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MYOGENIC SATELLITE CELLS: A BRIEF REVIEW

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ABSTRACT

Skeletal muscle has an amazing capacity to adapt him self to physiological and external stress as well as several types of injury. This capacity of overcome the injuries induced changes of skeletal muscle are part of the so call plasticity of the tissue.

There are several mechanisms involved in the regeneration and adaptation processes of skeletal muscle. Myogenic satellite cells have been known to play a key role is those events. Thus, among all the stem cells present in skeletal muscle, the satellite cells are crucial to repair and remodelling the injured skeletal muscle. In addition, there is considerable amount of information about these cells, however, some activation mechanisms are still to clarify as well as factors that can activate the myogenic satellite cells in skeletal muscle adaptations and/or injury.

These brief review aims to present some facts related to myogenic satellite cells and their role in some conditions of skeletal muscle changes.

KEY WORDS: Skeletal Muscle, Myogenic Satellite Cells, Skeletal Muscle Plasticity, Physical Exercise.

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INTRODUCTION

Skeletal muscle has a unique regenerative capacity, capable of return to maximal function after just 3 weeks of injury or severe damage. In addition, skeletal muscle can be repaired after repeated injury, requiring the generation of several myoblasts at each moment (Luz *et al.*, 2002). The structure responsible for this process is the myogenic satellite cells that are located between the basal lamina and sarcolemma of skeletal muscle fibres. Satellite cells split to provide myonuclei for muscle growth, before becoming mitotically quiescent as the muscle matures.

The homeostasis and repair of adult tissues depends mainly on stem cells (Zammit, 2008). These are undifferentiated cells allocated to completed differentiated tissues (Garcia-Prat *et al.*, 2013). Beside the myogenic regenerative ability, satellite cells can return to a progeny pool to produce new myofibres in case of injury. They are considered myogenic stem cells, derivative of its ability of self-renew, proliferation and differentiating into myoblasts (Shefer *et al.*, 2010). Satellite cells were first identified in 1961, speculating that were myoblast in a quiescent state until required for skeletal muscle repair. Although satellite had been related to the primary source of postnatal myoblasts. Nevertheless, several studies relay various stem cells non satellite cell myogenic precursors (Relaix & Zammit, 2012).

Characterization of Satellite Cells Function

The skeletal muscle contains quiescent stem cells which the proliferative activity is induced by injury or cellular stress. This quiescent state is considered like a protection mechanism of satellite cells, minimizing the stress induced by DNA replication and oxidative cellular processes (Garcia-Prat *et al.*, 2013). Since this and when a stimulus provided from injury or pathology occurs, satellite cells are activated followed different mechanisms of differentiation and maturation. After this, is it possible to proliferate and subsequently leave the cellular cycle to differentiate in new muscle fibres, repair injury tissue or can equally self-renew the quantity of satellite cells pool which are in quiescent state (Garcia-Prat *et al.*, 2013), according the defining criteria of a stem cell (Collins *et al.*, 2005).

Satellite cell not only generate myoblasts and myotubes, but could also maintained satellite cell pool (Relaix & Zammit, 2012). Beside this, satellite cells can also returns to their niche. In this way, isolating a myofibre with a small number of associated satellite cells or even a single activated cell, produces donor-derived satellite cells. This mechanism requires extensive proliferative ability from the donor cell, demonstrating that self-renew had occurred. Beside this, donor satellite cells remain viable they could participate in the regeneration process in case of muscle injury (Collins *et al.*, 2005). This donor cells can be also recovered after tissue transplantation followed recovery, showing the high potential for self-renew. So, this type of cells can be classified as myogenic stem cells because they not only generate differentiated progeny, but also keep their own population self-renew (Relaix

& Zammit, 2012). However, it not appears to be a universal feature due to heterogeneity in tissue transplantation studies (Collins *et al.*, 2005; Sacco *et al.*, 2008).

