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Perpective Article

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What happens when tendons bend and twist? Proteoglycans

K.G. Vogel

Department of Biology, The University of New Mexico, Albuquerque, NM, USA

Abstract

When tendons must bend or twist in order to fulfil their function of attaching muscle to bone they are subjected to forces that could damage the tendon. However, there are concomitant protective changes in the structure of the tendon at the location of bending. One of these changes involves increased synthesis and accumulation of the large proteoglycan aggrecan. The accumulation of aggrecan can protect the tendon by providing compressive stiffness, by allowing collagen fascicles to slide relative to one another, and by protecting vascular elements.

Keywords: Tendon, Load, Proteoglycans, Fibrocartilage

Introduction

Tendon is a soft connective tissue that usually experiences purely longitudinal/tensile forces as it transmits the contraction of muscle to bone. With its longitudinal collagen fibers, tendon is highly adapted for tensile strength. However, in locations where the tendon changes direction as it wraps around bone, passes through a pulley, experiences twisting, or when the action involves movement of independent subunits, the tissue experiences transverse/compressive and shear forces in addition to tension. These forces have the potential to seriously damage the tendon. And yet, fortunately, tendons do not rupture simply because they must bend or twist. The question is how tendons are altered in terms of structure and biochemical composition when subjected to compressive and shear loading *in situ*. For many animal and human tendons the answer is development of a protective region of fibrocartilage at the location of the compressive and shear stress[1,2].

Tendon proteoglycans

Proteoglycans make up less than 1% of the dry weight of most tensile tendons[3]. The predominant proteoglycan in tendon is a small molecule (small for a proteoglycan) named decorin. It is composed of a core protein (MW ~45kDa) to which is attached one dermatan sulfate chain near the N-terminus; the molecule migrates on SDS/PAGE with a molecular weight ~100,000 Da. The core protein of decorin belongs to a family of proteins that contain many leucine-rich repeat structures. Other members of this family are biglycan (having two dermatan sulfate chains) and the karatan sulfate-containing molecules fibromodulin and lumican. These molecules are sometimes called by the irreverent nickname of SLRPs (small leucine-rich proteins). All of these proteoglycans are found in tendons. When decorin is added to soluble type I collagen and fibrils are allowed to form *in vitro*, the fibrils are significantly thinner than those formed in the absence of decorin[4,5]. This *in vitro* result shows that small proteoglycans can affect collagen fibril formation. Tendon of the decorin knockout transgenic mouse showed morphological and mechanical deficiencies in collagen-rich connective tissues such as skin and tendon[6]. This *in vivo* result demonstrates that small proteoglycans play an important role in the development of normal tendon structure and function.

The most significant biochemical distinction between compressed and tensile regions of tendon is the greatly enhanced amount of the large proteoglycan aggrecan in compressed regions. Aggrecan, the major proteoglycan component of cartilage extracellular matrix, can have as many as 100 chondroitin sulfate chains and a MW of ~1 million Da. Aggrecan's large size and ability to hold water contributes to cartilage compressive stiffness. The aggrecan of compressed tendon has been shown to be identical to aggrecan in cartilage by a number of criteria including the presence of chondroitin sulfate and keratan sulfate chains, its ability to aggregate with hyaluronan, the presence of tryptic peptides from the G1, G2 and G3 domains,

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Corresponding Author: Kathryn G. Vogel, Ph.D., Department of Biology, University of New Mexico, Albuquerque, New Mexico 87131, USA
E-mail: kgvogel@unm.edu

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and definitive sequencing[7]. There is also a small amount of aggrecan in tensile tendon but this molecule appears to lack the G1 domains and also lacks keratan sulfate chains[7].

Tendon fibrocartilage

Fibrocartilage occurs in bovine deep flexor tendon both at its end (where tendon inserts into bone) and at a mid-substance location (at the point where tendon wraps under bone). The distinguishing characteristics of this mid-substance fibrocartilage are: 1) significant accumulation of the proteoglycan aggrecan; 2) collagen fibers running at angles to one another, i.e., not linear; 3) type II collagen as well as type I collagen; and 4) rounded cellular profiles. In significant ways, this tendon tissue takes on the characteristics of cartilage and the cells show characteristics of chondrocytes. It is suggested that the occurrence of fibrocartilage in tendon is the result of experiencing mechanical forces other than pure tension. That is, cells in tendon respond to compressive load by increasing their expression and synthesis of aggrecan. This suggestion is supported by both *in vitro* and *in vivo* experimental results. For example, application of cyclic compressive load to segments of fetal bovine flexor tendon *in vitro* for 72 h led to increased synthesis of the large proteoglycans and increased aggrecan mRNA levels[8,9]. Elimination *in vivo* of compressive loading to the fibrocartilage-rich zone of rabbit flexor digitorum profundus tendon resulted in rapid depletion of proteoglycans from the fibrocartilage and changes in the mechanical properties and microstructure of the tendon[10].

Mechanical roles for proteoglycan in tendon

Compressive Stiffness. Fibrocartilage develops in tendon at the point where the tendon bends around a bone or pulley. Aggrecan is the predominant proteoglycan in the extracellular matrix of tendon fibrocartilage. The collagen matrix with interfibriller aggregates of aggrecan is believed to be the basis for compressive stiffness in cartilage. By analogy, it is concluded that fibrocartilage in tendon can provide compressive stiffness to the tendon at exactly those locations where such mechanical reinforcement is needed. In addition, it has been suggested that compression in tendon is ultimately transferred to the collagen fibers resulting in an initial distension (loss of crimp). In this model, the proteoglycans have the function of providing a viscous environment, allowing the collagen fibers to stretch and dissipate the force of sudden loads[11].

Independent Movement of Fiber Bundles. The supraspinatus tendon of the human rotator cuff is an interesting tendon because it is made up of structurally independent fascicles. Loading of the fascicles depends upon the joint angle. This means there are times when some fascicles are loaded and others are not[12]. We have found large bands of proteoglycan accumulated in the supraspinatus tendon and suggest these are serving the role of lubrication when units slide relative to one another[13]. The regions of bovine deep flexor tendon located on the outer curvature of the tissue as it bends resemble tendon from tensile regions. That is, the collagen fibers are organized in linear rows. However, there is a key difference. Located between the collagen bundles are layers of a looser matrix that is stained with Alcian blue (indicating high glycosaminoglycan content). This material may be important in allowing slip planes between the fascicles as the tissue bends.

Protection of Vascular Elements. Transverse sections of adult bovine deep flexor tendon show an Alcian blue-stained structure of looser matrix at the point where several collagen bundles come together. This structure was only seen in the compressed region of the tendon, and only at the outer curvature of the bending tendon. This glycosaminoglycan-rich structure often appeared to surround vascular elements, possibly to protect them from twisting and shear damage.

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