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Fatty degeneration of the rotator cuff: pathogenesis, clinical implications, and future treatment

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Chronic rotator cuff pathology is often complicated by fatty degeneration of the rotator cuff (FDRC) muscles, an insidious process associated with poor prognosis with or without surgical intervention. Currently there is no treatment for FDRC, and many studies have described a natural course for this disease almost always resulting in further degeneration and morbidity. Recapitulating FDRC using animal injury models, and using imaging-based studies of human FDRC, the pathophysiology of this disease continues to be further characterized. Researchers studying mesenchymal stem cell–derived progenitor cells and known fibrogenic and adipogenic signaling pathways implicated in FDRC seek to clarify the underlying processes driving these changes. While new cell- and molecular-based therapies are being developed, currently the strongest available avenue for improved management of FDRC is the use of novel imaging techniques which allow for more accurate and personalized staging of fatty degeneration. This narrative review summarizes the evidence on the molecular and pathophysiologic mechanisms of FDRC and provides a clinical update on the diagnosis and management of this condition based on the existing knowledge. We also sought to examine the role of newer biologic therapies in the management of RC fatty degeneration and to identify areas of future research.

Fatty degeneration (FD) of the rotator cuff (RC) muscles in the setting of RC tears has been unequivocally linked to progressively worsening shoulder symptomology and poor outcomes after repair for more than thirty years.[2,5,6,15,17,25,51,54,58] Having proven a strong predictor of disease progression and surgical outcomes, scientists and clinicians have dedicated significant effort to elucidating the etiology of fibroadipogenic changes in the muscle that fall under the constellation of "fatty degeneration/fatty infiltration" of the RC.[27,39,41]

Research has evolved over the last years to better understand the pathophysiological mechanisms underlying the process of fatty degeneration of the rotator cuff. The clinical diagnosis and management of this condition is particularly challenging, and scientific efforts have focused on early recognition and/or reversal of fatty degeneration of the rotator cuff to optimize the outcomes of shoulder preservation therapies. One major area of interest is the role of mesenchymal stem cell (MSC)–derived progenitor cells in the RC as well as major signaling pathways regulating fibrogenesis and adipogenesis, such as transforming growth factor-β (TGF-β) and peroxisome proliferator-activated receptor γ (PPARγ).[29,41] There has also been great consideration of the pathophysiology of fatty degeneration of the rotator cuff (FDRC) and studies of associated structural and functional alteration patterns seen during progression of this disease.[1,20] Currently, clinical management of FDRC is guided by accurate and personalized staging of patients' RC pathology, including radiographic grading of the degree of FD.[80] Several groups have developed new methods and software for image capturing and analysis that report improved reliability in grading FDRC and can help clinicians better educate and counsel patients on their treatment options as per their unique presentation.[59,60] Recent advances have been made on the path to novel treatments developed in the research laboratory, focusing on modulating behavior of potent muscle-resident progenitor cells and chemically mitigating molecular cues that promote fibrosis and FD, but they remain more distant solutions.[8,29,42,47]

This narrative review summarizes the evidence on the molecular and pathophysiologic mechanisms of FDRC and provides a clinical update on the diagnosis and management of this condition

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based on the existing knowledge. We also sought to examine the role of newer biologic therapies in the management of RC fatty degeneration and to identify areas of future research.

Cellular and molecular etiology

Given the multifactorial causes of FD of the RC and varying phenotypes, the underlying cellular and molecular mechanisms driving this process are not fully understood.[27,41] Several cellular origins of adipose tissue in FDRC have been proposed, including expansion of existing adipocytes, migration of adipocytes from outside the RC, and differentiation of pluripotent MSC cells residing in the muscle.[71] While any or all of these scenarios may contribute to FDRC, recently a novel population of MSC-derived progenitor cells residing in RC muscle interstitium has been characterized and strongly implicated in fibrosis and FDRC after injury in a murine model.[8,29] These progenitor cells express the cell surface marker platelet-derived growth factor receptor α (PDGFRα$^+$) and have been dubbed "fibroadipogenic progenitor" (FAP) cells owing to their fibrogenic and adipogenic potential.[29]

