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Tendinopathy—from basic science to treatment

Graham Riley

SUMMARY

Chronic tendon pathology (tendinopathy), although common, is difficult to treat. Tendons possess a highly organized fibrillar matrix, consisting of type I collagen and various 'minor' collagens, proteoglycans and glycoproteins. The tendon matrix is maintained by the resident tenocytes, and there is evidence of a continuous process of matrix remodeling, although the rate of turnover varies at different sites. A change in remodeling activity is associated with the onset of tendinopathy. Major molecular changes include increased expression of type III collagen, fibronectin, tenascin C, aggrecan and biglycan. These changes are consistent with repair, but they might also be an adaptive response to changes in mechanical loading. Repeated minor strain is thought to be the major precipitating factor in tendinopathy, although further work is required to determine whether it is mechanical overstimulation or understimulation that leads to the change in tenocyte activity. Metalloproteinase enzymes have an important role in the tendon matrix, being responsible for the degradation of collagen and proteoglycan in both healthy patients and those with disease. Metalloproteinases that show increased expression in painful tendinopathy include ADAM (a disintegrin and metalloproteinase)-12 and MMP (matrix metalloproteinase)-23. The role of these enzymes in tendon pathology is unknown, and further work is required to identify novel and specific molecular targets for therapy.

KEYWORDS ADAMTS, matrix metalloproteinase, soft-tissue rheumatism, tendinopathy, tendon

REVIEW CRITERIA

PubMed and ISI Web of Science databases were searched for English-language papers using combinations of the following search terms: "tendon", "tendinopathy", "soft tissue rheumatism", "matrix remodeling", "matrix metalloproteinase" and "ADAMTS".

CME

G Riley is an Arthritis Research Campaign Senior Research Fellow and leader of the Soft Tissue Research Group in the School of Biological Sciences at the University of East Anglia, Norwich, UK.

Correspondence
Soft Tissue Research Group, School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ, UK
graham.riley@uea.ac.uk

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify the primary mechanism leading to tendinopathy.
2 Describe the prevalence of soft-tissue injury and tendinopathy in the United Kingdom.
3 Describe repair mechanisms after tendon injury.
4 List key elements of the extracellular matrix in tendon.
5 Describe the evidence for the efficacy of newer treatments for tendinopathy.

Competing interests

The author has declared an association with the following company/organization: Wyeth Pharmaceuticals. See the article online for full details of the relationship. Désirée Lie, the CME questions author, declared no relevant financial relationships.

INTRODUCTION

Soft-tissue disorders are the third most common rheumatologic condition in the UK, with a reported prevalence of 18 cases per 1,000 people.[1] These disorders, which primarily affect tendon, are the main reasons for a musculoskeletal consultation with a general practitioner, and comprised 30% of all such consultations in a 1-year study.[2] This is probably an underestimate of the scale of the problem, because only 40% of elderly individuals (over 70 years of age) with shoulder pain seek treatment.[3] Although many soft-tissue problems are treated by a general practitioner, often with NSAIDs, corticosteroid injection or physiotherapy, a substantial proportion of new patient consultations with rheumatologists

are for soft-tissue rheumatism. Secondary referral rates vary widely, but one study reported that 17% of new patients seen in a rheumatology clinic had soft-tissue complaints.[4]

Conditions affecting tendons, which include chronic pain and rupture, are now generally referred to as 'tendinopathies' in preference to terms such as 'tendinosis' and 'tendinitis', because this terminology makes no assumptions about the underlying pathology. Although the role of inflammation is still debated, it has long been known that tendinopathies are primarily degenerative conditions—there is usually an absence of inflammatory cells in or around the lesion.[5] Consequently, it should be no surprise that treatment with anti-inflammatory drugs showed little benefit in controlled trials.[6] In fact, there is remarkably little evidence that any conventional therapies are effective.[7] It has taken several years for research interest to grow, but the molecular mechanisms underlying the cause and progression of tendinopathy are beginning to be elucidated. This article will review the molecular pathology of tendon, and discuss how this knowledge might provide potential new targets for the treatment of chronic tendinopathies.

