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Cell and Biologic-Based Treatment of Flexor Tendon Injuries

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Abstract

The two primary factors leading to poor clinical results after intrasynovial tendon repair are adhesion formation within the digital sheath and repair-site elongation and rupture. As the outcomes following modern tendon multi-strand repair and controlled rehabilitation techniques are often unsatisfactory, alternative approaches, such as the application of growth factors and mesenchymal stem cells (MSCs), have become increasingly attractive treatment options. Successful biological therapies require carefully controlled spatiotemporal delivery of cells, growth factors, and biocompatible scaffold matrices in order to simultaneously (1) promote matrix synthesis at the tendon repair site leading to increased biomechanical strength and stiffness and (2) suppress matrix synthesis along the tendon surface and synovial sheath preventing adhesion formation. This review summarizes recent cell and biologic-based experimental treatments for flexor tendon injury, with an emphasis on large animal translational studies.

Keywords

flexor tendon repair; cell; growth factor; tissue engineering

Introduction

Among the most common and challenging hand injuries, intrasynovial flexor tendon transections have motivated over five decades of research designed to improve primary operative and rehabilitation techniques.[1–10] Finger lacerations are the most common upper extremity injury encountered in the emergency room, with an incidence of 221 per 100,000 person-years or 1 in 452 people per year,[11] mostly caused by glass or knives.[12] Even small

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lacerations < 2 cm presenting to the emergency room often cause deep tendon injuries (~60% of cases).[12] Major repair technique advances by Kessler,[9] then Pennington,[10] and then Winters and Gelberman[4] have changed Zone II intrasynovial flexor digitorum profundus (FDP) tendon treatment from an inoperable “no man’s land”[8] to a common surgical procedure. Following several decades of repair[3,4,9,10,13–22] and rehabilitation[23–25] improvements, we have reached a plateau in Zone II flexor tendon repair outcomes with current methods. Clincial outcomes remain highly variable, necessitating alternative approaches.[3,26,27]

The two primary factors leading to poor results are adhesion formation within the digital sheath and repair-site elongation and rupture. Adhesions severe enough to limit range of motion occur in up to 40% of flexor tendon repairs.[28] While adhesions can be decreased with passive motion rehabilitation,[6,29] they still occur frequently, even with closely controlled techniques.[25,30] Experimental studies report repair-site elongation and gap formation preventing satisfactory healing in up to 48% of canine FDP tendons undergoing state-of-the-art operative repairs. In a clinically relevant, controlled canine repair model, repair site gap formation during the first six postoperative weeks did not correlate with formation of intrasynovial adhesions or loss of digital motion.[31] In clinical settings, surgeons pursue a balance between repair and rehabilitation approaches promoting tendon strength and digital excursion.[32] Flexor tendon repair complications are attributed to a slow accrual of repair-site strength and stiffness and to an increase in gliding resistance within the digital sheath during the first few weeks following tendon suture.[31–39] The healing of paucicellular, hypovascular intrasynovial tendon appears to be limited by the relatively low levels of collagen synthesis and remodeling during the early stages of healing.[40,41]

Recent approaches in the canine model seek to increase time-zero strength, enabling better coaptation of tendon stumps, by increasing interaction between the suture and tendon tissue. Adhesive-coatings on sutures increase the interaction and distribute load transfer over a longer length of suture. Mechanically optimized adhesive coatings have potential to improve repair strength by several fold.[42] Experimental crosslinking agents coating sutures, including 1-ethyl-3-(3-dimethylaminopropyl) carbo-diimide hydrochloride (EDC) and cyanoacrylate, also increase suture-tendon interactions and crosslink the tendon tissue immediately adjacent to the suture.[43,44] These mechanical approaches offer an opportunity to improve repair strength, but do not inherently decrease adhesions or enhance the healing process.

Therefore, we look to biological approaches, such as the application of growth factors and mesenchymal stem cells (MSCs), for the next generation of approaches to improve tendon and ligament repair.[37,39,45–48] The goal of recent studies has been to: (1) promote matrix synthesis at the tendon repair site leading to increased biomechanical strength and stiffness and (2) suppress matrix synthesis along the tendon surface and synovial sheath preventing adhesion formation.[31,33,35,36] Biological approaches to augment repair have the potential to advance both of these goals. This review summarizes recent cell and biologic-based experimental treatments for flexor tendon injury, with an emphasis on large animal translational studies.

Flexor tendon natural healing response

Similar to healing paradigms in other tissues, intrasynovial flexor tendons follow three successive, overlapping stages of healing: acute inflammation (days 0–7 post injury), proliferation (days 3–14), and remodeling (days 10+).[32,35,49] The commonly injured region of the flexor tendon is intrasynovial, defined as Zone II by Kleinert and Verdan.[50] The tendon lies within a synovium-lined fibro-osseous sheath that extends from the distal aspect of the palm to the distal aspect of the A4 pulley. Intrasynovial flexor tendons are paucicellular[51] and hypovascular,[52,53] with limited blood supply delivered by long and short vinculae originating from the digital arteries and supplying the tendon segmentally.[41] In addition, the tendon receives nutrients and lubrication from the synovial fluid produced by the tendon sheath.[3,32] As healing intrasynovial tendon has few intrinsic cells and has limited vascularization, there is little intrinsic healing from tendon fibroblasts until delayed time points. At early time points, cell proliferation and matrix synthesis are dominated by cells that migrate to the injury site (Figure 1).[32,33,35] As a result, zone II flexor tendon injuries have substantially poorer healing outcomes following operative repair than do tendon injuries to extrasynovial flexor tendons.[3,8,15]

Acute inflammation in the first several days after tendon injury attracts circulating inflammatory cells to the injured tendon.[35,54,55] This inflammatory infiltration is dominated by polymorphonuclear cells during the first day, especially in the fibrin clot that forms at the repair site, followed by a transition to monocytes and macrophages by the third day.[49] Activated macrophages exhibit two major phenotypes: M1 and M2. The M1 macrophages, prevalent during acute inflammation,[56,57] promote extracellular matrix deposition (scar) and inflammation,[55,58] bridging the transected tendon ends but also leading to adhesions. Following acute inflammation, the proliferative phase of healing ensues. In addition to M1 macrophages,[55] there is an increase in the number of fibroblast-like cells synthesizing extracellular matrix at the proliferative phase.[49] Most of the fibroblast-like cells are likely derived from epitenon cells[49] and resident tendon fibroblasts.[59] Morphologic studies of repaired canine tendons at 7 days after tendon transection and repair show that regions with well coapted collagen fibers had a stronger endotendon response compared to those where the gap only had a few fibrinous strands serving as a scaffold for epitenon cell migration.[35] New blood vessels emerge at the surface of canine tendons 9 days following suture.[49] By 14 days, repaired canine tendon stumps show spontaneous neo-vascularization.[35] The final phase, remodeling, lasts many weeks to months, during which M1 macrophages subside and M2 macrophages appear. M2 macrophages suppress inflammation, promote matrix deposition, and facilitate tissue remodeling.[55,56,60] Reorganization of the granulation tissue at the repair site leads to improved tendon strength.

Animal models

The most commonly used animal models for studying flexor tendon repair and tendon rehabilitation[18,61] are the canine, mouse, horse,[62–64] rabbit,[65] and chicken.[66–69] The canine model for Zone II FDP tendon laceration and repair has been extensively used since 1962.[1,70] Canine flexor tendons are similar to human flexor tendons in both anatomy and function,[61,71] as well as in response to tendon injury, repair, and rehabilitation.[3,24] The

canine FDP tendon size is approximately one half the size of a human FDP tendon. Approximate size match enables surgeons both to perform surgical repairs identical to those performed clinically and to achieve similar time-zero mechanical strength to that seen in humans.[72,73] The canine Zone II FDP tendon repair surgical model allows direct testing of surgical modifications and biological approaches before performing clinical trials in humans.[24,25,43,48,74–76]

Several groups are currently investigating murine models for flexor tendon repair.[46,54,59,77–80] These models offer high genetic versatility and low cost, enabling *in vivo* studies of the healing response, biology of adhesion formation,[54,59,79] and effects of biological interventions.[46] However, the models and hypotheses tested need to be considered carefully due to anatomic and technical challenges that limit clinical relevance. Specifically, the small size of the tendon requires a simpler surgical technique using 8-0 caliber or smaller suture. Furthermore, to prevent repair rupture, all murine models to date require either partial laceration, which modifies the healing process, or proximal unloading. Wong and colleagues perform a partial laceration in Zone II in the murine digit.[54] Other groups opted to fully or partially lacerate the extrasynovial Zone III tendon and perform proximal transection to protect the repair,[59,78,80] leading to large scar formation between tendon ends.[79] Finally, rehabilitation postoperatively cannot be controlled due to the small size of the animal. Despite these limitations, the availability of transgenic mouse models opens up possibilities for mechanistic basic science experiments, including cell lineage tracing, gene deletion, and cell ablation.