The fibrotic and adipogenic potential of murine FAP cells has been demonstrated in vitro and in vivo using small animal injury models of FDRC.[8,29,42,47] Lineage tracing using transgenic reporter mice revealed significant expansion and differentiation of FAPs and their contribution to fibrotic and fatty tissue formation in a chronic RC injury model.[29] In 2020, the presence of FAPs in human RC muscle was first reported by Feeley et al[14] who also demonstrated that in human RC tears the number of FAP cells present correlated to tear size ($P < .01$) and Goutallier grade of FD ($P < .01$). FAP cells have been shown to primarily adopt a white adipose tissue (WAT) phenotype in FDRC marked by secretion of additional adipokines and further WAT expansion.[42] Recently FAP cells have been reported to possess the potential to adopt a beige adipose tissue (BAT) phenotype, described as being pro-myogenic via production of known anabolic cytokines such as follistatin and insulin-like growth factor 1 (IGF-1).[42,47] Further characterization of FAP cells and the signaling pathways that govern their commitment and cell fate is needed in order to better understand their role in FDRC and offer therapeutic avenues to modulate their effects.

Molecular signaling pathways that are involved in adipogenesis, lipid metabolism, fibrosis, myogenesis, muscle atrophy, and cellular apoptosis have been also been implicated in FDRC.[27,28,41] PPARγ is a canonical regulator of adipogenic differentiation, and is required for commitment of progenitor cells and pre-adipocytes to become mature adipocytes.[41] Increased expression of PPARγ has been consistently reported in the presence of FD in RC muscle.[28,31,86] Wnt signaling has also been implicated in adipogenesis within muscle tissue.[41] Activation of Wnt signaling by muscle stretch prevents myoblasts from differentiating into adipocytes; however, with the loss of mechanical stimulation or Wnt signaling this inhibitory effect is lifted and adipogenesis proceeds.[28,31] TGF-β signaling is considered a master regulator of fibrosis in many organs and has been shown to promote fibrosis and FD in RC injury.[41] Additionally, TGF-β signaling inhibited adipogenic differentiation in FAP cells in favor of fibrogenic differentiation, and has been shown to prevent FAP cell apoptosis.[8,41] Inhibition of TGF-β using a small molecule inhibitor has been shown to decrease muscle atrophy, fatty infiltration and fibrosis following a RC injury in a small animal model. The authors suggest mitigation of FD by inhibition of TGF-β signaling was achieved by increasing apoptosis of FAP cells, offering another avenue for limiting deleterious effects of FAP cells following RC injury.[8] The role of these major signaling pathways and other molecular mechanisms which result in induction of fibrogenic and adipogenic differentiation in FAPs and muscle resident cells remains a primary focus among researchers aiming to uncover the cellular etiology of FDRC.[14,29,41] Figure 1 presents a demonstration of key molecular pathways involved in the pathogenesis of fatty degeneration.

