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Scaffolds for Tendon and Ligament Repair and Regeneration

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Abstract

Enhanced tendon and ligament repair would have a major impact on orthopaedic surgery outcomes, resulting in reduced repair failures and repeat surgeries, more rapid return to function, and reduced health care costs. Scaffolds have been used for mechanical and biologic reinforcement of repair and regeneration with mixed results. This review summarizes efforts made using biologic and synthetic scaffolds using rotator cuff and ACL as examples of clinical applications, discusses recent advances that have shown promising clinical outcomes, and provides insight into future therapy.

Introduction

Tendons and ligaments can fail through chronic deterioration or trauma, and both pathways lead to substantial reduction in musculoskeletal function, resulting in reduced productivity and quality of life. There are over 400,000 shoulder tendon and ligament surgical repairs, more than 300,000 tendon and ligament surgical repairs for foot and ankle, and over 100,000 ACL repairs performed annually in the US²⁹. Surgery intended to replace, repair, or reinforce tendons and ligaments with autografts or allografts has provided effective therapeutic approaches, however major limitations remain (Table 1). Over several decades, biologic scaffolds derived from human and animal tissues have been generated, and synthetic scaffolds have been manufactured from absorbable and non-absorbable polymers to reinforce and replace tendons and ligaments. Until recently these approaches have resulted in modest or no improvement in clinical outcome. Improved understanding of the mechanics of repair, replacement requirements, the biologic activities and mechanical

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properties of the extracellular matrices (ECM), and synthetic devices, are now leading to new approaches to and improvement of surgical outcome. There is now the realistic potential for new technologies to significantly improve the clinical outcomes of previously challenging tendon and ligament pathology.

Tendon and Ligament Function

As novel scaffold materials are designed to directly repair or augment repair of tendon and ligament injuries (Figure 1) design criteria based on normal mechanics, matrix components and organization, and cellular phenotype, which includes the origin of stem/progenitor cells that contribute to these tissues become increasingly important.

When tendons and ligaments are exposed to the functional loads associated with activities of daily living (ADL) they do not routinely fail because they are strong enough to avoid trauma and stiff enough not to significantly deform (Figure 2). These functional characteristics have been difficult to measure in patients. However studies in various animal models have revealed several important results. Tendons experience larger in vivo percentages of failure force than ligaments (Figure 2). For example, goat patellar tendon forces increase with level of activity, achieving almost 40% of failure force for vigorous ADLs^{10,43}, while the anterior cruciate ligament in the same animal never exceeds 7-10% of failure force³². Thus, the safety factor for this tendon is only 2.5, while that of the ligament is approximately tenfold^{8,10}.

Tendon and ligament forces also vary with location in the body and with species (Figure 2)^{38,49} indicating the need to tailor repairs to the specific tissue of interest. Knowing these peak IVFs and the normal tendon stiffness also permits research to be conducted using novel functional tissue engineering strategies, including autologous mesenchymal stem cells, collagen scaffolds and mechanical preconditioning of the implant prior to surgery (Figures 3a and 3b)^{8,10}.

Scaffolds designed for repair and replacement of these injured tissues require that we account for these location- and ADL-related differences. Selected scaffolds must exceed known peak IVFs with added safety factors in case patients resume pre-injury activity level, experience unexpected loading, or demanding physical activities. If the scaffold provides only a proportion of the mechanical properties of the repair construct then the scaffold may provide lower levels of stiffness and strength, and the complete repair construct should be assessed for its mechanical properties.

Tendon and Ligament Biology

The structures of tendons and ligaments are well designed to serve their biomechanical functions, consisting of regions containing specialized cells that assemble aligned type I collagen fibers in the midsubstance to anchor to the adjacent bone or muscle through interface regions known as the enthesis and myotendinous junction (MTJ), respectively. The extracellular matrix includes collagens I, II, VI, and X, tenascin C, scleraxis, proteoglycans (aggrecan, biglycan and decorin), and cellular phenotype including tenocytes and progenitor cells with multi-phenotype potential of the three regions. The MTJ anchors the adjacent muscle¹² and the enthesis minimizes the stress that accumulates at the interface between the

relatively compliant tendon/ligament and bone. Direct attachment sites are organized into zones consisting of the bone, mineralized fibrocartilage, non-mineralized fibrocartilage, and finally the tendon/ligament midsubstance.

