The Achilles tendon: fundamental properties and mechanisms governing healing

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Summary

This review highlights recent research on Achilles tendon healing, and comments on the current clinical controversy surrounding the diagnosis and treatment of injury. The processes of Achilles tendon healing, as demonstrated through changes in its structure, composition, and biomechanics, are reviewed. Finally, a review of tendon developmental biology and mechano transductive pathways is completed to recognize recent efforts to augment injured Achilles tendons, and to suggest potential future strategies for therapeutic intervention and functional tissue engineering. Despite an abundance of clinical evidence suggesting that current treatments and rehabilitation strategies for Achilles tendon ruptures are equivocal, significant questions remain to fully elucidate the basic science mechanisms governing Achilles tendon injury, healing, treatment, and rehabilitation.

KEY WORDS: biomechanics, foot and ankle, tendinopathy, Achilles tendon rupture, injury, developmental biology, tissue engineering.

Introduction

The Achilles is the strongest and largest tendinous structure in the body. It is defined anatomically as the distal confluence of the gastrocnemius and soleus muscles and may also include the plantaris longus[1] (Fig. 1). During activity, the Achilles tendon can bear loads in excess of 3500 N[2,3], yet despite its tremendous strength, is frequently injured. Acute and chronic Achilles tendon pathology is estimated to be responsible for as much as 50% of all sports-related injuries[4]. 75% of Achilles tendon ruptures occur in middle-aged men between the ages of 30 and 49 while participating in sport[4-7] and the incidence is rising[4, 6-8]. The association of Achilles rupture with obesity, amongst a number of similarly trending parameters, may also play a role[7]. Chronic Achilles tendon injuries are generally defined by activity associated Achilles pain (e.g. swelling and tenderness) in conjunction with impaired performance during sporting activity[4], and asymptomatic degeneration may occur in 4% of active adults[9,10]. Rare causes of Achilles tendon rupture include fluoroquinalone-induced ruptures (0.02-2.0%) and those associated with systemic disease (2.0%)[4,7,11].

The primary means of diagnosing Achilles tendon rupture is through patient history and physical examination[12]. In acute Achilles ruptures, patients often present with a history of eccentric loading associated with a popping sensation, immediately followed by pain and difficulty during ambulation. In some cases of partial rupture where the diagnosis can be more difficult, MRI or advanced Doppler ultrasound may be beneficial[13]. Ultrasound may provide further benefit as a tool to monitor the healing process[14].

Meta-analyses evaluating treatment of the acute Achilles tendon rupture[15-18] have established the need for improved intervention given moderate outcomes[12]. Although early trials pointed to a decreased risk of re-rupture with surgical intervention at the cost of an associated increased risk of other major and minor complications[18], best practices regarding the treatment of Achilles tendon rupture remains an ongoing topic of debate[12,16] (Fig. 2). The known response of the Achilles tendon to mechanical stimulation[19-22] underlies the importance of rehabilitation in healing. In therapy initiated after rupture there is good evidence supporting early return to activity, however optimized protocols have not been defined and long term benefits have not been demonstrated[23-26]. Treatment of chronic Achilles tendinopathy remains challenging and usually consists of early rehabilitation with eccentric strengthening protocols but in intractable cases can result in continued symptoms eventually requiring surgical intervention[27, 28]. Therefore, well controlled basic science studies are important in resolving outstanding fundamental questions regarding means of treatment in a consistent and well established model. In this review we highlight recent

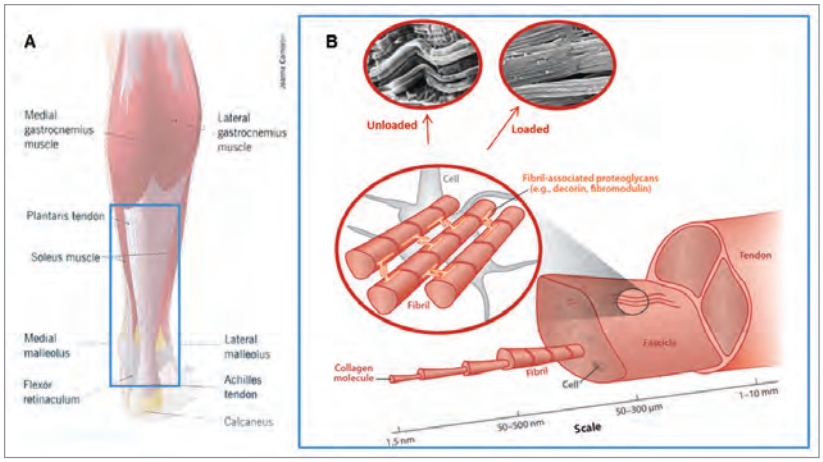

Figure 1. Gross anatomy and structure of the Achilles tendon.(A)The Achilles tendon emerges at the distal confluence of the gastrocnemius and soleus muscles and inserts into the calcaneus. (B) Similar to other tendons, the Achilles exhibits a hierarchical structure composed of fascicles, fibers, and fibrils. When loaded, fibrils straighten, decrease in crimp amplitude and frequency, and become more aligned.
Panel A: Image reproduced with permission from Joanna Cameron (2013). Panel B: Image reproduced with permission from Franchi et al. (2007)[38] and Voleti et al. (2012)[33].

