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Review

Is tendinitis an inflammatory disease initiated and driven by pro-inflammatory cytokines such as interleukin 1ß?

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Summary. Tendonitis and tendinitis are terms used to describe an inflamed and painful tendon. Tendinopathy, is a descriptive term for describing clinical conditions arising from tendon injury and overuse both within and around tendons. The aim of this mini-review is to explore the role of pro-inflammatory cytokines, particularly interleukin-1ß (IL-1ß) in tendon disorders. A number of investigators including our group have proposed that pro-inflammatory cytokines such as IL-1ß are initiators of tendinopathies, stimulating inflammation, apoptosis and extracellular matrix (ECM) degradation. This is one of the reasons why IL-1ß is frequently used in culture models of tendon inflammation to study the inflammatory and catabolic responses of tenocytes. However, some researchers oppose this view and suggest that although IL-1ß may play a role in rheumatoid arthritis (RA) and osteoarthritis (OA), the involvement of IL-1ß in the development of tendinopathy is questionable. This mini-review discusses the relevant papers published in this area and summarises the evidence for and against the involvement of pro-inflammatory cytokines such as IL-1ß in tendonitis. Reaching a consensus will be important for the development and refinement of biomimetic models of tendon inflammation and the formulation of new therapeutic strategies for the treatment of tendon injuries.

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Introduction

Tendons are tough white cords of fibrous connective tissue that join muscles to bones (Fig. 1A). Tendons are essential for locomotion in vertebrates because they have the mechanical capacity to transfer the force of muscle contraction to bones. However, they are prone to injury, particularly in athletic humans - especially when they overstretch themselves and overuse their load-bearing joints and muscles with repetitive impact forces. In humans tendon injuries are frequent and are responsible for substantial morbidity both in sports and in the workplace (Sharma and Maffulli, 2005, 2006). Tendonitis and tendinitis are terms that are often used to describe an inflamed and painful tendon. Tendonitis is a form of tendon inflammation, which causes pain and tenderness near to joints. Tendinopathy is the best generic descriptive term for the clinical conditions in and around tendons arising from overuse injury (Sharma and Maffulli, 2005; Battery and Maffulli, 2011).

Symptoms of tendonitis include pain and tenderness along a tendon, usually near a joint and pain that is worsened with movement or physical activity. Tendon pain can also be caused by small tears in the surrounding connective tissues or the gradual deterioration of a tendon at the point where it connects to bone. Tendonitis in humans is particularly common in shoulders, elbows, knees, hips, back of the heels, wrists and fingers. Other common examples of tendonitis in humans include tennis and golfer's elbow and Achilles tendonitis (Wong

et al., 2002). Tendinitis also occurs with aging as tendon loses elasticity. The global incidence of tendinitis is on the increase in line with the rise in ageing and inflammatory diseases. Rheumatologic and skeletal manifestations of diabetes are well recognised both in childhood (Rosenbloom, 1984) and adulthood (Rosenbloom and Silverstein, 1996). Like many other connective tissue, arthritic, rheumatic and musculoskeletal disorders associated with diabetes mellitus (Gray and Gottlieb, 1976; Rosenbloom and Silverstein, 1996), tendonitis is also linked with metabolic diseases such as diabetes.

In humans treatment can be broadly classified as operative (open or percutaneous) or non-operative (casting or functional bracing) (Khan et al., 2005). The goal of treatment for tendonitis is to relieve pain and reduce inflammation. In most cases a period of rest and immobilization of the affected tendons is essential for recovery after an acute injury. Non-steroidal anti-inflammatory drugs can reduce both pain and inflammation around the affected tendon. In more serious cases of tendon injury, corticosteroid injections can be given directly into the tendon sheath to reduce inflammation, control pain and enable physical therapy and rehabilitation to begin. Physical therapy that stretches and strengthens the muscle and tendon unit is essential and can restore the tendon function, improve healing, and prevent future injury. Surgery is a last resort can be used to remove the inflammatory tissue from around the tendon. Studies have shown that postoperative rehabilitation is a major factor in the success of an anterior cruciate ligament (ACL) reconstruction procedure (Beynnon and Johnson, 1996).

Healing of tendons and ligaments is a real challenge because healing by scar tissue compromises the function of these tissues. Rest is important for healing but long periods of immobilisation have been shown to be detrimental to healing of ligament (Montgomery, 1989). Prolonged rest may, in actual fact, delay recovery and adversely affect normal tissue turnover and controlled early resumption of physical activity can promote restoration of function and healing of musculoskeletal tissues (Buckwalter, 1996). Therefore it is important to consider a combination of rest and physical activity to maximise the chances of effective tissue repair.