Tendon and Ligament Repair: Function and Biology

Following injury, tendons and ligaments follow the normal stages of wound healing, including inflammation, repair, and remodeling⁷¹. As the blood clot forms, hematopoietic cells including macrophages and neutrophils regulate the inflammatory stages of healing. The blood clot is primarily fibrin based, but transitions to a matrix rich in tenascin C as surrounding mesenchymal progenitors, derived from the tendon's paratenon, infiltrate during the repair stage^{20,22} and form a callus with scleraxis-expressing cells (Figure 4) that mature the repair tissue. Finally, the cells organize the collagen during the remodeling stages to produce the final repair tissue that is often less organized than normal tendon/ligament with altered mechanics^{21,69}.

Given the variability in safety factors for different tendons and ligaments, scaffold-based repairs should be uniquely designed to tolerate different loading demands without stretching or failing. Two mechanical design targets for these repairs (Figures 3a and 3b) include the need to meet and even exceed peak IVFs and to match the shape of the normal loading curve up to these peak values and beyond^{8,10}. Partially-injured ligaments and tendons may tolerate the much lower peak IVFs that they routinely experience, however repeated loading can compromise the stiffness of these repairs, risking further tissue deformation. Larger forces can further slow the naturally healing tissue, thus preventing these structures from meeting design targets. Surgically repaired tendons can be vulnerable, especially when rehabilitation forces are imposed too quickly. Some animal studies suggest that repairs might never meet these design targets if the repair site is either overloaded, causing suture slippage, or underloaded, which shields stress from proper levels of force and deformation. Scaffolds have the potential via mechanical reinforcement to restore the functional biomechanics of these repairs; they also have the potential to enhance the biologic events of repair, to accelerate those events, or maximize their effectiveness. However when scaffolds are not sufficient then replacement may be needed.

A common replacement procedure is the anterior cruciate ligament (ACL) reconstruction. Although the success of this procedure has improved immensely over the past 20 years, the graft material can still lead to failure and other secondary complications, for example the early progression of osteoarthritis⁴⁸. Comparison of bilateral ACL reconstructions in the non-human primate using patellar tendon autografts revealed that the replacements were weak (low maximum force) and compliant (low stiffness) at 6 weeks after surgery, requiring 13 to 52 weeks to provide moderate values for these parameters⁹. Studies in other models (e.g. flexor tendon grafts) have shown similar results. Scaffolds used to reinforce or completely replace a ruptured tendon or ligament should be designed and manufactured at least based on estimates of the peak IVFs for anticipated vigorous ADLs. Further development of scaffolds could optimize both mechanical and biologic effects to maximize augmentation effectiveness.

Clinical Pathology, Treatment and Need for Enhanced Therapy

The rotator cuff tendons of the shoulder serve as an excellent example of an area in need of reinforcement (Table 1). The rotator cuff is composed of four muscles: the supraspinatus, the infraspinatus, the subscapularis, and the teres minor, and attach via their respective tendons to the greater tuberosity at the top of the humerus. These muscles function in concert to provide dynamic stabilization to the glenohumeral joint. Rotator cuff tears are a common cause of shoulder discomfort and dysfunction, most commonly in the supraspinatus, and increasing age has been correlated with the prevalence of tears^{72,82,83} (Figure 1).

Rotator cuff tears represent a prevalent medical condition especially for patients over the age of sixty years. A study of 588 patients with shoulder pain were examined by ultrasound imaging⁷² showed a 50% likelihood of bilateral tears in patients over the age of 60. When patients with bilateral tears were examined, more symptomatic shoulders were significantly more likely to have a larger tear, and patients who presented with a full thickness tear had a 35.5% prevalence of such on the contralateral side⁷². In asymptomatic patients, ultrasonographic examination showed 20% were in their sixties, 31% in their seventies and 51% in their eighties had evidence of a rotator cuff tear⁸².

Rotator cuff tears can be treated via non-operative methods or surgical repair depending on several factors. It is a general consensus that patients who sustain an acute, traumatic tear with loss of strength should be considered for a repair. However, degenerative tears causing patient discomfort are encountered more frequently. Non-operative management is a good choice for patients who have maintained good strength and for the elderly. Surgical management is indicated when non-operative treatment fails, with strength loss and with pain⁶².

