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The role of animal models in tendon research

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Tendinopathy is a debilitating musculoskeletal condition which can cause significant pain and lead to complete rupture of the tendon, which often requires surgical repair. Due in part to the large spectrum of tendon pathologies, these disorders continue to be a clinical challenge. Animal models are often used in this field of research as they offer an attractive framework to examine the cascade of processes that occur throughout both tendon pathology and repair. This review discusses the structural, mechanical, and biological changes that occur throughout tendon pathology in animal models, as well as strategies for the improvement of tendon healing.

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Introduction

Musculoskeletal pathologies account for more than half of chronic conditions for populations over the age of 50 in developed countries[1] and for 30% to 50% of all sports-related injuries.[2] In 2006, 15.6% of individuals surveyed in the United Kingdom reported the prevalence of a longstanding musculoskeletal disorders.[3] In the same year in the United States, musculoskeletal diseases and injuries resulted in direct healthcare costs and lost wages adding up to $950 billion.[1] Pathologies of the tendon, or tendinopathies, account for a substantial portion of musculoskeletal disorders. Their severity ranges from transient pain and inflammation, to chronic conditions involving partial or total ruptures of the tendon.

Tendons are soft tissues that transfer forces created by muscle to bones. Understanding the basics of mechanical function and structure of a healthy tendon is essential to re-establishing these attributes in the injured tendon. Damage to tendons often results in pain that impairs a person's ability to move in a smooth and coordinated manner. These changes have a cascading effect, leading to altered joint-loading patterns, which can ultimately result in mechanical degradation of joint integrity.[4]

A healthy mature tendon consists of a hierarchy of structured collagen intermingled with tenocytes and embedded in an extracellular matrix (Fig. 1).[5] At the macroscopic scale (1 mm to 10 mm), a tendon consists of bundles of fascicles that are covered by connective tissues known as the epitenon and endotenon, respectively. These connective tissues contain the neurovascular structures supplying the tendon. Tendon fascicles (50 µm to 300 µm) consist of bundles of collagen fibres with tenocytes between fascicles. The next level of tendon structure consists of parallel collagen fibrils (50 nm to 500 nm) that have a 'crimped' appearance in the absence of tensile load directed along the length of the tissue. At the smallest levels are microfibrils and tropocollagen molecules, which are around 1.5 nm in diameter.

Tendinopathy can be identified with a variety of assays. Through histology, tendinopathy can be identified by some or all of these characteristics: small tears and disorganisation of the collagen fibres, changes in cell number and shape, variations in vascularity, and varying glycosaminoglycan levels.[6] Biochemical tests can also identify tendinopathy by identifying the regulation of matrix metalloproteinases and their inhibitors.[7] Tendinopathy also leads to altered mechanical properties prior to tissue failure.[8] Due in part to the large spectrum of tendon pathologies, tendinopathic disorders continue to be a challenge to address clinically. The efficacious and long-lasting repair of tendons continues to challenge surgeons. For example, poor surgical

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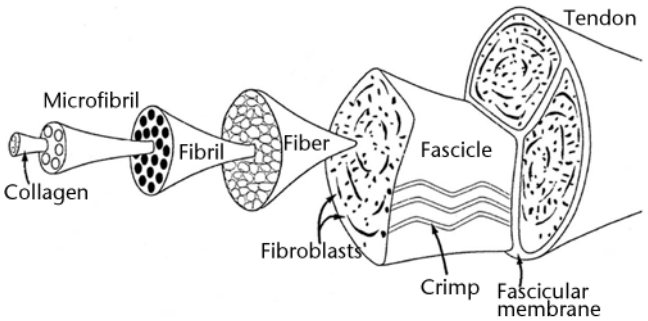

Fig. 1

Schematic representation of the hierarchical structure of a tendon. Reprinted from Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. The role of mechanobiology in tendon healing. J Shoulder Elbow Surg 2012;21:228-237[5] with permission from Elsevier.

