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Perspective Article

Hylonome

Tendon structure and response to changing mechanical load

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Introduction

Tendon is a soft connective tissue that usually experiences purely longitudinal/tensile forces as it transmits the contraction of muscle to bone. However, in locations where the tendon changes direction as it wraps around bone, passes through a pulley, experiences twisting, or the action involves movement of independent subunits, the tissue experiences transverse/compressive and shear forces in addition to tension. In many animal and human tendons a region of fibrocartilaginous tissue develops at this location[1,2]. The composition, development and roles of this fibrocartilaginous tissue is the focus of this summary.

Tendon structure and composition

Overall. The major constituents of tendon are water (~55% of wet weight) and type I collagen (~85% of dry weight). Triple-helical collagen molecules are assembled into fibrils with a D-periodicity of about 67 nm. Fibrils are assembled into fibers. Bundles of fibers are simply called fiber bundles or, sometimes, fascicles. The fiber bundles are delineated by a layer of endotenon. A whole tendon is composed of several fiber bundles and is surrounded by the epitenon. Some tendons (those not in a sheath or subjected to gliding) have a loosely associated layer of fibrous material outside the epitenon; this is called a paratenon. The paratenon may be quite vascular and is a source of the blood supply to the tendon itself. Table I provides a summary of the organization of Type I collagen molecules in tendon[3]. Other collagen types found in tendon include type III, type V, type VI, type XI and others.

The cells of tendon are fibroblasts. These elongated cells are found in the spaces between parallel bundles of collagen fibrils. Fibroblasts are responsible for the production and maintenance of tendon collagen and non-collagenous constituents. Although tendon fibroblasts appear to be quite isolated from each other, confocal microscopy has indicated that extended cell processes of tendon fibroblasts are in direct physical contact with one another through gap junctions[4]. Cells are also present in the endotenon and epitenon.

Proteoglycans. Proteoglycans make up less than 1% of the dry weight of most tensile tendons. The predominant proteoglycan in tendon is a small molecule (small for a proteoglycan, that is) 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. All of these proteoglycans are found in tendon. These molecules are sometimes called by the irreverent nickname of SLRPs (small leucine-rich proteins). 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[5]. The tendon of the decorin knock-out transgenic mouse showed morphological and mechanical deficiencies in collagen-rich connective tissues such as skin and tendon[6].

Fibrocartilage. Fibrocartilage occurs in the 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 fibrocartilage are 1) collagen fibers running at angles to one another, not linear; 2) type II collagen as well as type I collagen; 3) significant accumulation of the proteoglycan aggrecan; 4) rounded cellular profile. In significant ways, this tendon tissue takes on the characteristics of cartilage. It is the thesis of this presentation that the occurrence of fibrocartilage in tendon is the result of experiencing mechanical forces other than pure tension. 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

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Component	Description	Size/Mass	Method by Which It is Seen	Biochemical and Morphologic Characteristics	Clinical Significance
Pro-alpha chain	Polypeptide	150kd	--	Every third amino acid in helical region glycine; rich in hydroxyproline and hydrixylysine	Mutation in just one amino acid can affect subsequent levels of organization and ultimate function
Procollagen	Three pro-alpha chains	450kd	Electron microscopy (rotary shadowing)	Heterotrimer a1(l)2a2(l); secreted by fibroblasts	--
Collagen monomer (tropocollagen)	Triple helix; formed by cleavage of N- and C-terminal propeptides	300kd, 300nm x 2nm	Electron microscopy (rotary shadowing)	Length ~4.5 D	Mutations affecting propeptidase activity can impede fibril formation and ultimate function
Fibril	Regular lateral and axial aggregate of collagen monomers	D period= 67nm, diameter=50-200nm	Electron microscopy; negative or positive staining	Repetitive quarter-stagger banding pattern gap and overlap by negative stain, bands (a, B, C. D. e) by positive stain; stabilized by convalent cross-links between collagen monomers; heterotypic structure includes type V collagen and decorin	Change in structure or amount of fibril-associated molecules can affect fibril structure and ultimate function, e.g., fragile skin, osteochondrodysplasias
Fibril bundle = fiber	Group of fibrils delineated by a cleft containing interfibrillar material, fibroblasts, and extended cell processes	Width ~ 20 μm	Light microscopy; collagen pink and cell nuclei blue with H&E stain	Wavy crimp pattern seen; interfibrillar material may include large proteoglycans, type VI collagen, elastin; cell processes in direct contact with other cells	Too small to hold a suture
Fiber bundle = fascicle	Group of fibers surrounded by endotenon	Diameter ~ 1 mm	Visible	Visible, linear elements of tendon; endotenon contains loose connective tissue and vasculature	Delamination separates fascicles
Whole tendon	Connects muscle to bone; surround by epitenon	Diameter from 0.1 to round or flat	Visible	Pinkish white, firm and tough; water content 55%; fibrocartilage at ends and where under compressive load	Tears may occur at ends or midsubstance, partial or complete

Table 1. Organization of type I collagen in tendon[3].

flexor tendon *in vitro*, as in normal fetal development, led to increased synthesis of the large proteoglycans and increased aggrecan mRNA levels[7,8]. 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[9].

Mechanical roles for proteoglycan in tendon

Compressive Stiffness. Fibrocartilage develops in the tendon at the point where the tendon bends around a bone or pulley. Aggrecan is the predominant proteoglycan in the extracellular matrix of cartilage. When aggregated with hyaluronic acid, it forms a huge complex that cannot diffuse from the tissue. It has many glycosaminoglycan chains that carry negative charge and thus hold counter ions and water in the tissue. The collagen matrix with interfibriller aggregates of aggrecan is believed to be the basis for compressive stiffness in cartilage and, by extension, in the fibrocartilage of tendon. Others have suggested that in tendon, compression is ultimately transferred to the collagen fibers resulting in an initial distension (loss of crimp). The proteoglycans have the function of providing a viscous environment, allowing the collagen fibers to stretch and dissipate the force of sudden loads[10].

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[11]. 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[12]. 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 structure often appeared to surround vascular elements, possibly to protect them from twisting and shear damage.

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