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The Role of Mechanobiology in Progression of Rotator Cuff Muscle Atrophy and Degeneration

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Abstract

Rotator cuff (RC) muscles undergo several detrimental changes following mechanical unloading resulting from RC tendon tear. In this review, we highlight the pathological causes and consequences of mechanical alterations at the whole muscle, muscle fiber, and muscle resident cell level as they relate to RC disease progression. In brief, the altered mechanical loads associated with RC tear lead to architectural, structural, and compositional changes at the whole-muscle and muscle fiber level. At the cellular level, these changes equate to direct disruption of mechanobiological signaling, which is exacerbated by mechanically-regulated biophysical and biochemical changes to the cellular and extra-cellular environment (also known as the stem cell ‘niche’). Together, these data have important implications for both pre-clinical models and clinical practice. In pre-clinical models, it is important to recapitulate both the atrophic and degenerative muscle loss found in humans using clinically relevant modes of injury. Clinically, understanding the mechanics and underlying biology of the muscle will impact both surgical decision-making and rehabilitation protocols, as interventions that may be good for atrophic muscle will have a detrimental effect on degenerating muscle, and vice versa.

Keywords

Rotator Cuff; Muscle Mechanics; Skeletal Muscle Biology; Muscle Mechanobiology; Muscle Atrophy; Muscle Degeneration

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M.C.G. performed the literature search, manuscript synthesis, and figure preparation

A.S. participated in manuscript preparation and provided clinical and translational expertise/perspective for all sections

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Introduction

Rotator cuff tears affect over 20% of the general population, with prevalence increasing with age¹. Mechanical failure of the RC tendon, often preceded by pathological changes in the tendon microstructure²⁻⁶, is the primary cause of RC disease. Equally important from a clinical perspective are the resulting detrimental changes in RC muscle structure and composition, which play a prominent role in both the failure of RC tendon repairs as well as the persistent functional deficits observed in many patients⁷. Indeed, these muscular changes are a primary method by which RC disease is staged clinically⁸, based on the relative ease of noninvasive CT and MRI imaging of muscle compared to tendon and the negative relationship between intramuscular fat accumulation and clinical outcomes^{7;9}. Our understanding of the biological processes that govern the replacement of muscle by fat and fibrosis remains limited, but the role of altered mechanics in the progressive decline of RC muscle is central both to the existing data and prevailing hypotheses regarding RC muscle fate after tendon tear and/or repair. A summary of key factors involved in controlling and actuating skeletal muscle remodeling, which is arguably the most sensitive tissue to changes in mechanical loading in the RC, is outlined in Figure 1.

The phenotype of muscle disuse atrophy is primarily the result of mechanical unloading, which can occur via tendon failure, bed rest, casting, hindlimb suspension (in rodents), or otherwise decreased voluntary muscle activation¹⁰⁻¹⁴. Nerve injury or dysfunction may also cause atrophy, though the atrophy phenotype in denervation has a distinct molecular signature compared to disuse¹⁵. Regardless of the inciting event, atrophy is characterized by increased contractile protein turnover coupled with diminished protein synthesis¹⁵, leading to a reversible^{13; 16; 17} reduction in muscle force-producing capacity. In RC disease, disuse muscle atrophy, absent a nerve injury, appears to dominate the early phase of RC disease¹⁸⁻²¹ (Figure 2, *Atrophic Stage*).

Contrary to muscle atrophy, which is self-limiting and not thought to alter overall muscle fiber structure, organization, or number²², muscle fibers can also accumulate structural damage, leading to altered sarcomere structure, degeneration and ultimately muscle fiber death (Figure 1, *Damage/Degeneration*). Altered mechanics are also implicated in this mode of muscle loss, though the mechanism is more complex than the unloading-induced muscle atrophy described above. For example, in other muscle pathologies including Duchenne muscular dystrophy²³⁻²⁵, abnormal shear stress is implicated in sarcolemmal disruption. Muscle overloading, particularly during eccentric contraction, is known to induce muscle damage and regeneration^{16; 17; 26-29} (Figure 1, *Shear Stress or Overload*). However, in these and other examples there are several mediators of muscle degeneration-regeneration that influence the rate and degree of muscle injury and recovery. These include inflammation and resident stem cell function, which are themselves influenced by passive changes in the micromechanical environment^{26; 30-33} (Figure 1, *ECM Stiffening*). In advanced RC disease, muscle degeneration and reduced muscle fiber numbers driven by these mechanobiological changes appear to be the prominent mode of muscle loss³⁴ (Figure 2, *Degenerative Stage*).

