Current Updates in Stem Cell Research and Therapy

Review Article Open Access

Basking in their Niche: Stem Cells with Myogenic Potential as a Target to Combat Cachexia [Version 1, Awaiting Peer Review]

Alexandra Baccam[1,2], Medhi Hassani[1,2], Alexandra Sviercovich-Benoni[1], Sergio Adamo[2], Viviana Moresi[1,2] and Dario Coletti[1,2]*

[1]Department of Biological Adaptation and Aging, B2A (CNRS UMR 8256 - INSERM ERL U1164 -UPMC P6), Pierre et Marie Curie University, France
[2]DAHFMO - Unit of Histology and Medical Embryology, Sapienza University of Rome, and Inter-University Institute of Myology, Italy

*Corresponding author: Prof. Dario Coletti, Sapienza University of Rome, Istologia, Via Scarpa 16, 00185, Rome, Italy, Tel:. +39 06 49766643; Email: dario.coletti@uniroma1.it, dario.coletti@upmc.fr

Original Submission

Received: March 06, 2017
Accepted: March 20, 2017
Published: March 26, 2017

Open Peer Review Status: Awaiting Peer Review

How to cite this article: Alexandra Baccam, Medhi Hassani, Alexandra Sviercovich-Benoni, Sergio Adamo, Viviana Moresi, Dario Coletti. Basking in their Niche: Stem Cells with Myogenic Potential as a Target to Combat Cachexia [Version 1, Awaiting Peer Review]. Curr Updates Stem Cell ResTher. (2017) 1: 1.1

Acknowledgments: DC is funded by AFM (2012–0773), ANR (2013-J13R191), European Federation for Experimental Morphology (EFEM 2016), IBPS [2014), NIH (2013-1R01CA108857-01 subcontractor) and UPMC Emergence (2011-EME1115).
The PRIN 2012 Project # 2012N8YJC3_002 grant to S. Adamo is also acknowledged.

Abstract

Skeletal muscle contains several myogenic populations: satellite cells, muscle derived stem cells, PW1+ stem cells, mesoangioblasts / pericytes, fibroadipogenic progenitor cells, and hematopoietic stem cells. In response to muscle damage in cachexia, these myogenic populations proliferate, but fail to fuse into myofibers. Substantial evidence points to pro-inflammatory cytokines and other anti-myogenic factors, which apparently are responsible for this paradoxical increase in the muscle stem-cell pool in wasting muscle. Therapeutic efforts are currently aimed at counteracting myofiber catabolism and atrophy; nonetheless, functional myogenic cells could be an additional therapeutic targets. As in dystrophic muscles, myogenic cells can sustain muscle homeostasis for a long time, even in the presence of overt muscle damage and wasting. Many tools are already available to stimulate their differentiation, from exercise to the pharmacological removal of inhibitory signals blocking this very differentiation. However, an extended characterization of the various myogenic stem-cell populations, in search of the one resistant to cachectic factors, has not been performed to date. The identification of either an engineered or an endogenous myogenic cell type able to differentiate or fuse to cachectic myofibers in the presence of a non-permissive milieu would represent a revolutionary approach to counteract cachexia.

Keywords

Physical Activity; Stem Cell Niche; Adult Stem Cells; Satellite Cells; Striated Muscle Atrophy; Muscle Wasting; Myogenesis; Pro-Inflammatory Cytokines

Skeletal muscle mass and function are physiologically diminished with aging or, severely, in acute conditions such as severe injuries (burn, brain injury) or chronic conditions (cancer, organ failure, autoimmune diseases). The latter form of muscle wasting, known as cachexia, directly accounts for a significant percentage of deaths among patients and negatively affects survival and quality of life. So far, cachexia has been regarded primarily as a catabolic condition affecting the muscle mass, i.e. the myofibers. We and others demonstrated the importance in muscle wasting of factors within the muscle microenvironment surrounding the myofibers. With this view, it is of the greatest interest to shed light on the behavior of satellite cells and other stem cells with myogenic potential in muscle interstitial space upon the onset of cachexia.

Treatments against muscle wasting aimed at interfering with central mechanisms (such as the release of cytokines) or peripheral responses (such as myofiber protein catabolism) are promising, but an effective cure against cachexia is still lacking. In the light of the most recent findings on stem cells in cachexia, exploiting their myogenic potential would represent an alternative approach in order to counteract muscle wasting. This review focuses on the poorly explored domain of stem cell populations with myogenic potential as a target to combact cachexia.

Stem Cells with Myogenic Potential

At present, we know several stem cell populations which can be exploited to enhance muscle regeneration and homeostasis in pathological conditions, as reviewed by Sirabella as well as by Rinaldi [1,2]. Although these stem cell populations, including the satellite cell population, are all potentially myogenic, it is of pivotal importance to briefly summarize some differences among them.

Satellite Cells (SCs)

In 1961, by means of electron microscopy, Mauro first described the satellite cells as mononuclear cells located between the basal lamina and the sarcolemma [3]. By correlating their absence in the other striated muscle, i.e. cardiac muscle, and the lack of regenerative potential in this tissue, he speculated on the importance of SCs for muscle regeneration. These findings are now established and satellite cells are considered as the main source of new nuclei in skeletal muscle postnatal growth and repair, thus playing a major role in skeletal muscle plasticity [4]. Approximately 2.5–6% of nuclei in muscle belong to SCs [5,6]. SCs reside in a particular niche in proximity to the capillaries [7], allowing interactions between SCs, myofibers and endothelial cells on each side of the basement membrane [8,9]. SCs are in a quiescent state and are characterized by co-expression of the transcription factors Pax3 and Pax7 until they are activated by muscle damage, proliferate, and fuse to form new myofibers. The same processes also occurring during postnatal growth [10]. SC proliferative life span is limited, with the potential number of cell divisions decreasing considerably as a function of donor age in humans and animals [11]. Activated SCs re-enter the cell cycle and express Pax7, Myf5 and MyoD, thus becoming myoblasts. Their division can be symmetric, leading to two activated cells (Pax7+/Myf5+) or asymmetric, leading to one activated cell (Pax7+/Myf5+) and a quiescent cell (Pax7+/Myf5-), a process which replenishes the SC pool, and is a typical stemness feature [12]. Transcription factors such as Myf5, MyoD, myogenin, and MRF4 promote myogenic differentiation [13], while Pax7 and Pax3 expression progressively decreases upon SC differentiation [14]. The activated SCs fuse to existing damaged muscle fibers or fuse together to form nascent myofibers, or myotubes, expressing Mrf4 and the heavy chain of myosin (MHC), together with other markers of terminally differentiated myofibers [15-17]. Worth noting, whilst expressed in quiescent SCs, Pax7 maintains proliferation and prevents precocious differentiation, but does not promote quiescence, as elegantly demonstrated by Zammit [18]. In addition, one of the most striking stem cell features of SCs is the fact that a subpopulation of these cells retains all template DNA strands in their chromosomes after asymmetric cell division [19]. Other evidence of the heterogeneity of the SC subpopulations come from the studies of single myofiber grafting by Collins et al. in irradiated hosts, showing different muscle repopulation capacities displayed by SCs from different hind-limb muscles [20]. This and other studies globally highlighted the remarkable SC myogenic potential, showing that «as few as seven satellite cells associated with one myofiber can give rise to sufficient differentiation-competent progeny to generate thousands of myonuclei» [20].