In making the decision to repair a tear, the factors influencing tendon healing must be taken into account. These factors include age⁶, medical co-morbidities, smoking¹¹, tear size^{5,25,31,44}, muscle fatty infiltration²⁸, method of repair, and type of construct utilized. These factors are important, as studies have documented the correlation of successful rotator cuff healing with achievement of a more favorable functional outcome^{5,31,39}. It is likely that for some patients with compromised biologic repair mechanisms no surgical repair approach will result in a satisfactory outcome.

Failure of adequate tendon-to-bone ingrowth places the repair at risk for re-tear. Multiple studies have documented significant re-tear rates between 5% and 90% in arthroscopically-managed tears, with those of larger size being more at risk^{5,24,47} (Table 1). An analysis of 500 consecutive repairs showed that, as the tear size increased, the retear rate increase in a linear fashion Intraoperative determinants of rotator cuff repair integrity⁸⁰. An analysis of 1000 cases showed that the best independent predictors of retear were, in descending order, anterior-posterior tear length, tear size area, medial-lateral tear length, tear thickness and age of patient at time of surgery⁴⁴. Overall, they found that retears occur in 27% of full thickness tears. A study of arthroscopic repair for large and massive tears found only a 5% rate of healing²⁴. When a re-tear of the rotator cuff occurs, patient selection for revision repair is crucial and in order to give the patient the best chance of success, the revision

repair should be optimized to improve healing rates and mechanical stability. However, as stated previously, biological factors that can impact a specific patient's ability to repair can preclude the success of surgical intervention.

ACL reconstructions are typically replaced with either autografts or allografts, and both require sufficient revitalization of the graft since significant cell death typically occurs within the first four weeks after reconstruction³⁷. The necrotic response corresponds with a decrease in mechanical properties of the graft. Following this early necrotic response, cells that are either within the joint space and likely derived from the synovium and synovial fluid, or mesenchymal stem cells in the bone and bone marrow will begin to infiltrate the graft tissue and produce an attachment site to bone in the tunnel, a process that should follow normal enthesis development with anchoring of collagen, fibrocartilage formation, and mineralization of the fibrocartilage. Scaffolds have the potential to reinforce these grafts particularly during the phase where decrease in mechanical properties is experienced. They may also be used to reinforce a surgical repair of the native ACL. In either case the resultant construct should meet the design criteria for stiffness and strength throughout the recovery period.

Approaches to Support Tendon and Ligament Repair, Replacement and Regeneration

Optimization of the biologic environment is one way to improve the likelihood of a good clinical outcome. Multiple biologic solutions are currently being studied and employed for repairs. The concentrations and influence of bone morphogenetic proteins, matrix metalloproteinases, fibroblast growth factors, and transforming growth factor beta have been examined⁸¹. Several other studies have explored the influence of platelet rich plasma with rotator cuff repair in human subjects^{15,66}. Although these factors may be able to assist biologic healing, no consistent functional advantage has been achieved.

A method of improving the mechanical integrity and biologic environment of rotator cuff tendon repairs is the application of a reinforcement device or scaffold (Tables 2, 3). Scaffolds may provide structural support when applied appropriately, and may act as a vehicle for cells and new tissue formation. Reinforcement devices are used in several ways. (1) The device is used as an overlay on the surgical repair and functions in parallel with the repair to mechanically reinforce the repair by load sharing and protecting the suture attachment of the tendon to bone⁶⁴. (2) The reinforcement device is placed over the repair construct and acts as a scaffold to support new tissue formation and increasing the thickness of the tendon. (3) The device is placed between the sutures and the tendon, increasing the area of the tendon contacting the bone, and potentially enhancing the contact pressure and ultimate load to failure⁴; (4) the scaffold is placed between the repair tissues to enhance the biologic interaction.

The mechanical advantage of scaffolds has been demonstrated in several studies. Mathematical modeling demonstrated that the biomechanics of rotator cuff repairs could be improved with scaffolds that have tendon-like properties, but supra-physiologic scaffold stiffness did not translate into a stiffer or stronger repair¹. A study of the fatigue and failure of acellular dermis constructs for rotator cuff repairs using a range of pre-tensions showed significant elongation of the grafts¹⁸. A canine model of rotator cuff repair to study the

application of a poly-L-lactide woven device showed significant increase in successful repair at 12 weeks after surgery¹⁹. Similarly this canine shoulder model was used to study the application of a poly-L-lactic acid-reinforced human fascia patch². At time zero, the ultimate load of the repair construct was increased with the augmentation although no difference in stiffness was appreciated. At twelve weeks, however, the shoulders treated with fascia patch demonstrated reduced failure load compared to controls, even though the device showed a biocompatible host tissue response.

