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Chronic tendon pathology: molecular basis and therapeutic implications

Graham Riley

Tendons are frequently affected by chronic pain or rupture. Many causative factors have been implicated in the pathology, which until relatively recently was under-researched and poorly understood. There is now a greater knowledge of the molecular basis of tendon disease. Most tendon pathology (tendinopathy) is associated with degeneration, which is thought to be an active, cell-mediated process involving increased turnover and remodelling of the tendon extracellular matrix. Degradation of the tendon matrix is mediated by a variety of metalloproteinase enzymes, including matrix metalloproteinases and 'aggrecanases'. Neuropeptides and other factors released by stimulated cells or nerve endings in or around the tendon might influence matrix turnover, and could provide novel targets for therapeutic intervention.

Tendons are dense, fibrous connective tissues that connect muscle to bone and are essential for the transmission of force and the generation of movement at a joint. They are highly ordered composite materials consisting of collagens, proteoglycans and various glycoproteins, many of which have been poorly characterised. Tendon problems such as tendon rupture and chronic tendon pain are common, although the underlying pathology is not well understood and the conditions are often difficult to treat (Ref. 1). Terms such as tendonitis (or tendinitis) are traditionally used to describe a painful tendon, the name implying an inflammatory condition. This is contrary to the evidence from most histopathological studies, which describe a degenerative condition without inflammation that has been called tendinosis (Refs 2, 3, 4, 5, 6, 7, 8). In this review, the term tendinopathy is used for all forms of chronic tendon pathology, because it does not assume any knowledge of the underlying pathology.

Factors implicated in tendinopathy

It is increasingly recognised that most tendinopathies are not associated with any single factor, and tendon degeneration might result from various causes. Indeed, there is some evidence to suggest that the nature of the degenerative process varies at different sites (Ref. 3). Tendons at certain sites are more commonly affected, particularly the supraspinatus, extensor carpi radialis brevis, patellar and Achilles (at the shoulder, elbow, knee and ankle, respectively) (Refs 9, 10). These tendons

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are all exposed to relatively high mechanical demands, although additional factors are thought to be important. The majority of patients present in late middle age, often with no memory of any acute injury or trauma (Refs 10, 11). The condition usually has an insidious onset, with pain developing during or shortly after exercise. Tendon ruptures often occur during physical activity, typically in sports such as badminton (Ref. 12). Many cases of tendinopathy are ascribed to 'overuse', thought to result from repeated microstrain below the failure threshold, analogous to the fatigue failure that affects most materials placed under repetitive loading (Refs 10, 13, 14, 15).

It is generally assumed that tendon damage is the primary event, overwhelming the ability of the tendon cells (generally referred to as tenocytes) to repair structural defects in the tendon extracellular matrix (ECM). Alternatively, there is thought to be a failure to adapt to a change in physical demands. Tenocytes have a central role in the repair and maintenance of the tendon ECM, synthesising new proteins and producing the enzymes that degrade them. This continual process of matrix turnover is normally in balance, and changes in this activity in response to altered patterns of loading, for example, might precede any physical lesion or 'micro-injury'. Aside from microtrauma and hypoxia, factors that could potentially affect the tenocyte activity include age, temperature, drugs and the local activity of biochemical mediators produced by the resident cells. The potential roles of some of these factors are discussed in this review, which emphasises the importance of ECM turnover and matrix-degrading enzymes in tendon health and disease.

The structure and function of tendon

The principles of tendon structure and function have been comprehensively reviewed elsewhere (Refs 16, 17, 18, 19, 20). In general, tendon consists of successively larger structural units assembled in a highly ordered hierarchy of collagen molecules, microfibrils, subfibrils, fibrils, fibres and fascicles (fibre bundles) (Ref. 21) (Fig. 1). However, tendon is not a homogenous tissue: there are variations in structure and composition between tendons and at specific sites within tendons (Ref. 20).

The best-characterised regional variation within tendon is fibrocartilage, which is found at the insertion or where a tendon bends around a bony prominence or through a fibrous pulley (Refs 20, 22, 23). Fibrocartilage shares some similarities in structure and composition with articular cartilage, although it also retains essential characteristics of fibrous connective tissue. Its main function is to dissipate shear stress or resist compression, and the fibrocartilaginous region can vary greatly in size depending on factors such

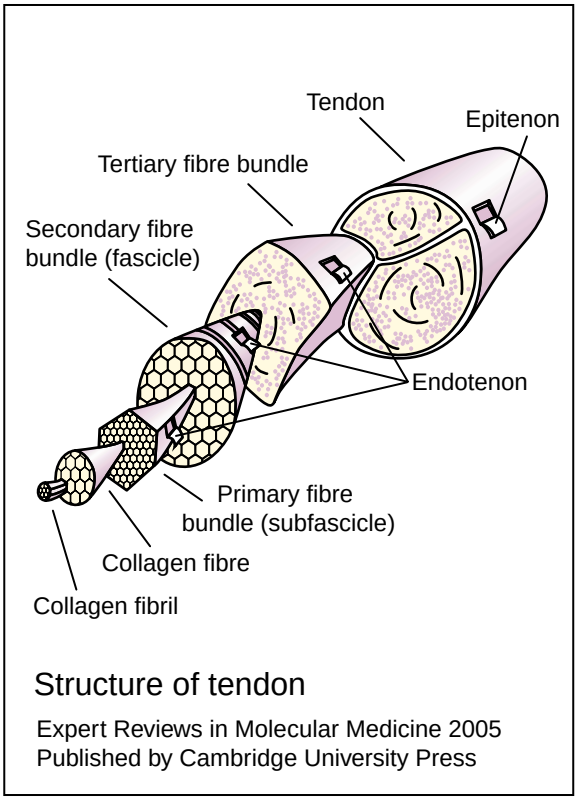


Figure 1. Structure of tendon. Tendon consists of a highly ordered hierarchy of successively larger structural units. Collagen molecules aggregate into fibrils, and bundles of fibrils form fibres, many of which are aggregated into primary fibre bundles or subfascicles. Multiple subfascicles form secondary fibre bundles or fascicles, and several fascicles form tertiary fibre bundles. Most tendons consist of multiple fascicles, which is thought to be a fail-safe mechanism so that failure of one or more fibre bundles does not compromise the tendon strength. Fibre bundles are surrounded by a thin layer of connective tissue known as the endotenon, through which pass blood vessels, lymphatics and nerves. The whole tendon is bound by another thin layer (contiguous with the endotenon) known as the epitenon. A loose outer layer known as the paratenon surrounds most tendons (not shown), and some tendons are also surrounded by a specialised synovial sheath. Figure modified from Ref. 21 (© 1978); reproduced by permission of Taylor & Francis, Inc., http://www.taylorandfrancis.com.

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as the range of movement and the angle of insertion (Refs 24, 25). Fibrocartilage is also thought to play a role in the migration of the insertion during skeletal growth, and to prevent narrowing of the stretched tendon at the interface with bone (Ref. 20).

The cell population in tendon is poorly defined, and there is no single marker of tenocytes (Refs 26, 27). The majority of cells have the appearance of fibroblasts, although there are also chondrocyte-like cells (fibrochondrocytes) within fibrocartilaginous zones, and a small number of capillary endothelial cells, smooth muscle cells and nerve cells, depending on the degree of vascularity and innervation (Ref. 18). There are regional differences in cell morphology and activity within tendons. Synovial-like cells found in the endotenon and epitenon surrounding the main fibre bundles (Ref. 28) possess a greater proliferative capacity and a different matrix-synthesising activity compared with the tenocytes within the fibres, and are the first cells to respond after acute tendon injury (Refs 28, 29, 30, 31, 32). Fibrochondrocytes from the fibrocartilaginous zones synthesise different matrix components (see below), an activity that is stimulated and maintained by the application of compressive load (Refs 33, 34, 35). A small proportion of cells are thought to be mesenchymal stell cells, capable of differentiating into chondrogenic, osteogenic and adipogenic cells when cultured in the appropriate conditions (Ref. 27).