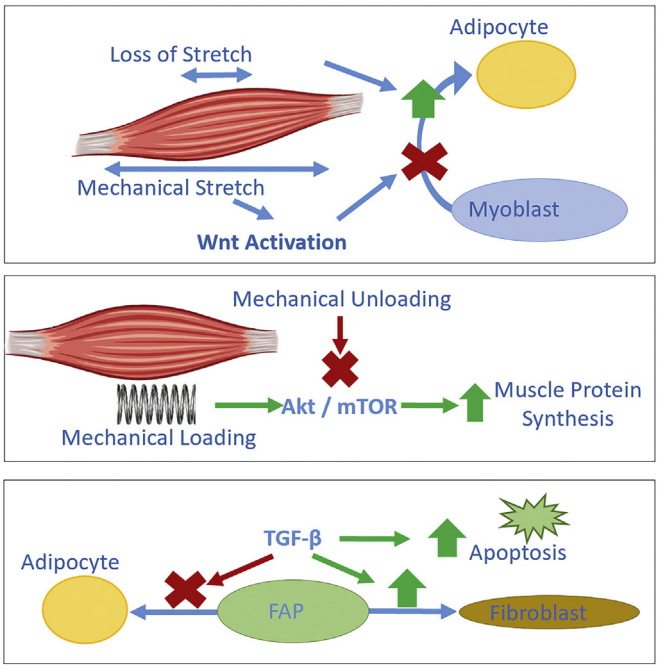

Figure 1 Key molecular pathways involved in the pathogenesis of fatty degeneration of the rotator cuff. *Akt*, protein kinase B; *FAP*, fibroadipogenic progenitors; *mTOR*, mammalian target of rapamycin; *TGF-β*, transforming growth factor β; *Wnt*, wingless-related integration site.

Pathogenesis

Currently the mechanisms underlying the pathophysiology of FDRC remain poorly understood, despite many novel findings and inroads being made by the research community.[29,39,41] What has become clear is that FD follows a progressive and heterogenous course based on a multitude of factors, some of which have been uncovered and will be discussed further in this section.[12,27,31,41] Despite its varied pathogenesis, there is seemingly a consensus that fatty degeneration is rarely reversible and likely to progress further to varying degrees with or without intervention.[11,17,24,42,86] Furthermore, to date there is no targeted treatment for FD and management typically consists of surveillance of low-grade FD and RC repair in the hopes of stopping or delaying FD progression.[1,48,59] In the setting of failed repair, re-tear with worsening symptoms, or severe FD leaving the RC muscles unsalvageable for repair, reverse total shoulder arthroplasty is among very few remaining surgical options to offer symptom relief and restore shoulder function now dependent on the deltoid muscle. Despite high grade FD's association with poor surgical outcomes and re-tears, it has been paradoxically reported that even with structural failure of the repair patients may continue to see stable or improved functional outcomes and mitigate progression of their FD.[3,24,26,69] A deeper understanding of the pathogenesis of FD remains critical to optimizing and innovating clinical management.

While FD changes in RC muscle have been reported sparingly in partial thickness tears, FD is classically associated with full thickness tears of one or more RC tendon and correlates significantly with tear size, such that one study found that 87.8% (43/49) of patients with large or massive RC tears had radiographic evidence of FD.[6,34,36,71] To better understand the relationship between large/massive full

thickness tears and FDRC, the structural and functional disturbances associated with this process have been carefully examined and tracked. Muscle denervation, suprascapular nerve (SSN) traction, and SSN neuropathy are reported to contribute to or elicit FD in subsets of patients with RC pathology, however the primary insult for the majority of patients is likely the gross anatomical and mechanical changes associated with musculotendinous unloading and retraction.[1,35,39,73] Nonetheless, understanding the consequences and interplay of both gross structural defects and SSN pathology may help delineate the varying FDRC phenotypes they give rise to and better guide clinical management.

Gerber et al studied the effect of infraspinatus tendon release and retraction on the architecture of the affected muscle in sheep via electron microscopy.[20] They demonstrated that muscle retraction increases the muscle fiber pennation angle, which decreases fiber length, and ultimately results in increased space between muscle fibers.[1,20] Over the course of 40 weeks following tendon release, the group would describe how myofibrillar volume decreased (but not myofibrillar density), and how fibrous extra cellular matrix (ECM) and adipose tissue would infiltrate and fill these growing interfascicular spaces.[20] Indeed, they characterized the typical fibrotic and adipogenic features that have become classically associated with FD: muscle retraction, atrophy and infiltration of resultant architectural defects by fibrotic ECM and fat.[1,31,39,41] Ultimately, muscle composition becomes significantly altered by disorganized myofibers and disordered fatty fibrosis, compromising the elasticity and structural integrity of the muscle eventually to an irreparable point.[39]