outcomes and re-tear rates of large rotator cuff tears have been reported to be between 76% and 94%.[9,10]

Animal models offer an attractive framework to investigate the etiology of tendinopathy. Unlike human tissue, which only can be examined during end-stage chronic pathology, animal models provide the opportunity to obtain tissue during all stages of tendinopathy. Additionally, animal models provide the ability to reproduce consistent and repeatable injuries that can be treated in a controlled and quantifiable manner and also allow the evaluation of invasive treatments and assessments that would be unethical with human subjects. Another unique advantage of animal models is the capability of modifying the genome, particularly in the murine model. This technology allows for comparison of tendon properties in mice with and without the ability to express a particular gene globally, in a particular tissue, or at a particular time. For example, Scleraxis-knockout mice demonstrate an inferior ability to generate healthy tendons at birth compared with controls, suggesting the important role of this molecule in tendon development.[11-13] Similar studies have been conducted to investigate the role of decorin (DCN), byglycan (BGN), mohawk (MKX), collagen V (COL V), collagen XI (COL XI), interleukin-4 (IL-4) and interleukin-6 (IL-6) to name a few.[14-21]

However, animal models of tendinopathy cannot truly replicate the human condition. Many lab animals are quadrupeds and subject their tendons to different magnitudes of load than their human counterparts, making it difficult to replicate the pathology seen clinically. Additionally, molecular differences between animals and humans further confound the ability to make direct comparisons between species. For example, the rat rotator cuff model does not fully represent the anatomy, movement kinematics, or kinetics that exist in the human shoulder[22] and rodents do not possess a homologue of the human MMP1 gene.[23] Despite these limitations, the rat model is still widely used, as it is considered a good choice given the practical considerations.[22] Overall, it is important to understand that while translational research is the goal, animal models allow researchers to understand cellular and tissue-level principles in the context of a living organism.[24,25]

This manuscript will review and evaluate animal models that have been developed to understand the aetiology and pathology of tendinopathy as well as some of their translational implications. To compile the list of the most relevant literature, the search term 'tendon animal model' was used in PubMed (1525 articles), in order to prevent inadvertent exclusion of articles of interest. These were then restricted to those from the last three years (423 articles). The three-year window of time was selected as our primary goal in order to provide a summary of the most recent literature. We excluded articles that did not use animal models and those that focused on ligaments. A small number of often referenced and highly regarded previous publications were included. Several review articles or book chapters were also included because they provide comprehensive overviews prior to the most recent literature, which is the focus of this article. This review is organised according to the four major tendon groups that are commonly studied with animal models: rotator cuff; flexor; achilles and patellar tendons.

Rotator cuff

Rotator cuff tendon tears are common shoulder injuries that often require surgical repair. Despite the advanced approaches to rotator cuff repairs and post-surgical rehabilitation, the rate of both failures and re-tears have been estimated to be as high as between 76% and 94%.[9,10] Animal models have been used extensively to investigate rotator cuff tendon repair, and a careful examination of over 30 species of animal concluded that the rat shoulder possesses an anatomic architecture that most resembles the human shoulder.[22] (Fig. 2) For this reason, the rat has been the most commonly used animal model in rotator cuff research, with more than 100 full-length, peer-reviewed publications to date. Nevertheless, a variety of other valuable animal models also continue to be used to replicate aspects of rotator cuff injury and repair, including murine,[26-28] rabbit,[29,30] ovine,[31-37] canine,[38,39] bovine,[40-43] and primate.[44,45]

Because of the high failure rates of rotator cuff repairs, the methods and materials employed in the surgical repair of rotator cuff tears continues to be an active field of research. Studies in this area often use *in vitro* ovine or bovine models, and focus on surgical variables during repair such as type of suture material[41]; number of sutures or rows of suture[29,32-39,42]; type of knot[36,37,42] and type and/or number of anchors[37,42,43] used in the repair. Several of these studies indicate that knot slipping may be the cause of repair failures, as this phenomenon occurs at substantially lower loads than anchor pull-out.[36,43] Additionally, it has been suggested that increases in the