Since RC disease progression can result in both unloading and overloading, the changing mechanobiological environment of the muscle can significantly impair the body's attempt at

regeneration, and this in turn may explain the irreversible loss of muscle and poor surgical outcomes that define RC disease. In this review, we summarize our current understanding of biomechanical environment changes and specific aspects of that environment that contribute to the clinically intractable deficits that result from chronic RC tear at the whole muscle, muscle fiber, and single cell levels. In this context, we will highlight differences between the atrophic and degenerative aspects of disease, focusing on the roles of mechanical unloading and matrix stiffening and their detrimental effects on muscle physiology at each length scale.

Whole Muscle Remodeling After RC Injury

As RC tendon tears progress over time, the RC muscles become mechanically unloaded and begin to retract. Mechanical unloading is potentially compounded by pain-induced diminution of voluntary muscle contraction. Suprascapular nerve dysfunction may also impact muscle remodeling, though the prevalence of neuropathy in RC tears appears to be limited³⁵. As the muscle retracts, muscle fibers shorten via serial sarcomere subtraction³⁶ and the muscle becomes fibrotic³⁷ (discussed in further detail below). This causes the working range of the muscle to decrease, and it has been hypothesized to increase RC muscles' susceptibility to injury during repair given the high muscle tension and strain required to repair the retracted tendon to its footprint^{38; 39}.

A second consequence of chronic muscle retraction is increased muscle fiber-bundle stiffness^{37; 40}. Because single fiber passive mechanics are not altered with RC tear, this stiffening is likely attributable to increased fibrosis, i.e. collagen content in the muscle⁴⁰ (Figure 1, *ECM Stiffening*). While fibrosis predicts stiffness to a degree^{37; 40}, the existing data suggests that muscle stiffness is dictated by additional variables. One possible contributor is reduced sarcomere number following tear, which would lead to higher average sarcomere strains for a given change in muscle length^{36; 41}. Another possibility is that ECM modification, and not just content, dictate total ECM stiffness (and cell-ECM interactions). Specifically, increased collagen cross-linking (associated with increased stiffness⁴²) has been demonstrated in degenerated RC tendon⁴³, though it has yet to be measured in RC muscle. Whether or not increased matrix stiffness is protective (via increased load distribution in passive stretch) or detrimental (via increased active shear stress) to muscle fibers remains unknown.

In contrast to tissue-level stiffening, changes in whole muscle biomechanics are more complicated. Similar to findings in fiber bundles, a human case series⁴⁴ and two separate animal models^{21; 45} found increased whole muscle stiffness over time following tendon transection. However, a cadaver study that involved samples with higher fat infiltration found that high fat accumulation correlated with softer muscle overall⁴⁶. A possible explanation for these findings is that whole muscle stiffness tracks with fiber bundle stiffness until muscle tissue loss hits a critical threshold, at which point whole muscle mechanics are dictated by a combination of muscle- and non-muscle tissue mechanics. Indeed, one prevailing hypothesis is that accumulation of adipose tissue serves as a necessary mechanical buffer to counter changes in muscle volume and pennation angle, in order to preserve a maximum possible amount of muscle force producing capacity⁴⁷. As RC disease progresses and stiff muscle^{40; 48} is replaced by more extensible fat⁴⁹, overall organ

extensibility increases, even though there is no evidence suggesting that remaining muscle tissue becomes more extensible itself. The resulting tissue is a complex and compartmentalized biomechanical system, which can in turn give rise to significant but localized changes in the micromechanical environment that impact both individual muscle fibers and resident stem cells.

Mechanical (Un)Loading Drives Muscle Fiber Pathology

The paradigm of mechanical unloading followed by muscle remodeling, progressive muscle atrophy, and fat accumulation has been central to RC muscle research for over two decades⁸. In the literature, this process is often interchangeably referred to as ‘fatty infiltration’, ‘fatty atrophy’, and ‘fatty degeneration’, with the latter two referencing specific modes of muscle loss. In this section, we discuss the effects of RC tear on individual muscle fibers, highlighting the biological importance of differentiating muscle atrophy from degeneration and focusing on the differential role that mechanical loads play in each of these distinct mechanisms of muscle loss.