Biologic treatments

A number of recent reports have indicated that biological approaches, such as the application of growth factors and mesenchymal stem cells (MSCs), have the potential to improve tendon and ligament repair.[37,39,45,47,48,81] By introducing cells into the paucicellular intrasynovial flexor tendon milieu and inducing a developmental paradigm between the repaired tendon ends, biological approaches attempt to accelerate healing and regenerate normal tissue. Multipotent MSCs from a variety of adult tissues have an excellent capacity to differentiate into the relevant tissue-specific phenotype and to provide potent immunosuppressive and anti-inflammatory effects.[82,83] However, MSC delivery has been ineffective in improving the strength and stiffness following the repair of intrasynovial tendons *in vivo*.[48] Similarly, likely due to the paucity of tendon fibroblasts in the region of repair, growth factor application in isolation has been unsuccessful in stimulating enhanced tensile properties following tendon suture, although some improvements have been achieved in digital range of motion.[37,39,84] This has led to more recent focus on combinations of growth factors, cells, and specialized delivery approaches to improve flexor tendon repair.

Delivery of biofactors

Several biofactor delivery approaches have been investigated to improve healing after flexor tendon suture. The simplest delivery method, systemic drug delivery, has not been widely adopted clinically due to low bioavailability at the tendon and concern of side effects. Oral nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen) have been used, with

varying results, to limit adhesions experimentally and clinically.[85–88] Local bolus delivery of cells[89] or growth factors[90,91] by simple injection has yielded limited results, since few cells graft to host tissue without a supporting scaffold and the delivered growth factor is rapidly cleared from the repair site[92]. Recent studies have shown that biological interventions require controlled spatiotemporal delivery to the repair site to improve tendon healing.[39,93–96]

In order to effectively deliver cells and growth factors to the repair site, two major tissue engineering paradigms have been investigated using a variety of scaffold biomaterials. Approaches typically either interpose cell- and/or growth factor-seeded scaffolds between the repaired tendon stumps[97–99] or deliver scaffolds on the surface of the repaired tendon.[48,100] Interposition delivers factors directly to the injury site where they are needed for repair, but scaffolds may form a barrier between the tendon stumps that is detrimental for healing.[101] Our group has explored scaffold delivery in a longitudinal slit made within the canine flexor tendon, enabling factor delivery to the injured site while retaining tendon stump coaptation. However, the slit was found to have injurious mechanical effects that must be overcome before improvement in healing can be achieved.[81,84,102] Alternatively, scaffolds placed on the surface of tendon adjacent to the repair site deliver factors to the general vicinity but rely on biofactor diffusion or migration to impact the repair itself. Furthermore, scaffolds wrapped around the tendon may induce adhesions or cause excessive bulking that limits tendon gliding within the fibro-osseous sheath. To minimize adhesion formation, lubricating biomaterials such as lubricin and hyaluronic acid[46,48,103–107] and anti-mitotic drugs such as 5-fluorouracil[33,108] have been successfully utilized in animal models. While these materials improve tendon gliding, some studies have shown deleterious effects on repair strength.[48,103,109] Other materials including silicone, polyethylene, and cellophane have been used clinically as an artificial sheath to reduce adhesions, but have not gained widespread acceptance in the United States.[2,3,110,111]

Biomaterial selection is crucial to the function of tissue engineered scaffolds. Fibrin delivery systems with heparin-bound growth factors have enabled sustained drug delivery during healing,[39,76,81,93,102,112,113] as have some microsphere-based approaches.[114–116] The scaffold backbone is also essential for promoting stem cell integration and differentiation. Scaffold mechanical properties and fiber diameter influence cell activity and differentiation.[117] Synthetic polymer approaches using electrospun polylactic co-glycolic acid (PLGA) nanofiber scaffolds have provided a strong, fibrous backbone and delivered viable cells and growth factors to the repair site (Figure 2). However, these scaffolds release acidic byproducts that increase the proinflammatory cytokine IL-1β and negatively impact healing.[81,102] Naturally occurring polymers, including collagen- and fibrin/heparin-based delivery systems, have been explored for their enhanced biocompatibility. Future delivery approaches should be biocompatible, appropriate for cell seeding, able to provide sustained growth factor delivery, and have appropriate surgical handling characteristics for implantation into the relatively dense tendon tissue.

Growth factor treatments

The growth factors bone morphogenic protein (BMP) 12, BMP13, and BMP14, (a.k.a., GDF7, GDF6, and GDF5, respectively) which are expressed in developing tendons and ligaments, have been shown to have the greatest potential for improving tendon healing.[45,118–122] These BMPs act by inducing tenogenesis in stem cells *in vitro* via Smad 1/5/8 phosphorylation.[45,118,121,123] BMP12 effectively increased the expression of the tendon markers scleraxis and tenomodulin in canine adipose-derived mesenchymal stromal cells (ASCs) *in vitro* at both mRNA and protein levels.[45] Consistent with these results, BMP12 induced scleraxis promoter driven-GFP and tenomodulin expression in mouse ASCs. BMP12 administration concurrently reduced expression of the bone marker osteocalcin, but not the osteogenic transcription factor runx-2. There was a mild increase in the expression of the cartilage matrix gene aggrecan, though still to considerably lower levels than those detected in tendon fibroblasts. BMP14 had similar but less potent effects.[45] However, these factors alone, without concurrent cell delivery, have not been sufficient to improve repair strength. Hayashi *et al.* interposed collagen gels with BMP14 without cells between cut ends of canine FDP tendon under *in vitro* tissue culture conditions, but this did not significantly change ultimate healing strength or stiffness compared to repaired controls.[47] Similarly, adenoviral-mediated gene transfer of human BMP13 did not improve healing in a rat rotator cuff repair model.[124]

Several other growth factor approaches have attempted to promote cell proliferation and matrix synthesis in order to improve flexor tendon healing. Exogenous basic fibroblast growth factor (bFGF) was shown to accelerate wound closure and promote fibroblast proliferation and matrix synthesis *in vitro* in rat patellar tendon fibroblasts and in canine tendon fibroblasts.[76,125,126] In an *in vivo* chicken flexor tendon injury and repair model, adeno-associated virus-2 carrying bFGF was directly injected into injured tendons. The bFGF treated chicken flexor tendons had significantly higher ultimate strength at 2, 4, and 8 weeks, fewer ruptures, and similar adhesion scores.[69] These promising *in vitro* and chicken *in vivo* studies motivated testing the effects of sustained bFGF delivery to injured flexor tendons in the clinically relevant canine large animal model. Sustained delivery of biologically active bFGF was achieved by incorporating bFGF into a fibrin delivery system. The bFGF release profile was tuned by bFGF dosage and heparin concentration, where increasing concentrations of heparin significantly slowed release. At a 1:1000 growth factor to heparin ratio, 37% of the loaded bFGF was released within the first 2 days and 71% was released within the first 10 days by passive release *in vitro* (i.e., mediated by diffusion and degradation of the fibrin carrier). Active bFGF release (i.e., mediated by canine tendon fibroblast cells) also achieved a sustained delivery profile over at least 10 days. The released bFGF stimulated increased cell number, increased gene expression of the extracellular matrix lubricating proteins lubricin and hyaluronic acid synthase 2, increased expression of the degradation proteins matrix metalloproteinase 1 and 13, and decreased expression of collagen I and III.[76] However, at 21 days *in vivo* in the canine flexor tendon injury and repair model, sustained bFGF delivery not only accelerated the cell-proliferation phase of tendon healing, but also promoted neovascularization and inflammation in the earliest stages following the suturing of the tendon. Despite a substantial biologic response, the administration of basic fibroblast growth factor failed to produce improvements in either the

mechanical or functional properties of the repair. Rather, increased cellular activity resulted in peritendinous scar formation and diminished range of motion (Figure 3).[84]