Identification Of Satellite Cells

Satellite cells can be identifying in human and several mammals skeletal muscle. The last years were focused in studying the behaviour of human skeletal muscle, namely mechanism of regeneration, atrophy and hypertrophy. In these different situations, it is crucial to identify the number of satellite cells. To perform this, markers were used to identify satellite cells in human skeletal muscle. M-cadherin (M-Cad) has been the alternative marker to NCAM/CD56 because this has been documented to stain positive against unmyelinated intramuscular nerves. However, NCAM/CD45 can be expressed in myoblasts, myotubes and muscle fibers during development/regeneration stages (Illa *et al.*, 1992). To prevent this, alternative markers like M-cadherin (M-Cad), c-Met and Pax-7 has been preferred instead NCAM/CD45 (Snijders *et al.*, 2015).

Additionally to the related facts, c-Met can be expressed in both quiescent and activated satellite cells, but according to literature (Lindstrom *et al.*, 2010) this marker can express small blood vessels, myofiber membranes and other muscular structures. With this, c-Met should not be preferred to identify/express satellite cells in muscle cryosections (Snijders *et al.*, 2015).

The last marker presented is Pax-7, knowing that can be expressed in the nucleus of myogenic progenitor cells during different stages, namely development and satellite cell mature muscle. It has been defined the most reliable satellite cell marker for mouse model, and in the last years, has been applied, also, in human studies (Snijders *et al.*, 2015). This marker is one of the most reliable concerning to satellite cell identification.

Mechanisms Of Satellite Cells Activation, Proliferation And Differentiation

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Satellite cell is linked to the transcription factor Pax7, since several studies affirmed that inactivation of Pax7 results in depletion of these muscle stem cells (Relaix & Zammit, 2012). Indeed, Pax7 was the first marker identified for satellite cell in both the quiescent and activated states, essential for satellite cell development and survival (Lepper *et al.*, 2009).

Pax3 is also expressed in satellite cells in some muscles, playing important roles in maintaining the proliferation and preventing early differentiation and cell death (Motohashi & Asakura, 2014).

Besides these transcription factors, there are other myogenic factors such as MyoD, Myf5, MRF4 and Myogenin, playing essential roles in myogenic specialization, differentiation, and maintenance during muscle development and regeneration (Tapscott, 2005). The transcription factor MyoD can reprogram several non-muscle cell type to a myogenic lineage, while in adult, Myf5 is expressed in the majority of quiescent satellite cells (Cornelison & Wold, 1997).

After injury, satellite cells begin the myogenic procedure by expression of MyoD, withdraw from quiescent state, and enter into the cell cycle as activated satellite cells. These proliferating activated cells are myogenic precursor cells known as myoblasts (Motohashi & Asakura, 2014).

During muscle regeneration, satellite cells can be distinguished based on Pax7 and MyoD protein expression. Cells with Pax7(+)MyoD(-) reflected a quiescent state, Pax7(+)MyoD(+) cells are in a proliferative state, and Pax7(-)MyoD(+) cells are in the process of myogenic differentiation followed by cell fusion to generated multinucleated myofibers (Zammit *et al.*, 2004). In addition, a minor group of activated cells give origin to Pax7(+)MyoD(-) non-dividing mononucleated cells, which revert to the quiescent state as a quiescent satellite cell (Yoshida *et al.*, 1998). This is a very important mechanism, because it maintains the satellite pool cell self-renewal process along adult life, making possible the regeneration of skeletal muscle cells. Thus, literature is unanimous that satellite cells are true functional muscle stem cells (Motohashi & Asakura, 2014).

Most of quiescent and proliferative satellite cells express Pax7, and is expected that these cells were considered a homogeneous population of muscle progenitor cells. However, recent studies prove through gene expression profile and cell surface marker analysis that satellite cells are a heterogeneous population. Besides Pax7, studies identified the fact that satellite cells may also express Myf5, M-cadherin, 7-integrin, CD34, Syndecan-3/4 or the calcitonin receptor (Motohashi & Asakura, 2014). Meanwhile, another study reported that a subpopulation of satellite cells do not express Myf5, CD34 or M-cadherin (Beauchamp *et al.*, 2000).

