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Cell and Biologic-Based Treatment of Flexor Tendon Injuries

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The 2 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 multistrand repair and controlled rehabilitation techniques are often unsatisfactory, alternative approaches, such as the application of growth factors and mesenchymal stem cells, have become increasingly attractive treatment options. Successful biological therapies require carefully controlled spatiotemporal delivery of cells, growth factors, and biocompatible scaffold matrices 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 article summarizes recent cell and biologic-based experimental treatments for flexor tendon injury, with an emphasis on large animal translational studies.
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Introduction

Among the most common and challenging hand injuries, intrasynovial flexor tendon transections have motivated over 5 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 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 et al[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 2 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] Although 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 6 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

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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 folds.[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 article 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 3 successive, overlapping stages of healing: acute inflammation (days 0-7 postinjury), 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 (Fig. 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 2 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 with 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 neovascularization.[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 because of anatomical 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 that modifies the healing