The molecular composition of tendon

Tendon is a highly ordered composite material consisting predominantly of collagen, with smaller amounts of various proteoglycans and glycoproteins, many of which are relatively poorly characterised (Table 1). Although many

Table 1. Molecular composition of tendon extracellular matrix

Molecule	Structure/type	Location and function
Collagen		
Type I	Fibril-forming	Main constituent of tendon (~95% of total collagen)
Type II	Fibril-forming	Restricted to fibrocartilage; forms less-organised meshwork
Type III	Fibril-forming	Normally restricted to endotenon; forms smaller, less-organised fibrils
Type IV	Forms meshwork	Basement membrane of blood vessels
Type V	Fibril-forming	Core of type I collagen fibril; forms template for fibrillogenesis
Type VI	Beaded filaments	Cell-associated; found in 'seams' between fibrils
Type IX	FACIT	Mediates cell–matrix interactions with type II collagen fibril surface
Type X	Forms meshwork	Restricted to insertion fibrocartilage; associated with mineralisation?
Type XI	Fibril-forming	Core of type II collagen fibril; forms template for fibrillogenesis
Type XII	FACIT	Mediates cell–matrix interactions with type I collagen fibril surface
Type XIV	FACIT	Mediates cell–matrix interactions with type I collagen fibril surface
Proteoglycan		
Decorin	SLRP	Binds collagen, affects collagen-fibril formation, binds growth factors
Biglycan	SLRP	Binds collagen, affects collagen-fibril formation, binds growth factors
Fibromodulin	SLRP	Binds collagen, affects collagen-fibril formation, binds growth factors
Lumican	SLRP	Binds collagen, affects collagen-fibril formation
Aggrecan	Hyalectan	Resists compression; most prominent in fibrocartilage
Versican	Hyalectan	Lubricates boundary between adjacent fibrils?
Glycoprotein		
Elastin	Branched network	Forms elastic fibres; provides elastic properties of tissue
Fibrillin	Linear arrays	Forms elastic fibres; provides elastic properties of tissue
Tenascin-C	Branched molecule	Mediates cell–matrix interactions; forms 'seams' with versican
COMP	Branched molecule	Mediates cell–matrix interactions; role in fibril formation?
Fibronectin	Modular protein	Mediates cell–matrix interactions; role in tendon healing
Laminin	Modular protein	Component of basement membranes
Link protein	Globular protein	Stabilises proteoglycan–hyaluronan interactions
Thrombospondin	Modular protein	Mediates cell–matrix interactions

Abbreviations: COMP, cartilage oligomeric matrix protein; FACIT, fibril-associated collagen with interrupted triple helix; SLRP, small leucine-rich repeat proteoglycan.

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constituents of tendon are present in very small amounts, they have important roles in the ECM, including modulating the formation of fibrils and mediating cell–ECM interactions. It is important to emphasise that the ECM does not merely fulfil a passive, structural role: many of its constituents also have an impact on tenocyte activity. Tendon is not an inert material, as the ECM can be continuously synthesised and replaced throughout life, although the rate of metabolism is much lower than in tissues such as muscle and bone (Ref. 36). There is also evidence of variation in the rate of turnover at different sites and in different tendons (Refs 37, 38). This activity is likely to be influenced by both internal and external factors, and is potentially a major factor in the development of tendinopathy.

Collagen

Extensive reviews of the synthesis, structure and function of collagen, particularly of collagen types I–XIX, have been published elsewhere (Refs 39, 40, 41, 42, 43, 44). In brief, each collagen consists of three polypeptide α-chains, which combine together as a homotrimer (three identical α-chains) or a heterotrimer (with two or three different α-chains). To date, 42 vertebrate α-chains have been sequenced, several of which can be differentially spliced, and these combine to form at least 27 different collagens (Refs 39, 40, 44). Each α-chain forms an extended left-handed helix, and contains a variable length of the repeated amino acid motif Gly-X-Y, where X and Y are commonly proline and hydroxyproline. This amino acid composition is an absolute requirement for the formation of the right-handed triple helix, a defining characteristic of collagenous (COL) protein domains. The collagens also possess globular, noncollagenous (NC) domains of variable size, number and location.

Although all collagens form highly organised polymers, the different collagen types can be grouped according to whether they form fibrils or other structures such as extended sheets or lattices. The classic fibril-forming collagens (types I, II, III, V and XI) comprise a single COL domain for almost the entire length of the molecule, with small NC domains at each end (Fig. 2). The newly discovered collagen types XXIV and XXVII have a similar molecular structure (Refs 45, 46). The nonfibrillar collagens are a heterogenous group with a variety of structures. Collagen types IV, VIII and X form extensive networks, whereas type VI collagen forms beaded microfilaments. Type VII collagen is essentially restricted to basement membranes where it forms anchoring filaments. Several collagens have transmembrane domains, including types XIII, XVII, XXIII and XXV, which mediate interactions between the cell and its external environment. Some collagens, designated FACIT (for 'fibril-associated collagens with interrupted triple helix'), are associated with the surface of fibrils and have several interruptions in the triple-helical structure. Collagen types IX, XII and XIV are the archetypal FACITs, although the more recently described collagen types XVI, XIX, XX, XXI, XXII and XXVI are thought to be related members.

The fibril-forming type I collagen is the major component of tendon; it is generally estimated to represent 95% of the total collagen, although it is difficult to be precise because of its insolubility, particularly in ageing tendon specimens (Ref. 47). Type III collagen is the next most abundant collagen in tendon, forming around 3% of the total in human supraspinatus and biceps brachii tendons (Ref. 47). In normal tendon, most type III collagen is found in the endotenon and epitenon (Ref. 48), although it is also found intercalated into the type I collagen fibril bundles, particularly in ageing tendons and at the insertion (Ref. 49). Other minor constituents of tendon are collagen types IV, V, VI, XII and XIV. Collagen types II, IX, X and XI, once thought to be restricted to cartilage, are found in the fibrocartilaginous regions of tendons and ligaments, where they are presumed to function to help resist compression and shear forces at these sites (Refs 50, 51).

Proteoglycans

ECM proteoglycans have been classified into two subfamilies: the small leucine-rich repeat proteoglycans (SLRPs) and the large modular proteoglycans. The latter are further divided into two subgroups: those that do not bind hyaluronan; and the 'hyalectans', which bind both hyaluronan and lectin (Refs 40, 52, 53). Only the SLRP and hyalectans are considered in this review, since these are the most abundant proteoglycans in the tendon ECM.