	Operative		Conservative			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Costa 2006	8	20	0	19	10.9%	16.19 [1.00, 262.45]	
Keating 2011	3	37	2	39	16.7%	1.58 [0.28, 8.93]	
Metz 2008	9	41	15	39	23.2%	0.57 [0.28, 1.15]	
Möller 2001	10	59	2	53	18.4%	4.49 [1.03, 19.58]	
Nilsson 2009	8	49	0	48	10.7%	16.66 [0.99, 280.85]	
Twaddle 2007	0	22	0	23		Not estimable	
Willits 2010	11	62	3	65	20.0%	3.84 [1.13, 13.13]	
Total (95% CI)		**290**		**286**	**100.0%**	**3.00 [0.88, 10.21]**	
Total events	49		22				

Heterogeneity: Tau² = 1.56; Chi² = 19.52, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 1.76 (P = 0.08)

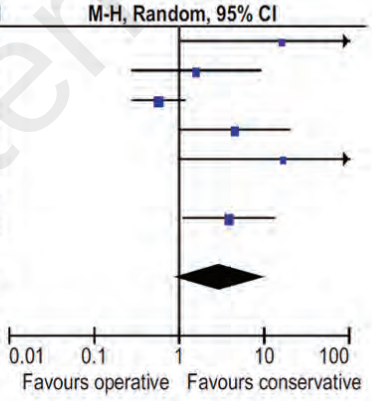

Figure 2. Summary of several randomized control trials (RCTs) highlighting the current clinical controversy surrounding surgical *versus* non-surgical treatment of Achilles tendon ruptures. This Table and Forest plot indicates that no significant difference in either major or minor complications exist between patients receiving operative and non-operative treatment.
Image reproduced with permission from van der Eng et al. (2011)[15].

research on Achilles tendon healing, and suggest potential strategies for therapeutic intervention and functional tissue engineering.

Compositional, structural, and biomechanical properties of normal Achilles tendon

Defining baseline compositional properties for normal tendon is necessary to set appropriate benchmarks for healing and to determine appropriate strategies for successful functional tissue engineering. Unfortunately, basic Achilles tendon compositional data is currently lacking, with the most thorough compositional studies performed using flexor tendons. As an extrapolation from data in other systems, Achilles tendons are thought to be composed of approximately 90% type I collagen that forms a hierarchical structure of fibrils, fibers, and fascicles bound together by small matrix molecules, such as proteoglycans[29]. The Achilles tendon insertion is composed of types II, IX, and X collagen, with type X collagen localized in the mineralized zone and type IX distributed throughout[30]. Although elastin only accounts for up to 2% of the tendon's dry mass, recent studies have shown it makes important contributions to the mechanical properties of tendons[31]. Digestion of glycosaminoglycans has been shown to decrease tendon modulus and ultimate load specifically at the tendon insertion site, suggesting a regional variance in composition that may mirror regional differences in structure and mechanical performance[32]. Alterations in tendon structure and loading elicit biochemical changes that are exacerbated in cases of injury and healing.

The structure of tendon directly relates to its mechanical function[33]. Baseline characterization of normal Achilles tendon structure is necessary to identify the mechanisms governing tendon injury and failure. Generally, tendon is an inhomogeneous, anisotropic, nonlinear[34], fiber-reinforced, biocomposite material[35] primarily composed of a collagen extracellular matrix[36] and non-collagenous molecules. The dry weight of tendon is primarily composed of longitudinal colla-

gen fibers that are believed to be the primary load bearing components in mature tissue[37]. At the most basic level, the collagen fibers in tendon are highly organized structures that demonstrate high strength in the direction of fiber alignment[36]. Under polarized light, tendons exhibit periodic banding due to its waveform configuration known as "crimp". This property extends down in a hierarchical fashion from macro- to nano-structural scales[38]. When initially loaded, the force-displacement curve demonstrates a distinct nonlinearity or "toe region" that arises from uncrimping and an associated increase in collagen alignment[39]. This concept is supported by the observed decrease in crimp frequency and amplitude in loaded Achilles tendons[38]. Glycosaminoglycans (GAGs) and structural proteins, such as elastin[31], connect adjacent fibrils. Such molecules may play a role in tendon structure-function relationships, though their specific role requires further elucidation[31,37]. Disruption to any of these load bearing elements may be detrimental to physiologic function, potentially leading to injury and failure.

