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韧带和肌腱的生物力学和力学生物学研究

李宗明[1]， 王慧聪[2]， 胡流源[3]

(1. Hand Research Laboratory, Departments of Biomedical Engineering, Orthopaedic Surgery, and Physical Medicine and Rehabilitation, Cleveland Clinic, Cleveland, Ohio, USA; 2. MechanoBiology Laboratory, Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA; 3. Musculoskeletal Research Center, Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA)

摘要: 国际韧带和肌腱研讨会(The International Symposium on Ligaments and Tendons, ISI&T)于2000年在美国佛罗里达州奥兰多市首次召开。研讨会的宗旨是引起对韧带和肌腱研究的重视,并为生物工程师、生物学家、临床医师提供一个可以分享、评论、讨论韧带和肌腱最新研究成果的论坛。从2000年起,国际韧带和肌腱研讨会已经开展了15届;每届研讨会上涌现了大量令人振奋的关于当前韧带和肌腱研究热点和未来挑战的讨论。多年来,韧带和肌腱领域内的研究数量大幅增加,研究质量不断提升。为纪念《医用生物力学》杂志创刊30周年,本文总结过去30年里韧带和肌腱研究的主要进展,包括组织力学、力学生物学、损伤与治愈机制、组织修复和再生。

关键词: 韧带; 肌腱; 生物力学; 力学生物学; 国际韧带和肌腱研讨会
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Biomechanics and mechanobiology of ligaments and tendons

LI Zong-Ming[1], WANG James H-C.[2], WOO Savio L-Y.[3] (1. *Hand Research Laboratory, Departments of Biomedical Engineering, Orthopaedic Surgery, and Physical Medicine and Rehabilitation, Cleveland Clinic, Cleveland, Ohio, USA*; 2. *MechanoBiology Laboratory, Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA*; 3. *Musculoskeletal Research Center, Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA*)

Abstract: The International Symposium on Ligaments and Tendons (ISL&T) was inaugurated in 2000 in Orlando, Florida, USA. The primary purpose of the ISL&T was to call attention to the importance of ligament and tendon (L&T) research and to bring together bioengineers, biologists, and clinician-scientists in a forum where the most current research findings could be shared, critiqued and discussed. In each symposium since 2000, there have been a number of stimulating, thought-provoking discussions on current hot topics and future challenges. The ISL&T has taken place for 15 years now, and as a result, the L&T field has significantly expanded in quantity while the quality of research has also been greatly improved. In commemoration of the 30th anniversary of the Journal of Medical Biomechanics, this article will highlight some of the major advances in L&T research over the past three decades. Topics to be covered include tissue mechanics, mechanobiology, injury and healing mechanisms, and tissue repair and regeneration.

Key words: Ligaments; Tendons; Mechanics; Mechanobiology; The International Symposium on Ligaments and Tendons (ISI&T)

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通信作者:李宗明,教授,E-mail: liz4@ccf.org。

Ligaments and tendons (L&T) are fibrous, connective tissues that are essential components of the musculoskeletal system. The constituent materials for L&T are water, collagen, elastin, fibroblasts, proteoglycans, and other non-collagenous proteins. Water occupies 70% of the weight of L&T, and collagen is the major solid component. The collagen content is over 75% of the dry weight and is somewhat greater in tendons than in ligaments. Elastin is present in much smaller amounts and has important elastic properties even though it has lower stiffness than collagen. Proteoglycans are non-collagenous macromolecules interwoven with the collagen fibers and elastin, contributing to the time-and history-dependent viscoelastic properties in L&T.

