THE ORTHOPAEDIC FORUM

Enthesis Repair

Challenges and Opportunities for Effective Tendon-to-Bone Healing

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Abstract: On May 22, 2017, the National Institutes of Health (NIH)/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) hosted a roundtable on "Innovative Treatments for Enthesis Repair." A summary of the roundtable discussion, as well as a list of the extramural participants, can be found at https://www.niams.nih.gov/about/meetings-events/roundtables/roundtable-innovative-treatments-enthesis-repair. This paper reviews the challenges and opportunities for developing effective treatment strategies for enthesis repair that were identified at the roundtable discussion.

Tendon attaches to bone across a specialized fibrocartilaginous tissue termed the *enthesis,* which is a frequent site of injury due to a variety of factors[1]. Injury may occur to a healthy tendon after acute trauma or to a degenerated tendon after normal activity or minor trauma. Common anatomic sites of injury include intra-articular entheses (e.g., the rotator cuff, the flexor tendon, the anterior cruciate ligament, and the meniscal root) and extra-articular entheses (e.g., the Achilles tendon, the patellar tendon, and the medial collateral ligament). Although certain factors may be common to all injuries (e.g., inflammation and paucity of cells), there are also factors (e.g., etiology, biology, and mechanical load) that are unique to the particular injury mechanism or the anatomic location. Regardless of the injury mechanism or the anatomic location, if surgical repair is required, the torn tendon is reattached to its osseous anatomic footprint, and healing relies on reincorporation of the tendon into the bone at the enthesis.

Clinically, enthesis-related pathologies include rotator cuff disease, tennis elbow (the medial epicondyle), jumper's knee (the inferior pole of the patella and the quadriceps insertion of the patella), and Achilles tendinosis. The most common, and perhaps the most challenging, pathology is rotator cuff disease. The rotator cuff is susceptible to degenerative changes related to its relative avascularity. There is a 30% prevalence of rotator cuff tears in asymptomatic shoulders in patients >60 years of age[2], as well as a high percentage of asymptomatic tears in patients with a painful tear in the opposite shoulder[3]. Many tears respond to nonoperative treatment, while others are treated operatively when nonoperative treatment is unsuccessful. The difference between the rotator cuff and the many other sites of enthesis degeneration is its intra-articular environment and its exposure to synovial fluid. Intra-articular soft tissues (i.e., the rotator cuff, the glenoid labrum, the anterior cruciate ligament, and the meniscus) do not heal as reliably as extra-articular structures (i.e., the distal biceps, the lateral collateral ligament of the knee, and the Achilles tendons). The roundtable group focused its discussion on the rotator cuff, with the understanding that many of the challenges and opportunities for developing effective treatment strategies for rotator cuff repair would be more broadly applicable to other enthesis sites.

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Clinical Research

The Need to Better Understand the Disease

Rotator cuff degeneration (tendinosis) is understood to commence in the early decades of life, with partial and full-thickness cuff tears increasing in frequency in the later decades. Occasionally, rotator cuff tears are truly traumatic in nature; however, they usually occur in the presence of some degree of degeneration. Historically, extrinsic damage related to acromial spurring was considered the primary etiology; however, current opinion places greater emphasis on the intrinsic nature of rotator cuff degeneration[4], including the inherent avascularity of the rotator cuff. Unfortunately, the fundamental pathoetiology of intrinsic tendinosis is not well-understood, which limits our ability to intervene early or rigorously inform research efforts.

