Overuse tendinopathies

Matrix metalloproteases: a role in overuse tendinopathies

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The balance between matrix metalloproteases and their inhibitors is important in maintaining healthy tendons

Tendinopathy is a broad term used to describe disorders in and around tendons, with absence of inflammatory cells and a poor healing response, demonstrated by collagen fibrils separated from each other lengthwise and disrupted in cross section. Tendinitis, tendinosis, and paratenonitis are all examples of tendinopathy.[1]

MATRIX METALLOPROTEASES (MMPS) AND TISSUE INHIBITORS OF METALLOPROTEASES (TIMPS)

MMPs, a family of zinc and calcium dependent endopeptidases active at a neutral pH, are involved in the remodelling of extracellular matrix (ECM) through their broad proteolytic capability.[2] Degradation of collagen in tendon ECM is initiated by MMPs.[3] Twenty three human MMPs have been identified,[2] with a wide range of extracellular substrates (table 1).[4 5] MMPs can be subdivided into four main groups: collagenases, which cleave native collagen types I, II, and III; gelatinases, which cleave denatured collagens and type IV collagen; stromelysins, which degrade proteoglycans, fibronectin, casein, collagen types III, IV, and V; membrane-type MMPs.[5]

The activity of MMPs is inhibited reversibly by TIMPs in a non-covalent fashion in a 1:1 stoichiometry.[5] There are four types of TIMP: TIMP1, TIMP2, TIMP3, and TIMP4.[5] The balance between the activities of MMPs and TIMPs regulates tendon remodelling, and an imbalance produces collagen disturbances in tendons.[6]

ROLE OF MMPS AND TIMPS IN TENDINOPATHY

MMP3 may play a major role in regulation of tendon ECM degradation and tissue remodelling. An increased expression of MMP3 may be necessary for appropriate tissue remodelling and prevention of tendinopathic changes.[7] The timing of MMP3 production is probably also critical in this process.[7] MMP3 and TIMP1, TIMP2, TIMP3 and TIMP4 are downregulated in tendinopathic tendons.[7 8] Decreased MMP3 expression may therefore lead to tendinopathic changes in tendons. The expression of MMP2 can be upregulated in Achilles tendinopathy,[8] although Ireland *et al*[7] showed no such upregulation in tendinopathic Achilles tendon. However, Ireland *et al*[7] used autopsy materials as control tissue, whereas Alfredson *et al*[8] used clinically normal looking tendon tissue in the same tendinopathic tendon. Also, interindividual variations could have produced different results. Physical exercise can influence local MMP and TIMP activities in human Achilles tendon[9] with a pronounced increase in local levels of pro-MMP9 after exercise. MMP9 may well have a role in a potential inflammation reaction in human Achilles tendon induced by intensive exercise. Also, exercise causes a rapid increase in serum MMP9,[10] a probable result of increased leucocytes in the circulation.[11]

Complete tears of the rotator cuff show no significant increase in MMP1 mRNA expression,[12] although the actual activity of MMP1 may be upregulated, with downregulation of MMP2 and MMP3 activity.[3] In animal models, the expression of MMP2 at the edges of an acute tear in the supraspinatus tendon is strongest at two weeks, and gradually reduces at three and six weeks,[13] suggesting that MMP2 degrades ECM at the tendon edges and reparative tissue.[13] TIMP1 is not present in normal tendons, but, after acute tears of the supraspinatus tendon, it is expressed in the tendon edges for two weeks.[13] By six weeks after the tear, there is no expression of TIMP1, implying that TIMP1 may inhibit excessive degradation of ECM by MMP2.[13] Contrary to the above findings, levels of TIMP1 are higher in normal than tendinopathic patellar tendon,[14] with a greater expression of MMP1 and suppressed expression of TIMP1 in tendinopathic patellar tendons.[14] This lack of TIMP1 activity in tendinopathic tendon perhaps causes a shift in the delicate balance in favour of greater collagenase activity, which would suggest that tendinopathy may be a disorder in healing of tendon with abnormal cellular responses to injury or repetitive stress which leads to tendon dysfunction, and may result in rupture. Although Choi *et al*[13] showed increased expression of TIMP1 two weeks after an acute supraspinatus tendon tear, that study was performed on an animal model, and it focused on the relation between MMP2 and TIMP1. Thus TIMP1 may be downregulated in chronic tendinopathy and upregulated in acute tears.

The expression of MMP3, TIMP2, TIMP3, and TIMP4 mRNA is decreased in torn rotator cuff tendons.[12] MMP3 may therefore play a role in the normal maintenance and remodelling of the rotator cuff tendon, and a decrease in normal MMP3 activity may represent a failure of normal matrix remodelling and maintenance.[3] Also, MMP13 is upregulated at the mRNA and protein level in patients with complete tears of rotator cuff tendons.[12]

DOES THE TYPE OF STRESS CHANGE MMP EXPRESSION?