Ultimately, Achilles tendon mechanical properties govern the tendon's ability to respond and adapt to its loading environment. Achilles tendon mechanical nonlinearity is shown through its stress strain curve at low strains[40]. At higher strains, Achilles tendons deform linearly prior to yield and rupture. Although the Achilles tendon is commonly referred to as a viscoelastic material containing both elastic (stress and strain occur in phase) and viscous (90 degree phase difference between stress and strain) components that store and release energy during loading to protect soft tissues from being damaged[41], recent evidence in humans has suggested that its elastic properties dominate[42]. These elastic spring-like properties allow the Achilles tendon to deliver explosive propulsion during ambulation as they may bear up to 3500 N before rupture[2]. Aside from cases of injury, Achilles tendon mechanical properties may be influenced by genetics[43], development[44], and aging[45].

Several studies have used conventional quasi-static methods to evaluate tendon mechanical properties[46,47]. However, given that the Achilles tendon typically performs at high and repetitive loads at or near failure, the clinical relevance of utilizing fatigue testing becomes increasingly important. Cadaveric and animal studies have shown that the response of tendon to fatigue loading is marked by three phases of damage[48]. In particular, stiffness initially increases, reaches a maximum, and then gradually decreases. This gradual decrease in stiffness is attributed to accumulated sub-rupture damage, which ultimately leads to the dramatic increase in peak deformation and decrease in stiffness prior to failure[48-50]. Interestingly, measured tendon fatigue *in vivo* in humans[51,52] has been less than that observed *in vivo* or *ex vivo* in animals[53]. Future work is necessary to fully evaluate this mechanism since these studies were not designed to control for the loads evaluated, which affects *ex vivo* fatigue damage[54].

Compositional, structural, and biomechanical properties of pathologic Achilles tendon

Following injury, Achilles tendons are biologically altered at both the cell and ECM levels[47], including a high density of inflammatory cells within the repair site[47,55]. Collagen content is decreased compared to control tendons[56], and is correlated with failure stress in ruptured tendons[56]. Within a few days of injury, tenocyte numbers are greatly reduced, expression of scleraxis (Scx, often used as a tenocyte marker) is substantially diminished, and apoptosis is evident[19]. Throughout early to intermediate healing, collagen-3 and biglycan have been shown to be upregulated[57]. In addition, in the middle-stages of healing, collagen-1[57], versican[57], decorin[57], matrix metalloproteinases (MMPs)[58,59], tissue inhibitory metalloproteinases (TIMPs)[58], and ADAMs[58] become upregulated, indicating further tissue remodeling. With healing, cell number and density return to baseline values[47]. Together, these findings suggest that healing results in altered Achilles tendon compositional properties that may reflect the structural and mechanical quality of the newly deposited tissue.

The Achilles tendon undergoes high repetitive loading demonstrated to influence tendon composition, suggesting the importance of the underlying mechanotransductive signaling response[19-22,57,60,61]. Harnessing the therapeutic effects of mechanical loading, as evidenced in normal tendon, may provide potentially transformative methods to enhance healing in injured tissues. Moderate running in mice was found to increase growth factor production, proliferation of tendon stem cells, expression of collagen-1 and tenomodulin, but had not effect on the expression of genes associated with cartilage and bone phenotypes[20]. However increasing the length of running episodes resulted in increased expression of both tendon, cartilage, and bone genes, indicating that excessive mechanical loading may cause metabolic changes and differentiation of TSCs into non-tenocyte lineages[20]. In a separate study, uphill running had a positive effects on tendon composition and mechanics, showing increased expression of collagen-3 and IGF-1, and decreased expression of fibromodulin, biglycan, degradative enzymes, TGF-β1, and CTGF[21]. Identifying changes in collagen synthesis in *in vivo* human studies has been more challenging. Following a 2-week single-limb immobilization period, humans were subjected to one hour of treadmill running[60]. After one hour of treadmill running, increased collagen synthesis was detected in both Achilles tendons. No changes were observed by Power Doppler ultrasound or in tendon cross-sectional area[60]. To further characterize the downstream signaling effects of mechanical loading, studies have investigated the role of TGF-β (Fig. 3A-C). Specifically, the effect of cyclic strain has been shown to mirror that of TGF-β stimulation[22]. In a related study, it was found that a single session of activity and treatment of TGF-β modulated the expression of collagen-1, Scx, and three mechanosensitive

miRNAs, suggesting a mechanism for tendon adaptation and healing[61]. Additionally, fluid shear stress used as a surrogate for cyclic strain, was found to induce Scx expression[19] (Fig.3D-F). Taken together, these studies demonstrate that mechanical loading and its downstream mediators directly affect tendon composition.