Similarly, exogenous platelet derived growth factor-BB (PDGF-BB) was shown to stimulate canine flexor tendon fibroblast proliferation, decrease collagen I and III gene expression, and increase lubricin, hyaluronic acid synthase-2, and matrix metalloproteinase 1 and 13 gene expression *in vitro*.[76,93,126] Sustained delivery of PDGF-BB using a fibrin/heparin based delivery system in canine flexor tendon repairs *in vivo* consistently improved range of motion, collagen remodeling, and cell proliferation at 14, 21, and 42 days following suture. However, PDGF-BB delivery did not increase repair strength at any timepoint.[37,39,40,81]

Transforming growth factor β (TGFβ) has also produced mixed effects on flexor tendon healing: while TGFβ isoforms are important during flexor tendon healing to stimulate collagen production, they also lead to fibrosis and scar formation.[38,127–131] While some studies used TGFβ with the goal of improving strength,[118] many have attempted to inhibit TGFβ in order to reduce adhesions, albeit at the cost of reducing repair strength.[132–136] This decrease in repair strength precludes the use of TGFβ inhibitors as a standalone therapy. Successful TGFβ-modulating treatments would require controlled spatiotemporal activity to enhance collagen production in the healing tendon itself, but decrease scar and adhesion formation at the tendon surface.

A promising recent growth factor approach is based on connective tissue growth factor (CTGF), which has been shown to induce MSC differentiation into tendon fibroblasts and/or chondrocytes.[137–139] Similar to BMP12 and positively promoting BMP12 effects, *in vitro* CTGF effectively increased the expression of the tenocyte lineage markers scleraxis and tenomodulin, as well as the fibroblast proteins collagen I and tenascin-C.[138] During rat rotator cuff healing, CTGF is highly expressed in the tendon midsubstance and at the tendon-to-bone insertion for several weeks following injury.[140] In chicken flexor tendons, CTGF is relatively highly expressed in normal tendons and throughout healing.[141] CTGF and cell combination studies are described below.

Cell treatments

As noted above, early enthusiasm for cell therapy, based on patellar tendon[89,142] and Achilles tendon[143] results, has been largely unsuccessful in rotator cuff[144] and flexor tendon animal models. In two studies using a canine *in vitro* tissue culture model, interposition of a multilayered collagen patch seeded with bone marrow-derived MSCs into the repair site did not improve flexor tendon healing mechanics compared with control repairs without interposed patches.[47,145] MSC implantation *in vivo* in rabbits decreased adhesions but did not improve biomechanical properties 3 or 8 weeks after surgery.[146] Racehorses that received direct injection of bone marrow-derived MSCs during superficial digital flexor tendon repair had reduced re-injury rates compared with historical controls,[147–149] however, the equine superficial digital flexor tendon has substantially different functional, structural, and material properties from human FDP tendon.[63,150]

Cell-growth factor combination treatments

Though cells and growth factors in isolation have not markedly improved flexor tendon healing, combination therapies offer greater potential to improve outcomes. While interposition of bone marrow-derived MSCs only or BMP14 only did not improve repair mechanics in an *in vitro* canine flexor tendon tissue culture model, the combination of MSCs with BMP14 or platelet-rich plasma on collagen patches improved strength and stiffness.[47,145] This approach, combined with surface lubricin for *in vivo* canine flexor tendon repairs to decrease adhesions, unfortunately resulted in substantially worse repair strength 42 days after repair.[48] Similarly, application of adipose-derived MSCs in combination with BMP12 in an *in vivo* canine Zone II flexor tendon repair using PLGA and fibrin scaffolds led to increased total collagen compared to repairs with acellular scaffolds, but did not improve tensile properties at 28 days after surgery compared to the acellular group. The delivery method used in these studies was a critical component driving the outcomes: the PLGA-fibrin scaffolds had a deleterious effect that may have counteracted any beneficial effects from the MSCs and/or BMP12.[102] A previous study delivering the same PLGA-fibrin scaffolds containing MSCs and PDGF-BB demonstrated retained cell viability after 10 days, but also mild inflammatory reactions, possibly due to the PLGA scaffold (Figure 2).[81]

Connective tissue growth factor and cell combination approaches have not been thoroughly evaluated in flexor tendon *in vivo*, but CTGF-based approaches show promise in other tendon repair scenarios. Tendon-derived CD146+ stem cells cultured with CTGF promoted tenogenic differentiation *in vitro*.[151] Tendon-derived stem cell sheets stimulated with CTGF promoted improved anterior cruciate ligament graft healing and biomechanics *in vivo* in rats, including improved osteointegration.[152] Similarly, cell sheets with CTGF and ascorbic acid enhanced biomechanical and histology-based outcomes at 8 weeks in an *in vivo* rat patellar tendon repair model. Further studies introducing CTGF and/or BMP growth factors with cells and biocompatible matrices will be important for defining the next generation of therapies for flexor tendon repair.

Conclusions

Intrasynovial flexor tendons are notoriously challenging to repair, with highly variable clinical outcomes due to the competing requirements for repair strength to avoid rupture and minimal adhesion formation to maintain adequate range of motion. Advances in rehabilitation protocols have led to significant improvements in tendon healing and gliding outcomes, but post-operative complications remain. Biological approaches have potential to simultaneously tackle both of these problems. Successful biological therapies will require carefully controlled spatiotemporal delivery of cells, growth factors, and biocompatible scaffold matrices in order to simultaneously promote matrix synthesis at the tendon repair site to improve strength and suppress matrix synthesis along the tendon surface to prevent adhesion formation.

