Published in final edited form as:

Tech Shoulder Elb Surg. 2017 September ; 18(3): 84–90. doi:10.1097/BTE.0000000000000124.

Targeting Inflammation in Rotator Cuff Tendon Degeneration and Repair

Adam C. Abraham, PhD¹, Shivam A. Shah, PhD³, and Stavros Thomopoulos, PhD^{1,2}

¹ Department of Orthopedic Surgery, Columbia University, Black Building 1408, 650 W 168 ST, New York, NY, 10032, USA.

² Department of Biomedical Engineering, Columbia University, New York, NY, USA

³ Department of Orthopaedic Surgery, Washington University, 660 South Euclid, Campus, Box 8233, St. Louis, MO, 63110, USA

Abstract

Rotator cuff degeneration is a common affliction that results in pain and disability. Tendinopathy was historically classified with or without the involvement of the immune system. However, technological advancements in screening have shown that the immune system is both present and active in all forms of tendinopathy. During injury and healing, the coordinated effort of numerous immune cell populations work with the resident stromal cells to break down damaged tissues and stimulate remodeling. These cells deploy a wide array of tools, including phagocytosis, enzyme secretion, and chemotactic gradients to direct these processes. Yet, there remains a knowledge gap in our understanding of the sequence of critical events and regulatory factors that mediate this process in injury and healing. Furthermore, current treatments do not specifically target inflammation at the molecular level. Typical regimens include non-steroidal anti-inflammatory drugs or corticosteroids; however, researchers have found irrevocable functional deficits following treatment, and have disputed their long-term efficacy. Therefore, developing therapeutics that specifically consider the nuances of the immune system are necessary to improve patient outcomes.

Keywords

Tendinopathy; Enthesis; Immune; Cytokine

1 Introduction

Over 20% of all consultations made to a general practitioner are related to musculoskeletal diseases and 30% of these are associated with tendon injuries.^{1,2} In the shoulder, the rotator cuff is a frequent source of pain and disability. Furthermore, the incidence of injury increases with age: over 50% of the population over the age of 65 has a rotator cuff tear.³⁻⁵

Corresponding Author: Stavros Thomopoulos, PhD, Columbia University, 1406 Black Building, 650 W 168th Street, New York, NY 10032, Fax Number: Phone Number: sat2@columbia.edu.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Loss of strength and function due to rotator cuff tears results in disability and leads to lost days from work, occupational challenges, and recreational limitations for patients.⁶ Rotator cuff repair to recover shoulder function is one of the most common orthopedic surgical procedures, with over 250,000 repairs performed each year in the United States.⁶⁻⁸ It is the most common shoulder condition, with more than 17 million individuals in the United States affected. Healing after rotator cuff repair is a well-known clinical challenge. Tears occur at the tendon-to-bone insertion site, and the goal of rotator cuff repair is anatomic restoration of the tendon attachment. However, clinical studies have shown failure rates ranging from 20-94%.⁹⁻¹² Factors associated with failure include tear size, chronicity, patient age, and other environmental factors.^{5,11,13} Understanding the process of rotator cuff degeneration will allow clinicians to implement preventative early interventions.

Prior to the 1990s, tendon injuries were often classified as tendinitis, with the “itis” suffix resulting in a misleading emphasis on inflammation.¹⁴ However, even as early as the 1970s, some research groups presented a lack of acute inflammatory cells in chronic tendon injuries.¹⁵ More recently, Khan *et al.* reported an increase in the presence of fibroblastic and myofibroblastic cells accompanied by a distinct lack of inflammatory cells in tendons of athletes with overuse injuries.¹⁶ Khan advocated for the use of the term “tendinopathy” to refer to overuse injuries which were previously considered tendinitis. Researchers in the last two decades have advocated the separate use of the terms “tendinitis” and “tendinosis” to describe tendon injuries with inflammation and without inflammation, respectively. Lost in the nomenclature debate and classification of inflammatory vs. non-inflammatory responses has been an appreciation of a spectrum of inflammatory responses across the various tendon pathologies.

As immunohistochemistry and gene expression analysis techniques have improved, mounting evidence supports some level of inflammation in all tendon injuries.^{17,18} For example, improved histological techniques were used to show the presence of B and T lymphocytes, suggesting the presence of inflammation, in chronic Achilles tendon injury.¹⁹ Tenocytes became more metabolically active in response to inflammatory cytokines and increased in number and size in pathologic tendon.²⁰ A systematic review of the literature in 2015 suggested that increased numbers of inflammatory cells are present in pathological tendons.²¹ Therefore, inflammation plays a role in the development and progression of tendon injuries, and particularly during an injured tendon's healing response.

Despite the evidence that inflammation is involved in tendinopathy, there is a lack of consensus regarding inflammation-targeting treatments. There is an emerging trend among researchers and clinicians supporting the use of biological treatment coupled with surgical intervention to improve patient outcomes. The need for targeted therapeutics in tendon healing and degeneration, with known mechanisms that effect particular cells, has become clear.^{2,22} Specifically, there is a need for more data on cellular and molecular aspects of tendon development, signal transduction, mechanotransduction, and basic mechanisms underlying tendon degeneration and healing. This review will first briefly describe our current understanding of tendon degeneration and treatment approaches and then focus on inflammation-related strategies to treat tendinopathies.