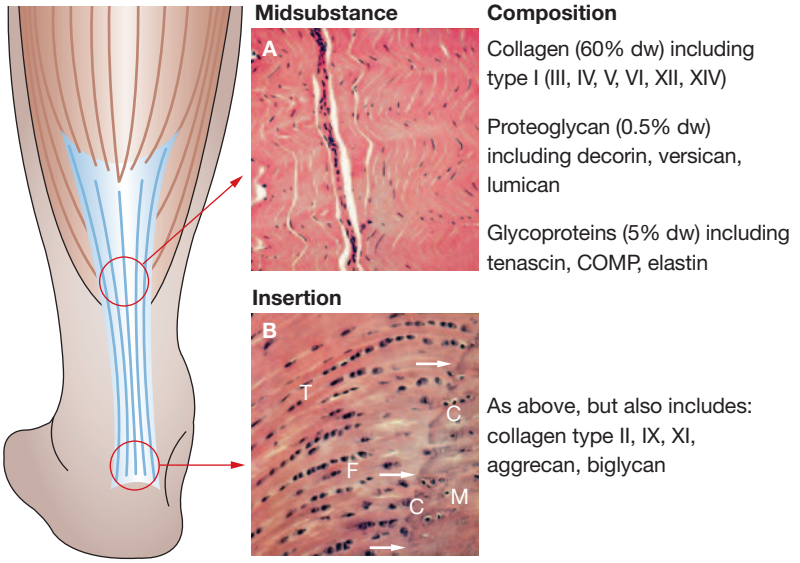

Figure 1 Schematic of tendon structure and composition. The tendon midsubstance (**A**) is a dense, fibrous connective tissue of crimped fiber bundles, mostly aligned with the long axis of the tendon. The matrix consists predominantly of type I collagen, with lesser amounts of 'minor' collagens, proteoglycans and other glycoproteins. The tendon–bone insertion (enthesis) (**B**) shows more rounded cells with an Indian-file appearance and a gradual transition from tendon (T) to fibrocartilage (F) to calcified fibrocartilage (C) to mineralized bone (M). The matrix composition of the enthesis is similar to the tendon midsubstance but also contains additional 'minor' collagens and increased quantities of the proteoglycans aggrecan and biglycan. Photomicrographs (A) and (B) are H&E-stained sections of tendon midsubstance and insertion, respectively. Abbreviations: COMP, cartilage oligomeric matrix protein; dw, dry weight; H&E, hematoxylin and eosin.

MOLECULAR COMPOSITION OF TENDON

The main principles of tendon structure and composition are shown schematically in Figure 1, and have been reviewed elsewhere.[8,9] Key elements of the extracellular matrix are the dense, fibrillar network of predominantly parallel-aligned collagen fibers, principally consisting of type I collagen but also containing lesser amounts of various 'minor' collagens, several proteoglycans and a growing list of glycoproteins.[8] Although the role and function of many of these components are still poorly defined, the molecular architecture of the matrix is ideally suited primarily for the transmission of tensile load; however, tendons also function to stabilize joints and absorb large shocks, protecting muscles from damage.

There are variations in structure and composition within a tendon, particularly at the myotendinous junction and bone insertion sites (enthesis) but also at sites where the tendon is compressed, passes through soft-tissue pulleys, abuts against ligaments or traverses bony prominences.[9] Fibrocartilaginous regions are formed in tendons in response to compressive load or shear, an adaptive response that protects the tendon from damage. The molecular architecture of tendon fibrocartilage has been extensively studied, demonstrating increased expression of molecules normally associated with articular cartilage, including type II collagen and aggrecan.[9]

CELL POPULATIONS OF TENDON

The fibroblast-like cells that populate tendon are known as 'tenocytes', which are thought to be distinct from other connective tissue cells, although there are currently no specific molecular markers that can be used to characterize them.[10] There are a variety of cell phenotypes described in histologic studies of tendon, with more rounded 'fibrochondrocyte' cells in fibrocartilaginous regions, often arranged in columns at the insertion, compared with elongated and dispersed fibroblasts within fibers in the tensile-load-bearing regions of the tendon midsubstance.[11] There are synovial-like cells in the endotenon and epitenon, the thin layers of

loose connective tissue that surround the fiber bundles or fascicles.[12] The different cell populations have distinct activities in matrix synthesis, and are responsive to cytoskeleton-mediated matrix interactions and changes in their mechanical environment.[12–14] Additional cells include smooth muscle and endothelial cells associated with blood vessels, which can be found passing through the endotenon and epitenon. Fine nerve processes and nerve endings are sparse but also present, usually in proximity to the blood vessels, which are more abundant in the epitenon and enveloping paratenon.[15]

