Human Muscle Stem Cells and the Effect of Aging

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Editorial

The skeletal muscle tissue is able of maintaining its mass during adulthood thanks to the role played by myogenic precursors, activated under certain stimuli. In the adult skeletal muscle, the primary role to perform this process is due to Satellite Cells (SCs), a population of quiescent and undifferentiated cells that start the mitotic process in the form of myoblasts, fuse with each other or with pre-existing fibers and differentiate as myotubes in response to specific stimuli such as fiber damage or muscle tension increase or in conditions of chronic inflammation [1]. Blau defined the Muscle Stem Cells (MuSCs) as the satellite cells that reside in anatomically defined niches within muscle tissues [2]. In particular, it has been observed that the stimuli that alter the quiescent niche and contribute to SC activation include degenerative diseases (such as muscular dystrophy), denervation, injury to myofibers and exercise [3]. Also during aging changes occur in the key niche elements, the myofibers and the basal lamina that are in intimate contact with satellite cells. These elements are influenced by factors secreted by interstitial cells, immune system cells, and cells associated with the vasculature, all of which change with age [4]. Senescence goes along with a less effective regeneration of skeletal muscle tissue mainly due to the decreased myogenic capability of satellite cells, in part because of the niche aging and partly due to the intrinsic aging of the satellite cell. This occurrence impedes proper maintenance and contributes to the age-associated decline in muscle mass, known as sarcopenia. The myogenic potential impairment depends mainly on the difficulty of SCs to complete a differentiation program [5]. The activated SCs can lose the expression of myogenic markers or eventually leave the cell cycle showing that they are a heterogeneous mixture of stem cells and committed progenitors. The muscle has a different composition of myogenic cell pool due to individual variety but above all of the stimuli, environmental conditions and age. Apart from SCs, other stem/progenitor cells such as Mesenchymal Stem Cells (MSCs), interstitial stem cells called PICs (PW1+/PAX7-interstitial cells), together with fibro/adipogenic progenitors/mesenchymal stem cells, muscle side population cells (Sca-1+ and CD45+) and pericytes, actively participate in the muscle regeneration process, if properly addressed [6,7]. As among MSCs Muscle Derived Stem Cells (MDSCs) have been included, expressing CD13 and to a lesser extent CD10 and CD56 as well as the lack of hematopoietic marker expression, including CD45 [8]. These cells were considered mesenchymal stem cells for their ability to differentiate into the mesodermal phenotypes. In a recent paper the authors indentify the muscle-derived stem cells, termining MuStem cells. These cells reside in human skeletal muscle and display a long-term ability to proliferate, allowing generation of a clinically relevant amount of cells. Cultured Human MuStem (hMuStem) cells do not express hematopoietic, endothelial or myo-endothelial cell markers and reproducibly correspond to a population of early myogenic-committed progenitors with a perivascular/mesenchymal phenotypic signature, revealing a blood vessel wall origin. Importantly, they exhibit both myogenesis *in vitro* and skeletal muscle regeneration after intramuscular delivery into immunodeficient host mice [9]. These populations act as myogenic precursors but are able to generate also other tissue types [10]. The characterization and/or identification of myogenic stem cells utilizing specific surface markers may also depend on the method of isolation, as reported in a review Burdzinska et al. [11]. It is also noteworthy that there is considerable plasticity of myogenic stem cells. Whereas cell precursors of muscle tissue can give rise to adipogenic or osteogenic cells, various types of stem cells [such as those deriving from bone marrow, blood vessels (mesoangioblasts) or circulating blood (AC133+)] may give rise to skeletal muscle through two different mechanisms: *via* the direct fusion of newly formed fibers (if this is an active or passive process) and/or occupying the niche of resident stem cells (like satellite cells) [12]. The SC are difficult to isolate, and it is improbable to identify a single marker discriminating quiescent satellite cells from proliferating myogenic precursor cells, because several markers may only identify specific subpopulations of satellite cells or stage of satellite cell activation [13,14]. Together more markers help to understand what stage the cells stay. Some markers characterize specific subpopulations of SCs, but in literature there are controversial results. CD34 is considered one of muscle markers most represented, but