2 Pathogenesis of Rotator Cuff Degeneration and Current Treatment Approaches

Rotator cuff injuries can occur due to years of degeneration (e.g., associated with overuse), sports (e.g., due to collision), accident (e.g., due to a laceration), and/or disease. Both intrinsic and extrinsic factors contribute to tendon injury.²³ Intrinsic factors for chronic and acute injury include age, gender, obesity, type 2 diabetes, and genetics. With regard to age, the incidence of rotator cuff repairs increased by 238% from 1995 to 2009 in New York, in part due to the increase in the percentage of the population between 45-65 years of age rising from 53.0 to 62.4%.²⁴ With regard to genetics, six single nucleotide polymorphisms (SNP) of the TNC gene were recently associated with full-thickness rotator cuff tears.²⁵ In particular, a missense SNP in exon 10 varied the amino acid sequence close to the TNF-FNIII5 domain, which binds with numerous growth factors during tendon healing.²⁶ Variants of SAP30BP, SASH1, and ESRRB were also associated with full-thickness tears.²⁷⁻²⁹ These genes are part of apoptosis pathways, and an increase in apoptotic cells are found in torn rotator cuffs, which is also associated with increases in pro-inflammatory cytokines.^{30,31} Rotator cuff disease defined by full- or partial-thickness tears or tendinosis was associated with SNPs of DEFB1, DENND2C, ESRRB, FGF3, FGF10, and FGFR1 genes, all of which are implicated in tissue degenerative and repair processes, including inflammatory cascades.³²

Extrinsic factors leading to injury differ between chronic and acute injury. These factors include exercise regimens, occupation, nutrition, medication, and smoking.^{23,33,34} Chronic injuries are associated with repetitive mechanical strain and loading.³⁵ Acute injuries are associated with sudden eccentric movement that causes the tendon to tear or rupture from the bone.³⁶ A common thread that runs through many of the risk factors for rotator cuff degeneration is inflammation. Aging, obesity, type 2 diabetes, and smoking are all associated with increases in circulating inflammatory factors which are believed to contribute to a state of low-grade chronic inflammation leading to various diseases.³⁷ More researchers are attempting to close this potential loop with tendinopathy and explore the role of the immune system during degeneration and healing.¹⁸

The high prevalence of tendon injuries has influenced the development of various treatment strategies. Surgical repair is necessary to re-attach tendon ends in cases of mid-substance tears or lacerations and tendon-to-bone ruptures. However, most surgical treatments have shown only moderate success rates.^{38,39} Patients may experience pain relief and demonstrate improved outcomes in clinical assessments, but the surgical repair may only deliver a short-term solution.³⁸ The poor surgical failure rates can partially be attributed to a variety of patient factors, including patient age, size of injury, chronicity of injury, systemic diseases, diabetes, and smoking. Surgical technique has improved along with our understanding of tendon mechanics, but an inherent difficulty lies in recreating the complex tendon-to-bone attachment or the structure of tendon midsubstance following injury.

More conservative non-surgical interventions for tendon injuries have shown mixed success.² Rest alone does not heal chronic tendinopathies, but can help manage the pain associated with the injury and may prevent re-injury. Eccentric exercise (EE) therapy has

shown some success for Achilles tendinopathy, but less so for tendinopathy at other sites.⁴⁰ Extracorporeal shock wave (ESW) therapy for chronic tendon injuries is an attractive non-surgical treatment option which showed some success in early clinical use, but its mechanism of action still remains to be defined.⁴¹ Finally, the use of platelet rich plasma (PRP) injections to treat tendinopathies has shown very limited success.^{18,42} The patient's age, demographics, pain and risk tolerance help clinicians decide whether or not non-surgical intervention should be pursued. Eventually, if the tendon injury progresses and/or patient discomfort increases, surgical intervention is necessary.

3 Immune cell types and signaling pathways involved in tendon disease and healing

3.1.1 Immune cells involved in the inflammatory response

Immune cells are present in pathologic tendons due to the generation of alarmins, an endogenous set of biomolecules which can recruit and activate cells of the innate and adaptive immune systems.⁴³ There are two main types of inflammatory responses – acute and chronic. Acute inflammation is the initial response to harmful stimuli and mediated primarily by innate immune cells such as mast cells, macrophages, and neutrophils. Their general purpose is to eliminate or minimize additional damage from the stimuli, remove dying cells and damaged tissue, and initiate tissue repair. Chronic inflammation has a delayed onset and is mediated primarily by mononuclear cells like macrophages and lymphocytes.

Within the innate cell population, mast cells increase in density during the early stages of the disease and can persist in patients with longstanding symptoms.⁴⁴⁻⁴⁶ These pro-inflammatory cells secrete immune mediators that recruit other immune cells and suppress collagen synthesis of tendon fibroblasts via prostaglandin E2 signaling.⁴⁷ Macrophages are also present during all stages of disease, however, their functionality changes as they guide the healing process towards resolution. Initial macrophage infiltrate and resident expansion adopt an M1 pro-inflammatory phenotype.⁴⁸⁻⁵⁰ In contrast, late stage healing of tendon is marked by a phenotypic switch to anti-inflammatory M2 macrophages.^{48,51} However, this switch may not occur in non-resolving patients, leading to chronic degeneration and pain.^{22,48} Other innate immune cells that are known to be present during tendon pathology include neutrophils, dendritic cells, and natural killer cells; however, their specific roles remain undefined in tendinopathy.⁵²

Adaptive immune cells such B and various T cells are also known to be present during tendinopathy and in healing, but little is known regarding their roles in these processes.^{19,20} Importantly, lymphocytes are extremely diverse and few studies have screened for specific markers in the rotator cuff. However, several unique subpopulations of T cells residing within musculoskeletal tissues have been identified. Exploring the mechanisms of spondyloarthritis led to the discovery of a tendon enthesis-specific population of T cells that are ROR- γ t+ CD3+ CD4- CD8- and respond to interleukin-23, producing downstream inflammatory mediators.⁵³ Specifically, these cells secrete interleukin-22 which activates signal transducer and activator of transcription 3-dependent osteoblast-mediated bone

remodeling, resulting in osteophyte formation. Skeletal muscle specific regulatory T cells were found to mediate tissue repair processes following injury by reducing late stage inflammation and secreting the growth factor amphiregulin, which acts directly on satellite cells.⁵⁴ Studies like these shed light on the phenotypic heterogeneity *within* immune cell populations that are driven by their unique niches within tissues. Furthermore, their specificity to the interface between tendon and bone is particularly relevant to rotator cuff repair, which relies on re-integration of the two tissues for functional success.