Unloading of the muscle directly disrupts regulation of muscle size via the Akt-mammalian target of rapamycin (mTOR) signaling pathway whose physiologic role includes transduction of mechanical loads to signals upregulating muscle protein synthesis.[41] In a rat massive RC tear injury model, Laron et al observed altered Akt/mTOR signaling and “increased muscle atrophy”, in accordance with Gerber et al’s report of decreased myofibrillar volume following infraspinatus release in sheep.[20,41] Muscle atrophy further complicates architectural changes associated with retraction and significantly affects shoulder function.

Disturbance of the SSN and innervation of the supraspinatus and/or infraspinatus has been described as a consequence of RC retraction, with proposed mechanisms of injury including SSN traction and entrapment at the suprascapular or spinoglenoid notch.[1,35,38,41] SSN neuropathy in the absence of RC tears has been demonstrated to induce RC atrophy and FD, following a well-described model of peripheral nerve injury leading to aberrant energy metabolism and disuse atrophy in the affected muscle.[1,35,38] Highly variable rates of SSN neuropathy associated with RC tears have been reported, ranging from 2%-100% of patients depending on the study.[38] Further complicating matters, FD caused by SSN neuropathy or RC tears have distinguishing features and patterns on radiographic imaging reflecting unique mechanisms of FD for each injury type, which may be occurring concurrently in some patients.[1] This again emphasizes the heterogenous etiologies and phenotypes of FD associated with RC tears, and further explains why establishing a definitive disease model remains challenging.

Diagnosing fatty degeneration

While many physical exam tests exist to detect rotator cuff pathology, only the “dropping” and “hornblower’s” lag signs have been shown to correlate with fatty degeneration (FD) in the corresponding muscle.[70] When either of these signs are positive, a large rotator cuff tear, often coupled with extensive FDRC (Goutallier stage 3 or 4) is suspected.[83] Radiographic studies are normally performed in evaluation of chronic RC pathology, but only one finding (acromiohumeral distance <8mm on anteroposterior view) has been shown to be predictive of a large RC tear with FD and its reliability has not been confirmed.[76] Ultrasonography (US) is an inexpensive and readily accessible diagnostic tool whose use in rotator cuff imaging was first described by Wiener et al and Takagishi et al in the 1990s.[50,79,87] In 2005, Strobel et al evaluated muscle pennate architecture and echogenicity of the supraspinatus (SSP) and infraspinatus (IS) using US and developed a three-point scale which has been used by other groups to confirm comparable US results to standard magnetic resonance imaging (MRI).[33,46,64,66,68,72,78,84] Despite promising results, drawbacks of US include the inability to distinguish moderate from severe fatty infiltration, problems with US wave penetrance in deep tissue and obese patients, and dependence on operator expertise.[33,39,67]

Due to the lack of accurate clinical tests for mild or moderate FDRC, standard imaging modalities such as computerized tomography (CT), and MRI have been widely used to diagnose and classify rotator cuff FD.[16,23,25,80] Goutallier et al initially proposed a five-stage semi-quantitative classification system based upon CT images (stage 0, no fatty streaks; stage 1, minor fatty streaks; stage 2, less fat than muscle; stage 3, as much fat as muscle; stage 4, more fat than muscle), which Fuchs et al later adapted for use in standard T1-weighted spin-echo sequence MRI.[16,25] Fuchs et al proposed a simplified 3-grade scale whose reliability compared to the traditional Goutallier scheme has been extensively studied and shown to be largely comparable but not necessarily better (Table I).[7,16,30,59,60,63,75,77,78,84,88] Additionally, radiographical rotator cuff atrophy signs such as the occupation ratio (SSP muscle surface area/SSP fossa surface area) and tangent sign (SSP does not intersect the line from the coracoid’s superior aspect to the superior border of the scapular spine on sagittal MRI) have been shown to correlate strongly with FDRC and may provide quick indications of muscle quality.[37,69,81,88]