Compositional property changes stimulated through variations in loading protocols may allow for potentially therapeutic treatment strategies. In a study examining the effects of post rupture mobilization, late changes in ECM in addition to a 14-fold increase in mRNA expression of collagen-I, collagen-II, versican, decorin and biglycan were observed when compared to an immobilized group[57]. Such compositional findings were confirmed with histological evidence that showed increased blood vessel, fibroblast, and new collagen formation[57]. Conversely, stress deprivation via Achilles tendon detachment resulted in increased MMP-13, MMP-3, TIMP-2 in culture, and the addition of cyclic hydrostatic compression had no effects on subsequent gene expression[63]. Surrogate measures for *in vivo* composition such as tendon strength, stiffness, and ultrasound echo intensity have been correlated with collagen type and content[47]. Although several studies have aimed to demonstrate the potential clinical benefit of load dependent therapies, additional characterization is warranted prior to translation into humans.

Compositional changes with healing are mirrored by structural and biomechanical alterations. Following complete Achilles transection in animal models, tendon stumps remain well defined. During healing the gross appearance of the tendon changes, becoming wider, denser, and less translucent with time[64]. The reduction in tendon transparency occurs in conjunction with deposition of new fibrils with altered diameter distributions[19] and decreased longitudinal organization[55,65] (Fig.4). With healing, new fibers gradually become more aligned[65,66] and with this altered structure, tendons may elongate[67]. Notably, Achilles tendon elongation has been correlated with poor clinical outcomes[68]. Despite the increased alignment of newly deposited elements, scarred portions may remain non-recoverably disorganized with associated inferior mechanical properties[69].

Promising new imaging methods have proven effective in assessing structural components and predicting mechanical properties. Tissue birefringence, a measure of structural organization, was able to predict tendon modulus throughout healing[69]. Similarly, echo intensity using low frequency B-mode ultrasound is correlated with tendon stress and normalized stiffness during healing[70]. This method may also measure strain directly and be useful to identify partially torn Achilles or those susceptible to rupture[71]. Taken further, high frequency ultrasound has been able to directly measure fiber alignment[72] a critical property in determining mechanical performance of tissue[36]. Such imaging techniques capable of structural and mechanical analysis offer an exciting means of monitoring tissue healing as well as risk of injury or re-injury.

The specific effects of mechanical loading on structural remodeling in healing Achilles tendon remain controversial. Structural adaptation to mechanical load is evident through increased tendon thickness following exercise in rats[73]. Consistently, after prolonged ankle immobilization in multiple species, structural organization is known to decrease[57,74]. Attempts at creating a mod-

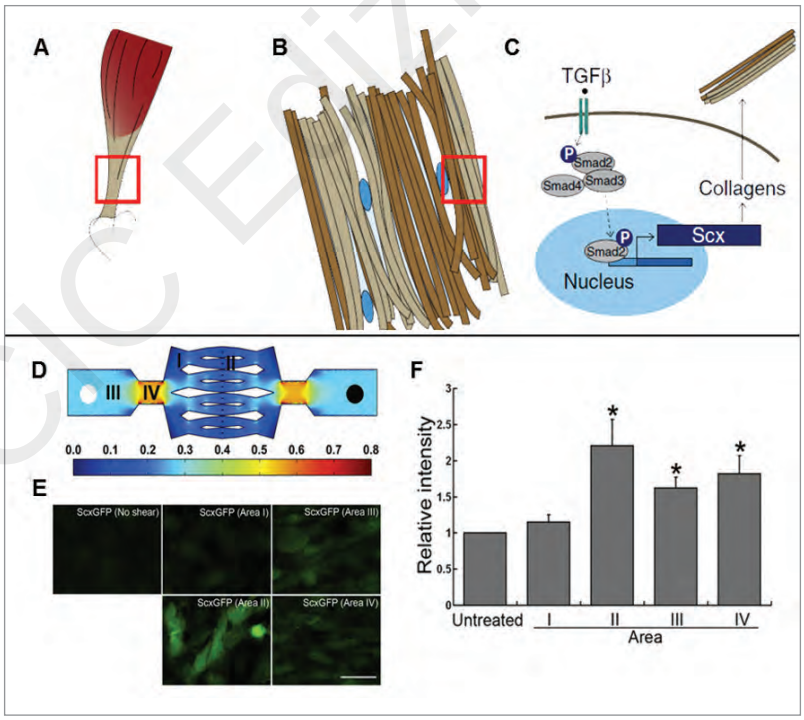

Figure 3A-F. Effects of mechanical loading on Achilles tendon composition. (A-C): The Achilles tendon (A) is composed of an extracellular matrix (B) containing cells known as tenocytes. (C) TGF-β signaling leads to downstream activation of the smad proteins, leading to expression of scleraxis (Scx) and collagens. (D-F): To elucidate the effects of fluid shear stresses on the downstream expression of Scx, a microfluidics device was used to provide a dose dependent response of fluid shear stresses (D, regions I-IV). (E,F) Moderate shear stresses promote increased expression of Scx, whereas removal of shear stress resulted in no expression of Scx. Collectively, these studies suggest that mechanical loading and its downstream mediators directly affect tendon and may be partially mediated by TGF-β signaling.
Panels A-C: Image reproduced with permission from Sharir et al. (2011)[62].
Panels D-F: Image reproduced with permission from Maeda et al. (2011)[19].