In parallel with alterations at the whole muscle level, individual muscle fibers undergo several detrimental changes as a result of chronic unloading, with distinct stages across the disease spectrum. In terms of muscle architecture, muscle fibers in full-thickness tears have decreased sarcomeric order and increased accumulation of small (<1µm) intracellular lipid droplets⁵⁰, but normal sarcomere length⁴¹ is maintained via serial sarcomere subtraction^{36; 51}. However in large or massive (>5cm retraction) RC tears, normal sarcomere remodeling is not observed, and sarcomeres are significantly shorter than in either intact or full thickness tears³⁶. The implications of these findings are two-fold: first, this suggest that muscle with moderate tears are more likely than larger tears to remodel and remain functional after repair, and second, that repair of massive tears may fail due to a combination of over-strained sarcomeres immediately after repair and failure to adapt sarcomere length over time³⁶.

Beyond architectural changes, RC muscle undergoes continuous muscle loss throughout the course of disease. In the ‘early’ phase of disease, radial atrophy of the RC muscle occurs as mechanical load is reduced following smaller and/or less chronic RC tendon tear^{18; 19} (Figure 1, *Mechanical Unloading, Atrophy*; Figure 2, *Atrophic Stage*), possibly heightened by passive stress shielding resulting from the stiffer matrix discussed above, or inflammatory signals known to activate catabolic pathways within muscle discussed below^{10; 11; 15; 52}. This atrophic muscle loss encompasses a cell-intrinsic, self-limiting process where protein turnover is tightly controlled by the interplay of anabolic⁵² and catabolic¹⁵ pathways; it is not generally considered a putative mechanism of muscle fiber deletion²². With decreased load, strain-dependent signaling proteins at the Z-disk⁵³ and costamere⁵⁴ become less active, leading to decreased anabolic signaling^{52; 55} and increased signaling and activity of the two principal mechanisms of protein degradation in the cell: the ubiquitin-proteasome^{55–57} and the autophagosome/lysosome¹⁵ (Figure 1, *Protein Synthesis, Proteasome/ Autophagosome*). In muscle atrophy, proteins are freed from the Z-disk via the combined action of calpains^{58; 59} and muscle-specific E3 ubiquitin ligases⁵⁶. These freed contractile proteins are subsequently degraded, thus reducing the force-producing capacity of the muscle.

Importantly, protein loss in muscle atrophy is highly specific; only ubiquitinated proteins are degraded, while proteins still anchored to the Z-disk are protected from the catabolic machinery and overall muscle architecture is preserved.

As RC disease progresses, the muscle is more likely to experience higher axial loads (due to diminished total cross-sectional area)⁶⁰ and higher shear forces when activated (due to increased stiffness of the matrix)^{61; 62}. Both axial and shear stress are known to cause direct mechanical injury to the sarcolemma^{23; 27} (Figure 1, *Shear Stress or Overload*). This, along with potential increases in permeability caused by local inflammatory cells (discussed below)^{61; 63}, leads to increased calcium in the muscle fiber because of direct diffusion and sarcoplasmic reticulum disruption^{64; 65}. Increased calcium may then increase calcium-sensitive calpain activity, which along with their role in contractile protein turnover in atrophy^{65; 66} are also implicated in cellular apoptosis^{67; 68} and necrosis⁶⁹. Together with the direct overload/shear injury, these indirect mediators of protein turnover and cell death (as well as the hypothesized increase in oxidative stress and a protease-rich inflammatory environment discussed below) likely explain the recently described muscle damage and degeneration of muscle fibers found in advanced rotator cuff disease³⁴ (Figure 1, *Damage and Degeneration*).

Can Satellite Cells Maintain Muscle Homeostasis Post-Injury?

Satellite cells (SCs), the primary myogenic stem cell of adult muscle, play an integral role in adult myogenesis and homeostasis, particularly in the context of muscle's response to exercise/reloading^{26; 70} and recovery from damage or injury^{31; 71} (Figure 1, *Quiescent Satellite Cells, Satellite Cell Proliferation/Differentiation*). Notably, while SCs are required for muscle regeneration, they are dispensable in the context of fiber hypertrophy^{72; 73}. Given the muscle degeneration present in advanced RC disease³⁴, understanding the fate of SCs in RC disease is paramount to understanding why muscle loss is generally irreversible after RC tear.