Scaffolds have also been examined in human cadaveric studies. Eight paired human cadaveric shoulders underwent rotator cuff repairs, one shoulder of each pair was repaired with the poly-L-lactic acid woven device and one was not, and initial stiffness, yield load, ultimate load and failure mode were determined⁵¹. The results demonstrated a significant increase in the yield load and ultimate load in rotator cuff repairs, with no significant impact on initial stiffness and a significant reduction in failure by suture pulling through the tendon. A similar study was performed using the fascia lata patch⁵². After repair, the cyclic gap formation and the failure points were examined between 5 and 180 N for 1000 cycles. The data illustrated significantly less gaping with the augmented repair and all augmented repairs were able to complete all 1000 cycles, whereas only three of nine non-augmented repairs were able to make it to 1000 cycles.

Biologic Scaffolds for Tendon and Ligament Repair

A range of biologic scaffolds has been generated from xenogeneic or allogeneic tissues and processed to remove cells for use in tendon and ligament repair. The tissue processing may involve chemically crosslinking the collagenous matrix, the outcome being to increase tensile properties and to reduce rate of degradation. The human-derived matrices may be regulated as allograft material and classified as human tissue for transplantation. The number of grafts used to reinforce shoulder soft tissue repair exceeds 30,000 per year, and grafts used in foot and ankle soft tissue repair exceed 20,000 per year²⁹, indicating a significant clinical need. A list of some of the matrices that are cleared or approved by the FDA and commercialized is provided in Table 2.

The ECM patches consist primarily of type I collagen, and are likely to contain smaller amounts of collagen III, IV, elastin, and proteoglycans although thorough analysis of the biochemical composition varies depending on the product. These materials are frequently provided in multiple layers to enhance the mechanical properties of the product to try and realistically provide mechanical reinforcement to repair sites. Matrices derived from dermis, small intestinal submucosa, and other tissues that do not bear substantial loads have been found to have low mechanical strength, stiffness, and suture pull-out strength, requiring that they be used in multiple layers or enhanced by chemical crosslinking. Advantages include delivering a biologic scaffold that should provide a local environment for rapid cell attachment and enhanced new tissue formation. Disadvantages include poor mechanical properties, poor suture retention strength, risk of disease transmission, variability of product, and necessary harvest from animals or humans.

Synthetic Scaffolds for Tendon and Ligament Repair

Synthetic scaffolds have been manufactured for tendon and ligament repair using a variety of polymers and fabrication methods, with the potential to optimize to particular desired features. Aligned fibers in various conformations have also been used, including attempting to replicate the fiber organization of an ACL. Knitted mesh offers the surgeon the ability to cut and trim the material to a desired size, although these knitted materials have poor tensile properties (strength and stiffness). Woven mesh can provide high tensile strength and stiffness, and high suture retention strength, although cutting the device may not be possible.

Replacement synthetic ACL replacements have been explored, largely without success. A carbon fiber-based implant resulted in carbon particles within the joint, implant stretching and rupture with corresponding long term failure. Gore-Tex and Dacron implants provided high tensile strength but poor long-term stability. Other artificial ligaments have similarly resulted in poor long-term function. However more recently the LARS Ligament has been reported to provide a functional replacement, although long term outcomes have yet to be determined⁵⁷.

Several synthetic scaffolds are presently marketed for tendon and ligament reinforcement. X-Repair is a complex multilayer woven mesh, slowly degradable and with tensile strength and stiffness similar to human tendons. Artelon is a partially degradable knitted mesh that can be cut by the surgeon, although it has modest tensile properties. Recently there have been reports of biocompatibility issues, particularly when used to provide an articular repair of the carpometacarpal phalangeal joint (base of the thumb)^{14,67}. Biofiber has a special open woven structure that has suture pullout strength similar to Graftjacket, and is also available with a collagen coating. The Leeds-Keio artificial ligament and the LARS ligament are made from non-degradable PET, and are not available within the US^{55,57}.

Advantages of synthetic scaffolds include safety (no risk of disease transmission), potential to specify and control features, defined and narrow specifications of manufacture, ability to provide terminal sterilization, controlled degradation rate and high biocompatibility. Disadvantages are few, although some non-degradable and partially degradable devices have shown long term (>2 years) problems that may be related to long-term fatigue of the materials. Synthetic materials are perceived to provide less support for tissue ingrowth and new tissue formation, although evidence suggests some materials support autologous cell homing for new tissue formation¹⁹. The degradation products of synthetic devices must be considered. PLGA and PLLA devices generate lactic acid and glycolic acid, two simple and naturally occurring molecules that have substantial safety profiles when used in soft tissues. Non-natural synthetic polymer degradation products should be understood in significant detail.