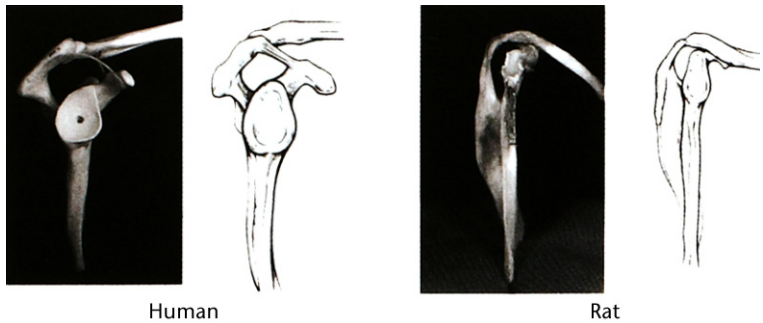

Fig. 2

Photographs and schematic representations showing the similiarities of human and rat shoulders from a lateral view. In both anatomies, the supraspinatus tendon passes through the enclosed arch of the acromion. Reprinted from Soslowsky LJ, Carpenter JE, DeBano CM, Banerji I, Moalli MR. Development and use of an animal model for investigations on rotator cuff disease. J Shoulder Elbow Surg 1996;5:383-92[22] with permission from Elsevier.

number of stitches used during the repair is the determining factor in the failure load.[32] On the other hand, it has been suggested that the contact area and failure strength is dependent upon the number of rows used in the repair.[33,35,37] In general, although each study makes a compelling argument for the preferred protocol, there is still no clear consensus on the best materials and methods to employ.

The rat model is used to investigate rotator cuff pathology in animals and to better understand the cascade of biological processes that occur in the shoulder joint after a rotator cuff tear. To create a model, the most common practice is a surgical transection of one or several tendons in the shoulder.[46-49] To replicate the chronic effects of tendinopathy and rotator cuff tears more closely, a tendinopathic condition can be created by overuse, in which rats are run on downward-sloping treadmills to impose eccentric forces on the tendon.[50] Alternatively, a combination of overuse followed by acute injury has also been used to model rotator cuff tendinopathy.[51,52] Use of these paradigms has led to the conclusion that damage to rotator cuff tendons leads to an increase in atrophy and/or fatty infiltration of the muscle.[46-48] It has also been discovered that acute rupture of the tendon leads to decreased regulation of the signaling pathway that maintains muscle mass in response to mechanical loading (Akt/mTOR), but denervation without transection of the tendon leads to upregulation in this pathway.[47] Interestingly, rotator cuff tears can have a direct effect on neighbouring intact tendons, such as the biceps, and can include decreased collagen organisation, more rounded cell shape, increased Aggrecan expression and decreased modulus.[53] Finally, it has also been shown that the glenoid cartilage is also altered by a rotator cuff tear, as significant decreases in mechanical properties and thickness have been measured regionally in the glenoid.[54]

To date, the synergistic effects of repair techniques and various rehabilitative protocols on rotator cuff healing is still a debated topic. Current research has not clearly elucidated the role of mechanical loading in the pathological shoulder joint, but also the benefits/drawbacks of post-operative immobilisation continue to be confounding.[5] Methods such as casting immobilisation,[49,55] botulinum toxin injections,[56,57] and overuse activity[51,52] have been used to alter the mechanical loads imparted upon the shoulder joint before and after surgical intervention. Results suggest that pre-operative immobilisation may have beneficial effects on long-term healing because this approach has resulted in improved cellularity and collagen organisation, while simultaneously increasing the Collagen I:Collagen III ratio, which is indicative of the end stages of tendon healing.[57] Decreased post-operative loading has been shown to result in increased organisation of collagen, decreased cellularity and a more elongated cell shape.[49] While the benefit of post-operative immobilisation of the shoulder seems to be beneficial, the effectiveness of such a strategy is limited to discrete time frames.[55] It has also been suggested that myogenic and adipogenic genes are influenced by mechanical loads, as they are upregulated in muscle when unloaded, but tendon-specific genes are more influenced by the presence of the injury.[57] Overuse of the shoulder following a rotator cuff repair also causes significant changes in transcriptional regulation of chondrogenic genes, while also resulting in deleterious changes to the mechanical integrity of the tendons and cartilage within the shoulder. Surprisingly, joint function is not affected by these changes.[51,52]