SLRPs

SLRPs are found in most connective tissues and include decorin, biglycan, fibromodulin and lumican. They all possess a small protein core (36–42 kDa), with an N-terminal domain for

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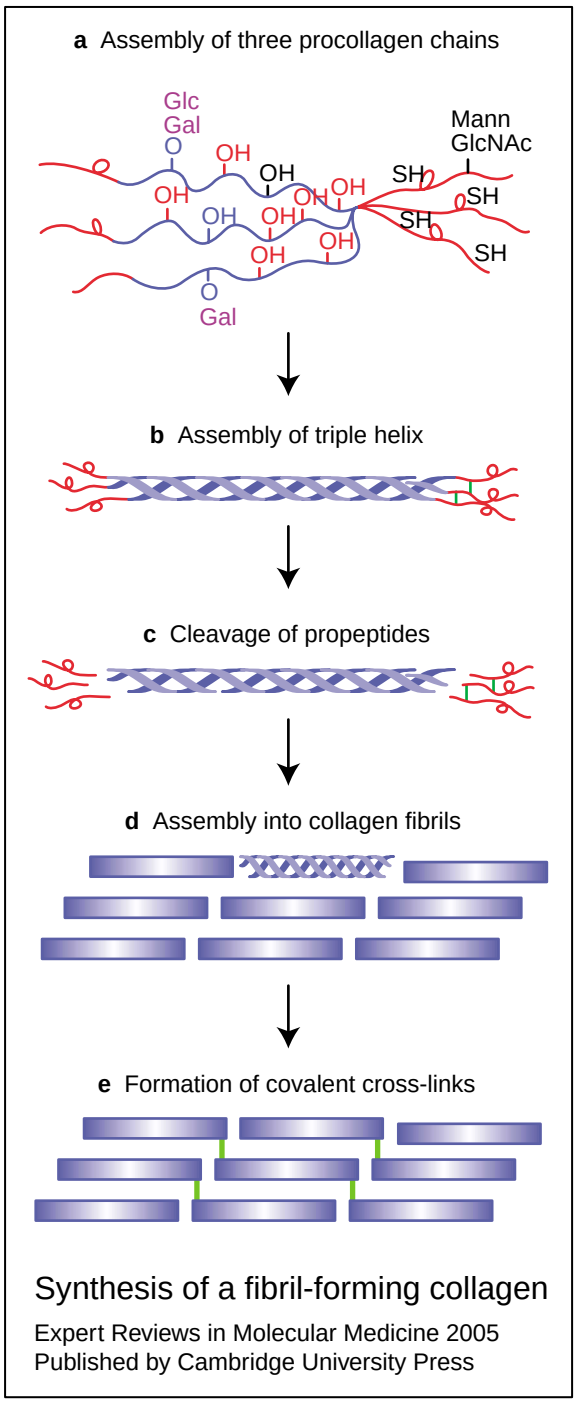


Figure 2. Synthesis of a fibril-forming collagen. *(See next column for legend.)*

Figure 2. Synthesis of a fibril-forming collagen. (a) Following synthesis, the three collagen α-chains undergo extensive post-translational modification, including hydroxylation of lysine residues and glycosylation. (b) The α-chains wrap around each other to form a tightly wound, right-handed triple helix which is secreted as a procollagen monomer. (c) The N- and C-terminal propeptides are cleaved by specific peptidases. (d) The processed collagen forms multimolecular aggregates, which are aligned end-to-end to form banded fibrils. (e) Crosslinks are formed between specific amino acids, which stabilise the collagen fibril and provide tensile strength. Abbreviations: Gal, galactose; Glc, glucose; Mann, mannose; GlcNAc, *N*-acetylglucosamine; OH, hydroxyl group; SH, sulphydryl group. Figure modified from Ref. 44 (© 2004), with permission from Elsevier.

binding of glycosaminoglycan (GAG) chains, a central region of leucine-rich repeats flanked by clusters of cysteines, and a C-terminal domain (Ref. 52) (Fig. 3a). The protein core is compact and horseshoe shaped, which might be important for protein–protein interactions (Ref. 54). SLRPs carry one to four chains of GAG, which can be keratan sulphate (KS), dermatan sulphate (DS) or chondroitin sulphate (CS). The type of GAG depends on the tissue, with decorin containing CS in bone and DS in tendon (Ref. 55). Fibromodulin and lumican have a similar protein core structure to decorin, but contain KS. (Ref. 56).

The most abundant proteoglycan in tendon is decorin, although biglycan is also present in small amounts (Ref. 57). All the SLRPs are now thought to have some role in collagen-fibril formation (fibrillogenesis), acting in a sequential and orchestrated fashion during development and repair to control the growth and ultimate diameter of the collagen fibres (Refs 58, 59). Decorin, for example, is found attached to collagen fibres at specific sites every 64–68 nm, where it acts to modulate (limit) collagen-fibril formation (Refs 60, 61). Modulation of this activity using antisense gene therapy to inhibit decorin gene transcription has been shown to promote the formation of larger collagen fibrils in healing ligament, thus improving the strength of repair (Ref. 62). Biglycan binds only weakly to type I collagen and has a much greater affinity for type VI collagen, promoting the rapid formation of hexagonal networks (Ref. 63).

Apart from their role in ECM organisation, the SLRPs can also modulate various cell activities (Refs 64, 65, 66). Decorin, fibromodulin and biglycan, for example, might modulate the activity of the resident cell population by binding to and sequestering growth factors such as transforming growth factor β (TGF-β) (Refs 65, 66).

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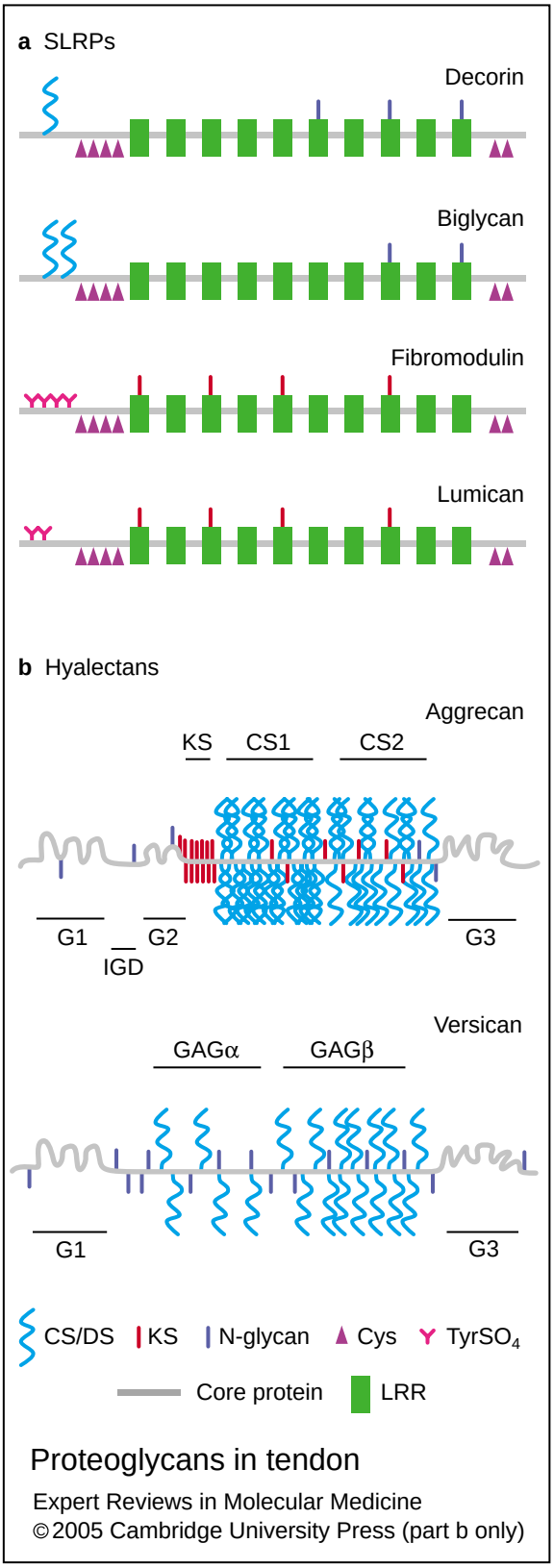


Figure 3. Proteoglycans in tendon. *(See next column for legend.)*

Figure 3. Proteoglycans in tendon. (a) Small leucine-rich repeat proteoglycans (SLRPs). SLRPs in tendon include decorin, biglycan, fibromodulin and lumican. They share a common core protein structure with ten leucine-rich repeats (LRRs) and at least one chain of glycosaminoglycan (GAG). Decorin in tendon has one dermatan sulphate (DS) chain, whereas biglycan has two chondroitin sulphate (CS) chains. Fibromodulin and lumican have up to four keratan sulphate (KS) chains and some tyrosine (Tyr) residues are sulphated. Part a of figure reproduced, with permission, from the Glycoforum website (http://www.glycoforum.gr.jp). (b) Hyalectans. The hyalectans in tendon are versican and aggrecan, with versican predominant in tensile-loaded regions and aggrecan in compressed, fibrocartilaginous regions. All hyalectans contain a G1 domain, a GAG-attachment region and a G3 domain that has similarities with selectin. Aggrecan also has a G2 domain, separated from G1 by an interglobular domain (IGD), and the molecule contains approximately 100 CS chains and 30 KS chains. Versican contains up to 21 CS chains, clustered within two GAG domains known as GAGα and GAGβ. One or both of the GAG domains might be removed by alternative splicing of the mRNA transcript, forming four versican splice variants.