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References

1. Potenza AD. Tendon healing within the flexor digital sheath in the dog. J Bone Jt Surg Am. 1962; 44-A(1):49–64.
2. Kessler I, Nissim F. Primary repair without immobilization of flexor tendon division within the digital sheath. An experimental and clinical study. Acta Orthop Scand. 1969; 40:587–601. [PubMed: 4907784]
3. Boyer MI, Strickland JW, Engles DR, Sachar K, Leversedge FJ. Flexor Tendon Repair and Rehabilitation: state of the art in 2002. Instr Course Lect. 2003; 52:137–61. [PubMed: 12690845]
4. Winters SC, Gelberman RH, Woo SL, Chan SS, Grewal R, Seiler JG III. The Effects of Multiple-Strand Suture Methods on the Strength and Excursion of Repaired Intrasynovial Flexor Tendons : A Biomechanical Study in Dogs. J Hand Surg Am. 1998; 23(1):97–104. [PubMed: 9523962]
5. Woo SL-Y, Gelberman RH, Cobb NG, Amiel D, Lothringer K, Akeson WH. The importance of controlled passive mobilization on flexor tendon healing. Acta Orthop Scand. 1981; 52(6):615–622. [PubMed: 7331798]
6. Gelberman RH, Woo SL, Lothringer K, Akeson WH, Amiel D. Effects of early intermittent passive mobilization on healing canine flexor tendons. J Hand Surg Am. 1982; 7(2):170–175. [PubMed: 7069172]
7. Verdan CE. Primary repair of flexor tendons. J Bone Jt Surg. 1960; 42(4):647–657.
8. Bunnell, S. Surgery of the Hand. 3. Lippincott, J., editor. Philadelphia: JB Lippincott; 1956.
9. Kessler I. The “grasping” technique for tendon repair. Hand. 1973; 5(3):253–255. [PubMed: 4583860]
10. Pennington DG. The locking loop tendon suture. Plast Reconstr Surg. 1979; 63(5):648–52. [PubMed: 372992]
11. Ootes D, Lambers KT, Ring DC. The epidemiology of upper extremity injuries presenting to the emergency department in the United States. Hand. 2012; 7(1):18–22. [PubMed: 23449400]
12. Tuncali D, Yavuz N, Terzioglu A, Aslan G. The rate of upper-extremity deep-structure injuries through small penetrating lacerations. Ann Plast Surg. 2005; 55(2):146–148. [PubMed: 16034243]
13. Fufa DT, Osei DA, Calfee RP, Silva MJ, Thomopoulos S, Gelberman RH. The effect of core and epitendinous suture modifications on repair of intrasynovial flexor tendons in an in vivo canine model. J Hand Surg Am. 2012; 37(12):2526–31. [PubMed: 23174065]
14. Diao E, Hariharan S, Soejima O, Lotz JC, Francisco S. Effect of Peripheral Suture Depth on Strength of Tendon Repairs. J Hand Surg Am. 1996; 21(2):234–239. [PubMed: 8683052]
15. Nelson GN, Potter R, Ntouvali E, et al. Intrasynovial flexor tendon repair: a biomechanical study of variations in suture application in human cadavera. J Orthop Res. 2012; 30(10):1652–9. [PubMed: 22457145]
16. Wade PJF, Wetherell RG, Amis AA. Flexor tendon repair: Significant gain in strength from the halsted peripheral suture technique. J Hand Surg J Br. 1989; 14(2):232–235.
17. Hatanaka H, Manske PR. Effect of suture size on locking and grasping flexor tendon repair techniques. Clin Orthop Relat Res. 2000; (375):267–274. [PubMed: 10853178]
18. Strickland JW. Development of flexor tendon surgery: Twenty-five years of progress. J Hand Surg Am. 2000; 25(2):214–235. [PubMed: 10722813]
19. Savage R, Risitano G. Flexor tendon repair using a “six strand” method of repair and early active mobilisation. J Hand Surg Br. 1989; 14(4):396–9. [PubMed: 2621398]
20. Becker H, Davidoff M. Eliminating the Gap in Flexor Tendon Surgery: A New Method of Suture. Hand. 1977; 9(3):306–311. [PubMed: 344167]
21. Wagner WF, Carroll C, Strickland JW, Heck DA, Toombs JP. A biomechanical comparison of techniques of flexor tendon repair. J Hand Surg Am. 1994; 19(6):979–83. [PubMed: 7876500]
22. McLarney E, Hoffman H, Wolfe SW. Biomechanical analysis of the cruciate four-strand flexor tendon repair. J Hand Surg Am. 1999; 24(2):295–301. [PubMed: 10194013]
23. Silva MJ, Boyer MI, Ditsios K, et al. The insertion site of the canine flexor digitorum profundus tendon heals slowly following injury and structure repair. J Orthop Res. 2002; 20:447–453. [PubMed: 12038617]

24. Boyer MI, Gelberman RH, Burns ME, Dinopoulos H, Hofem R, Silva MJ. Intrasynovial flexor tendon repair. An experimental study comparing low and high levels of in vivo force during rehabilitation in canines. J Bone Jt Surg. 2001; 86(6):891–899.
25. Silva MJ, Brodt MD, Boyer MI, et al. Effects of increased In vivo excursion on digital range of motion and tendon strength following flexor tendon repair. J Orthop Res. 1999; 17:777–783. [PubMed: 10569491]
26. Boyer MI, Goldfarb CA, Gelberman RH. Recent progress in flexor tendon healing: The modulation of tendon healing with rehabilitation variables. J Hand Ther. 2005; 18:80–86. [PubMed: 15891963]
27. Khanna A, Friel M, Gougoulias N, Longo UG, Maffulli N. Prevention of adhesions in surgery of the flexor tendons of the hand: What is the evidence? Br Med Bull. 2009; 90(1):85–109. [PubMed: 19395470]
28. Aydin A, Topalan M, Mezdeği A, et al. Single-stage flexor tendoplasty in the treatment of flexor tendon injuries. Acta Orthop Traumatol Turc. 2004; 38(1):54–9. [PubMed: 15054299]
29. Lister GD, Kleinert HE, Kutz JE, Atasoy E. Primary flexor tendon repair followed by immediate controlled mobilization. J Hand Surg Am. 1977; 2(6):441–451. [PubMed: 336675]
30. Lieber RL, Silva MJ, Amiel D, Gelberman RH. Wrist and digital joint motion produce unique flexor tendon force and excursion in the canine forelimb. J Biomech. 1999; 32(2):175–181. [PubMed: 10052923]
31. Gelberman RH, Boyer MI, Brodt MD, Winters SC, Silva MJ. The Effect of Gap Formation at the Repair Site on the Strength and Excursion of Intrasynovial Flexor Tendons. J Bone Jt Surg Am. 1999; 81-A(7):975–982.
32. Beredjiklian PK. Biologic aspects of flexor tendon laceration and repair. J Bone Jt Surg Am. 2003; 85-A(3):539–550.
33. Khan U, Kakar S, Akali A, Bentley G, McGrouther DA. Modulation of the formation of adhesions during the healing of injured tendons. J Bone Jt Surg Br. 2000; 82-B(7):1054–1058.
34. Matthews P, Richards H. Factors in the adherence of flexor tendon after repair: an experimental study in the rabbit. J Bone Jt Surg Br. 1976; 58(2):230–6.
35. Gelberman RH, Vande Berg JS, Manske PR, Akeson WH. The early stages of flexor tendon healing: a morphologic study of the first fourteen days. J Hand Surg Am. 1985; 10(6 Pt 1):776–784. [PubMed: 2416800]
36. Zhao C, Amadio PC, Paillard P, et al. Digital resistance and tendon strength during the first week after flexor digitorum profundus tendon repair in a canine model in vivo. J Bone Jt Surg Am. 2004; 86-A(2):320–7.
37. Thomopoulos S, Das R, Silva MJ, et al. Enhanced flexor tendon healing through controlled delivery of PDGF-BB. J Orthop Res. 2009; 27(9):1209–1215. [PubMed: 19322789]
38. Beredjiklian PK, Favata M, Cartmell JS, Flanagan CL, Crombleholme TM, Soslowsky LJ. Regenerative versus reparative healing in tendon: A study of biomechanical and histological properties in fetal sheep. Ann Biomed Eng. 2003; 31(10):1143–1152. [PubMed: 14649488]
39. Gelberman RH, Thomopoulos S, Sakiyama-Elbert SE, Das R, Silva MJ. The Early Effects of Sustained Platelet-Derived Functional and Structural Properties of Repaired Intrasynovial Flexor Tendons: An In Vivo Biomechanic Study at 3 Weeks in Canines. J Hand Surg Am. 2007; 32A(3): 373–379.
40. Thomopoulos S, Zaegel MA, Das R, et al. PDGF-BB released in tendon repair using a novel delivery system promotes cell proliferation and collagen remodeling. J Orthop Res. 2007; 25(10): 1358–68. [PubMed: 17551975]
41. Gelberman RH, Amiel D, Gonsalves M, Woo SL, Akeson WH. The Influence of Protected Passive Mobilization on the Healing of Flexor Tendons: A Biochemical and Microangiographic Study. Hand. 1981; 13(2):120–128. [PubMed: 7286796]
42. Linderman SW, Kormpakis I, Gelberman RH, et al. Shear lag sutures: Improved suture repair through the use of adhesives. Acta Biomater. 2015; 23:229–39. [PubMed: 26022966]
43. Zhao C, Sun Y, Zobitz ME, An K, Amadio PC. Enhancing the Strength of the Tendon–Suture Interface Using 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide Hydrochloride and Cyanoacrylate. J Hand Surg Am. 2007; 32A(5):606–611.