3.2 Signaling pathways and cytokines involved in the inflammatory response

The inflammatory response can be modulated by targeting components of the nuclear factor- κ -B (NF- κ B) pathway (Figure 1). NF- κ B is an evolutionarily conserved transcription factor that plays a role in multiple biological processes, but most notably in the development and function of the immune system.^{55,56} The transcription factor also has a significant role in the development and function of the epithelium and skeletal system and has been linked to a variety of disease states.^{57,58} Most of the disease states are related to chronic inflammatory and autoimmune diseases, where sustained NF- κ B signaling leads to a pathophysiology. The pathway's capacity to link "physiology to pathology" has increased the number of research studies and publications describing the mechanism of the pathway.

Activation of the NF- κ B pathway is described through two pathways – canonical (classical) and non-canonical (alternative).⁵⁹ The canonical pathway is activated by ligands binding to receptors for TNF or IL-1, pattern recognition receptors, or antigen receptors and is marked by activation of the I κ B kinase (IKK) complex. These receptors are present in resident tendon fibroblasts and expression of the complimentary cytokines are increased in tendinopathy.⁶⁰⁻⁶² Recently, interleukin-33 (IL-33) was found to stimulate canonical NF- κ B signaling via ST2 in early rotator cuff tendinopathy (Figure 2).⁶³ This resulted in suppression of micro-RNA-29a in tendon cells and subsequent production of scar-forming type III (Figure 2). The non-canonical pathway is induced by specific members of the TNF cytokine family such as CD40 ligand, BAFF, and lymphotoxin- β .^{64,65} The NF- κ B inducing kinase (NIK) stimulates IKK α activation (independent of NEMO) leading to phosphorylation of p100 and the generation of RelB/p52 complexes. It has not yet been shown if non-canonical NF- κ B signaling has any role in rotator cuff tendinopathy.

One downstream effect of NF- κ B signaling is the production of the cytokine interleukin-6 (IL-6). Classically, IL-6 is considered pro-inflammatory, as it stimulates T-cell and macrophage activation and osteoclast formation. However, it is now known to also be an anti-inflammatory myokine that responds to physical exercise and promotes secretion of inhibitory factors such as interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10).⁶⁶ The bias towards pro-inflammatory behavior has been shown to be tumor necrosis factor alpha (TNF α) dependent.⁶⁷ In patients with rotator cuff tears, IL-6 gene expression and cytokine production have been shown to correlate with the extent of degeneration and genes associated with tissue remodeling.⁶⁸⁻⁷¹ One study examined patients following rotator cuff repair surgery and found increased joint stiffness was associated with polymorphisms of the IL-6 gene.⁷²

Another signaling downstream cytokine implicated in rotator cuff disease is interleukin 17A (IL-17A). This cytokine is known to be secreted from various immune cells, and binding of its receptor results in the production of pro-inflammatory cytokines, chemokines, inducible nitric oxide synthase, and MMPs. Modulation of IL-17A is dependent on synergistic activation of interleukin-23, STAT3, and NF- κ B or TGF- β and IL-6. Patients with early rotator cuff tendinopathy show increased expression of IL-17A. Furthermore, culturing tenocytes with rhIL-17A induced production of proinflammatory cytokines and increased expression of apoptosis related genes.⁷³

4 Therapeutic Potential of Targeting Inflammation

4.1 Broad approaches

Some clinicians use non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to treat early tendon injuries. However, most researchers argue against the use of NSAIDs for tendinopathy.⁷⁴ NSAIDs block the production of prostaglandins from arachidonic acid, which leads to an overall decrease in the inflammatory response. However, too much arachidonic acid could also lead to tissue damage. Therefore, NSAIDs are believed to have a positive effect on patient symptoms, but may be deleterious to tissue and tendon healing in the long term. Similarly, the use of corticosteroids offers some short term pain relief, but has limited long-term benefits for tendon healing.⁷⁵ Corticosteroids inhibit the accumulation of neutrophils and synthesis of inflammatory cytokines. They have been shown to decrease pain and improve abduction in rotator cuff tendon injury, but not in Achilles tendon injury.^{76,77} There is concern about an association with increased risk of tendon rupture with the frequent use of corticosteroid injections.⁷⁸ NSAIDs and corticosteroids are the predominant anti-inflammatory options available to clinicians today. There is a need for the development of therapeutics that could provide finer control and mediation of inflammation in tendon healing.