Like many other adult stem cells, the SC is highly dependent on its physical environment, i.e. niche⁷⁴. This niche consists of the region between the sarcolemma and the basal lamina of the muscle fiber⁷⁵, with SC fate determined by dynamic interactions with each structure⁷⁶ (Figure 1, *Basal Lamina, ECM*). The physical and biochemical composition of the niche is important in the maintenance of SC quiescence⁷⁷, potency⁷⁸, and possibly even myogenic fate⁷⁹, with ECM proteins and particularly collagens IV and VI playing a notable role in the regulation of SCs by the basal lamina^{80; 81}. The dependency of SC function on niche composition suggests a central role of force transmission in the maintenance of SC stemness. Changes in matrix composition directly alter the way SCs experience load based on local niche stiffness⁷⁸, and may also affect SC focal adhesions based on altered integrin-binding substrate availability⁸². Alterations in the matrix may also alter SC function indirectly because the matrix serves as a local reservoir and co-modulator of growth factors critical to SC modulation^{78; 83; 84} (Figure 1, *IGF1/MGF+, Myostatin/GDF's+*). As mechanical loads change, the matrix undergoes damage and remodeling which determine the rate of release and/or sequestration of these factors^{85; 86}.

Indeed, SC function is highly dependent on niche stiffness (Figure 1, *ECM Stiffening*). During *in vitro* culture, SCs proliferate, self-renew, and differentiate best on substrates with normal muscle stiffness (~1 kPa)^{48; 87}. On stiff substrates (~10⁶ kPa) differentiation into myotubes is favored⁸⁷, while the maintenance of quiescence is favored on softer substrates (~2 kPa)⁷⁷. In RC disease, increased matrix stiffness may skew SCs toward differentiation and away from self-renewal, which may deplete the SC pool and diminish the muscle's regenerative capacity in the long run⁸⁸. However, evaluation of this hypothesis is difficult, because although RC muscles have reduced SC populations compared to other muscles⁸⁹, once SCs are removed from the pathological environment of the torn RC, their proliferation, differentiation, and fusion characteristics are not different between no-tear and full-thickness tears⁸⁹.

Beyond the static stiffness of the niche, mechanical loading is also important in the maintenance and activation of the SC pool (Figure 1, *Exercise, Mechanical Unloading, Satellite Cell Proliferation/Differentiation*). SCs can be activated by mechanical loading *in vitro*³² and exercise *in vivo*, though the effects of exercise are multifactorial and the relative contribution of mechanical load to overall exercise-induced activation is difficult to determine *in vivo*^{16; 26; 90} (Figure 1, *Exercise*). The complementary finding is also true; in most models, unloading reduces total SC number and potency of remaining SCs¹¹. Therefore, reduced muscle activity levels following RC tear in the atrophic stage of disease may ultimately contribute to diminished regenerative capacity in the degenerative phase of disease.

Further complicating the evaluation of SCs in the context of RC disease are other potential environmental contributors to SC dysfunction known to occur in the torn RC. The torn RC environment demonstrates altered expression of soluble factors⁹¹⁻⁹⁴ as well as increased inflammation^{34; 95; 96} and oxidative stress⁹⁷⁻⁹⁹, which are all potent mediators of SC function^{30; 100; 101} that may be exacerbated by muscle injury. Pro-inflammatory signaling and oxidative stress stimulate SC proliferation, but blocks differentiation^{100; 101} and self-renewal¹⁰² via the TNF/TWEAK/NF- κ B and Notch signaling axes, while anti-inflammatory signals aid in differentiation¹⁰³ (Figure 1, *Monocytes, M1/M2 Macrophages, Eosinophils, Neutrophils, Pro-Inflammatory Cytokines/Proteases, Oxidative Stress, Anti-Inflammatory Cytokines*). These effects may also be modulated by interplay of other myogenic regulatory factors that are likely altered in the torn RC, including members of the TGF- β superfamily (GDF and BMP subfamilies in particular)^{52; 104} and IGF/GH axis¹⁰⁵⁻¹⁰⁷, all of which influence SC dynamics (Figure 1, *IGF1/MGF/+, Myostatin/GDF's/+*). While classically 'pro-' and 'anti-' inflammatory or myogenic signaling suggests a binary effect (i.e. either 'good' or 'bad'), the effects of these factors on muscle homeostasis are dependent on the environment as a whole. For example, in acute inflammatory situations, these factors are coordinated to promote muscle homeostasis, as proliferation of SCs occurs prior to fusion, regeneration, and return to quiescence^{30; 76; 108; 109}. However, with chronic inflammation, prolonged pro-inflammatory and anti-myogenic signaling may simultaneously inhibit muscle regeneration and SC pool maintenance, leading to both short- and long-term deficits in muscle regenerative capacity.

