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Inflammation in tendinopathy

Alessio D'Addona^{a,*}, Nicola Maffulli^{b,c}, Silvestro Formisano^d,
Donato Rosa^a^a Department of Public Health, Section of Orthopaedic and Trauma Surgery, School of Medicine and Surgery,
University of Naples "Federico II", Via Pansini 5, 80131, Naples, Italy^b Centre for Sports and Exercise Medicine, Barts and The London School of Medicine and Dentistry, Mile End Hospital,
275 Bancroft Road, London, E1 4DG, England, UK^c Department of Musculoskeletal Disorders, Faculty of Medicine and Surgery, University of Salerno, Salerno, Italy^d Department of Molecular Medicine and Medical Biotechnology, School of Medicine, Federico II University of Naples,
Via Pansini 5, 80131, Naples, Italy

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ABSTRACT

Pain and functional limitation are frequent in symptomatic tendinopathy. The essential lesion of tendinopathy is a failed healing response. Understanding the cellular and molecular mechanisms involved in a failed healing response during the early stages of pathogenesis of tendinopathy would help to develop new and effective treatments. The role of inflammation in the development of tendon pathologies has been revived during the last few years, in particular during the first phases of tendinopathies, when "early tendinopathy" may not be clinically evident. This review outlines the possible molecular events that occur in the first phases of tendinopathy onset, stressing the role of pro-inflammatory cytokines, proteolytic enzymes, growth factors and healing genes in the development of tendon disorders.

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Introduction

Tendinopathy is the best generic descriptive term for the clinical conditions in and around tendons arising from over-use.^{1,2} The term "tendinopathy" defines the clinical syndrome characterised by a combination of pain, swelling and impaired performance.³ Tendon injuries produce considerable morbidity, and the disability that they cause may last for several months despite what is considered appropriate management. The aetiology of tendinopathy remains unclear, and

many causes have been hypothesised.⁴ Hypoxia, ischaemic damage, oxidative stress, hyperthermia, impaired apoptosis, inflammatory mediators, fluoroquinolones, and matrix metalloproteinase imbalance have all been implicated as mechanism of tendinopathies.⁴ Biomechanical factors, functional alterations, repetitive mechanical loading, aging and metabolic disorders may predispose to tendinopathy, with high risk of re-injury.^{1,2,5}

The process of tendinopathy involves both the collagen matrix and the tenocytes.⁶ Normally, collagen fibers in tendons are tightly bundled in a parallel fashion, but

* Corresponding author. Fax: +39 081 7463722.

E-mail addresses: alessio.daddona@gmail.com (A. D'Addona), n.maffulli@qmul.ac.uk (N. Maffulli), sformisano@unisa.it (S. Formisano), drosa@tin.it (D. Rosa).
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tendinopathic samples show unequal and irregular crimping, loosening and increased waviness of collagen fibers, with an increase in type III reparative Collagen (COL-III).^{6–8}

Overloading of tendons after intensive exercises and training induces micro-rupture of tendon,⁹ with the expression of damage associated molecular patterns (DAMPs) in an attempt to produce tissue healing.¹⁰ The essential lesion of tendinopathy is not of a degenerative nature: it has the features of a failed healing response, in which the tendon attempts to heal, but, for some reason, including, possibly, continuous inappropriate mechanical stimuli, the healing process appears non-finalised.³ Several models have recently implicated pro-inflammatory cytokines to initiate the catabolic process, such as Tumor Necrosis Factor- α (TNF- α), Interleukin-1 β (IL-1 β) and Interleukin-6 (IL-6), Growth Factors such as Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), TGF- β , EGF, IGF-1,¹ and transcriptional factors such as Nuclear Factor-kappa B (NF- κ B), especially in the earlier phases of the process.¹¹

In the acute phase, it is possible to find signs of inflammations with a huge release of cytokines and immunomodulating factors able to cause inflammation with cellular proliferation, onset of pain and ECM degradation with necrosis.^{12,4,12–15} This phase could be considered a prelude to the clinical condition, in which there is an initial production and release of cytokines and attempts at healing.¹⁶ When the amount of inflammatory cells, derived from overloading and mechanical stress, becomes relevant, there is an imbalance between pro-inflammatory factors with degradation of ECM, and protective factors, causing onset of pain, by the release of Substance P and glutamate and the production of COX2 and PGE2.^{3,16,17}