Animal systems have been used routinely to investigate the use of potential regenerative agents (i.e., growth factors,[40,58] platelet-rich plasma (PRP),[30,59,60] hormones,[61,62] bone morphogenetic protein,[63] autologous cell seeding,[64] and stem cells[65-68])while the design, implementation, and translational viability of engineered tissue constructs have

been concurrently developed. These studies simulated an acute rupture of the rotator cuff tendon(s) of rats,[69] rabbits,[30] canines,[39] or primates[45] and regenerative agent(s) were subsequently applied directly to the injury site,[30] injected into the joint space,[59] delivered via subcutaneous injection,[61] osmotic pump,[58] or scaffolds/grafts.[40,45,60,63,64,70] Scaffold designs are not limited to the purpose of delivering agents in a controlled manner, as some have also been proven to improve mechanical strength at the repair site[39] and remodel to tendon-like architecture while integrating bone and tendon.[45] The scope of this review does not permit a full exploration of the effects of all of the regenerative agents used in tendon research, so we will only briefly review a few studies examining the use of PRP and stem cells, which have recently garnered considerable interest as potential therapy modalities. Research investigating the effects of PRP has yielded mixed results. In some cases, it has been shown that the addition of PRP has decreased inflammation, improved tendon thickness and continuity, and increased biomechanical strength,[30,59] but other studies have shown that the presence of PRP did not have any substantial phsyiological effects and the failure load of rotator cuff repairs was not altered by PRP augmentation.[60] The healing potential of mesenchymal and adipose-derived stem cells has recently been tested with rabbit and rat models[65-68,70] and results of such experiments have provided more consistent results than PRP-based studies. Results suggest that stem cell-based therapeutic modalities have the potential to decrease fatty infiltration after cuff repair,[66] offer improvement in tendon-to-bone healing,[65,70] increase generation of collagen I[67,68] and improve the tendon's mechanical properties.[68] For a more thorough review of the use of engineered regenerative agents in the rotator cuff, the reader is referred to Isaac et al.[71]

Achilles

The Achilles tendon is the largest and strongest tendon in the human body, routinely experiencing loads up to 12.5 times the weight of the individual.[72] This, along with other factors, likely contributes to substantial Achilles tendon pathology and highlights the need for both surgical and conservative Achilles tendon research.

Rats have been used frequently to model Achilles tendon rupture and tendinopathy, using primarily one of two methods of inducing injury; mechanical or chemical. Mechanical induction of tendinopathy has proven to be dependent on activity level. For example, rats that ran on a 10° incline at 17 m/min to 20 m/min for 60 min/day showed only slight adaptive changes in their Achilles tendons,[73] however, a slight increase in speed and duration resulted in signs of tendinosis such as fibrillar mirotearing, hypercellularity and increased GAG deposition.[74] Alternatively, tendinopathy has been generated by having rats run in a bipedal position,[75] or with repetitive electrically-induced eccentric contraction of the calf.[76] Alternatively, chemically-induced models of tendinopathy are attractive because they require less time and resources. Although the collagenase-induced Achilles tendinopathy model has been the most widely used approach, several new methods have recently been proposed. For example, after an intratendinous injection of TGF-β1, Achilles tendons show both attenuated material properties and a gene expression profile consistent with chronic tendinopathy, with a reverse seen to both changes after exercise.[77] Another novel approach to chemical induction of tendinopathy consists of using injections of Substance P, a well-known neuropeptide and modulator of pain that encourages tenocyte proliferation and neovascularisation. Although the presence of Substance P seems like it would be beneficial to tendon healing, it has been shown that repeated injections of Substance P followed by exercise elicits an exacerbated inflammation-repair response, which leads to a tendinopathic condition.[78] The role of Subtance P in tendinopathy is therefore particularly intriguing as it can be effectively added or blocked,[78] potentially leading to clinical applications.

