Muscular injuries after tendon rupture in the rotator cuff of animal models. Systematic review

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Summary

Introduction: Atrophy, fatty infiltration and fibrosis are irreversible changes of the muscle after chronic retraction of a torn tendon. These changes result in further loss of function and are prognostic factors for worse clinical outcomes after surgical repair, making such approach ineffective. Currently, there is no clinical treatment to reverse this degenerative condition. This review addresses the findings of experimental studies in the context of the molecular regulation and the cellular origin of the local fibro/adipogenic progenitors and satellite cells.

Methods: We systematically reviewed studies on animal models of muscular degeneration after lesion of the tendons of the rotator cuff. We used PubMed as data source. Eligibility criteria were animal models assessing the degeneration of rotator cuff muscles after tendon injury or repair. The articles were reviewed for experimental methodology of the lesion, control group and timing of repair.

Results: The experimental studies addressing muscle-tendon retraction have reproduced and described muscular changes at the macroscopic, histologic, biochemical and genetic level. With the aim to improve this condition, some possible surgical and pharmacological approaches have been investigated.

Conclusion: Animal models for muscular degeneration after rotator cuff tears have been well established and described. The next challenge is the achievement of a therapeutic target that could be transferred to the clinical setting.

Level of evidence: Not applicable.

KEY WORDS: fatty infiltration, fibro/adipose progenitors, fibrosis, muscle atrophy.

Introduction

The degeneration of the muscles of the rotator cuff worsens the function of the shoulder after tendon rupture and jeopardizes the results of surgical treatment. To date there is not an established clinical treatment for the prevention or improvement of muscular degeneration 1.

The objective of this review is to compile the current knowledge in animal models of the muscular consequences of rotator cuff tendon tears, specially atrophy, how it starts and progresses, the role of muscular stem cells, and how fibrosis and fatty infiltration compromise muscle regeneration. We also review the influence of surgical repair and pharmacological interventions as compared to experimental control groups. The outcome of interest is the effect on atrophy, fibrosis and fatty infiltration. We include all the experimental studies and some clinical studies relevant to the question. Thus, the review will start with the observations from human samples and then goes into details of the current animal models. Finally, the features of muscular degeneration are discussed.

Materials and methods

According to PRISMA guidelines a systematic strategy was used for previous publications on animal models were searched in the PubMed database (September 8th 2017) 2. The search strategy was tendon AND
(rotator cuff OR supraspinatus) AND [(fatty OR adipoc*) OR (atrophy) OR (fibrosis)]. The selection criteria were original studies on animal models assessing the degeneration of rotator cuff muscles in experimental modelling or treatment of muscle degeneration, tendon injury or repair. Articles in English or French were included. The study selection was done by one of the Authors (JPV). References within articles were also screened for inclusion. The references of review articles were also screened. The data was collected by two of the Authors (VMT, JPV). The articles were reviewed for experimental methodology of the lesion, intervention, control group, timing of repair (when applicable). The variability in animal species, methodologies and timing precluded quantitative summarizing of data.

Studies on human samples indirectly detected by means of this search strategy have been included for detailing of background information. This research was conducted according to the international standards.

Results

The search strategy yielded 655 references. The flow diagram of study selection is detailed in Figure 1.

Basic-science studies of the muscle of the torn rotator cuff in human samples

The presence of apoptosis, necrosis, protein catabolism, loss of satellite cells and changes in molecular receptors determine the atrophic muscular injuries. This process is further aggravated by the development of fibrotic and adipose cells within the muscle. Biopsies from patients have shown that muscle atrophy is characterized by accumulation of fibers with decreased cross sectional area and increased percentage of small-diameter fibers. Lundgreen et al. studied the distribution and fiber composition by immunohistochemistry. In full thickness tears, both MHC1+ and MHC2+ fibers have smaller average diameters than in partial thickness tears, with a decreased proportion of type I (MHC1+) fibers. Using electron microscopy, Steinbacher et al. observed that the decrease in cross sectional area is exclusive of type I (slow) fibers. In addition they have higher mitochondrial volume density, a common feature of atrophic muscle. Fuchs et al. demonstrated upregulation of myosin heavy polypeptide-1 mRNA expression levels, which expresses type IIx myosin characteristic of type II (fast) fibers.

One of the key factors in skeletal muscle maintenance and repair is the presence of the satellite cells. In comparison with partial thickness tears, full thickness tears have a smaller population of satellite cells, and these cells are less actively replicating in injured tendons. This is in accordance to the findings of Gigliotti et al., who observed that non-proliferating satellite cells (Pax7*/BrdU*) were more abundant than the proliferating Pax7+/BrdU+ ones. However, satellite cells which lack a proliferating stimulus in this specific clinical entity maintained their ability to differentiate, fusing in culture and generating new fibers when delivered into injured muscles. In conclusion, the progenitor cells population is less abundant and more compromised to replicate rather than to regenerate.

Fibrosis and fatty infiltration are two cellular processes which characterize human muscle response in rotator cuff tears, as well as in other pathologies such as bursitis and tendinopathy. The tissue samples of injured rotator cuffs show increased fibrosis and fat tissue composition. Curiously, muscles from massive tears show downregulated fibrogenic, adipogenic and myogenic genes, while those from full thickness tears upregulate fibrotic and adipogenic genes and down regulate myogenic genes. These changes correlate with MRI imaging. Muscles from shoulders with bursitis or tendinopathy still express myogenic genes. Fatty infiltration is mainly located between fibers, and it is more noticeable in full thickness tears than in partial thickness tears. Consequently, lipid content is also increased inside the cells, specifically in type I fibers. Fibrosis is characterized by an increase in collagen content, which may be explained by the upregulation of alpha smooth muscle actin (αSMA) (implied in pro-fibrotic processes). In addition, collagen deposition may explain the biomechanical response of the musculotendinous unit to chronic ruptures: an increased passive tension, indicating tendon retraction. It requires greater force to reduce the tendon stump to its original insertion. The late stage shows further degeneration with the presence of macrophages.

