Exploring Stem Cells and Inflammation in Tendon Repair and Regeneration

A. Vinhas, M.T. Rodrigues, and M.E. Gomes

Abstract

Tendon injuries are frequent and are responsible for substantial morbidity both in sports and in the workplace. Despite the endogenous mechanisms of tendon repair and regeneration, tendon healing upon injury is slow and often insufficient to restore complete biomechanics functionality.

Inflammation has a pivotal role in tendon healing and failed healing responses contribute to the progression of tendinopathies. However, the molecular and cellular mechanisms involved are poorly understood requiring further insights.

During inflammation, bioactive molecules such as cytokines secreted locally at the injury site, influence resident stem cells that contribute as modulatory agents over the niche towards homeostasis, holding great promise as therapeutic agents for tendon pathological conditions associated to unresolved inflammation and failed healing.

This review overviews the role of cytokines and resident cells, focusing on the participation of tendon stem cell population in inflammation and tendon healing upon injury and their potential action in resolution of pathological conditions.

A. Vinhas, M. T. Rodrigues, and M. E. Gomes (✉)
3B's Research Group, I3Bs – Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, Guimarães, Portugal

ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal

The Discoveries Centre for Regenerative and Precision Medicine, Headquarters at University of Minho, Guimarães, Portugal
e-mail: megomes@i3bs.uminho.pt

Abbreviations

CTGF	connective tissue growth factor
ECM	extracellular matrix
MMPs	matrix metalloproteinases
MSCs	mesenchymal stem/stromal cell
NO	nitric oxide
STAT3	activator of transcription 3
TDSCs	tendon-derived stem cells

1 Introduction

1.1 Tendon Niche

Tendons are dense connective tissues that connect muscles to bone and transmit the mechanical forces generated during contraction to the

skeleton, therefore essential for locomotion (Liu et al. 2014; Subramanian and Schilling 2015). Tendons are hypocellular tissues mainly composed of tenocyte, and a stem and progenitor cell population (Bi et al. 2007). However, other cell types may be also present, for instance endothelial cells, mast cells, chondrocytes, synovial and vascular cells. Tenocytes are responsible for extra cellular matrix (ECM) maintenance, which is mainly composed of collagen, in particular fibrillar collagens, namely collagen type I and III, although other types of collagen are also present, such as collagen type III, V, VI, XII, XIV and XV (James et al. 2008; Millar et al. 2015; Rodrigues et al. 2013). Tendon ECM is also composed of proteins and proteoglycans, such as decorin, biglycan, aggrecan and elastin (Aparecida de Aro et al. 2012; Docheva et al. 2015; James et al. 2008; Tan et al. 2015; Subramanian and Schilling 2015).

Morphologically, tendons follow a hierarchical architecture of collagen molecules that gather to form collagen fibrils. These fibrils assemble into fibers to form collagen fiber bundles. Finally, the bundles organize into tendon fascicles. The presence and alignment of collagen fibers is oriented for providing resistance to tendon and increased tensile strength (Docheva et al. 2015; Killian et al. 2012; Lui 2015; Durgam and Stewart 2016), while reducing stress during muscle contraction (Ho et al. 2014).

In tendon milieu, tendon cells and the ECM coordinate actions in promoting damage repair and tissue regeneration. Since vascular supplies in tendon are confined to endotenon and epitenon, it is likely that stem cell recruiting through the vascular system may be restricted to the surrounding areas of these layers. Thus, the resident cell populations, stem cells and tenocytes, have a critical role in physiological homeostasis and regulation of the tendon matrix. When this delicate fine-tuned balance is disturbed the susceptibility to tendon damage increases (Cadby et al. 2014).

Growing evidence supports tendon stem cells, rather than tenocytes, as the main responsible for the healing response in acute injuries. Beyond the self-renewal capacity, proliferation and multi-lineage potential, stem cells are a secretory source of cytokines and growth factors with paracrine and autocrine activities. These soluble factors support the growth and differentiation of stem and progenitor cells and have a angiogenic, chemotatic, anti-apoptotic, anti-scarring or immunomodulatory activity (Meirelles et al. 2009) in local environments. The secretion of a broad range of bioactive molecules with paracrine effects resulting from the dynamic communication between stem cells and niche environment is believed to be the main mechanism by which mesenchymal stem cells achieve their therapeutic effect (Meirelles et al. 2009).

Other intrinsic agents such as age, genetics, nutrition, body habitus and metabolic diseases are also involved in homeostasis as well as extrinsic factors namely pharmacological influences and mechanical stresses, including loading, disuse, compression and exogenous damage (Abate et al. 2009; Riggin et al. 2015). When tendon injuries occur, there is a local failure in physiological conditions, whose attempt to be solved is mediated by tendon healing and regeneration processes.