44. Thoreson AR, Hiwatari R, An K-N, Amadio PC, Zhao C. The Effect of 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide Suture Coating on Tendon Repair Strength and Cell Viability in a Canine Model. J Hand Surg Am. 2015; 40(10):1986–1991. [PubMed: 26304735]
45. Shen H, Gelberman RH, Silva MJ, Sakiyama-Elbert SE, Thomopoulos S. BMP12 induces tenogenic differentiation of adipose-derived stromal cells. PLoS One. 2013; 8(10):e77613. [PubMed: 24155967]
46. Hayashi M, Zhao C, Thoreson AR, et al. The effect of lubricin on the gliding resistance of mouse intrasynovial tendon. PLoS One. 2013; 8(12):e83836. [PubMed: 24349551]
47. Hayashi M, Zhao C, An K-N, Amadio PC. The effects of growth and differentiation factor 5 on bone marrow stromal cell transplants in an in vitro tendon healing model. J Hand Surg Eur. 2011; 36(4):271–9.
48. Zhao C, Ozasa Y, Reisdorf RL, et al. Engineering Flexor Tendon Repair With Lubricant, Cells, and Cytokines in a Canine Model. Clin Orthop Relat Res. 2014; 472(9):2569–78. [PubMed: 24906811]
49. Manning CN, Havlioglu N, Knutsen E, et al. The early inflammatory response after flexor tendon healing: a gene expression and histological analysis. J Orthop Res. 2014; 32(5):645–52. [PubMed: 24464937]
50. Kleinert HE, Verdan C. Report of the Committee on Tendon Injuries. J Hand Surg Am. 1983; 8(5): 794–798. [PubMed: 6630960]
51. Gelberman RH, Vandeberg JS, Lundborg GN, Akeson WH. Flexor tendon healing and restoration of the gliding surface. An ultrastructural study in dogs. J Bone Jt Surg Am. 1983; 65(1):70–80.
52. Lundborg G, Rank F. Experimental intrinsic healing of flexor tendons based upon synovial fluid nutrition. J Hand Surg Am. 1978; 3(1):21–31. [PubMed: 621365]
53. Fenwick SA, Hazleman BL, Riley GP. The vasculature and its role in the damaged and healing tendon. Arthritis Res. 2002; 4(4):252–60. [PubMed: 12106496]
54. Wong JKF, Lui YH, Kapacee Z, Kadler KE, Ferguson MWJ, McGrouther DA. The Cellular Biology of Flexor Tendon Adhesion Formation. Am J Pathol. 2009; 175(5):1938–1951. [PubMed: 19834058]
55. Dakin SG, Werling D, Hibbert A, et al. Macrophage sub-populations and the lipoxin A4 receptor implicate active inflammation during equine tendon repair. PLoS One. 2012; 7(2):e32333. [PubMed: 22384219]
56. 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. J Orthop Res. 2014; 32(7):944–951. [PubMed: 24700411]
57. Marsolais D, Côté CH, Frenette J. Neutrophils and macrophages accumulate sequentially following Achilles tendon injury. J Orthop Res. 2001; 19(6):1203–1209. [PubMed: 11781025]
58. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol. 2013; 229(2):176–185. [PubMed: 23096265]
59. Hasslund S, Jacobson JA, Dadali T, et al. Adhesions in a murine flexor tendon graft model: autograft versus allograft reconstruction. J Orthop Res. 2008; 26(6):824–33. [PubMed: 18186128]
60. Loiselle AE, Kelly M, Hammert WC. Biological Augmentation of Flexor Tendon Repair. J Hand Surg Am. 2016; 41(1):144–149. [PubMed: 26652792]
61. Gelberman RH, Manske PR, Vande Berg JS, Lesker PA, Akeson WH. Flexor tendon repair in vitro: a comparative histologic study of the rabbit, chicken, dog, and monkey. J Orthop Res. 1984; 2(9): 39–48. [PubMed: 6491797]
62. Thorpe CT, Birch HL, Clegg PD, Screen HRC. The role of the non-collagenous matrix in tendon function. Int J Exp Pathol. 2013; 94(4):248–59. [PubMed: 23718692]
63. Thorpe CT, Klemt C, Riley GP, Birch HL, Clegg PD, Screen HRC. Helical sub-structures in energy-storing tendons provide a possible mechanism for efficient energy storage and return. Acta Biomater. 2013; 9(8):7948–56. [PubMed: 23669621]
64. Cadby JA, Buehler E, Godbout C, van Weeren PR, Snedeker JG. Differences between the Cell Populations from the Peritenon and the Tendon Core with Regard to Their Potential Implication in Tendon Repair. PLoS One. 2014; 9(3):e92474. [PubMed: 24651449]

65. Chang J, Most D, Thunder R, Mehrara B, Longaker MT, Lineaweaver WC. Molecular studies in flexor tendon wound healing: the role of basic fibroblast growth factor gene expression. J Hand Surg Am. 1998; 23(6):1052–8. [PubMed: 9848558]
66. Halikis MN, Manske PR, Kubota H, Aoki M. Effect of immobilization, immediate mobilization, and delayed mobilization on the resistance to digital flexion using a tendon injury model. J Hand Surg. 1997; 22(3):464–472.
67. Wray RC Jr, Holtman B, Weeks PM. Clinical treatment of partial tendon lacerations without suturing and with early motion. Plast Reconstr Surg. 1977; 59(2):231–234. [PubMed: 834778]
68. Chow SP, Yu OD. An experimental study on incompletely cut chicken tendons--a comparison of two methods of management. J Hand Surg Br. 1984; 9(2):121–125. [PubMed: 6747408]
69. Tang JB, Cao Y, Zhu B, Xin K-Q, Wang XT, Liu PY. Adeno-Associated Virus-2-Mediated bFGF Gene Transfer to Digital Flexor Tendons Significantly Increases Healing Strength. J Bone Jt Surg Am. 2008; 90(5):1078.
70. Potenza AD. Detailed evaluation of healing processes in canine flexor digital tendons. Mil med. 1962; 127:34–47. [PubMed: 14488262]
71. Horibe S, Woo SL, Spiegelman JJ, Marcin JP, Gelberman RH. Excursion of the flexor digitorum profundus tendon: a kinematic study of the human and canine digits. J Orthop Res. 1990; 8(2): 167–74. [PubMed: 2303949]
72. Zhao C, Amadio PC, Zobitz ME, An KN. Gliding characteristics of tendon repair in canine flexor digitorum profundus tendons. J Orthop Res. 2001; 19(4):580–6. [PubMed: 11518265]
73. Zhao C, Amadio PC, Momose T, Couvreur P, Zobitz ME, An KN. The effect of suture technique on adhesion formation after flexor tendon repair for partial lacerations in a canine model. J Trauma. 2001; 51(5):917–921. [PubMed: 11706340]
74. Zhao C, Moran SL, Cha SS, Kai-Nan-An, Amadio PC. An analysis of factors associated with failure of tendon repair in the canine model. J Hand Surg Am. 2007; 32(4):518–25. [PubMed: 17398363]
75. Noguchi M, Seiler JG, Gelberman RH, Sofranko RA, Woo SL. In vitro biomechanical analysis of suture methods for flexor tendon repair. J Orthop Res. 1993; 11(4):603–11. [PubMed: 8340832]
76. Thomopoulos S, Das R, Sakiyama-Elbert SE, Silva MJ, Charlton N, Gelberman RH. bFGF and PDGF-BB for tendon repair: Controlled release and biologic activity by tendon fibroblasts in vitro. Ann Biomed Eng. 2010; 38(2):225–234. [PubMed: 19937274]
77. Wong J, Bennett W, Ferguson MWJ, McGrouther DA. Microscopic and histological examination of the mouse hindpaw digit and flexor tendon arrangement with 3D reconstruction. J Anat. 2006; 209(4):533–45. [PubMed: 17005025]
78. Beason DP, Kuntz AF, Hsu JE, Miller KS, Soslowsky LJ. Development and evaluation of multiple tendon injury models in the mouse. J Biomech. 2012; 45(8):1550–1553. [PubMed: 22405494]
79. Loiselle AE, Bragdon GA, Jacobson JA, et al. Remodeling of murine intrasynovial tendon adhesions following injury: MMP and neotendon gene expression. J Orthop Res. 2009; 27(6):833–840. [PubMed: 19051246]
80. Hasslund S, O'Keefe RJ, Awad HA. A mouse model of flexor tendon repair. Methods Mol Biol. 2014; 1130:73–88. [PubMed: 24482166]
81. Manning CN, Schwartz AG, Liu W, et al. Controlled delivery of mesenchymal stem cells and growth factors using a nanofiber scaffold for tendon repair. Acta Biomater. 2013; 9:6905–6914. [PubMed: 23416576]
82. Yañez R, Lamana ML, García-Castro J, Colmenero I, Ramírez 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]
83. Cui L, Yin S, Liu W, Li N, Zhang W, Cao Y. Expanded adipose-derived stem cells suppress mixed lymphocyte reaction by secretion of prostaglandin E2. Tissue Eng. 2007; 13(6):1185–1195. [PubMed: 17518704]
84. Thomopoulos S, Kim HM, Das R, et al. The Effects of Exogenous Basic Fibroblast Growth Factor on Intrasynovial Flexor Tendon Healing in a Canine Model. J Bone Jt Surg Am. 2010; 92A(13): 2285–2293.

