J Musculoskel Neuron Interact 2003; 3(4):333-334

Hylonome

Perspective Article

Summary - Tendon Biology

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Tendons are a critical connective tissue with a major role in the transmission of contractile forces from the muscle to the bone. Like many connective tissues of the musculoskeletal system, tendon is organized in a hierarchical manner: oriented type I collagen fibers are clustered into micro-fibrils, sub-fibrils, fibrils, and fascicles. Cells, predominantly fibroblasts, are present in relatively small numbers between collagen fibers and blood vessels, lymphatics and nerves run longitudinal to the fascicles. Tendons arise deep within muscle at a transition termed the myotendinous junction and insert into bone either directly (where loading is in tension perpendicular to the insertion) or angularly (where loading is mediated through fibrocartilage from variable angles). Tendons are also found in regions of compression such as in the foot. The extracellular matrix of tendons varies based on these loading conditions, as do the ability and mechanisms of healing. In a manner similar to bone, tendons repair through the formation of callus tissue. Although poorly understood, this process appears to be regulated by both mechanical and growth factor signaling. There are significant similarities between bone and tendon with regard to the biochemical make up and response to and reliance on mechanical forces. The purpose of the tendon session at Sun Valley was to open discussion and raise awareness of this very critical connective tissue amongst meeting participants.

Load leads to changes in tendon strength in tendon in a manner very similar to bone. The increased strain in response to load leads to increased fluid flow that results in signals to the cells in tendon. Like bone, it is a fatigue prone material with cellular mechanisms to detect microdamage and repair such damage. It is possible that the principles that control bone structure apply to tendon. Thus, it appears that load determines strength in both tendon and bone. Based on these observations, load-bearing collagenous tissues appear to be controlled by mechanostats that adapt the strength of the tissue to the exposed mechanical load. Further research needs to be carried out related to understanding the nature and control of the putative tendon/connective tissue mechanostat.

There are distinct regional variations in the histological appearance of tendon that relate to the load to which the tendon is exposed. Most tendons are exposed to tensile load. However regions of the tibialis posterior tendon that passes under the medial malleolus are exposed to transverse compressive forces. There are significant differences in the proteoglycan make up and concomitant gene expression in these tendons with specific responses relating to the load environment. Not surprisingly, all proteins identified in cartilage are also present in tensile tendon with expression of these proteins regulated by the specific mechanical environment of the tendon. Fibrocartilage develops in tendon at the points of compressive force resulting in the expression of aggrecan and formation of a "cartilage-like" matrix. Elimination of compressive loading results in rapid depletion of proteoglycans from the fibrocartilage and dramatic changes in the mechanical properties and microstructure of the tendon.

Significant advances in the understanding of repair and rehabilitation of intrasynovial flexor tendon have been made in recent years. The concept of adhesion-free, or intrinsic tendon healing – that tendons could heal primarily without the ingrowth of fibrous adhesions from the surrounding sheath -- has proven to be true. More recent attempts to understand and improve the results of intrasynovial flexor tendon repair have focused upon restoration of the gliding surface, repair site biomechanics and on the molecular biology of early tendon healing. The overall goals of the surgical treatment of tendon lacerations remain unchanged, however: to achieve a primary tendon repair of sufficient tensile strength to allow post-operative rehabilitation that will inhibit adhesion formation and restore gliding surfaces. Some investigators have emphasized the use of increased force during rehabilitation of repaired tendons; however, recent studies with a canine model show that rehabilitation that produced increased tendon excursion did not influence range-of-motion or tensile properties and that tensile properties were not different between low- and high-force rehabilitation regardless of repair technique. Increasing the level of force within the

The author has no conflict of interest.

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Accepted 15 August 2003

range that can be applied with passive mobilization (i.e., 5 to 17 N) did not accelerate the time-dependent accrual of stiffness and strength in the canine model. Taken together with the previous finding that increased tendon excursion did not enhance tendon healing, these findings suggest that the widely held concept, increases in force and motion produced by more vigorous mobilization protocols are beneficial to tendon healing, should be re-examined. While more vigorous rehabilitation may help improve overall function, there is no current evidence that it enhances tissue healing or strength when combined with modern suture repair techniques. To increase the sensitivity of the repair site to increased force levels, it may be necessary to alter the biochemical environment by increasing expression of integrins or other force-sensitive molecules. Future strategies to accelerate tissue healing may therefore require manipulation of both biochemical and rehabilitation variables.

Tendons have the same length and cross-sectional area throughout normal adulthood. However, there are circumstances where individuals experience pain or rupture of tendons with little effort. This is surprising in that tendons have a built-in safety margin: maximal activation of muscle can only load the tendon to 10-25% of its ultimate tensile strength. So why do tendons rupture? It has been shown that 97% of ruptured tendons have degenerative changes in the biochemical make up of the matrix. Thus, it appears that rupture is an end-stage result of the degenerative process. Generally, the weakest region of the bone-tendon-muscle unit is the interface between the muscle and tendon. For a tendon to fail mid-substance, it must have become weaker than this interface. If one thinks of tendon ruptures as fatigue failure of the tendon, then it can be hypothesized that tendinopathies are due to the accumulation of fatigue or microdamage of the matrix and are manifest by pain. Normally, cells of the tendon are able to repair routine damage due to physical activity. However, failure to repair damage in tendon, as in bone, can ultimately result in tendon rupture. Unfortunately, there are little experimental data to support these hypotheses. Microdamage has not been demonstrated in tendon *in vivo* with repeated loading although it can be observed with *in vitro* loading. Is microdamage a stimulus for the cells to remodel or repair the matrix? Do the tendon fibroblasts have any way to evaluate the integrity of the matrix surrounding them? Clearly the tendon cells in culture have a sensitive cytoskeleton that can alter collagenase expression based on surrounding tension. Such observations suggest that these cells may have a biological set point for "normal" tension (i.e., a mechanostat). Further studies need to be carried out to ascertain the role of microdamage and repair to tendinopathies and the mechanisms that control the mechanosensitivity of tendon. Is there a "normal" turnover process in tendon that is accelerated by the presence of microdamage? Could alterations in this turnover process relate to tendon injury? Once information becomes available on the capacity of the tendon cells to sense and repair damage, pharmacological modifications could be made to modify this process and improve treatment of tendon injuries.