2   Tendon Repair Mechanisms

The healing process is a prolonged and complex response of the host to injury and is crucial for the mechanisms of tissue regeneration. It is also a window of opportunity envisioning new therapies for improving impaired healing (Stalman et al. 2015) and understanding the molecular entities and mechanisms behind regeneration. Because tendons possess a limited intrinsic regeneration capacity with low cellularity, low vascularization and poor innervation, tendon healing results in healed tissues with impaired mechanical capabilities. The potential of tendon healing also depends on the anatomical location and local environment (Thomopoulos et al. 2015).

Most tendons heal spontaneously upon injury but the load-bearing functions are frequently dominated by fibrotic scaring, which can result

in adhesion formation and consequent failure to achieve proper biomechanics (Sharma and Maffulli 2005). Thus, a major challenge in tendon healing is to control the scar tissue formed (over scar remodeling) that deeply compromises the normal function (Rodrigues et al. 2013). Overuse or repetitive stretching during physical activities, which are the major cause of tendon lesions leading to microdisruption of tendon fibers, are known to trigger the release of pro-inflammatory mediators (Rileya et al. 2002; Yang et al. 2005). Increase levels of inflammatory cytokines have been associated to tendon degeneration and disease (Millar et al. 2009).

The lack of understanding on the cell mediated mechanisms disturbing the endogenous repair/regeneration process results in limited knowledge for effective treatment. The inflammation process has a pivotal role in the healing upon injury and failed healing responses contribute to the progression of tendinopathies, which represent a significant medical problem worldwide. The development of tendinopathy compromises tendon structure and function and is characterized by pain, swelling and dysfunction (Magnusson et al. 2010; Zhang et al. 2016), affecting athletes and general population.

The mechanisms supporting tendon healing are still a subject of debate. Two types of tendon healing were proposed: intrinsic and extrinsic. In intrinsic healing, tenocytes from the epitenon and endotenon migrate and proliferate into the site of injury, reorganizing the ECM and giving support to the internal vascular networking (Muller et al. 2015). Conversely, extrinsic healing is achieved by the invasion of cells from the surrounding sheath and synovium. Extrinsic healing has been associated to facilitate scar formation and, consequently inferior biomechanics. Other studies suggest that both intrinsic and extrinsic pathways are fundamental to the early stages of tendon healing (Harrison et al. 2003).

The tendon healing process typically includes three main phases: inflammation, proliferation and remodeling (Docheva et al. 2015) influenced by a temporal and spatially controlled array of mediators and the microenvironment events (Thomopoulos et al. 2015) (Fig. 1).

The first phase is often rapid and of short duration and characterized by the infiltration of inflammatory cells like monocytes, macrophages, neutrophils and platelets. These cells release chemotactic factors that favor the migration and activation of tendon cells from nearby regions of the injury and from tendon sheaths. In the next phase, tendon cells proliferate and produce a collagen rich ECM, re-establishing the alignment of tenocytes between collagen fibrils. Finally, during the remodeling phase, ECM becomes more organized with axial arrangement of collagen fibers. In rat flexor tendons, MMP-9 and MMP-13 mediate tissue degradation, while MMP-2, MMP-3 and MMP-14 were associated to the remodeling phase (Buono et al. 2013). The remodeling of the ECM is a crucial process of tendon healing for gaining biomechanical competence.

During healing, the inflammatory mediators such as Il-6 and TNF-α are secreted by tendon cells (Bauge et al. 2015; Wynn and Vannella 2016) assisting the crosstalk between cells and the ECM synthesis and arrangement contributing for the reparative versus degenerative process that drives tendon remodeling (Dakin et al. 2014; Dean et al. 2017).

Inflammation is the physiological response to injuries and is part of tendon healing process. If the injury is not resolved, the response becomes chronic and pathologic. The magnitude and duration of the inflammatory response is adjusted by regulatory mechanisms at the injury site (Andia et al. 2010; Prisk and Huard 2003).

Persistent inflammation disrupts the balance between MMPs and TIMPs contributing to scared tendon healing and chronic matrix degradation (D'Addona et al. 2017; Tarafder et al. 2017). Scared tissue results in poor rearrangement of collagen fibrils and separation of collagen bundles. The rupture on collagen fibers may be resulted in calcifications (Zabrzyński et al. 2016). Thus, modulation of the inflammatory response is necessary for recovery of tendon function (Shen et al. 2016).

