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Tendon Basic Science: Development, Repair, Regeneration, and Healing

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Abstract

Tendinopathy and tendon rupture are common and disabling musculoskeletal conditions. Despite the prevalence of these injuries, a limited number of investigators are conducting fundamental, basic science studies focused on understanding processes governing tendinopathies and tendon healing. Development of effective therapeutics is hindered by the lack of fundamental guiding data on the biology of tendon development, signal transduction, mechanotransduction, and basic mechanisms underlying tendon pathogenesis and healing. To propel much needed progress, the New Frontiers in Tendon Research Conference, co-sponsored by NIAMS/NIH, the Orthopaedic Research Society, and the Icahn School of Medicine at Mount Sinai, was held to promote exchange of ideas between tendon researchers and basic science experts from outside the tendon field. Discussed research areas that are underdeveloped and represent major hurdles to the progress of the field will be presented in this review. To address some of these outstanding questions, conference discussions and breakout sessions focused on six topic areas (Cell Biology and Mechanics, Functional Extracellular Matrix, Development, Mechano-biology, Scarless Healing, and Mechanisms of Injury and Repair), which are reviewed in this special issue and briefly presented in this review. Review articles in this special issue summarize the progress in the field and identify essential new research directions.

Keywords

New Frontiers; tendon conference; tendinopathy; tendon injury

Tendinopathies and tendon tears are common musculoskeletal injuries that account for over 30% of all musculoskeletal consultations.[1] Despite the prevalence of these injuries, a limited number of investigators are conducting fundamental basic science studies that are focused

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on understanding processes governing tendinopathies and tendon healing. Several obstacles innate to a young and developing field must be overcome to allow for the necessary growth and progress. For instance, the small size of the field limits the amount of complementary research between investigators, resulting in limited progress that can be built on related achievements. In addition, the small number of researchers in the tendon field promotes individual-driven rather than team-driven progress. A shift in research approach to one that is more multidisciplinary, driven by collaboration of individuals with divergent ideas and methodologies might foster both individual growth and in the field at large.

To propel much needed progress in the field of tendon research, the New Frontiers in Tendon Conference, co-sponsored by NIAMS/NIH, the Orthopaedic Research Society, and the Icahn School of Medicine at Mount Sinai, was held to promote exchange of ideas between tendon researchers and experts from outside the tendon field. This special issue, edited by the authors of this review, is one outcome from that meeting. This review will highlight some of the numerous questions that remain unanswered and present hurdles to progress in the field. To address some of these questions, the conference discussions and breakout sessions focused on six topic areas which are reviewed in this special issue are briefly presented below.

HURDLES TO PROGRESS IN THE TENDON FIELD

Tendons are load bearing structures that transmit forces from muscle to bone. Their hierarchical collagen structure is interlaced with numerous non-fibrillar proteins, which are essential to the ability of tendons to support load with stability. Tenocytes, the main resident cells of the tendon, “sense” loads from the extracellular matrix (ECM), and in turn modulate the ECM. Loading therefore, is essential for the maintenance of tendon homeostasis, but can readily promote remodeling or degeneration. Despite essential progress of research in the field, the factors and mechanisms that define the effect of loading as “healthy” versus overuse for particular tendons are largely unknown. In addition, after tendon degeneration leads to rupture, healing, even after apparently secure surgical repair, does not effectively restore the native structure and function of the tendon. Therapeutics have been largely ineffective because fundamental mechanisms that underlie pathogenesis of tendon injury and impaired healing remain unknown.

Remodeling or Degeneration From Loading

Repetitive healthy loading, as in exercise, can promote remodeling in the tendon, leading to long-term structural and functional improvements. The process of tendon remodeling involves both synthesis and degradation of collagen with a net degradation that begins immediately after exercise and then shifts to a net synthesis.[2] The observed breakdown of the ECM suggests that matrix metalloproteinases (MMPs) likely play a role in tendon adaptation.[3] Thus, a fundamental question that remains unanswered is whether overloading inhibits the necessary modulators of MMP activity, shifting the response of the tendon from adaptive to degenerative. In addition, the mechanistic relationship between MMP activity and loading remains unknown.

Studies using animal models have shown that physiological exercise leads to an enhanced cell proliferation rate, particularly of tendon-derived progenitor cells, and increased production of collagen.[4] Treadmill running leads to increased presence of myofibroblasts, suggesting that myofibroblasts are key players in tendon remodeling.[5] Physiological exercise leads to enhanced expression of tenocyte-related genes, such as tenomodulin, but does not affect expression of genes associated with adipocytes (LPL), chondrocytes (Sox9), or osteocytes (Runx2 and Osterix),[6] suggesting that the resident tendon cells are likely also responding to loading. Clearly, an unanswered question is which cell types are responsible for remodeling and degeneration in the tendon. Therapeutics targeting the implicated cell type will likely be more effective than non-specific interventions. In addition, activity of several growth factors, such as TGF-β, FGF, and VEGF have been implicated in tendon remodeling[7] but, not surprisingly, have also been correlated with tendinopathy, suggesting that the role of these key growth factors is highly contextual, both spatially and temporally. An important unanswered question is how are these growth factors regulated in homeostasis, remodeling, and degeneration.

