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Impaired Regeneration: A Role for the Muscle Microenvironment in Cancer Cachexia

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Abstract

While changes in muscle protein synthesis and degradation have long been known to contribute to muscle wasting, a body of literature has arisen which suggests that regulation of the satellite cell and its ensuing regenerative program are impaired in atrophied muscle. Lessons learned from cancer cachexia suggest that this regulation is simply not a consequence, but a contributing factor to the wasting process. In addition to satellite cells, evidence from mouse models of cancer cachexia also suggests that non-satellite progenitor cells from the muscle microenvironment are also involved. This chapter in the series reviews the evidence of dysfunctional muscle repair in multiple wasting conditions. Potential mechanisms for this dysfunctional regeneration are discussed, particularly in the context of cancer cachexia.

INTRODUCTION

Significant loss in body mass, termed cachexia, is a common side effect of many disease states, including renal disease, chronic obstructive pulmonary disease (COPD), chronic heart failure, diabetes, and advanced cancer [1–5]. These decreases in body mass are often severe and result from loss of both adipose tissue and skeletal muscle [6]. Skeletal muscle loss is particularly problematic, as it is associated with decreased patient quality of life [7]. In some diseases, including cancer, skeletal muscle loss contributes to decreased patient treatment tolerance and survival, with perhaps more than one quarter of all cancer-related deaths resulting from muscle wasting, rather than tumor burden [8, 9].

Skeletal muscle wasting due to cachexia results from atrophy of individual muscle fibers. Despite decades of research, the complete mechanism by which skeletal muscle wastes due to cancer remains unknown. At current, the primary mechanism of muscle wasting across conditions that induce muscle atrophy is thought to involve an imbalance between muscle protein synthesis and degradation [10, 11]. When the synthesis of muscle protein is

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equivalent to the breakdown of muscle protein, muscle fiber size remains constant. Similarly, decreases in muscle protein synthesis and increases in muscle protein degradation both lead to decreases in muscle fiber cross-sectional area. The serine-threonine kinase Akt (also called protein kinase B, PKB) and its downstream effectors, including the mammalian target of rapamycin (mTOR), glycogen synthase kinase-3beta (GSK-3β), and Forkhead Box O (FoxO) proteins, play important roles in maintaining the balance of muscle protein synthesis and degradation [12, 13].

Like for many atrophy conditions, much of what we know about cancer-induced muscle wasting comes from animal models of the condition. Protein synthesis has been reported to decrease in cachectic rodents [14–16]. Additionally, the activation of Akt and its downstream effectors are altered in mice with cachexia, which is consistent with a decrease in protein synthesis [16–18]. Increases in muscle protein degradation also contribute to the imbalance of protein synthesis and degradation in rodents with cancer cachexia [16]. In addition to direct measures, increased expression of the components of the ubiquitin proteasome system, a key proteolytic pathway involved in muscle degradation, is commonly used as a surrogate marker for protein degradation. Specifically, increases in the muscle-specific E3 ubiquitin ligases atrogin-1 (also known as Muscle Atrophy F-box, MAFBx) and Muscle Ring Finger-1 (MuRF-1) are consistently seen in cachectic rodents [17, 19]. Additionally, authors consistently report increased expression of genes associated with the autophagy pathway, another key mechanism through which muscle protein is degraded [12, 16, 17, 19]. Thus, an imbalance of protein synthesis and protein degradation does seem to contribute to cancer-induced muscle wasting in the traditional animal models of cachexia.

While at least part of the mechanism by which muscle protein is lost in rodents experiencing cancer cachexia is understood, the manner in which patients suffering from cancer lose muscle protein remains less defined. Several studies have reported that muscle protein synthesis is decreased in patients suffering from cancer [20–22]. However, opposing evidence also exists to suggest that muscle protein synthesis is not impacted by cancer [23]. Work conducted by Williams et al., demonstrates that while protein synthesis in cancer patients did not differ from control individuals in the fasted state, cancer patients failed to increase protein synthesis following feeding like control subjects [21]. Importantly, these same patients demonstrated a significant post-feeding increase in protein synthesis following curative tumor resection, providing clear evidence that tumors do alter muscle protein synthesis, at least in response to feeding. Consistent with the controversy about changes in muscle protein synthesis in patients with cancer, the Akt signaling pathway is commonly believed to be either downregulated or dysfunctional in patients with cancer, but the evidence for changes in this pathway is not compelling [24–26].