The linear organization of type I collagen fibres in tendon results in optimal stiffness and strength at low strains under tensile load. However, this structural organization combined with the poor vascular supply to the tissue makes repairing ruptured or lacerated tendons difficult (Koob, 2002). This is why biomimetic approaches to tendon repair have not been able to produce constructs with biomechanical properties of native tendon. Even natural scar tissue is mechanically weaker, more elastic and less compliant than the tissue it replaces (Montgomery, 1989). Scar tissues require a long time to revascularize and heal, and the biomechanical behaviour of the repair tissue never returns to normal (Beynnon and Johnson, 1996). Therefore, scar tissue will never be able to recapitulate the biomechanical properties of the original tendon.

A number of research groups have proposed that pro-inflammatory cytokines such as IL-1ß are involved in inflammation, apoptosis and ECM degradation in tendon. However, there is the opposing view that the involvement of IL-1ß in the development of tendon inflammation is questionable. The aim of this paper is to review the literature and summarise the evidence for and against the involvement of pro-inflammatory cytokines in tendonitis. We also highlight the link between tendinopathy and the use of fluoroquinolone antibiotics. Although this paper may not be able to establish a definitive consensus statement with regard to the involvement of pro-inflammatory cytokines in tendonitis, it represents an important step forward in the resolution of this debate.

Pro-inflammatory and anti-inflammatory cytokines

Cytokines are signaling molecules and major mediators of inflammatory responses. They are small proteins and signaling molecules produced by a variety of different cell types. They control many different cellular functions, including proliferation, differentiation and cell survival/apoptosis. Cytokines play an indispensable role in cell signaling and communication, and possess potent immunomodulatory properties. They are also involved in a plethora of pathophysiological processes, including viral infections, autoimmune diseases, arthritis and cancer. Cytokines are synthesized under various stimuli by a variety of cells of both the innate (monocytes, macrophages, dendritic cells) and adaptive (T- and B-cells) immune systems. They have been classified as lymphokines, interleukins, and chemokines, based on their functions. The term "interleukin" was initially used by researchers for those cytokines whose presumed targets were principally leukocytes. In contrast the term "chemokine" refers to a specific class of cytokines that mediate chemoattraction (chemotaxis) of on the immune cells. In many publications cytokines are listed along with hematopoietic growth factors, interferons, lymphokines, monokines, chemokines, and other cytokines (Liles and Van Voorhis, 1995). Cytokines have been classified into two groups: pro-inflammatory and anti-inflammatory. Pro-inflammatory cytokines, including interferon-γ (IFN-γ), IL-1ß, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), are predominantly derived from the innate immune cells and Th1 cells. Anti-inflammatory cytokines, including interleukin-10 (IL-10), interleukin-4 (IL-4), interleukin-13 (IL-13) and interleukin-5 (IL-5), are produced by Th2 immune cells. The role of pro-inflammatory cytokines in RA is very well established (Feldmann et al., 1996). Anti-cytokine therapy for RA has become a clinical treatment for aggressive forms of the disease (Maini and Taylor, 2000). However, pro-inflammatory cytokines also contribute to the pathogenesis of OA. In OA cell stress, injury or damage

in response to chronic inflammation and exposure to cytokines, chemokines, and proteases is thought to drive disease progression (Loeser, 2011).

IL-1ß is produced during infection, injury, or immunologic challenge (Dinarello, 1989; Dinarello and Savage, 1989). It is a protein synthesised by activated macrophages as a pro-protein, which is then proteolytically processed to its active form by caspase 1 (CASP1/ICE). It is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. IL-1ß is produced by activated macrophages, and stimulates thymocyte proliferation by inducing interleukin-2 (IL-2) release, B-cell maturation and proliferation, and fibroblast growth factor activity. IL-1ß was originally thought to be produced by monocytes and macrophages but is now known to be produced by many cell types in arthritic diseases, including synovial cells (Bunning et al., 1986), chondrocytes (Pelletier et al., 1991, 1993) and many other connective tissue cells.