Similar to the rotator cuff, animal models have been used extensively to improve Achilles tendon repair methods through improvements in material and techniques. For example, impregnating a suture with Butyric acid has shown improved biomechanical and histological properties in a rabbit model,[79] while coating a suture with mesenchymal stem cells appears to improve repair strength in the period when a repair is typically the weakest (7 to 10 days).[80] Demonstrating the importance of suture technique, a bovine model showed that the triple-strand technique provided greater mean peak load to failure, and greater resistance to gapping when compared with Dresden, Krackow, and modified oblique Dresden techniques (Fig. 3).[81] This result likely reiterates the well-known tenet

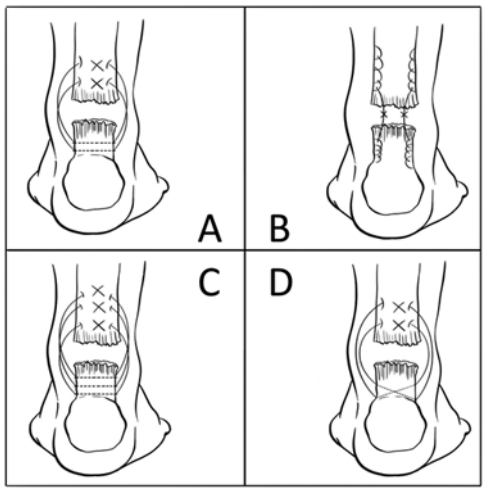

Fig. 3

Diagram showing the suture configurations of the a) Dresden, b) Krackow, c) triple and d) oblique technique (figure modified from original with permission).[81]

of tendon repair – repair strength correlates to the number of sutures crossing the repair site.

There is a variety of rehabilitation protocols for Achilles tendon repair, and animal models have been valuable in defining areas for human study. Examination of the biological processes that occur in the rabbit under various rehabilitation protocols has led to the understanding that protein expression profiles in the Achilles tendon are significantly affected by early movement when compared with immobilisation.[82] Moreover, the effect of a single loading episode on healing Achilles tendon results in significant, yet short-lived changes in the expression of inflammatory, healing and coagulation markers in a rat model.[83] In addition, it appears that the magnitude of the loading episode after repair may play a role in determining tissue quality and callus formation, which define the mechanical integrity of the healing Achilles tendon.[84] These studies suggest that frequent, short, early loading after an Achilles tendon injury is important in improving and expediting tendon healing.[85]

The use of imaging modalities varies depending on the pathology, but the superficial location of the Achilles tendon makes it a particularly attractive tendon for examination with ultrasound. Ultrasound has the potential to be a cost-effective, non-invasive method of determining degree and location of Achilles tendon disease. Sonoelastography is an ultrasound based imagine technique which has demonstrated an ability to track tendon elasticity - a possible surrogate for healing.[86] As another example, chronic local hypervascularity has been linked to the pain associated with tendinopathy, and contrast-enhanced sonography is proving efficacious in grading vascularity after induced tendinopathy.[87]

Tissue engineering approaches using the rabbit model have been commonly used to address sequelae of Achilles pathology such as adhesions[88] and tendon defects.[89] For example, a recently developed electrospun silk wrap has been shown to be effective in providing significant reduction in adhesion formation in rabbit Achilles tendons, while also improving the biomechanical properties of the repaired tendon.[88] Conversely, a new equine collagen membrane has shown histological signs of integrating into a rabbit Achilles tendon defect; however, the graft's effects on resultant material properties or healing remains unknown.[89] As Achilles tendon ruptures appear to be on the rise,[90,91] this work could prove instrumental in improving both the strength and quality of operative tendon repair.