Pw1+ Interstitial Cells (PICs)

PICs are characterized by expression of PW1, aka Peg3, a zing finger protein which regulates two major cell-stress pathways, the Tumor Necrosis Factor (TNF)- and the p53-dependent signaling, both involved in muscle atrophy [21-23]. Several studies demonstrated that PICs are not derived from the same embryonic lineage of satellite cells [24,25]. Naive PICs do not express any gene involved in the myogenic lineage like Pax7 or MyoD, but in vitro, in a pro-myogenic environment, PICs are able to form myotubes by fusion. In vivo PICs are able to regenerate muscle fibers and reform PICs and the SC pool when they are injected in injured muscle [25]. Differently from SCs, PICs are multipotent and can differentiate into both skeletal and smooth muscle [26].

Muscle-Derived Stem Cells (MDSC)

MDSC are another multipotent stem cell population, originally identified in the interstitial space of murine muscles [27].

The characteristic weak adhesion to plastic in culture shown by MDSC provides an easy way to isolate this stem cell population ex vivo. Interestingly, MDSC have a good myogenic potential, in addition to having 10 times higher efficiency in hematopoiesis than hematopoietic stem cells themselves [28,29]. MDSC are also able to differentiate into mesenchymal tissues regenerating bone and muscle [27]. Clones of MDSCs express some stem cell markers, such as CD34, Bcl-1 and Sca-1, and myogenic markers, such as MyoD. Mouse MDSCs can be expanded in vitro without undergoing senescence [30]. For all of the above, MDSC and SCs are clearly distinct populations. The long-term self-renewal process of postnatal MDSC, and their embryonic origin, are not known yet. Interestingly, MDSC isolated from female mice have a higher regeneration capacity than their male homologues [31].

Mesoangioblasts (MABs) / Pericytes

MABs and pericytes are multipotent stem cells [32] which contribute to muscle regeneration [33]. Pericytes and mesoangioblasts co-express endothelial and myogenic markers, since they derive from the embryonic dorsal aorta. Later on, they take place along blood vessels. Indeed, pericytes are adult MABs and they differ from MABs inasmuch as their express Alkaline Phosphatase, Platelet-Derived Growth Factor (PDGGF) receptor, and Neural/Glial antigen 2 [34]. Pericytes locate onto the basement membrane, rely on type VI collagen for cell adhesion to the extracellular matrix (ECM) [35] and on PDGFR to bind PDGF-b expressed by endothelial cells for cell-cell interactions [36]. Pericytes directly participate to muscle fiber formation and can differentiate in satellite cells during postnatal development [37]. Mesoangioblasts proliferate and maintain the ability to differentiate into different mesoderm cell types, like skeletal and smooth muscle, osteoblasts or adipocytes [32].

Fibroadipogenic Progenitors Cells (FAPs)

FAPs have been recently added to the list of stem cells with myogenic potential. FAPs do not arise from the myogenic lineage and can also differentiate into adipocytes and fibroblasts [38, 39]. They are abundant in healthy muscle, recruited upon injury, and enhance pro-myogenic signals [39]. FAPs are located in the interstitial space between myofibers, next to blood vessels. They express PDGFRα and produce IL-6, and IGF1, thus modulating myogenesis [39]. In IL-4/IL-13 dependent fashion, FAPs contribute to necrotic debris clearance and promote muscle regeneration [38]. However, FAPs can also trigger fibrosis in muscles upon myostatin stimulation, through Smad3 signaling, in the presence of chronic kidney disease [40].

Hematopoietic stem cells (HSC)

HSC are located in red bone marrow and originate all blood cell lineages in hematopoiesis. Strikingly, bone marrow cells can contribute to skeletal muscle fiber formation, but it is not well known which subpopulation plays a major role in muscle regeneration. It was suggested that either HSC, mesenchymal stem cells, myelo-monocytic cells or even macrophages are implicated in this phenomenon; however, HSC appear the major contributors to muscle regeneration [41]. Noteworthy studies showed that a single HSC transplanted into sublethally-irradiated recipient, can give rise to a mixed progeny reconstituting both blood cells and myogenic cells that integrate into regenerating myofibers[42].

Muscle Homeostasis in Health and Disease

Skeletal Muscle Regeneration After Injury

Skeletal muscles regenerate following muscle damage, thus maintaining functional muscle mass throughout life. Skeletal muscle is composed of bundles of multinucleated cells, called myofibres, surrounded by ECM. During embryonic development muscles fibers derive from the fusion of precursors know as myoblasts, a process which is somehow recapitulated in adult life during muscle regeneration, even though this paradigm has been elegantly challenged [43,44]. The syncytial nature of myofibers determines some peculiar features of muscle regeneration, recently reviewed by Coletti et al. [45]. The fine regulation of a sequence of phases following acute injury is of pivotal importance to grant fully, effective regeneration [46]. The latter requires the following steps: 1) Innate immune system recruitment: inflammatory cells of the innate immune system, such as neutrophils, are attracted to the damaged site, and, in turn, recruit monocytes; the latter convert initially to pro- and later to anti-inflammatory macrophages, phagocyte debris of necrotic tissue and stimulate myogenesis and muscle regeneration [47]. Regulatory signals are represented by chemotactic growth factors released by ECM fragmentation or by growth factors of macrophagic origin. 2) Angiogenesis: angiogenesis is necessary to restore blood vessels that ensure supply of oxygen and nutrients to myofibers. Skeletal muscle regeneration is strongly enhanced by Angiopoietin-1 (Ang-1, a ligand secreted by satellite cells) after injury, inducing the angiogenic program in endothelial cells. Also, recombinant Ang-1 increases survival, proliferation, migration and differentiation into myotubes in human skeletal myofibers [48]. Prolonged ischemia, favors fibroblast proliferation and fibrosis development, instead of muscle formation. 3) SC activation: upon SC activation and proliferation myoblasts express MyoD and divide asymmetrically or symmetrically. 4) SC differentiation: SCs quit the mitotic cycle and switch to differentiation expressing specific muscle proteins. Differentiating myoblasts line up and fuse to form multinucleated myotubes characterized by seriatim central nuclei [49]. It has been recently shown, for instance, that stabilin 2 (type 1 transmembrane receptor of phosphatidylserine) contributes to cell-cell interaction, apoptotic cell clearance and especially to myoblasts fusion. This interaction, which requires phosphatidylserine in the myoblast membrane, promotes myoblast fusion into myotubes [50]. 5) Reinnervation: innervation

by motor neurons is required to complete the regeneration of mature, fully functional myofibers. In fact, denervation leads to skeletal muscle atrophy and functional impairment [51]. Motor neuron axons end on the basal lamina of the myofiber forming the neuromuscular junctions, thus innervation is much more likely to be successful if the basal lamina integrity is preserved.