Ligament connects bone to bone and provides joint stability as well as guides normal joint motion. For example, the anterior cruciate ligament attaches between the distal femur and anterior tibia eminence which protects the tibia from excessive anterior translation and medial rotation in the knee joint. Tendon connects muscle to bone and transmits muscular forces to the insertion sites at distant locations without extending muscles all the way from origin to insertion. For example, of the 29 muscles controlling the hand, 80% of the muscle mass is located in the forearm, so that the muscle power for the hand is achieved by long tendons. Such a musculotendinous arrangement effectively reduces the bulk of the hand without sacrificing hand strength. In addition to the biomechanical function, L&T also contain a variety of neural elements for proprioceptive responses that help maintain joint integrity and protecting the tissues against injuries. Reflex pathways in ligaments allow strain signals to be communicated to the nervous system, causing muscles to contract and prevent excessive ligament elongation and joint displacement. Tendons contain Ruffini corpuscles, Pacinian corpuscles, and Golgi tendon organs, which function as force sensors responding to displacement, velocity, acceleration, and force.

In this article, we briefly highlight some of the major advances in L&T biomechanics and mechanobiology research over the past three decades. We then discuss clinical and translational aspects of L&T research in terms of injury, degeneration, healing mechanisms, and tissue repair and regeneration. Lastly, we present a brief history on the International Symposium on Ligaments and Tendons (ISL&T), a forum that has brought together bioengineers, biologists, and clinician-scientists to solve challenging scientific and clinical problems.

1 Biomechanical properties of ligaments and tendons

The biomechanical properties of L&T are commonly determined by force-elongation or stress-strain curves via in vitro uniaxial tensile testing. A force-elongation curve characterizes structural properties that depend on the geometric configuration of the tested specimen, whereas a stress-strain relationship reflects mechanical properties of tissues that are independent of their dimensions. Force-elongation and stress-strain curves are typically characterized in terms of four regions. The initial (toe) region, with low stiffness, indicates the straightening and successive recruitment of the crimped fiber structure. The second (linear) region is the elastic part of the curve. where the tissue becomes stiffer as collagen fibers are stretched and become taut. The third (yield) region is where fibers undergo microscopic tearing as the tissue is further stretched. The last (failure) region indicates continued over-stretching and resultant progressive fiber disruption, leading to complete tissue rupture.

The mechanical properties of L&T can vary considerably to suit the needs of their anatomical location. The elastic modulus for ligaments ranges from 250 to over 1 600 MPa, tensile strength 35-125 MPa, and ultimate strain 12%-18%. The elastic modulus for tendons ranges from 1 200 to 1 800 MPa, tensile strength 50-105 MPa, and ultimate strain 9%-35%. During daily activities, L&T operate in the toe and lower linear regions of the curve. For example, the anterior cruciate ligament functions in the early part of the linear region, even during strenuous activities such as fast cutting or running. Loading of this ligament beyond the linear region occurs during a ski accident, football tackle, or a fault landing in gymnastics.

The attachment site of a ligament or tendon to the bone, or called enthesis, involves a gradual and continuous change of fibrous to fibrocartilaginous tissues to effectively transfer the load between them. In addition, L&T enlarge their cross-sectional areas as they approach the bones as a means of mitigating a localized stress concentration. The attachment of a tendon to muscle at the myotendinous junction comprises highly folded interdigitation between tendon collagen fibrils and muscle sarcolemma to maximize the junction area and minimize tissue stress.

Measurements of the *in situ* force in ligaments, particularly in the knee and shoulder joints, have been implemented using six degrees of freedom robotic arms instrumented with force-moment transducers. The superposition principle is applied to determine the amount of force exerted on a ligament *in situ*, assuming that for the same joint position and motion, the change in joint force before and after a ligament is sectioned is equal to the force carried by the intact ligament. Additionally, computational approaches using finite element models have been used to investigate ligament, tendon, and joint mechanics. These models have varying degrees of complexity and reliability, and efforts are ongoing for their rigorous validation and clinical translation. Imaging modalities such as magnetic resonance, ultrasound, and elastographic imaging have provided noninvasive investigation of the mechanical behaviors of the L&T to address more physiologically and clinically relevant problems. Currently, there is limited knowledge pertaining to *in vivo* mechanical behaviors of the L&T, and technological advancements will continue to provide many opportunities for basic and applied research in the field.