Although the five-stage Goutallier classification with MRI remains the most popular method of evaluating FDRC, it is not without limitations. Assessment of fatty infiltration from a single, static, two-dimensional MRI or CT image may not be representative of heterogenous muscle and fat volume.[82] Furthermore, the variability in interrater agreement (Table I) and subjectivity present in the semi-quantitative Goutallier scale stresses the need for more objective quantitative metrics.[39,76,77] Lee et al measured Hounsfields Units (HU) and found a significant correlation between HU measurements and Goutallier grade in CT images ($P < .05$).[44] Two other studies used different specialized software to quantitatively grade standard MRI sequences and reported excellent reliability (ICC 0.947[10], ICC 0.997[43]) and comparable results to newer Dixon MRI fat fractions and MR spectroscopy fat/water ratios.[10,43] Both these computer-based techniques present viable alternatives to the Goutallier scale without the need for new imaging modalities, although accessibility of specialized computer programs may be an issue.

Advanced MRI techniques for fat quantification are also being developed.[10,59,60] Dixon MRI sequences use chemical shift-based water-fat separation and can produce a 3D spatial image of intramuscular fat.[32,49] This technique has been shown to be reliable and predictive of re-tear after repair, and fat quantification can be normalized to account for age and other confounding factors.[9,55,60] A pilot study by Davis et al found significant inverse correlation with range of motion (ROM) measures for Dixon fat fractions ($P < .01$) compared to Goutallier MRI scale (no significance).[9] Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) MRI sequence is another water-fat imaging technique that correlates strongly with tendon tear severity and other clinical parameters.[40,45,59] Nardo et al evaluated 57 shoulders and found that fat fractions measured using IDEAL

Table 1
Reliability of imaging-based grading of fatty degeneration of the rotator cuff.

Study (Year)	Imaging protocol	Grading scale	Interobserver reliability (test)
Magnetic resonance imaging (MRI)			
Fuchs et al. (1999)[56]	T1 weighted	3-grade scale	0.82-0.93 (weighted kappa)
Spencer et al. (2008)[57]	T1/T2 weighted	5-grade scale	0.1 (kappa)
Oh et al. (2010)[58]	T1/T2 MRA	3-grade scale	0.6-0.75 (ICC)
		5-grade scale	0.60-0.72 (ICC)
Slabaugh et al. (2012)[59]	T1 weighted	3-grade scale	0.61 (kappa)
		5-grade scale	0.43 (kappa)
Wall et al. (2012)[48]	T1/T2 weighted	5-grade scale	0.59-0.77 (weighted kappa)
Jo et al. (2013)[62]	T1 weighted	5-grade scale	0.55-0.79 (kappa)
Nardo et al. (2014)[18]	T1/T2 IDEAL	Quantitative Fat Fraction in Muscle	0.81-0.91 (kappa)
Nozaki et al. (2016)[17]	Two-point Dixon MRI	Quantitative Fat Fraction in Muscle	0.80-0.94 (ICC)
Collin et al. (2017)[61]	T1-weighted	3-grade scale	0.56 (kappa)
Computed tomography (CT)			
Fuchs et al. (1999)[56]	CT	5-grade scale	0.68-0.83 (weighted kappa)
Williams et al. (2009)[60]	Three-plane	3-grade scale	0.46-0.62 (kappa)
		5-grade scale	0.37-0.52 (kappa)
Oh et al. (2010)[58]	CTA	3-grade scale	0.43-0.63 (ICC)
		5-grade scale	0.43-0.6 (ICC)
Ultrasonography			
Strobel et al. (2005)[46]	Two-plane	3-grade scale for echogenicity and contour	0.55-0.71 (kappa)
Wall et al. (2012)[48]	"	"	0.65-0.72 (weighted kappa)