Several contributing factors have been proposed to influence a shift in the response of tendon from healthy remodeling to degeneration. For instance, the absence of a recovery period during an exercise regimen,[8] smoking,[9] obesity,[10] and high cholesterol[11] promote degeneration instead of adaptation. Increase in age has been clinically correlated with higher incidence of tendon injury,[12] with animal studies showing correlations between increase in age and both a decrease in the number of viable tenocytes and increased MMP activity.[13] Gender has also been shown to be a significant intrinsic contributor to development of degeneration instead of remodeling, with tendons from females exhibiting decreased collagen synthesis rate in response to acute exercise and dampened hypertrophy in response to habitual exercise.[14] However, while correlations between incidence of injury or retear and these contributing factors have been identified, the mechanisms by which these factors alter the biological environment or govern the mechanosensitivity of the responding cells remains unknown.

Biology of Tendinopathy

The biological environment associated with development of tendinopathy has been largely described from late stage disease: The time when patients seek medical interventions. Molecular inflammation with elevated inflammatory cytokines has been associated with development of tendinopathy,[15,16] but it is generally accepted that development of tendinopathy does not include an overt inflammatory cell response; however several recent studies have challenged this premise.[17] Interestingly, therapeutic interventions to diminish inflammation have been explored with mixed success, likely because inflammation, when present, is a component of a “healthy” biological response that ushers in a healing cascade.[18,19] Therefore, a remaining unanswered fundamental question is whether inflammation is implicated in tendon degeneration and if so, what role it may play.

Expression of 983 genes differed between tendinopathy and healthy tendons suggesting that tendinopathy significantly alters the biomechanical environment of the tendon.[20] For instance, the expression of several matrix proteins, cytokines, signaling factors, and enzymes

have been shown to be altered in tendinopathic tendons.[21] A significant hurdle to utilizing these observed changes to inform therapeutics is that it is largely unknown whether they are causative or manifestations of the disease. Therefore, an attempt to inhibit a gene that has been observed to be upregulated in tendinopathy could have a detrimental effect if its upregulation is a critical component of an attempt to repair. We expect that animal models of tendinopathy,[22,23] particularly ones that readily allow genetic manipulations,[24] will be integral to providing context for the observed clinical manifestations.

Ineffective Healing From Surgical Repair

Surgical repairs of ruptured tendons have re-tear rates of up to 35 and 94% of small and large rotator cuff tears,[25,26] respectively. Several factors associated with failure of surgical repair have been reported, including advanced patient age, large size of tear, severe muscle atrophy and fatty infiltration, systemic diseases, and smoking.[27] Elevated levels of MMP-1 and MMP-9 have been shown to be correlated with re-tear of surgical repair of the rotator cuff.[28] Animal models of tendon healing have shown that several growth factors and cytokines, including TGF-β1, BMPs, VEGF, and PDGF, are modulated throughout tendon healing.[29] However, extending these biological observations from animal models to explain clinical healing or basic mechanisms governing failure has been limited.

Nevertheless, numerous investigators have evaluated therapeutic modulations to improve tendon healing in animal models. Evaluated treatments have led to mixed outcomes, likely due to differences in tendons, animals, and time course of evaluation between studies. For instance, addition of platelet rich plasma to healing tendons has resulted in an improvement in the rotator cuff of Wistar rats[30] but a negative effect in the FDL of New Zealand white rabbits.[31] The addition of TGF-β3 improved tendon-to-bone healing in one rat rotator cuff study[32] but showed no effect in another.[33] The addition of mesenchymal stem cells to healing rat Achilles tendons led to an improvement in some studies,[34] a negligible effect in others,[35] and a negative effect in some.[36] The addition of doxycycline has led to improved healing in the rat rotator cuff[37] but led to mixed outcomes in the rat Achilles tendon.[38,39] The addition of BMP-2 has led to improved tendon-to-bone healing in the rabbit patellar tendon[40] but no improvement in canine FDLs.[41] These mixed outcomes suggest that further investigation of the basic underlying mechanisms is integral to inform modulations and foster focused research in these areas. Indeed, therapeutics that are more targeted, so as to impact a particular cell population during a specific time in the healing or degeneration cascade, should be explored.

IDENTIFIED SIX SIGNIFICANT TOPIC AREAS

Six topic areas that are essential to advancement of the tendon field towards prevention and treatment of tendinopathies and promoting effective tendon healing were identified for the New Frontiers in Tendon Research Conference. The scope of the topics chosen encompasses the basic science of tendon function, development of pathologies and biologic healing response. The six topics were the subject of additional reviews in this issue: Cell Biology and Mechanics (Sun et al.), Functional Extracellular Matrix (Screen et al.), Development (Huang et al.), Mechano-biology (Lavagnino et al.), Scarless Healing (Galatz et al.), and Mechanisms of Injury and Repair (Thomopoulos et al.).