Mechanical Augmentation of the Surgical Repair

The primary rationale for using synthetic or ECM devices in tendon and ligament repair has been for mechanical reinforcement, providing additional mechanical support to the original repair, allowing the biologic repair to proceed without experiencing excessive and disruptive loads. As such the device design requirements include strength, stiffness, and absorption

rates that are appropriate for the tissue repair. The strength of the device should be greater than the peak in vivo loads experienced by the repair tissue and preferably similar to the tissue itself, therefore ensuring that the device will not fail under normal loads. The device should have stiffness that allows for substantial load sharing, providing reinforcement and at the same time ensuring some load will be applied across the repair site, required for optimal biologic repair. At the same time, the device should not stretch more than within the toe region of a load-displacement curve rather than experiencing loads in the linear stiffness region (Figure 2). Tendon and ligament have normal function between 7% to 40% of failure loads depending on ligament or tendon type^{8,10,32,43}. Several products used for reinforcement have strength and stiffness that are substantially less than human tendon values (Figure 5), and require being stretched substantially (30 - >100%) before developing a measurable load¹⁸, although a synthetic device has been designed with a short toe region and stiffness and strength that closely match human tendon properties (Figure 5)^{19,51}.

Suture retention strength is an additional feature that is critical to product function, as it is the link between the tendon, ligament, or bone and the device and allows the device to function. The suture pull out strength should be high enough to allow the product to resist functional loading, and, simultaneously, the elongation required to impose that load should be very low. Multiple sutures are usually used to attach the device in place and the accumulative stiffness and strength of the sutures should provide appropriate fixation. Since ligament and tendon normally function with up to 10% and 40% of tissue failure load, respectively¹⁰, it therefore can be estimated that combined suture retention strength should be a minimum of 30% of the failure load of the tissue. For rotator cuff this would approximate to a requirement of 100 – 200 N per suture. While suture pullout strength is frequently measured for repair devices, the stiffness of the suture attachment is rarely if ever reported.

The device should impose these mechanical properties over a period of time that allows for functional repair to occur. While younger individuals may regain good functionality relatively quickly (3 – 4 months), mature and older individuals require longer repair times of 9 – 12 months. Therefore, the device should be slowly degrading and preferably retain the majority of its mechanical properties for the same time period. The device and its degradation products should not induce any adverse reactions. The non-crosslinked extracellular matrix products are likely to remodel rapidly and quickly lose their mechanical properties. Of the synthetic products, X-Repair is slowly degrading and retains 80% of its properties for approximately 8-9 months. It is then slowly absorbed with the degradation product lactic acid being rapidly absorbed by the soft tissue environment and no evidence or any reports of any local effect. Artelon is a partially degradable product (50% remains after 6 years).

The primary repair of tendon and ligament is via sutures that have substantial strength, although the suture-repair construct is relatively weak. It has been proposed that this attachment has potential for improvement by using additional reinforcement devices placed between the suture and the tendon and acting primarily in compression. In an ovine cadaveric study of rotator cuff repair, placing a PTFE membrane strip between the suture and the tendon was shown to increase footprint contact pressure and increase load to failure

by almost 50%⁴. An additional feature of this approach is to increase the footprint contact area by modulating compressibility and thickness of the device. It seems likely that appropriate devices have the potential to increase footprint area by several fold. It remains to be seen if this approach can influence the rate of clinical success.

Biologic Augmentation of Tendon and Ligament Repair

It has been recognized that scaffolds have the potential to augment the biologic features of tendon and ligament repair by improving the quality and quantity of the tendon and ligament tissue, and by enhancing the biologic events at the repair site. Extracellular matrices can provide an excellent scaffold for cell attachment and consequent matrix formation, and as an overlay over tendon and ligament have the potential to increase the volume and thickness of tissue and overall quality of tissue¹³. The biologic events at the junction of ACL repair has been proposed to be enhanced by platelet-rich plasma combined with a collagen scaffold, although the use of a more natural blood clot or fibrin clot may be more effective⁵⁶. Enhanced biologic repair at the interface between tendon and bone would be a major advance. A fibrin clot has also been used to enhance the biologic repair of rotator cuff tears⁶³. In animal studies demineralized bone positioned between the tendon and bone has been shown to enhance that biologic interaction⁷⁰. These studies indicate there is substantial potential for enhanced biologic repair of tendons and ligaments. The repair site should remain stable and tissues held in close proximity to allow the biologic events to occur, either by sutures or mechanical reinforcement. It seems likely that a combined mechanical and biologic approach will have the most effectiveness in enhancing tendon and ligament repair.