4.2 MSC-mediated modulation of inflammation

The complex mechanisms of inflammation and tissue repair make it difficult to identify a single target for rotator cuff degeneration and tendinopathy. However, several treatment modalities have been attempted with various degrees of therapeutically-defined mechanisms. Prior *in vivo* and *in vitro* studies have suggested that the application of mesenchymal stromal cells (MSCs) may improve the healing response via their capacity to modulate the inflammatory environment.^{79,80} MSCs influence local tissue environments through the secretion of soluble factors and exert protective effects on local cells. This aspect of MSC function has been exploited to enhance tissue repair in animals.^{81,82} In a recent study, ASCs co-cultured with M1 (pro-inflammatory) macrophages successfully suppressed the effects of M1 macrophages on tendon fibroblasts by inducing a phenotypic switch from a pro-inflammatory macrophage phenotype to an anti-inflammatory macrophage phenotype.⁸³ This led to decreased exposure of tendon fibroblasts to pro-inflammatory cytokines such as IL-1 β and increased production of extracellular matrix proteins. ASCs, delivered in a cell sheet to a tendon repair site in an *in vivo* animal model, also modulated the inflammatory response.⁸⁴ When examining the effect of ASCs on macrophage phenotype, gene expression and immunohistochemistry results after 7 days of healing were consistent with the *in vitro*

results. Similar results were reported in a small animal study using MSCs primed with the cytokine TNF α .⁸⁵ These studies suggest that, by controlling inflammation, ASCs may improve tendon healing outcomes.

4.3 Signaling Inhibition

A more granular approach to treatment is to target specific immune signaling pathways. NF- κ B functions as a master regulator and is typically activated by TNF and IL-1 signaling cascades. Therefore, several studies have attempted to modulate these pathways to treat disease or improve healing. Inhibiting TNF is currently used as treatment for autoimmune diseases such as rheumatoid arthritis and ankylosing spondylitis.⁸⁶ Low-dose inhibition could improve tendinopathy without increasing the risk of infection.¹⁸ In a pilot study, peritendinous injection of adalimumab, a monoclonal TNF α antibody, was administered to the Achilles of symptomatic athletes.⁸⁷ Walking and resting pain was reduced over the 12 week course of treatment and tendon thickness remained constant, while blood flow decreased. In a rat rotator cuff repair model, blockade of TNF α using pegylated TNF receptor type 1 improved the biomechanical strength and reduced pro-inflammatory macrophages at early time points (< 4 weeks).⁸⁸ However, these effects normalized to the non-treated controls by 8 weeks. Knocking out TNF α using lenti-virus mediated siRNA in a rat model of carrageenan-induced subacromial bursitis muted the inflammatory response at 5 weeks and reduced fibro-cartilaginous metaplasia.⁸⁹

Inhibition of the IL-1 signaling pathway is also used to treat autoimmune diseases and has served as another therapeutic candidate for rotator cuff disease. In the aforementioned athlete study, the investigators also applied anakinra, a recombinant form of interleukin-1 receptor antagonist (IL-1ra), to treat Achilles tendinopathy.⁸⁷ However, it was not as effective as the TNF α inhibitor. Suppressing IL-1 did not significantly reduce pain or blood flow and increased tendon thickness after 12 weeks of treatment.⁸⁷ Recent animal studies have shown more promise for inhibiting IL-1. In a rabbit model of stress-shielding induced patellar tendinopathy, treatment with IL-1ra prevented mechanical deterioration.⁹⁰ Similarly, IL-1ra prevented collagen disruption and maintained matrix metalloproteinase-1 and -3 expression in stress-shielded rat Achilles tendons.⁹¹ Lastly, in carrageenan-induced rat patellar tendinopathy, IL-1ra maintained the tissue geometry and collagen activity relative to controls and reduced inflammatory cell infiltrate.⁹² Seemingly, no work focusing specifically on the rotator cuff has been attempted using this treatment axis. Although these results are encouraging, more work is needed to realize the therapeutic potential of this approach.

An alternative approach is to suppress extracellular matrix-degrading enzymes downstream of the inflammatory response. Along these lines, modulation of matrix metalloproteinases (MMPs) has been used in various musculoskeletal degenerative diseases as a treatment approach.⁹³ Doxycycline, an antibiotic that inhibits MMPs, was found to improve healing in rats following rotator cuff repair. The animals exhibited an increase in tissue strength, and this was associated with decreased levels of MMP-13 over a two week time period. However, using the same approach for Achilles tendons in rats, one group reported positive effects⁹⁴ while another group reported negative effects with treatment.⁹⁵ Another non-

specific inhibitor of MMP activity, recombinant α -2-macroglobulin, appeared to improve regeneration of the tendon-to-bone interface following acute rotator cuff repair based on histologic outcomes.⁹⁶ The mechanism of inhibition using these approaches remains unclear, and the results have been limited to repair of acute injuries rather than the more clinically relevant chronic injuries. One limitation of focusing solely on a specific signaling pathway or cytokine as an axis of treatment ignores the spatial and temporal heterogeneity of the immune and stromal cell responses, and the cross-talk between them.

5 Conclusion

The inflammatory cascade during rotator cuff degeneration and after surgical repair is a dynamic process involving a complex set of cells and signaling pathways. Therefore, success of inflammation-focused treatment strategies hinges on understanding the temporal nuances of the immune-mediated program. Thorough phenotyping of tissue-resident and infiltrating cell populations in clinical samples can guide more mechanistic approaches, leveraging lineage-specific deletion of inflammatory signals in order to understand the mechanisms of rotator cuff disease. Furthermore, understanding how these factors change in response to an individual's environment, lifestyle, and genetics will advance patient care in the growing era of precision medicine.

Acknowledgments

Source of Funding

This work was supported in part by the National Institutes of Health (R56 AR057836, F31 AR066452).