Conservative treatments for tendon healing fight inflammation with anti-inflammatory drugs for tissue recovery in an attempt to diminish an
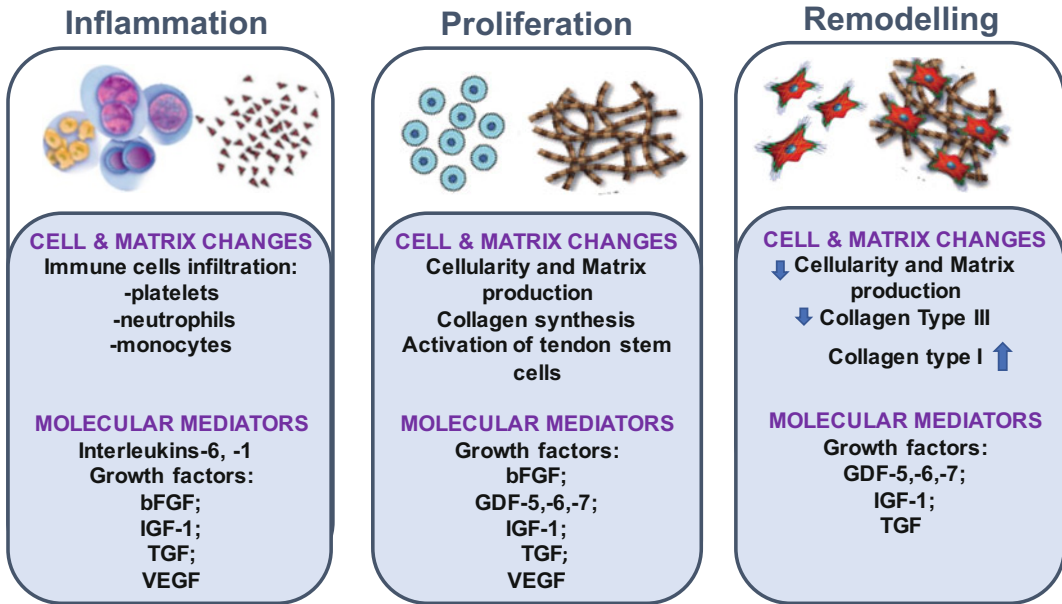
Fig. 1 Representation of the main phases of tendon repair. Inflammation, proliferation and remodeling phases and molecular, cellular and matrix changes during these phases

abnormal or prolonged inflammation often associated to pathophysiology conditions. However, interrupting inflammation overruns important beneficial effects that are required for proper healing to occur.

The role of inflammation in tendinopathy is a subject of debate. Although several studies point a relation between inflammation and tendinopathy (D'Addona et al. 2017; Dakin et al. 2014; Dean et al. 2017; Rees et al. 2014), the onset and development of tendinopathy are poorly understood. Growing evidence suggests that inflammation may not be the cause of several tendinopathies but the failure to resolve inflammation will likely contribute to a complex environment of inflammatory mechanisms (stromal, immune-sensing and infiltrating compartments such as immune cells) (Millar et al. 2017) affecting tendon homeostasis and exacerbating symptoms and tissue degeneration.

Tendinopathies are associated to changes in cellularity and in the remodeling activity of tendon ECM resulting in significant structural and biomechanical alterations of the host niche (Lui and Chan 2011; Tempfer and Traweger 2015).

Histological examination of tendinopathy tissues showed collagenolytic injuries and an active healing process, focal hypervascularity and metaplasia. Moreover, the collagen fibers show unequal and irregular crimping, loss the transverse bands, separations and rupturing of the fibers with an increase of type III collagen. The type III collagen is deficient in the number of cross-links between and within the tropo-collagen units (Abate et al. 2009; D'Addona et al. 2017; Zabrzyński et al. 2016).

Inflammatory mediators including, IL-1, IL-6 and COX-2 were reported to be increased in Achilles tendinopathy (Legerlotz et al. 2012). In a degenerative tendon model, the expression of IL-6, IL-11, IL-15 and TNF-α was up-regulated and accompanied by increased expression of MMP-13 and IL-1β (Dakin et al. 2014; Legerlotz et al. 2012). MMP-13 levels were also increased in human cuff tendon injuries. MMP-13 together with MMP-1 and MMP-8 participate in the cleavage of type I collagen present in tendons. The excessive collagen degradation during turnover results in chronic injuries (Buono et al. 2013).

2.1 Role of Cytokines in Tendon Healing

Cytokines are small proteins with the ability to influence and regulate biological activities (Dakin et al. 2014; Evans 1999) of cells that contribute to the healing response (Barr and Barbe 2004; Lin et al. 2006; Muller et al. 2015). Cytokines constitute the major mediators of inflammatory response with a relevant role in cell signaling and communication, holding potent immunomodulatory properties. An endogenous expression of inflammatory cytokines, namely TNF-α, IL-1β, IL-6, IL-4 and IL-10 has been demonstrated in human injured and healthy tenocytes (Ackermann et al. 2013; Mobasheri and Shakibaei 2013). Additionally, some of these cytokines may also be involved in the (self)regulation of tenocyte processes as IL-6 stimulation was reported to increase the proliferation capacity of tenocytes and inhibition expression of tendon cell markers (Thomopoulos et al. 2015). Cytokine expression is also affected by external stimuli as mechanical stimuli/exercise, which impacts the cytokine profile (including IL-1β and TNFα) during the tendon healing process (Morita et al. 2017).