Satellite cells can also be distinguished depending on muscle types with the distinct differences of gene expression and cell behaviour *in vitro* and *in vivo*: experiments of gene expression profile have revealed differences between satellite cells from head muscles and others (Harel *et al.*, 2009). These studies suggest that satellite cells have different characteristics depending on the origin of muscle. According with this, is it possible to claim that satellite cells are a heterogeneous populations expressing high potency of self-renew *in vivo* not only genetically but also functionally, affected by their development origins, environments and niches (Motohashi & Asakura, 2014).

Most of the literature characterize satellite cells like a potential stem cell, while other studies have proposed that satellite cells are composed of two different populations: one population consists of myogenic satellite cells, possessing potential myogenic differentiation. The other population is an undifferentiated subgroup, which retains the satellite stem cell profile but could be differentiated in other cells then myoblasts (Collins *et al.*, 2005; Kuang *et al.*, 2007; Ono *et al.*, 2010). Previous studies identified this population as muscle side population cells, which can participate in muscle regeneration, originating satellite cells like. Satellite Cells side population cells can interact into injury muscles following systemic delivery. Moreover, it seems that the main goal of this type of cells comprise on repopulation of the satellite cell niche among the potential for long term muscle regeneration (Tanaka *et al.*, 2009).

According with this, several studies suggest a dual dividing rate, whereas slow-dividing minor population exhibits the high potency to self-renew and the fast-proliferating cell population tends to undergo myogenic differentiation. This finding was supported by a study in which satellite cells could be distinguished as fast and slow-dividing cells through fluorescent markers. Fast dividing cells origin a higher number of myogenic differentiated cells, while slow dividing cells represents quiescent-like self-renew cells (Ono *et al.*, 2012).

Another feature related with satellite cell niche is related with non-satellite cells namely, bone marrow derived stem cells, side population cells, mesoangioblasts/pericytes and CD133⁺ cells, where they can contribute to the myotubes formation as well as satellite cell reconstitution during muscle regeneration. Initially, these cells don't express Pax7, but when they enter in the satellite cell niche, they can fuse with other myogenic cells to form muscle fibres. At the same time this cells can differentiate into Pax7-expressing cells, contributing muscle satellite cells heterogeneity (Motohashi & Asakura, 2014). This subgroup population as the side population myogenic cells can undergo myogenic differentiation upon muscle injurie. At the same time, they can also express Pax7, like satellite cells, and contribute to muscle fibre regeneration.

The Wnt signalling pathway plays a central role in the regulation of several processes concerning myogenic stem cells. These mechanism controls several biological processes, such as cell proliferation, cell fate determination, cell adhesion, cell polarity, and morphology (Yin *et al.*, 2013). It acts as a promotor for myogenic specification in muscle resident stem cells, initiated through binding with the G-protein coupled receptor proteins of the Frizzled (Fzd) family (Motohashi & Asakura, 2014). The Wnt signalling branches can be activate into two distinct pathways: the canonical Wnt/ β -catenin pathway, and the non-canonical or β -catenin-independent pathway that can divide into planar cell polarity (PCP) and the Wnt/Ca²⁺ pathway (Komiya & Habas, 2008).

The canonical pathway induces satellite cell proliferation during muscle regeneration (Otto *et al.*, 2008), while the non-canonical Wnt pathway induces myocyte growth in the developing fibres (Gros *et al.*, 2009). The key point of the canonical Wnt pathway is the accumulation and translocation of the adherent's junction associated-protein β -catenin into the nucleus. Without signalling, cytoplasmic β -catenin is degraded by a β -catenin destruction complex. Inside nucleus, β -catenin exerts on gene transcription by acting as a transcriptional co-activator. The canonical Wnt signalling had an important and crucial role in cell fate phases during early embryogenesis (Komiya & Habas, 2008).