At the molecular level, excessive protein destruction resulting from accelerated turnover of proteins by the ubiquitin-proteasome pathway, often coupled with diminished rates of protein synthesis seems to be the main mechanism behind muscle atrophy. The Forkhead box O (FOXO) family proteins promote muscle atrophy not only by inducing the proteasome pathway, but also acting on the autophagy lysosomal system, indicating that these two catabolic pathways often work together. In addition, the caspase and calpain protein families, commonly known for their role in initiating apoptosis, are proteolytic enzymes which participate in protein catabolism. Human biopsies of massive rotator cuff tears exhibit upregulation of some genes involved in protein degradation. Atrogin-1 (MAFbx) has been shown to be increased, and expression levels of Capn1, Ube2b, and Ube3a were upregulated more than two-fold after injury.

Denervation secondary to musculo-tendinous injury

Warner et al. raised the concern that repair of a retracted rotator cuff could lead to indirect iatrogenic injury of the supraspinatus nerve (SSN). In fact, Goutallier et al. observed SSN injury after repair of retracted supraspinatus tendons. However Mallon et al. observed re-innervation after repair of massive rotator cuff tears with concomitant SSN injury.
Despite studies showing a low incidence of SSN injury in rotator cuff tears and the presence of SSN injury being independent of the fatty infiltration, retraction of the rotator cuff has been postulated to lead to secondary compression neuropathy of the SSN. Interestingly, Beeler et al. observed that the pattern of fatty infiltration in rotator cuff tears is different from the one found associated to SSN injury. Other studies showing a higher prevalence of SSN are subject to selection bias. Gigliotti et al. didn't find any differences between the neuromuscular junctions (Acetylcholine receptor) AChR cluster pattern in torn supraspinatus and healthy deltoid muscle. However, the muscle of torn supraspinatus showed a tendency toward a higher γ/ε AChR subunit ratio, which suggests that there is denervation of the muscle.
In conclusion, in humans, after rotator cuff injury, muscle atrophy is characterized by decreased diameter of muscular fibers, especially type I fibers, and increase in the proportion of type II fibers. The population of satellite cells is small and show less replication. These changes are aggravated by fibrosis and fatty infiltration. Finally, there is an upregulation of the expression of genes mediating protein degradation and an increase of protein catabolism.

**Experimental models of muscular lesion of the rotator cuff**

**Methods used for the description of the phenomenon**
The high variability among the studies due to the animal model used, injury method, timing and analysis technique makes difficult to summarize the design of different animal models and surgical procedures that assess the changes in the muscle after a tendon lesion (Tab. I).

The main animal models have been developed in sheep, rabbit and rat. More recently, a mouse model has been described. The surgical methods to produce a tendon tear include osteotomy, simple transection, resection, transection and release from neighbouring tendons of the rotator cuff and wrapping of the tendon to prevent healing (Tab. I). Some studies assessed the effect of surgical repair on muscle response at different time points after the initial injury: straightaway after injury, early or late, depending on the animal model. Another variability factor between animal models is the timing of sampling since the injury or repair surgery.

The muscle atrophy, fatty infiltration, muscle retraction, fibrosis, denervation, and inflammation were assessed using a variety of methods including macroscopic description, CT imaging, MRI, histology and electron microscopy. Recently, the presence of different proteins has been assessed by immunohistochemistry, immunofluorescence, western blot and quantitative PCR.

Changes after experimental lesions in different animals have different time course and intensity, therefore the most relevant aspects will be commented stratified by animal species.

**Atrophy**

**Sheep.** In sheep, the muscle atrophy after tenotomy develops increased fiber diameter while the mean muscle fiber length decreases due to the change in the pennation angle34,36. Although atrophy lingers after late repair, it improves after continuous traction with an increase in type II fibers35,36. At the molecular level, these changes are correlated with changes of some myogenic transcription factors as well as with muscle growth related factors. Expression of Myf5 increases, while myogenin and myostatin remained unchanged37, which suggests that satellite cells are in a quiescent-like state rather than cycling and undergoing differentiation. The atrophic changes are much increased when a lesion to the suprascapular nerve is added to the animal model41.

**Rabbit.** In rabbits, there is also muscle atrophy with decreased volume, tissue weight, fiber cross sectional area and Type I fibers47,48. These changes occur earlier and are more pronounced in large tendon releases (free retraction tenotomy), progressing up to 12 months after tenotomy46,50. Twelve weeks after surgical repair, the muscle atrophy persists but it may be reversed 24 weeks after repair47,57.

**Rat.** Triggering lasting muscular changes in rats requires lesion and release of at least two tendons. When a simple SSP release is done, some of the muscle atrophic changes recover healing spontaneously eight/nine weeks after injury58,59,64. Ward et al. found a decrease in cross sectional area of myofibers together with a reduced number of sarcomeres when the supraspinatus tendon is released69. The decreased fiber cross sectional area found at earlier stages, further decreased in later stages70. As in rabbits, muscle atrophy was characterized by higher ratio of type Iib fibers66. Additional histological analysis showed absence of fibers with shrunken centralized nuclei, which are forming clusters twelve weeks after tendon injury, demonstrating the absence of a regeneration process66,70.

Atrophic muscles characterize the muscular degeneration after tenotomy with a higher proportion in type II fibers66. However, when suprascapular neurectomy is added to the tenotomy, the fiber type distribution pattern is completely different (with increased type I fibers) to the one found in muscles after simple tenotomy. Following double injury, Myh7 (MHC I) expression first decreases and finally increases, while expression levels of Myh4 (MHC Iib) starts increasing and then decreases66. These changes correlate with an upregulation of MyoD1 expression, and a down-regulation of Myf5 and myostatin.