The homeostasis of tendons results from a continuing remodeling process mediated by MMPs (matrix metalloproteases) and TIMPs (inhibitors of MMPs), with the apposition of new extracellular matrix (ECM), in particular with the production of Collagen type I (COL-I) (the principal constituent of collagen fibrils), decorin, biglycan, versican, scleraxis, tenascin C and aggrecan (constituents of ECM) by tenocytes.^{2,9,15,18–21} Mechanical loads play a key role in the maintenance of tissue homeostasis²²: sedentary individuals present high levels of pro-inflammatory cytokines, such as TNF- α , IL-1 β and VEGF, and low levels of COL-I, which improve the state of inflammation and prelude to an increased activity of MMPs (MMP-2, -9, -13) with a degenerative response and an higher risk of tendon rupture.¹⁴ Without initial inflammation, the healing process and the subsequent changes that characterize chronic tendinopathies (>12 weeks) can not take place.¹⁶

Early tendinopathy: the role of inflammation

Inflammation may play a role in the early initiation of tendon pathologies.²³ It has been hypothesised that inflammation begins earlier than fibrotic and other degenerative tendon changes.¹⁷ Tendon injuries are accompanied by inflammation, with endogenous expression of various mediators of inflammation by tenocytes, including pro-inflammatory and anti-inflammatory cytokines, and some Growth Factors, such

as TNF- α , IL-1 β , IL-6, IL-10, VEGF, TGF- β ,^{10,23–25} COX-2 expression and PGE₂ production.^{12,13,26} Among the pro-inflammatory cytokines, TNF- α and IL-1 β are the most potent inducers of chemokines.²⁷ Repetitive mechanical overloading and hypoxic injury have long been suggested as the main causes of tendinopathy, leading to elevated inflammatory markers.^{10,28} Repetitive mechanical overloading, in particular, leads to elevated inflammatory markers such as PGE₂, IL-1 β and TNF- α .¹⁵ Furthermore, various intracellular stressors, both physiological and pathological, induce the activation of NF- κ B.²⁹ In the acute phase of the inflammation response, these cytokines are synthesised by a variety of cells including lymphocytes, monocytes and endothelial cells.²⁴ This involves tenocytes in the secretion of pro-inflammatory cytokines in the early phases of inflammation, with a positive feedback, resulting in edema and hyperemia, detectable in this phase only using US.^{1,14} The reason why tendinopathy will become chronic is still debated, but injuries, repeated mechanical stresses and hypoxia seem to predispose to chronicity.⁵ Increased oxygen demand by tenocytes during overload, coupled with individual susceptibility, cause a state of hypoxia that produces free radicals (ROS),⁶ one of the most important immunogenetic stimulants, and the release of VEGF.^{10,30}

The role of IL-1 family

The family members of IL-1 are considered the most potent cytokines produced by innate immunity.³¹ This family is composed of IL-1 α , IL-1 β , IL-18^{29,31} and IL-33.^{10,25} Both IL-1 α (IL-1F1) and IL-1 β (IL-1F2) are synthesized as precursor, and they are cleaved respectively by Calpain^{10,30} and Caspase 1 (IL-1 β converting enzyme).³² The intracellular signaling involves adapter proteins MyD88 (myeloid differentiation factor 88), IRAK (IL-1-receptor-associated-kinase) and TRAF6 (TNF-receptor associated factor 6), and leads to the activation of NF- κ B, JNK (c-Jun N-terminal-kinase) and MAPK.³¹ Necrosis causes release of alarmins, such as IL-1 α and IL-33, that, by binding to different receptors of NF- κ B, enhance the inflammatory response.¹⁰ NF- κ B activation regulates the expression of more than 500 different gene products linked with inflammation, tumor cell transformation, survival, proliferation, invasion, angiogenesis, metastasis and chemoresistance.¹¹ IL-1 α and IL-33 are currently considered classical cytokine alarmins.¹⁰ Alarmins are the equivalent of damage-associated molecular patterns (DAMPs), but are endogenous molecules found in a variety of organelles in all cell types studied, and maintain normal cell homeostasis.^{10,31} Currently, alarmins include defensins, cathelicidins, eosinophil-associated ribonucleases, HMGB (high mobility group box-1) proteins, granulysin, and iron-binding proteins (e.g. lactoferrin).³¹ An alarmin is released rapidly during necrosis, is sequestered in apoptosis, has potential for active secretion by immune cells, and ultimately promotes homeostasis.¹⁰ IL-1 α affects inflammatory and immune responses, angiogenesis and haematopoiesis.¹⁰ IL-33 (IL-1F11), a cytokine associated with Th₂ response, is preferentially expressed in vascular endothelial cells, with constitutive expression also in epithelial surfaces and lymphoid organs.³¹ The increase of mRNA level of IL-33 in tenocytes *in vitro* seems to be an important early signal in

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