Veterinary Immunology and Immunopathology 158 (2014) 121–127

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Review Paper

Resolving an inflammatory concept: The importance of inflammation and resolution in tendinopathy

Stephanie G. Dakin*, Jayesh Dudhia, Roger K.W. Smith

Royal Veterinary College, Department of Clinical Sciences and Services, North Mymms, Hatfield, Hertfordshire AL9 7TA, United Kingdom

ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form
19 December 2013
Accepted 6 January 2014

Keywords:
Tendon
Injury
Tendinopathy
Pathogenesis
Inflammation
Resolution

ABSTRACT

Injuries to the superficial digital flexor tendon (SDFT) are an important cause of morbidity and mortality in equine athletes, but the healing response is poorly understood. One important drive for the healing of connective tissues is the inflammatory cascade, but the role of inflammation in tendinopathy has been contentious in the literature. This article reviews the processes involved in the healing of tendon injuries in natural disease and experimental models. The importance of inflammatory processes known to be active in tendon disease is discussed with particular focus on recent findings related specifically to the horse.

Whilst inflammation is necessary for debridement after injury, persistent inflammation is thought to drive fibrosis, a perceived adverse consequence of tendon healing. Therefore the ability to resolve inflammation by the resident cell populations in tendons at an appropriate time would be crucial for successful outcome. This review summarises new evidence for the importance of resolution of inflammation after tendon injury. Given that many anti-inflammatory drugs suppress both inflammatory and resolving components of the inflammatory response, prolonged use of these drugs may be contraindicated as a therapeutic approach. We propose that these findings have profound implications not only for current treatment strategies but also for the possibility of developing novel therapeutic approaches involving modulation of the inflammatory process.

Contents

Abbreviations: COX, cyclooxygenase; ECM, extracellular matrix; FPR2/ALX, lipoxin A_4 receptor; IFN-γ, interferon gamma; IL-1β, interleukin-1beta; LXA_4, lipoxin A_4; Mφ, macrophage; mPGES-1, microsomal prostaglandin E synthase-1; MMP, matrix metalloproteinase; NSAIDs, non-steroidal anti-inflammatory drugs; PGE_2, prostaglandin E_2; SDFT, superficial digital flexor tendon; TNF-α, tumour necrosis factor alpha.

* Corresponding author. Current address: Botnar Research Centre Institute of Musculoskeletal Sciences, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford OX3 7LD, United Kingdom. Tel.: +44 1865 223423.
E-mail address: stephanie.dakin@ndorms.ox.ac.uk (S.G. Dakin).

0165-2427/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.vetimm.2014.01.007

1. Introduction

Pathologic changes in tendons due to repetitive use are a significant cause of morbidity in athletic humans and horses (Avella et al., 2009; Kujala et al., 2005; Thorpe et al., 2010). The importance of inflammation in both the pathogenesis of tendon injury and the healing process has been contentious in recent years and is poorly understood. Equine clinicians are familiar with the clinical signs of inflammation immediately after a tendon injury occurs, but these signs are not so evident during the chronic phase of injury. Overstrain injury in humans is generally considered to result from a primarily degenerative condition where clinical signs of inflammation and invading inflammatory cells are rarely observed (Alfredson and Lorentzon, 2002; Astrom and Rausing, 1995; Jarvinen et al., 1997; Jozsa et al., 1990; Kannus and Jozsa, 1991; Webbon, 1978). However, this lack of perceived clinical inflammation may be attributable to factors such as the later presentation of human patients, frequently with recurrent injury and the availability of tissues for analysis at different times after injury. Furthermore, the absence of clinically evident inflammation does not preclude an integral role for inflammatory mediators during the pathogenesis and healing of tendon injuries at a cellular level. Current controversy regarding the role of inflammation in tendon injury and healing is similar to that previously debated in joint disease. Use of the term 'arthritis' with its emphasis on inflammation, has generally replaced the term 'arthrosis' when referring to a wide variety of joint disease conditions (Attur et al., 2002). This change in terminology reflects the fact that inflammatory cytokines have recently been shown to play a pivotal role in the development of joint disease even when clinical signs of inflammation may not be detected. Terminology commonly used to refer to tendon pathology is further described in Box 1.

Several laboratory animal models have been used to investigate tendon injury; however, these induced injury models do not accurately reproduce the naturally occurring conditions that are detected in human and equine patients (Lui et al., 2011). Horses, on the other hand suffer a high frequency of clinical overstrain injury involving a wide spectrum of tendons and ligaments. Therefore the horse presents an attractive large animal model not only for equine related studies but also as a relevant model of human injury due to the shared characteristics of aging phenotypes (Dudhia et al., 2007; Strocchi et al., 1991), elastic energy storing function common to the weight-bearing tendons of both species (Ker et al., 2000; Wilson et al., 2001) and injury induced by natural athletic activity. Equine tendon healing processes are traditionally classified into three distinct but overlapping phases in naturally occurring injury; the acute inflammatory phase occurs immediately after the initial trauma lasting only a few days, followed by the sub-acute reparative phase (peaking at 3–6 weeks but lasting several months and chronic remodelling phase (>3 months after injury) (Dowling et al., 2000). Whilst this temporally coordinated but overlapping sequence of events describes very well the clinical progression of SDFT lesions and other injuries such as some suspensory branch desmopathies in the horse, injuries to the human Achilles tendon manifest differently with less well defined phases characterised by persistent pain and 'failed healing' (Longo et al., 2009). These clinical descriptions of the healing phases suggest that inflammation drives acute and chronic phases of injury. However recent insights into the underlying molecular events suggest that some components of the inflammatory cascade are necessary for resolution of injury. This review will discuss the inflammatory mediators relevant to tendon disease and illustrate that in addition to pro-inflammatory roles, inflammation triggers important resolution processes, which can potentially be harnessed for beneficial therapeutic effect.

2. Inflammation related mediators in tendon health and disease

2.1. Cytokines in tendinopathy

Cytokines are small proteins with the ability to influence the biological activities of cells and operate in an autocrine/paracrine manner. They are highly potent and exert their effects at picomolar concentrations. The interaction between a cytokine and its receptor triggers a series of intracellular signalling events culminating in a physiological response (Evans, 1999). Cytokines are reported to have important roles in tendon and ligament homeostasis by regulating cellular differentiation and activity (Evans, 1999; Lin et al., 2006; Molloy et al., 2003) and the synthesis of tendon matrix (Millar et al., 2009; Riley, 2005; Sun et al., 2008). However, samples of injured equine SDFT stain positively for pro-inflammatory cytokines IL-1α, IL-1β, TNF-α and IFN-γ which were not found in normal tendons (Hosaka et al., 2002). Hence in conjunction with

Box 1: Terminology

The terms below are used commonly in a variety of clinical scenarios but have not been well defined. For the purposes of this review, we have attempted to clarify what would be considered the most appropriate use of these terms.

'**Tendinopathy**' is used to describe disorders affecting tendons, including tendon rupture and chronic pain. This term does not assume any knowledge about the underlying pathology.

'**Tendonitis**' is used to describe a painful tendon and implies that tendon injury is accompanied by an inflammatory response.

'**Tendinosis**' is used to describe a painful tendon and implies that tendon injury develops as a consequence of a degenerative process and implies absence of inflammation.

'**Tendon disease**' implies that injury develops as a consequence of repetitive cyclic loading and the effects of ageing resulting in cumulative microdamage. Often exacerbated by overstrain injury, the most common manifestation in the horse is a central core lesion.

'**Tendon injury**' encompassing tendon disease but also occurs as a consequence of traumatic injury when the tendon is lacerated after cutaneous injury.