Regarding the mechanisms responsible of muscle atrophy, it has been shown that tenotomy is followed by a decrease in protein levels of p-AKT, p-mTOR, p-70S6 Kinase and p-FOXO1, despite having unchanged total levels of protein67. Expression of MAFbx and MuRF-1, two muscle-specific ubiquitin ligase genes, remains unchanged after tenotomy65,67. The AKT/mTOR pathway is a central regulator of muscle atrophy due to its ability to regulate muscle protein synthesis and degradation, and S6K1 and FOXO translocations. Once AKT becomes activated, mTOR phosphorylates and activates, which further regulates protein synthesis via 4E-BP-1 and S6K1. Furthermore, decreased activation and phosphorylation of AKT promotes reduced phosphorylation of FoxO, which is able to translocate to the nucleus and initiate the transcription of autophagy-related genes. In summary, muscle atrophy after tenotomy seems related to reduction of protein synthesis via decreased S6K1 activity rather than protein catabolism.
Table I. Animal models for muscle injury after rotator cuff tendon injury.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Reference</th>
<th>Tenotomy</th>
<th>Control</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>Coleman et al. 2003 33</td>
<td>ISP release and cover in gore-tex</td>
<td>W0</td>
<td>W0, W6, W18</td>
</tr>
<tr>
<td></td>
<td>Meyer et al. 2004 34</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>W40</td>
</tr>
<tr>
<td></td>
<td>Gerber et al. 2004 35</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>W40</td>
</tr>
<tr>
<td></td>
<td>Gerber et al. 2009 36</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>Failed repairs</td>
</tr>
<tr>
<td></td>
<td>Frey et al. 2009 37</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>W22</td>
</tr>
<tr>
<td></td>
<td>Zumstein et al. 2012 38</td>
<td>ISP tenotomy</td>
<td>CLS</td>
<td>W6</td>
</tr>
<tr>
<td></td>
<td>Meyer et al. 2011 39</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Luan et al. 2015 40</td>
<td>ISP tenotomy</td>
<td>CLS</td>
<td>W0</td>
</tr>
<tr>
<td></td>
<td>Gerber et al. 2017 41</td>
<td>ISP osteotomy, encased in silicon tube</td>
<td>CLS</td>
<td>W6</td>
</tr>
<tr>
<td>Dog</td>
<td>Safran et al. 2005 42</td>
<td>ISP release+wrap with polymer membrane</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Bjorkenheim 1989 43</td>
<td>SSP release and allowed to freely retract</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Fabis et al. 1998 44</td>
<td>Supraspinatus detachment</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Fabis et al. 2000 45</td>
<td>SSP detachment</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Fabis et al. 2001 46</td>
<td>SSP detachment</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Matsumoto et al. 2002 47</td>
<td>SSP detachment + wrapping</td>
<td>SG (no repair)</td>
<td>W12</td>
</tr>
<tr>
<td></td>
<td>Uhthoff et al. 2003 48</td>
<td>SSP detachment + wrapping</td>
<td>CLS detachment SG (no repair)</td>
<td>W6</td>
</tr>
<tr>
<td></td>
<td>Gupta et al. 2007 49</td>
<td>SSC detachment</td>
<td>Partial or complete or neurotomy</td>
<td>CLS</td>
</tr>
<tr>
<td></td>
<td>Rubino et al. 2007 50</td>
<td>SSP detachment and release</td>
<td>CLS intact</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Rubino et al. 2008 51</td>
<td>SSP detachment and release</td>
<td>CLS intact</td>
<td>W6</td>
</tr>
<tr>
<td></td>
<td>Rowshan et al. 2010 52</td>
<td>SSP superior section or Complete or nerve section</td>
<td>CLS sham surgery</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Trudel et al. 2010 53</td>
<td>SSP detachment &amp; wrapping</td>
<td>SG intact</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Trudel et al. 2012 54</td>
<td>SSP detachment</td>
<td>SG intact</td>
<td>W4, W8, W12</td>
</tr>
<tr>
<td></td>
<td>Gayton et al. 2013 55</td>
<td>SSP detachment and release</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Uhthoff et al. 2014 56</td>
<td>Detachment + repair</td>
<td>SG</td>
<td>W0</td>
</tr>
<tr>
<td></td>
<td>Fabis et al. 2016 57</td>
<td>SSP, fibrocartilaginous pad was resected</td>
<td>CLS</td>
<td>W12</td>
</tr>
<tr>
<td>Rat</td>
<td>Barton et al. 2005 58</td>
<td>SSP tenotomy (no release)</td>
<td>SG</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Ward et al. 2010 59</td>
<td>SSP release</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Buchman et al. 2011 60</td>
<td>SSP TT</td>
<td>CLS intact</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Itoigawa et al. 2011 61</td>
<td>SSP ISP resection, SSC detachment</td>
<td>CLS sham surgery</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Farshad et al. 2011 62</td>
<td>SSP tenotomy</td>
<td>CLS sham surgery</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Liu et al. 2011 63</td>
<td>SSP + SP + TM resection or SSP + SP + TM resection+SSN neurotomy</td>
<td>CLS sham surgery</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Mannava et al. 2011 64</td>
<td>SSP tenotomy</td>
<td>SG</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Gumucio et al. 2012 65</td>
<td>SSP + ISP resection</td>
<td>CLS sham surgery</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Kim et al. 2012 66</td>
<td>SSP</td>
<td>SG</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSP + ISP</td>
<td>SG</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSP + ISP+SSN Control (no surgery)</td>
<td>SG</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Liu et al. 2012 67</td>
<td>SSP + ISP resection or SSN neurotomy Control (unoperated)</td>
<td>SG intact</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Joshi et al. 2013 68</td>
<td>SSP + ISP + SSN</td>
<td>CLS</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Killian et al. 2013 69</td>
<td>SSP TT or SSP TT + repair or SSP TT + repair + botulinum toxin</td>
<td>SG intact, Saline injection, Toxin injection</td>
<td>D0</td>
</tr>
</tbody>
</table>

To be continued
After denervation, both anabolic and catabolic pathways become activated with an increase expression of p-AKT, p-mTOR, p-70S6 Kinase, p-FOXO1 and up-regulation of the MuRF1 and MAFbx catalytic genes, which leads to severe muscle atrophy. The up-regulation of AKT/mTOR/S6K1 signalling pathway may be compensatory due to the protein degradation caused by the increase of ubiquitin-proteasome activity. Thus, rotator cuff muscle atrophy following nerve injury is primarily caused by increased protein degradation instead of decreased protein synthesis, although the up-regulation of MuRF1 and MAFbx genes seems to be independent of FOXO activation. As described in other injuries, muscle atrophy induced by mTOR, which is also associated to upregulation of PPARγ and SREBP-1, can be modified by blocking mTOR signalling with Rapamycin. Surgical repair induces damage to the membrane of muscle fibers.