Multipotent Progenitors – Potential Sources of Fat and Fibrosis

Progressive fat accumulation and fibrosis in RC tears at the whole-muscle level is indisputable, but the cell population(s) responsible remain unresolved. Further complicating our understanding of fat accumulation mechanisms is the finding that lipid-filled cells accumulate in distinct locations (epimuscular, interfascicular, and intrafascicular) within the muscle structure^{34; 110}, where lipid in different anatomical locations may be the result of disparate cellular processes or cell populations. SCs are theoretically capable of adopting an adipogenic fate^{111; 112}, and the lipid content of mature muscle fibers is known to increase with tear⁵⁰. However, there is no current consensus on whether SCs can trans-differentiate into adipocytes *in vivo*^{113; 114}, and at a minimum the niche must be significantly manipulated *in vitro* to alter SC fate^{115; 116}.

Multipotent adipose stem cells (ASCs) have also been implicated in fat accumulation, particularly at the epimuscular border¹¹⁰. In this region, adjacent to existing fat depots, there is evidence that RC tear leads to a whitening of the normally beige epimuscular fat depot, with implications for paracrine signaling that may affect muscle regeneration¹¹⁰. Yet fat accumulation does not strictly proceed from the muscle border, particularly in more advanced disease¹¹⁷. As such, two additional native muscle stem cell populations, fibro/adipogenic progenitors (FAPs) and perivascular stem cells/pericytes have been the focus of research into the source of fat in torn RC muscle. A comprehensive discussion of the role of these cell types in skeletal muscle is beyond the scope of this review and can be found elsewhere^{118; 119}.

The bipotent FAP population, first described independently by Uezumi¹²⁰ and Joe¹²¹ in 2010, is the most attractive candidate of the muscle resident cells implicated in RC disease progression (Figure 1, *Quiescent FAPs*). With an indispensable role in normal muscle regeneration (where they synthesize new, regenerative matrix)^{122; 123} and ability to differentiate into either adipocytes or fibroblasts^{120; 121} (Figure 1, *Pro-Myogenic FAPs*, *Adipogenic FAPs*), dysfunction of FAP's could be implicated in all three detrimental changes in torn RC (muscle loss, fibrosis/stiffening, and fat accumulation). Indeed, the conditions under which FAPs take on an adipogenic fate exist in the inflammatory environment of the torn human RC¹²³, and a small animal model has shown potential for adipogenic differentiation of FAPs in the context of RC tear¹²⁴.

Unlike FAPs, pericytes are a heterogeneous population¹²⁵, are not muscle specific, and are capable of differentiating into a wider array of mesenchymal cells, including skeletal muscle¹²⁶, adipocytes¹²⁷, fibroblasts^{128; 129}, and others^{127; 130}. In non-muscle tissues, matrix stiffening causes pericytes to adopt a myofibroblast/fibrotic phenotype^{128; 129}, which leads to a positive fibrotic feedback loop¹³¹. In the same small animal RC tear model used to evaluate FAP fate, pericytes were found to contribute to both adipogenic and fibrogenic cell populations¹²⁴, though more stringent cell classification and more clinically relevant models (discussed below) are needed to definitively characterize and study the source(s) of adipocytes in RC disease.

A caveat to the findings presented in this section is that, due to a lack of a definitive marker for either FAPs or pericytes, studies of these cell populations are inherently studies of mixed populations that share a small number of specific markers. Of particular note is the overlap between markers for pericytes, FAPs, and many other subpopulations that are generally considered mesenchymal stem cells¹³². One such marker, PW1, is a good example of this conundrum; PW1+ stem cells have been found in many tissue types¹³³ and share many other markers and characteristics with pericytes, including myogenic potential¹³⁴, yet PW1+ cells and classical pericytes are distinct populations¹³⁵. As such, differentiating between these cell populations remains a challenge, and complicates efforts to identify or describe a unique cell population primarily responsible for fat accumulation in RC disease, if such a population exists.