Pro-inflammatory cytokines and activation of NF-κB

Nuclear factor-κB (NF-κB) is a rapidly acting primary transcription factor found in all cell types. It is involved in cellular responses to pro-inflammatory stimuli such as cytokines and stress and plays a key role in regulating the immune response to infection. NF-κB can be triggered by a host of stress-related stimuli including pro-inflammatory cytokines, excessive mechanical stress and ECM degradation products (Marcu et al., 2010). In unstimulated cells NF-κB dimers are sequestered inactively in the cytoplasm by a protein complex called inhibitor of NF-κB (IκB). IκB inactivates NF-κB by masking the nuclear localization signals (NLS). Activation of NF-κB occurs via degradation of IκB, a process that is initiated by its phosphorylation by IκB kinase (IKK). Phosphorylated IκB becomes dissociated from NF-κB, unmasking the NLS. Phosphorylation also results in IκB ubiquitination and targeting to the proteasome. NF-κB can now enter the nucleus and regulate gene expression. In addition, NF-κB turns on expression of IκB forming a negative feedback loop.

Does inflammation play a role in tendonitis?

It is generally accepted that pro-inflammatory cytokines are pleiotropic contributors to synovial joint pathology in OA, RA and many other connective tissue and musculoskeletal diseases. However, is there evidence to support the notion that inflammation is important in tendon diseases and pro-inflammatory cytokines are involved in tendonitis?

Tenocytes are specialized, fibroblast-like cells of mesenchymal origin that constitute the cellular component of periarticular tendons (Fig. 1B,C). They play an important role in producing tendon ECM - a mechanically unique matrix capable of withstanding the high shear forces subjected to tendon in vivo (Amiel et al., 1984). Tenocytes are spindle-shaped fibroblast-like cells within an extensive three-dimensional network of ECM components consisting predominantly of collagen type I fibrils (>95% of tendon collagen), other collagen types (type III and type V collagen), proteoglycans (decorin and aggrecan), elastin, tenascin, fibronectin and water (approximately 55% of the weight of tendon) (Bernard-Beaubois et al., 1997; Kannus, 2000). The parallel organization of collagen fibrils and intermolecular cross-linking between them leads to an increase in tendon tensile strength and biomechanical stability and loading (Kannus, 2000). Collagen fibrils in tendon are 100-500 nm in diameter and are bundled into large fibers that are visible using light and electron microscopy (Jarvinen et al., 2004; Raspanti et al., 2005). Interactions between collagen fibrils at the macromolecular level dictate the strength of tendon. Spindle-shaped tenocytes are embedded within collagen fibers and synthesize and maintain the tendon specific ECM (Fig. 1B). The collagen fibers (Fig. 1A) are bound into units by the endotenon to give higher structural units called fascicles, which in turn are bound together by epitenon to form the tendon (Kastelic et al., 1978). The endotenon contains the vascular, lymphatic, and neural structures to maintain the specialized tenocytes (Ochiai et al., 1979).

Typical phenotypic markers of tenocytes include type I collagen (COL1), tenomodulin (TNMD) and scleraxis (SCX). Tenomodulin (Fig. 1D) is a type II transmembrane glycoprotein predominantly expressed in tendons and ligaments (Shukunami et al., 2001). It is required for tenocyte proliferation and collagen fibril maturation in tendon (Docheva et al., 2005). Scleraxis is a basic helix-loop-helix (bHLH) transcription factor and a specific marker for tendons and ligaments (Cserjesi et al., 1995; Schweitzer et al., 2001). Monolayer (Herrmann et al., 1980) and high-density (Schwarz and Bissell, 1977; Schulze-Tanzil et al., 2004) tenocyte culture systems have been established. However, the phenotype of tenocytes in culture rapidly drifts with progressive passage (Yao et al., 2006). Therefore, tenocytes markers should be used in all in vitro studies to monitor the expression of at least two phenotypic markers and high-density cultures should be adopted as the most biomimetic models for tendon.