The 'hyalectans'

The hyalectan subgroup of large proteoglycans comprises aggrecan, versican, brevican and neurocan (Refs 40, 52). Neurocan and brevican are thought to be restricted to brain and neural tissues. The hyalectans possess a large protein core (100–370 kDa) consisting of a C-terminal domain with epidermal growth factor (EGF)-like repeats, a central domain carrying the majority of GAG chains, and an N-terminal hyaluronan-binding domain (Ref. 56) (Fig. 3b).

Aggrecan, the major proteoglycan of articular cartilage but also found in tendon, forms multimolecular aggregates with the nonsulphated GAG hyaluronan. Aggrecan is reported to be present throughout tendon, although it is generally thought to be more abundant in regions of fibrocartilage. Aggrecan has three globular domains (G1, G2 and G3) and contains many GAG chains (CS and KS) attached to specific sites in the GAG-binding domain between the G2 and G3 domains (Ref. 67). The high fixed negative charge of the GAG attracts counter-ions and functions to hold water within the tissue. Swelling of the tendon is restrained by the collagen meshwork, and the resulting turgor functions to resist

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compressive load. Thus, the expression of aggrecan in compressed regions of tendon, or areas subjected to shear forces such as the insertion, is thought to be a functional adaptation that protects the tissue from damage.

Versican has been identified in many soft connective tissues and has a similar structure to aggrecan, although it lacks a G2 domain and contains much less GAG, all of which is CS (Ref. 68). Its precise role in tendon is unknown, although it is found associated with seams of microfibrils between fibres and it might function to facilitate the sliding of adjacent fibre bundles.

Glycoproteins

The noncollagenous components of tendon are relatively poorly characterised. Elastin, thought to make up less than 2% of the tendon dry weight, is a component of the elastic fibres that are thought to maintain the tendon crimp and to be responsible for the elastic properties of the ECM (Refs 13, 69). Fibrillin is also a major component of the elastic microfibril, and is thought to form a template for tropoelastin and the assembly of the elastin multimer (Refs 70, 71). Elastic microfibrils are present in most connective tissues and contain polymers of fibrillin-1 and fibrillin-2 (Refs 70, 71). Mutations in fibrillin-1 have been linked to Marfan's syndrome and associated disorders of various connective tissues (Ref. 72). Fibrillin-1 is associated with type XVI collagen in the dermis (but not in cartilage), and other proteins such as versican, fibulin, matrix-associated glycoprotein (MAGP)-1, MAGP-2 and emilin (Refs 73, 74, 75, 76). The microfibril structures that are formed have been divided into essentially three types on the basis of structure and appearance – oxytalan, elaunin and elastic – which differ in the relative amounts of elastin (from lowest to highest, respectively). Elastic fibres, predominantly oxytalan, are reportedly more homogenous and abundant in developing tendon, less common in adult tendon and absent from fibrocartilage (Ref. 77).

Fibronectin mediates cell interactions with the ECM, and affects a range of cell functions including cell adhesion, cell migration, differentiation, haemostasis, phagocytosis and chemotaxis (Refs 40, 78). Present at low levels in normal tendon, fibronectin is massively increased after tendon injury and consequently has been implicated in cell adhesion, migration and differentiation at the site of injury (Refs 79, 80, 81).

Tenascin-C is a disulphide-linked hexameric protein with subunits of 200–300 kDa in humans, created by alternative splicing of a single gene transcript (Refs 82, 83). In normal fibrous tendon, tenascin-C might have a role in maintaining the interface between fibrils and adjacent structures (Ref. 84). In fibrocartilaginous regions of tendon, tenascin-C is predominantly cell-associated (similar to type VI collagen) and is implicated in the development of the chondrocyte cell phenotype (the expression of type II collagen and aggrecan) in response to compressive load (Ref. 84). Tenascin-C is transiently increased after tendon injury, and is thought to modulate cell activities in the developing scar (Refs 85, 86).

Cartilage oligomeric matrix protein (COMP), despite its name, is not restricted to cartilage and is a major component of tendon, representing up to 3% of the dry weight (Ref. 87). A member of the thrombospondin gene family (thrombospondin 5), it is a large (524 kDa) pentameric molecule composed of five disulphide-bonded subunits (Ref. 88). Like tenascin-C and the other thrombospondins, it is thought to have both a structural role and an interactive role with the cell population. There is a strong positive correlation of COMP expression with the levels of mechanical load, with higher levels in flexor tendons compared with extensors (Ref. 89). Levels of COMP increase with age up to skeletal maturity, although only in weight-bearing tendons (Ref. 89). The structural importance of COMP is shown by the condition of pseudoachondroplasia, a genetic disorder caused by a mutation in the COMP gene, resulting in short stature, lax joints and early-onset osteoarthritis (Ref. 90).

In addition to serum proteins such as albumin, other glycoproteins in tendon include: laminin, which is found as a major constituent of basement membranes; link protein, which stabilises hyalectan–hyaluronan interactions (Refs 6, 91); and other multidomain adhesive glycoproteins, including members of the thrombospondin family, that, like COMP, tenascin and fibronectin, mediate cell–matrix interactions in normal and injured tissues (Refs 92, 93, 94).

The molecular pathology of chronic tendinopathy

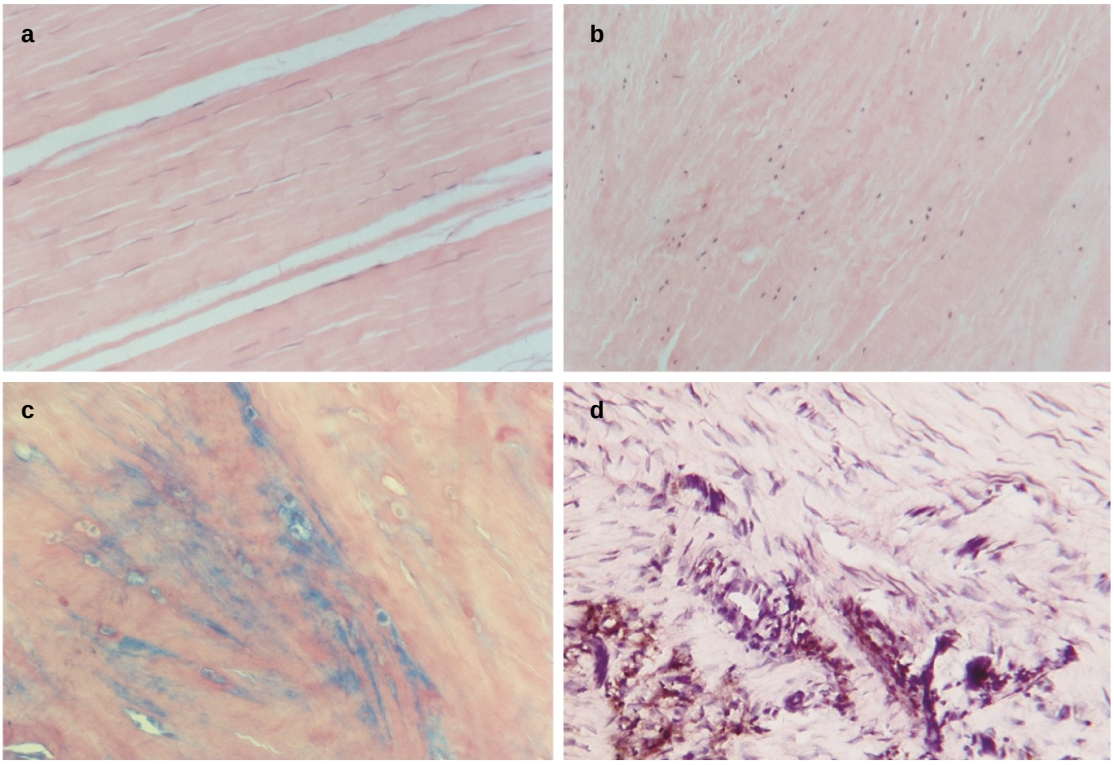
Histopathological studies of tendinopathy have shown an absence of inflammatory cell infiltration and the presence of many features thought to be characteristic of ECM degeneration. These include