Autophagy is the process by which cells remove organelles and other cell components using lysosomal machinery to adapt to a new environment. It can be triggered by oxidized lipid accumulation, inflammation, macrophage recruitment, or endoplasmic reticulum or metabolic stress. This degradation process is crucial in muscle remodelling and atrophy. The increase in macrophage recruitment and lipid accumulation in torn rotator cuff has driven Authors to study muscle atrophy induced by mTOR, which is also associated to upregulation of PPARγ and SREBP-1, can be modified by blocking mTOR signalling with Rapamycin. Surgical repair induces damage to the membrane of muscle fibers.

Table I.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Treatment</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditsios et al. 2014 70</td>
<td>SSP + ISP detachment</td>
<td>CLS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gumucio et al. 2014 71</td>
<td>SSP + ISP resection</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ichinose et al. 2014 72</td>
<td>SSP release and resection</td>
<td>SG intact</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Joshi et al. 2014 73</td>
<td>SSP ISP tendon resection</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Killian et al. 2014 74</td>
<td>SSP + ISP TT + chronic repair</td>
<td>SG acute injury+repair</td>
<td>W0, W8, W16</td>
<td>-</td>
</tr>
<tr>
<td>Liu et al. 2014 75</td>
<td>SSP + ISP + SSN transection</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sato et al. 2014 76</td>
<td>SSP ISP TT + saline</td>
<td>SG intact</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Davies et al. 2015 77</td>
<td>SSP ISP TT + SSN</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Davis et al. 2015 78</td>
<td>SSP TT</td>
<td>SG</td>
<td>D28</td>
<td>-</td>
</tr>
<tr>
<td>Killian et al. 2015 79</td>
<td>SSP IST TT + botulinum toxin+W8 repair</td>
<td>CLS acute repair</td>
<td>W0, W8</td>
<td>-</td>
</tr>
<tr>
<td>Liu et al. 2015 80</td>
<td>SSP + ISP resection + SSN neurotomy</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melamed et al. 2015 81</td>
<td>SSP TT</td>
<td>CLS (group B)</td>
<td>W0</td>
<td>-</td>
</tr>
<tr>
<td>Sahin et al. 2015 82</td>
<td>SSP TT</td>
<td>SG intact</td>
<td>W0</td>
<td>-</td>
</tr>
<tr>
<td>Sevivas et al. 2015 83</td>
<td>SSP ISP detachment</td>
<td>SG sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Davies et al. 2016 84</td>
<td>SSP ISP TT + SSN resection</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hashimoto et al. 2016 85</td>
<td>SSP ISP TT</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thangarajah et al. 2017 86</td>
<td>SSP TT</td>
<td>CLS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kim et al. 2012 86</td>
<td>SSP + ISP detachment or SSP + ISP detachment + SSN neurotomy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liu et al. 2012 87</td>
<td>SSP + ISP resection or SSN or both</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Samagh et al. 2013 88</td>
<td>SSP + ISP resection or SSN lesion or both</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kuenzler et al. 2016 89</td>
<td>SSP + ISP TT + SSN neurotomy</td>
<td>CLS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liu et al. 2016 90</td>
<td>SSP, ISP TT + SSN neurotomy</td>
<td>CLS sham surgery SG (C57BL/6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Davies et al. 2017 91</td>
<td>SSP + ISP resection</td>
<td>CLS sham surgery</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Klomps et al. 2017 92</td>
<td>SSP + ISP resection</td>
<td>SG</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lee et al. 2017 93</td>
<td>SSP TT</td>
<td>CLS</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SSP supraspinatus, ISP: infraspinatus, SSC: subscapularis, SSN: supraescapular nerve, CLS: contralateral side; SG, specific group. D, day; W, week; M, month; S, sacrifice.
Vsp34 and Beclin-1, initiation components of autophagy. Both have been found to be induced in torn rotator cuff muscles in adult rats, suggesting that its remodelling uses autophagocytic pathways. The same Authors didn’t find changes in the autophagy related transcripts Afg16L1, Afg5, Beclin-1 and Vps34 doing the same injury to older rats. Several Authors have studied the molecular mechanisms behind the autophagy processes. Their results show that when atrophy is only preceded by tendon transection, LC3B, ATG12 and the LC3BII/LC3BI index are increased. This suggests that muscle atrophy after tendon transection, with no denervation associated is also mediated by autophagy. Moreover, mTOR, that suppresses the autophagy initiation complex, has been shown to be decreased in rotator cuff muscle following tendon transection and increased after denervation. Therefore, autophagy may be suppressed after denervation, due to the inhibition of the activation complex by mTOR, which increases after denervation.

Rapid onset of atrophy can also be triggered by blocking the release of the synaptic vesicles with botulinum neurotoxin, or blocking of ACHR with alpha bungarotoxin at the synaptic junction, which may be followed by an increased myogenic and adipogenic response.

**Mouse.** As in rats, tenotomy also produced muscle atrophy, increased by the addition of suprascapular nerve neurotomy. The changes were more severe in the infraspinatus. Davies et al. showed that although the relative population of muscular stem cells is constant after injury, their activation is only transient.

**Retraction and fibrosis**

**Sheep.** After tenotomy, the muscle retracts. This phenomenon increases during the first 16 weeks after damage and there is more retraction in the tendon than in the muscle. Post-injury continuous traction can recover the original muscle length. This retraction can also be observed as an increase in the pennation angle, which is posteriorly recovered after continuous tensioning of the muscle. The increase in interstitial fibrous tissue is present even after immediate repair phase, suggesting that SSP retraction is not essential for the development of fatty infiltration.