Like alterations in muscle protein synthesis, whether patients experiencing cancer cachexia demonstrate increases in muscle protein degradation remains unclear. Studies calculating protein breakdown rates in cancer patients vary in their outcome, with some reporting increased protein breakdown and others failing to find significant changes [23, 27]. Some studies report increases in proteasome gene expression in muscle of humans suffering from diseases associated with muscle loss [28–30], but other, more recent studies, including ones conducted in cancer patients with cachexia, fail to demonstrate the large increases in

expression of these genes commonly seen in rodents models of cancer cachexia [31, 32]. Further, although limited data exist, autophagy markers also do not appear to increase in cancer patients with cachexia [24].Taken together, whether alterations in protein synthesis and protein degradation in skeletal muscle are driving forces of cachexia in cancer patients, as seen in rodent studies, remains controversial. Clearly, more patient studies will be needed to clarify this issue.

Regardless of whether increased protein degradation, decreased protein synthesis, or a combination of both is ultimately responsible for inducing muscle atrophy in cancer patients, the regulation of these mechanisms of atrophy is firmly considered to reside within muscle fibers. However, over the past several decades there has been a sparse, but growing body of literature suggesting that events surrounding muscle fibers also play an important role in the process of muscle fiber atrophy. In this chapter of the series, we will review the evidence pointing to the importance of the muscle microenvironment in cancer-induced muscle atrophy, with a particular focus on the role of the muscle regeneration program.

The Extracellular Environment of Muscle

The environment surrounding muscle fibers is a complex mixture of structural proteins, blood vessels, and nerves that support muscle's primary purpose of force production for movement. In addition to these components, the extracellular matrix of skeletal muscle is home to several different types of mononuclear cells. Many of these cell types have been demonstrated to proliferate following muscle injury and either have the capacity to become myogenic and contribute to skeletal muscle or remain non-myogenic but nevertheless support the process of muscle regeneration (reviewed in [33–35]). Cells such as satellite cells, pericytes and mesoangioblasts, side population cells, PW1+ cells, and CD133+ progenitor cells can become myogenic and fuse into injured skeletal muscle [36–47]. Additionally, fibro-adipogenic (FAP) cells support muscle repair by promoting the differentiation of other muscle precursor cells [48, 49]. Importantly, the resident population of Pax7+ satellite cells appears to provide the majority of muscle precursor cells necessary for repairing muscle, while other populations contribute fewer cells to regenerating adult muscle under physiological conditions [50–54].

Satellite cells were originally described based on their location, as they reside outside the sarcolemma, but under the basal lamina [55]. Besides their anatomical position, satellite cells are best identified by their expression of the transcription factor, Pax7. When muscle fibers become damaged, whether due to small perturbations of the sarcolemma caused by everyday wear and tear or large injuries which will require the formation of new muscle fibers, satellite cells become activated, enter the cell cycle, and begin to proliferate to produce muscle precursor cells, which are called myoblasts [56].These Pax7+ cells commit to the myogenic linage by expressing other transcription factors including MyoD [56]. Following a decline of Pax7 expression within myoblasts, muscle is repaired by myoblast differentiation, where myoblasts fuse with each other to form de novo skeletal muscle fibers or fuse to existing muscle fibers in need of repair [57–59]. Indications of ongoing muscle repair include the presence of centrally located nuclei within muscle fibers, the expression of the embryonic isoform of myosin heavy chain, the presence of small muscle fibers, and

increases in the expression of transcription factors such as MyoD and myogenin [56]. A subpopulation of Pax7+ cells will continue to have high Pax7 expression and remain MyoD −, which signals these cells to self-renew and reacquire their anatomical position as satellite cells, poised for the next round of injury and repair [60, 61]. Together, this process of muscle regeneration is quite similar to the stepwise events that occur during embryonic and fetal muscle development, called myogenesis [33].

