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ABSTRACT

All tissues and organs undergo a progressive regenerative decline as they age. This decline has been mainly attributed to loss of stem cell number and/or function, and both stem cell-intrinsic changes and alterations in local niches and/or systemic environment over time are known to contribute to the stem cell aging phenotype. Advancing in the molecular understanding of the deterioration of stem cell cells with aging is key for targeting the specific causes of tissue regenerative dysfunction at advanced stages of life. Here, we revise exciting recent findings on why stem cells age and the consequences on tissue regeneration, with a special focus on regeneration of skeletal muscle. We also highlight newly identified common molecular pathways affecting diverse types of aging stem cells, such as altered proteostasis, metabolism, or senescence entry, and discuss the questions raised by these findings. Finally, we comment on emerging stem cell rejuvenation strategies, principally emanating from studies on muscle stem cells, which will surely burst tissue regeneration research for future benefit of the increasing human aging population.

1. Introduction

The incidence of tissue dysfunction and diseases, including cancer, cardiovascular pathologies or diabetes, exponentially increases with age. However, aging is still a largely mysterious process. Why do we age? Which are the molecular mechanisms regulating aging? Is there a limit to how long we can live?

Over the years, many theories have emerged to explain what processes and mechanisms drive aging. In fact, almost every important discovery in molecular or cellular biology has led to a new family of theories of aging. It is widely accepted that the ability of an organism to ensure healthy function during aging depends on mechanisms regulating homeostasis (Goodell and Rando, 2015). In many organs of mature vertebrates, resident stem cells participate in tissue homeostasis and regeneration after injury or disease, with variations in their roles across different tissues and organs (Jones and Rando, 2011; Bell and Van Zant, 2004). Nowadays, we know that the function, and in some cases the number, of adult stem cells declines during the aging process of an organism (Garcia-Prat et al., 2013). Their position at the base of cellular lineages makes dysfunction of stem cells potentially more impactful than in other cell types, and their exhaustion is the consequence of integration of multiple types of aging-associated damages (Lopez-Otin et al., 2013). Hence, some issues still need to be addressed, such as which are the factors that maintain the fitness of stem cell populations over time, what blunts their regenerative potential, and what drives their terminal dysfunction. Investigating on stem cell biology and aging should help clarify these issues and provide the basis of novel strategies to sustain healthy aging (Goodell and Rando, 2015).

In this review, we will discuss stem cell aging as a multifactorial process induced by different alterations in various molecular systems, their exact nature and relative contribution to age-associates dysfunction, while taking into account important tissue-particularities. We will pay special attention to the combined effects of age-dependent damages such as mutations, DNA damage, epigenetic modifications, senescence arrest and dysregulated metabolism to stem cell aging, focusing particularly on the possible causes that may explain the age-associated dysfunction of stem cells in skeletal muscle.

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2. The aged phenotype in skeletal muscle

Muscle stem cells (also called satellite cells, SCs) are essential for skeletal muscle formation, regeneration and homeostatic turnover caused by daily wear and tear (Yin et al., 2013). As their name implies, SCs are located outside the myofiber plasma membrane, in a "satellite" position, surrounded by basal lamina. SCs remain mitotically quiescent throughout life and only activate in response to muscle damage or stress. Upon activation, SCs start to proliferate and their progeny contributes both to the differentiated nuclei within the growing muscle fibers and to replenishment of the SC compartment in a process known as self-renewal (Chang and Rudnicki, 2014). Nonetheless, it has been shown that aged SCs decline in number and functionality (Garcia-Prat et al., 2013; Chakkalakal et al., 2012; Conboy et al., 2003; Roth et al., 2000; Wagers and Conboy, 2005; Shefer et al., 2006; Shefer et al., 2010; Zammit et al., 2002; Day et al., 2010), which are consequences of a combination of different factors, including mechanistic defects in self-renewing, quiescence and myogenic regenerative capacity, as well as alterations in apoptosis and senescence (Sousa-Victor and Munoz-Canoves, 2016; Blau et al., 2015). Furthermore, it is now widely accepted that aged SCs show a tendency to adopt fibroblastic and adipogenic fates in vitro and in vivo, particularly in diseased aging muscle, which explains the increased levels of higher fat deposition and fibrotic tissue in muscles of aged (and dystrophic) mice (Sousa-Victor et al., 2015; Taylor-Jones et al., 2002; Shefer et al., 2004; Brack et al., 2007). Nowadays, the causes of these age-associated changes are under intensive investigation and recent promising studies suggest that stem cell rejuvenation may reverse this aging phenotype at the organismal level.

3. Blueprints of aging stem cells: focus on muscle stem cells

3.1. DNA damage and mutations in old stem cells

Strong evidences indicate that DNA damage contributes to stem cell and tissue aging.