The histologic and molecular characteristics of human rotator cuff disease were recently summarized in a systematic review[5]. Rotator cuff disease is associated with changes to cells, vascularity, extracellular matrix (ECM) components, enzymes, cytokines, growth factors, neuronal factors, and apoptosis/cell-cycle-related factors. Relatively few studies have reported on the pathology that is specifically associated with increasing levels of severity of rotator cuff disease. The current literature on biomarkers of disease severity in human subjects is summarized in a recent review[6], and points toward inflammatory markers (e.g., interleukin [IL]-1β, IL-1ra [receptor antagonist], tumor necrosis factor [TNF]-α, cyclooxygenase [COX]-2, inducible nitric oxide synthase [iNOS])[7,8] and matrix remodeling markers (in particular, members of the collagen and matrix metalloproteinase [MMP] families)[7,9-12] as possible biomarkers of rotator cuff disease progression. Future work should seek to identify prognostic biomarkers of rotator cuff disease and its progression, which would allow improved diagnosis and management of patients and help to identify possible targets for disease-modifying interventions (which may include drugs, growth factors, cells, matrices, etc.) aimed to reduce progression and induce repair. Ideally, these efforts would utilize a large, multicenter longitudinal cohort and adopt a systematic and standardized approach that focuses on a few relevant tissue targets and common analytical methods. The Multicenter Orthopaedic Outcomes Network (MOON), which to date has enrolled over 3,500 anterior cruciate ligament reconstruction patients from 7 centers (https://www.vumc.org/orthopaedics/moon-knee-project), offers a successful and highly productive approach for performing multicenter longitudinal studies in orthopaedics[13].

The Need for Better Outcome Measures

A recent meta-analysis of Level-I and II studies investigating outcomes after full-thickness rotator cuff repair concluded that "there is not a clinically important difference in validated functional outcome scores or pain for patients who have undergone rotator cuff repair regardless of the structural integrity of the repair."[14] The current weak correlation between patient-reported outcome measures (PROMs) and structural outcomes following rotator cuff repair indicates a need for more precise imaging techniques to measure and define structural outcomes, as well as an opportunity to develop more discriminating PROMs. One possible area for improvement is to explore which subsections or individual questions in current PROMs most closely correlate or associate with structural integrity. There also is a need to better understand and differentiate the sources of shoulder pain other than that from rotator cuff pathology, and the influence of these sources of pain on the clinical outcome of rotator cuff surgery, regardless of the healing status of the rotator cuff after repair. In addition, enhanced and well-defined outcomes and consistent methods to measure shoulder range of motion and strength (including intrarater and interrater agreement and validation) should be adopted. Newer approaches for measuring shoulder range of motion using smartphone digital clinometer applications[15] or wearable technologies with remote monitoring capability[16] are attractive alternatives to traditional manual goniometer methods, but their reliability and validity need to be demonstrated in large patient cohorts. There also is a need to develop and validate a functional active shoulder test or assessment that provides a better measure of rotator cuff function than isometric strength testing. For example, an assessment of shoulder fatigue strength using repetitive, low-weight movements commensurate with activities of daily living, or development and validation of return-to-work or return-to-sport functional performance testing following rotator cuff repair, may better assess rotator cuff integrity and function.

Magnetic resonance imaging (MRI)[17-19], MR arthrography[20,21], and ultrasound[22-24] are routinely used for diagnosing rotator cuff tears or retears. Excellent sensitivities and specificities have been reported for each technique[25], yet none offers perfect reliability or the ability to discern tissue type or quality; thus, each has challenges of clinical interpretation. The Sugaya classification system is currently the most commonly used method for the evaluation of healing quality following rotator cuff repair[26], but it provides only an indirect, subjective assessment. Hence, another avenue of investigation should include understanding the relationship between objective mechanical properties and imaging characteristics of healed tendon repairs compared with those that have failed in continuity (tendon retraction and attenuation without a recurrent defect)[27] because the intervening scar tissue may not withstand load to the same degree that a healed tendon would. This would enhance existing forms of imaging assessment, like the Sugaya classification, and may elucidate why patients who are considered healed by imaging still report weakness. Improved imaging modalities and discriminating imaging outcomes (including intrarater and interrater agreement and validation) must be developed and adopted.

Demonstrating efficacy of repair augmentation strategies (scaffolds, growth factors, platelet-rich plasma, etc.) in clinical trials may prove elusive without patient-reported, clinical, and imaging outcomes that are sensitive to the spectrum of repair healing and function. Once the methods of evaluating these outcomes have improved, well-designed clinical trials can rigorously test the efficacy of strategies to improve the healing of debilitating rotator cuff tears. These trials should employ sample sizes that are large enough to allow for adequate power and

multivariate analyses, likely requiring a multicenter approach as described above.