The biochemical profile within a tissue niche during healing and other physiological events is of ultimate importance as it can be indicative of homeostatic, inflammatory or pathological conditions. Thus, the biochemical relevance of soluble factors as cytokines in tendon niches anticipates their application as potential diagnosis and therapeutic tools for repair and regeneration strategies (Table 1).

3 Tendon Derived-Stem Cells (TDSCs) to Modulate Inflammation and Improve Tendon Healing

The interplay of mesenchymal stem/stromal cell (MSCs) with the tendon niche is essential for the modulation of the inflammatory response following injury (Lui and Chan 2011; Zhou et al. 2010) and is strongly dependent on a balance of soluble factors, cell-cell communication and cell-matrix interactions. During inflammation, MSCs interact with resident cells to promote cell migration and proliferation, which could allow a faster re-colonization of the defect, and matrix synthesis (Proffen et al. 2013).

The crosstalk between inflammation cues and stem cells is important to elucidate the mechanisms of how stem cells respond to tissue damage avoiding scar formation and tuning cell-based mechanisms for regenerative approaches.

Previous studies with non-tendon mesenchymal stem/stromal cell suggested that a MSCs treatment could attenuate scar formation and compromised function by improving tissue strength after ligament and tendon injuries. This was due to a paracrine-mediated immunosuppressive effect, through which MSCs modulate macrophage phenotypes (Proffen et al. 2013; Thomopoulos et al. 2015). It is expected that local stem cell populations within different tissues may also exert a similar effect. Thus, tendon stem/progenitor cells hold potential to contribute to the resolution of inflammation and pathophysiology of tendinopathies modulating biological responses at the injury site (Fig. 2).

A local tendon stem cell population could be beneficial over other stem cell sources due to their inherent pro-tenogenic abilities, which are likely more prone to produce tendon components under the influence of tendon environments (Dakin et al. 2014; Snedeker and Foolen 2017).

In 2007, a population of tendon stem/progenitor cells was firstly identified in tendons from mouse and humans, by Bi et al. (Bi et al. 2007). Tendon-derived stem cells (TDSCs) present universal stem cell characteristics such as the ability to self-renewal, clonogenicity and multi-lineage differentiation capacity (Bi et al. 2007). TDSCs were reported to *in vitro* differentiate into tenocytes, chondrocytes, osteocytes and adipocytes and to originate tendon, cartilage, bone and tendon-to-bone tissues in several animal models such as, nude mouse and rat, rabbit patellar and Achilles tendon (Lui 2013; Zhang and Wang 2010).

Table 1 Cytokines in homeostasis, inflammation and pathogenesis of tendon tissues

Cytokine	Function in homeostasis	Function in inflammation	Pathogenesis	References
IL-1β	Regulation of temperature, sleep and feeding Modulation of cellular metabolism	Stimulation of MMPs production Synthesis of pro-inflammatory cytokines (e.g. TNF-α, IL-6 and IL-8)	Acute and chronic inflammatory disorders	Ren and Torres (2009)
TNFα		Favors ECM degradation (MMPs) Induction inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-10) Suppression of collagen type I Increases the elasticity (reduction of ECM stiffness)	Participates in degeneration of tendon	Dohnert et al. (2015)
IL-6	Maintain metabolic homeostasis	Increases collagen synthesis Amplifies the inflammatory response Induction of VEGF and IL-10	Induces acute-phase responses	Ackermann et al. (2013)
IL-4	Associated to ECM homeostasis in may disease models	Modulates and suppresses pro-inflammatory cytokines Decreases the synthesis of inflammatory cytokines (TNF-α, IL-1β, IL-6) and inhibits the secretion of MMPs Reduces tendon strength		Courneya et al. (2010), John et al. (2010), Schulze-Tanzil et al. (2011), Wojdasiewicz et al. (2014)
IL-10		Inhibition of the synthesis of inflammatory cytokines (TNF-α and IL-2) and MMPs Synthesis of collagen type II and aggrecan Induces proliferation and survival of tenocytes		Ackermann et al. (2013)
IL-17A		Promote tissue destruction and degeneration Induces the production of cytokines (IL-1, IL-6, TNF-α), MMPs and NO synthase in tenocytes	Early inflammatory response in human tendinopathy Mediates inflammation and tissue remodeling in human tenocytes	Millar et al. (2015)