Stem cells, like other cells in the body, are frequently exposed to DNA damaging agents (Friedberg et al., 2006). Exogenous sources of DNA damage include ultraviolet (UV) radiation, ionizing radiation (IR) or chemical exposure can damage DNA. Endogenous agents such as reactive oxygen species (ROS) generate DNA damage by oxidative modification of DNA bases or by spontaneous hydrolysis of nucleosides. Both IR and ROS can lead to the formation of DNA double-strand breaks (DSBs). In order to maintain genomic integrity after DSBs, cells activate a highly organized and complex program, called the DNA damage response (DDR) (Nagaria et al., 2013; Khanna and Jackson, 2001).

It is widely accepted that there is a general age-dependent decline in the efficiency of normal DNA repair mechanisms and an increased accumulation of DNA damage that have important consequences on stem cell functionality (Sperka et al., 2012; Rube et al., 2011). In hematopoietic stem cells (HSCs) and SCs, histone H2AX phosphorylation and comet tails, both of which are indicative of DNA damage, increase with age (Rube et al., 2011; Oh et al., 2014; Rossi et al., 2007; Sinha et al., 2014; Garcia-Prat et al., 2016a,b,c). Furthermore, cycling old HSCs in mice have high levels of replication stress associated with cell cycle defects and chromosome gaps, which are due to decreased expression of mini-chromosome maintenance (MCM) helicase components and altered dynamics of DNA replication forks (Flach et al., 2014). Analysis of the functional defects observed in HSCs of mice deficient in DNA repair proteins such as FANCD1(Navarro et al., 2006), MSH2(Reese et al., 2003) or ERCC1(Prasher et al., 2005) has also provided further support for a DNA damage-associated mechanism underlying stem cell aging (Garcia-Prat et al., 2013). Moreover, premature aging syndromes, or progeroid syndromes, are mainly caused by defects in DNA repair genes, strengthening the idea that the aging rate is determined in part by a balance between DNA damage and repair (Oh et al., 2014; Hasty et al., 2003).

In old stem cells, however, high levels of damaged DNA may arise from build-up of continuous injuries throughout lifetime, a rise in the injury rate, a decline in the repair rate, or a compound of all (Oh et al., 2014). The levels of ROS also increase during aging in human mesenchymal stem cells and SCs, and the frequency of blood-forming HSCs with low ROS levels declines with age in mice(Garcia-Prat et al., 2016a,b,c; Stolzing et al., 2008; Jang and Sharkis, 2007). This excessive cellular ROS concentration leads to aberrant proliferation, malignancy and compromised self-renewal capacity in HSCs and neural stem cells (NSCs), and senescence in SCs(Ito et al., 2004). Mouse lines with ablation of antioxidant genes such as Foxo1, Foxo3a, Foxo4 and Sod2 in HSCs and NSCs results in high levels of ROS and disruption of stem cell quiescence and increase in apoptosis, further demonstrating the correlation between excessive levels of ROS and stem cell dysfunction (Bigarella et al., 2014; Rossi et al., 2008; Paik et al., 2007; Paik et al., 2009; Tothova and Gilliland, 2007; Miyamoto et al., 2007; Yalcin et al., 2008; Renault et al., 2009; Golden et al., 2002).

Analysis of DDR pathways in HSCs indicates that, independent of age, quiescent stem cells, such as HSCs and SCs, are restricted to use the error-prone non-homologous end-joining pathway (NHEJ) for repairing DSBs, and this process could introduce mutations and promote genomic instability (Vahidi Ferdousi et al., 2014; Mohrin et al., 2010). Consistent with this notion, mouse HSCs forced to proliferate show fewer mutational events after exposure to DNA-damaging radiation, suggesting that, in certain instances, a break from quiescence enables the cell to engage the high-fidelity homologous recombination (HR) pathway, which will help to maintain stem cell's genomic integrity (Oh et al., 2014; Beerman et al., 2014). In addition, other studies have demonstrated that in certain instances quiescence can promote accumulation of DNA damage and mutations by allowing the survival of damaged cells (Sperka et al., 2012). On the other hand, each time that a fast-dividing stem cell replicates its DNA, the likelihood of a mutation increases. For instance, a recent study proposed that the accumulation of mutations through stem cell divisions is a major determinant of lifetime cancer risk (Adams et al., 2015).

In contrast, quiescence can also protect stem cells from DNA damage accumulation and functional decline by increased expression of specific stress-protection genes and prevention of cell proliferation and DNA replication (Montarras et al., 2013; Pallafacchina et al., 2010). Indeed, SCs in quiescence are known to have elevated expression of genes coding for antioxidant enzymes, for solubilization of xenobiotics, for multidrug resistance and for elimination of toxic debris, among others (Montarras et al., 2013). A better understanding of the causes of DNA damage, endogenous sources of ROS and the cellular compartments in which they act is important for clarifying the stem cell regulatory actions and potential therapeutic value of ROS modulating agents.

3.2. Epigenetic modifications in old stem cells

Epigenetic regulation is a term used to classify heritable changes of gene expression that are not attributed to changes in DNA sequence and refers mainly to DNA methylation and post-translational histone modifications (Goldberg et al., 2007). The epigenetic landscape of stem cells not only regulates the transcriptional program that dictates the function of the stem cells themselves but has also the potential to coordinate cellular differentiation towards distinct effector lineages. Stem cells heritably