Satellite cells are surrounded by an environment that defines the “niche” of these resident stem cells. The composition of this niche plays an important role in the maintenance, activation, and function of satellite cells [62]. In particular, laminin is required for myoblast proliferation and differentiation, while fibronectin promotes satellite cell proliferation, but inhibits differentiation, and is likely needed for the self-renewal process [63–65]. Additionally, muscle precursor cells are particularly sensitive to the tension of their environment, which is most commonly regulated by collagen levels [66]. Perturbations to the satellite cell niche are a common signal of muscle damage in need of repair, which leads to activation of the myogenic program. While less appreciated than the more common acute injuries to skeletal muscle, muscle atrophy is also related to muscle damage, a point that will be discussed in the next section.

Muscle Damage and Regeneration in Atrophy

Muscle damage, particularly to the muscle membrane, or sarcolemma, is a feature of muscle atrophy described in the literature, particularly in regards to denervation [67–69]. Most commonly, these changes were visualized by electron microscopy and are purely descriptive. Reports state that the sarcolemma changed from a smooth, flat appearance in control muscle to a ridged, uneven surface in denervated muscle. Perhaps the greatest evidence that muscle atrophy is associated with muscle damage is the multitude of studies that describe different aspects of the muscle regeneration program, including centrally located nuclei within muscle fibers, embryonic myosin heavy chain expression, small muscle fibers, and increased MyoD and myogenin expression [68–76]. Additionally, a number of studies have demonstrated an increase in the number of muscle precursor cells present in atrophying muscle, with many of these increases quantified using electron microscopy. For instance, Ferreria et al. reported that a 3-fold increase in proliferating Pax7+ cells occurs following a mere six hours of hindlimb suspension, before declining to control levels after 48 hours, with further declines after 72 hours and 1 week of suspension [77]. Similar phenotypic events seem to occur in denervated muscle, with multiple groups reporting initial increases in satellite cell numbers, followed by later declines [68, 78–80].

While many causes of muscle atrophy appear to associate with the initiation of the muscle regeneration program, a prevailing hypothesis in the field is that muscle regeneration is impaired in atrophying muscle. This idea originated from a number of studies that reported that the number of precursor cells decline in atrophied muscle [81–85]. More recent work supports this hypothesis by demonstrating that muscle atrophied by hindlimb suspension prior to cardiotoxin injury exhibited a block in regeneration that impairs any gain in muscle mass even six weeks following acute injury [86].

In addition to denervation and disuse, other conditions of atrophy, such as chronic obstructive pulmonary disease (COPD) [87–92], chronic kidney disease [93, 94], burn injury [95, 96], diabetes [97–102], and cancer [103–107], have also been associated with the impairment of muscle regeneration. However, missing from these studies is an understanding of whether the impairment of muscle regeneration is simply a consequence of muscle atrophy, or instead a contributing factor leading to the loss of muscle mass and function. Evidence that impaired regeneration is indeed causal to muscle atrophy was recently provided in the cancer-induced muscle wasting condition of cachexia that we expand upon in the following section. The evidence demonstrating activation and dysfunction of the muscle regeneration program in conditions inducing muscle atrophy, including cancer cachexia, is summarized in Table 1.

Muscle Regeneration is Activated but Dysfunctional in Cancer Cachexia

Similar to more traditional methods of inducing muscle atrophy, muscles undergoing cancer cachexia clearly become damaged. Electron micrographs, laminin staining, IgG staining, and the leakage of Evan's Blue dye into muscle fibers of patients and animals with tumors all indicatean ultrastructural alteration to the sarcolemma of muscle fibers [19, 104, 108]. Importantly, this damage phenotype appears to derive from circulating tumor factors rather than from metastatic tumor cells directly infiltrating into the muscle [104]. Consistent with this damage, two independent groups identified an increase in the number of mononuclear cells within the muscle microenvironment in cachectic animals, with similar findings reported by our group in cachectic patients with pancreatic cancer [104, 107].