85. Rouhani A, Tabrizi A, Ghavidel E. Effects of Non-Steroidal Anti-Inflammatory Drugs on Flexor Tendon Rehabilitation After Repair. Arch Bone Jt Surg. 2013; 1(1):28–30. [PubMed: 25207280]

86. Hsu C, Chang J. Clinical implications of growth factors in flexor tendon wound healing. J Hand Surg Am. 2004; 29(4):551–563. [PubMed: 15249076]

87. Kulick MI, Smith S, Hadler K. Oral ibuprofen: evaluation of its effect on peritendinous adhesions and the breaking strength of a tenorrhaphy. J Hand Surg Am. 1986; 11(1):110–20. [PubMed: 3511134]

88. Tan V, Nourbakhsh A, Capo J, Cottrell JA, Meyenhofer M, O'Connor JP. Effects of nonsteroidal anti-inflammatory drugs on flexor tendon adhesion. J Hand Surg Am. 2010; 35(6):941–7. [PubMed: 20513575]

89. Awad HA, Butler DL, Malaviya P, Huibregtse B, Caplan AI. Autologous Mesenchymal Stem Cell-Mediated Repair of Tendon. Tissue Eng. 1999; 5(3):267–277. [PubMed: 10434073]

90. Woo SLY, Smith DW, Hildebrand KA, Zeminski JA, Johnson LA. Engineering the healing of the rabbit medial collateral ligament. Med Biol Eng Comput. 1998; 36(3):359–364. [PubMed: 9747578]

91. Hildebrand KA, Woo SL, Smith DW, et al. The effects of platelet-derived growth factor-BB on healing of the rabbit medial collateral ligament. An in vivo study. Am J Sports Med. 1998; 26(4): 549–54. [PubMed: 9689377]

92. Robinson SN, Talmadge JE. Sustained release of growth factors. In Vivo. 2002; 16(6):535–40. [PubMed: 12494898]

93. Sakiyama-Elbert SE, Das R, Gelberman RH, Harwood F, Amiel D, Thomopoulos S. Controlled-Release Kinetics and Biologic Activity of Platelet-Derived Growth Factor-BB for Use in Flexor Tendon Repair. J Hand Surg Am. 2008; 33A(9):1548–1557.

94. Butler DL, Goldstein SA, Guilak F. Functional tissue engineering: the role of biomechanics. J Biomech Eng. 2000; 122(6):570–5. [PubMed: 11192376]

95. Butler DL, Juncosa-Melvin N, Boivin GP, et al. Functional tissue engineering for tendon repair: A multidisciplinary strategy using mesenchymal stem cells, bioscaffolds, and mechanical stimulation. J Orthop Res. 2008; 26(1):1–9. [PubMed: 17676628]

96. Breidenbach AP, Gilday SD, Lalley AL, et al. Functional tissue engineering of tendon: Establishing biological success criteria for improving tendon repair. J Biomech. 2013:1–8. [PubMed: 23259938]

97. Spalazzi JP, Doty SB, Moffat KL, Levine WN, Lu HH. Development of controlled matrix heterogeneity on a triphasic scaffold for orthopedic interface tissue engineering. Tissue Eng. 2006; 12(12):3497–508. [PubMed: 17518686]

98. Lu HH, Subramony SD, Boushell MK, Zhang X. Tissue engineering strategies for the regeneration of orthopaedic interfaces. Ann Biomed Eng. 2010; 38(6):2142–2154. [PubMed: 20422291]

99. Uehara K, Zhao C, Gingery A, Thoreson AR, An K-N, Amadio PC. Effect of Fibrin Formulation on Initial Strength of Tendon Repair and Migration of Bone Marrow. J Bone Jt Surg Am. 2015; 97(21):1792–1798.

100. Zhao C, Chieh H-F, Bakri K, et al. The effects of bone marrow stromal cell transplants on tendon healing in vitro. Med Eng Phys. 2009; 31(10):1271–1275. [PubMed: 19736035]

101. Qu F, Lin J-MG, Esterhai JL, Fisher MB, Mauck RL. Biomaterial-mediated delivery of degradative enzymes to improve meniscus integration and repair. Acta Biomater. 2013; 9(5): 6393–402. [PubMed: 23376132]

102. Gelberman RH, Shen H, Kormpakis I, et al. Effect of adipose-derived stromal cells and BMP12 on intrasynovial tendon repair: A biomechanical, biochemical, and proteomics study. J Orthop Res. 2015:1–11. [PubMed: 25312837]

103. Zhao C, Sun Y-L, Kirk RL, et al. Effects of a Lubricin-Containing Compound on the Results of Flexor Tendon Repair in a Canine Model in Vivo. J Bone Jt Surg Am. 2010; 92(6):1453.

104. Zhao C, Sun Y-L, Jay GD, Moran SL, An K-N, Amadio PC. Surface modification counteracts adverse effects associated with immobilization after flexor tendon repair. J Orthop Res. 2012; 30(12):1940–4. [PubMed: 22714687]

105. Amiel D, Ishizue K, Billings E, et al. Hyaluronan in flexor tendon repair. J Hand Surg Am. 1989; 14(5):837–43. [PubMed: 2794401]

106. Wiig M, Abrahamsson SO, Lundborg G. Tendon repair-cellular activities in rabbit deep flexor tendons and surrounding synovial sheaths and the effects of hyaluronan: An experimental study in vivo and in vitro. J Hand Surg Am. 1997; 22(5):818–825. [PubMed: 9330139]

107. Miller JA, Ferguson RL, Powers DL, Burns JW, Shalaby SW. Efficacy of hyaluronic acid/nonsteroidal anti-inflammatory drug systems in preventing postsurgical tendon adhesions. J Biomed Mater Res. 1997; 38(1):25–33. [PubMed: 9086414]

108. Khan U, Occleston NL, Khaw PT, McGrouther DA. Single exposures to 5-Fluorouracil: A possible mode of targeted therapy to reduce contractile scarring in the injured tendon. Plast Reconstr Surg. 1997; 99:465–71. [PubMed: 9030156]

109. Cerovac S, Afoke A, Akali A, McGrouther DA. Early breaking strength of repaired flexor tendon treated with 5-fluorouracil. J Hand Surg Br. 2001; 26:220–223. [PubMed: 11386771]

110. Stark HH, Boyes JH, Johnson L, Ashworth CR. The use of paratenon, polyethylene film, or silastic sheeting to prevent restricting adhesions to tendons in the hand. J Bone Jt Surg Am. 1977; 59(7):908–913.

111. Eskeland G, Eskeland T, Hovig T, Teigland J. The ultrastructure of normal digital flexor tendon sheath and of the tissue formed around silicone and polyethylene implants in man. J Bone Jt Surg Br. 1977; 59(2):206–212.