NO nitric oxide, *ECM* extracellular matrix, *MMPs* matrix metalloproteinases

TDSCs have also shown evidence as cell source for tendon repair (Lui et al. 2016; Mienaltowski et al. 2014; Tarafder et al. 2017) (Table 2). TDSCs cultured in fibrin glue constructs were shown to promote earlier and improved tissue repair assessed by increased collagen production and fiber alignment in a patellar tendon window defect model (Ni et al. 2013). The

TDSCs seeded in knitted silk-collagen sponge scaffolds also demonstrated ability to promoting regeneration of rotator cuff in rabbit model by inducing tenogenic differentiation and secretion of anti-inflammatory cytokines that prevented immunological rejection. (Shen et al. 2012).

The resident stem cell populations present in different regions of the tendon can be subject to
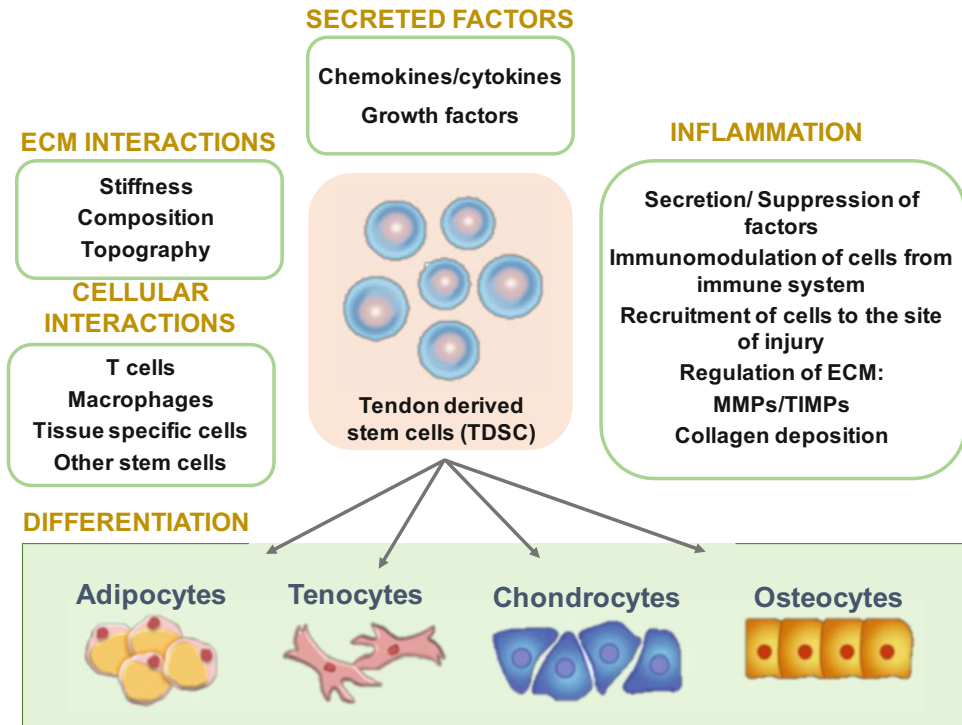
Fig. 2 Schematic representation of the TDSCs in tendon niches as modulators of tissue repair and regeneration

different biochemical stimuli and contribute in distinctive ways for the reparative response to injury, and thus play different yet interactive roles in inflammation and healing.

A study by Mienaltowski *et al.* compared the properties of proper-(TPs) and peritenon-(TPes) derived progenitor cells from embryonic Achilles tendon in an *in vitro* regenerative tendon construct model. The anatomical origin of TSCs (TPs or TPes) contributed differently for tendon-like tissue formation and the secretome of TPes bolster the expression of tenogenic differentiation markers and matrix assembly genes in TPs and tenocytes. These findings highlight an additional potential role of TPes in tendon repair besides the synthesis of provisional matrix (Mienaltowski et al. 2014).

TDSCs also participate in the regulation of inflammation during healing of acute tendon injuries (Tarafder et al. 2017). Connective tissue growth factor (CTGF) enriched CD146+ TDSCs were shown to reduce pro-inflammatory M1 cells in the early healing phase and express anti-inflammatory IL-10 and TIMP-3 vis JNK/signal

transducer and activator of transcription 3 (STAT3) signalling (Tarafder et al. 2017).

The immunomodulatory action and trophic signaling on cytokine modulation are TDSCs parameters to be taken in consideration as they are proposed to impact cellular immunity and immune associated processes, controlling cell responses and holding great promise for a variety of pathologies where inflammation and failed healing could be problematic. Therefore, TDSCs therapy is promising for regenerative medicine approaches aiming to repair tendon injuries to tissues pre-injury functional stage.