With the onset of lineage tracing using a Pax7-ERCre;Rosa26-Tomato reporter mouse line that specifically marks Pax7+ cells, it was possible to determine using a combination of single myofiber immunostaining and FACS analysis that in addition to the increase in satellite cells, non-satellite, interstitially-located cells expressing Pax7 also expand in cachectic muscles of tumor bearing mice [104]. The majority of these non-satellite Pax7+ cells expressed the stem cell marker Sca1. Further investigation from single myofiber staining revealed distinct Pax7+;Sca1+ populations, with a portion of these cells marked either by the FAP cell marker PDGFRα, or NG2, a proteoglycan associated with pericytes. Muscle from control mice did not demonstrate similar co-localization of Pax7 and PDGFRα or NG2, suggesting that these cell types may be "called upon" to enter a myogenic linage in response to the tumor-induced damage. However, whether these non-satellite cell populations assist satellite cells in attempting to repair damaged muscles to prevent atrophy has not yet been resolved. This combination of increased satellite cell numbers and non-myogenic populations appearing to be called to a myogenic linage results in large increases in Pax7 protein expression in cachectic muscle [104].

Importantly, several genetic manipulations were used to reduce the amount of Pax7 expressed specifically in precursor cells by tumor-bearing mice. In two different animal models of cancer cachexia, depletion of Pax7 was sufficient to attenuate muscle wasting by rescuing the muscle regeneration program [104]. This firmly demonstrated that deregulated levels of Pax7 contribute to muscle wasting in cancer cachexia. However, the mechanism by

which muscle regeneration, and by extension Pax7, becomes dysregulated remains unknown, although two possibilities are discussed below.

Myoblast Fusion Defects

While no definitive evidence exists, potential causes of dysfunctional muscle regeneration during cancer-induced muscle atrophy have been identified. These include defects in myoblast fusion and an inability of muscle fibers to shed their “stemness” and progress through the regeneration process. For various atrophy conditions including cancer, there is an increase in muscle precursor cell number as muscle mass is lost [68, 77–79, 104]. Such results indicate that the muscle regenerative program is active during muscle wasting, suggesting that the ability of satellite cells to be activated is not the limiting factor during the impairment of the muscle regeneration program. Several groups, including our own, have postulated that the accumulation of muscle precursor cells seen in atrophying muscle is actually the result of a fusion defect, which prevents myoblasts from differentiating into muscle fibers and repairing the damage induced by the original atrophy signal.

Early suggestions of a fusion defect in atrophying muscle came from Mozdziaket. al., who demonstrated that muscle regenerating from a snake venom injection contained more proliferating nuclei when the muscle was also subjected to hindlimb suspension [109]. Thus, myoblast proliferation was actually greater during conditions of disuse, yet muscle loss was increased. *In vitro* data demonstrating delayed fusion of myoblasts isolated from animals who had undergone disuse compared to cells from control animals also support the concept of a fusion defect in atrophying muscle, with similar data in myoblasts isolated from denervated muscle [81, 110].

In cancer cachexia, muscle atrophy induces substantial increases in both the expression of Pax7 protein and the number of Pax7+;BrdU+ cells, suggesting that proliferation of muscle precursor cells is not the limiting factor of muscle regeneration in this condition [19, 104]. However, in the case of cancer, the microenvironment appears to play a prominent role in regulating fusion as a terminal stage of differentiation. For example, we showed that muscle precursor cells isolated from non-tumor bearing mice fuse into cardiotoxin-injured muscle of tumor-bearing mice at a reduced frequency compared to regenerating muscle from a non-tumor-bearing mouse, suggesting that the environment of cachectic muscle is not conducive to myoblast fusion [104]. Similarly, while proliferating Pax7+ cells were unable to fuse into muscle of cachectic mice, these cells readily fused into muscle fibers following the resection of the tumor. Thus, tumor-derived factors that influence the muscle microenvironment appear responsible for preventing the fusion of Pax7+ precursor cells into muscle, which is necessary to complete their differentiation program [104]. Similar conclusions were reached with *in vitro* assays. Here, our laboratory demonstrated that muscle precursor cells isolated from tumor-bearing mice actually differentiate more readily than cells from control mice. This was consistent with other data showing that muscle precursor cells from cachectic mice enter into a regenerative program due to muscle damage caused by tumor-derived circulating factors. Thus, the ability for these cells to complete differentiation *in vitro* faster than control muscle precursor cells argues that their fusion defect *in vivo* is not due to a cell autonomous

effect but rather a property of the muscle microenvironment influenced by the presence of tumor-derived factors [104].