Muscle Atrophy and Hypertrophy: Not Just a Matter of Protein Metabolism

Muscle Hypertrophy

Muscle hypertrophy is obtained by an expansion of myofiber size («true» hypertrophy) or an increase in myofiber number (hyperplasia). It has been demonstrated that myonuclear addition on to human myofiber by SC recruitment may achieve substantial myofiber growth. This is the rationale for proposing SC expansion and incorporation into myofiber as an intervention against muscle atrophy [52]. It is generally accepted that the phosphatidylinositol 3-kinase(PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway is implicated in this phenomenon, being sensitive to mechanical pressure, and leads to translation initiation during hypertrophy [53,54]. In addition, incorporation of new myonuclei, likely from satellite cells, has been associated to IGF-1 -dependent muscle hypertrophy, suggesting that myofiber growth is achieved by a combination of metabolic and cell dependent phenomena [53,54].

Muscle Atrophy

Two major pathways are involved in muscle fiber atrophy following denervation, malnutrition, disuse, or cachexia: the ATP-dependent ubiquitin/proteasome and the autophagy lysosome systems, both leading to loss of muscle mass and reduction of contractile strength. FoxO3 has been shown to be sufficient and necessary to induce atrophy in skeletal muscle by controlling these two pathways [55]. Despite the contribution of autophagy in muscle atrophy is still debated, impaired proteasome activation clearly is protective for skeletal muscle subjected to atrophying conditions [56,57]. Nonetheless, events independent of protein catabolism could participate in myofiber atrophy, by involvement of nuclear loss such as in denervation [58]. Even though this notion is controversial, failure to maintain the regular turnover of myonuclei into muscle fibers could contribute to muscle atrophy [59].

Cachexia and its Effects on Myogenic Cells

Cachexia is a muscle wasting syndrome associated to acute or chronic diseases like AIDS, some organ failure, chronic inflammation due to burning or infection, metabolic diseases [60]. This syndrome is characterized by severe body weight loss of at least 5% in 6 months in the presence of illness. Anorexia and abnormal biochemistry can be associated to cachexia [61,62]. The consequent muscle wasting decreases muscle strength and fatigue. In both cachectic patients and animals the atrophying muscle shows deregulation of muscle homeostasis, due to increased activity of the ubiquitin-proteasome system and induction of defective autophagy, but also to decreased myofibrillar proteins synthesis and mitochondrial content and function. The latter contributes to the increase of stress oxidation in myofibers, further exacerbating myofiber damage and wasting.

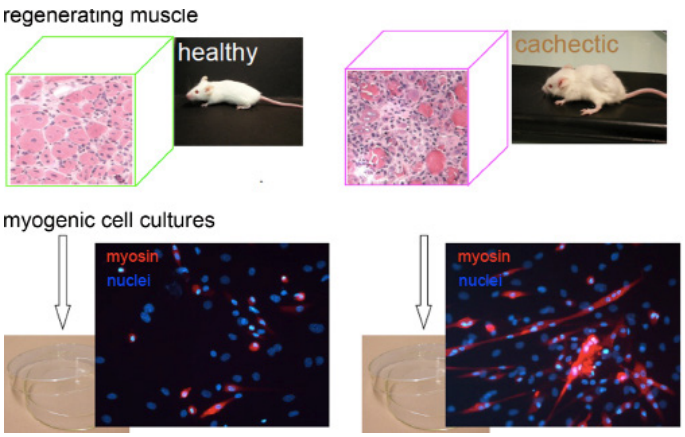

Figure 1: Loss of myogenic potential is not cell intrinsic in cachexia. Upon focal injury healthy muscles regenerate, showing robust formation of myofibers characterized by central nuclei; on the contrary, muscles from tumor-bearing mice have delayed/hampered regeneration. Nonetheless, this deficit is not due to a cell intrinsic decrease in myogenic potential, as shown by primary cultures obtained by isolating myogenic cells from injured muscle of control and cachectic murine muscle. The latter contains cells capable to express myosin starting from 2 days of culture in vitro in differentiation medium (DMEM supplemented with 2% horse serum) by the time cells from control muscles begin the process of myogenic differentiation, parallel cell cultures from cachectic muscle show even bigger myotubes, suggesting an accelerated differentiation. In the photomicrographs myosin is stained in red and nuclei in blue. This suggests that the myogenic potential is not lost in cachexia and is fully expressed once the cells are removed from the inhibitory environment represented by a tumor-conditioned organism.

Additional studies pinpoint the potential contribution of altered muscle regeneration in cachexia. Indeed, skeletal muscle is damaged in cachexia, due to an acquired downregulation of dystrophin [63]. Likely, in response to damage, stem cells proliferate in the musculature in cachectic conditions, thus being even more abundant than in healthy subjects, but clearly fail to support muscle regeneration and homeostasis [64,65]. As shown in Figure 1, a regeneration assay following focal injury highlight the hampered regeneration potential of cachectic muscles. However, this is not due to a myogenic deficit intrinsic to muscle stem cells, since these cells are perfectly capable to form myotubes in differentiation assays in vitro, i.e. once extracted from the pro-cachectic environment. One potential inhibitory cue for muscle regeneration is represented by pro-inflammatory cytokines, which are elevated in cachectic patients and animal models. Figure 2 shows the inhibitory effects of the serum from tumor-bearing mice on myogenic cells and how

this is mimicked by recombinant TNF, a pro-inflammatory cytokine. This kind of evidences suggest the hypothesis that a major limitation to muscle homeostasis in cachexia is not the lack of myogenic stem cells but the fact that their myogenic potential is significantly reduced due to the environmental cues linked to chronic pro-inflammatory state. This issue, is further discussed below.

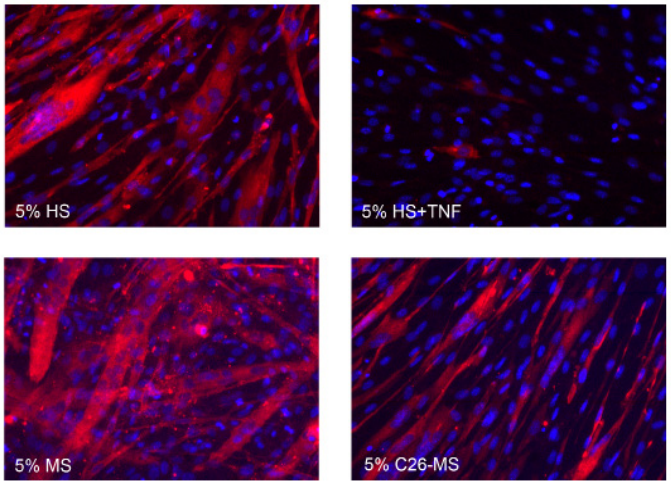

Figure 2: Myogenic differentiation in vitro is inhibited by factors present in the serum of tumor-bearing mice and mimicked by pro-inflammatory cytokines. The myogenic cell line C2C12 can be cultured for 3 days in vitro in the presence of a differentiating medium, constituted by DMEM supplemented as follows: 5% horse serum; 5% horse serum plus 20 ng/ml TNF; 5% murine serum from control, healthy animals; 5% murine serum from C26 tumor-bearing animals. In the photomicrographs myosin is stained in red and nuclei in blue. Low concentrations of either homologous or heterologous serum prompt robust myotube formation, a phenomenon which is diminished in the presence of serum obtained from tumor-bearing, cachectic mice. This effects mimics the well know inhibitory effect of recombinant TNF added to the cell culture, suggesting that the serum from cachectic mice contains pro-inflammatory cytokine(s) or other factor(s) which hamper the myogenic potential of muscle cells.