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a loss of fibre organisation, decreased fibril diameter, changes in cell density (both increased and decreased), cell rounding, GAG accumulation, lipid accumulation and calcification (Refs 3, 4, 5, 7, 95) (Fig. 4). Although similar changes are commonly found in normal tendons, they are generally less severe, and it is assumed that ECM degeneration precedes the onset of the clinical condition (Refs 3, 7, 96).

There have been few biochemical studies of chronic tendinopathy. In ruptured supraspinatus tendons there was a small but significant decrease in the total collagen content, and an increased proportion of type III collagen relative to type I collagen (Ref. 47). The collagen had a high content of hydroxylysine and there were greater than normal levels of the mature collagen crosslinks hydroxylyslpyridinoline (HP) and lysylpyridinoline (LP) (Ref. 97). These and other crosslinks greatly affect the solubility of the collagen, making it difficult to assess the collagen type, even using chemical methods such as cyanogen bromide peptide mapping. However, the changes in the tendon ECM are characteristic of scar tissue, and the levels of type III collagen and HP tend to diminish as healing proceeds, although high levels often persist because of incomplete remodelling (Ref. 98). Similar ECM



Histopathology of tendinopathy

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Figure 4. Histopathology of tendinopathy. (a) Normal flexor tendon histology, showing organised parallel fibre bundles and long thin tenocytes dispersed throughout the matrix [stained with hematoxylin and eosin (H&E)]. (b) Ruptured supraspinatus tendon, showing hyaline (glassy) appearance, loss of matrix organisation and rounded, shrunken nuclei (H&E). (c) Glycosaminoglycan (GAG) accumulation ('mucoid degeneration') in supraspinatus tendon, showing GAG (blue) surrounding rounded cells in the matrix (Alcian Blue and H&E). (d) 'Angiofibroblastic' change in painful Achilles tendinopathy, showing increase in cell number and blood vessels (H&E). Part c of figure reprinted from Ref. 4 (© 1994); reproduced with permission from the BMJ Publishing Group.

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changes have since been reported in studies of posterior tibialis tendon dysfunction and Achilles tendon rupture (Refs 99, 100). These data are consistent with the gradual accumulation of type III collagen over a relatively long time period, allowing the maturation of collagen crosslinks and stabilisation of the ECM. The gradual incorporation of type III collagen into the main fibre bundles is consistent with a reduction in the average fibril diameter (Ref. 101), a change that is thought to weaken the tendon and to precede tendon rupture (Ref. 102).

Other biochemical studies have shown an increase in the amount of hyaluronan and various proteoglycans in degenerate tendons, although the latter have not yet been fully characterised (Refs 103, 104). An increased water content, typically 10% above normal, is commonly found in tendinopathy, associated with the increased proteoglycan content. Consequently, the specimen dry weight or collagen (hydroxyproline) content is a better reference point for composition studies than the tissue wet weight. Differences in the sugar moieties expressed in ruptured tendons compared with normal were revealed by changes in lectin-staining properties (Ref. 105). Glycoproteins such as tenascin-C were increased in ruptured supraspinatus, with different protein isoforms expressed as well as numerous small peptide fragments, the latter consistent with enzyme-mediated cleavage in the tissue (Ref. 84). Fibronectin immunostaining was significantly increased in ruptured tendon, and there was accumulation of necrotic tissue and fibrin (Ref. 106).

Several studies have shown differences in the expression of various genes encoding matrix proteins in tendinopathy (Refs 107, 108, 109). In one study, for example, 23 genes were found to be upregulated and 17 genes were downregulated in degenerate Achilles tendon (Ref. 107). Although potentially very informative, relatively few of these changes have been confirmed by more rigorous techniques, and the levels of cognate proteins for many of these genes have not been investigated. There were no changes detected in the expression of cytokines and cytokine receptors, consistent with the absence of any ongoing inflammatory process, as confirmed by an analysis of the fluids surrounding painful tendons (Ref. 110). However, these data do not rule out the involvement of inflammation at earlier stages of the disease. It is possible, for example, that the tendon fails to recover after the inflammatory reaction has subsided.

In summary, the ECM changes described in chronic tendinopathy are consistent with a cell-mediated remodelling process occurring in degenerate tendon, without inflammation. The process is similar in many respects to the later stages of a wound-healing response, albeit with impaired or incomplete remodelling, rather than any functional adaptation. The evidence generally supports the hypothesis that there is gradual deterioration in the quality of the ECM, which predisposes to tendon pathology. A key element of this process is thought to be the cellular expression of proteolytic activities and their effects on tendon ECM turnover.

Role of MMPs in tendon collagen degradation and tendinopathy

Proteolytic activity is an essential component of tissue maintenance and repair. After injury, proteolysis is required to remove any damaged ECM and remodel the newly formed scar so that it more closely resembles the normal tissue. Some collagen in tendon is probably degraded intracellularly after phagocytosis, with fibroblasts and macrophages engulfing collagen molecules that are then digested by lysosomal enzymes, comprising mainly cysteine and aspartate proteases (Refs 111, 112). This is a major activity in the rapidly remodelling peridontal ligament, although few (if any) studies have investigated the function of lysosomal enzymes and serine proteases in tendon matrix turnover. Most published studies have focused on collagen degradation occurring in the extracellular environment and mediated by secreted metalloenzymes known as the MMPs.