Importantly, the existence of a fusion defect during regeneration in atrophied muscle should not preclude efforts to establish if a satellite cell proliferation defect also exists in atrophied muscle. While clear evidence exists that satellite cells do indeed become activated during muscle atrophy, the majority of these reports involve muscle that is currently undergoing atrophy. As discussed above, while satellite cell number increases early in the process of muscle atrophy, the number of satellite cells is reduced in late-stage atrophy caused by disuse or denervation [68, 77–79, 81–84]. Satellite cells from muscle denervated for greater than five days are unable to proliferate and express myogenin or to uptake BrdU [111, 112]. Further, in a study of cardiotoxin injections during continued hindlimb suspension, no proliferation of Pax7+ cells occurred [86]. Thus, in addition to a fusion defect, a satellite cell proliferation defect may also exist in atrophied muscle.

At current, no evidence exists to indicate that cancer induces a decrease in satellite cell number. However, our own data demonstrate that tumor factors can induce satellite cell apoptosis *in vitro*, which has been suggested as a mechanism by which satellite cell numbers decline in other atrophy conditions [84, 113]. Additional experiments will be required to determine the relative importance of apoptosis in cancer-induced muscle wasting.

Maintaining Stemness in Cancer Cachexia

A characteristic of satellite cells that is common to all stem cells is their ability to self-renew in order to be able to repair muscle following repeated injuries. Pax7+ cells appear to do this by undergoing asymmetrical divisions, with one daughter cell maintaining a less-committed phenotype than the other [60]. During a physiological response of muscle regeneration, the less committed daughter cell (Pax7+,Myf5−) is able to occupy the satellite cell niche and replenish the satellite cell pool, while the more committed Pax7+,Myf5+ cells undergo symmetric cell division, which produces two identical daughter cells that will either continue to proliferate or proceed to differentiate into muscle fibers. Thus, satellite cell activation and division produces a heterogeneous population to meet the need of the muscle to both maintain the satellite cell pool and repair damage.

During disuse atrophy, the expression of Pax7 remains high, yet expression of transcription factors like Myf5, which is associated with myogenic commitment, is decreased [81, 114]. Thus, in this condition of muscle atrophy muscle precursor cells fail to commit to differentiation potentially due to a continued stemness of the Pax7+ cells. Similarly, muscles from tumor-bearing mice exhibit many-fold increases in Pax7 protein levels without increases in other myogenic transcription factor coding genes like MyoD and myogenin, which under physiological conditions would be induced to regulate the completion of differentiation [19, 104, 106].

The relative expression of Pax7 and MyoD appears to determine whether or not a satellite cell proceeds forward in the regeneration program towards differentiation. When the Pax7 to MyoD ratio is low, differentiation is promoted, allowing MyoD to induce the expression of myogenin, which functions in myoblast fusion [115, 116]. Myogenininduction has been

shown to promote differentiation in part through a negative feedback response on Pax7. The decrease in Pax7 signals the cell to proceed to differentiation rather than self-renew [58, 117]. If the ratio of Pax7 to MyoD remains high, satellite cells cannot progress through myogenesis and eventually exit the cell cycle, returning to quiescence [115]. While this mechanism is important to maintain a population of satellite cells, too many satellite cells prone to returning to quiescence reduces the number of committed cells needed for effective muscle repair.

One reason that the ratio of Pax7 to MyoD can remain high is due to continued expression of Pax7, which either prevents or delays the expression of myogenin and muscle precursor cell differentiation [58, 59]. Thus, failure of activated satellite cells to downregulate Pax7 or to express MyoD or myogenin leads to a block in muscle regeneration, as muscle precursor cells appear to maintain their stemness and are unable to fuse into muscle fibers.