Additionally, one of the Wnt receptors, Fzd7, is highly expressed in Pax7(+)Myf5(-) quiescent satellite stem cells, and so, Wnt7 is a ligand for Fzd7. This interaction promote the symmetric division of a Pax7(+)Myf5(-) satellite stem cell population through the activation of the non-canonical Wnt pathway (Le Grand *et al.*, 2009), while overexpression of Wnt7 enhanced muscle regeneration with an increase of satellite stem cell number. However, overexpression of Wnt3, which stimulate the canonical Wnt pathway, impaired muscle regeneration (Motohashi & Asakura, 2014).

Another important signalling pathway is the Notch process, which develop important roles in skeletal muscle regeneration. Is known for various cell functions, including cell-cell interaction and cell fate determination during tissue development, homeostasis and regeneration (Lai, 2004), and is also implied in cell proliferation and differentiation (Yin *et al.*, 2013). Activated by muscle injury, the Notch ligand Delta (family of ligands to Notch transmembrane receptors) is rapidly upregulated in both activated satellite cells and in myofibres (Conboy & Rando, 2002). This Delta upregulation in satellite cells is followed by the appearance of the NICD (Notch intracellular domain), indicative of activated Notch signalling. NICD consist in a sequential enzymatic cleavage of the Notch receptor and release of an active truncated form of Notch (Yin *et al.*, 2013).

The activation of this signalling process stimulates the proliferation of satellite cells and their progeny, leading to the increment of proliferating myoblasts. In normal condition, Notch mechanism prevents myoblast differentiation and promote satellite cell self-renew by limiting MyoD activity through up-regulation of HES proteins, an inhibitor of MyoD (Kuroda *et al.*, 1999). Attenuation of Notch signalling by Numb (Notch inhibitor), results in the progression of myogenesis from myoblast proliferation to differentiation (Conboy & Rando, 2002). Considering this, is important to keep the balance between Notch1 and Numb to allow satellite cell proliferation, differentiation and self-renew.

With aging, a dysfunction on Notch activity impairs muscle regeneration mediated by supressing satellite cell activation, whereas normal activation of notch signalling promotes muscle regeneration (Conboy *et al.*, 2003).

Another important feature about satellite cell distribution is related with the interaction between endothelial cells and satellite cells. Since satellite cells are anatomically close to capillaries, the paracrine signalling of endothelial cells stimulates the muscle satellite cell to growth (Christov *et al.*, 2007). Additionally, a recent study related that stem cell niches can be generated by endothelial cells that surrounds satellite cells (Gomez-Gaviro *et al.*, 2012).

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Satellite Cells Self-Renew

Satellite cells have the ability to differentiate into new myofibers and also self-renew, being essential to keep the satellite cell pool homeostasis, as we referred above. When a defect in the last process occurs it can results in a depletion of the satellite cell pool as well as in reduced muscle regeneration capacity. Thus the self-renew can be defined by the satellite cells return from an active to a quiescent state.

There are two mechanisms that must be taking into account concerning the regulation of satellite cell self-renew: one is the asymmetric division, whereas a major population of cells generates daughter's cells committed to myogenic differentiation and, so, the small cell population give rise to a self-renew daughter cells; the second mechanism is through symmetric division, in which one stem cell population generates two identical functional daughter stem cells (Motohashi & Asakura, 2014).

It was already described the importance of the myogenic factors Myf5, MyoD, MRF4 and Myogenin in the myogenic processes of specialization, differentiation and maintenance during muscle development and regeneration. Even so, Pax3 and Pax7 are also essential in the same processes (Lagha *et al.*, 2008). Meanwhile, a recent study suggest that Myf5 is one of the key modulators of satellite cell self-renew (Gayraud-Morel *et al.*, 2012). In addition, down-regulation of MyoD expression is an important event for the satellite cell self-renew process. The anti-apoptotic property of *MyoD*^{-/-} myoblasts is mediated by up-regulation of Pax3, where this last factor acts like an anti-apoptotic factor in myoblasts. (Crist *et al.*, 2009).