After tendon injury, most repair activity is associated with cells from the epitenon and endotenon, which migrate to the lesion and synthesize new matrix.[16] A proportion of these cells is thought to be derived from a resident population of stem cells, which can differentiate into a variety of mesenchymal tissues, such as bone, fat and cartilage, in addition to tendon.[10]

TENDON MATRIX ADAPTATION AND REMODELING

In addition to internal variations within tendon, there are variations in structure, composition and cell phenotype between tendons from different sites, and, increasingly, it is recognized that tendons are 'engineered' according to the functional demands on them in specific anatomic locations.[17] There are variations in the content of proteoglycan and collagen, and there is evidence of different rates of matrix turnover. Highly stressed tendons, such as the supraspinatus in the rotator cuff, show increased levels of collagen remodeling compared with those that are not under high stress, for example the distal biceps tendon in the forearm, which has much lower rates of collagen turnover.[18,19] The continual process of matrix remodeling is a constitutive (albeit slow) activity in normal tendons, affecting proteoglycans in addition to collagen,[20,21] and is thought to be primarily mediated by metalloproteinases acting in the extracellular environment, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS).

MMPs and ADAMTS have been reviewed elsewhere.[22,23] Briefly, there are 23 MMPs in humans, which have a wide range of matrix substrates. Several of these enzymes (MMP1, MMP2, MMP8, MMP13 and MMP14) have activity against fibrillar collagen. Because few enzymes can cleave fibrillar collagen at neutral pH, regulation of this activity is thought to be a key step in the remodeling process in both health and disease. Proteoglycans are primarily degraded by enzymes of the ADAMTS family known as 'aggrecanases', which include ADAMTS1, ADAMTS4, ADAMTS5, ADAMTS8 and ADAMTS9, although precisely which enzyme is involved in the turnover of tendon proteoglycan is currently unknown. The activity of metalloproteinases is highly regulated at multiple levels, including transcription, activation and inhibition by tissue inhibitors of metalloproteinase (TIMPs).[22]

Analysis of metalloproteinase gene expression in human Achilles tendon showed that almost all of the 23 MMP and 19 ADAMTS family members were detectable in normal tendon, although levels of expression varied widely.[24] These enzymes are important in regulating cell activity as well as matrix degradation, and they have roles in growth, development and repair, and also pathologic processes, including inflammation and degeneration.[25] Evidence of their importance in tendon health is provided by the observation that broad-spectrum metalloproteinase inhibitors used in clinical trials caused a musculoskeletal syndrome similar to tendinopathy that resolved after treatment ended.[26] Fluoroquinolone antibiotics, such as ciprofloxacin, can also induce tendinopathy in some patients, and these drugs can modulate MMP expression by tenocytes, at least *in vitro*.[27] Doxycycline, which inhibits several MMPs, significantly reduced the mechanical properties of healing tendons, demonstrating the importance of MMPs in tendon repair.[28]

MACROSCOPIC AND MICROSCOPIC OBSERVATIONS OF TENDINOPATHY

Tendons commonly affected by tendinopathy include the supraspinatus and long head of biceps in the shoulder, medial and lateral extensors of the elbow, the patellar, the Achilles tendon and the posterior tibialis. In most cases, with the notable exception of the Achilles tendon, the site affected is at or near the insertion in a fibrocartilaginous region of the tendon.[29] There are several common features of these sites: they are more highly stressed than other tendons, often exposed to repeated strains, including shear or compressive forces, and relatively less vascularized than the tendon midsubstance.