112. Sakiyama-Elbert SE, Hubbell JA. Controlled release of nerve growth factor from a heparin-containing brin-based cell ingrowth matrix. J Control Release. 2000; 69:149–158. [PubMed: 11018553]

113. Sakiyama-Elbert SE, Hubbell JA. Development of fibrin derivatives for controlled release of heparin-binding growth factors. J Control Release. 2000; 65:389–402. [PubMed: 10699297]

114. Solorio LD, Phillips LM, McMillan A, et al. Spatially organized differentiation of mesenchymal stem cells within biphasic microparticle-incorporated high cell density osteochondral tissues. Adv Healthc Mater. 2015; 4(15):2306–13. [PubMed: 26371790]

115. Solorio LD, Dhami CD, Dang PN, Vieregge EL, Alsberg E. Spatiotemporal regulation of chondrogenic differentiation with controlled delivery of transforming growth factor-β1 from gelatin microspheres in mesenchymal stem cell aggregates. Stem Cells Transl Med. 2012; 1(8):632–639. [PubMed: 23197869]

116. Jeon O, Wolfson DW, Alsberg E. In-Situ Formation of Growth-Factor-Loaded Coacervate Microparticle-Embedded Hydrogels for Directing Encapsulated Stem Cell Fate. Adv Mater. 2015; 27(13):2216–2223. [PubMed: 25708428]

117. Erisken C, Zhang X, Moffat KL, Levine WN, Lu HH. Scaffold fiber diameter regulates human tendon fibroblast growth and differentiation. Tissue Eng Part A. 2013; 19(3–4):519–28. [PubMed: 23150905]

118. Wolfman NM, Hattersley G, Cox K, et al. Ectopic induction of tendon and ligament in rats by growth and differentiation factors 5, 6, and 7, members of the TGF-beta gene family. J Clin Invest. 1997; 100(2):321–30. [PubMed: 9218508]

119. Tashiro T, Hiraoka H, Ikeda Y, et al. Effect of GDF-5 on ligament healing. J Orthop Res. 2006; 24(1):71–79. [PubMed: 16419971]

120. Lou J, Tu Y, Burns M, Silva MJ, Manske P. BMP-12 gene transfer augmentation of lacerated tendon repair. J Orthop Res. 2001; 19(6):1199–202. [PubMed: 11781024]

121. Hoffmann A, Pelled G, Turgeman G, et al. Neotendon formation induced by manipulation of the Smad8 signalling pathway in mesenchymal stem cells. J Clin Invest. 2006; 116(4):940–952. [PubMed: 16585960]

122. Park A, Hogan MV, Kesturu GS, James R, Balian G, Chhabra AB. Adipose-Derived Mesenchymal Stem Cells Treated with Growth Differentiation Factor-5 Express Tendon-Specific Markers. Tissue Eng Part A. 2010; 16(9):2941–2951. [PubMed: 20575691]

123. Lee JY, Zhou Z, Taub PJ, et al. BMP-12 treatment of adult mesenchymal stem cells In Vitro augments tendon-like tissue formation and defect repair In Vivo. PLoS One. 2011; 6(3):1–7.

124. Gulotta LV, Kovacevic D, Packer JD, Ehteshami JR, Rodeo SA. Adenoviral-mediated gene transfer of human bone morphogenetic protein-13 does not improve rotator cuff healing in a rat model. Am J Sport Med. 2011; 39(1):180–187.

125. Chan BP, Chan KM, Maffulli N, Webb S, Lee KKH. Effect of basic fibroblast growth factor. An in vitro study of tendon healing. Clin Orthop Relat Res. 1997; 342:239–247.

126. Thomopoulos S, Harwood FL, Silva MJ, Amiel D, Gelberman RH. Effect of several growth factors on canine flexor tendon fibroblast proliferation and collagen synthesis in vitro. J Hand Surg Am. 2005; 30(3):441–447. [PubMed: 15925149]

127. Juneja SC, Schwarz EM, O'Keefe RJ, Awad HA. Cellular and molecular factors in flexor tendon repair and adhesions: A histological and gene expression analysis. Connect Tissue Res. 2013; 54(2):218–226. [PubMed: 23586515]

128. Farhat YM, Al-Maliki AA, Chen T, et al. Gene Expression Analysis of the Pleiotropic Effects of TGF-β1 in an In Vitro Model of Flexor Tendon Healing. PLoS One. 2012; 7(12):e51411. [PubMed: 23251524]

129. Klein MB, Pham H, Yalamanchi N, Chang J. Flexor tendon wound healing in vitro: The effect of lactate on tendon cell proliferation and collagen production. J Hand Surg Am. 2001; 26(5):847–854. [PubMed: 11561237]

130. Katzel EB, Wolenski M, Loiselle AE, et al. Impact of Smad3 loss of function on scarring and adhesion formation during tendon healing. J Orthop Res. 2011; 29(May):684–693. [PubMed: 20842701]

131. Farhat YM, Al-Maliki AA, Easa A, O'Keefe RJ, Schwarz EM, Awad HA. TGF-beta1 Suppresses Plasmin and MMP Activity in Flexor Tendon Cells via PAI-1: Implications for Scarless Flexor Tendon Repair. J Cell Physiol. 2014; (June):318–326.

132. Zhou Y, Zhang L, Zhao W, Wu Y, Zhu C, Yang Y. Nanoparticle-mediated delivery of TGF-β1 miRNA plasmid for preventing flexor tendon adhesion formation. Biomaterials. 2013; 34(33): 8269–8278. [PubMed: 23924908]

133. Wong JKF, Metcalfe AD, Wong R, et al. Reduction of Tendon Adhesions following Administration of Adaprev, a Hypertonic Solution of Mannose-6-Phosphate: Mechanism of Action Studies. PLoS One. 2014; 9(11):e112672. [PubMed: 25383548]

134. Chang J, Thunder R, Most D, Longaker MT, Lineaweaver WC. Studies in flexor tendon wound healing: neutralizing antibody to TGF-B1 increases postoperative range of motion. Plast Reconstr Surg. 2000; 105(1):148–155. [PubMed: 10626983]

135. Loiselle AE, Yukata K, Geary MB, et al. Development of antisense oligonucleotide (ASO) technology against Tgf-β signaling to prevent scarring during flexor tendon repair. J Orthop Res. 2015; 33(6):859–66. [PubMed: 25761254]

136. Wu YF, Mao WF, Zhou YL, Wang XT, Liu PY, Tang JB. Adeno-associated virus-2-mediated TGF-β1 microRNA transfection inhibits adhesion formation after digital flexor tendon injury. Gene Ther. 2016; 23(2):167–175. [PubMed: 26381218]

137. Lee CH, Shah B, Moioli EK, Mao JJ. CTGF directs fibroblast differentiation from human mesenchymal stem/stromal cells and defines connective tissue healing in a rodent injury model. J Clin Invest. 2010; 120(9):3340–3349. [PubMed: 20679726]

138. Liu J, Tao X, Chen L, Han W, Zhou Y, Tang K. CTGF Positively Regulates BMP12 Induced Tenogenic Differentiation of Tendon Stem Cells and Signaling. Cell Physiol Biochem. 2015; 35(5):1831–1845. [PubMed: 25833297]

139. Fukunaga T, Yamashiro T, Oya S, Takeshita N, Takigawa M, Takano-Yamamoto T. Connective tissue growth factor mRNA expression pattern in cartilages is associated with their type I collagen expression. Bone. 2003; 33(6):911–918. [PubMed: 14678850]

140. Würgler-Hauri CC, Dourte LM, Baradet TC, Williams GR, Soslowsky LJ. Temporal expression of 8 growth factors in tendon-to-bone healing in a rat supraspinatus model. J Shoulder Elb Surg. 2007; 16(5 Suppl):S198–203.

141. Chen CH, Cao Y, Wu YF, Bais AJ, Gao JS, Tang JB. Tendon healing in vivo: gene expression and production of multiple growth factors in early tendon healing period. J Hand Surg Am. 2008; 33(10):1834–1842. [PubMed: 19084187]

142. Juncosa-Melvin N, Boivin GP, Gooch C, et al. The effect of autologous mesenchymal stem cells on the biomechanics and histology of gel-collagen sponge constructs used for rabbit patellar tendon repair. Tissue Eng. 2006; 12(2):369–79. [PubMed: 16548695]

143. Young RG, Butler DL, Weber W, Caplan AI, Gordon SL, Fink DJ. Use of mesenchymal stem cells in a collagen matrix for Achilles tendon repair. J Orthop Res. 1998; 16(4):406–413. [PubMed: 9747780]

144. Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. Am J Sports Med. 2009; 37(11):2126–33. [PubMed: 19684297]

145. Morizaki Y, Zhao C, An K-N, Amadio PC. The effects of platelet-rich plasma on bone marrow stromal cell transplants for tendon healing in vitro. J Hand Surg Am. 2010; 35(11):1833–41. [PubMed: 20951509]

146. He M, Gan AWT, Lim AYT, Goh JCH, Hui JHP, Chong AKS. Bone Marrow–Derived Mesenchymal Stem Cell Augmentation of Rabbit Flexor Tendon Healing. J Hand Surg Am. 2015; 20(3):421–429.