References

1. Jordan KP, Jöud A, Bergknut C, et al. International comparisons of the consultation prevalence of musculoskeletal conditions using population-based healthcare data from England and Sweden. *Annals of the Rheumatic Diseases*. 2014; 73(1):212–218. [PubMed: 23345602]
2. Riley G. Tendinopathy--from basic science to treatment. *Nature clinical practice Rheumatology*. 2008; 4(2):82–89.
3. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg*. 1999; 8(4):296–299. [PubMed: 10471998]
4. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. *J Shoulder Elbow Surg*. 2001; 10(3):199–203. [PubMed: 11408898]
5. Lehman C, Cuomo F, Kummer FJ, Zuckerman JD. The incidence of full thickness rotator cuff tears in a large cadaveric population. *Bull Hosp Jt Dis*. 1995; 54(1):30–31. [PubMed: 8541777]
6. Mather RC 3rd, Koenig L, Acevedo D, et al. The societal and economic value of rotator cuff repair. *J Bone Joint Surg Am*. 2013; 95(22):1993–2000. [PubMed: 24257656]
7. Vitale MA, Vitale MG, Zivin JG, Braman JP, Bigliani LU, Flatow EL. Rotator cuff repair: an analysis of utility scores and cost-effectiveness. *J Shoulder Elbow Surg*. 2007; 16(2):181–187. [PubMed: 17399623]
8. Jain NB, Higgins LD, Losina E, Collins J, Blazar PE, Katz JN. Epidemiology of musculoskeletal upper extremity ambulatory surgery in the United States. *BMC Musculoskelet Disord*. 2014; 15:4. [PubMed: 24397703]
9. Harryman DT 2nd, Mack LA, Wang KY, Jackins SE, Richardson ML, Matsen FA 3rd. Repairs of the rotator cuff. Correlation of functional results with integrity of the cuff. *Journal of Bone & Joint Surgery*. 1991; 73(7):982–989.

10. Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. *J Bone Joint Surg Am*. 2004; 86-A(2):219–224. [PubMed: 14960664]
11. Clement ND, Nie YX, McBirnie JM. Management of degenerative rotator cuff tears: a review and treatment strategy. *Sports Med Arthrosc Rehabil Ther Technol*. 2012; 4(1):48. [PubMed: 23241147]
12. Rhee YG, Cho NS, Yoo JH. Clinical outcome and repair integrity after rotator cuff repair in patients older than 70 years versus patients younger than 70 years. *Arthroscopy*. 2014; 30(5):546–554. [PubMed: 24630958]
13. Mall NA, Kim HM, Keener JD, et al. Symptomatic progression of asymptomatic rotator cuff tears: a prospective study of clinical and sonographic variables. *J Bone Joint Surg Am*. 2010; 92(16):2623–2633. [PubMed: 21084574]
14. Khan KM, Cook JL, Kannus P, Maffulli N, Bonar SF. Time to abandon the “tendinitis” myth. *Bmj*. 2002; 324(7338):626–627. [PubMed: 11895810]
15. Puddu G, Ippolito E, Postacchini F. A classification of Achilles tendon disease. *Am J Sports Med*. 1976; 4(4):145–150. [PubMed: 984291]
16. Khan KM, Cook JL, Bonar F, Harcourt P, Åstrom M. Histopathology of Common Tendinopathies. *Sports Medicine*. 1999; 27(6):393–408. [PubMed: 10418074]
17. Hashimoto T, Nobuhara K, Hamada T. Pathologic evidence of degeneration as a primary cause of rotator cuff tear. *Clin Orthop Relat Res*. 2003; (415):111–120.
18. Rees JD, Stride M, Scott A. Tendons - time to revisit inflammation. *Br J Sports Med*. 2013; 48(21):1553–1557. [PubMed: 23476034]
19. Schubert T, Weidler C, Lerch K, Hofstadter F, Straub R. Achilles tendinosis is associated with sprouting of substance P positive nerve fibres. *Annals of the Rheumatic Diseases*. 2005; 64(7):1083–1086. [PubMed: 15958764]
20. Scott A, Cook JL, Hart DA, Walker DC, Duronio V, Khan KM. Tenocyte responses to mechanical loading in vivo: A role for local insulin-like growth factor 1 signaling in early tendinosis in rats. *Arthritis & Rheumatism*. 2007; 56(3):871–881. [PubMed: 17328060]
21. Dean BJF, Gettings P, Dakin SG, Carr AJ. Are inflammatory cells increased in painful human tendinopathy? A systematic review. *British Journal of Sports Medicine*. 2015
22. Thomopoulos S, Parks WC, Rifkin DB, Derwin KA. Mechanisms of tendon injury and repair. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 2015; 33(6):832–839. [PubMed: 25641114]
23. Nho SJ, Yadav H, Shindle MK, MacGillivray JD. Rotator Cuff Degeneration: Etiology and Pathogenesis. *The American Journal of Sports Medicine*. 2008; 36(5):987–993. [PubMed: 18413681]
24. Ensor KL, Kwon YW, DiBeneditto MR, Zuckerman JD, Rokito AS. The rising incidence of rotator cuff repairs. *Journal of Shoulder and Elbow Surgery*. 2013; 22(12):1628–1632. [PubMed: 23466172]
25. Kluger R, Burgstaller J, Vogl C, Brem G, Skultety M, Mueller S. Candidate Gene Approach Identifies Six SNPs in Tenascin-C (TNC) Associated With Degenerative Rotator Cuff Tears. *Journal of Orthopaedic Research*. 2016 n/a-n/a.
26. UdaloVA IA, Ruhmann M, Thomson SJP, Midwood KS. Expression and Immune Function of Tenascin-C. 2011; 31(2):115–145.
27. Tashjian RZ, Granger EK, Farnham JM, Cannon-Albright LA, Teerlink CC. Genome-wide association study for rotator cuff tears identifies two significant single-nucleotide polymorphisms. *Journal of Shoulder and Elbow Surgery*. 2016; 25(2):174–179. [PubMed: 26350878]
28. Tashjian RZ, Granger EK, Zhang Y, Teerlink CC, Cannon-Albright LA. Identification of a genetic variant associated with rotator cuff repair healing. *Journal of Shoulder and Elbow Surgery*. 2016; 25(6):865–872. [PubMed: 27066960]
29. Teerlink CC, Cannon-Albright LA, Tashjian RZ. Significant association of full-thickness rotator cuff tears and estrogen-related receptor- β (ESRRB). *Journal of Shoulder and Elbow Surgery*. 2015; 24(2):e31–e35. [PubMed: 25219474]