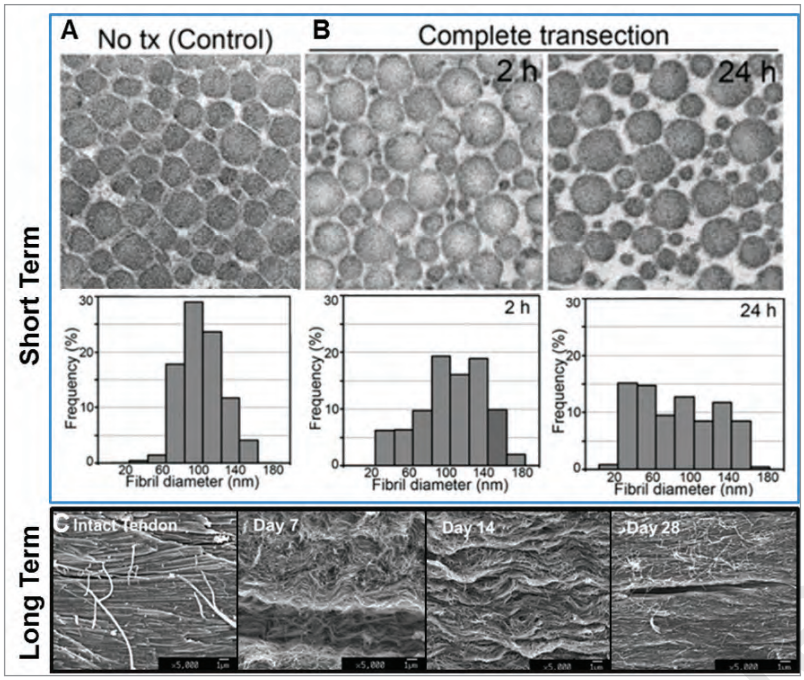

Figure 4. Effects of injury on Achilles tendon structural properties.(A-B) Within 24 hours of complete Achilles tendon transection, fibril diameter distributions show a greater number of large and small diameter fibrils, indicating a structural change in response to injury. (C) In the longer term, transverse SEM data indicates that the initial disorganization observed gradually leads to more longitudinally aligned collagen fibrils with healing.
Panels A-B: Image reproduced with permission from Maeda et al. (2011)[19]. Panel C: Image reproduced with permission from Sasaki et al. (2012)[65].

el to explore how excessive loading may participate in Achilles tendinopathy has generated mixed histological results[21,73,75-77]. These varied results[21,73,75-77] suggest that the response of tendon to mechanical load is protocol dependent and that histological evidence alone is insufficient to fully characterize tendinopathy. Determining the optimum loading conditions and the mechanisms by which this impacts tendon remodeling requires careful evaluation, with particular focus on load magnitude, frequency, and duration.

Injured Achilles tendons display inferior mechanical properties and increase in cross sectional area during healing[46,47,56]. Examples of inferior quasi-static mechanical properties following injury include decreased ultimate stress, maximum load, stiffness (Fig. 5A), elongation to failure, modulus, and percent relaxation (a measure of tendon viscoelasticity)[46,47,69]. Although conventional quasi-static mechanical tests have shown inferior material properties following injury, they lack the clinical parallel to *in vivo* tendon performance observed in fatigue testing. In particular, the number of cycles to failure, as a result of fatigue testing, has been shown to decrease dramatically following injury[69] (Fig. 5B) and may better mirror the collagen breakdown process observed with repeated loading *in vivo*[78]. The mechanisms driving mechanical changes in tendons likely stem from changes in structure and composition with injury. For example, it is believed that viscoelastic properties that decrease in injured tendon[79] may be a result of alterations in collagen structure[80] that, in turn, affect friction between collagen fibers and ECM[41], fluid flow through the ECM[81], and cross links between molecules[82]. With healing, tendon mechanical properties may demonstrate partial recovery[47], but complete recovery is not achieved.

To evaluate the effects of dose-dependent loading on healing, tail suspension[83,84], Botox[85], immobilization[74], whole body vibration[86], and exercise[21,83] have been used as model systems. Collectively, these studies have demonstrated that Achilles tendon mechanics are highly influenced by the magnitude[83-85], timing[83], and duration[21] of loading. Specifically, tendon mechanics were shown to improve with just four loading periods for both early and late healing[83] and inhibition of loading via treatment with Botox and tail suspension could reduce quasi-static mechanical properties by up to 80%[85]. Dynamic mechanical properties, such as the loss and storage modulus, were inferior in Achilles tendons that were immobilized[74]. Interestingly, one study attempting to create degenerate conditions in the Achilles tendon via uphill running found that the loading protocol actually led to improved tendon modulus and failure stress[21]. To determine if animal-based findings supporting the positive impact of loading during tendon healing translate to humans, a randomized control trial was conducted where subjects were randomized into an early tensional loading or cast immobilization[87]. The groups showed no differences in functional outcomes measured by the Achilles Tendon Total Rupture Score (ATRS) or heel-raise index after 52 weeks, but the elastic modulus was improved. This further supports the concept that simple *in vivo* assays do not directly assess tendon function suggesting the need for *in vivo* image-based assays that assess tendon structure-function relationships.