147. Godwin EE, Young NJ, Dudhia J, Beamish IC, Smith RKW. Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet J. 2012; 44(1):25–32. [PubMed: 21615465]

148. Smith RKW. Mesenchymal stem cell therapy for equine tendinopathy. Disabil Rehabil. 2008; 30(20–22):1752–1758. [PubMed: 18608378]

149. Pacini S, Spinabella S, Trombi L, et al. Suspension of bone marrow-derived undifferentiated mesenchymal stromal cells for repair of superficial digital flexor tendon in race horses. Tissue Eng. 2007; 13(12):2949–55. [PubMed: 17919069]

150. Thorpe CT, Clegg PD, Birch HL. A review of tendon injury: why is the equine superficial digital flexor tendon most at risk? Equine Vet J. 2010; 42(2):174–80. [PubMed: 20156256]

151. Lee CH, Lee FY, Tarafder S, et al. Harnessing endogenous stem/progenitor cells for tendon regeneration. J Clin Invest. 2015; 125(7):2690–2701. [PubMed: 26053662]

152. Lui PPY, Wong OT, Lee YW. Application of tendon-derived stem cell sheet for the promotion of graft healing in anterior cruciate ligament reconstruction. Am J Sports Med. 2014; 42(3):681–9. [PubMed: 24451112]

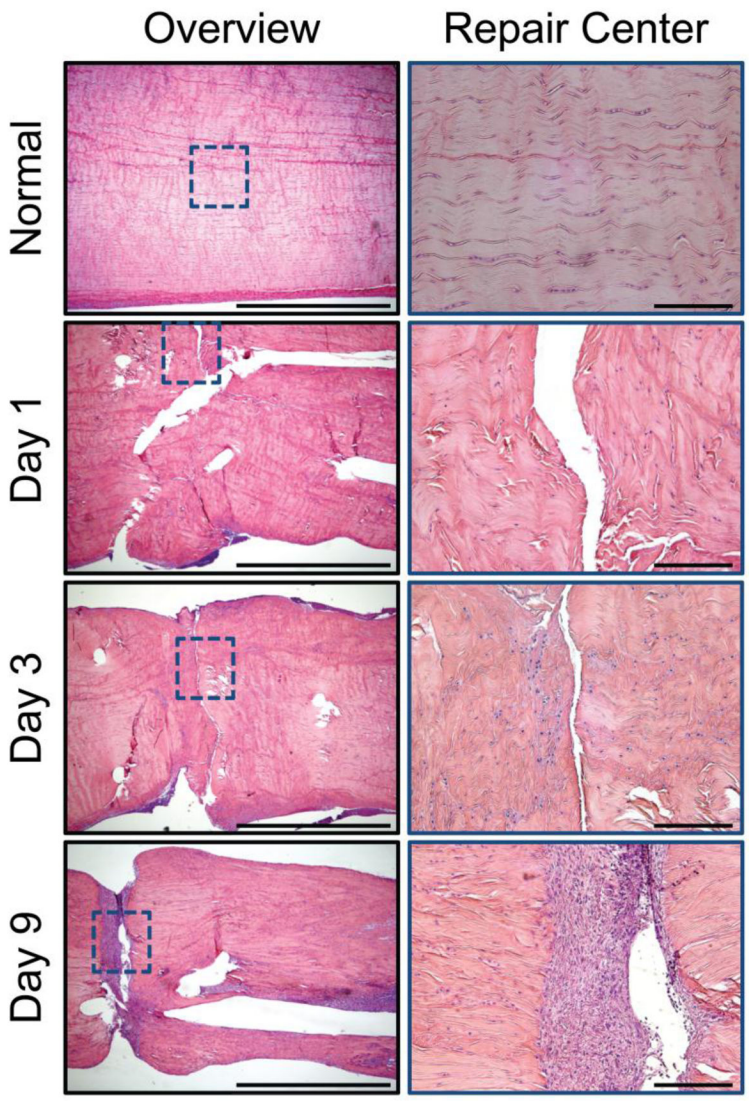

Figure 1.

Representative histologic sections of healthy and repaired canine flexor tendons 1, 3, and 9 days post-operatively. The sections were stained with H&E and viewed under bright field for cell identification. An overview of a representative section from each time point is shown to the left (4x objective, 2mm scale bar). High magnification images (20x objective, 200mm scale bar) of the section outlined in blue are shown to the right. Inflammatory cells are seen infiltrating the repair site via the tendon surface.

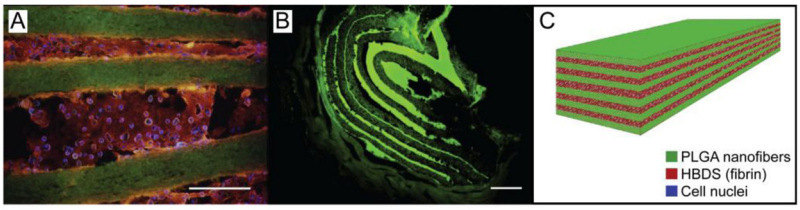

Figure 2.

A representative PLGA-fibrin scaffold with 11 alternating layers of aligned electrospun PLGA nanofiber mats separated by fibrin containing adipose-derived MSCs. **(A)** Micrograph showing the scaffold *in vitro*; the PLGA was labeled with FITC (green), the fibrin was labeled with Alexa Fluor 546 (red) and the adipose-derived MSC nuclei were labeled with Hoechst 33258 (blue) (scale bar = 200 μm). **(B)** Micrograph showing the scaffold in vivo 9 days after implantation in a canine flexor tendon repair (scale bar = 100 μm). **(C)** A schematic of the layered scaffold is shown.

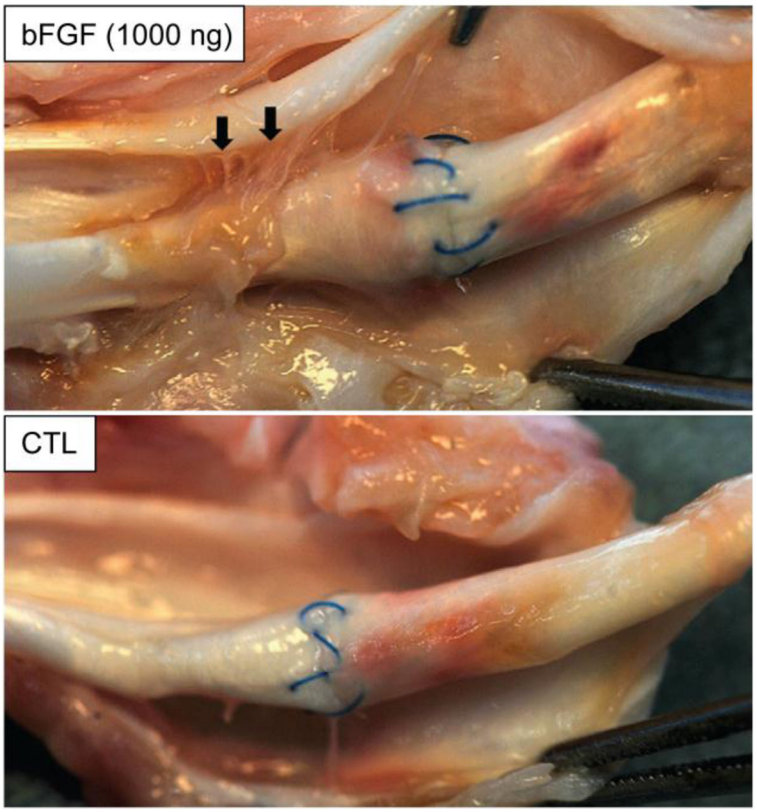

Figure 3.

There were more adhesions (arrows) between the flexor tendon surface and its surrounding sheath in the bFGF-treated tendons (top panel) than there were in the non-bFGF-treated control (CTL) tendons (bottom panel). Arrows indicate adhesions proximal to the repair site in a tendon treated with 1000 ng bFGF. The paired control tendon did not have any apparent adhesions.