30. Yuan J, Murrell GAC, Wei A-Q, Wang M-X. Apoptosis in rotator cuff tendonopathy. *Journal of Orthopaedic Research*. 2002; 20(6):1372–1379. [PubMed: 12472255]
31. Fabi J, Szemraj J, Strek M, Fabi A, Dutkiewicz Z, Zwierzchowski TJ. Is resection of the tendon edge necessary to enhance the healing process? An evaluation of the homeostasis of apoptotic and inflammatory processes in the distal 1 cm of a torn supraspinatus tendon: part I. *Journal of Shoulder and Elbow Surgery*. 2014; 23(12):1772–1778. [PubMed: 24927882]
32. Motta, GdR, Amaral, MV., Rezende, E., et al. Evidence of genetic variations associated with rotator cuff disease. *Journal of Shoulder and Elbow Surgery*. 2014; 23(2):227–235. [PubMed: 24129055]
33. Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S. Nicotine Delays Tendon-to-Bone Healing in a Rat Shoulder Model. *The Journal of Bone & Joint Surgery*. 2006; 88(9):2027–2034. [PubMed: 16951120]
34. Wani Z, Abdulla M, Habeebullah A, Kalogriantis S. Rotator cuff tears: Review of epidemiology, clinical assessment and operative treatment. *Trauma*. 2016; 18(3):190–204.
35. McMaster WC, Troup J. A survey of interfering shoulder pain in United States competitive swimmers. *The American Journal of Sports Medicine*. 1993; 21(1):67–70. [PubMed: 8427371]
36. Mall NA, Lee AS, Chahal J, et al. An Evidenced-Based Examination of the Epidemiology and Outcomes of Traumatic Rotator Cuff Tears. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. 2013; 29(2):366–376. [PubMed: 23290186]
37. Franceschi C, Campisi J. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2014; 69(Suppl 1):S4–S9.
38. Bishop J, Klepps S, Lo IK, Bird J, Gladstone JN, Flatow EL. Cuff integrity after arthroscopic versus open rotator cuff repair: a prospective study. *Journal of Shoulder and Elbow Surgery*. 2006; 15(3):290–299. [PubMed: 16679227]
39. Galatz LM, Griggs S, Cameron BD, Iannotti JP. Prospective longitudinal analysis of postoperative shoulder function: a ten-year follow-up study of full-thickness rotator cuff tears. *J Bone Joint Surg Am*. 2001; 83-A(7):1052–1056. [PubMed: 11451975]
40. Rompe JD, Nafe B, Furia JP, Maffulli N. Eccentric loading, shock-wave treatment, or a wait-and-see policy for tendinopathy of the main body of tendo Achillis: a randomized controlled trial. *Am J Sports Med*. 2007; 35(3):374–383. [PubMed: 17244902]
41. Seil R, Wilmes P, Nuhrenborger C. Extracorporeal shock wave therapy for tendinopathies. Expert review of medical devices. 2006; 3(4):463–470. [PubMed: 16866643]
42. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2010; 303(2):144–149. [PubMed: 20068208]
43. Millar NL, Murrell GAC, McInnes IB. Alarmins in tendinopathy: unravelling new mechanisms in a common disease. *Rheumatology*. 2013; 52(5):769–779. [PubMed: 23362223]
44. Millar NL, Hueber AJ, Reilly JH, et al. Inflammation Is Present in Early Human Tendinopathy. *The American Journal of Sports Medicine*. 2010; 38(10):2085–2091. [PubMed: 20595553]
45. Pingel J, Wienecke J, Kongsgaard M, et al. Increased mast cell numbers in a calcaneal tendon overuse model. *Scandinavian Journal of Medicine & Science in Sports*. 2013; 23(6):e353–e360. [PubMed: 23889295]
46. Scott A, Lian Ø, Bahr R, Hart DA, Duronio V, Khan KM. Increased mast cell numbers in human patellar tendinosis: correlation with symptom duration and vascular hyperplasia. *British Journal of Sports Medicine*. 2008; 42(9):753–757. [PubMed: 18308880]
47. Behzad H, Sharma A, Mousavizadeh R, Lu A, Scott A. Mast cells exert pro-inflammatory effects of relevance to the pathophysiology of tendinopathy. *Arthritis Research & Therapy*. 2013; 15(6):R184–R184. [PubMed: 24517261]
48. Dakin SG, Martinez FO, Yapp C, et al. Inflammation activation and resolution in human tendon disease. *Science Translational Medicine*. 2015; 7(311)
49. Kawamura S, Ying L, Kim H-J, Dynybil C, Rodeo SA. Macrophages accumulate in the early phase of tendon–bone healing. *Journal of Orthopaedic Research*. 2005; 23(6):1425–1432. [PubMed: 16111854]