CTA, computed tomographic arthrography; *ICC*, interclass correlation coefficient; *IDEAL*, iterative decomposition of water and fat with echo asymmetry and least-squares estimation; *MRA*, magnetic resonance arthrography.

significantly correlate ($P < .0001$, $k > 0.9$) with Goutallier grades.[59] Many of these new imaging techniques demonstrate better reliability (Table I) and clinical correlations than traditional Goutallier MRI evaluation, but must be further refined in speed, availability, and ease of use before widespread clinical adoption.[39]

Clinical management

In the context of clinical decision making, imaging studies for tear evaluation and FD grading play a critical role in determining appropriate management, in addition to consideration of shoulder function and patients' activity level, quality of life and expectations with treatment.[60] Strong correlations between the severity of FD and patient age, chronicity of symptoms, and size of RC tear have been extensively documented, and preoperative FDRC levels have been shown to independently predict poor surgical outcomes.[6,17,21,22,36] Gladstone et al evaluated 38 patients and reported that FDRC at Goutallier stage two or higher greatly increases risk of re-tear, and thus may constitute a "point of no return".[24] Similarly, Nozaki et al used Dixon MRI imaging to quantify preoperative fat fractions (FF) in 50 patients, and found significantly higher preoperative supraspinatus fat fractions in the failed-repair group compared to the intact-repair group (37.0% vs. 19.5%, $P < .01$). This group was the first to report quantitative preoperative FF cutoff points that predict re-tears in both the supraspinatus (26.6%, sensitivity = 0.706; specificity = 0.80) and infraspinatus (31.0%, sensitivity = 0.931; specificity = 0.65).[60]

Preoperative FDRC has also been shown to correlate with postoperative clinical patient reported outcome scores.[40,56,65] Ohzono et al performed receiver operative characteristic (ROC) curve analysis to show that Goutallier stage 2 represents a cutoff point in both supraspinatus and infraspinatus for unsatisfactory outcomes after surgery.[65] Because the natural history of FDRC is one of increasing severity over time, several groups have recommended early surgical intervention to achieve the best possible functional and structural outcomes.[22,24,52,53] Another goal of surgical repair is to prevent or delay progression of FDRC, although several studies have shown that it may continue to progress following repair.[11,16,22,24,25,67] Deniz et al reported on 87 patients undergoing RC repair and found that none showed improvement in muscle atrophy or fatty infiltration, and that patients with re-tears had more severe progression of FD ($P = .0001$).[11]

Even if FDRC does not reverse following surgical repair, functional improvements may occur without accompanying muscle quality improvement.[3,24,26,69] Burkhart et al evaluated 22 patients with Goutallier stage 3 and 4 infraspinatus FDRC, and reported significant improvements in range of motion, UCLA score (preoperative 12.3 and postoperative 29.5), and Constant score (preoperative weighted score 74.8, postoperative 88.5).[3] Another study found that ASES, Constant, and pain scores improved significantly ($P < .0001$) while muscle degeneration did not improve following repair, although preoperative fatty infiltration and muscle atrophy were independent predictors of ASES and Constant scores.[24] Higher preoperative fatty infiltration may correlate with higher re-tear rates and sub-optimal outcomes, but symptomatic improvements may still be achieved. To this point Fermont et al demonstrated that preoperative FDRC was not a predictor of quality of life following repair as measured by the Western Ontario Rotator Cuff Index (WORC).[15]

It has been suggested that patients with operable RC tears with low grade FD, and no functional deficits can be conservatively managed with non-operative therapy and radiographic surveillance for progression of FD and tear size.[48] On long-term follow-up of patients managed non-operatively, Maman et al reported progression of tear size in 40-60% of cases, while Zingg et al reported progression of FD in three RC muscles by an average of one Goutallier stage after 48 months.[48] Zingg et al also demonstrated that 48 months is the average duration patients with a massive rotator cuff tear can be managed non-operatively before shoulder function becomes unsatisfactory. The severity of morphologic and anatomic changes in the RC muscle by this point typically exclude repair as an advisable surgical option. Management of cases that have progressed to severe and irreparable degeneration is limited to RC débridement, muscle transfers, or reverse total shoulder arthroplasty.