Current Research on Stem Cell Impairment in Cachexia

Satellite Cells are Activated but Fail to Fuse in Cachexia

Cachexia is associated with muscle damage resulting in activation of both satellite and non satellite muscle progenitor cells [63,65]. In agreement, it was shown that the number of SCs increases in cachexia [65]. However, in the presence of a tumor SC myogenic potential is reduced. These data, along with the observation that the same SCs retain their differentiation capacity in vitro, suggest that in cachexia satellite cells proliferate but the microenvironment inhibits their differentiation, which prompts further investigation on the underlying mechanisms.

In patients and animal models of cachexia SCs overexpress Pax7, which represents an inhibitory signal for their differentiation [65,66]. NFkB activity mediates Pax7 dysregulation and inhibits myogenic differentiation [65,66]. Both in cell culture and in vivo, the amount of MyoD mRNA decreases when NFkB is activated [67]. NFkB can translocate in nuclei and recognizes FoxO. The latter intervenes in the regulation of atrogenic gene, such as the ubiquitin ligase MuRF1. Thus, in cachexia, NFkB activity increases and keeps satellite cells in an undifferentiated state and, at the same time, participates to protein degradation in myofibers.

Many studies demonstrated that NFkB activity is associated with inflammatory factors like TNF, angiotensin II (Ang II), TGF family members, and to the production of reactive oxygen species (ROS) in cancer cachexia. This is particularly relevant, since in cachexia pro-inflammatory cytokines significantly increase. Several studies showed that TNF is sufficient to inhibit myogenic differentiation in vitro [68] and to induce myofiber atrophy in vivo by a blockage of the myogenic program [69] and a negative effect on muscle regeneration [70]. Some groups showed that TNF-mediated blockage of muscle regeneration requires NFkB activity [67,71]. We demonstrated that TNF inhibits myogenic differentiation and muscle regeneration through the p53 cell death pathway including PW1/Peg3, bax, and caspases-dependent signaling [22,23,72]. Studies on IL-6, a pro-inflammatory cytokine elevated in cachexia, and its effects on SCs and muscle homeostasis are more controversial. IL-6 activates the JAK/STAT3 pathway [73,74], but also the ERK and PI3K/AKT pathways, which are typically active in response to exercise and hypetrophying stimuli. IL-6 also induces myostatin expression [75] and, in vitro, impairs myogenic differentiation by modulation of p90RSK/eEF2 and mTOR/p70S6K [73]. Ang II increases in animal models of cancer cachexia by inhibition of the angiotensin converting enzyme [76]. An increase of Ang II in the SC microenvironement induces activation of smad2/3 which plays a catabolic function by blockage of AKT/ mTOR signaling [77]. Consistently with a role in cachexia, Ang II promotes NFkB activity [78], but it is still unknown whether this occurs in cancer cachexia. The smad2/3 complex is activated by Ang II as well as by the TGF family member Myostatin. The latter inhibits MyoD expression in satellite cells [79]. In addition, Myostatin can induce TNF expression by NFkB and ROS mediation in vitro, highlighting potential crosstalk among pro-catabolic factors [80]. The CCAAT/enhancer binding protein beta (C/EBPβ) is a bZIP transcription factor expressed in satellite cells, it inhibits myogenic differentiation and prevents the myogenic regeneration in cancer cachexia in vivo and in vitro; in fact, C/EBPb is normally downregulated in myogenic differentiation [81]. Many studies have been done on the role of C/EBP b in adipogenesis and osteogenesis but not on myogenesis of satellite cells, thus, its role in the inhibition of myogenic differentiation in cachexia is still poorly characterized.

In conjunction with an altered humoral milieu, an increase in oxidative stress seems to play a role in cachexia. TNF increases reactive oxygen species (ROS) in C2C12 cells, revealing that cytokines are able per se to increase oxidative stress in muscle

cells [82]. Consistently, oxidative stress is elevated in cancer patients [83], likely due to a decrease of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase. Inducible nitric oxide synthase/nitric oxigen (iNOS/NO) pathway also affects the fate of satellite cells. In cachexia this pathway could induce muscle wasting [84]. NO released by fibers can mediate SC activation [85,86]. A recent study on aged cancer patients showed a loss of oxidative defense inducing a blockage of SC maturation in skeletal muscle [87].

The Wnt/β-catenin pathways promotes SC differentiation [88] and the Notch signaling pathways represses differentiation of satellite cells [89]. In cachexia, Wnt signaling declines [90] and notch signaling is unchanged [91], suggesting another molecular mechanism for the observed decrease of SC myogenic activity.

Studies on HSC in Cachexia are Scarce

Decreased DNA content proportional to muscle mass wasting in cancer cachexia was observed by our group: this reduction was associated to a decrease in the number of nuclei occurring in the muscular but not in the stromal compartment [64]. In the same study, a statistically significant enrichment in Sca-1+, CD45+ HSC in the cachectic muscle [64], suggesting that this could represent an attempt to maintain muscle homeostasis by recruitment and/or activation of stem cells of various origin along with SCs [64]. We are not aware of other studies addressing the abundance or functional status of HSC in cachexia are missing. Various studies suggest that muscle mass and activity affects HSC survival and function in different pathological settings (HSC transplantation), highlighting, nonetheless, the crosstalk between the two tissues was reported [92].

PICs are Potent Myogenic Cells but Very Sensitive to Cytokines

As described above, PICs express PW1, which participates in both intrinsic (p53) and extrinsic (inflammatory cytokine signaling) cell stress responses [22,23,93]. A recent study showed that PICs contribute to preserve the integrity of myofibers and SCs: PICs expresse follistatin (FST), which in turn neutralizes myostatin, and insulin-like growth factor-1 (IGF-1) that account, in part, for their promyogenic activity [94]. The PW1(+)/Pax7(-) PICs show myogenic potential in vitro, efficiently contribute to skeletal muscle regeneration and are able to generate SCs and other PICs in vivo. They are therefore potentially very interesting as a therapeutic target against muscle atrophy. However, PICs are very sensitive to cytokines, in particular to TNF, as shown by our pioneeristic studies regarding an interstitial myogenic stem cell population, which clearly corresponds to PICs, even though this name was not in use at that time. By exploiting an animal model of muscle regeneration in the absence or presence of TNF (such as it occurs in cachexia), we noticed striking caspase activity localized in interstitial cells, which expressed Sca-1, CD34, and PW1 [95]. Perturbation of PW1 activity blocked caspase activation and improved regeneration, indicating on the one hand the importance of PICs in muscle regeneration, on the other a novel regulatory mechanism whereby TNF inhibits muscle regeneration through caspase activation [96]. Worth noting, caspase activation was independent of their classical, pro-apoptotic role and did not simply deplete muscle of myogenic cells; caspase activation appeared to control myogenesis by an unconventional pathway [96]. The treatment with a potent pro-myogenic factor, such as vasopressin, abolished caspase activation in the putative PICs and rescued muscle regeneration [95], showing that PICs - and myogenic stem cells in general - can be a target for pharmacological or hormonal intervention in conditions characterized by altered muscle homeostasis and regeneration.