4 Conclusions and Future Directions

Despite the insights from recent years on the cellular and molecular cues involved in tendon healing, the knowledge on biological mechanisms to recapitulate tendon regeneration remains at the infancy.

Table 2 The role of tendon derived stem cell populations in tendon healing and repair

TDSCs in tendon healing and repair		Model	References
TPes	Reinforces tendon differentiation genes synthesis of matrix	*In vitro*	Mienaltowski et al. (2014)
CTGF enriched CD146^{+} TDSCs	Induced anti-inflammatory factors: IL-10 and TIMP-3 expression Reduced pro-inflammatory M1 in the early healing phase	Full-transected patellar tendons (rat)	Tarafder et al. (2017)
TDSCs in fibrin glue	Increased collagen production and fiber alignment Earlier and improved tissue repair	Patellar window defect (mouse)	Ni et al. (2013)
Allogenic TSC in silk–collagen scaffold	Reduced number of lymphocytes	Rotator cuff (rabbit)	Shen et al. (2012)

TPes peritenon-(TPes) derived progenitor cells from embryonic tendon, *CTGF* connective tissue growth factor, *TDSCs* tendon-derived stem cells

Findings on tendon (stem cell) biology will likely contribute for better understanding of tendon homeostasis and proper healing. Inflammation as a necessary step for healing to occur should not be blocked but modulated and controlled. New studies are required to insight on the role of the mediators involved in unresolved and chronic inflammation to unveil new homeostatic or pathological markers and assist diagnosis tools for the treatment of tendon conditions. Ultimately, the knowledge gathered would enable the control of tendon healing response to injury toward a complete restoration of functional biomechanical cues.

References

Abate M, Gravare-Silbernagel K, Siljeholm C, Iorio AD, Amicis DD, Salini V, Werner S, Paganelli R (2009) Pathogenesis of tendinopathies- inflammation or degeneration? Arthritis Res Ther 11:1–15

Ackermann PW, Domeij-Arverud E, Leclerc P, Amoudrouz P, Nader GA (2013) Anti-inflammatory cytokine profile in early human tendon repair. Knee Surg Sports Traumatol Arthrosc 21:1801–1806

Andia I, Sanchez M, Maffulli N (2010) Tendon healing and platelet-rich plasma therapies. Expert Opin Biol Ther 10:1415–1426

Aparecida de Aro A, Vidal Bde C, Pimentel ER (2012) Biochemical and anisotropical properties of tendons. Micron 43:205–214

Barr AE, Barbe MF (2004) Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders. J Electromyogr Kinesiol 14:77–85

Bauge C, Leclercq S, Conrozier T, Boumediene K (2015) TOL19-001 reduces inflammation and MMP expression in monolayer cultures of tendon cells. BMC Complement Altern Med 15:217

Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, Li L, Leet AI, Seo BM, Zhang L, Shi S, Young MF (2007) Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat Med 13:1219–1227

Buono AD, Oliva F, Osti L, Maffulli N (2013) Metalloproteases and tendinopathy. Muscles Ligaments Tendons J 3:51–57

Cadby JA, Buehler E, Godbout C, van Weeren PR, Snedeker JG (2014) Differences between the cell populations from the peritenon and the tendon core with regard to their potential implication in tendon repair. PLoS One 9(3):e92474

Courneya J-P, Luzina IG, Zeller CB, Rasmussen JF, Bocharov A, Schon LC, Atamas SP (2010) Interleukins 4 and 13 modulate gene expression and promote proliferation of primary human tenocytes. Fibrogenesis Tissue Repair 3:2–8

D'Addona A, Maffulli N, Formisano S, Rosa D (2017) Inflammation in tendinopathy. Surgeon 15(5):297–302

Dakin SG, Dudhia J, Smith RK (2014) Resolving an inflammatory concept: the importance of inflammation and resolution in tendinopathy. Vet Immunol Immunopathol 158:121–127

Dean BJF, Dakin SG, Millar NL, Carr AJ (2017) Review-emerging concepts in the pathogenesis of tendinopathy. Surgeon J R Coll Surg Edinb Irel 15 (6):349–354

Docheva D, Muller SA, Majewski M, Evans CH (2015) Biologics for tendon repair. Adv Drug Deliv Rev 84:222–239

Dohnert MB, Ferreira GK, Silveira PC, Zanoni ET, Dohnert LH, de Souza CT, Paula MM (2015) Inflammatory cytokines content in Achilles tendinopathy after phonophoresis treatment combined with gold nanoparticles and diclophenac diethylammonium in rats. Inflammation 38:1044–1049

Durgam SS, Stewart MC (2016) Tendon-derived progenitor cells: in vitro characterization and clinical applications for tendon repair. J Stem Cell Res Med 1:8–17