According with the literature, the factors that down-regulate MyoD and up-regulate Pax7 could be importantly to return satellite cells from an active to a quiescent state. Although, there's a lack of studies to identify the factors that selectively induce asymmetric or symmetric division of myogenic precursor cells (Motohashi & Asakura, 2014).

Implication Of Satellite Cells In Skeletal Muscle Regeneration

It is now a proved fact that skeletal muscle has the unique ability to regenerate from injurie (Wang & Rudnicki *et al.*, 2012). Severe muscle injurie can be due to either traumatic injuries (e.g., extensive physical activity such as resistance training or exposure to myotoxin) or genetic defects (e.g., muscular dystrophies). In both cases can occurs myofibre necrosis, inflammatory responses, activation of satellite cells, proliferation and differentiation of satellite cell-derived myoblast. The whole process beginning with myofibre necrosis and ending with new myofibre formation is called muscle regeneration (Yin *et al.*, 2013). This unique muscular process implies the activation and proliferation of myogenic satellite cells (Wang & Rudnicki *et al.*, 2012), being a fundamental factor to promote a successful regeneration.

Muscle regeneration proceeds in three sequential but overlying stages starting with inflammatory response followed by activation, differentiation, and fusion of satellite cells, and for last, maturation and remodelling of newly formed myofibres (Yin *et al.*, 2013). At the end of this complex mechanisms, newly formed myofibres increase in size, and the myonucleus move to the periphery of the muscle fibre. In normal conditions, the newly muscle fibres are morphologically and functionally indistinguishable from undamaged muscles (Yin *et al.*, 2013).

Satellite cell activation is manage by several niche factors and signalling pathways described previews. This activation is not only restricted to the site of muscle damage, but also along the same myofibre and migration of these satellite cells to the regeneration site (Schultz *et al.*, 1985). The activation process is also accompanied by extensive cell mobility/migration. It has been described that satellite cells can also migrate between myofibres and even muscles across barriers of basal lamina and connective tissues during muscle development, growth, and regeneration (Yin *et al.*, 2013).

The presence of MyoD, desmin, Myogenin in satellite cells was observed as early as 12h after injury, which is before any noticeable sign of satellite cell proliferation. This early expression of MyoD is associated with a subpopulation of committed satellite cells, which differenti-

ate without proliferation (Rantanen *et al.*, 1995). In contrast, it occurs an expression of MyoD or Myf5 by the majority of satellite cells 24h following injury and subsequently co-express both factors by 48h (Cornelison & Wold, 1997). Since satellite cells had an ability to upregulate either MyoD or Myf5, it suggests that these two transcription factors may have different functions in adult myogenesis (Yin *et al.*, 2013). According this facts, Myf5 is implied in adult myoblast proliferation, while MyoD is essential for differentiation. It has been suggested that satellite cells enter different myogenic programs depending on whether Myf5 or MyoD expression predominates. Predominance of MyoD expression would induce the program to early differentiation. In contrast, predominance of Myf5 expression would follow the program into enhanced proliferation and delayed differentiation. At last, myoblasts co-expressing both Myf5 and MyoD would exhibit the intermediate growth and differentiation characteristics as shown by most of satellite cell-derived myoblasts. According with this, is expected that disruptions in the MyoD/Myf5 ratio may determine the choice of myogenic mechanisms (Yin *et al.*, 2013).

Since the ratio of Pax7 and MyoD activities are critical for satellite cell fate determination (Olguin *et al.*, 2007), a higher proportion of Pax7 to MyoD keeps satellite cells in their quiescent state. In addition, an intermediate relation of Pax7 to MyoD allows satellite cells to proliferate, but not differentiate. Satellite cells with a low Pax7 to a MyoD ratio begin to differentiate, and further decrease in Pax7 levels are observed following activation of Myogenin. After this several mechanisms and programs, the majority of satellite cells enter in the myogenic differentiation and begin to fuse to damaged myofibers or fuse to each other to form nascent multinucleated myofibres (Yin *et al.*, 2013).