Very Little is Known on Other Stem Cells Populations in Cachexia

To the best of our knowledge, the only study showing a direct tumor cell effect on muscle stem cells was done on MDSC and indicates, again, that tumor cells inhibit MDSC myogenic potential. Indeed, it was shown that the myogenic potential of MDSCs decreases when these cells are cocultured with osteosarcoma cells, a response rescued by Notch inhibition [97].

Rationale for Stem Cell Based Interventions Against Cachexia

The main axes of intervention against cachexia and the underlying strategies have recently been reviewed [98]. While most of the current approaches are based on pharmacological treatments, nutritional supplementation or multimodal approaches including exercise, stem cells do not seem to be a major nor a specific target for intervention to date. Some of the main avenues for intervention are suggested by current phase III clinical trials and are based on pro-anabolic agents (which often also have a pro-myogenic effect) such as androgen receptor or ghrelin receptor agonists (reviewed by Crawford [99]). Ghrelin treatments are paradigmatic of hormone-based interventions, since they counteract cachexia by promoting myogenic differentiation and fusion of muscle stem cells, besides having multiple tissue targets [100,101]. In parallel, exercise has been often proposed as a intervention against cachexia, since it counteracts cachexia, a systemic syndrome, thanks its pleiotropic effects including muscle stem cell mobilization [102].

As described in detail above, in the last few years we have shown the importance of the environmental cues for myogenic stem cell function impairment in cachexia. From a therapeutic standpoint, this would emphasize the necessity to exploit population(s) more resistant to the inhibitory cues of a cachectic environment, rather than to transplant myogenic stem cells. In addition, one can foresee that modifying the stem cell niche in cachectic patients would favor stem cell activation and myogenic differentiation, by either inducing pro-myogenic sig-

nals or by removing negative signal which block myogenesis. In this regard, physical activity is a promising approach, since it modulates the inflammatory status of different tissues and organs, favoring resolution of inflammation, promoting muscle homeostasis and increasing survival in the presence of a tumor [66,103].

Which are the major issues related to the myogenic stem cell populations here reviewed? Advantages and disadvantages of SCs for cell-based therapies have been reviewed by Kuang and Rudnicki [104]. Briefly, these cells have been widely studied and they have been already used in clinical trials; however, they seem unsuitable for systemic delivery and have limited expansion potential in vitro; furthermore, their myogenic program is inhibited by pro-inflammatory cytokines. PICs are present in big mammals, such as swine and humans, but they are a far less represented population in muscles as compared to SCs [105]. MDSC are attractive as a therapeutic myogenic source, and have already been used against muscle diseases [106], even though currently there is a large variability in their purification and expansion in vitro, so that the possibility of setting up standard quality control procedures for their use in clinical practice is still a challenge [107]. MABs have been isolated from humans or other mammals and used for intra-arterial transplantation [108]; however, nothing is known about MABs behavior in pathological settings other than dystrophies.

Not all stem cell populations have been characterized bearing in mind their potential sensitivity to circulating factors, which are the most likely candidates to mediate the anti-myogenic, atrophying responses in cachexia. For instance, activin plays a role in cachexia by binding to its type 2 receptor B (ActRIIB) [109]; however, ActRIIB expression in the different stem cells populations has not been fully elucidated by proteomic, comparative analysis. Identifying a myogenic population expressing low levels or no ActRIIB would hamper its sensitivity to activin making it the ideal candidate for a cell based therapy of cachexia, as the latter is characterized by high activin levels.

Independently of the specific stem cell population of choice, other neglected but substantial differences may exist in the myogenic potential of different stem cells, especially in pathological conditions and upon stress. A striking work by Deasy et al. reported that MDSC isolated from male or female differ in their myogenic capacity, with the latter being slower but significantly more robust to produce myotubes, a response due to resistance to oxidative stress [31].

Conclusion

Muscle fiber growth can occur by cytoplasmic increase following anabolism (hypertrophy) or by incorporation of precursor cells into damaged myofibers. Pro-hypertrophic treatments are promising for the rescue of muscle homeostasis in cachexia, but still not routinely used in clinic practice. Stem cell based therapies are not currently foreseen for cachexia, even though they would represent an interesting approach and an alternative to metabolism stimulation. Which would be the ideal candidate for a cell based therapeutic intervention against cachexia? An autologous, possibly recombinant, or an exogenous stem cell, with a potent myogenic potential, reliably and repeatedly expandable in culture, which could be directed toward a myogenic program independently of the presence of factors inhibiting myogenic differentiation. We are not aware of any research group having addressed this question by comparing different types of myogenic stem cells and their behavior in cachexia. Using a genomic or proteomic, comparative approach stem cell populations could be possibly identified which retain their myogenic potential even in adverse conditions such those occurring in cachexia.

References

1. Sirabella D, De Angelis L, Berghella L. Sources for skeletal muscle repair: from satellite cells to reprogramming. J Cachexia Sarcopenia Muscle. 2013; 4: 125-136.
2. Rinaldi F, Perlingeiro RC. Stem cells for skeletal muscle regeneration: therapeutic potential and roadblocks. Translational research: The journal of laboratory and clinical medicine.2014; 163:409-417.
3. MAURO A. Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol. 1961; 9: 493-495.
4. Yablonka-Reuveni Z. The skeletal muscle satellite cell: still young and fascinating at 50. J Histochem Cytochem.2011; 59:1041-1059.
5. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. J Appl Physiol (1985). 2001; 91: 534-551.
6. Schultz E. A quantitative study of the satellite cell population in postnatal mouse lumbrical muscle. Anat Rec. 1974; 180: 589-595.
7. Joshua PN, Sophie J, Tim S, Victoria I, Steven KB, et al. Skeletal muscle satellite cells are located at a closer proximity to capillaries in healthy young compared with older men. J Cachexia Sarcopenia Muscle.2016; 7:547-554.
8. Montarras D, L'honoré A, Buckingham M. Lying low but ready for action: the quiescent muscle satellite cell. FEBS J. 2013; 280: 4036-4050.
9. Yin H, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. Physiol Rev. 2013; 93: 23-67.
10. Collins CA, Gnocchi VF, White RB, Boldrin L, Perez-Ruiz A. Integrated functions of Pax3 and Pax7 in the regulation of proliferation, cell size and myogenic differentiation. PLoS One. 2009; 4: e4475.
11. Decary S, Mouly V, Hamida CB, Sautet A, Barbet JP, et

al. Replicative potential and telomere length in human skeletal muscle: implications for satellite cell-mediated gene therapy. Human gene therapy.1997; 8:1429-1438.