**Mouse.** There is increased fibrosis after tendon section, denervation or combined injury. It would be related to upregulation of aSMA and Vimentin.

**Fatty infiltration**

**Sheep.** The increase in interstitial fat after osteotomy of the infraspinatus insertion is both inter- and intra-fascicular. Two studies have assessed the effect of fatty infiltration after immediate repair. By using Osmium tetroxide analysis, Coleman et al. did not observe significant increase of adipose tissue but Luan et al. found a relevant increase in adipogenic genes by RT-PCR six months after immediate repair. When the tendon repair is done at 6 or 18 weeks after release, fatty infiltration decreases, but it takes longer to recover in more chronic injuries. In the case of late repair (40 weeks), fatty infiltration first increases and then improves up to similar levels than those found at the time of repair. However, it does not improve after continuous traction and repair. At the molecular level, these changes are related to increased expression of PPARγ and C/EBPβ after tendon release, and a decrease of PPARγ after repair. Fatty infiltration is mostly related to tendon than neuronal injury.

**Rabbit.** Fatty infiltration is present four weeks after detachment of the supraspinatus. This change is more intense in the lateral than in the medial region of the muscle and is localized within and around the muscle, and inside myocytes. Fatty infiltration does not spontaneously disappear, it even progresses with the chronicity of the lesion, and does not completely reverse after repair. Fatty infiltration was not observed in partial tears. Interestingly, fatty infiltration was also seen in a model of acute (immediate) repair, suggesting that SSP retraction is not essential for the development of fatty infiltration.

**Rat.** To induce a stable fatty infiltration, both the supraspinatus and infraspinatus must be tenotomized and released to allow tendon retraction. Simple supraspinatus tenotomy only produces an early transient fatty infiltration. Fatty infiltration is more severe when suprascapular neurotomy is added. As observed in rabbits, fatty infiltration is more pronounced in the musculotendinous junction at 4 weeks. The deposition of lipids is also present within the muscle fibers. Fatty infiltration progresses with chronicity and is localized principally in the infraspinatus. These changes are similar in young and adult rats. At molecular level, PPARγ and C/EBPα are increased, as well as the lipid marker perilipin-1, which accumulates earlier in the distal...
Portion\textsuperscript{61,65,66,77}. Joshi et al. found that after tenotomy with denervation there was an increase in PPARγ and SREBP-1, which was associated to upregulation of the mTOR signalling\textsuperscript{98}. Leptin, another marker of adipose tissue, is also upregulated\textsuperscript{98}.

Fatty infiltration can be related to BMPs. Inhibition of BMP signalling with intraperitoneal injection of LDN-193189 reduces supraspinatus fatty infiltration, as seen with Oil Red staining and decreased expression of SREBP1\textsuperscript{80}. Davies et al. showed that the fatty infiltration, associated to upregulated adipogenic pathways, appeared after rotator cuff section, but not after gastrocnemius muscle section in rats, suggesting that the rotator cuff has a differential response to lesions\textsuperscript{77}.

Mouse. Also showed fatty infiltration, increased by the addition of neurotomoty to tenotomy\textsuperscript{90,96}. Although fatty infiltration was more intense in the infraspinatus, this process was found together with upregulation of PPAR-γ, adiponectin and perilipin A\textsuperscript{66,90}. Klopm et al. showed that the fatty tissue does not come from circulating bone marrow stem cells\textsuperscript{92}. Kuenzler et al. found that this change is related to PARP-1\textsuperscript{89}. Lee et al. showed that fatty infiltration is mediated by FABP4, which is, itself, regulated by HIF1\textsuperscript{93}.

Inflammation

Gumucio et al., in a rat model of tenotomy without neurotomy, found macrophages in areas of fatty degeneration. Also the expression of IL-10 was decreased, while IL-6 and IL-1β levels were unaltered\textsuperscript{65}. The same model with older rats (24 months) showed the same findings. The pro-inflammatory macrophage 1 (M1) subpopulation marker CCR7 was unchanged, but CD11b and CD68 were increased. The anti-inflammatory M2 macrophage marker, CD168 was unchanged\textsuperscript{71}. This is in agreement with the facts that the process of atrophy after tenotomy without denervation seems to be autophagy and macrophages are responsible for phagocytosis in autophagy\textsuperscript{65,71,87}. When muscle tissue is damaged, an inflammatory process is triggered and it is necessary to regenerate and heal the tissue. However, it has to be perfectly regulated, because a prolonged inflammatory response can stimulate excessive tissue remodelling causing fibrosis. The M1 subpopulation of macrophages are responsible for the initial inflammatory response and the M2 subpopulation come into play in later repairing and remodelling stages\textsuperscript{96,97}. However, the macrophages are responsible for the increase in RhoA expression, which is associated with the increase in TNF-α and TGF-β1, and atrophy, fibrosis and fatty infiltration\textsuperscript{98}.

Muscular function

Muscular function has also been studied in experimental models both in vitro and in vivo. In one of the earliest experimental studies, Bjorkenheim et al. showed that the section of the supraspinatus tendon in rabbits leads to changes in the contractile re-

response with increased fatigue and muscular insufficiency after repeated stimulation, in line with the atrophy observed\textsuperscript{25}. Fabis et al. described a loss of twitch tension and a decrease in the fatigue index after the detachment of the supraspinatus muscle in rabbits, that was markedly present 6 weeks after detachment and continued increasing slowly after six months\textsuperscript{44,45}. In vivo, the average force of infraspinatus muscle contraction in a sheep model decreased by a 48% six weeks after tendon detachment, and 52% after 18 weeks\textsuperscript{14}. An immediate repair after detachment prevented muscle force loss. A delayed 6 weeks repair of the tendon partially reverted the force decrease at 12 (22% recovery) and 20 weeks (36% recovery). However, a delayed repair at 18 weeks after detachment needed 30 weeks to show some improvement. Meyer et al. showed that, in sheep, tendon tears were not only related to fatty infiltration, retraction and atrophy, but also to loss of strength and contractile amplitude of muscle. The loss of muscle work correlated with the fatty infiltration\textsuperscript{39}.