In contrast to a tendon, in which the tensile force generated by muscles tends to be unidirectional, a ligament can have anatomically distinct bundles and be subjected to varying directions of tensile force, depending on joint position. For example, the posterior fibers of the medial collateral ligament of the knee are under tension in joint extension, whereas the middle fibers are under tension when a varus load is applied. The collagen fibers in tendons have uniform alignment along the tensile forces, but a ligament can have a more complex fiber arrangement. For example, the transverse carpal ligament in the wrist has a fibrous network with fibers orientations in the transverse, longitudinal, and oblique directions. The interosseous ligament in the forearm connect the radius and ulna in an oblique direction from the longitudinal axis, providing force transmission from bone to bone in the longitudinal direction and stabilization force at the radioulnar joints. As such, two- or three-dimensional mechanical properties are needed to characterize the complex biomechanical functions of some ligaments.

L&T further exhibit viscoelastic behaviors resulting from collagen, water, and interactions between collagenous and non-collagenous proteins. The viscoelasticity of a ligament or tendon is characterized by stress-relaxation, creep, and hysteresis. When a ligament or a tendon is stretched rapidly, the ground substance has less time to flow, and consequently, the tissue stiffens and thus becomes more effective in transmitting high-level force. Conversely, at low strain rates, L&T are more deformable, absorb more energy, and are less effective in transferring loads. Hysteresis of L&T demonstrates time-dependent loading and unloading behavior; more work is done in stretching the tendon than is recovered when the tissue is allowed to relax. This state occurs because some of the work supplied to stretching is dissipated by causing the flow of the fluid within the ground substance. Some tendons (e. g., Achilles tendon) are highly elastic, with the ability to store and recover energy at high efficiency, while others (e. g., digit flexor tendons) are more viscoelastic for fine control of movement. Among the many modeling work, a representative mathematical representation for L&T viscoelasticity is the quasilinear viscoelasticity model, which includes a convolution of the independent elastic response and a relaxation function.

2 Mechanobiology of ligaments and tendons

L&T are subjected to mechanical loading and respond to mechanical loading by changing their metabolism and remodeling their structure; therefore, they can be called as “mechano-responsive systems”. In tendons, appropriate levels of mechanical loading during normal activities and moderate exercise can produce multiple benefits, including increases in its cross-sectional area and stiffness of tendons. This strengthening occurs also because of the anabolic responses in tendons such as an increase in collagen type I in peritendinous tissues. However, excessive, vigorous physical use-whether a very high mechanical load or a moderate but repetitive mechanical load with high frequency and/or for long durations-may induce tendinopathy, which is characterized by tendon inflammation and then follow by degeneration. Similarly, ligament cells such as those from the anterior cruciate and medial collateral ligaments of the knee, are also mechano-responsive. Their gene expression of collagen types I and III changes when various magnitudes of mechanical loading are placed on them. Thus, mechanical loading placed on the anterior cruciate and medial collateral ligaments also affects their homeostasis as well healing response after injury.

It is clear that cells in L&T regulate the physiology and pathology of these tissues. Tendons have long been thought to contain mainly tenocytes, the resident cells that maintain and repair tendons. Recently, tendon stem/progenitor cells have been identified in humans, mice, rats and rabbits. These tendon-specific stem cells differ from tenocytes in their ability to self-renew and form colonies in culture. They can also multi-differentiate into tenocytes and non-tenocytes (including adipocytes, chondrocytes and osteocytes) under appropriate conditions. In parallel, stem cells have also been identified in both anterior cruciate and medial collateral ligaments. Studies have shown that stem cells in the anterior cruciate ligament have much lower growth and reparative potential and differentiation capacity when compared to those in the medial collateral ligament; hence, the differences in these properties may contribute to the known disparity in healing capabilities between these two ligaments.