A more thorough understanding of the biological interplay between tendinopathy and other disease states remains elusive. For example, the effects of hypercholesterolemia on the rotator cuff and patellar tendons have been studied in several animals[44,92,93] In regards to the Achilles tendon, a rat model has been used to elucidate the deleterious effect of diabetes on tendons and tendinopathy. In a diabetic state, activity improves material properties of the Achilles tendon,[94] while that same state attenuates expression of several healing markers after an acute injury.[95] This work points to the importance of moderate exercise in diabetic patients, while also suggesting that the healing response of tendons in such patients is indeed impaired.

Flexor

The full recovery of digit function following a flexor tendon injury remains a clinical challenge, with suboptimal repair rates ranging up to 31%.[96,97] The most common complication is caused by deformation or gapping between tendon stumps, which leads to decreased mechanical properties and increased potential for rupture of the repaired tendon.[98] Even if gapping does not occur, curbing the formation of peritendinous adhesions following repair remains difficult. These adhesions inhibit the smooth gliding of the tendon past surrounding tissues, which leads to reduced mobility, pain, and the inability to perform activities of daily living.[99] In the past, the canine model was relied upon to perform research on flexor tendons.[98-100] More recently, a wider variety of animals have been used to characterise flexor tendon injury and repair, including chicken,[101] canine,[102-104] ovine,[105] porcine,[106,107] and rabbit[105-110] models. The best choice of model system will depend on the essential characteristics that must be mimicked for a particular research question.

Many flexor tendon studies have focused on improving the fixation methods and rehabilitation protocols used to prevent gapping and subsequent formation of an adhesion. Recently, an *ex vivo* uniaxial test demonstrated that the Yotsumoto-Dona technique, a side-locking loop structure paired with a horizontal mattress peripheral suture, performed significantly better in 2 mm gap force, yield force, ultimate force, stiffness, energy to yield, and energy to failure tests when compared with the often-used modified Kessler technique, which consists of a grasping type structure, paired with a running peripheral suture.[106] In a separate *ex vivo* study, pulley-wrapped tension was applied to the tendon to better simulate gliding over bony surfaces.[107] In this case, the interrupted horizontal mattress technique proved to be significantly more effective in regards to ultimate tensile strength and resistance to gapping. An *in vivo* approach to this problem provides a more comprehensive perspective on this issue, as biological healing factors and cyclic loading are taken into account. It was recently demonstrated that extending the core suture purchase and deepening the epitendinous suture repair was critical in improving repairs, as this strategy significantly reduced the incidence of gap formation and tendon rupture in a canine model. As far as rehabilitation protocols are concerned, several studies have suggested that early active mobilisation leads to more effective tendon gliding, less adhesion formation and more joint mobility[108,109]; however, this type of approach may lead to unacceptably high rupture rates.[99] It has

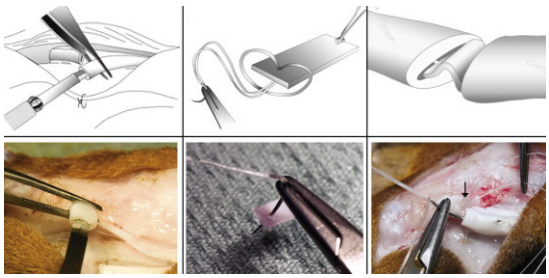

Fig. 4

Schematic and photographic representations of the surgical protocol used to secure a mechanically rigid scaffold into the core of a flexor tendon. Reprinted from 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;9:6905-14[104] with permission from Elsevier.