Role of NF-κB in Dysfunctional Muscle Regeneration

In an effort to determine the upstream signal leading to dysfunctional muscle regeneration in cancer cachexia, our group investigated the NF-κB signaling pathway. NF-κB is a family of transcription factors which playsmultiple roles in promoting cell survival and proliferation [118]. NF-κB signaling, through what is now referred to as the classical pathway, is activated in cachectic myofibers and this activation contributes to tumor-induced muscle wasting [104, 119]. In culture, activation of the same classical pathway in myoblasts has been shown by multiple groups, including our own, to negatively regulate differentiation. In fact, in conditions such as muscular dystrophy, the constitutive activation of NF-κB in muscle was shown to function as a major inhibitor of muscle regeneration, which is one of the hallmark features of degenerative muscles in this pathology [120, 121]. In cancer cachexia, we showed that NF-κB activity was absent in quiescent satellite cells, but highly induced within Pax7+ cells in tumor-bearing mice [104]. Further, we found that deletion of NF-κB signaling specifically from Pax7+ cells is sufficient to rescue cancer-induced muscle wasting. This rescue is associated with increased fusion of Pax7+ cells into muscle fibers, suggesting that in cancer, NF-κB plays a role in the muscle microenvironment to dysregulate the expression of Pax7, which subsequently leads to impaired muscle regeneration and muscle atrophy.

While NF-κB signaling clearly appears to contribute to cancer-induced muscle wasting, both by operating in the myofiber and in Pax7+ precursor cells, the mechanism by which NF-κB is activated during muscle wasting remains unknown. Several well-studied inflammatory factors such as Tumor necrosis factor-alpha (TNF), angiotensin II (Ang II), and the TGF family member myostatin have been linked to cancer cachexia and have been associated with NF-κB activity [122–127]. Below we discuss each of these cytokines in more detail, including their potential roles in cancer cachexia.

TNF

TNF is a pro-inflammatory cytokine that was originally called “cachectin” because of its association with cachexia [128]. TNF has been associated with increased muscle protein breakdown, and also plays an important role in the progression of the muscle regeneration

program [129–134]. An increase in TNF signaling is required for muscle regeneration to occur, but TNF also appears to prevent myoblasts from differentiating normally [135, 136].

The first suggestion of an association between TNF and dysfunctional muscle regeneration came from simple studies utilizing cultured muscle cells, including work by Miller et al., who demonstrated that TNF inhibits human myoblasts from differentiating into myotubes [137]. Additionally, TNF specifically prevents the expression of both MyoD and myogenin, two proteins required for the progression of muscle regeneration, as well as induces cyclinD1 to prevent myoblasts from exiting the cell cycle, which is a requirement for differentiation [121, 138–141]. NF-κB activity appears to be required for TNF-induced blockage of the myogenic program [139, 142, 143], although another group has suggested that caspase activity, and not NF-κB activity, is required for dysfunctional regeneration induced by TNF [144, 145]. In addition to *in vitro* work, *in vivo* animal studies have also demonstrated that TNF has an effect on muscle regeneration. Overexpression of TNF in muscle is sufficient to both induce muscle wasting and decrease muscle regeneration, as shown following cardiotoxin injury and in a model of COPD [87, 146].

Specifically in cancer cachexia, inhibition of TNF, either through overexpression of a soluble receptor, or administration of an anti-TNF antibody, attenuates muscle loss in rodent models of cachexia [104, 126]. However, it remains unknown whether this sparing of muscle resulted from improved muscle regeneration, and whether this activity required NF-κB.

The role of TNF in inducing cachexia in cancer patients is less clear. Although serum TNF from cancer patients sometimes correlates with the stage of their disease, a correlation with cachexia does not seem to exist [25, 134, 147–149]. Thus, many individuals have speculated about the role TNF in cancer patients suffering from cachexia. Clinical results are somewhat mixed, as blocking the TNF receptor reduced fatigue in patients undergoing chemotherapy for advanced non-small cell lung cancer, but inhibiting TNF was not successful in preventing weight loss of cancer patients [150, 151]. These data support the increasing view in the field that elevated TNF is not a requirement for cancer cachexia [133, 152]. Additional work will be required to fully elucidate the role of this cytokine in cancer and other chronic illnesses that promote muscle wasting.