Defining Which Factors Influence Healing

Patient factors such as age, tear size and chronicity, muscle atrophy and degeneration, tendon quality, repair technique, occupation, smoking status, and Workers' Compensation status have been shown to influence healing following rotator cuff repair[28]. However, these factors alone do not explain all of the variation in healing that is observed. It is unclear, for example, whether sex influences rotator cuff healing. Furthermore, postoperative rehabilitation is assumed to influence healing, yet there remains insufficient evidence to define the optimal protocol. While physical therapy protocols have been developed based on rigorous systematic review of the literature[29], clinical evidence for improved tendon healing with a particular approach has not been definitively reported. For example, 1 randomized controlled trial in patients <60 years of age with smaller tears showed no difference between early and late range-of-motion protocols in ultimate healing[30]. The value of postoperative cold therapy, the optimal method for postoperative bracing, and the efficacy of home-based exercise programs versus facility-based rehabilitation after rotator cuff surgery also are not firmly established[4]. The optimal rehabilitation program for rotator cuff healing may depend on patient factors and should be a focus of future investigation.

Variable healing rates after rotator cuff repair also may be influenced by differences in the intrinsic healing potential of the patient, yet relatively few studies have investigated biomarkers that are specifically associated with varying levels of rotator cuff healing[6]. Inflammatory markers (COX-2)[31] and matrix remodeling markers (in particular, members of the collagen and MMP families)[31,32] have been shown to be associated with rotator cuff healing in human subjects. One recent study identified a significantly increased risk for a rare allele involving the single-nucleotide polymorphism (SNP) rs17583842 in the ESRRB (estrogen-related receptor beta) gene in patients who experienced lateral rotator cuff retears compared with healed patients[33], while to our knowledge no studies have directly investigated cellular metrics as biomarkers of healing. Future work should seek to identify intrinsic biomarkers that predict healing after rotator cuff repair, adopting a multicenter, systematic, and standardized approach as described above. Identifying biomarkers as prognostic factors of healing after rotator cuff repair would inform current practice and possibly identify modifiable predictors of outcome, as well as provide a scientific premise for future research into modifiable variables or interventions in the treatment of rotator cuff tears.

Basic and Translational Research

Challenges of Enthesis Repair

The fundamental difficulty with repairing a tendon back to bone is the mechanical challenge of attaching a compliant material (tendon) with a modulus on the order of 200 MPa to a stiff material (bone) with a modulus on the order of 20 GPa[1]. In the uninjured state, the tendon-bone enthesis has a fibrocartilage transitional region that exhibits gradations in cell phenotype, matrix composition, tissue organization, and mechanical properties[1,34,35]. These natural gradations facilitate the effective transfer of load between the 2 materials by reducing the potentially damaging stress concentrations that would otherwise arise at their interface. There are a number of mechanical mechanisms that are conserved across species[36] at various hierarchical levels that allow for effective stress transfer between tendon and bone. On the millimeter scale, stresses can be reduced by optimization of the shape of the attachment[36,37]. On the micrometer scale, interdigitation, fiber orientation, and a compliant band increase the toughness of the interface[34,38]. On the nanometer scale, spatial gradients in mineralization stiffen the matrix[39]. None of these mechanisms are recreated after tendon-to-bone healing[40-42]. These multiscale features are consistent across fibrocartilaginous entheses, including the rotator cuff, the Achilles tendon, the patellar tendon, the flexor tendon, and the meniscal root. At the rotator cuff, repair techniques focus on secure attachment of tendon to bone using sutures and bone anchors, but have not been effective in promoting regeneration of the native enthesis structure. Therefore, the mechanical properties of the fibrovascular scar tissue that forms at the interface do not approximate those of the normal tendon enthesis. Failure to recreate the structure and mechanics of the healthy enthesis may predispose the repair site to failure in continuity, gapping, or frank rupture.