Mechanobiology of Inflammatory Cells – Regulating the Regulators

Infiltration and persistence of inflammatory cells is a key feature of the RC disease process in both tendon^{5; 136} and muscle^{34; 95}. Understanding inflammatory cell population dynamics is particularly important given the complex role of timing and specific inflammatory milieu in modulating the changes in muscle fibers and resident stem cells described in the preceding sections. Here, we will highlight findings in the broad field of inflammatory cell mechanobiology^{137; 138} as they relate to the pathology of RC tears.

Inflammatory cells are known to accumulate in the tendon in the earliest stages of disease, where they are thought to modulate the degeneration of the tendon that eventually leads to muscle unloading^{3; 96; 98; 139}. Therefore, it is possible that the original inflammatory response observed in RC muscles is the result of local degeneration-related signaling from the tendon. While it is unclear if RC tendon and muscle share common degenerative mechanisms at the cellular or molecular level, based on the high degree of physical and biochemical cross-talk between the two tissues^{140; 141} it is possible that inflammatory or degenerative findings in muscle may inform research in tendon, and vice versa.

Of the inflammatory cell populations, the myeloid class generally and monocyte/macrophage subpopulation in particular is commonly implicated in modulating skeletal muscle responses to injury and disease¹⁴² (Figure 1, *Monocytes, Eosinophils, Neutrophils, M1/M2 Macrophages*). While the complexity of the inflammatory milieu is beyond the scope of this review and has been reviewed elsewhere^{143; 144}, in general, when muscle fibers and surrounding matrix are damaged in healthy muscle, myeloid cells are recruited to the injury region by a combination of released cytokines/chemokines and subsequent increased matrix permeability¹⁴⁵. This acute inflammation is marked by M1 macrophage polarization¹⁴⁶ and release of pro-inflammatory cytokines¹⁴² and proteases¹⁴⁷. Resolution, characterized by M2 macrophage polarization¹⁴⁶ and expression of anti-inflammatory and often pro-fibrotic and pro-survival cytokine and growth factor release, quickly follows in non-pathological situations¹⁰³. This normal regenerative cascade appears to be altered in RC disease.

Increased matrix stiffening and matrix remodeling in RC disease likely influence both inflammatory cell migration¹⁴⁸ and cytokine release profile, skewing toward reduced

migration speed¹⁴⁹ and prolonged, enhanced release of pro-inflammatory cytokines¹⁵⁰ on stiffer matrix (though these findings have not been evaluated specifically in RC muscle). While in some diseases abnormal inflammation alone is enough to drive muscle damage and degeneration¹⁵¹, it remains to be seen whether pro-inflammatory cells and signals are active participants in RC muscle degeneration, or if persistent inflammation is the result of continual muscle injury.

Clinical Considerations and Concerns of Pre-Clinical Models

These findings have important clinical significance, but many questions still remain. Muscle atrophy and degeneration are fundamentally different mechanisms of muscle loss, and must thus be treated with fundamentally different interventions. From a rehabilitation perspective, selecting the correct intervention is complicated by the existence of both modes of muscle loss along the spectrum of disease. Mechanical reloading (i.e. exercise and/or tendon repair) is generally sufficient to recover from atrophy^{13; 16; 17; 152}, including limited evidence for this finding in RC¹⁵³. But in a stiff, degenerating muscle, exercise and the damage that may result from mechanical overload may accelerate the pace of muscle loss^{23; 25; 34}. In torn RC this is particularly concerning, as the normal inflammatory and regenerative processes that are associated with positive muscle changes following exercise are likely impaired^{30; 102; 150}.

In terms of surgical intervention and repair, the altered muscle architecture and increased stiffness must be considered, particularly in chronic, massive tears^{154–156}. These pathological changes suggest that repair of large tears may be futile from a functional standpoint, as repair may cause more damage³⁸ and the muscle may not adapt sarcomere number and length normally³⁶. Tendon repair alone is also unlikely to ameliorate the pro-degenerative/anti-regenerative environment of the chronically torn cuff, further diminishing the likelihood of successful functional restoration in large and massive tears. Given these findings, two issues still remain: our ability to reliably measure these important biological phenomena clinically, and a framework in which this type of biomechanical and biological information can be used for clinical and surgical decision-making.