Several studies have utilized sophisticated biomechanical tests to characterize injured and healing tendons, but, due to their high cost and complexity these have remained research tools. Three dimensional

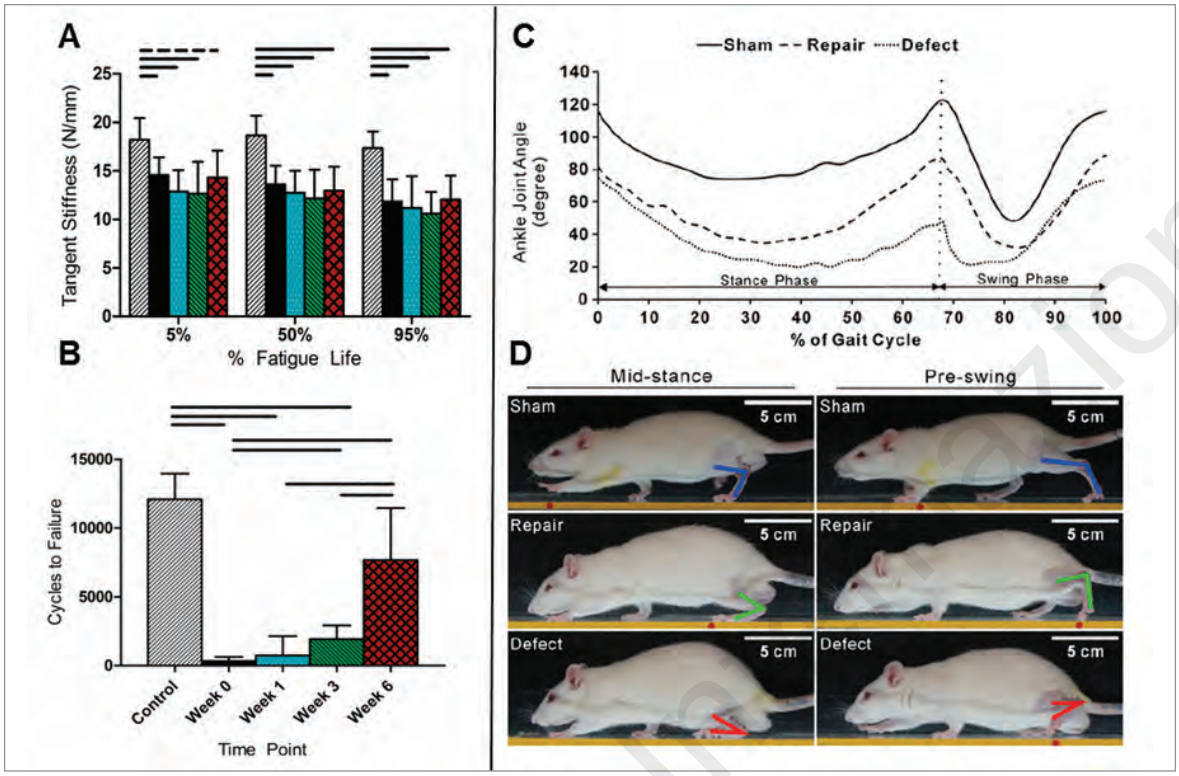

Figure 5A-D. Biomechanical response of the Achilles tendon to injury and healing. (A-B) Following an acute injury, the tangent stiffness (A) and the number of cycles to failure (B) decreased. (C-D) Video-based measures to evaluate rat gait following injury demonstrated that injured and repaired animals ambulated with lower ankle joint angles compared to normal controls. When quantified over the course of healing, the ankle joint angle was shown to be a more sensitive metric compared to the Achilles Functional Index.
Panels A-B: Image reproduced with permission from Freedman et al. (2013)[69]. Panels C-D: Image reproduced with permission from Liang et al. (2013)[90].