12. Gurevich DB, Nguyen PD, Siegel AL, Ehrlich OV, Sonntag C, et al. Asymmetric division of clonal muscle stem cells coordinates muscle regeneration in vivo. Science. 2016; 353: aad9969.
13. Zammit PS, Golding JP, Nagata Y, Hudon V, Partridge TA, et al. Muscle satellite cells adopt divergent fates: a mechanism for self-renewal? The Journal of cell biology.2004; 166:347-357.
14. Oustanina S, Hause G, Braun T. Pax7 directs postnatal renewal and propagation of myogenic satellite cells but not their specification. The EMBO journal.2004; 23:3430-3439.
15. Le Grand F, Rudnicki MA. Skeletal muscle satellite cells and adult myogenesis. Curr Opin Cell Biol. 2007; 19: 628-633.
16. Wang YX, Rudnicki MA. Satellite cells, the engines of muscle repair. Nat Rev Mol Cell Biol. 2011; 13: 127-133.
17. Brack AS, Rando TA. Tissue-specific stem cells: lessons from the skeletal muscle satellite cell. Cell Stem Cell. 2012; 10: 504-514.
18. Zammit PS, Partridge TA, Yablonka-Reuveni Z. The skeletal muscle satellite cell: the stem cell that came in from the cold. J Histochem Cytochem. 2006; 54: 1177-1191.
19. Rocheteau P, Gayraud-Morel B, Siegl-Cachedenier I, Blasco M, Tajbakhsh S. A subpopulation of adult skeletal muscle stem cells retains all template DNA strands after cell division. Cell.2012;148:112-125.
20. Collins CA, Olsen I, Zammit PS, Heslop L, Petrie A, et al. Stem cell function, self-renewal, and behavioral heterogeneity of cells from the adult muscle satellite cell niche. Cell. 2005; 122: 289-301.
21. Relaix F, Wei XJ, Wu X, Sassoon DA. Peg3/Pw1 is an imprinted gene involved in the TNF-NFkappaB signal transduction pathway. Nat Genet. 1998; 18: 287-291.
22. Schwarzkopf M, Coletti D, Sassoon D, Marazzi G. Muscle cachexia is regulated by a p53-PW1/Peg3-dependent pathway. Genes Dev. 2006; 20: 3440-3452.
23. Schwarzkopf MCD, Marazzi G, SassoonD. Chronic p53 activity leads to skeletal muscle atrophy and muscle stem cell perturbation. Basic Applied Myology.2008; 18:8.
24. Pannerec A, Formicola L, Besson V, Marazzi G, Sassoon DA. Defining skeletal muscle resident progenitors and their cell fate potentials. Development.2013; 140:2879-2891.
25. Mitchell KJ, Pannérec A, Cadot B, Parlakian A, Besson V, et al. Identification and characterization of a non-satellite cell muscle resident progenitor during postnatal development. Nature cell biology.2010; 12: 25-266.
26. Vanessa B, Piera S, Amélie W, Frédéric R, Brahim NO, et al. PW1 gene/paternally expressed gene 3 (PW1/Peg3) identifies multiple adult stem and progenitor cell populations. Proceedings of the National Academy of Sciences of the United States of America.2011; 108:11470-11475.
27. Qu-Petersen Z, Deasy B, Jankowski R, Ikezawa M, Cummins J, et al. Identification of a novel population of muscle stem cells in mice: potential for muscle regeneration. J Cell Biol. 2002; 157: 851-864.
28. Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, et al. Pax7 is required for the specification of myogenic satellite cells. Cell.2000; 102:777-786.
29. Baohong Cao, Bo Zheng, Ron J Jankowski, Shigemi Kimura, Makoto Ikezawa, et al. Muscle stem cells differentiate into haematopoietic lineages but retain myogenic potential. Nature cell biology.2003; 5:640-646.
30. Deasy BM, Gharaibeh BM, Pollett JB, Jones MM, Lucas MA, et al. Long-term self-renewal of postnatal muscle-derived stem cells. Mol Biol Cell. 2005; 16: 3323-3333.
31. Deasy BM, Lu A, Tebbets JC, Feduska JM, Schugar RC, et al. A role for cell sex in stem cell-mediated skeletal muscle regeneration: female cells have higher muscle regeneration efficiency. J Cell Biol. 2007; 177: 73-86.
32. Minasi MG, Riminucci M, De Angelis L, Borello U, Berarducci B, et al. The meso-angioblast: a multipotent, self-renewing cell that originates from the dorsal aorta and differentiates into most mesodermal tissues. Development.2002; 129:2773-2783.
33. Luciana DA, Libera B, Marcello C, Laura L, Malvina Z, et al. Skeletal myogenic progenitors originating from embryonic dorsal aorta coexpress endothelial and myogenic markers and contribute to postnatal muscle growth and regeneration. The Journal of cell biology.1999; 147:869-878.
34. Ozerdem U, Grako KA, Dahlin-Huppe K, Monosov E, Stallcup WB. NG2 proteoglycan is expressed exclusively by mural cells during vascular morphogenesis. Dev Dyn.2001; 222:218-227.

35. Tillet E, Ruggiero F, Nishiyama A, Stallcup WB. The membrane-spanning proteoglycan NG2 binds to collagens V and VI through the central nonglobular domain of its core protein. The Journal of biological chemistry.1997; 272:10769-10776.

36. Hellstrom M, Kalen M, Lindahl P, Abramsson A, Betsholtz C. Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse. Development.1999; 126:3047-3055.

37. Dellavalle A, Maroli G, Covarello D, Azzoni E, Innocenzi A, et al. Pericytes resident in postnatal skeletal muscle differentiate into muscle fibres and generate satellite cells. Nat Commun. 2011; 2: 499.

38. Heredia JE, Mukundan L, Chen FM, Mueller AA, Deo RC, et al. Type 2 innate signals stimulate fibro/adipogenic progenitors to facilitate muscle regeneration. Cell. 2013; 153: 376-388.

39. Joe AW, Yi L, Natarajan A, Le Grand F, So L,, et al. Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis. Nature cell biology.2010; 12:153-163.

40. Dong J, Dong Y, Chen Z, Mitch WE, Zhang L, et al. The pathway to muscle fibrosis depends on myostatin stimulating the differentiation of fibro/adipogenic progenitor cells in chronic kidney disease. Kidney Int. 2017; 91: 119-128.

41. Abedi M, Foster BM, Wood KD, Colvin GA, McLean SD, et al. Haematopoietic stem cells participate in muscle regeneration. Br J Haematol. 2007; 138: 792-801.