The poor vascularization of tendon seems to be a major reason for its limited healing capacity (Favata et al., 2006) (Fig. 2). Overuse tendon injury and tendinopathies are a growing problem in sports medicine and orthopaedic practice that affects a large proportion of the ageing Western population (Anitua et al., 2005; Jarvinen et al., 2005). They have major influence on quality of life for the general population and competitive athletes (Lian et al., 2005). Tenocytes undergo apoptosis in response to hypoxia, oxidative stress, or excessive tensile load (Scott et al., 2005). Moreover, evidence suggests that genes encoding many pro-inflammatory

proteins are regulated by NF-κB (Ding et al., 1998; Tak et al., 2001). The over-expression of catabolic enzymes by pro-inflammatory mediators is initiated by a set of pro-inflammatory signaling pathways. Among them, the activation of NF-κB, is critical in the pathophysiology of tendinitis (Tang et al., 2004). Matrix metalloproteinase enzymes (MMPs) play an important role in the tendon matrix and are responsible for the degradation of collagens and proteoglycans (Riley, 2008). The MMP that shows increased expression in painful tendinopathy are MMP-2, MMP-13 and MMP-23 (Riley, 2008; Corps et al., 2012). Changes in proteoglycan and collagen levels in tendinopathy have been proposed to be a consequence of changes in the metabolic turnover of these macromolecules in tendon (Samiric et al., 2009).

Arguments against a role for interleukin 1ß in tendonitis

A number of investigators do not agree that pro-inflammatory cytokines such as IL-1ß could be initiators of tendinopathies, stimulating inflammation, apoptosis and ECM degradation (Riley, 2004, 2008). They claim that IL-1ß has not been identified as the main initiator of tendinopathies and argue that while IL-1ß may play a role in RA and OA, the involvement of IL-1ß in the development of tendinopathy is questionable. The rationale for this argument is that tendinopathy is considered, by some clinicians, not to be an inflammatory condition in contrast to RA and OA. Histological examination of pathological tendon reveals significant structural disruption with a notable absence of inflammation, and it was in response to such findings that the generic term 'tendinopathy' was adopted in replace of 'tendinitis' (Riley, 2004, 2008). However, extensive immunohistochemical studies of pro-inflammatory cytokines in tendon are largely lacking due to the challenges associated with performing immunohistochemical studies on tendon samples. Furthermore, some of the molecular studies that have been carried out on tendon tissue in search of pro-inflammatory mediators have been flawed in terms of experimental design. Nevertheless, it has been argued that the actual cellular behaviour in the development of