Rowshan et al. found that the complete section of the subscapularis tendon in rabbits induced histologic changes in the muscle, that were very similar to those observed after muscle denervation. This supports the hypothesis that nervous damage may be induced by a tendinous lesion\textsuperscript{52}. However, Gayton et al. examined in detail the histology of the supraspinatus muscle of rabbits three months after tendon section, and they saw no evidence of denervation, despite that atrophy and fatty degeneration were evident\textsuperscript{55}.

Mannava et al. studied in rats the effect of the tension required to repair an acute or chronic supraspinatus tendon tear, based on the amplitude of the maximal tetanic contraction and the compound motor action potential of the muscle (CMAP). They observed that chronic lesions, that required a higher tension in the repair, had lower muscle force and CMAP than acute lesions, highlighting the better functional prognosis of an early repair after injury\textsuperscript{64}. Gumucio et al. studied the force production of a single rat muscle fibre 30 days after supraspinatus and infraspinatus tendon section. They observed a decrease in force production associated to an induction of fibrogenic, adipogenic, and inflammatory gene expression\textsuperscript{65}. In a subsequent study, they found that the extent of degenerative changes in old rats was greater than that found in adults\textsuperscript{71}. Ditsios et al. also described a marked decrease in force after supraspinatus and infraspinatus section in rats. In a detailed 3D histological study, they observed that the degeneration and the fatty infiltration were more evident near the tendon and at the dorsal side in both muscles\textsuperscript{70}.

Therapeutic research

This section is summarized in Table II. Within the different pharmacological therapies, Gerber et al. first observed that in sheep, intramuscular injection of nandrolone decanoate, administered in the muscle belly of the infraspinatus, was unable to regenerate the muscle when degenerative changes are pre-
sent. The anabolic steroid administered *alia loco* prevented fatty infiltration, reducing functional muscle damage in rabbits and sheep. It prevents fatty infiltration when administered after tendon release and also prevents further degenerative changes after surgical repair if administered after tendon repair, but cannot reverse it when already present. The same group showed that anabolic steroids and IGF-I, a growth factor with muscle anabolic properties, had no beneficial effect in a sheep model of muscle degeneration. Analyzing the effect of 5-LOX, COX-1, and COX-2 inhibition with licofelone, Oak et al. targeted the fibrogenic process of muscle injury. They observed a marked reduction in fibrosis and lipid content in supraspinatus muscles with reduced expression of several genes involved in fatty infiltration. Cho et al. studied the effect of tamoxifen, an estrogenic agonist with anabolic effects. Although it produced decreased atrophy and endomysial inflammation, there were no significant differences in the amount of intramuscular adipocytes and lipid droplets nor in the expression of adipogenic genes. With

Table II. Therapeutic studies.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Reference</th>
<th>Injury</th>
<th>Intervention</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>Gerber et al. 2012&lt;sup&gt;99&lt;/sup&gt;</td>
<td>ISP osteotomy + lengthening at week 16 for 6 weeks</td>
<td>Nandrolone decanoate / IGF-1-PLGA microsphere</td>
<td>W22</td>
</tr>
<tr>
<td></td>
<td>Gerber et al. 2015&lt;sup&gt;100&lt;/sup&gt;</td>
<td>ISP osteotomy and wrapping</td>
<td>Nandrolone decanoate (injection W16 into gluteus maximus)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flück et al. 2017&lt;sup&gt;101&lt;/sup&gt;</td>
<td>ISP osteotomy and wrapping</td>
<td>Nandrolone decanoate (injection W16 into gluteus maximus)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ruoss et al. 2018&lt;sup&gt;102&lt;/sup&gt;</td>
<td>ISP osteotomy and wrapping</td>
<td>Nandrolone decanoate (injection W16 into gluteus maximus)</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>Gerber et al. 2011&lt;sup&gt;103&lt;/sup&gt;</td>
<td>SSP release</td>
<td>Nandrolone decanoate</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Oh et al. 2014&lt;sup&gt;104&lt;/sup&gt;</td>
<td>Subscapularis detachment and wrapping</td>
<td>Heterologous ADSC</td>
<td>W6</td>
</tr>
<tr>
<td></td>
<td>Kim et al. 2014&lt;sup&gt;105&lt;/sup&gt;</td>
<td>SSP detachment</td>
<td>ADMSC</td>
<td>W3</td>
</tr>
<tr>
<td></td>
<td>Gilotra et al. 2015&lt;sup&gt;106&lt;/sup&gt;</td>
<td>SSP transection and wrapping</td>
<td>Botulinum toxin</td>
<td>W12</td>
</tr>
<tr>
<td></td>
<td>Chung et al. 2016&lt;sup&gt;107&lt;/sup&gt;</td>
<td>SSP detachment</td>
<td>Simvastatin</td>
<td>W10</td>
</tr>
<tr>
<td>Rat</td>
<td>Oak et al. 2014&lt;sup&gt;108&lt;/sup&gt;</td>
<td>SSP TT and wrapping</td>
<td>Licofelone</td>
<td>W4</td>
</tr>
<tr>
<td></td>
<td>Davis et al. 2015&lt;sup&gt;109&lt;/sup&gt;</td>
<td>SSP TR</td>
<td>Simvastatin</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Gumucio et al. 2016&lt;sup&gt;110&lt;/sup&gt;</td>
<td>SSP TT</td>
<td>Stromal vascular fraction of adipose tissue</td>
<td>W4</td>
</tr>
<tr>
<td>Mouse</td>
<td>Wilde et al. 2016&lt;sup&gt;111&lt;/sup&gt;</td>
<td>SSP TT and wrapping</td>
<td>Intraperitoneal SB203580</td>
<td>D30</td>
</tr>
<tr>
<td></td>
<td>Sevivas et al. 2016&lt;sup&gt;112&lt;/sup&gt;</td>
<td>SSP + ISP TT</td>
<td>Secretome from human MSCs</td>
<td>- - -</td>
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<tr>
<td></td>
<td>Takase et al. 2016&lt;sup&gt;113&lt;/sup&gt;</td>
<td>SSP + ISP TT</td>
<td>Subacromial PRP</td>
<td>- - -</td>
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<tr>
<td></td>
<td>Gumucio et al. 2017&lt;sup&gt;114&lt;/sup&gt;</td>
<td>SSP TT and wrapping</td>
<td>PHD inhibitor GSK1120360A</td>
<td>W4</td>
</tr>
<tr>
<td></td>
<td>Cho et al. 2015&lt;sup&gt;115&lt;/sup&gt;</td>
<td>SSP + ISP TR + SSN NT</td>
<td>Tamoxifen</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Davies et al. 2016&lt;sup&gt;116&lt;/sup&gt;</td>
<td>SSP + ISP TT + SSN NT</td>
<td>Intraperitoneal SB431542</td>
<td>TGF-β inhibitor</td>
</tr>
<tr>
<td></td>
<td>Eliasberg et al. 2017&lt;sup&gt;117&lt;/sup&gt;</td>
<td>SSP + ISP TT or SSP + ISP TT + NT</td>
<td>Allogenic perivascular stem cells</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Shirasawa et al. 2017&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Whole rotator cuff transection + SSN NT + humeral head resection</td>
<td>Imatinib mesylate</td>
<td>(PDFGR inhibitor)</td>
</tr>
</tbody>
</table>