MMPs: a brief overview

Comprehensive reviews of the MMPs have been published elsewhere and only salient points are reviewed here (Refs 113, 114, 115, 116, 117, 118, 119, 120). MMPs are members of the 'MB' clan of metallopeptidases, generically referred to as 'metzincins' because they contain zinc at the active site and a conserved methionine eight residues downstream. There are 23 MMPs found in humans, each comprising a multidomain structure and with activity at neutral pH against a broad spectrum of different ECM substrates (Refs 114, 116, 118) (Table 2; Fig. 5a). Although important in ECM degradation, MMPs also have

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Table 2. Major known or putative substrates of the matrix metalloproteinases

Family/type	MMP	Descriptive name(s)	Principal or major known substrates
Collagenases	MMP-1	Interstitial collagenase 1	Fibrillar collagens types I, II, III
	MMP-8	Neutrophil collagenase	
	MMP-13	Collagenase 3	
Gelatinases	MMP-2	Gelatinase A, 72 kDa gelatinase	Nonfibrillar collagens, gelatin
	MMP-9	Gelatinase B, 92 kDa gelatinase	
Stromelysins	MMP-3	Stromelysin 1, transin	Proteoglycans, fibronectin, laminin, nonfibrillar collagens, pro-IL-1, collagen type III
	MMP-10	Stromelysin 2, transin-2	
Matrilysins	MMP-7	Matrilysin, PUMP-1	Proteoglycans, link protein, fibronectin, laminin, nonfibrillar collagens, gelatin, fibrin, entactin
	MMP-26	Matrilysin 2, endometase	
Elastase	MMP-12	Macrophage elastase, metalloelastase	Elastin, nonfibrillar collagens
Transmembrane	MMP-14	MT1-MMP	Pro-MMP-2, (MMP-13), gelatin, tenascin, fibronectin, vitronectin, aggrecan
	MMP-15	MT2-MMP	
	MMP-16	MT3-MMP	
	MMP-24	MT5-MMP	
GPI anchored	MMP-17	MT4-MMP	Pro-MMP-2, gelatin
	MMP-25	MT6-MMP	
Miscellaneous	MMP-11	Stromelysin-3	α1-Proteinase inhibitor, IGFBP-1
	MMP-19	RASI-1	Gelatin, aggrecan, COMP, fibrin, tenascin
	MMP-20	Enamelysin	Amelogenin, aggrecan, COMP
	MMP-21	xMMP	Not known
	MMP-23A	CA-MMP	Gelatin
	MMP-23B		Not known
	MMP-27	MMP-22, cMMP	Gelatin, casein
	MMP-28	Epilysin	Not known

Abbreviations: CA, cysteine array; cMMP: chicken MMP; COMP, cartilage oligomeric matrix protein; GPI, glycosylphosphatidylinositol; IGFBP-1, insulin-like growth factor binding protein 1; MBP, myelin basic protein; MMP, matrix metalloproteinase; MT, membrane-type; pro-IL-1, pro-interleukin 1; PUMP, putative metalloproteinase; RASI-1, rheumatoid arthritis synovium inflamed 1; TNF, tumour necrosis factor; xMMP, *Xenopus* MMP.

activity against cell-surface receptors and growth factor precursors (Ref. 119). Consequently, these enzymes also have an important role in the regulation of numerous cellular activities including cell proliferation, cell death (apoptosis), cell migration and chemotaxis (Ref. 119).

The activities of MMPs are normally tightly controlled in vivo, with regulation at the levels of gene transcription, protein translation, activation and inhibition. In general, expression and activity of the MMPs is stimulated by pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumour necrosis factor (TNF), and is inhibited by growth factors such as TGF-β. MMPs are potently inhibited by α_2-macroglobulin in the serum, and also by a family of specific inhibitors produced by cells within the tissues known as tissue inhibitors of metalloproteinases (TIMPs) (Refs 115, 116, 121). Four TIMPs have been characterised to date, and each TIMP binds to active MMPs in a stoichiometric (1:1) ratio, resulting in a stable, inactive complex.

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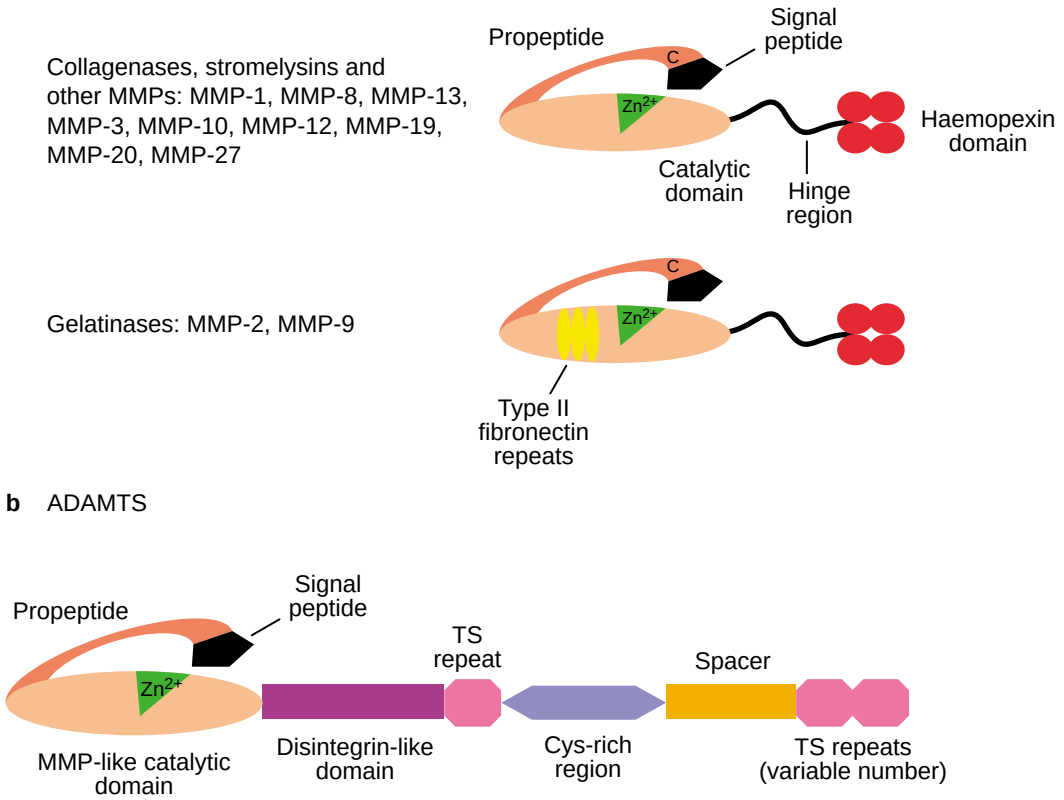


Figure 5. Domain structure of matrix metalloproteinases (MMPs) and ADAMTS. (a) MMPs. The archetypal MMPs such as the collagenases and stromelysins share common domains: a signal peptide that is cleaved prior to synthesis, a propeptide that renders the enzyme inactive until removed by proteolysis, a catalytic domain with a zinc-binding site, a hinge region, and a haemopexin domain that confers substrate specificity. Gelatinases have an additional, gelatin-binding domain consisting of fibronectin type II repeats. Other MMPs have additional domains (not shown, but see Ref. 120). (b) ADAMTS. The ADAMTS family share a common domain structure, with a prodomain that is cleaved within the cell to activate the enzyme, a metalloproteinase catalytic domain, a disintegrin domain, a cysteine (Cys)-rich domain and a variable number of thrombospondin (TS) type I repeats. Several additional C-terminal domains have been found downstream of the variable TS type 1 repeats in some ADAMTS molecules (not shown, but see Ref. 120). Modified figure reproduced from Ref. 120, published in this journal.

MMPs in tendon

The MMPs are implicated in both the physiological and pathological turnover of the tendon ECM. Pieces of normal tendon placed in explant culture produce collagenase and gelatinase activities, degrading the collagen matrix after two to three weeks in culture, and this process is stimulated by the addition of inflammatory cytokines such as IL-1 (Refs 122, 123, 124, 125). MMPs are also implicated in the remodelling of tendon that follows immobilisation (Refs 126, 127, 128, 129). MMP-1 is thought to be one of the key mediators of tendon fibrillar collagen degradation, at least in explant culture, and this activity can be inhibited by the application of cyclical strain, an effect though to be mediated via the tenocyte cytoskeleton (Refs 130, 131, 132, 133, 134). Isolated tenocytes respond to strain and shear forces by

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upregulation of MMP, demonstrating that mechanical strain is likely to be a major stimulus for ECM remodelling in tendon (Refs 135, 136). MMP expression was stimulated in rabbit tendon in vivo by extended periods of cyclical loading, although there was no sign of injury as assessed by histological examination (Ref. 137). Intense physical training was also shown to increase MMP-2 and MMP-9 activities in the fluid surrounding human Achilles tendon (Ref. 138).