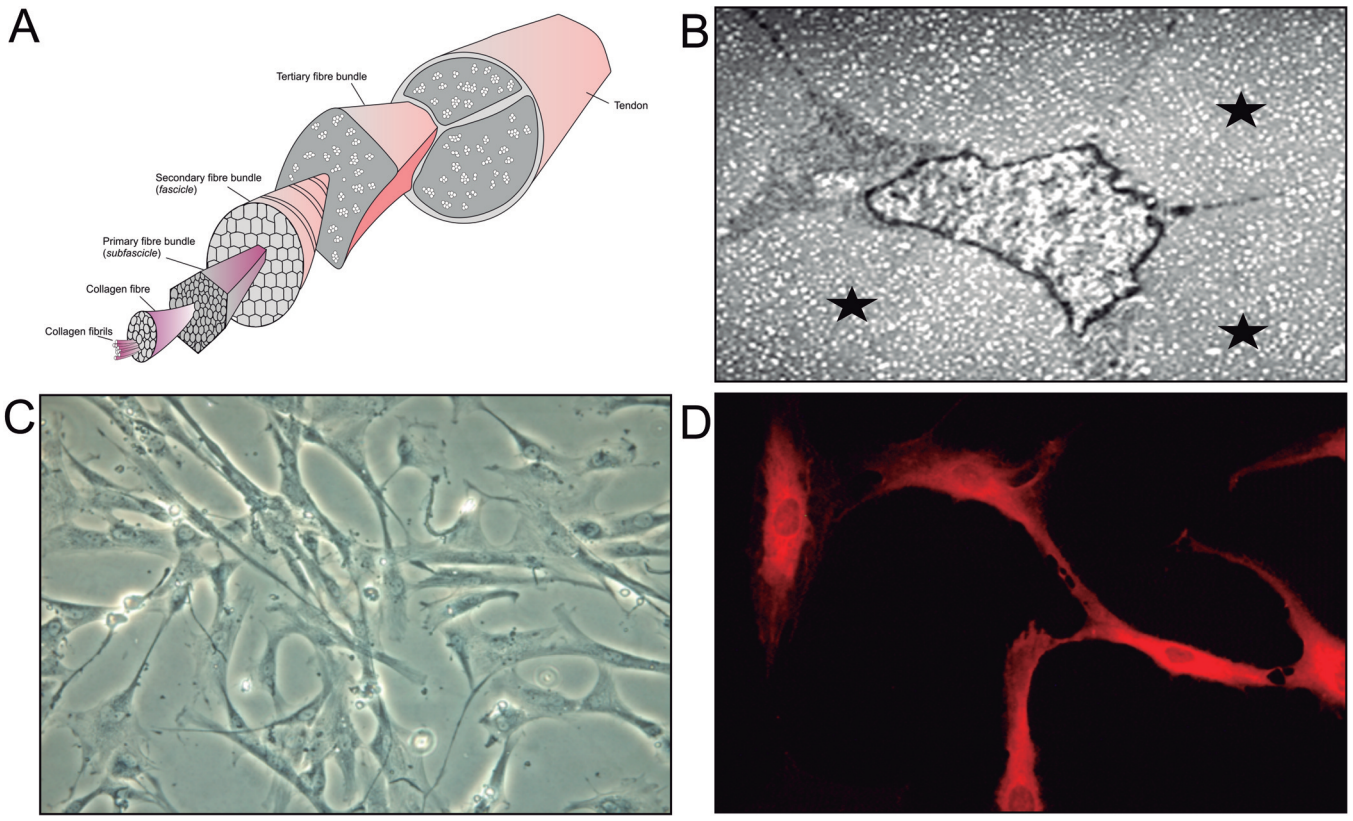

Fig. 1. A. Schematic illustration of collagen fibrils, fibres and bundles in tendon. **B.** Transmission electron micrograph of a tenocyte from rat Achilles tendon. The cell shown in this micrograph exhibits typical morphological features of a tenocyte including cytoplasmic processes and a spindle-shaped nucleus. It is surrounded by a well-developed and organized extracellular matrix (*) with thick collagenous fibrils. The nucleus contains high quantities of active euchromatin. x 10000. **C.** Phase contrast micrograph of isolated human tenocytes in monolayer culture. **D.** Immunofluorescent labelling of the tenocyte marker tenomodulin in primary human tenocytes in monolayer culture.