Evans CH (1999) Cytokines and the role they play in the healing of ligaments and tendons. Sports Med 28:71–76

Harrison R, Jones M, Grobbelar AO, McGrouther DA, Brown RA, Mudera V (2003) Tendon healing intrinsic or extrinsic? Direct evidence for dual mechanisms in early stages of tendon injury. Tissue Eng 9(4):852–852

Ho JO, Sawadkar P, Mudera V (2014) A review on the use of cell therapy in the treatment of tendon disease and injuries. J Tissue Eng 5:204173141454967

James R, Kesturu G, Balian G, Chhabra AB (2008) Tendon: biology, biomechanics, repair, growth factors, and evolving treatment options. J Hand Surg 33:102–112

John T, Lodka D, Kohl B, Ertel W, Jammrath J, Conrad C, Stoll C, Busch C, Schulze-Tanzil G (2010) Effect of pro-inflammatory and Immunoregulatory cytokines on human tenocytes. J Orthop Res 28:1071–1077

Killian ML, Cavinatto L, Galatz LM, Thomopoulos S (2012) The role of mechanobiology in tendon healing. J Shoulder Elb Surg 21:228–237

Legerlotz K, Jones ER, Screen HR, Riley GP (2012) Increased expression of IL-6 family members in tendon pathology. Rheumatology 51:1161–1165

Lin TW, Cardenas L, Glaser DL, Soslowsky LJ (2006) Tendon healing in interleukin-4 and interleukin-6 knockout mice. J Biomech 39:61–69

Liu H, Zhu S, Zhang C, Lu P, Hu J, Yin Z, Ma Y, Chen X, Ouyang H (2014) Crucial transcription factors in tendon development and differentiation: their potential for tendon regeneration. Cell Tissue Res 356:287–298

Lui PP (2013) Identity of tendon stem cells--how much do we know? J Cell Mol Med 17:55–64

Lui PP (2015) Stem cell technology for tendon regeneration: current status, challenges, and future research directions. Stem Cells Cloning Adv Appl 2015:163

Lui PP, Chan KM (2011) Tendon-derived stem cells (TDSCs): from basic science to potential roles in tendon pathology and tissue engineering applications. Stem Cell Rev 7:883–897

Lui PPY, Wong OT, Lee YW (2016) Transplantation of tendon-derived stem cells pre-treated with connective tissue growth factor and ascorbic acid in vitro promoted better tendon repair in a patellar tendon window injury rat model. Cytotherapy 18:99–112

Magnusson SP, Langberg H, Kjaer M (2010) The pathogenesis of tendinopathy: balancing the response to loading. Nat Rev Rheumatol 6:262–268

Meirelles LS, Fontes AM, Covas DT, Caplan AI (2009) Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine Growth Factor Rev 20:419–427

Mienaltowski MJ, Adams SM, Birk DE (2014) Tendon proper- and peritenon-derived progenitor cells have unique tenogenic properties. Stem Cell Res Ther 5:1–15

Millar NL, Wei AQ, Molloy TJ, Bonar F, Murrell GAC (2009) Cytokines and apoptosis in supraspinatus tendinopathy. J Bone Joint Surg 91:417–424

Millar NL, Akbar M, Campbell AL, Reilly JH, Kerr SC, McLean M, Frleta-Gilchrist M, Fazzi UG, Leach WJ, Rooney BP, Crowe LAN, Murrell GAC, McInnes IB (2015) IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. Sci Rep 6:1–11

Millar NL, Murrell GA, McInnes IB (2017) Inflammatory mechanisms in tendinopathy – towards translation. Nat Rev Rheumatol 13:110–122

Mobasheri A, Shakibaei M (2013) Is tendinitis an inflammatory disease initiated and driven by pro-inflammatory cytokines such as interleukin 1ß? Histol Histopathol 28:955–964

Morita W, Dakin SG, Snelling SJB, Carr AJ (2017) Cytokines in tendon disease. Bone Joint Res 6:656–664

Muller SA, Todorov A, Heisterbach PE, Martin I, Majewski M (2015) Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. Knee Surg Sports Traumatol Arthrosc 23:2097–2105

Ni M, Rui YF, Tan Q, Liu Y, Xu LL, Chan KM, Wang Y, Li G (2013) Engineered scaffold-free tendon tissue produced by tendon-derived stem cells. Biomaterials 34:2024–2037

Prisk V, Huard J (2003) Muscle injuries and repair. Histol Histopathol 18:1243–1256

Proffen BL, Haslauer CM, Harris CE, Murray MM (2013) Mesenchymal stem cells from the retropatellar fat pad and peripheral blood stimulate ACL fibroblast migration, proliferation, and collagen gene expression. Connect Tissue Res 54:14–21