50. Manning CN, Havlioglu N, Knutsen E, et al. The early inflammatory response after flexor tendon healing: A gene expression and histological analysis. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 2014; 32(5):645–652. [PubMed: 24464937]
51. Sugg KB, Lubardic J, Gumucio JP, Mendias CL. Changes in Macrophage Phenotype and Induction of Epithelial-to-Mesenchymal Transition Genes Following Acute Achilles Tenotomy and Repair. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 2014; 32(7):944–951. [PubMed: 24700411]
52. Kragstnaes MS, Fredberg U, Stribolt K, Kjaer SG, Bendix K, Ellingsen T. Stereological Quantification of Immune-Competent Cells in Baseline Biopsy Specimens From Achilles Tendons: Results From Patients With Chronic Tendinopathy Followed for More Than 4 Years. *The American Journal of Sports Medicine*. 2014; 42(10):2435–2445. [PubMed: 25081311]
53. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthritis by acting on ROR- γ CD3+CD4-CD8-entheseal resident T cells. *Nat Med*. 2012; 18(7):1069–1076. [PubMed: 22772566]
54. Burzyn D, Kuswanto W, Kolodin D, et al. A Special Population of Regulatory T Cells Potentiates Muscle Repair. *Cell*. 2013; 155(6):1282–1295. [PubMed: 24315098]
55. Janeway CA, Medzhitov R. Innate Immune Recognition. *Annual Review of Immunology*. 2002; 20(1):197–216.
56. Hayden MS, Ghosh S. Signaling to NF- κ B. *Genes & development*. 2004; 18(18):2195–2224. [PubMed: 15371334]
57. Ben-Neriah Y, Karin M. Inflammation meets cancer, with NF- κ B as the matchmaker. *Nature immunology*. 2011; 12(8):715–723. [PubMed: 21772280]
58. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nature Reviews Immunology*. 2011; 11(2):98–107.
59. Brasier AR. The NF- κ B regulatory network. *Cardiovascular Toxicology*. 2006; 6(2):111–130. [PubMed: 17303919]
60. Voloshin I, Gelinas J, Maloney MD, O'Keefe RJ, Bigliani LU, Blaine TA. Proinflammatory Cytokines and Metalloproteases Are Expressed in the Subacromial Bursa in Patients With Rotator Cuff Disease. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. 2005; 21(9):1076.e1071–1076.e1079. [PubMed: 16171632]
61. John T, Lodka D, Kohl B, et al. Effect of pro-inflammatory and immunoregulatory cytokines on human tenocytes. *Journal of Orthopaedic Research*. 2010; 28(8):1071–1077. [PubMed: 20127972]
62. Tsuzaki M, Guyton G, Garrett W, et al. IL-1 β induces COX2, MMP-1, -3 and -13, ADAMTS-4, IL-1 β and IL-6 in human tendon cells. *Journal of Orthopaedic Research*. 2003; 21(2):256–264. [PubMed: 12568957]
63. Millar NL, Gilchrist DS, Akbar M, et al. MicroRNA29a regulates IL-33-mediated tissue remodelling in tendon disease. *Nature Communications*. 2015; 6:6774.
64. Hayden MS, Ghosh S. NF- κ B, the first quarter-century: remarkable progress and outstanding questions. *Genes & development*. 2012; 26(3):203–234. [PubMed: 22302935]
65. Sun S-C. Non-canonical NF- κ B signaling pathway. *Cell research*. 2011; 21(1):71–85. [PubMed: 21173796]
66. Petersen A, Pedersen B. The anti-inflammatory effect of exercise. *Journal of Applied Physiology*. 2005; 98(4):1154–1162. [PubMed: 15772055]
67. Brandt C, Pedersen BK. The Role of Exercise-Induced Myokines in Muscle Homeostasis and the Defense against Chronic Diseases. *Journal of Biomedicine and Biotechnology*. 2010:2010.
68. Abrams GD, Luria A, Carr RA, Rhodes C, Robinson WH, Sokolove J. Association of synovial inflammation and inflammatory mediators with glenohumeral rotator cuff pathology. *Journal of Shoulder and Elbow Surgery*. 2016; 25(9):1076.e1071–1076.e1079. [PubMed: 26810016]
69. Ko J-Y, Wang F-S, Huang H-Y, Wang C-J, Tseng S-L, Hsu C. Increased IL-1 β Expression and Myofibroblast Recruitment in Subacromial Bursa Is Associated with Rotator Cuff Lesions with Shoulder Stiffness. *Journal of Orthopaedic Research*. 2008; 26(8):1090–1097. [PubMed: 18327798]