The Need to Better Understand the Mechanisms of Enthesis Development

Understanding how a complex enthesis is formed by a pool of progenitor cells during development may inform strategies for enhanced healing at the surgically repaired enthesis. The tendon enthesis initially organizes as an unmineralized cartilaginous attachment unit in utero, and then mineralizes via endochondral ossification postnatally[43-45]. A number of key factors have been defined as necessary for chondrogenesis (e.g., Sox9) and tenogenesis (e.g., Mohawk [Mkx][46] and Scleraxis [Scx][47]). Growth factors in the transforming growth factor-beta (TGF-β) and bone morphogenetic protein (BMP) families likely regulate early enthesis formation[43,44], and molecules such as Indian hedgehog (Ihh) and parathyroid hormone-related protein (PTHrP) likely regulate late mineralization events[48,49]. A synergy between these growth factor cues and mechanical cues then gives rise to the complex structure and composition of the mature tendon enthesis. The mature enthesis maintains a gradient of cell phenotypes, from tendon fibroblast to chondrocyte to mineralizing chondrocyte to osteoblast/osteocyte. It is unclear how this gradient in cell phenotypes develops and how it is regulated by the local environment (e.g., ECM, muscle loading, and growth factors). Understanding the molecular mechanisms that control the formation of an interface with a gradient of cellular phenotypes and ECM will allow us to develop regenerative strategies for enhanced tendon-to-bone healing in the adult setting.

The Need to Better Understand the Mechanisms of Enthesis Pathology

Although the histologic and molecular characteristics of human rotator cuff disease have been described, the molecular events leading to tendinopathy and subsequent enthesis rupture are poorly understood. Rodent models have been particularly valuable for the study of tendinopathy, particularly related to the rotator cuff. Previous work established the similarity of the rodent rotator cuff anatomy to the human anatomy[50]. Rotator cuff tendinopathy has been induced in rodent models by overuse, disuse, surgery, chemical insult, and genetic manipulation[51-53]. Each of these models simulates aspects of tendon pathology and allows for exploration of disease mechanisms. Basic and clinical studies have implicated inflammatory processes in tendinopathy and crosstalk between tendon, bone, and muscle[54]. Although not yet fully elucidated, the immunobiology of tendinopathy involves infiltrating cells such as macrophages, resident responding cells such as mast cells, and resident tenocytes. Inflammatory mechanisms typically involve cytokines such as IL-1, IL-6, IL-17, and IL-21. For example, IL-17 and IL-21 were shown to be elevated in human tendinopathic samples, and IL-17 regulated proinflammatory cytokines in tendon fibroblasts in vitro[55,56]. Much work remains, however, to determine the mechanistic roles of inflammation and crosstalk in rotator cuff tendinopathy and how treatment strategies can target these processes. Animal studies in rodents also have explored outcomes after a rotator cuff enthesis repair, including the effect of tear chronicity on tendon, muscle, and bone health, and the roles of inflammation and bone loss during tendon-to-bone healing. Further exploration of enthesis pathogenesis and repair is needed to drive new treatment approaches, not only for the rotator cuff, which has been the focus of most of the translational animal model work, but also for other clinically relevant entheses, such as the Achilles tendon[57], the patellar tendon[58], the flexor tendon[41], and the meniscal root[59].

Developing Novel Strategies for Enthesis Repair

Mouse models are useful to study the fundamental mechanisms of tendon and enthesis development, growth, and pathology; however, the small size of the mouse precludes the use of clinically relevant repair techniques, making it difficult to test translational treatment strategies. However, the rat is large enough to examine tendon-to-bone healing using clinically relevant repairs[40]. In the rat rotator cuff, multiple studies have examined novel strategies for improving tendon-to-bone healing. For example, treatment strategies have targeted bone loss during healing[60], examined the role of loading after repair[40], and tested various cellular and growth factor approaches[61-64]. Compared with large animal models, the cost of rat studies is relatively low, and there are fewer ethical concerns. Although the rat is an excellent model for the initial testing of novel strategies for rotator cuff repair, its small size still limits its potential for translation directly to human trials. Furthermore, to date, researchers have largely focused injury models, treatment strategies, and outcomes on tendon-to-bone healing, and have not considered the complete rotator cuff muscle-tendon-enthesis-bone unit. There is a need to develop models and repair strategies aimed to treat and restore function to the entire connective tissue unit (i.e., muscle-tendon-enthesis-bone).