Since stem cells are essential for maintaining L&T homeostasis and mechanical load plays a critical role in soft tissue metabolism, understanding of L&T stem cell mechanobiology is of particular importance. *In vitro* studies show that in response to low mechanical loading, tendon stem cells undergo tenogenic differentiation by expressing tenocyte-related genes, collagen type I, tenomodulin and tenascin C. However, under high mechanical loading conditions, tendon stem cells also express non-tenocyte related genes, PPAR, Sox9 and Runx-2, the markers for adipocytes, chondrocytes and osteocytes, respectively, which may produce harmful effects to the tissue tissues (e.g. lipid deposits, proteoglycan accumulation, and calcification) typically observed in tendinopathic tendons. Thus, tendon stem cells may play a key role in the development of degenerative tendinopathy following excessive mechanical loading.

The following future directions for L&T research are indicated. First, the stem cell based mechanisms of tendinopathy should be investigated as *in vivo* studies using animal running on a treadmill as an experimental model to gain better understanding of the development as well as to design new strategies for the effective prevention and treatment of tendinopathy. Second, even though aging is now known to be a major causative factor of degenerative tendinopathy, the senescence of tendon cells are known to cause inflammatory/catabolic responses that may lead to tendon inflammation and degeneration in aging patients. Thus, it is necessary to investigate the aging-induced mechanisms of tendinopathy, Third, moderate levels of exercise have been recommended clinically for treating tendinopathy as such exercises could reduce tendon inflammation. Nevertheless, the precise characterization of cellular and molecular mechanisms that could prove these beneficial effects secondary to exercise on young adult and aging tendons are still lacking. Concommitently, the mechanobiology of ligament stem cells in ligaments also need to be studied in order to better understand the mechanisms responsible for the ligament homeostasis, injuries and subsequent healing.

3 Injuries, healing and repair of ligaments and tendons

When L&T are subjected to excessive and repetitive mechanical loads, injuries can occur by overstretching or tearing of the tissue substance and/or their attachment sites. The healing process of an injured ligament or tendon involves three overlapping phases. In the first phase, bleeding and clotting occur, inflammation of tissues takes place at the injury site, and new blood vessel and collagen formation begin. In the second phase, the fibroblastic cells replicate excessively and reticular fibers reproduce rapidly. In the final phase, the matrix remodels itself and eventually matures over time. On the other hand, the healing of their attachment sites is more involved because different type of tissues are involved.

The concept of "controlled motion is good" for management of L&T injuries has fundamentally impacted sports medicine and orthopaedic rehabilitation. In the past, joint immobilization by plaster casting had led to joint contracture, tissue adhesion, reduced lubrication, bone resorption at the insertion sites and deterioration of biomechanical properties of L&T. Controlled mobilization after the inflammatory phase enhances the quality of healing L&T. In these circumstances, mechanical loading enhances tissue repair and remodeling by stimulating fibroblast proliferation, collagen synthesis and fiber alignments. For example, early mobilization of injured digital flexor tendons helps increase the tensile strength, reduce tissue adhesion, facilitate gliding and excursion, improve functional outcomes and relieve clinical symptoms.

Some L&T have limited healing capability. In these cases, surgical repair and/or replacement by other tissue grafts are performed to restore function. Treatment of an anterior cruciate ligament rupture, one of the most common injuries in sports is a good example. In recent years, novel experimental devices, such as robot in couple with force-moment transducers have been used to gain new knowledge. The data obtained from these biomechanical experiements have been successfully applied to improve methods to reconstruct the ligament and restore/reproduce knee joint function. Some important factors affecting the surgical outcome of the reconstruction of the anterior and posterior cruciate ligaments of the knee include graft selection, number of tunnels, tunnel placement, initial graft tension, graft fixation and graft tunnel motion. If a tendon is torn or cut, the ends of the tendon will be pulled apart by muscle tension, necessitating surgical repair. Tendon grafting is commonly required to repair an injury to a digital flexor tendon, but post-repair tissue adhesion continues to be an unsolved problem. Endesis injuries require tendon reattachment to bone using suture anchors, but it creates a scarred, weak zone at the tendon-bone interface and does not reproduce the unique native transition zone at the interface.