42. Camargo FD, Green R, Capetanaki Y, Jackson KA, Goodell MA. Single hematopoietic stem cells generate skeletal muscle through myeloid intermediates. Nature medicine.2003; 9:1520-1527.

43. Lepper C, Conway SJ, Fan CM. Adult satellite cells and embryonic muscle progenitors have distinct genetic requirements. Nature.2009; 460:627-631.

44. Wang J, Conboy I. Embryonic vs. adult myogenesis: challenging the 'regeneration recapitulates development' paradigm. J Mol Cell Biol. 2010; 2: 1-4.

45. Coletti D, Teodori L, Lin Z, Beranudin JF, Adamo S. Restoration versus reconstruction: cellular mechanisms of skin, nerve and muscle regeneration compared. Regen Med Res.2013; 1:4.

46. Grounds MD, Shavlakadze T. Growing muscle has different sarcolemmal properties from adult muscle: a proposal with scientific and clinical implications: reasons to reassess skeletal muscle molecular dynamics, cellular responses and suitability of experimental models of muscle disorders. BioEssays : news and reviews in molecular, cellular and developmental biology.2011; 33:458-468.

47. Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, et al.Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. The Journal of experimental medicine.2007; 204:1057-1069.

48. Mofarrahi M, McClung JM, Kontos CD, Davis EC, Tappuni B, et al. Angiopoietin-1 enhances skeletal muscle regeneration in mice. Am J Physiol Regul Integr Comp Physiol. 2015; 308: R576-589.

49. Mazzotti AL, Coletti D. The Need for a Consensus on the Locution "Central Nuclei" in Striated Muscle Myopathies. Front Physiol. 2016; 7: 577.

50. Park SY, Yun Y, Lim JS, Kim MJ, Kim SY, et al. Stabilin-2 modulates the efficiency of myoblast fusion during myogenic differentiation and muscle regeneration. Nat Commun. 2016; 7: 10871.

51. Larsson L. Motor units: remodeling in aged animals. The journals of gerontology. Series A, Biological sciences and medical sciences.1995; 50:91-95.

52. Petrella JK, Kim JS, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. Journal of applied physiology.2008; 104:1736-1742.

53. Musarň A, Giacinti C, Pelosi L, Dobrowolny G, Barberi L, et al. Stem cell-mediated muscle regeneration and repair in aging and neuromuscular diseases. Eur J Histochem. 2007; 51 Suppl 1: 35-43.

54. Barberi L, Scicchitano BM, De Rossi M, Bigot A, Duguez S, et al. Age-dependent alteration in muscle regeneration: the critical role of tissue niche. Biogerontology. 2013; 14: 273-292.

55. Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, et al. FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab. 2007; 6: 458-471.

56. Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001; 294: 1704-1708.

57. Moresi V, Williams AH, Meadows E, Flynn JM, Potthoff MJ, et al. Myogenin and class II HDACs control neurogenic muscle atrophy by inducing E3 ubiquitin ligases. Cell. 2010; 143: 35-45.

58. Dupont-Versteegden EE, Murphy RJ, Houle JD, Gurley CM, et al. Activated satellite cells fail to restore myonuclear number in spinal cord transected and exer-

cised rats. The American journal of physiology.1999; 277: C589-597.

59. Bruusgaard JC, Gundersen K. In vivo time-lapse microscopy reveals no loss of murine myonuclei during weeks of muscle atrophy. The Journal of clinical investigation.2008; 118:1450-1457.

60. Coletti D, Adamo S. Highlights on Cachexia, from the 4th Cachexia Conference. Tampa (FL), 6-9 Dec 2007. European Journal of Translational Myology.2008; 18:109-114.

61. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, et al. Cachexia: a new definition. Clin Nutr. 2008; 27: 793-799.

62. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011; 12: 489-495.

63. Acharyya S, Butchbach ME, Sahenk Z, Wang H, Saji M, et al. Dystrophin glycoprotein complex dysfunction: a regulatory link between muscular dystrophy and cancer cachexia. Cancer cell.2005; 8:421-432.

64. Berardi E, Aulino P, Murfuni I, Toschi A, Padula F, et al. Skeletal muscle is enriched in hematopoietic stem cells and not inflammatory cells in cachectic mice. Neurol Res. 2008; 30: 160-169.

65. He WA, Berardi E, Cardillo VM, Acharyya S, Aulino P, et al. NF-kappaB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. The Journal of clinical investigation.2013; 123:4821-4835.

66. Coletti D, Aulino P, Pigna E, Barteri F, Moresi V, et al. Spontaneous Physical Activity Downregulates Pax7 in Cancer Cachexia. Stem Cells Int. 2016; 2016: 6729268.

67. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS, Jr. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. Science.2000; 289:2363-2366.

68. Miller SC, Ito H, Blau HM, Torti FM. Tumor necrosis factor inhibits human myogenesis in vitro. Molecular and cellular biology.1988; 8:2295-2301.

69. Ramon CJL, Annemie MWJS, Marco CJMK, Jos LJ van der Velden, Emiel FMW, et al. Muscle wasting and impaired muscle regeneration in a murine model of chronic pulmonary inflammation. American journal of respiratory cell and molecular biology.2006; 35:689-696.

70. Coletti D, Moresi V, Adamo S, Molinaro M, Sassoon D. Tumor necrosis factor-alpha gene transfer induces cachexia and inhibits muscle regeneration. Genesis.2005; 43:120-128.

71. Ladner KJ, Caligiuri MA, Guttridge DC. Tumor necrosis factor-regulated biphasic activation of NF-kappa B is required for cytokine-induced loss of skeletal muscle gene products. The Journal of biological chemistry.2003; 278:2294-2303.

72. Coletti D, Yang E, Marazzi G, Sassoon D. TNFalpha inhibits skeletal myogenesis through a PW1-dependent pathway by recruitment of caspase pathways. The EMBO journal.2002; 21:631-642.

73. Pelosi M, De Rossi M, Barberi L, Musarň A. IL-6 impairs myogenic differentiation by downmodulation of p90RSK/eEF2 and mTOR/p70S6K axes, without affecting AKT activity. Biomed Res Int. 2014; 2014: 206026.

74. Bonetto A, Aydogdu T, Jin X, Zhang Z, Zhan R, et al. JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. American journal of physiology.2012; 303: E410-421.

75. Rodríguez A, Becerril S,. Crosstalk between adipokines and myokines in fat browning. Acta Physiol (Oxf). 2017; 219: 362-381.

76. Sanders PM, Russell ST, Tisdale MJ. Angiotensin II directly induces muscle protein catabolism through the ubiquitin-proteasome proteolytic pathway and may play a role in cancer cachexia. British journal of cancer.2005; 93:425-434.

77. Rommel C, Bodine SC, Clarke BA, Rossman R, Nunez L, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nat Cell Biol. 2001; 3: 1009-1013.

78. Marta RO, Oscar L, Mónica R, Sven K, Burghardt W, et al. Angiotensin II activates nuclear transcription factor kappaB through AT(1) and AT(2) in vascular smooth muscle cells: molecular mechanisms. Circulation research.2000; 86:1266-1272.