Clinical Use of Scaffolds for Tendon and Ligament Repair

Primary surgical repair of selected ligament and tendon ruptures has historically proved problematic, with high associated failure rates. Even though autograft and allograft reconstruction techniques have improved the surgical outcomes, they also have shortcomings. Autografts have graft site morbidity and reduced tensile strength during graft remodelling³⁷. Allografts, meanwhile, carry the potential for infection and have higher failure rates⁵⁰. In an effort to improve surgical outcomes, provide a more rapid return to function, and reduce healthcare costs, different scaffold materials have been developed and used clinically to provide both a mechanical and biological augmentation of tendon and ligament repairs and reconstructions. Scaffold materials that have been used include synthetic non-absorbable, synthetic absorbable, and biologic acellular ECM (Table 2)^{3,23,64}. Synthetic materials are designed to mechanically augment the repair by load sharing while host tissue heals and may integrate with and thicken the host tissue. By contrast, biologic materials are thought to augment the repair by improving the healing process and, to some degree, may also provide mechanical augmentation.

Polyethylene terephthalate (PET) is a non-absorbable material with the desired properties of excellent tensile strength while potentially allowing for tissue ingrowth. The Leeds-Keio artificial ligament was developed from mesh-like PET and used as a graft in ACL reconstructions, although studies demonstrated there was an unacceptably high long-term failure rate⁶⁵, and over 50% having increased laxity and 100% osteoarthritis at 10-16-year follow-up⁵⁵. More recently, another PET ligament, the Ligament Augmentation and

Reconstruction System (LARS) was designed in hopes of overcoming the previous problems.. Short-to-medium term results using LARS have demonstrated results comparable to published autograft techniques⁵⁷. However, high-quality, long-term follow-up studies have not been performed, and there have been two recent reports of failures associated with significant synovitis^{27,46}. Use of the LARS has also been reported for other soft tissue repairs including posterior cruciate ligament reconstruction and massive rotator cuff tears. In addition to PET, use of a nondegradable polycarbonate polyurethane patch has been reported to augment surgical repair of small and medium-sized rotator cuff tears with 90% intact at 12 months²³.

Absorbable scaffold materials, including poly-L-lactic acid, poly(urethaneurea), and polycarbonate poly(urethaneurea), have been used as scaffolds for ligaments and tendons, although very few clinical studies have evaluated these materials. One of the first was a polylactic acid-polycaprolacton co-polymer with carbon fiber allowing for collagen ingrowth used for ACL reconstruction with good reported results at 24 months follow-up⁷⁷, although carbon fiber-based implants had poor long term outcome¹⁶. More recently, a woven mesh of absorbable poly-L-lactic acid (X-Repair, Synthasome) was designed specifically to reinforce tendon repair with mechanical properties similar to human tendon and supported cell infiltration and matrix deposition^{19,51,75} with integration with adjacent host tendon. When used to augment large and massive rotator cuff tears, 78% of the repairs remained intact at 42 months after surgery⁶⁴.

There are a number of biologic scaffold devices utilizing mammalian ECM of small intestinal submucosa (SIS), dermis, and pericardium used as scaffolds to enhance tendon and ligament repair. Despite the current interest, availability, and use of these ECM scaffold devices, clinical outcome assessment is limited with mixed results. A number of studies have investigated the use of ECM scaffolds for rotator cuff repair augmentation and interposition grafting. Those using non-cross-linked porcine SIS did not show improved outcome and had an unacceptably high rate of post-operative inflammatory reaction^{34,76}. A recent prospective randomized study of rotator cuff repairs augmented with non-cross-linked human dermis ECM scaffolds (GraftJacket, Wright Medical) showed intact repairs in 85% of the augmented group and 40% of the nonaugmented group³ and these findings are consistent with the retrospective studies using this scaffold⁷⁹. Augmentation of Achilles tendon repairs with non-cross-linked human dermis ECM scaffolds has also been retrospectively reported with no re-rupture or complications at the 20-month postoperative follow-up⁴⁵.