Cell Biology and Mechanics

Several aspects of cellularity contribute to the progression of tendon injury and repair mechanisms. For instance, the round morphology of native tenocytes that is commonly observed in tendinopathic tendons[42] may contribute to further matrix degradation and ineffective ECM synthesis.[43,44] In addition, various factors affect the ability of cells to respond to physiological loading, injury, and therapeutics. For instance, while gap junctions differentially modulate the response of tenocytes to loading,[45] the association of gap junctions with actin is essential for their stability during prolonged periods of intense mechanical loading.[46] It is likely that failure of such interaction is a contributing factor to onset of tendon degeneration. In addition to the native tenocyte population, recent studies have shown that there is a resident stem cell population in the tendon[47] which becomes less responsive with age.[48] It is likely that tendon stem cells contribute to repair and injury mechanisms but the molecular and cellular nature of undifferentiated stem cells in tendon injury, healing, and adaption have not been well characterized.

Functional Extracellular Matrix

Understanding the role of various components of the extracellular matrix in promoting functional load transmission from muscle to bone is essential to assessing the onset of damage and the risk of further progression. In addition to the role of the extracellular matrix in initiating cellular and biologic responses through deformations of the cells,[49] extracellular matrix components can directly affect cell signaling.[50] Injured tendons do not fully restore the native extracellular matrix, leading to an altered biologic and mechanical environment. Consequently, several investigators have sought to recapitulate fetal fibrillogenesis in injured adult tendons to restore functional extracellular matrix in healing tendons.

Development

Fully elucidating the mechanisms that govern tendon fibrillogenesis could be integral to development of therapeutics that promote effective fibrillogenesis in tendon healing. Early in vitro studies[51] and studies utilizing chick embryos[52] have been foundational to demonstrating collagen matrix formation. Recently, Kalson et al. described “fibripositors” as the sites of collagen assembly and transport.[53] New insights have been gained through development of novel imaging techniques, such as serial block face-scanning electron microscopy.[54] In addition, fetal studies have also provided insight into functional structural development.[55] Interestingly, in contrast to adult tendon healing, injured fetal tendons restore the native structure of injured tendons, motivating an understanding of the biologic environment associated with healthy tendon development. The fetal environment that is permissive to effective fibrillogenesis is not fully understood. The extent to which regenerative aspects from the fetal environment can be applied to regenerate adult tendons has not been fully explored.

Mechano-Biology

Mechanical loading is essential for tendon development,[56] homeostasis, and repair.[57] Loading induces a tensile stretch to tenocytes, activating protein kinases[58] and various biologic responses. For instance, physiological exercise has been shown to increase turnover

of Collagen I and promote an anabolic response.[59] In contrast, overloading or underloading has been shown to have detrimental effects on the tendon, resulting in a biologic response that is catabolic.[60,61] Studies have shown that loading history affects the mechanical sensitivity of tenocytes, causing a change in their response to the same applied strain,[62] presenting further complexity to the relationship between tissue load and biologic response. The method by which mechanical modulations from the ECM translate into biochemical signals that drive the biological response of the tendon is not well understood.

Scarless Healing

Adult tendon healing is characterized by scar formation with disorganized tissue and diminished mechanical properties. In contrast, regeneration, as seen in fetal healing and non-mammalian vertebrates, is characterized by restoration of the native structural and functional properties of the tissue, without scar. While therapeutic interventions to improve scar-mediated healing are an advancement to the field, the ultimate unmet goal is to promote regenerative healing.

Mechanisms of Injury and Repair

Tendinopathies leading to tendon rupture most commonly result from sub-rupture damage accumulation. The underlying mechanisms associated with pathogenesis of tendinopathies are largely unknown. It is thought that MMPs, thrombospondin motifs (ADAMTs), and TIMPs contribute to healing and degeneration.[63,64] The extent of inflammation, an integral component of the wound healing process in tendinopathic tendons, remains a subject of much debate.

CONCLUSION

Therapeutic measures for effective intervention and prevention of tendon injuries have progressed with limited success because of the scarcity of data that describes basic mechanisms for effective tendon function and response to injuries. In addition, the success of tendon surgical repair has been limited by the diminished ability of degenerated tissue to heal. Accordingly, several research areas that are underdeveloped and represent major hurdles to the progress of the tendon field were highlighted in this review. To address some of the outstanding fundamental questions, six topic areas, discussed at the New Frontiers in Tendon Research conference and reviewed in this special issue, summarize the progress in the field and identify essential new directions for research. Development of effective therapeutics is hindered by the lack of guiding data on the cellular and molecular aspects of tendon development, signal transduction, mechanotransduction, and fundamental mechanisms underlying tendon pathogenesis and healing.

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