Tissue engineering approaches have been used to accelerate L&T repair. These tissue engineering approaches include the use of growth factors, mesenchymal stem cells, and biological and synthetic scaffolds. When tested on animal models, these methods have been shown some promise to enhance L&T healing. On the other hand, tissue engineering approaches also have inherent drawbacks, For example, the use of exogenous growth factors raises safety concerns especially when it comes to timing and dosages levels; using mesenchymal stem cells in clinical settings may not be feasible because of the need for special equipment and experienced personnel to perform stem cell isolation, culture and expansion. Additionally, the use of biological and synthetic scaffolds for repair can cause safety concerns in patients. Until these issues are resolved, tissue engineering approaches as treatment solutions in clinical settings remain to be limited.

In recent years, a biologic treatment, namely platelet-rich plasma (PRP), has become a popular option to treat L&T injuries particularly for professional athletes. PRP has a number of advantages that substantiates its use to treat musculoskeletal tissue injuries. PRP is autologous, i. e. it is prepared from a patient's own blood by centrifugation to achieve a high platelet concentration within a small volume of plasma. Platelets in PRP function are natural reservoir of growth factors that are essential to the repair of injured tissues. Once activated, PRP becomes a gel-like material, called fibrin gel. Platelets in the gel slowly release growth factors that stimulate the healing of injured L&T. Besides, the fibrin matrix itself may also contribute to tendon healing by providing a conductive scaffold for cell migration and new matrix formation.

As a biologic agent, PRP is now widely used in orthopaedic surgery and sports medicine to augment the healing of injured musculoskeletal tissues, including L&T. However, the efficacy of this PRP treatment for L&T injuries remains controversial. While many basic science studies show that PRP promotes L&T wound healing, more basic science studies should be done in future to elucidate the PRP mechanisms on injured L&T. On the other hand, most clinical studies use PRP, prepared from a commercial kit and a pre-determined dose is administered for all types of L&T injuries in all patients irrespective of age, gender, disease history, etc. This "one-size-fits-all" approach may be one of the main reasons for the conflicting PRP treatment results in clinical studies. Therefore, we propose the use of an individualized approach based on the conditions of individual patients. Such efforts may improve the efficacy of PRP treatment efficacy in clinical trials. Also, the rehabilitation protocol following such biologics treatments should be individually customized to promote full recovery of injured L&T.

4 The International Symposium on Ligaments and Tendons

In the 1970s, L&T gained significant attention in the orthopaedic, bioengineering and other research communities. For example, at the Orthopaedic Research Society, one of the four concurrent sessions was always devoted to ligaments, tendons and their contribution to joint mechanics. Bioengineers, scientists and surgeons would be in the same room to listen, learn and discuss with each other on the current issues. Meanwhile, the US National Institute of Health (NIH) regularly funded L&T research. This was the best of times for those doing L&T work and a lot of seminal papers were published.

Then, the orthopaedic field had an explosion on biological research that attracted many biologists to the L&T

field. Unlike those that are involved in bone and cartilage research, the L&T researchers had not paid sufficient attention to this change. By the turn of the century, the ratio of biologists involved in bone research vs. L&T research reached 50∶1. As a result, the number of NIH grants to support bone and cartilage research was 15 and 4 times, respectively, over those for L&T research. Further, the podium presentations on L&T at the annual Orthopaedic Research Society meeting had fallen to much lower levels. Thus, the senior author (SW) felt that there was a dire need to bring together those in the L&T field, to get ourselves organized and to work together to advocate our cause! We must create a forum to promote our field and to attract new and young investigators. In addition, we must extend this movement by reaching out to our colleagues from around the world. With the help of his team, as well as endorsement by a number of leaders in our field, a blue ribbon International Advisory Committee was formed and the inaugural International Symposium of Ligaments and Tendons (ISL&T-I) was held in Orlando, Florida in March of 2000.