Though various scaffolds are clinically available to aid tendon and ligament repair and regeneration, few high-quality, long-term studies exist. Future research should evaluate the long-term results including outcomes like clinically relevant effectiveness, safety, cost effectiveness, and ability to exceed pre-determined mechanical design criteria.

Future Directions

An improved understanding of the mechanics of tendon and ligament repair, using specific design criteria to enhance the repair construct has resulted in improved clinical outcomes. This general approach of biomimicry for reinforcement now has the potential to

substantially improve both rehabilitation and final clinical outcome in a variety of surgical repairs of tendons and ligaments. The ability to accurately determine in vivo forces and changes during injury and repair with different therapies (in experimental and clinical settings) is an important next step in developing future advances in functional treatment. When the goal is to restore the defect to normal function then it is likely that strategies for selecting suitable biologic and synthetic devices require their material properties closely match that of the native tissue (Figure 1) and that the material retains its initial stiffness and strength over the period of time required for the biologic repair to be completed, probably for several to many months. More modest clinical requirements may provide less mechanically demanding repair constructs. Setting clinical goals individualized for patients, particularly the level of functionality required, is likely to influence the repair approach, and a clinical algorithm for this would be valuable. Enhancing the biologic events to speed repair, when necessary in combination with mechanical reinforcement remains a major need. The potential to use scaffolds for delivery of active agents (growth factors, drugs, etc) that can provide the biologic stimulus offers substantial research and clinical opportunities.

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Figure 1.

Images of arthroscopic surgery of rotator cuff tear (a), repair of the tendon back to the bone (b) and reinforcement with a synthetic patch (c). Figure 1a shows the rotator cuff tendon detached (white arrows) from the top of the humerus exposing the bone attachment site (black arrow). Figure 1b shows the surgical repair where the tendon has been reattached to the bone using sutures attached to suture anchors. Figure 1c shows a reinforcement patch⁶⁴ overlaid on the surgical repair and fixed in place medially to the tendon and laterally to the bone.

Figure 2.

Defining functional design criteria for tendon and ligament repairs. A relative load-displacement curve for tendons and ligaments is depicted with load on the y-axis and displacement on the x-axis displayed as percentage of maximum load and displacement, respectively. When the tissue is first elongated (origin of curve) the force slowly develops in the so-called nonlinear “toe region.” With further elongation the tissue experiences a constant slope, called the linear stiffness. Upon further elongation, the tissue undergoes partial failures before achieving the highest point on the failure curve (the maximum force or strength). Tendons and ligaments typically do not experience loads approaching the failure region during normal activities. Instead they experience much lower loads that define the functional region. We have labeled peak in vivo forces recorded in the goat patellar tendon (PT)⁴³, rabbit flexor digitorum profundus (FDP) tendon⁴⁹, rabbit Achilles tendon (AT)⁷⁸, rabbit PT³⁸, and goat anterior cruciate ligament (ACL)³² via horizontal bars on the plot. These peak in vivo loads range anywhere from 10% (goat ACL) up to 40% (goat PT)

of maximum load. Therefore, researchers should design their repairs to match the shape of this loading curve (red arrow) up to and beyond peak in vivo forces to provide an additional safety factor.

Figure 3.

Force-displacement curves are shown for the normal uninjured rabbit patellar tendon compared to the a) naturally healing PT and one tissue-engineered repair of a central, full-length defect in the PT (autologous mesenchymal stem cells in a collagen gel) and b) two tissue-engineered repairs (autologous MSCs in collagen sponge scaffolds exposed to mechanical preconditioning) at 12 weeks post surgery. a) Note that the naturally healing tendon and the tissue engineered repair fail both criteria as they neither exceed peak in vivo forces nor match the slope or “tangent stiffness” of the normal patellar tendon. b) By

contrast, the tissue engineered repairs using autologous bone marrow-derived progenitor cells meet both criteria: using one collagen scaffold, the repair curve matches the tangent stiffness of the normal patellar tendon up to 25% beyond peak in vivo forces. When a stiffer collagen scaffold is used, the repair curve matches the tangent stiffness of the normal curve to 50% beyond peak IVFs. Figures adapted from Butler et al^{8,10}.

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Figure 4.