Establishing Relevant Animal Models for Translation of Novel Treatments

Large animals (e.g., sheep, dogs, goats, and rabbits) have been used for translational research investigations, bridging rodent models and human patients. Because of their size, many standard-of-care surgical techniques can be reasonably reproduced in large animals. As such, large animal models have been used to study surgical techniques[65] and regenerative strategies for rotator cuff repair, including growth factors[66], scaffold interposition[67], and scaffold augmentation[68]. However, reports have shown that rotator cuff repairs, at least in sheep and canines, uniformly undergo retearing in the very early postoperative period, yet form robust gap scar tissue that is grossly and histologically similar in appearance to a tendon[69-71]. The instability of the initial repair construct combined with robust gap tissue formation in spite of repair failure confounds the interpretation of studies investigating repair strategies. Future work should carefully explore the extent to which this limitation (ubiquitous retearing with robust gap tissue formation) occurs in the rabbit model since this has not been previously reported and might lend support for using the rabbit model instead of the sheep or canine models for translational research studies of rotator cuff repair.

Arguably, there are fundamental differences in intra-articular anatomy, pathogenesis, chronicity, biomechanical loading, and age between all animal models and the human rotator cuff. These differences limit the translational value of even large animal models for studying the etiology, pathology, or repair of the rotator cuff. It may be that a particular animal model may provide clinically relevant translational information on only a portion of the factors that need to be considered. The field as a whole, including researchers, providers, and regulatory agencies, should develop a consensus on which, if any, standardized animal models and outcomes are relevant for translational investigations.

Conclusions

This paper reviews the challenges and opportunities for developing effective treatment strategies for enthesis repair. The paper focuses particularly on the rotator cuff, with the understanding that many of the challenges and opportunities for developing these strategies will be more broadly applicable to other enthesis sites. Advances in both clinical and basic/translational research are needed. Some key areas for future research include:

Clinical Research

The Need to Better Understand the Disease

- Define the fundamental pathoetiology of intrinsic tendinosis.

- Identify prognostic biomarkers of rotator cuff disease and its progression.

The Need for Better Outcome Measures

- Explore which subsections or individual questions in current PROMs most closely correlate with structural integrity following rotator cuff repair.
- Better understand and differentiate the sources of shoulder pain, other than that from rotator cuff pathology, and the influence of pain on the clinical outcome of rotator cuff surgery.
- Develop enhanced and well-defined outcomes and consistent methods to measure shoulder function (e.g., range of motion, strength, and functional activity).
- Develop improved imaging modalities and discriminating imaging outcomes.
- Understand the mechanical properties and imaging characteristics of healed tendon repairs compared with those that have failed in continuity.
- Once the methods of evaluating outcomes have improved, design clinical trials to rigorously test the efficacy of strategies to improve the healing of rotator cuff tears.

Defining Which Factors Influence Healing

- Define optimal rehabilitation programs for rotator cuff healing.
- Identify intrinsic biomarkers that predict healing after rotator cuff repair.
- Determine the role of sex on healing after rotator cuff repair.

Basic and Translational Research

The Need to Better Understand the Mechanisms of Enthesis Development

- Understand the cellular, molecular, and biophysical mechanisms that control enthesis formation.

The Need to Better Understand the Mechanisms of Enthesis Pathology

- Determine the roles of inflammation and crosstalk between muscle, tendon, and bone in rotator cuff tendinopathy.

Developing Novel Strategies for Enthesis Repair

- Develop models and repair strategies aimed to treat and restore function to the entire connective tissue unit (i.e., muscle-tendon-enthesis-bone).

Establishing Relevant Animal Models for Translation of Novel Treatments

- Explore the extent to which ubiquitous retearing with robust gap tissue formation occurs in the rabbit rotator cuff repair model.
- Develop a consensus on which, if any, standardized animal models and outcomes are appropriate for translational investigations of rotator cuff repair and the repair of other clinically relevant entheses.
- Include sex as a variable in animal model study designs. ■

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