rarely some CD34+ cells are observed in a satellite position and, although CD34 is a marker of satellite cells in murine models, in human CD34 expression is not the hallmark of satellite cells [15]. According to other researchers, not all the SCs express CD34 or M-cadherin, have an active Myf5 locus, or have previously expressed Myf5. Other studies show that human satellite cells express CD56, M-cadherin as well as commitment and differentiation factors (PAX7, Myf5, MyoD) either *in situ* or upon dissociation. Indeed, CD56 is chosen as it has been validly used to identify satellite cells in the majority of human studies [16]. Further a recent observation shows that in human muscles a subpopulation of cells expressing the myogenic marker CD56 and co-expressing CD34 contains cells with adipogenic potential further support this possibility [17]. The skeletal muscles analyzed during my studies have shown a little percentage of CD34+ cells only in young subjects and disappear in elderly ones (data unpublished). Resident CD133+ cells have also been reported to take part to muscle regeneration, but they are practically absent in the elderly [18]. There have been reports in the literature showing a difficulty in identifying the various types of stem cells that make up the myogenic precursor pool and that perhaps the same cell typology based on the markers with which it is identified may have different names. Stem cells ensure tissue regeneration; whiles overgrowth of adipogenic cells may compromise organ recovery and impair function. In myopathies and muscle atrophy associated with aging, fat accumulation increases dysfunction and after chronic injury, the process of fatty degeneration, in which muscle is replaced by white adipocytes, further compromises tissue function and environment. Aging skeletal muscle is also characterized by a decreasing efficiency in repair and regeneration, together with a decline in the number of adult stem cells. Several studies demonstrate that human SCs (which can be considered CD56+ cells) in the elderly show a lower differentiation capacity and consequently could contribute less to muscle regeneration [19]. Furthermore, during aging the SCs show greater susceptibility to apoptosis and in particular the intrinsic apoptotic mithocondrial pathway [20,21]. The intercellular communication may play a role in muscle aging, from hormonal and other circulating endocrine factors to local paracrine and autocrine secretory environment of the stem cell niche that may also modify the intrinsic properties of the stem cells themselves [22]. As already mentioned above, besides the CD56+ cells in the muscle there is a population of interstitial stem cells. Interstitial cells, including pericytes and Fibro Adipogenic Progenitors (FAPs), can likely contribute to the reduced muscle regeneration and increased fat deposition which are hallmarks of aging [23,24]. Indeed, during aging the complete regenerative program may not be permitted due to fat and fibrotic tissue formation by resulting in functional impairment of the skeletal muscle. Some studies suggest that pericytes may contribute to muscle regeneration as well as fat formation. Type-2 pericytes expressing CD146 marker participate only to the muscle regeneration after injury, while type-1 pericytes expressing the adipogenic progenitor marker PDGFRα contribute to fat accumulation [23]. An increase of pericyte population is found in neuromuscular disorders as support for their role in muscle regeneration [25]. The elderly interstitial cell population contains higher number of CD15+ and PDGFRα+ cells when compared to young samples [26]. In addition, the authors found that the CD56–/ALP+ (alkaline phosphatase positive) cells were well represented as a multipotent stem cell population inside the CD56– fraction. CD56–/ALP+/CD15– cells were clonogenic, and since they were myogenic and expressed NG2 (neural/glial antigen 2), α-SMA (alpha Smooth Muscle Actin) and PDGFRβ (Platelet- Derived Growth Factor Receptor Beta), can be considered mesoangioblasts (MABs). Interestingly, despite the number of MABs and their typical pericyte markers were not affected by aging, elderly MABs displayed a dramatic impairment in the myogenic differentiation ability *in vitro* and when they have been transplanted in dystrophic immunodeficient Sgcb-null Rag2-null *cc-null* mice. In addition, elderly MABs proliferated less, but yet they retained other multiline age capabilities [5,26]. Overall, these studies indicate that aging negatively impacts on the regenerative potential of SCs and interstitial stem cell, among which MABs and this may in part justify the difficulty of aged skeletal muscle regeneration.

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