SSP supraspinatus, ISP: infraspinatus, SSN: supraescapular nerve, TT tenotomy, TR tendon resection, NT neurotomy, CLS contralateral side, SG: specific group, W: week, D: day.

ADSC adipose tissue derived stem cell, MSC mesenchimal stem cell, PRP platelet rich plasma.
the previous observations indicating that hypercholesterolemia impairs tendon to bone regeneration, and that statins prevent fibrosis and inflammation in other diseases, Davis et al. investigated the effect in a model of rotator cuff repair in rats. They observed that simvastatin increased fiber specific force and reduced collagen content, but without significant effect on atrophy or triglyceride content. Simvastatin down-regulated PPARy, C/EBPα, CD68, eMHC, and most of the genes involved in ECM synthesis, fibrosis, and fibroblast proliferation. Recently, Chung et al. observed that treatment with statins was beneficial in a rabbit model of fatty infiltration. Davies et al. showed that blocking the pro-fibrotic factor TGF-β down regulates the expression of fibrotic, adipogenic, and atrophy-related genes, reducing the number of fibro/adipogenic progenitor cells by promoting their apoptosis; thus, fibrosis, fatty infiltration, and muscle weight loss were reduced. Wilde et al. demonstrated that blocking p38 MAPK signalling, involved in the regulation of adipocyte activity, decreased the adipose and collagen content. Hypoxia-inducible factor-1 alpha has also been shown to be positively involved in the prevention of degenerative changes after tendon injury. More recently, Shirasawa et al. showed that the inhibition of PDGFR was able to suppress the muscular fibro-fatty degeneration.

Gilotra et al. described the damaging effects of botulinum toxin in the muscle after tendon repair confirming the previous reports that used botulinum toxin as a mechanism of injury. After tendon detachment in rabbits, Oh et al. showed a decrease of fatty infiltration if repair was complemented with muscular injection of adipose-derived stem cells. Similarly, Kim et al. observed that transplanted adipose-derived stem cells produced a higher expression of IGF1R and MHC. The positive effect of stem cells was also observed by Eliasberg et al. when injecting allogenic perivascular stem cells to mice with chronic rotator cuff injury. Other Authors have studied the effect of stromal vascular fraction cells of adipose tissue, the secretome from mesenchymal stem cells and platelet rich plasma to improve muscle recovery.

Discussion

The purpose of this review was to recapitulate the most significant findings on animal models of the muscular degeneration after rotator cuff injury, to get a better understanding of one of most common muscle pathologies in orthopaedic patients. Most of the reviewed works are focussed on the muscular atrophy of the rotator cuff muscles after tendon injury, mainly characterized by changes in fiber type composition, with muscles accumulating more type IIb fibers. This fiber shift from type I towards type II suggests that the muscles of rotator cuff change from an endurance muscle (predominant type I muscular fibers) to a resistance muscle (predominant type IIB fibers) after tendon injury, since type II fibers are strength training, glycolytic fibers, unable to maintain sustained contraction.

Among the different animal models of tendon tears, dysregulation of the principal proteolytic systems implicated in protein quality control, namely, the autophagy-lysosomal system and the ubiquitin-proteasome system, leads to atrophy. Ubiquitin-proteasome is the main mechanism in animal models that included neurotomy, while autophagy-lysosomal system seems to be predominant in those using simple tendon section or resection. In human, Schmutz et al. found that CAPN1, APN1, UBE2B, and UBE3A genes were up-regulated after tendon injury, supporting proteolysis as the main process leading to muscular atrophy. However, the relevance of neuropathy is still under discussion in the clinical field and the mechanisms leading to atrophy need to be profoundly explored. Autophagy-lysosomal and ubiquitin-proteasome systems are connected upstream, as they are both promoted by FOXO 1/3. In addition, AKT/PKB signalling can block the activity of FOXO 1/3 and autophagy through the activation of mTOR. Thus, one possible explanation for the differences between tenotomy and neurotomy is that in simple tenotomy decreases anabolism and increases autophagy as a consequence of mTOR pathway down-regulation to avoid cellular apoptosis, which in turn is congruent with the role of mTOR as an autophagy inhibitor. In the case of neurotomy, both the AKT/mTOR (protein synthesis) and ubiquitin/proteasome (Murf1, MAFbx) pathways are up-regulated, and thus autophagy is inhibited by mTOR. This scenario may explain why autophagy is the main responsible for muscle atrophy after tenotomy, while ubiquitin/proteasome system is the most common after tenotomy with denervation. However, other possibility to explain these differences could be related to the age of the animals, since aging is associated with perturbed proteostasis. Gumucio et al. showed activation of autophagy in a 6 month-old-rat model of tenotomy without SSN section, but not in 24 months aged rats. Muscular atrophy means that the coordinated muscle repair response after tendon injury is lost, and the function of different cell populations within the skeletal muscle is completely impaired. Immediately after tendon injury, muscular degeneration triggers accumulation and activation of the inflammatory cells, which should activate the quiescent satellite cells to start muscle repair. However, the increase of pro-inflammatory M1 macrophages is not switched off and followed by accumulation of anti-inflammatory M2 macrophages. This excess of the inflammatory response worsen the injury, stimulating a disproportionate tissue remodelling causing fibrosis. The mechanisms underlying fibrosis in rotator cuff injuries are not well understood, but the pathological prevalence of fibroblasts around and within the muscle after tendon injury has linked poor muscle function to increased expression of fibrotic markers. Similarly, the presence of adult adipose cells, which is excep-
Muscular degeneration in rotator cuff tears