Histopathology of painful tendons shows changes in cellularity (both increased and

decreased), cell rounding, decreased matrix organization and increased infiltration of blood vessels.[30] The abnormal vascularity has been associated with tendon pain.[31] Ruptured tendons show similar degenerative features, although there is generally reduced cellularity and little evidence of neovascularization.[32] The absence of new blood vessels and associated nerves might account for the absence of pain in 'spontaneous' tendon ruptures, which have no preceding clinical symptoms. Most of the cells in tendinopathy specimens are fibroblast-like, albeit generally more rounded or ovoid, and few studies have identified inflammatory cells, at least in the tendon substance.[30]

MOLECULAR PATHOLOGY OF TENDINOPATHY

Biochemical and molecular studies of chronic tendinopathy during the past 15 years have increased our understanding of the underlying pathology; the main findings are summarized in Figure 2. In pathologic human tendon, there is increased expression of the messenger RNA of collagen types I and III, and increased amounts of type III collagen protein are found in the tendon matrix.[33] The levels of fibronectin and tenascin C are also increased, consistent with a healing response.[33] There is an increased level of glycosaminoglycan in the matrix[33] and increased expression of the chondroitin sulfate proteoglycans, aggrecan and biglycan, even in the midsubstance of the Achilles tendon (in which fibrocartilage is not normally found), consistent with an adaptive response to shear or compression.[34] Versican messenger RNA levels were unchanged in painful tendons, although there were changes in splicing of the gene that would affect the quantity of glycosaminoglycan attached to the mature protein.[35]

There are changes in the expression and activity of various metalloproteinases, and changes in the level of TIMPs that are consistent with increased proteolytic activity in degenerate tendons.[33] Pathologic (torn) rotator cuff tendons showed greatly increased collagenase (MMP1) activity and reduced gelatinase (MMP2) and stromelysin (MMP3) activity compared with normal tendons; these changes correlated with levels of collagen turnover in the tissues.[19] A study of gene expression in Achilles tendons showed that painful and ruptured tendons had distinct patterns of expression, consistent with quantitative and qualitative differences in catabolic activity in the different clinical entities.[24] Ruptured tendons showed increased levels of expression of MMP1, MMP9, MMP19, MMP25 and TIMP1 and decreased levels of expression of MMP3, MMP7, TIMP2, TIMP3 and TIMP4. Painful tendons showed reduced expression of MMP3, MMP10 and TIMP3 and increased expression of ADAM12 and MMP23. Little is known about the role and function of ADAM12 and MMP23 in tendon, although both have been associated with changes in cell phenotype: ADAM12 with myogenesis and lipidogenesis, and MMP23 with endochondral ossification.[36,37] In summary, the changes in the composition of tendon matrix are consistent with changes in cell-mediated matrix remodeling that precede the onset of clinical symptoms, and these changes are mediated, at least in part, by metalloproteinase enzymes.

The cellular and molecular processes that drive the changes in the remodeling of tendon matrix in tendinopathy are yet to be determined.