Two final confounding issues in studying the biomechanical and cellular regulators of RC disease are discrepancies between animal models and human patients or patient-derived cells, and inconsistencies in findings between different laboratories. Briefly, while large animal models recapitulate the muscle stiffening and atrophy found in the early phase of RC disease^{18; 19; 21; 40; 45}, small animal models require a nerve injury (denervation) to achieve a similar phenotype^{157–159}. However, nerve injury (denervation in particular) is a relatively rare feature of clinical RC disease, and may confound results from such models as the mechanisms of denervation atrophy and disuse atrophy are not equivalent¹⁵. To date, no animal model has demonstrated the accumulation of muscle damage and cellular degeneration found in humans, and only the sheep model seems to accumulate fat to a degree that is similar to patients with advanced disease²¹. This is problematic when trying to translate animal research to the clinic, as preclinical models do not share the disease processes that govern the most intractable clinical cases. Complicating this issue are differences in cell markers and behavior between humans and animals, differences in patient

demographics between human studies, and inconsistencies in isolation methods that are used to identify SCs, FAPs, and pericytes. This leads to potentially significant and confounding discrepancies between the cell populations evaluated from model to model and study to study, and likely contributes to the conflicting effects of various factors on resident cell dynamics reported in different publications.

Conclusions

Skeletal muscle is in a constant state of dynamic equilibrium between contractile protein gain and loss. In RC disease, the role of the macro- and micro-mechanical environment is paramount. The initial insult to the muscle is fundamentally an unloading event, where tendon tear and pain lead to direct mechanical unloading and indirect disuse, both of which lead to muscle atrophy. The secondary and tertiary effects of the initial unloading insult are also mechanically sensitive. With prolonged retraction of the muscle, the matrix becomes stiff, leading to potentially increased incidence of muscle damage while simultaneously creating an environment in which regeneration is likely inhibited, which may help explain the progressive, irreversible muscle loss due to degeneration observed in RC disease.

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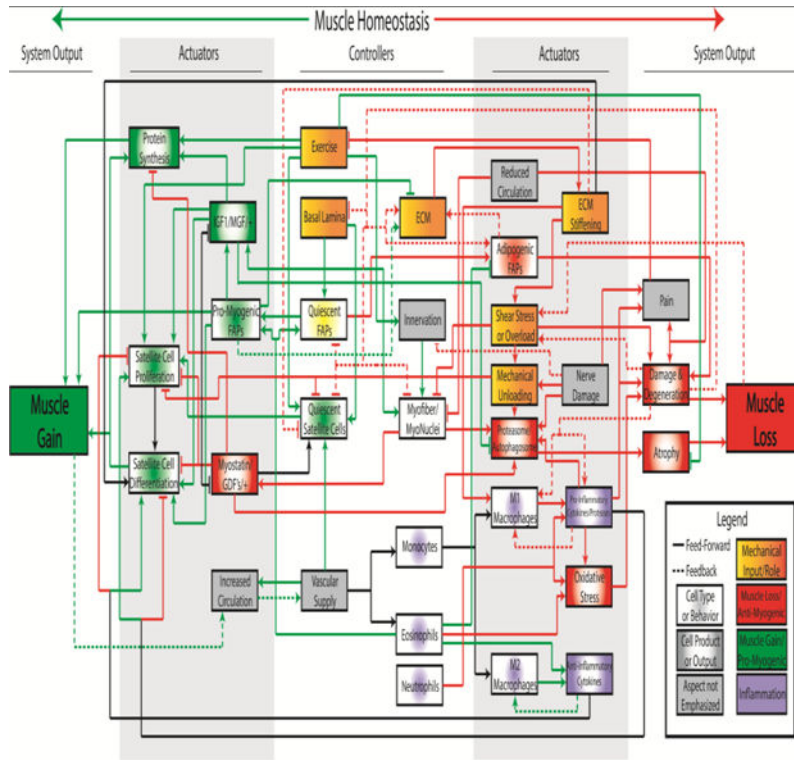


Figure 1. Conceptual control system diagram representing 33 key controllers and actuators of muscle gain (green) and loss (red) that may be affected in rotator cuff muscle pathology. Black lines represent processes that may contribute to muscle gain or loss, depending on context. Lines ending in arrowheads indicate a proliferative, intensifying or otherwise increasing effect on the indicated element, while lines ending in perpendicular lines indicate an inhibitory or otherwise diminishing effect. Dashed lines denote downstream processes that feed backward through the system to modulate upstream cell populations or processes. Additionally, system elements are color-coded by predominant functional category and shaded to indicate biological category, though again some elements may contribute to gain or loss in a context dependent manner. It is important to note that this is *not* a comprehensive map and does not show all known or possible interactions.