Several MMPs have been identified in acute tendon injuries, with differences in the timing and location of expression that suggest different roles in the healing process. Levels of MMP-9 and MMP-13 peaked 7–14 days after injury, whereas MMP-2, MMP-3 and MMP-14 increased and were maintained at high levels until at least day 28 (Ref. 139). Thus, it appears that MMP-9 and MMP-13 are involved in the degradation of collagen in the initial inflammatory phase, whereas MMP-2, MMP-3 and MMP-14 have a role in the remodelling of the scar tissue.

A comparison of human tendons showed evidence of substantial differences in the rate of collagen turnover between tendons from different sites (Ref. 38). There was very little collagen turnover in normal biceps brachii tendons, which contained no significant levels of MMP activity and a linear accumulation of pentosidine crosslinks with increasing age (Ref. 38). By contrast, supraspinatus tendons obtained from normal shoulders showed relatively high levels of collagen turnover, and there were correspondingly high levels of MMP-1, MMP-2 and MMP-3 activity (Ref. 38). In ruptured supraspinatus tendon, there was increased activity of MMP-1, reduced activity of MMP-2 and MMP-3, and evidence of increased turnover of the collagen network (Ref. 38). Levels of expression of MMP-1 and MMP-3 in shoulder fluids were shown to correlate with the size of the tendon tear, and MMP-1 was expressed by cells within the ruptured tendon (Refs 140, 141).

Studies of painful Achilles tendons using cDNA arrays have identified several differences in MMP gene expression, although many of these findings need to be confirmed by RT-PCR analysis (Refs 107, 108). The absence of MMP-1 and MMP-8 expression was consistent with an absence of inflammation, and there was a small but variable increase in MMP-2 and MMP-14 in degenerate tendons, whereas MMP-9 and MMP-13 were detected only in ruptured tendons (Refs 107, 108). The greatest difference between normal and pathological tendon specimens was the level of MMP-3, which was absent or significantly less abundant in painful tendinopathy (Refs 107, 108). A similar change was reported in degenerate supraspinatus tendons (Ref. 38), consistent with a role for MMP-3 in the maintenance of the normal tendon ECM, at least in highly stressed tendons such as the supraspinatus and the Achilles. The loss of MMP-3 activity in tendinopathy could account for the increase in proteoglycan commonly found in tendon lesions, since proteoglycans are potential substrates for the enzyme. However, since most proteoglycan degradation in vivo is attributed to aggrecanases (see below), more research is required to identify the role of MMP-3 in tendon.

Role of aggrecanases in tendon proteoglycan degradation and tendinopathy

Proteoglycans are turned over much more rapidly than the fibrillar collagens. Although some members of the MMP family, for example MMP-3, can degrade proteoglycans such as aggrecan in vitro, most proteoglycan-degrading activity in vivo is associated with a related but distinct group of metallo-endopeptidases, commonly known as aggrecanases.

Aggrecanases were first identified on the basis of their ability to cleave aggrecan at specific Glu-Xaa bonds. The core protein is cleaved at several sites, resulting in the shortening of the core protein or the complete loss of the GAG-rich portion of the molecule from the tissue (Ref. 142). This activity was associated with the loss of cartilage proteoglycan that accompanies osteoarthritis (Ref. 143). Aggrecanases were subsequently identified as members of the ADAMTS family, a subgroup of ADAM (for 'a disintegrin and metalloproteinase') with thrombospondin (TS) type I motifs (Refs 144, 145) (Fig. 5b).

Aggrecanases and the ADAMTS family

To date, 19 mammalian ADAMTS enzymes have been identified, many of which are not yet fully characterised (Refs 144, 145). ADAMTS-2, ADAMTS-3 and ADAMTS-14 are procollagen peptidases, and function as regulators of collagen-fibril assembly (Refs 146, 147, 148). ADAMTS-4 (aggrecanase 1) and ADAMTS-5 (aggrecanase 2) were the first aggrecanases to be identified (Refs 144, 149, 150), although ADAMTS-1 and other

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phylogenetically related enzymes (ADAMTS-8, ADAMTS-9, ADAMTS-15 and ADAMTS-20) might also have aggrecanase activity (Refs 151, 152, 153, 154). Best known for their activity against aggrecan, ADAMTS-1 and ADAMTS-4 are also capable of cleaving other ECM proteoglycans such as versican and brevican (Ref. 155), and glycoproteins such as COMP (Ref. 156), at least in vitro. Although inhibition of ADAMTS-4 and ADAMTS-5 can prevent cartilage degradation in tissue culture models (Ref. 157), the enzymes responsible for proteoglycan degradation in osteoarthritis and other diseases of connective tissues have yet to be identified.

Aggrecanase activity is thought to be regulated at multiple levels, although the mechanism is currently poorly understood. Differential regulation of ADAMTS mRNAs has been deduced from analysis of their expression in cell and explant cultures, albeit with considerable variation between studies (Refs 157, 158, 159, 160, 161). A study of human tendon cells has reported small and variable effects of IL-1 on ADAMTS-4 expression (Ref. 161).

In addition to regulation at the level of gene transcription, the activities of ADAMTS enzymes are also subject to post-translational regulation. The noncatalytic ancillary domains of ADAMTS-4 are required for both catalytic activity and substrate specificity (Refs 162, 163). Full-length enzyme is sequestered in the ECM via GAG-binding sequences in the spacer domain, and sulphated GAGs attached to the aggrecan core protein are required for ADAMTS-4 activity (Ref. 163). Deletion of the C-terminal spacer domain increased the efficiency of hydrolysis of aggrecan at Glu373-Ala374 bonds, and revealed new activities against fibromodulin, decorin and a general protein substrate (Ref. 163). Several short forms of ADAMTS-4, thought to be generated by autocatalytic C-terminal truncation, are found in cartilage, and these potentially contribute to the degradation of a broad range of protein substrates in addition to proteoglycans (Refs 162, 163). The enzymes are thought to be secreted in an active form after cleavage of the prodomain within the cell by furin, which might be followed by C-terminal truncation by MMP-17 at the cell surface (Refs 164, 165). Aggrecanases such as ADAMTS-4 are inhibited by the general proteinase inhibitor α_2-macroglobulin and by the specific endogenous inhibitor TIMP-3, but not by other TIMPs (TIMP-1, -2 and -4) (Ref. 166).

Aggrecanase activities in tendon

Studies of normal (bovine) tendon have shown that proteoglycans are constitutively turned over relatively rapidly, with hyalectans breaking down more rapidly than the SLRPs (Refs 167, 168, 169). Proteolytic fragments of proteoglycans such as aggrecan were present in both young and mature tendon, in both tensional and compressed regions. Much of the aggrecan in tendon appears to lack the G1 domain, but the molecule might be retained in the tissue by interactions of the G3 domain with an unidentified matrix component. Cultured tendon explants released cleavage products into the culture medium and there was no significant stimulation of this activity by IL-1 (Ref. 167). There was no evidence of MMP-mediated proteoglycan turnover, although aggrecan turnover did not directly correlate with the levels of expression of either ADAMTS-4 or ADAMTS-5 mRNA. However, gene expression might play a relatively minor role in the regulation of aggrecanase activity, and further studies are required to identify the enzyme activities present in human tendon and their role in tendinopathy. Since levels of proteoglycan are increased in the degenerate tendon lesion (unlike osteoarthritic cartilage), it will be interesting to determine whether this is caused by an increase in proteoglycan synthesis or a decrease in proteoglycan degradation.