In order to avoid progression of debilitating shoulder symptoms or the need for more intensive surgical procedures, patient education on the natural history of RC tears and FD progression is critical to managing expectations and ensuring the best possible outcome.[48,51-53] Clinicians must use all the tools available at their

disposal to thoroughly characterize RC injury and associated FD, which may convey a more personalized clinical picture of a patient's course with this dynamic and heterogenous disease. For example, FD of the infraspinatus has proved an even stronger predictor of repair failure and poor outcomes than that of the other RC muscles.[6,38,65] While the reason for this is not fully understood, the FDRC phenotype that involves the infraspinatus is thought to be especially deleterious, and patients with evidence of infraspinatus FD should be advised of the increased urgency for surgical intervention.

Future treatment

Recent cell-based approaches in developing new therapies to combat rotator cuff fatty degeneration have centered around a subset of PDGFRα^+ muscle resident MSC-derived progenitor cells, or 'fibro-adipogenic progenitors' (FAPs).[8,29,42,47] These cells have been inextricably linked to fibrosis and fatty degeneration following RC tears in small animal injury models, and have now been shown to participate in the same process in humans suffering from chronic rotator cuff tears with FD.[14] FAPs demonstrate significant expansion following RC injury and their progeny constitute to some degree the fibroblasts and adipocytes seen in degenerated muscle.[8,14,29,86] These progenitors also have other more positive physiologic roles in the muscle milieu, where they act as support cells for myogenic differentiation and help maintain muscle homeostasis.[29,47] Efforts are ongoing to better understand FAPs and related progenitor cell subsets residing in muscle with the hope of uncovering physiologic or pathologic cellular and molecular pathways with strong therapeutic potential in FDRC. The discovery of FAPs with a pro-myogenic beige adipose tissue (BAT) phenotype in lieu of the more ubiquitous and adipogenic white adipose tissue phenotype has offered a novel and exciting avenue for modulation of the deleterious response of FAPs to RC injury.[14,42,47] Lee et al[42] isolated and expanded FAPs expressing uncoupling protein-1, a reliable marker for BAT FAPs, and transplanted them into mouse RCs two weeks after inducing injury using their tendon transection and denervation chronic injury model. BAT FAPs, which produce promyogenic follistatin and IGF-1, when transplanted reduced muscle atrophy and fatty infiltration and increased angiogenesis via vascular epithelial growth factor expression.[42] Strategies are now being developed to induce white adipose tissue FAPs into becoming more BAT-like or to "brown" deleterious white fat in the RC. Trichostatin A (TSA) and β_3 adrenergic receptor agonists have been shown to "brown" fat and demonstrated similar promising effects on muscle atrophy and degeneration as BAT FAP transplantation in murine chronic RC injury models.[14,47] While the therapeutic potential of TSA and β_3 agonists is limited, others are being designed to modulate these same pathways and hopefully to benefit patients in the future.[14,47]

While FAPs coexpressing PDGFRβ and PDGFRα have been demonstrated to contribute significantly to fibroadipogenesis in FDRC, Mosich et al[57] recently detailed a novel PDGFRβ^+/PDGFRα^- subset of perivascular cells with antifibroadipogenic potential.[29,74] These cells (PDGFRβ^+CD146$^+$CD34$^-$CD56$^-$) were derived from human embryonic stem cells using a reliable induction and purification protocol and transplanted into murine RCs after injury in a chronic RC injury model.[57] Transplantation of these non-FAPs resulted in decreased fibrosis and adipogenesis, while also markedly reducing muscle atrophy, which was also observed in in vitro cultures treated with non-FAP cultured medium alone.[57] In addition to PDGFRα's role in determining the phenotype adopted by FAPs, Sharma et al[74] demonstrated that aged mice experienced significantly increased fibrosis and FDRC than younger mice in a chronic RC injury model. PDGFRβ^+/PDGFRα^+ FAPs displayed an amplified response to RC injury in aged mice, whose more severe FD was reflected by an increase in collagen deposition and number of adipocytes, possibly indicating a more profibroadipogenic cellular environment associated with aging.[74] These novel findings concerning the different phenotypes of FAPs, their behavior, and the milieu they reside in must continue to be characterized with the goal of developing tools that may sway this balance more favorably and offer therapeutic benefit.[74]