Thus, the regeneration processes imply the formation of a new myofibre during muscle regeneration happens in two stages. First, individual differentiated myoblasts fuse to one another and generate nascent myotubes with few nuclei. In the following step, additional myoblasts incorporate into the nascent myotubes, creating a mature myofibre with increased size and expression of contractile proteins (Horsley & Pavlath, 2004).

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Physical Exercise And Satellite Cells

Until recent, there's no pharmacological offer that improves the recovery ability after a process of atrophy (Bodine, 2013) that can be due to a several conditions including aging. Meanwhile, past studies demonstrate that aerobic exercise have the ability to modulate fibre type and interfere in several muscular mechanisms, including number and activation of satellite cells, as well as several proteins involved in muscular vascularization and regeneration. So, physical activity, more specifically aerobic exercise, can constitute a non-pharmacological therapeutic against muscular atrophy. Past studies with *Wistar* rats and practise of aerobic exercise, induce an increment in myogenic clones, reflecting an improvement of satellite cells function. This myogenic improvement can result in a possible mechanism where practise of aerobic exercise induce a progress in quality and quantity in skeletal muscle mass in oldery people (Shefer *et al.*, 2010).

Resistance Exercise

It is clear that resistance type exercise training is an effective strategy to increase muscle mass and strength in older subjects. In order to occur muscular fibre hypertrophy, the addition of new myonuclei to fibers is essential, and this can be facilitated by the proliferation of satellite cells and the differentiation of their progeny into new myonuclei that fuse with existing fibres (Snijders *et al.*, 2009). With this exercises, myogenic regulatory factors mRNA expression appears to increase following the resistance exercise in both young and older subjects (Costa *et al.*, 2007). In addition, the literature is precise about impaired aged Notch pathway. So, the resistance exercise downregulates the myostatin mRNA expression in response to exercise training in both young and older individuals (Snijders *et al.*, 2009). Several studies suggest an increase in satellite cell content just in 24h after 92 of eccentric contractions in both young and elderly. Although, the increment was greater in the young against the older subjects, suggesting that satellite cell response to exercise is impaired in the elderly (Dreyer *et al.*, 2006). Besides this impairment, the reduced satellite cell pool size does not prevent the capacity to allow extensive muscle hypertrophy even at an advanced aged (Snijders *et al.*, 2009). Several theories had been related with the last facts, but the most consensual proofs that skeletal muscle hypertrophy in older subjects is accompanied by an increase in myonucleus domain size, whereas myonucleus number remains equal throughout the training period (Petrella *et al.*, 2006). Besides this, resistance exercise training in older subjects can increase satellite cell content even in the absence of muscle fibre hypertrophy (Mackey *et al.*, 2007).

In summary, resistance exercise training had positive effects against myofibre atrophy on older subjects, whereas occurs hypertrophy as well as a considerable increase in muscle strength and improved functional capacity. Additionally, concerning myogenic regulator factors and Notch signalling those were upregulated in response to resistance training. However, and on a microscopic level, satellite cells number does not increase to the same extent when compared with young individuals (Snijders *et al.*, 2009).

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Endurance Exercise

Concerning endurance exercise training, the literature is poor in describing the effects on aged skeletal muscle and satellite cell content/function. However, recent studies suggest that endurance exercise training also influences satellite cell activation and proliferation. In this case, all studies reported an increase in satellite cell activation and content after a period never shorter than 10 weeks. In addition, aerobic capacity (VO_{2max}) also increase after the period of training. Although, the increase in myonucleus number and muscle fibre volume don't achieve statistical significance (Snijders *et al.*, 2009).

Independent of the type of exercise, resistance or endurance, the practise of each or both has positive effects on skeletal muscle hypertrophy and increase muscle function in older subjects. Both exercises increases satellite cell content specifically in the type II

muscle fibres, accompanied by an increase in satellite cell activation and proliferation factors in skeletal muscle fibres. According the literature, the myogenic satellite cell co-regulates myogenesis, having an equal important function in the mechanism of atrophy with aging.