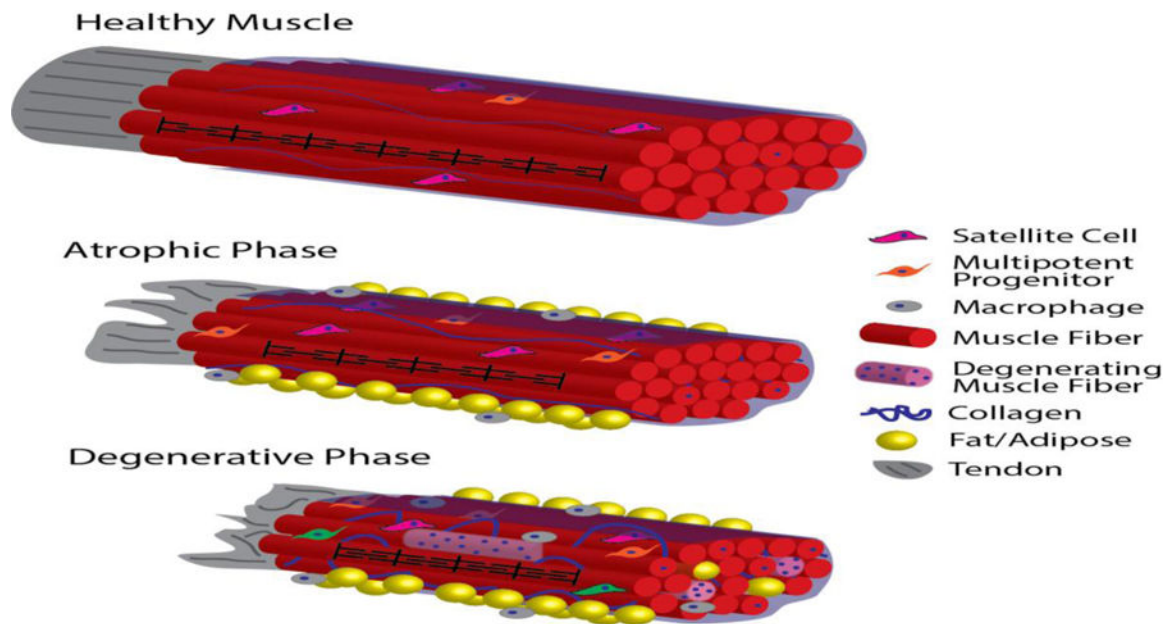


Figure 2.

Schematic of progression of muscle pathology through different stages of RC disease. In healthy muscle with intact tendon (represented as a single fascicle connected to a tendon for simplicity), densely-packed muscle fibers are organized into fascicles by perimycium (translucent blue sheath), sarcomere length is maintained (black pattern on center-front fiber, not to scale), and muscle resident cells remain quiescent (note that cells are not to scale). With tendon disruption, RC muscle progresses to the atrophic disease stage, where muscle fibers become shorter, fiber cross-sectional area is reduced, and fat, fibrosis, and inflammation appear, while muscle architecture and overall muscle fiber and satellite cell numbers remain relatively constant. In the advanced, degenerative stage of RC disease, muscle fiber architecture is altered as sarcomeres remain chronically short, and damage and degeneration-regeneration becomes apparent (represented by the heterogeneous, hypercellular/myophagocytic light-pink fibers and centrally-nucleated, otherwise healthy fibers, respectively). The accumulation of inflammatory cells, collagen, and fat in both the inter-fascicular space (yellow spheres outside blue perimycium) and intra-fascicular space (yellow spheres between fibers) is more pronounced in the degenerative phase. Resident stem cell function is also disrupted in this stage of disease (represented in green in this schematic).