Angiotensin II

Angiotensin II (Ang II) is a humoral factor commonly associated with congestive heart failure, but has also been shown to induce skeletal muscle loss. Although the muscle wasting effects of Ang II have generally been thought to be due to alterations in the balance of protein synthesis and protein degradation, recent work demonstrates that Ang II also impacts muscle by affecting myogenesis and regeneration [7, 153]. Treatment with Ang II significantly decreases the ability of muscle to regenerate following cardiotoxin injury. This failed regeneration is associated with a failure to upregulate MyoD and myogenin, and is associated with an Ang II-mediated decline in satellite cell numbers. However, conflicting evidence suggests that inhibition of Ang II prevents muscle regeneration, which highlights that elucidating the role of Ang II in skeletal muscle is complex [154].

Inhibition of angiotensin converting enzyme during cancer cachexia to reduce Ang II has been shown to prevent cancer-induced muscle wasting in an animal model of cancer cachexia [127]. However, this treatment also significantly decreased tumor growth, which is a confounding issue when attempting to ascertain a bona fide “anti-cachexia” effect. Additional studies will be required to determine if Ang II plays an important role in muscle wasting in cancer cachexia, including if Ang II contributes to dysfunctional muscle regeneration in cachexia or if circulating Ang II levels are increased in cachectic patients. Since Ang II has also been shown to promote NF-κB activity, it will be interesting to determine whether in the context of tumor-induced muscle wasting, the discovered activation of NF-κB in muscle progenitor cells might derive from elevated levels of Ang II [122, 155].

Myostatin

Myostatin is a TGF-β family member associated with muscle atrophy due to a variety of conditions in both humans and rodents [156–160]. Myostatin is a negative regulator of skeletal muscle size, as overexpression of myostatin is sufficient to cause muscle wasting [161]. Much of the effect of myostatin on muscle size is related to its known effects on both muscle protein synthesis and protein degradation [162]. However, in addition to altering the balance of protein synthesis and protein degradation, myostatin has also been shown to impair muscle regeneration. Specifically, myostatin prevents satellite cells from expressing MyoD [163]. As discussed above, without the expression of MyoD, muscle regeneration is compromised due to an inability of satellite cells to commit to a myogenic fate and differentiate into damaged muscle.

Myostatin is a soluble cytokine which functions through activation of the ActRIIB receptor [162]. Multiple pharmacological strategies have been tried to decrease myostatin signaling, including the use of soluble ActRIIB receptors and myostatin antibodies [125, 164–166]. Specifically in cancer cachexia, a multitude of studies demonstrate that inhibition of myostatin is sufficient to prevent muscle wasting [125, 164–167]. In addition to a rescue of muscle mass, Zhou et al. demonstrated that inhibiting myostatin signaling correlated with an increase in the number of BrdU+, Pax7+ cells in tumor-bearing mice [125]. This suggests the possibility that myostatin acts in a similar manner to NF-κB by upregulating Pax7 to impair the regenerative process. Work from our own laboratory and others has been unable to find evidence of myostatin acting upstream of NF-κB, but some evidence does suggest that NF-κB can induce expression of myostatin family members [124, 168–170]. Further work will be required to determine the relationship between NF-κB and myostatin and if the impact of myostatin on muscle regeneration is a major contributing factor in cancer cachexia.

Considerations of Age in Cancer-induced Muscle Wasting

Many of the cancers that are associated with cachexia, including gastric, esophageal, and pancreatic cancers, occur in older individuals [5, 171]. While our laboratory has demonstrated that older mice develop cachexia in a manner similar to the younger mice typically used to study cancer-induced muscle wasting, admittedly separating the effects of advanced aged on muscle from the impact of cancer is difficult [19]. This is particularly true

when considering the role that dysfunctional muscle regeneration plays in cancer cachexia, as muscle regeneration is defective in sarcopenic individuals [172].

The balance of signaling through the Notch and Wnt signaling pathways controls the fate of satellite cells, with Notch signaling repressing the differentiation of satellite cells and Wnt signaling promoting satellite cell proliferation [117]. Both decreased Notch signaling [173] and increased Wnt signaling [172] have been implicated in the age-related decline in muscle regeneration. In animal models of cancer cachexia, Wnt signaling seems to decline [174], while Notch signaling appears to be unchanged (Kuang and Guttridge, unpublished data). Thus, the relevance of changes in both Notch and Wnt signaling pathways during cachexia remains unknown. Additional studies will be required to determine whether these pathways play a role in dysfunctional muscle regeneration induced by cachexia and if the age-related changes in these pathways exacerbate cancer cachexia in older individuals.