gait analysis found that individuals with Achilles tendinopathy had less tibial external rotation moment and peak internal rotation compared to healthy runners[88]. Although this study gives insight into the prospect of future exercise programs that may avoid such potentially harmful movements, it is unknown whether the change in gait was due to aberrant running biomechanics or was followed by the Achilles tendinopathy. In a separate study, runners with a non-rearfoot strike exhibit a higher Achilles tendon impulse during running, which may contribute to injury[89]. In rats, a video-based gait system detected differences in healing Achilles tendons that showed improvement with healing[90] (Fig.5C,D). Still, the severity of injury remains unknown since no uninjured controls were included in the study[90]. In another *in vivo* functional assay, the passive elastic properties as assessed by ankle equilibrium position and dynamic torque of the rat ankle were affected by torn dorsiflexor and extensor ankle muscles[91]. This technique may have significant application in the clinic, where a constant effort exists to link *in vivo* ankle properties to tissue level mechanics. Finally, ultrasound-based measures of tendon mechanics have been investigated. For example, conventional and shear wave elastography have shown that tissue elasticity decreases in ruptured Achilles tendons, thus highlighting potential clinical utility[92,93]. However, such methods assume that material properties and wave velocity remain constant with loading, which therefore may restrict application of these techniques to small strains. Other ultrasound-based methods may overcome such limitations, such as the acoustoelastic strain gauge that relates changes in echo intensity during movement to tissue mechanical properties and has shown excellent reliability and agreement between limbs[94].

Biological augmentation for tendon healing

Overview

Tendon development and healing is a well-orchestrated process requiring highly ordered molecular signaling events influenced by mechanical stimulation and surrounding environmental factors[95]. To best augment Achilles tendon healing through targeted therapeutics and tissue engineering strategies requires sufficient understanding of the *in vivo* milieu that dictates tendon development. Importantly, tendons injured during early phases of development heal without scar at an accelerated rate[96,97].

Tendon Development

In early studies regarding tendon formation, there was substantial emphasis on the extracellular matrix[98]. Recent work has focused on tenocyte differentiation, and requisite molecular and mechanical signaling. Axial tendon formation has been shown to require early FGF signaling for induction of Scx expression, an early marker of commitment to the tenocyte lineage that persists through maturation[99-101]. In chick wing buds, BMP over expression decreased Scx expression, while Noggin over expression, a BMP antagonist, had the converse effect. Despite over expression of Scx in the presence of Noggin no ectopic tendon formation occurred[100]. These studies suggest that although Scx may be necessary for tendon formation, it is not sufficient. TGF-β signaling is also required for tendon formation. In mouse limb buds, removal of TGF-β signaling resulted in absent expression of Scx and tenomodulin, a downstream differentiation marker[102]. Interestingly, mechanical stimulation in mouse tendons resulted in TGF-β signaling and downstream Scx expression. Many other factors influence this process, and the detailed biological program responsible for healthy tendon formation remains a highly active field of research.

Molecular biology of tendon healing

Numerous signaling pathways have been demonstrated to participate in the orchestration of tendon healing. It is no surprise that several such pathways shown to have a significant impact on healing are also key regulators of development (e.g., BMP, TGF-β, and early growth response (EGR)[103]. In the rat, over expression of BMP-14 at the Achilles tendon during healing resulted in increased tendon tensile strength as compared to control tendons[104]. As BMP signaling has been demonstrated to interfere with Scx expression, this highlights the intricate and not always straight forward nature of healing. In contrast, EGR1, a transcription factor that unlike BMP has been demonstrated to participate in tendon differentiation, also promoted healing of the Achilles tendon in a rat model. Further, and similar to development, there are numerous other molecular signaling pathways involved in healing (e.g., CTGF, VEGF, TGF-β, IGF-1, and FGF)[105]. As each of these pathways appears to play a specific role in development, exploration of their function in healing as well as tissue engineering remains critical.

Therapeutics and tissue engineering

Several studies have used therapeutics and tissue engineering approaches in attempts to reduce signs of tendinopathy and to enhance Achilles tendon healing following rupture. Several studies have suggested the prospect of stem cell therapies in the treatment of tendinopathy[106]. When seeded on decellularized tendon matrices[107,108] these cells produced a surrounding environment very similar to native tissue. In addition, compared to traditional culture, MSCs maintained under hypoxic conditions[109] were found to demonstrate a more physiologic phenotype. Other therapeutics such as amnion derived multipotent progenitor cells demonstrated improved mechanical properties after application in injured rat Achilles tendons[110]. Finally, although whole blood injection[111], Platelet Rich Plasma (PRP)[27,112], and other adjuvant therapies have demonstrated potential clinical use[113], some even supported by small trials, none has a sufficiently consistent track record to merit a consensus recommendation.

Tissue engineering strategies utilizing 3D scaffolds have been engineered to integrate between ruptured ends of Achilles tendons in rats[114] and rabbits[115] (Fig. 6). For example, *in vivo* and *ex vivo* experiments demonstrating that collagen-PDF implants recapitulate the structural, compositional, and mechanical properties of control tendons, and show capacity for good integration *in vivo*[116]. Incorporation of biodegradable synthetic scaffolds may present an additional strategy for future research[117,118].