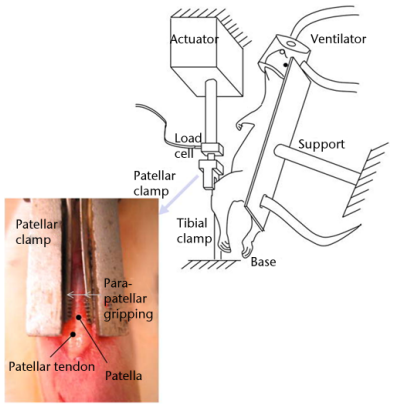

Fig. 5

Image demonstrating the experimental set-up for *in vivo* fatigue testing of the patellar tendon. This allowed *in vivo* tendon loading without interfering with the movement of the tendon. Reprinted from Fung DT, Wang VM, Andarawis-Puri N, et al. Early response to tendon fatigue damage accumulation in a novel in vivo model. J Biomech 2010;43:274-9[117] with permission from Elsevier.

been suggested more recently that a well-controlled rehabilitation protocol may result in a somewhat limited range of movement, but this measured approach to remobilisation lowered the risk of rupture, perhaps making this option preferable.[101]

Similar to other tendons, the role of regenerative agents such as BMP-2, MSCs, and PRP have been examined to determine if they have the ability to augment scar formation in flexor tendon, but these approaches have been met with very limited success.[103,105,110] On the other hand, although it is not typically used in the treatment of other tendons, the paired use of sodium hyaluronate (NaH) and human recombinant basic fibroblast growth factor has recently provided intriguing results regarding repair of a flexor tendon. Continued subcutaneous injections of these agents on a rabbit flexor repair site significantly reduced tendon diameter, increased ultimate tensile strength and yield strain, enhanced the maturation rate of the tenoblasts, and increased the diameter and density of the collagen fibrils.[111-113] Additionally, a one-time direct application of NaH with Lactoferrin Peptide (PXL01) dissolved into solution curbed the need for repeated subcutaneous injections, and significantly increased the mobility of the rabbit paw, while having no adverse effects on the mechanical strength of the tendon.[114]

The use of tissue engineering applications has been investigated in flexor tendons, as the release of growth agents over extended periods of time may be beneficial in preventing gapping and rupture. Soft or absorbable constructs, such as calcium phosphate matrices, collagen sponges, and bioabsorbable membranes, have been developed to introduce growth factors to repaired flexor tendon sites.[103,115] Such approaches have provided limited positive results, but can be easily adapted to accommodate different choices of regenerative agents. Rigid scaffolds offer a similar ability to reliably deliver growth factors and cells in a controlled manner, but they are also able to maintain a rigid form suitable for tendon repair surgery and long-term mechanical strength to prevent gapping (Fig. 4).[104] Overall, these approaches are still in developmental phases, but the use of such technologies is promising.

Patella

The human patellar tendon is also susceptible to tendinopathy. However, the patellar tendon is of particular interest not only because it regularly experiences high-force cyclical loading, but also because portions of the tendon are commonly harvested during anterior cruciate ligament repairs. The patellar tendon is amenable to study with animal models because the tendon readily undergoes experimental cyclical loading, is easily dissected, and portions of the tendon are easily harvested to replicate a clinically relevant injury.

Because of the emerging evidence pointing to the importance of tendon fatigue as a precursor to tendinopathy and possibly tendon rupture, the patellar tendon of rats and mice has been used in the development of an *in vivo* fatigue model[116,117] (Fig. 5). Results from this model have suggested that the initial accumulation of sub-rupture damage caused by *in vivo* cyclic loading leads to subsequent changes in mechanical function.[116] Furthermore, like in the Achilles tendon, the upregulation of genes such as collagen I (Col I), collagen XII (Col XII), matrix metalloproteinase 2 (MMP2), and tissue inhibitor of

metalloproteinase (TIMP3) shows an initially adaptive response to cyclic loading that is attenuated after a certain amount of damage.[118] However, while a fatigue model evokes a different molecular response than an acute rupture, structural restoration of an overly fatigued tendon may never be complete.[117,119] This points to the importance of developing better tools for recognising tendon fatigue in the clinical setting, as irreversible tendon damage may occur earlier than the consensus suggests.