In 2017, Eliasberg et al[13] attempted human lipoaspirate-derived perivascular stem cell transplantation in a murine massive RC tear model, which resulted in reduced muscle atrophy in all groups, as well as reduced adipogenesis in mice undergoing tendon transection without denervation. In mice undergoing tendon transection and denervation, perivascular stem cell transplantation resulted in increased muscle wet weight and cross-sectional area, but neither increased nor decreased fibrosis and adipogenesis, highlighting the potent effects of denervation on FDRC.[13] While autologous perivascular stem cells can be made readily available from lipoaspirate, further studies are ongoing to optimize the source and preparation of cells used for transplantation.

Oh et al[62] used adipose-derived stem cell (ADSC) transplantation in a rabbit chronic subscapularis tear model and demonstrated significantly improved tendon-to-bone healing and decreased FD. These cells were postulated to directly differentiate into tenocytes, fibroblasts, myofibers, and other mesenchymal-derived cells needed for regeneration and to support surrounding cells in the milieu via TGF-β and vascular epithelial growth factor signaling.[62] Despite promising effects, bringing stem cell transplantation to therapeutic fruition remains a very challenging task.[85] Recently, Wang et al[85] developed a "cell-free" therapeutic candidate using ADSC-derived exosomes, which are 30-nm to 150-nm vessels used by ADSCs for cellular communication and transport of proteins, lipids, RNAs, and more. In a rabbit chronic RC injury model, ADSC exosomes were able to replicate the improved tendon-to-bone healing and decrease in FD reported by Oh et al[62] using ADSCs themselves. These exosomes are thought to be less immunogenic than ADSCs and thus present a safer therapeutic option, although they must continue to be characterized and studied further in animal models.[85]

As Wang et al[85] describes, several small molecule drugs including Licofelone, an inhibitor of 5-lipoxygenase, cyclooxygenase-1, and cyclooxygenase-2, and SB431542, a TGF-β1 inhibitor, have demonstrated the ability to improve RC healing and decrease FDRC, but their clinical potential is low given their pleiotropic effects and safety profile.[8,61] Anabolic steroids have also shown decreased muscle atrophy and FD in small animal RC injury models, while tamoxifen, an estrogen receptor modulator, decreased muscle atrophy and inflammation but did not affect FD.[4,18,19] As for the experimental small molecule therapies, it can be said that anabolic steroids and tamoxifen are also poor candidates for therapeutic use in FDRC given their potent and widespread action. Although these agents are not feasible for therapeutic use, they provide invaluable mechanistic insight into the diverse processes governing FDRC and may help usher in efficacious and more refined drug candidates in the future.

Conclusion

FDRC has proven a significant contributor to worsening RC pathology, morbidity, and poor outcomes after RC repair. No solution appears imminent, as the mechanisms driving FDRC are not fully understood. Canonical fibrogenic and adipogenic signaling pathways continue to be studied in the context of FDRC, but their widespread and dynamic effects complicate determining a definitive pathophysiological mechanism. Cell-based therapies using

MSC-derived progenitors, as well as chemical strategies to modulate their behavior in situ, have been shown to be effective in animal RC injury models but are currently still in the experimental stages. Basic science researchers and clinicians must continue their efforts to fully characterize FDRC, validate imaging protocols using readily available techniques, and develop novel therapies to improve the quality of life for patients with RC disease.

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