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Review: Emerging concepts in the pathogenesis of tendinopathy

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ABSTRACT

Tendinopathy is a common clinical problem and has a significant disease burden attached, not only in terms of health care costs, but also for patients directly in terms of time off work and impact upon quality of life. Controversy surrounds the pathogenesis of tendinopathy, however the recent systematic analysis of the evidence has demonstrated that many of the claims of an absence of inflammation in tendinopathy were more based around belief than robust scientific data. This review is a summary of the emerging research in this topical area, with a particular focus on the role of neuronal regulation and inflammation in tendinopathy.

Introduction

Tendinopathy is a common clinical problem, the three most common sites affected are the Achilles, patellar and rotator cuff tendons.[1] The rotator cuff tendons are the most commonly affected with an annual incidence of over 1% that increases with age[2,4] and consequently there is a rising rate of surgery for rotator cuff tears.[5] Others include the tendons around the elbow (golfer's and tennis elbow) and the tendons around the wrist. There is a significant disease burden attached to painful tendinopathy, not only in terms of health care costs, but also for patients directly in terms of time off work and impact upon quality of life. The primary purpose of this review is not to give an overall summary relating to all tendinopathies, it is to summarise specific emerging areas relating to tendinopathy pathogenesis research in which the authors have a particular expertise while giving a brief overall context this recent research.

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Aetiology and pathogenesis

The pathogenesis of tendinopathy is certainly multifactorial and complex.[6,7] Increased age is a key risk factor for the development of tendinopathy,[8,9] although the commonly affected tendons all experience high levels of mechanical stress[10] and over-use is a frequently implicated risk factor.[8,11] The mechanism of overuse has been well demonstrated in animal models,[12,13] while both metabolic and vascular risk factors are associated with the development of tendinopathy.[9,14] Inactivity and the unloading also have an effect on tendon collagen homeostasis.[15]

Recent systematic reviews have clearly demonstrated that patients with high cholesterol and diabetes are at significantly higher risk of developing tendinopathy,[14,16] while recent review has demonstrated that an association exists between the metabolic-hormonal imbalances and tendon degeneration.[17] Hypercholesterolaemia has also been demonstrated to have a significant impact upon tendon repair *in vivo*,[18] while the clear link between hypercholesterolaemia and inflammation has been long known.[19] This emerging link between metabolic dysregulation and chronic inflammation in tendinopathy has also been supported by a recent study using Achilles tendon biopsies from a group of patients.[20]

The historical context relating to the rotator cuff provides an interesting insight into the frequent debates and changing viewpoints as regards tendinopathy pathogenesis. Codman initially proposed in 1934[21] that degeneration within the tendon was the 'intrinsic' primary causal factor. The 'extrinsic' theory relating to tendon damage secondary to attrition by surrounding structures was popularised by Neer[22] and the term 'impingement' was coined. Broadly the modern consensus recognises both the role of intrinsic and extrinsic factors, but sees the intrinsic factors as being more dominant overall[23] with the use of the term 'impingement' appearing increasingly baseless.[24] It is probable that different patients have different disease phenotypes with different intrinsic and extrinsic factors playing variable roles. Certainly not all tendinopathies are identical, as represented by differences in both the tendon's local anatomy and epidemiological profile.

Histopathology and clinical features

Tendinopathy has characteristic histopathological, clinical and radiological findings.[25] The histopathological changes include collagen disorganisation, the increased deposition of mucoid ground substance, increased overall cellularity, as well as the appearance of round and plump 'chondroid' type cells.[26,27] These features of apparent attempted healing diminish as degree of tendon degeneration increase. The overall picture is one of pathological chondroplasia in which tissue which normally exhibits a tensional morphology is replaced by tissue of a fibrocartilage-like phenotype.[26,28] Historically several different words have been used to described tendon related pathology including 'tendinosis' (implying degenerative aetiology), 'tendinitis' (implying inflammatory aetiology) and the more recently favoured and less aetiologically specific 'tendinopathy'.[29] This diversity of language reflects a historical disagreement within the scientific community as to the exact role of inflammation in the aetiology of 'tendinopathy'. Recent evidence has shown that tendon overload is linked to alterations in cell shape, as well as increased markers of inflammation and matrix degradation.[30] The way in which the cells interact with the extracellular matrix is an area of much interest[31,32]; inflammation and damage-induced matrix remodelling seem to be concentrated in, or in the vicinity of, the highly cellular interfascicular matrix.[33] It may be therefore be postulated that interactions between the tendon, the interfascicular matrix and adjacent fat pads are instrumental in the development of tendinopathy, with the latter being a key potential source of key cytokines and inflammatory cells.[34] This may help explain the presence of persistent inflammation in tendinopathy,[35] a phenomenon which has been shown to have important effects on tendon cells *in vitro*.[36,37]

Clinical symptoms including pain are frequently poorly matched to the histopathological and radiological findings, meaning that a high proportion of patients with a tendon that is both histopathologically and radiologically degenerate experience have no related pain or symptoms.[38] The reasons for this mismatch between pathology and perceived pain are poorly understood, however recent research has identified the peripheral and central pain processing pathways as good candidates for an explanation.[39,40] It appears that the presence of pain in tendinopathy not only relates to mechanical changes in the tendon but also changes to the ways in which the local cells and the peripheral nerves react to this change, thus contributing to the nociceptive pathways to higher centres being activated. Overall the vast majority of tendon ruptures (97%) occur in patients with histopathologically abnormal tendons.[41]

Neuronal pathways and glutamate

The neuronal response to tendon injury involves nerve in growth during the initial inflammatory phase; the subsequent proliferative and remodelling phases are regulated by sensory nerves, as well as the glutaminergic and autonomic systems.[42] Glutamate is an important amino acid involved in many key physiological processes including cell metabolism, pain sensitization and collagen synthesis.[39,43] Glutamate receptors can be broadly broken down into two major types: inotropic, which are glutamate-gated ion channels (iGlu), and metabotropic, which are G-protein coupled receptors that modulate signal transduction cascades (mGlu).[44] The inotropic receptors include Kainate (KA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and N-Methyl-D-Aspartate (NMDA) receptors.[45] Glutamate has been shown to induce pain and hyperalgesia when injected around human tendon tissue.[46] An upregulation of the glutaminergic signalling has been linked to inflammatory change in a rat supraspinatus model.[47]

The first study to recognize the presence of glutamate in tendinopathy used a microdialysis technique in chronic painful Achilles tendinopathy.[48] Glutaminergic changes have since become increasingly described in painful tendinopathy,[42] including an increase in extracellular glutamate

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