Satellite Cells And Muscle Aging

The progressive loss of strength and skeletal muscle mass is a characteristic of normal aging. With aging comes a continuing and gradual muscle atrophy denominated sarcopenia, which result in a skeletal muscle and performance decline. This reflects on a disability and the subsequence loss of independence and quality of life. Several factors can contribute to this state, but partially related with decline in physical activity, malnutrition and the prevalence of diseases (Snijders *et al.*, 2009).

The function of satellite cells in this physiological condition continues to be controversial whether satellite cells decrease in number during aging and/or their capacity to become activated. These alterations might contribute to the development of a sarcopenic state. Although, recent studies suggest that in elderly individual occurs an atrophy in type II muscle fibers type and a decline in satellite cells essentially in lower limb muscle, whereas no such alterations evident in upper limb (Snijders *et al.*, 2009).

Several studies suggested that during aging, satellite cells display reduced proliferative response after damage and reduced regenerative capacity (Pallafacchina *et al.*, 2012). Despite the number of skeletal muscle satellite cells appears to reduce with aging, basal myogenic regulatory factors mRNA expression appears to be upregulated in senescent muscle (Edstrom & Ulfhake, 2005). The myogenic regulatory factors activity is required for satellite cells to enter and/or complete their cell cycle. In an animal model, the intensity of up-regulation of myogenic regulatory factors mRNA expression tends to be similar to the degree of sarcopenia (Edstrom & Ulfhake, 2005). So, is expected that senescence skeletal muscle fails in it regenerative effort (Kosek *et al.*, 2006).

The Notch signalling mechanism is a key role on the satellite cells function. In contrast with up-regulation of myogenic regulatory factors, Notch signalling has been reported to decline with aging. Being essential in the regulation of the satellite cell activation, proliferation, and differentiation, elderly individuals have a reduced Notch gene expression at all moments when compared with young subjects (Snijders *et al.*, 2009). Thus, it may be logic to suggest that satellite cell number and their activation mechanisms appear to be altered in aging muscle.

The progressive physiological and cellular decline associated aging is in the most of the cases a consequence of degenerative state. So, the decrease in satellite cells functionality is much related with the process of aging, resulting in a deficit capacity of self-renew. In several cases it occurs depletion of stem cells or these cells may loses the activation/proliferation potential resulting in a skeletal muscle deficient regenerative process.

The literature is precise on the progressive decline of functional capacity of satellite cells during aging. This process can be seen easily in sarcopenic people, where this type of cells loses its regenerative, proliferative and differentiation capacity (Garcia-Part *et al.*, 2013).

The state of the art suggests several fundamentals for this process, including reducing in satellite cells number and incapacity to perform the return pool stock of quiescent cells. It's also suggested a decrease on myogenic colonies formation, dysfunction in differentiation and myotube fusion and reduction on satellite cells reserve formation (Baj *et al.*, 2005; Collins *et al.*, 2007). In same line, some authors acclaim that in older skeletal muscle, satellite cells trends to differentiate in fibroblastic or fat tissue in response an injurie or cellular aggression. These facts confirm the increase in intermuscular fat and fibrogenic tissue in aged skeletal muscle (Garcia-Part *et al.*, 2013).

Satellite cells presented in aged skeletal muscle also develop a tendency to differentiate into non myogenic cell, adopting adipogenic and fibrogenic phenotype that could contribute to muscle fibrosis (Taylor-Jones *et al.*, 2002; Brack *et al.*, 2007).

There is others mechanisms and processes related in decrease of satellite cells efficiency, namely accumulation of oxidative aggression, dysfunction in the mechanism that keep the genomic integrity and change of the mitochondrial functions which probably reduce the oxidative phosphorylation and mitochondrial biogenesis, resulting in a increment of reactive oxygen species (Hasty *et al.*, 2003; Ames, 2004).

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