Rees JD, Stride M, Scott A (2014) Tendons--time to revisit inflammation. Br J Sports Med 48:1553–1557

Ren K, Torres R (2009) Role of interleukin-1beta during pain and inflammation. Brain Res Rev 60:57–64

Riggin CN, Morris TR, Soslowsky LJ (2015) Tendinopathy II: etiology, pathology, and healing of tendon injury and disease. In: Reis M, Rodrigues MRT (eds) Tendon regeneration understanding tissue physiology and development to engineer functional substitutes. Elsevier, San Diego

Rileya GP, Currya V, Degrootb J, Bv E, Verzijlb N, Hazlemana BL, Bankb RA (2002) Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. Matrix Biol 21:185–195

Rodrigues MT, Reis RL, Gomes ME (2013) Engineering tendon and ligament tissues: present developments

towards successful clinical products. J Tissue Eng Regen Med 7:673–686

Schulze-Tanzil G, Al-Sadi O, Wiegand E, Ertel W, Busch C, Kohl B, Pufe T (2011) The role of pro-inflammatory and immunoregulatory cytokines in tendon healing and rupture: new insights. Scand J Med Sci Sports 21:337–351

Sharma P, Maffulli N (2005) Basic biology of tendon injury and healing. Surgeon 3:309–316

Shen W, Chen J, Yin Z, Chen X, Liu H, Heng BC, Chen W, Ouyang HW (2012) Allogenous tendon stem/progenitor cells in silk scaffold for functional shoulder repair. Cell Transplant 21:943–958

Shen H, Kormpakis I, Havlioglu N, Linderman SW, Sakiyama-Elbert SE, Erickson IE, Zarembinski T, Silva MJ, Gelberman RH, Thomopoulos S (2016) The effect of mesenchymal stromal cell sheets on the inflammatory stage of flexor tendon healing. Stem Cell Res Ther 7:144

Snedeker JG, Foolen J (2017) Tendon injury and repair – a perspective on the basic mechanisms of tendon disease and future clinical therapy. Acta Biomater 63:18–36

Speed C (2016) Metabolic influences on risk for tendon disorders. In: Ackermann PW, Hart D (eds) Metabolic influences on risk for tendon disorders, Advances in Experimental Medicine and Biology. Springer, Cham

Stalman A, Bring D, Ackermann PW (2015) Chemokine expression of CCL2, CCL3, CCL5 and CXCL10 during early inflammatory tendon healing precedes nerve regeneration: an immunohistochemical study in the rat. Knee Surg Sports Traumatol Arthrosc 23:2682–2689

Subramanian A, Schilling TF (2015) Tendon development and musculoskeletal assembly: emerging roles for the extracellular matrix. Development 142:4191–4204

Tan SL, Selvaratnam L, Ahmad TS (2015) A mini review on the basic knowledge on tendon: revisiting the normal & injured tendon. JUMMEC 18:1–14

Tarafder S, Chen E, Jun Y, Kao K, Sim KH, Back J, Lee FY, Lee CH (2017) Tendon stem/progenitor cells regulate inflammation in tendon healing via JNK and STAT3 signaling. FASEB J 31:3991–3998

Tempfer H, Traweger A (2015) Tendon vasculature in health and disease. Front Physiol 6:330

Thomopoulos S, Parks WC, Rifkin DB, Derwin KA (2015) Mechanisms of tendon injury and repair. J Orthop Res 33:832–839

Wojdasiewicz P, Poniatowski LA, Szukiewicz D (2014) The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediat Inflamm 2014:561459

Wynn TA, Vannella KM (2016) Macrophages in tissue repair, regeneration, and fibrosis. Immunity 44:450–462

Yang G, Im HJ, Wang JH (2005) Repetitive mechanical stretching modulates IL-1beta induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. Gene 363:166–172

Zabrzyński J, Zabrzyńska A, Grzanka D (2016) Tendinopathy – a disease of tendons. J Orthop Trauma Surg Relat Res 3:024–030

Zhang J, Wang JH-C (2010) Characterization of differential properties of rabbit tendon stem cells and tenocytes. BMC Musculoskelet Disord 11:1–11

Zhang X, Lin YC, Rui YF, Xu HL, Chen H, Wang C, Teng GJ (2016) Therapeutic roles of tendon stem/progenitor cells in tendinopathy. Stem Cells Int 2016:4076578

Zhou Z, Akinbiyi T, Xu L, Ramcharan M, Leong DJ, Ros SJ, Colvin AC, Schaffler MB, Majeska RJ, Flatow EL, Sun HB (2010) Tendon-derived stem/progenitor cell aging: defective self-renewal and altered fate. Aging Cell 9:911–915