In an animal model, increased fluid flow produced upregulation of the genes for MMP1 and MMP3.[15] Thus, shear stress on tenocytes may potentially contribute to tendinopathy through the action of MMPs and cyclo-oxygenase II.[15] However, stress deprivation has been shown to upregulate MMP1 expression in tenocytes in an animal model.[16] Increasing the cyclic strain frequency totally eliminated MMP1 mRNA expression at low amplitude strain levels.[16] Also, when a static tensile load is applied to rat tail tenocytes, MMP1 mRNA expression is inhibited in a dose dependent manner.[17] Thus the type of force may influence the expression of MMP1: shear forces upregulate MMP1,[15] whereas cyclical strain and static tensile loads downregulate MMP1.[16 17]

RELEVANCE FOR CLINICIANS

The clinical applications of MMPs in the treatment of various orthopaedic conditions, including tendinopathies, are constantly being explored. Multiple steps in their regulation may offer potential targets at which future drug therapy may be aimed. Such drugs, which will have inhibitory activity against specific MMPs, will need to undergo stringent testing for absorption, bioavailability, metabolism, and excretion before the treatment is clinically approved. Although the discovery of specific, synthetic, orally active MMP inhibitors is still in its early days, they will have a huge impact in the management of tendinopathies, despite varying opinions on the best MMP to inhibit.[4] The

Table 1 The main components of the matrix metalloprotease (MMP) family

Name	Synonym	Degrades	Other actions
MMP1	Collagenase-1 Interstitial collagenase Fibroblast collagenase	Collagens type III (preferentially), I, and II Collagens type VII, VIII, and X	
MMP2	72 kDa gelatinase A 72 kDa type IV gelatinase	Gelatin, collagens type IV, V, VII, X, and XI Fibronectin, elastin, proteoglycans	Synergistic with MMP1
MMP3	Stromelysin-1 Transin, proteoglycanase Procollagen activating factor	Proteoglycans, laminin, fibronectin, gelatin Collagens III, IV, V, and IX Core protein of cartilage proteoglycans	Broad substrate specificity Activates pro-MMPs
MMP7	Matrilysin Pump-1 Small uterine proteinase	Gelatin, proteoglycans, fibronectin, elastin, casein	Activates pro-MMP1
MMP8	Neutrophil collagenase	Collagens type I (preferentially), II, and III Aggrecan	
MMP9	92 kDa gelatinase-B 92 kDa type IV gelatinase	Collagens type IV, V, X, XI Gelatin	
MMP10	Stromelysin-2 Transin-2	Gelatin, fibronectin, collagens type III, IV, and V	Activates pro-MMPs
MMP11	Stromelysin-3	Aggrecan, fibronectin, laminin	
MMP12	Macrophage metalloelastase	Elastin, collagen types I and IV, aggrecan, fibronectin, laminin, entactin, gelatin type I, vitronectin, fibrillin	
MMP13	Collagenase-3	Collagens type II (preferentially), I, and III Gelatin	

potential of drugs that decrease MMP activity to basal levels and therefore reduce excessive tissue degradation will have a profound impact on the management of tendinopathies in the near future. The two principal ways to decrease concentrations of MMPs are inhibition of enzyme activity and inhibition of enzyme synthesis.[4] It is uncertain whether administration of exogenous TIMPs will be useful therapeutically. However, increasing the local production of TIMPs may be an alternative therapeutic option.[4]

An inhibitor of MMPs, aprotinin, has been used in musculoskeletal practice to decrease bleeding from scoliosis surgery.[18] We and other authors have used it peritendinously in the management of Achilles[19] and patellar[20 21] tendinopathy, with good middle term success compared with peritendinous injections of corticosteroids. We are also aware of further studies being conducted using aprotinin (http://www.users.bigpond.com/msn/johnorchard/aprotinin_study.htm).

CONCLUSIONS

Tendon matrix is not static; it is constantly remodelled, with higher rates of turnover at sites exposed to high level strain. MMPs and their inhibitors are crucial to ECM remodelling, and a balance exists between them in normal tendons. Alteration of MMP and TIMP expression from basal levels leads to alteration of tendon homoeostasis. Tendinopathic tendons have an increased rate of matrix remodelling, leading to a mechanically less stable tendon which is more susceptible to damage. Table 2 highlights the role played by various MMPs and TIMPs in the pathogenesis of tendinopathy. Current concepts on the role of MMPs in tendinopathy have mostly been derived from in vitro or animal model studies, and may not accurately reflect the behaviour of MMPs in vivo. Also, clinical studies have numerous variables that may affect the outcome of results obtained, leading to conflicting results in some cases. More research is required to understand the complexities of interplay between the different MMPs and their inhibitors in the pathogenesis of tendinopathy to devise specific therapeutic strategies in these patients.

Table 2 Main roles of some matrix metalloproteases (MMPs) and tissue inhibitors of metalloproteases (TIMPs)

MMP1	• Upregulated in acute tendon tears[3] • Upregulated in tendinopathy[14] • Upregulated in response to shear stress[15] • Downregulated in response to cyclical strain and static tensile load[16 17]
MMP2	• Upregulated in tendinopathy[8] • May be upregulated[13] or downregulated[3] in complete tendon tears • Inhibits TIMP1 and TIMP2 in response to exercise[10]
MMP3	• Plays a major role in maintenance and remodelling of normal tendon[3 7] • Downregulated in tendinopathy and complete tendon tears[3 6 8 12] • Upregulated in response to shear force[8]
MMP13	Upregulated in complete tendon tears[12]
MMP9	Upregulated following exercise[9 10]
TIMP1	• Downregulated in tendinopathy[7 14] • Upregulated transiently following an acute tendon tear[13] • Inhibits excessive degeneration of ECM by MMP2[13]
TIMP2, TIMP3, TIMP4	Downregulated in tendinopathy[7] and complete tendon tears[12]

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