Adult tendons do not heal through a regenerative process, but rather a scarring process[120]; therefore, understanding the biological underpinnings of tendon healing has become a significant vein of research, commonly employing the patellar tendon as a model. In comparison with tendinopathy of the patellar tendon, acute defects of the patellar tendon are commonly iatrogenic when the tendon is harvested for the purposes of anterior cruciate ligament reconstruction surgery. Therefore, those studying the reasons for inefficient tendon healing have employed a similar approach, where the central third of the patellar tendon is removed, known as the 'window defect' model. As sometimes observed in patients,[121] rat tendons exhibit ectopic chondrogenesis and ossification following this injury as well, while expression of biglycan increases and levels of aggrecan and decorin decrease.[122] Although the function of these proteoglycans is not fully understood, these changes may, in part, explain the poor tissue quality that is often observed after this injury. Indeed, despite some histological and molecular indications of healing, ultimate load and stiffness only reach 48% and 63% of baseline respectively.[123] Thus, efforts have been made to recoup the mechanical deficiencies that occur as a result of harvest of the patellar tendon. For example, after the introduction of tendon-derived stem cells to a window defect in a rat model, tendons exhibited increases in collagen production and improvement in resultant alignment and material properties.[124]

Physical therapy is currently a mainstay of non-operative treatment for patellar tendinopathy. Specifically, eccentric training has shown significant increases in failure load, failure stress, and vascularisation, while concentric training only significantly improved failure stress.[125] Nevertheless, alternatives to physical therapy have recently been studied as viable options for tendon rehabilitation. Laser, light emitting diode, radiofrequency ablation, hyperbaric oxygen and autologous tenocyte therapies have all shown some promise with respect to improving the mechanical or histological properties of healing tendon,[126-128] while the beneficial effects of high-energy extracorporeal shockwave therapy have not shown as much benefit in tendon repair as in the treatment of other musculoskeletal disorders.[129-131] In general, the goal is to improve the quality of tendon tissue after injury and allow earlier and more aggressive rehabilitation protocols to speed recovery.

The effects of age on tendon mechanics and metabolism continue to be elucidated through animal models. The Achilles tendon has been used to understand better prenatal tendon properties, which have the ability to undergo scarless repair, forming a structurally uninjured tendon. Not surprisingly, as a neonatal mouse Achilles tendon matures, collagen content increases, fibril diameter increases, and the tendon becomes stronger.[132] On the other end of the age spectrum, a study of both the murine patellar tendon and *in vivo* rat Achilles tendon has suggested that an aged tendon has inferior mechanical and histological properties.[14] Specifically, it is the maladaptive changes in passive biomechanical properties of an aged tendon, such as increased stiffness, increased peak tension and increased estimated modulus that are most interesting, as they are postulated to be part of the reason why the incidence of Achilles tendon ruptures is more common in middle-age. Thus, the ability to predict the viscoelastic behavior of a tendon could have clinical applications. This highlights the importance of a recently developed empirical model which uses *in vivo* measurements to accurately predict the viscoelastic properties of damaged or aged murine patellar tendons based on a single stress measurement.[133]

Conclusion

Tendinopathy can result in significant pain and disability, which has driven the need for research dedicated to tendon repair and healing. In comparison to other fields, tendon research is still in its infancy, and the complex nature of the tissue continues to provide intriguing answers to pointed research questions. This review discusses the role of animal models in regards to the current understanding of the mechanical, structural and biological changes that occur during tendon repair and healing. The unique benefits of animal modeling techniques will continue to be used in the future to promote experimental endeavours in this field of study. Through the use of such models, it is expected that translation to the human tendon will be successful and that therapeutics, diagnostics and clinical outcomes will continue to improve.

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