79. Langley B, Thomas M, Bishop A, Sharma M, Gilmour S, et al. Myostatin inhibits myoblast differentiation by down-regulating MyoD expression. J Biol Chem. 2002; 277: 49831-49840.

80. Sriram S, Subramanian S, Sathiakumar D, Venkatesh R, Salerno MS, et al. Modulation of reactive oxygen species in skeletal muscle by myostatin is mediated through NF-ÎşB. Aging Cell. 2011; 10: 931-948.

81. Marchildon F, Lamarche É, Lala-Tabbert N, St-Louis C, Wiper-Bergeron N, et al. Expression of CCAAT/Enhancer Binding Protein Beta in Muscle Satellite Cells Inhibits Myogenesis in Cancer Cachexia. PLoS One. 2015; 10: e0145583.

82. Kosmidou I, Vassilakopoulos T, Xagorari A, Zakynthinos S, Papapetropoulos A, et al. Production of interleukin-6 by skeletal myotubes: role of reactive oxygen species. Am J Respir Cell Mol Biol. 2002; 26: 587-593.

83. Mantovani G, Macciň A, Madeddu C, Mura L, Gramignano G, et al. Quantitative evaluation of oxidative stress, chronic inflammatory indices and leptin in cancer patients: correlation with stage and performance status. Int J Cancer. 2002; 98: 84-91.

84. Hall DT, Ma JF, Marco SD, Gallouzi IE. Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cachexia. Aging.2011; 3:702-715.

85. Kobzik L, Reid MB, Bredt DS, Stamler JS. Nitric oxide in skeletal muscle. Nature. 1994; 372: 546-548.

86. Anderson JE. A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Molecular biology of the cell.2000; 11:1859-1874.

87. BrzeszczyĹ„ska J, Johns N, Schilb A. Loss of oxidative defense and potential blockade of satellite cell maturation in the skeletal muscle of patients with cancer but not in the healthy elderly. Aging (Albany NY). 2016; 8: 1690-1702.

88. Fujimaki S, Machida M, Hidaka R, Asashima M, Takemasa T, et al. Intrinsic ability of adult stem cell in skeletal muscle: an effective and replenishable resource to the establishment of pluripotent stem cells. Stem Cells Int. 2013; 2013: 420164.

89. Olguín HC, Pisconti A. Marking the tempo for myogenesis: Pax7 and the regulation of muscle stem cell fate decisions. J Cell Mol Med. 2012; 16: 1013-1025.

90. Bonetto A, Aydogdu T, Kunzevitzky N, Guttridge DC, Khuri S, et al. STAT3 activation in skeletal muscle links muscle wasting and the acute phase response in cancer cachexia. PLoS One. 2011; 6: e22538.

91. Talbert EE, Guttridge DC. Impaired regeneration: A role for the muscle microenvironment in cancer cachexia. Seminars in cell & developmental biology.2016; 54:82-91.

92. Takekiyo T, Dozono K, Mitsuishi T, Murayama Y, Maeda A, et al. Effect of exercise therapy on muscle mass and physical functioning in patients undergoing allogeneic hematopoietic stem cell transplantation. Support Care Cancer.2015; 23:985-992.

93. Frédéric Relaix, Xiao-jun Wei, Wei Li, Jianjing Pan, Yahong Lin, et al. Pw1/Peg3 is a potential cell death mediator and cooperates with Siah1a in p53-mediated apoptosis. Proceedings of the National Academy of Sciences of the United States of America.2000; 97:2105-2110.

94. Formicola L, Marazzi G, Sassoon DA. The extraocular muscle stem cell niche is resistant to ageing and disease. Front Aging Neurosci. 2014; 6: 328.

95. Moresi V, Garcia-Alvarez G, Pristerŕ A, Rizzuto E, Albertini MC, et al. Modulation of caspase activity regulates skeletal muscle regeneration and function in response to vasopressin and tumor necrosis factor. PLoS One. 2009; 4: e5570.

96. Moresi V, Pristerà A, Scicchitano BM, Molinaro M, Teodori L, et al. Tumor necrosis factor-alpha inhibition of skeletal muscle regeneration is mediated by a caspase-dependent stem cell response. Stem cells (Dayton, Ohio).2008; 26:997-1008.

97. Mu X, Agarwal R, March D, Rothenberg A, Voigt C, et al. Notch Signaling Mediates Skeletal Muscle Atrophy in Cancer Cachexia Caused by Osteosarcoma. Sarcoma. 2016; 2016: 3758162.

98. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013; 10: 90-99.

99. Crawford J. Clinical results in cachexia therapeutics. Current opinion in clinical nutrition and metabolic care.2016; 19:199-204.

100. Porporato PE, Filigheddu N, Reano S, Ferrara M, Angelino E, et al. Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice. J Clin Invest. 2013; 123: 611-622.

101. Filigheddu N, Gnocchi VF, Coscia M, Cappelli M, Porporato PE, et al. Ghrelin and des-acyl ghrelin promote differentiation and fusion of C2C12 skeletal muscle cells. Mol Biol Cell. 2007; 18: 986-994.

102. Alves CR, da Cunha TF, da Paixão NA, Brum PC. Aerobic exercise training as therapy for cardiac and cancer cachexia. Life Sci. 2015; 125: 9-14.

103. Lira FS, Rosa JC, Zanchi NE, Yamashita AS, Lopes RD, et al. Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. Cell Biochem Funct. 2009; 27: 71-75.

104. Kuang S, Gillespie MA, Rudnicki MA. Niche regulation of muscle satellite cell self-renewal and differentiation. Cell Stem Cell. 2008; 2: 22-31.

105. Lewis FC, Henning BJ, Marazzi G, Sassoon D, Ellison GM, et al. Porcine skeletal muscle-derived multipotent PW1pos/Pax7neg interstitial cells: isolation, characterization, and long-term culture. Stem cells translational medicine.2014; 3: 702-712.

106. Torrente Y, Belicchi M, Marchesi C, D'Antona G, Cogia-

manian F, et al. Autologous transplantation of muscle-derived CD133+ stem cells in Duchenne muscle patients. Cell Transplant. 2007; 16: 563-577.

107. Wang JJ, Gao XN, Chen SS, Zhang PP, Wang T, et al. [Progress of Experimental Research on Differentiation of Muscle-Derived Stem Cells into Haematopoietic Lineages in Vitro -Review]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2016; 24: 1897-1900.

108. Giulio C, Stefano CP, Sara N, Maria PC, Francesco ST, et al. Intra-arterial transplantation of HLA-matched donor mesoangioblasts in Duchenne muscular dystrophy. EMBO molecular medicine.2015; 7:1513-1528.

109. Hatakeyama S, Summermatter S, Jourdain M, Melly S, Minetti GC, et al. ActRII blockade protects mice from cancer cachexia and prolongs survival in the presence of anti-cancer treatments. Skelet Muscle. 2016; 6: 26.