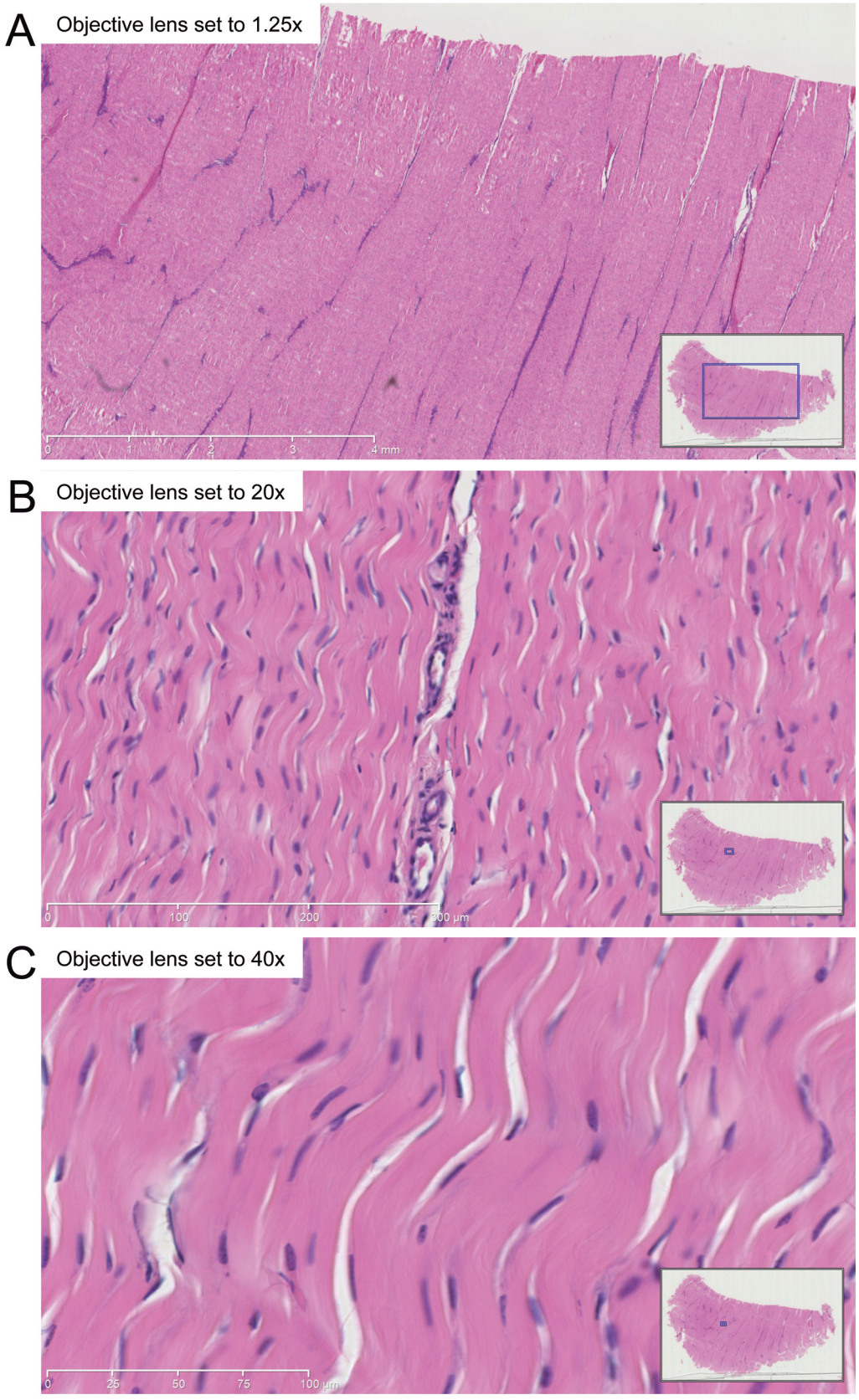

Fig. 2. Microscopic morphology of equine tendon. The three images in this figure show increasing magnifications of a section of equine tendon stained with haematoxylin and eosin. A, x 1.25; B, x 20; C, x 40

tendinopathy remains largely unknown, although inflammation may still play an important role in the early initiation of the disease. It is possible that IL-1ß may be involved in the early initiation of the disease, but this has yet to be proven. Microarray analysis of tendinopathic tendon has not detected IL-1ß (Molloy et al., 2006; Jelinsky et al., 2011). Therefore it has been questioned if adding IL-1ß to tenocyte cultures represents a genuine in vitro model of tendinitis. It should be noted that adding a single pro-inflammatory cytokine to an in vitro model of tendon might, in fact, be an oversimplification; many more pro-inflammatory cytokines may be involved at different stages of tendonitis.

Arguments in favour of the involvement of interleukin 1ß in tendonitis

Some of the evidence in favour of pro-inflammatory cytokines being involved in tendon inflammation comes from anatomical studies. By definition tendonitis and bursitis are inflammation and degeneration of the soft tissues around muscles and bones. This clearly implies that tendon disease is a disease of tendon and surrounding tissues rather than tendon in isolation from adjacent anatomical structures. Although pro-inflammatory cytokines such as IL-1ß may not be the main initiators of tendinopathies, they are likely to be present in tissues surrounding mechanically injured tendon. This is an important but often overlooked consideration. Mechanical injury is likely to be one of the main factors involved in the pathogenesis of tendinopathies. A number of papers have been published to support the use of IL-1ß in cultures of tenocytes (Tsuzaki et al., 2003; Uchida et al., 2005; Qi et al., 2006; Thampatty et al., 2007; Fedorczyk et al., 2010). These papers illustrate a diverse number of studies that have employed IL-1ß in vitro. There are a number of published papers that have used IL-1ß on tendon cells. There are two papers that have used microarrays to study tendon degeneration to argue for the absence of IL-1ß in tendon inflammation. One of these studies used a rat model of tendinopathy and the other examined tendons from 23 human patients undergoing surgical procedures for the treatment of chronic tendinopathy. The authors argue that microarray analysis of tendinopathic tendon has not picked up IL-1ß expression (Molloy et al., 2006; Jelinsky et al., 2011). This is by itself is a relatively weak argument and cannot be used as concrete evidence for the absence of IL-1ß in tendinopathy. Global gene expression profiling is not a satisfactory method for ruling out the presence of gene transcripts. Quantitative PCR and western blotting are more appropriate methods for detecting and measuring transcripts and their expression at the protein level. Therefore, microarray analysis by itself cannot be used as evidence for the absence of IL-1ß expression or indeed any other gene. There are other published papers that have detected and measured IL-1ß in tendon (Uchida et al., 2005; Wang et al., 2010). Furthermore, recombinant interleukins, including IL-1ß, have been used by numerous investigators in culture models of tendon inflammation (John et al., 2010). Increased expression of IL-1ß has also been shown in the subacromial bursa in rotator cuff lesions in human patients (Ko et al., 2008). In this study the authors evaluated whether pro-inflammatory cytokine expression and myofibroblast recruitment in subacromial bursa was linked to rotator cuff lesions with shoulder stiffness. They analyzed expression of IL-1ß, IL-6 and TNF-α in subacromial bursa and joint fluid collected from 14 patients with cuff tears with stiffness as a study group and 14 patients with rotator cuff tears without shoulder stiffness as a control group using real-time RT-PCR, immunohistochemistry, and ELISA. The study group showed higher mRNA expression and immunoreactivity for IL-1ß. These patients also had higher levels of IL-1ß, IL-6, and TNF-α in their joint fluids. Interestingly increased IL-1ß mRNA expression in the subacromial bursa and actual IL-1ß levels in joint fluid correlated with a preoperative deficit in shoulder motion. The study concluded that increased expression of IL-1ß and myofibroblast recruitment in the subacromial bursa in rotator cuff lesions are linked to shoulder stiffness.