Paratenon progenitor cells expressing SMA contribute to patellar tendon healing. Triple transgenic mice containing 1) SMA-CreERT2 construct to drive Cre enzyme expression in a cell population in the paratenon, 2) Ai9-tdTomato Cre-reporter mice that once activated by Cre will express constitutively express tdTomato fluorescence, and 3) ScxGFP construct that is expressed in tendon cells. A lineage trace was conducted where tamoxifen was delivered to the mice prior to injury in order to label the SMA+ population (SMA9 in red). The healing process was assessed at 1, 2, and 5 weeks post-injury. The SMA9 cells form an

anterior bridge over the defect space at 1 week (A-J) but only 10% of these cells are ScxGFP+ (V). These cells differentiate into ScxGFP+ cells at 2 weeks (K-T) with over 60% of SMA9+ cells are also ScxGFP+. These SMA9 cells reduce their level of Scx expression by 5 weeks (V), which corresponds with a plateau in mechanical properties. Scale bars = 100 μ m. *significantly different than 1 and 5 weeks, ^significantly different than 1 week ($p < 0.05$). Error bars denote SD. Figure adapted from Dymant et al²².

Figure 5.

Stress-strain curves for human and canine infraspinatus tendon (IFS) of the rotator cuff, and for products used for reinforcement of rotator cuff surgical repair. Note that the human and canine IFS tendons demonstrate steep stress-strain curves indicating they undergo only a small amount of strain under these loads. In contrast some of the reinforcement products undergo substantial strain when under load. Adapted from Derwin et al^{18,19}.

Table 1

The success rates for surgical repair of rotator cuff. A review of the literature was performed to determine success rates for rotator cuff repair where imaging (ultrasound or MRI) was used to determine repair of the tendon to the bone. The data is presented using the size of the tears in the specific patient population assessed. The success rate is presented as mean + SD with the range of success rates in the different studies also shown. The data shows that attachment of the tendon to bone is not always achieved even in patients with small tears, and that this rate decreases to 54% for large tears and 42% for massive tears. This data suggests that the methods used in surgical repair would benefit from modification.

Tear Size	Published Studies	Success by imaging Mean $\pm$ SD (Range)
Small to medium (1 –	5-7,17,26,31,33,35,40,41,44,53,58-60,68,74	78 $\pm$ 7 % (60 - 90%)
Large (3 - 5 cm)	5,24,25,31,34,40,42,54,84	54 $\pm$ 21% (5 - 90%)
Massive (2 or more tendons)	25,31,34,59,61,73	42 $\pm$ 12% (24 - 63%)

Table 2

Scaffolds for Tendon and Ligament Repair

Biologic Scaffolds Product	Species	Tissue	Company
Allopatch HD	Human	Dermis	MTF
ArthroFlex	Human	Dermis	Arthrex
BioArthro	Human	Amniotic membrane	BioArthro
Connexa	Porcine	Dermis	Tornier
Dermaspan	Human	Dermis	Biomet
Graftjacket	Human	Dermis	Wright Medical
Integra	Porcine	Dermal collagen, multiple layers, crosslinked	Integra
Restore	Porcine	Small intestinal submucosa	DePuy Synthes
TissueMend	Bovine	Fetal dermis	Stryker Orthopaedics
Zimmer Collagen Patch	Porcine	Dermis, cross-linked	Zimmer
Synthetic Scaffolds			
Artelon	Polyurethane urea block polymer	Knitted mesh	Artelon
Biofiber	Poly-4-hydroxybut (P4HB)	Leno weave	Tornier
Biofiber-CM	P4HB with type 1 bovine collagen	Leno weave	
X-Repair	Poly-L-lactic acid (PLLA)	Multilayer woven mesh	Synthesome

Table 3

Mechanical properties of reinforcement patches

Tissue/Product	Tensile strength [N]	Tensile stiffness [N/mm] (range)	Suture pull-out strength [N]: simple suture	Suture pull-out strength [N]: mattress suture
Rotator cuff: infraspinatus ³⁰	2005	574 (343 - 843)	-	-
Supraspinal ³⁶	652	289 (228 - 427)	-	-
subscapulars ³⁰	1,724	594	-	-
Allopatch HD 2 (20 mm wide)	350	91.5	99.9	n/a
Artelon (SportMesh) (20 mm wide)	160	19.6	72.6	82
Graftjacket MaxForce (20 mm wide)	313	83.3	84.7	182
GraftJacket Extreme (20 mm wide)	532	146.6	106.5	229
X-Repair (bilayer) (20 mm wide)	2024	650	220	280