Future perspective and conclusion

There is much information regarding the anatomy, diagnosis, treatment, and biomechanics of normal and healing Achilles tendons, however there remains many research areas requiring further investigation. Although well controlled basic science studies are not a direct substitute for large scale clinical trials, they are important in resolving outstanding fundamental questions regarding means of treatment in a consistent and well established model. This includes studies designed to determine whether non-operative treatment of Achilles tendon ruptures is equivalent to operative treatment, and identification of the optimal rehabilitation protocol. For example, the benefits of eccentric exercise on Achilles tendon healing have only been performed in the context of tendinopathy[12,118-124], and its potentially therapeutic effects following injury or repair require further evaluation. Future studies should provide a comprehensive approach to study tendon healing, through careful evaluation of mechanical, structural, compositional, and functional tissue properties. In particular, it will be informative to relate image-based modalities evaluating tendon structure to dynamic mechanical properties. These studies should be prioritized due to their potentially translatable nature. Additionally, there is a need for greater characterization of the dose-dependent response of mechanical load on tendon. Results from such studies would further allow for much needed research into development of effective adjuvant therapies that could be translated into improved outcomes.

Continued investigation into promising direct biologic interventions, such as BMP, EGR1 or other combinations of cells and cytokines would seem capable of generating useful therapies in a reasonable time

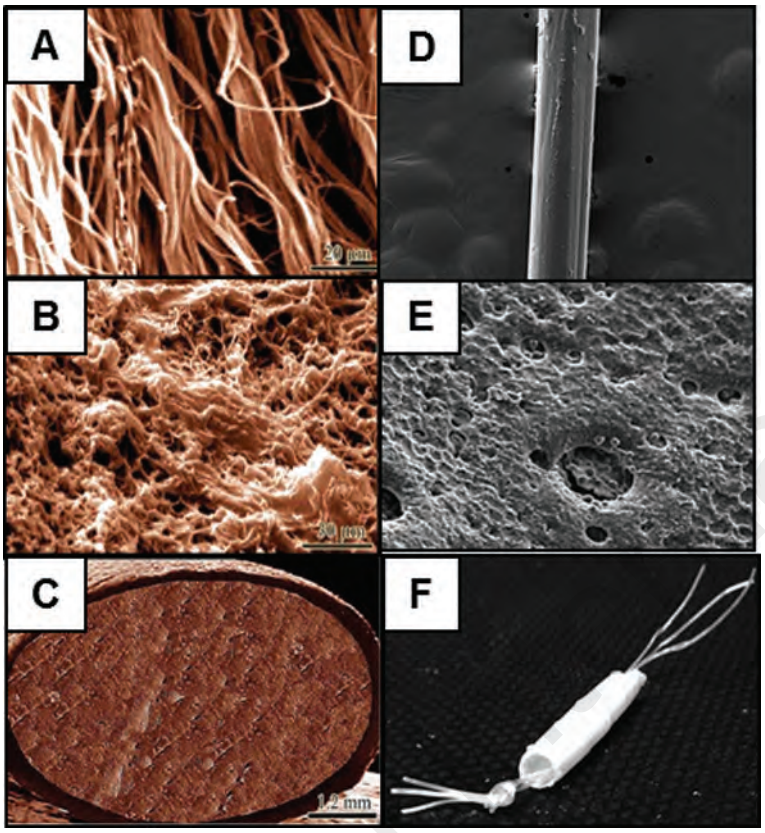

Figure 6A-F. Tissue Engineering Strategies to Repair Ruptured Achilles Tendons. Tissue engineering strategies utilizing 3D scaffolds have been engineered to integrate between ruptured ends of Achilles tendons. (A-C) The collagen-PDS implant engineered demonstrated fibril-like characteristics when viewed in the transverse direction (A, scale: 20μm) and porous morphology with fibers connected by cross links in the transverse direction (B, scale: 20μm). *In vivo* and *ex vivo* experiments demonstrated that collagen-PDS implants recapitulate the structural, compositional, and mechanical properties of control tendons, and show capacity for good integration[116]. (C) SEM showing the entire collagen-PDS implant (scale: 1.2 mm). (C-F) In a separate approach, poly(3-hydroxybutryrate-co-3-hydroxyhexanoate) (PHBHHx) was evaluated as a potential scaffold for rat Achilles tendon healing. SEM images demonstrated that the fibers (D; scale: 200x magnification)used to construct the PHBHHx tubular scaffold also contained surface pores (E; scale: 500x). (F) SEM showing entire PHBHHx implant. Once implanted, these scaffolds showed comparable mechanical properties to rat tendon, no secondary immune response, evidence of tissue remodeling and cell alignment, and a return to normal animal load bearing.
Panels A-C: Image reproduced with permission from Meimandi-Parizi et al. (2013)[115]. Panels D-F: Image reproduced with permission from Webb et al. (2013)[114].

course. Lessons from development may continue to expand this list of putative treatments, as well as our fundamental understanding of the healing process. Cell based therapies and tissue engineering also represent a related avenue well suited to facilitate Achilles tendon healing. While none of these promising therapies has had a marked impact on patient outcomes thus far, recent and ongoing work offers reasons to be optimistic regarding facilitation of Achilles tendon healing and coming improvements in patient centered outcomes.

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