tional in healthy muscles, notably increases after tendon injury, contributing to muscle repair failure. Fatty infiltration, normally associated to an upregulation of adipogenic genes \(^{56,68,71}\), is mainly dependent on tendon retraction, progresses after tendon injury and becomes not reversible with tendon repair. Nevertheless, tendon retraction is not indispensable for the development of fatty infiltration, as it is also present after immediate tendon repair \(^{40,48}\). Fat infiltration strongly correlates with poor clinical outcomes and success rates of rotator cuff repair, because further to impair muscle function, there is a level of fat infiltration that is irreversible even following repair. Inadequate inflammatory response, accumulation of fibrotic tissue and fatty infiltration after tendon injury exceed the regenerative capacity of the satellite cells, as it has been demonstrated in human muscles with full thickness tendon tear \(^{7,8,12,13}\). However, an increased satellite cell population, with less replicative potential, is described in tendons with partial tears \(^{7,8,12}\). Similarly, in sheep and rat experimental models, there is upregulation of Myf5 when neurotomy of the SSN is added to tenotomy \(^{37,66}\). Since Myf5- satellite cells are committed to differentiation rather to maintain the reservoir of the satellite cells \(^{123}\), we may speculate that loss of asymmetric satellite cell divisions is the cause of stem cell depletion in the rotator cuff, contributing to the development of muscular atrophy \(^{124}\). All these evidences suggest a cellular relation between inflammation, fibrosis and fatty infiltration after tendon injury. Within the normal interfibrillar component of the skeletal muscle there are quiescent cells, which do not derive from myogenic progenitors and are unable to differentiate into muscle cells \(^{125,126}\). Because these cells have the potential to differentiate into fibrous and adipose lineages upon activation \(^{128}\), they are called fibro-adipogenic progenitors (FAPs). FAP cells promote muscle repair after injury through interacting with the satellite cells \(^{126,127}\) and, interestingly, FAP cells may be regulated by immune cells. Infiltrating monocytes induce the apoptosis of FAPs as they produce TNF, while macrophages prevent FAPs death and induce their differentiation by expressing TGF-β \(^{116,127-130}\). Recently, these FAP cells have been identified in the muscles of the rotator cuff \(^{116,8,125}\), supporting that they generate the fibrous and adipose tissues after tendon injury \(^{126,133}\). Expression of platelet-derived growth factor receptor alpha (PDGFRα), characteristic of the FAPs cells \(^{129,131}\), is highly increased in rat muscles of tendon tears, correlating with high fibrosis and fatty infiltration \(^{65}\), while inhibition of PDGFR\(^ +\) cells in tendon injury mouse models prevents muscle fatty infiltration \(^{85}\). These findings demonstrate that fibrosis and adipocyte accumulation in rotator cuff muscles after damage mainly comes from PDGFR\(^ +\) mesenchymal cells, the FAPs \(^{90}\). Although these evidences rise the possibility that fibrosis and fatty infiltration leads to muscular atrophy, some investigators have suggested these are different cellular processes. Liu et al. showed that blocking BMP signalling results in increased muscle atrophy and decreased fatty infiltration in rotator cuff \(^{80}\), and clinically, atrophy comes first, followed later by fatty infiltration.

Different therapeutic strategies such as pharmacological and cell therapy approaches have been developed to counteract rotator cuff muscles after tendon tears by reducing fatty infiltration and fibrogenic process or increasing the regenerative response of the satellite cells and muscular mass. However, they are no effective treatment for these muscle pathologies. The identification of FAPs as the major cellular sources of rotator cuff muscles fibrosis and fatty infiltration, with the potential to drive satellite cell to promote myogenesis opens new perspective for developing cellular targeted treatments for these diseases. The limitations of this study are derived of the heterogeneity of the different studies in the field. In consequence, although there are multiple mechanisms with potential as targets for efficient therapies in the treatment of tendon tears and recovery of muscular injuries, their translation to clinical settings seems still far away.

Conclusion

Muscular degeneration after tendon injury is still an unsolved problem. There have been established animal models in sheep, rabbit, rat and mouse to model human disease and assess the effect of different therapeutic strategies. A key factor of these animal models of tendon injury is whether they include or not the resection of the supraspinal nerve, because the type and mechanism of muscle atrophy is different. In recent years there are more studies focusing on the cellular origin of the fibrous and adipose tissue, since they are hallmark of muscle degeneration and prevent muscle repair. Clarification of the molecular and cellular interrelations of the muscular phenomena, – atrophy, fibrosis, fatty infiltration and inflammation – and how they affect satellite cell function, could make more targeted therapies possible.

Conflict of interest

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39. Meyer DC, Gerber C, Von Rechenberg B, Wirth SH, Farshad M. Amplitude and strength of muscle contraction are educed in...
Muscular degeneration in rotator cuff tears