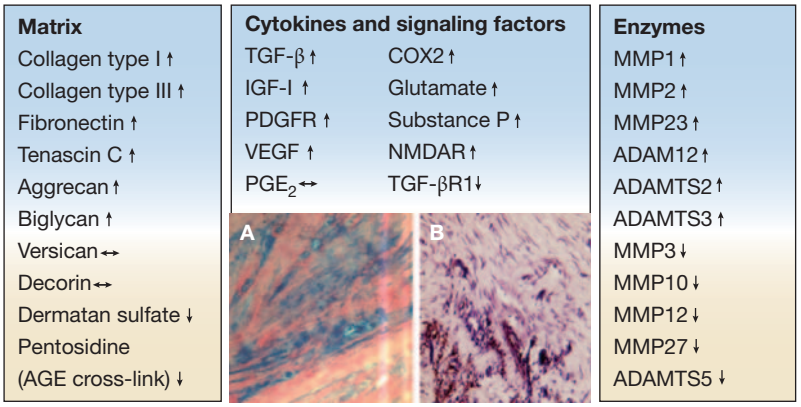

Figure 2 Major structural and molecular changes in chronic tendinopathy. Typical features of tendinopathy are cell rounding and increased cell number, proteoglycan content and vascularity. Major molecular changes that have been identified by gene-expression studies, protein analysis or both are summarized. Molecules for which expression levels are increased are denoted by an upwards arrow, molecules for which expression levels are decreased are denoted by a downwards arrow and molecules for which expression levels remain unchanged are denoted by a horizontal arrow. Note that not all the changes shown have been rigorously confirmed, particularly at the protein level. Photomicrograph (**A**) is an alcian blue/H&E-stained section of supraspinatus tendinopathy, showing proteoglycans stained blue. Photomicrograph (**B**) is an H&E-stained section of Achilles tendinopathy, showing increased cellularity and proliferation of blood vessels. Abbreviations: ADAM, a disintegrin and metalloproteinase; ADAMTS, ADAM with thrombospondin motifs; AGE, advanced glycation end product; COX2, cyclo-oxygenase 2; H&E, hemotoxylin and eosin; IGF-I, insulin-like growth factor 1; MMP, matrix metalloproteinase; NMDAR, *N*-methyl-D-aspartate receptor; PDGFR, platelet-derived growth factor receptor; PGE_2, prostaglandin E_2; TGF-β, transforming growth factor β; TGF-βR1, TGF-β type 1 receptor; VEGF, vascular endothelial growth factor.

Table 1 Conservative treatments for chronic tendinopathy.[a]

Treatment	Putative target or mode of action
Rest or modification of activity	Removal of precipitating factors and prevention of reinjury
Orthotics (e.g. heal inserts)	As above
Cryotherapy (e.g. ice packs and baths)	Reduction of acute inflammation and decrease in cell metabolism
Heat treatment	Stimulation of cell activity and increase in blood flow
Physiotherapy (including massage and controlled motion)	As above
Electrical stimulation	Reduction of pain perception, stimulation of blood flow and increase in cell activity
Laser treatment (pulsed or continuous)	Possible analgesic effects and unspecified (unknown) effects on cell activity
Pulsed electromagnetic fields	As above
Ultrasound (0.75–3.0 MHz; pulsed or continuous)	Thermal effects on tissue, stimulation of cell activity and increased blood flow
Extracorporeal shock-wave therapy	As above, with possible stimulatory effects on neovascularization and inhibition of nociception
NSAIDs	Reduction of inflammation through inhibition of prostaglandin synthesis
Corticosteroid injection (peritendinous)	Reduction of inflammation and other unknown effects (generally inhibitory of protein synthesis)
Low-dose heparin	Effect on tendon blood flow; possibly results in improved healing
Actovegin (deproteinized extract of calf's blood)	Unknown (suggested to promote glucose uptake and other effects on tendon cell metabolism that promote repair and resolution)
Glycosaminoglycan polysulfate	Inhibition of inflammation, possibly also acting to inhibit metalloproteinase enzyme activity
Eccentric exercise therapy	Thought to promote restoration of normal tissue structure, possibly through an effect on cell activity and matrix remodeling
Sclerosant injection (ultrasound-guided)	Blocks tendon blood flow (targets neovascularization and associated nerve in-growth)
Platelet-rich plasma injection	Contains growth factors (e.g. transforming growth factor β and platelet-derived growth factor) that promote matrix synthesis and tissue repair

[a]Few treatments for chronic tendinopathy are targeted against specific molecular processes. In most cases, there is little or no evidence of therapeutic effectiveness, especially in the long term. Large, appropriately controlled clinical trials with extended follow-up are required.

It is uncertain to what extent the remodeling represents a limited repair response to microscopic fiber damage or an adaptive response to changes in cell-loading patterns. Excessive microstrain or 'overuse' acting on the tenocytes has been shown to elicit the expression of several inflammatory mediators and MMPs, at least *in vitro*, and it is suggested that this might trigger increased proteolytic activity in the tendon;[38] however, the levels of strain required to elicit this response are high, potentially much higher than the strains experienced by cells *in vivo*. More recently, it has been shown that rat tenocytes cultured in three-dimensional collagen gels will upregulate their expression of MMP13, the major rodent collagenase, if the gels become free floating and contract.[39] These studies were extended to a study of stretched tendons *in vitro*, and it was shown that upregulation of MMP13 occurred after failure of one or more of the fiber bundles.[40] Thus, it seems that MMP output is attenuated by strain on the tendon cells through the cytoskeleton, and damage to tendon fibers results in the release of the cells from this strain regulation, resulting in increased collagenase activity and matrix degradation.