A study by Miyatake and colleagues has suggested that IL-1ß plays an important role in the deterioration of the mechanical properties of patellar tendon and IL-1 receptor antagonist inhibits these changes although it does not affect the tendon fascicles themselves (Miyatake et al., 2008). Therefore, we need to consider the tangible possibility that IL-1ß and other pro-inflammatory cytokines are present in tissues surrounding mechanically injured tendon and that the receptors for pro-inflammatory cytokines may show altered expression and responsiveness at different stages of the disease.

A study by Uchida and co-workers (2005) actually recommended the possible application of an anti-IL-1ß or anti-TNF-α strategy for reducing the mechanical deterioration of tendons and ligaments in response to stress deprivation.

The studies reviewed in this section provide evidence in support of the idea that pro-inflammatory cytokines are involved in tendon inflammation and can be used in culture models of tendon inflammation.

Fluoroquinolone induced tendinopathy

There is evidence to suggest that some antibiotic drugs can induce tendinopathy. One good example is the fluoroquinolone class drug Levofloxacin, which is a synthetic chemotherapeutic antibiotic used to treat severe or life-threatening bacterial infections or bacterial infections that have failed to respond to other antibiotic classes. Fluoroquinolones are active antibacterial agents against a broad spectrum of bacteria and possess favourable pharmacokinetic properties, in particular, a good tissue penetration which is reflected by a high

volume of distribution. Therefore, the use of these agents has increased significantly over the last few decades. However, the increased incidence of tendinopathies associated with fluoroquinolone therapy suggests that the use of these drugs can compromise tendon function (Kahn and Hayem, 1997; van der Linden et al., 1999, 2001). Fluoroquinolones cause molecular changes in the extracellular matrix, signalling proteins, MMPs and caspase-3 in cultured human tendon cells (Sendzik et al., 2005). Fluoroquinolone action on tenocytes decreases the diameter of collagen fibrils and increases the distance between the collagen fibrils and the tenocytes. Disturbances in cell-cell and cell-matrix interactions stimulate apoptosis in physiologically relevant fluoroquinolone concentrations (i.e. equivalent to those achieved in plasma after drug therapy) (Sendzik et al., 2005). These findings have led to the suggestion that tenocytes apoptosis is as a late but important event in the pathogenesis of fluoroquinolone-induced tendinopathies.

In 2002 the Belgian Pharmacovigilance Centre received 161 reports of levofloxacin - associated tendinopathy, including 68 reports of tendon rupture, during the period that this drug was marketed in 2000 through to 16 April 2002. The average age of patients with levofloxacin-associated tendinopathy was 69 years and about half of them were receiving concomitant corticosteroid treatment. The average time between the start of levofloxacin treatment and the development of tendinopathy and tendon rupture was 8.4 and 10 days, respectively, with tendon rupture occurring within 48 hours in some cases. Although data from spontaneous reports are insufficient for risk comparisons, the number of cases of tendon disorders reported in association with levofloxacin to date is much higher than that for ciprofloxacin (22 cases), norfloxacin (8), ofloxacin (63) and pefloxacin (16), all of which have been on the market for > 10 years. The most common indications for which levofloxacin was prescribed in patients who experienced tendon rupture were chronic bronchitis (32%) and chronic obstructive pulmonary disease (28%). Therefore it has been recommended by the World Health Organization (WHO) that patients receiving levofloxacin treatment should contact their doctor if tendon pain occurs.