The objectives of the ISL&T were (and continue to be) to be an attractive venue for students, research fellows, bioengineers, biologists, clinicians and surgeons to congregate in the same room for an entire day to present novel ideas and to address current and difficult problems related to L&T research and clinical management. The meeting format had to be friendly and conducive to free exchange of ideas, to learn from each other as well as to come up with new research directions. It was also important to create opportunities for the younger investigators to interact with the more seasoned investigators, as well as for those from the West to meet those from the East, the North and the South. It was the intent that at the end of each ISL&T meeting, new friendships would be fostered and collaborations established. To accomplish the above objectives, we limited the attendance to be around 150 as the size is small enough to facilitate good discussion. Special attention was given to ensure that at least half of the participants were students and research fellows, and that the attendees were a good mix of bioengineers, biologists and clinicians.

For each symposium, an International Program Committee is selected by the International Advisory Committee and the organizers of the ISL&T. Each International Program Committee selects three or four thematic topic areas for that symposium. A world-renowned orthopaedic surgeon is invited to give an opening lecture on his/her years of clinical experience, as well as to suggest new research needs and directions. Members of the International Program Committee also review and select podium and poster papers with a goal that a large number of attendees have the opportunity to share their new findings in a short, summary format. Sufficient time is set aside for everyone to join in for a good scientific exchange. After a very long day, we all go together to enjoy a delicious meal of Chinese cuisine. At the banquet, we also give recognition to the best papers delivered by our young investigators with awards.

To date, we have had fifteen successful ISL&Ts, plus three satellite meetings. We are also delighted to share the following findings from a survey of attendees: 82% came because of the meeting content and would definitely return to another ISL&T. Also, over 50% came because of the keynote speakers, networking and personal growth and development. An astonishing 87% are interested in playing a leadership role should the ISL&T become a society. For interested readers, we refer you to the website (www.pitt.edu/~msrc and click on ISL&T) to learn more about our history, view past programs and abstracts and notice a number of other symposium features.

The ISL&T has served as an important platform for our field. The symposia have defined a number of future directions for L&T research. Topics such as homeostatic responses in the transition zones, the interface between muscle and tendon, enthesis, markers for cell based therapies, *in vivo* mechanics, bioscaffold based treatment of L&T injuries and so on. These topics have also helped the NIH and other funding organizations to prioritize important research grants to support. Further, some of our regular participants have gone on to organize additional "think tank" and "focus group" meetings for their professional societies. As a result, new multidisciplinary, collaborative projects to address key issues have started with societal seed funding. Finally, we have noticed that papers that were presented at the ISL&T are regularly quoted at the Orthopaedic Research Society and other meetings. These days, a number of new sessions related to special topics on L&T research have begun to surface at a number of conferences.

It is gratifying that the ISL&T has accomplished a number of its original objectives. More importantly, there are enthusiastic responses from our international communities in Europe and Pacific regions. Indeed, we have brought the world together! The success of ISL&T can also be attributed to a number of organizations who have provided the needed financial support to enable younger investigators to join us at the ISL&T as well as to provide prize money for awards.

The ISL&T has had an auspicious beginning, thanks to the many who have believed in it. Building on this solid foundation, we are ready to move forward and upward in the coming years. Much work still remains for L&T research to reach its full potential. The future of the ISL&T as an international force for science and translation depends on our reaching out to colleagues and young investigators worldwide to form effective partnerships, explore new funding sources, and ensure the training and mentoring of future investigators. Together, we will then be able to further elevate the science of L&T and bring the latest in biomedical science and engineering to serve patients.

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