CONCLUDING REMARKS

Dysfunctional muscle regeneration is only beginning to emerge as an important contributor to muscle wasting induced by disease. Additional well-designed studies using both human subjects and animal models are required to fully elucidate the causes of dysfunctional muscle regeneration during disease-induced muscle wasting including cachexia caused by cancer. Of particular interest is the involvement of the microenvironment of skeletal muscle and the roles of non-satellite progenitor cells, which in cancer cachexia appear to be undergoing a lineage switch and adopting a myogenic fate for reasons that currently are not known.

While muscle regeneration can be discussed as a discreet entity, it is important to remember that signaling pathways may play distinct roles in both muscle regeneration and the balance of protein synthesis and protein degradation. For example, animals lacking myogenin exhibit decreased expression of the E3 ligase MuRF1 following denervation, suggesting that myogenin is upstream of at least one component of the proteasome system [175]. Additionally, although the E3 ligase TRIM32 has been suggested to be responsible for the loss of actin during at least some atrophy-inducing conditions [176], TRIM32 is also required for functional muscle regeneration in adult mice [177]. Finally, as discussed above, the transcription factor NF-κB plays a prominent role in the control of muscle regeneration. However, NF-κB is also tied to an increase in protein degradation through upregulation of muscle-specific E3 ligases [119]. Thus, the relationship between muscle regeneration and the balance of protein synthesis and degradation is complex, and additional work will be required to delineate the specific roles of individual signaling pathways in muscle atrophy.

In summary, we would like to propose that in addition to understanding the processes regulating muscle atrophy from within the myofiber, consideration should be given to events occurring outside the fiber in the muscle microenvironment. The role of this environment, at least in cancer, appears to compromise regenerative cues inherent in normal muscle repair. Whether similar effects of non-satellite progenitor cells observed in murine models of cancer cachexia are observed in non-cancer atrophy conditions will be interesting to discover. An

additional interest will be to see if our understanding of the regeneration program, or lack thereof in cancer, can be targeted for a therapeutic benefit.

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Table 1

Evidence for Altered Muscle Regeneration in Various Atrophy/Cachexia Conditions

							Regeneration Markers			
	Altered Sarcolemma	**Increased/ Decreased SC's**	**Increased/ Decreased Pax7 Expression**	**Proliferation Defect**	**Differentiation Defect (in vitro)**	**Differentiation Defect (in vivo)**	**New Muscle Fibers**	**Centrally Located Nuclei**	**eMHC Expression**	**References**
Denervation										
≤7 days		+	+	−	+	−				
10–30 days	+	+		+	+		+		+	
2–4 months	+	+			−	+	++	+	+	68–72, 74–76, 78–80, 111
7 months		**NC**					+		+	
≥9 months		−					+/−	+		
Hindlimb Suspension										
≤12 hours		+		−				+		
≥2 weeks		−	−	+	+	+		−		77, 81–82, 85–86, 109
Cancer Cachexia										
APC$^{min/+}$								+	+	
LLC Model	+	+	+	−		+				
C-26 Model	+	+	+	−	−	+				19, 103–104, 106–107
Cancer Patients	+	+	+			+				
Chronic Renal Disease										
Subtotal Nephrectomy		**NC**	+		+	+				93–94
COPD										

							Regeneration Markers			
	Altered Sarcolemma	**Increased/ Decreased SC's**	**Increased/ Decreased Pax7 Expression**	**Proliferation Defect**	**Differentiation Defect (in vitro)**	**Differentiation Defect (in vivo)**	**New Muscle Fibers**	**Centrally Located Nuclei**	**eMHC Expression**	**References**
COPD Patients		**NC**			+	+		+	−	88–92
Burn Injury										
2 days		+	+	−						95–96
Burn Patients					+					
Diabetes										
STZ rats			−		+	+		−	−	98–102

+: increased or present

−: decreased or absent

+/−: conflicting evidence

NC: no change