Khaliq and Zhanel have reviewed the literature to investigate the frequency and strength of this association. Ninety-eight case reports were evaluated. The incidence of tendon injury associated with fluoroquinolone was low in a healthy population but it increased in older patients and patients with renal dysfunction, especially those undergoing haemodialysis, or those who had renal transplants. Tendon injury associated with fluoroquinolone use is significant, and risk factors such as renal disease or concurrent corticosteroid use must be considered when these agents are prescribed (Khaliq and Zhanel, 2003). Therefore, patients receiving fluoroquinolone treatment should be informed about the increased risk associated with age and the presence of simultaneous corticosteroid therapy (http://www.who.int/medicines/publications/newsletter/en/news2002_4.pdf)

These studies highlight the unique sensitivity of tendon to fluoroquinolone antibiotics and corticosteroids suggesting that tendon health is influenced by other medications and systemic factors.

Perspectives and areas for future research

IL-1ß has been referred to as the "gatekeeper of inflammation". There is a large body of evidence for the involvement of IL-1ß and favourable clinical results of reducing IL-1ß activity in a broad spectrum of inflammatory and rheumatic diseases (Dinarello, 2011). In RA and OA IL-1ß is an important pro-inflammatory cytokine responsible for the degeneration of articular cartilage matrix. This makes IL-1ß and its cell surface receptor as well as downstream inflammatory signaling pathways prime targets for therapeutic strategies (Kapoor et al., 2011). In vivo evidence suggests that increased subchondral bone resorption occurs at an early stage in the development of RA and OA, and that blocking bone-resorbing cytokines can prevent cartilage damage (Funck-Brentano and Cohen-Solal, 2011).

The association between tendonitis and metabolic diseases such as diabetes suggests that tendon is sensitive to systemic factors involved in metabolic disease. Arthritis diseases are increasingly considered to be systemic diseases because of their associations with overweight and obesity. Diabetes is associated with RA, OA, carpal tunnel syndrome, osteoporosis, diffuse idiopathic skeletal hyperostosis, crystalline arthropathy, neuropathic arthropathy, and tendinopathy (Burner and Rosenthal, 2009). Prolonged, systemic, low-grade inflammation and impaired insulin sensitivity are important risk factor for a failed healing response after an acute tendon insult in humans, and predispose to the development of chronic overuse tendinopathies in susceptible individuals (Del Buono et al., 2011). In obesity, macrophages migrate to adipose tissue and accumulate, resulting in the decreased availability of immune circulating cells. One interpretation of this phenomenon is that in cases of acute tendon injury there will be less effective immune responses (Del Buono et al., 2011). In humans elevated adiposity is a risk factor for tendon injury and is frequently associated with tendon injury (Gaida et al., 2009). Therefore tendonitis is also likely to be influenced by systemic factors, some of which include adipokines, originating from adipose tissue in overweight individuals. It is now recognised that obesity and hypertension can cause diminution of local microvasculature (Holmes and Lin, 2006). Tendon is poorly vascularised and this is one of the main reasons why tendon injuries heal slowly. The correlations between obesity, metabolic disease and tendinopathy highlight links that need to be further explored in future studies. One of the most important links in the context of this review is the presence of pro-inflammatory cytokines such as IL-1ß in tendon and its elevated levels

in obesity.

Conclusions

Many scientists and clinicians agree that pro-inflammatory cytokines are involved in diseases of connective tissues such as cartilage, intervertebral disc and bone. It is therefore highly unlikely that tendon is an exception. There is ample published evidence that supports the expression and functional involvement of pro-inflammatory cytokines such as IL-1ß in tissues surrounding mechanically injured tendon. This review is entitled: "Is tendinitis an inflammatory disease initiated and driven by pro-inflammatory cytokines such as IL-1ß?" Based on the papers reviewed in this article we propose that IL-1ß is involved in tendon inflammation. The role of the surrounding tissues needs to be considered in any connective tissue disease. For example, the role of the synovium cannot be ignored in cartilage damage in OA. Therefore, pro-inflammatory cytokines such as IL-1ß can and should be used within in vitro models of tendon inflammation to study the mechanisms involved and screen for new anti-inflammatory compounds that can block or counteract the effects of inflammatory cytokines. More research is needed to understand the basic cell biology of tendon and how tenocytes respond to pro-inflammatory cytokines, bioactive lipids and MMPs. Further work is also required to identify novel and specific molecular targets for treating tendonitis.

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