70. Nakama K, Gotoh M, Yamada T, et al. Interleukin-6-induced Activation of Signal Transducer and Activator of Transcription-3 in Ruptured Rotator Cuff Tendon. *The Journal of International Medical Research*. 2006; 34(6):624–631. [PubMed: 17294994]
71. Shindle MK, Chen CCT, Robertson C, et al. Full-thickness supraspinatus tears are associated with more synovial inflammation and tissue degeneration than partial thickness tears. *Journal of Shoulder and Elbow Surgery*. 2011; 20(6):917–927. [PubMed: 21612944]
72. Ling Y, Peng C, Liu C, Zhang N, Yue S. Gene polymorphism of IL-6 and MMP-3 decreases passive range of motion after rotator cuff repair. *International Journal of Clinical and Experimental Pathology*. 2015; 8(5):5709–5714. [PubMed: 26191285]
73. Millar NL, Akbar M, Campbell AL, et al. IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. *Scientific Reports*. 2016;6. [PubMed: 28442741]
74. Magra M, Maffulli N. Nonsteroidal antiinflammatory drugs in tendinopathy: friend or foe. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine*. 2006; 16(1):1–3. [PubMed: 16377967]
75. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet*. 2010; 376(9754):1751–1767. [PubMed: 20970844]
76. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev*. 2003; 1(1)
77. DaCruz D, Geeson M, Allen M, Phair I. Achilles paratendonitis: an evaluation of steroid injection. *British Journal of Sports Medicine*. 1988; 22(2):64–65. [PubMed: 3167505]
78. Paoloni JA, Orchard JW. 1. The use of therapeutic medications for soft-tissue injuries in sports medicine. *Medical Journal of Australia*. 2005; 183(7):384. [PubMed: 16201960]
79. Yanez R, Lamana ML, Garcia-Castro J, Colmenero I, Ramirez M, Bueren JA. Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of the graft-versus-host disease. *Stem Cells*. 2006; 24(11):2582–2591. [PubMed: 16873762]
80. Gao F, Chiu SM, Motan DA, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. *Cell Death Dis*. 2016; 7:e2062. [PubMed: 26794657]
81. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem*. 2006; 98(5): 1076–1084. [PubMed: 16619257]
82. Mathiasen AB, Haack-Sorensen M, Kastrup J. Mesenchymal stromal cells for cardiovascular repair: current status and future challenges. *Future Cardiol*. 2009; 5(6):605–617. [PubMed: 19886787]
83. Manning CN, Martel C, Sakiyama-Elbert SE, et al. Adipose-derived mesenchymal stromal cells modulate tendon fibroblast responses to macrophage-induced inflammation in vitro. *Stem Cell Res Ther*. 2015; 6(1):74. [PubMed: 25889287]
84. Shen H, Kormpakis I, Havlioglu N, et al. The effect of mesenchymal stromal cell sheets on the inflammatory stage of flexor tendon healing. *Stem Cell Research & Therapy*. 2016; 7(1):144. [PubMed: 27677963]
85. Aktas E, Chamberlain CS, Saether EE, et al. Immune modulation with primed mesenchymal stem cells delivered via biodegradable scaffold to repair an Achilles tendon segmental defect. *Journal of Orthopaedic Research*. 2016
86. Feldmann M, Maini RN. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nat Med*. 2003; 9(10):1245–1250. [PubMed: 14520364]
87. Fredberg U, Ostgaard R. Effect of ultrasound-guided, peritendinous injections of adalimumab and anakinra in chronic Achilles tendinopathy: a pilot study. *Scandinavian Journal of Medicine & Science in Sports*. 2009; 19(3):338–344. [PubMed: 18492052]
88. Gulotta LV, Kovacevic D, Cordasco F, Rodeo SA. Evaluation of Tumor Necrosis Factor α Blockade on Early Tendon-to-Bone Healing in a Rat Rotator Cuff Repair Model. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. 2011; 27(10):1351–1357. [PubMed: 21705172]
89. Wang Y, Li Q, Wei X, et al. Targeted knockout of TNF- α by injection of lentivirus-mediated siRNA into the subacromial bursa for the treatment of subacromial bursitis in rats. *Molecular Medicine Reports*. 2015; 12(3):4389–4395. [PubMed: 26130073]

90. Miyatake S, Tohyama H, Kondo E, Katsura T, Onodera S, Yasuda K. Local administration of interleukin-1 receptor antagonist inhibits deterioration of mechanical properties of the stress-shielded patellar tendon. *Journal of Biomechanics*. 2008; 41(4):884–889. [PubMed: 18062978]
91. Ma Y, Yan X, Zhao H, Wang W. Effects of Interleukin-1 Receptor Antagonist on Collagen and Matrix Metalloproteinases in Stress-shielded Achilles Tendons of Rats. *Orthopedics*. 2012; 35(8):e1238–e1244. [PubMed: 22868612]
92. Berkoff DJ, Kallianos SA, Eskildsen SM, Weinhold PS. Use of an IL1-receptor antagonist to prevent the progression of tendinopathy in a rat model. *Journal of Orthopaedic Research*. 2016; 34(4):616–622. [PubMed: 26418607]
93. Bedi A, Fox AJS, Kovacevic D, Deng X-h, Warren RF, Rodeo SA. Doxycycline-Mediated Inhibition of Matrix Metalloproteinases Improves Healing After Rotator Cuff Repair. *The American Journal of Sports Medicine*. 2010; 38(2):308–317. [PubMed: 19826139]
94. Kessler MW, Barr J, Greenwald R, et al. Enhancement of Achilles tendon repair mediated by matrix metalloproteinase inhibition via systemic administration of doxycycline. *Journal of Orthopaedic Research*. 2014; 32(4):500–506. [PubMed: 24346815]
95. Pasternak B, Fellenius M, Aspenberg P. Doxycycline impairs tendon repair in rats. *Acta Orthopaedica Belgica*. 2006; 72(6):756–760. [PubMed: 17260615]
96. Bedi A, Kovacevic D, Hettrich C, et al. The effect of matrix metalloproteinase inhibition on tendon-to-bone healing in a rotator cuff repair model. *Journal of Shoulder and Elbow Surgery*. 2010; 19(3):384–391. [PubMed: 19800260]

Figure 1.

An inflammatory stimulus activates the NF-κB pathway, leading to recruitment of the IKK complex, phosphorylation of IκB, and translocation of NF-κB subunits – p50 and p65 – into the nucleus.

Figure 2.

In early rotator cuff tendinopathy interleukin-33 (IL-33) activates NF-κB signaling via ST2/IL-1RA which suppresses micro-RNA-29a (miR-29a) expression resulting in production of type III collagen and soluble ST2 which competitively binds to circulating IL-33, potentially acting as a protective feedback mechanism. (Figure reprinted from Millar et al⁶³ and is distributed openly under Creative Commons Attribution 4.0 International Public License)