Although there is an absence of inflammatory cells in or around the lesion, this does not mean that inflammatory mediators are not implicated in tendinopathy, at least at some stage in the disease. Although levels of prostaglandin E_2 were not significantly higher in the fluids surrounding painful tendons,[41,42] levels of prostaglandin E_2 and several other inflammatory mediators, such as thromboxane, bradykinin and interleukin (IL)-6, are increased in peritendinous tissue after prolonged exercise.[43–45] Other studies have reported increased levels of IL-1 in the tissues surrounding painful tendons, such as the bursa in the shoulder.[46] Increased expression

of cyclo-oxygenase 2 was associated with patellar tendinopathy,[47] and repeated injection of prostaglandin around the tendon has been shown to induce a degenerative tendinopathy in animal models.[48] The expression of growth factors and other potential modulators of tendon cell activity has been shown to increase in tendinopathy, including transforming growth factor β, platelet-derived growth factor receptor and neurotransmitters, such as glutamate and substance P.[42,47,49–51] These changes might, however, be part of the healing response of the tissue and a requisite for tendon repair.[52,53]

NEW TREATMENTS FOR TENDINOPATHY AND FUTURE RESEARCH DIRECTIONS

A summary of current treatments and new therapies in development is shown in Table 1. Exercise is important in both prevention and treatment of tendinopathy. Eccentric exercise therapy has been reported to have some effect in prospective, randomized trials in athletic patients;[54,55] however, a review of 20 published trials found that there was little evidence of a positive effect on clinical outcomes, such as reduction of pain, return to function and patient satisfaction.[56] Shock-wave therapy, which is thought to function on the tenocytes to stimulate repair, might be effective in a carefully selected group of patients,[57] although other studies have reported no significant effect.[58,59] Growth factors have been used for several years in an attempt to improve tendon healing, but there is currently no evidence that these are effective in tendinopathies. Nitric oxide, applied using topical nitroglycerin patches, has been shown to improve outcomes in randomized, double-blind, placebo-controlled trials, possibly by enhancing collagen synthesis.[60–62] Sclerosant injections have been shown to give at least short-term benefit,[63] and might provide a rational basis for targeting neovascularization in painful tendinopathy, which might be triggered initially by hypoxia and regulated by levels of endostatin and vascular endothelial growth factor.[64,65] Aging might reduce the ability of tenocytes to remodel and repair lesions, supporting the use of stem-cell therapies that involve the injection of bone-marrow-derived cells into injured or degenerate tendon; this approach is currently being used to treat equine tendinopathy.[66] Gene therapy to introduce specific anabolic or anti-catabolic factors shows promise, and preparatory studies have demonstrated the feasibility of this approach in animal tendons.[67] Tissue engineering constructs are also being developed to repair or replace damaged tendons, although much more work is required before these constructs are used in humans.[68]

CONCLUSIONS

Future work is required to fully define the etiology of tendinopathy, including the development and validation of both *in vitro* and *in vivo* models. *In vitro* models will enable the investigation of the regulation of tenocyte activity by factors such as mechanical strain, cell–matrix interactions, cytokines, soluble factors, enzymes and signaling molecules. There are now several promising animal models,[69,70] and further work using genome-wide screening and specific gene knockouts or transgenic animals should yield exciting new insights into the cause and progression of the disease. Metalloproteinases might be important in tendon pathology, but there are other classes of protease (e.g. cysteine, aspartate and serine proteases) that have, so far, received little attention. Because some enzyme activities are required in healthy and repairing tendon, it is essential to differentiate 'good' enzymes from those that are 'bad', so that drugs targeting specific activities can be developed for the treatment of tendinopathy.

KEY POINTS

- Tendon disorders are common, often under-reported and a major clinical problem
- Most current treatments for tendinopathy are neither effective nor evidence-based
- Molecular processes underlying tendinopathy are now being elucidated: metalloproteinase enzymes are thought to have a key role in the regulation of the activity of tendon cells and matrix remodeling in both normal and pathologic tendon
- The potential roles of neuropeptides, inflammatory mediators and mechanical strain (either too much or too little) acting on the resident tenocytes are the source of some controversy and require in-depth investigation using *in vitro* and *in vivo* models
- Excessive or inappropriate activity of destructive matrix-degrading enzymes might be a novel therapeutic target for tendinopathy; other treatments in development include the injection of stem cells, gene therapy and tissue engineering to repair or replace damaged tendon tissue

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Competing interests

The author has declared an association with the following company/organization: Wyeth Pharmaceuticals. See the article online for full details of the relationship.