Clinical implications

Anti-inflammatory drugs: do they have a role in the treatment of tendinopathy?

The absence of inflammatory cells, at least at later stages of the disease, would suggest that there is no rational basis for the treatment of chronic tendinopathy with anti-inflammatories such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections, both of which are commonly used even though there are limited data to demonstrate their effectiveness (Ref. 1). However, it has recently been argued that the definition of inflammation should be reappraised, since inflammatory mediators can be produced by a variety of cell types, and not just by infiltrating leukocytes (Ref. 170). Degenerative conditions such as osteoarthritis can be considered inflammatory diseases on this basis, with the expression of cytokines and nitric oxide by chondrocytes and/or synovial cells (Refs 170, 171, 172). In a similar fashion, it is possible that mediators of inflammation might be involved in

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chronic tendinopathy, although produced by the resident cell population or surrounding connective tissues (Refs 173, 174, 175, 176). For example, prostaglandins and other inflammatory mediators were found to be increased in the fluids surrounding tendons following vigorous exercise and are implicated at least in the adaptive response of the tissue (Refs 177, 178, 179). Increased expression of the inducible cyclooxygenase (COX-2) in patellar tendinosis suggests some involvement of prostaglandins in the disease (Ref. 175). Several studies have shown IL-1 was more abundant in the endotenon, vascular endothelium and synovial tissues surrounding affected tendons (Refs 174, 176). Inflammatory mediators might also be transiently produced by the tenocytes, which can be induced to express IL-1β and COX-2 under the influence of mechanical strain, providing a theoretical basis for the development of 'overuse' tendinopathy (Refs 180, 181, 182, 183). However, most molecular studies of tendinopathy have so far provided no conclusive evidence for the involvement of inflammatory mediators and cytokines such as prostaglandin E_2 and IL-1 (Refs 107, 108, 184, 185).

Enzymes as potential targets for therapy

In degenerative conditions such as osteoarthritis, one of the targets for drug therapy is the increased cartilage ECM degradation mediated by enzymes such as MMPs and ADAMTS (Refs 118, 186). Various therapeutic approaches have been attempted, including selective inhibition of collagenases or broad-spectrum inhibition of many different MMPs, although none has yet been successful in clinical trials (Ref. 118).

The pathology of tendinopathy is evidently different from osteoarthritis, with increased cell activity, neovascularisation, and accumulation of proteoglycan within the lesion, in addition to increased turnover of the matrix collagen. Indeed, it would appear that some ECM turnover is required for maintaining the health of the tendon, at least in highly stressed tendons such as the supraspinatus and Achilles. This hypothesis is consistent with data obtained from clinical trials with broad-spectrum MMP inhibitors, which were found to cause an unwanted side effect described as a 'musculo-skeletal syndrome' in the tendons of the patients' shoulders and hands, which recovered after the cessation of therapy (Refs 187, 188). Compounds selective for collagenases or gelatinases did not induce the condition, and the precise cause of the syndrome remains unidentified. Additional activity against 'sheddases' (members of the ADAM family of metalloproteases involved in the processing of cell-surface receptors) might explain the development of the syndrome, although there is no consensus of opinion. Because there are many different enzymes, a solution to this problem will require an analysis of all the metalloproteinase enzymes that are expressed and active in healthy and degenerate tendon.

Neuropeptides and tendon ECM turnover: a novel therapeutic target for tendinopathy?

If inflammation is not associated with the development of chronic tendinopathy, other causes of tendon pain and ECM degeneration must be considered. Recent studies have suggested that nerves, and small peptides ('neuropeptides') produced by nerve endings, might have a role in tendinopathy, similar to that described in intervertebral disc degeneration (Refs 189, 190).

In studies of 'tennis elbow' lesions, nerve endings and neuropeptides were found at the site of the lesion, although it was unclear if this distribution was different to normal (Ref. 191). Studies of fluids obtained from around painful tendons using a microdialysis technique have shown that levels of the neurotransmitter glutamate were significantly increased in tendinopathy relative to controls (Refs 110, 184, 192). Both free glutamate and glutamate receptors (NMDAR1) have also been detected within Achilles tendons, located to nerve fibres, both in tendinopathy specimens and in controls (Ref. 193). Since glutamate is a potent mediator of pain in the central nervous system, it was suggested that NMDAR1 antagonists might be useful in the treatment of tendon pain.

It has also been reported that substance P, another neuropeptide associated with the sensation of pain, is increased in the subacromical bursa in patients with rotator cuff tendinopathy (Ref. 194). The amount of substance P was shown to correlate with the degree of motion pain as assessed by a visual analogue scale. Whether this was due to an increase in the release of substance P or an increase in the number of nerve fibres was not clear, although immunohistochemistry showed more nerve fibres in bursal tissues of patients with a perforated rotator cuff (Ref. 194). Apart from the modulation of pain, substance P and other

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neuropeptides might have additional effects, regulating the local circulation and stimulating neurogenic inflammation in and around the tendon (Refs 195, 196).

Hart et al. have proposed that regulatory units composed of nerve endings and mast cells reside in and around the tendon (Ref. 197). The release of neurotransmitters stimulates mast-cell degranulation, releasing a variety of mediators including growth factors that influence oedema, angiogenesis, fibroblast proliferation and many other aspects of cell activity. Biomechanical stimulation of these nerve–mast-cell units might form part of the normal regulatory system, maintaining the tissue and also contributing to the adaptive response to load. Excessive stimulation of neural–mast-cell units might contribute to overuse tendinopathy. Since the extent of innervation and vascularisation varies between different tendons, the potential for the development of neurogenic dysfunction also varies. This theory potentially links mechanical stimulation of the paratenon, which is more richly innervated, and tissue changes in the tendon mid-substance. The association of neuropeptides with tissue remodelling has not been conclusively proved, although substance P and calcitonin-gene-related peptide (CGRP) were shown to modulate directly the expression of MMP-1 and MMP-3, at least in vitro (Refs 195, 198). Thus innervation, and the stimulation of neuropeptide release by strain or friction at the tendon surface, is thought to be important for both normal tendon function and tendinopathy, affecting remodelling events in the tissue. Since peptide antagonists of substance P are already available, having been used in clinical trials for the treatment of pain, emesis and depression, it is possible that they could prove useful for the treatment of chronic tendinopathy.

Concluding remarks

Most tendinopathy is associated with degeneration, which is thought to be an active, cell-mediated process involving increased turnover and remodelling of the tendon ECM. There is a gradual transformation in the quantity and quality of the ECM that precedes tendon rupture. However, some ECM turnover might be required to maintain the health of the tendon, particularly at sites exposed to high mechanical strain, such as the shoulder and ankle. Degradation of the tendon ECM is mediated by a variety of metalloproteinase enzymes, including MMPs and aggrecanases. Some enzymes are thought to be responsible for repair and maintenance of the tendon, and others are implicated in the pathological destruction of the ECM: these enzymes need to be identified so that new drugs can be developed. There are a variety of factors that might influence ECM turnover in tendon, although a major factor in most tendinopathy is thought to be repeated minor mechanical strain or 'overuse'. Although infiltrating inflammatory cells are probably not involved in chronic tendinopathy, neuropeptides and other mediators of pain and inflammation produced in or around the tendon might be implicated, and could provide novel targets for therapeutic intervention.

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Figures

Figure 1. Structure of tendon.
Figure 2. Synthesis of a fibril-forming collagen.
Figure 3. Proteoglycans in tendon.
Figure 4. Histopathology of tendinopathy.
Figure 5. Domain structure of matrix metalloproteinases (MMPs) and ADAMTS.

Table

Table 1. Molecular composition of tendon extracellular matrix.
Table 2. Major known or putative substrates of the matrix metalloproteinases.

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