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Review

The role of pro-inflammatory and immunoregulatory cytokines in tendon healing and rupture: new insights

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Owing to limited self-healing capacity, tendon ruptures and healing remain major orthopedic challenges. Increasing evidence suggests that post-traumatic inflammatory responses, and hence, cytokines are involved in both cases, and also in tendon exercise and homeostasis. This review summarizes interrelations known between the cytokines interleukin (IL)-1β, tumor necrosis factor (TNF)α, IL-6 and vascular endothelial growth factor (VEGF) in tendon to assess their role in tendon damage and healing. Exogenic cytokine sources are blood-derived leukocytes that immigrate in damaged tendon. Endogenous expression of IL-1β, TNFα, IL-6, IL-10 and VEGF was demonstrated in tendon-derived cells. As tendon is a highly mechanosensitive tissue, cytokine homeostasis and cell survival underlie an intimate balance between adequate biomechanical stimuli and disturbance through load deprivation and overload. Multiple interrelations between cytokines and tendon extracellular matrix (ECM) synthesis, catabolic mediators e.g. matrix-degrading enzymes, inflammatory and angiogenic factors (COX-2, PGE2, VEGF, NO) and cytoskeleton assembly are evident. Pro-inflammatory cytokines affect ECM homeostasis, accelerate remodeling, amplify biomechanical adaptiveness and promote tenocyte apoptosis. This multifaceted interplay might both contribute to and interfere with healing. Much work must be undertaken to understand the particular interrelation of these inflammatory and regulatory mediators in ruptured tendon and healing, which has relevance for the development of novel immunoregulatory therapeutic strategies.

Tendon injury such as rupture induces a local inflammatory response, characterized by the induction of pro-inflammatory cytokines (Berglund et al., 2007; Tohyama et al., 2007; Akesen et al., 2009). Tendon overuse is accompanied by repetitive microtraumata and can lead to tendinopathy or rupture (Allenmark, 1992; Sun et al., 2008). Blood-derived leukocytes attracted by tendon tissue trauma and released into the tissue during bleeding might represent an important exogenic source for pro-inflammatory cytokines (Tsuzaki et al., 2003b; Chbinou & Frenette, 2004). However, the highly specialized resident fibroblasts in tendon, the tenocytes, are well known to produce several endogenic cytokines and growth factors acting in an auto- and paracrinic manner on tenocytes (Pufe et al., 2001; Tsuzaki et al., 2003b; John et al., 2010). Tendon cell proliferation and synthesis of a neo-matrix are essential factors in tendon healing (Chan et al., 2000; Sharma & Maffulli, 2005). The strictly linear uniaxial organization of collagen fibrils as main constituents of the extracellular tendon matrix (ECM) and the linear alignment of tenocytes between them (Fig. 1a and b) have to be re-established in tendon during healing (Loiselle et al., 2009) – remodeling processes, which might be further influenced in a post-traumatic inflammatory microenvironment. Tendon repair leads to scar formation. Tendon scars provide inferior or altered biomechanical properties (Nakamura et al., 2000; Loiselle et al., 2009).

The aim of this review is to summarize the effects of pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)α and other important mediators such as vascular endothelial growth factor (VEGF) in terms of their putative influence on tendon healing or degeneration. It is necessary to elucidate the precise multifaceted interplay of cytokines and growth factors in damaged tendon to find strategies for improvement of tendon healing and to impair scar and adhesion formation.

Tendon organization

The hypocellular histological structure (Meller et al., 2009), poor blood supply under physiological

conditions and the low metabolic activity of tendons and ligaments are major reasons for their limited self-healing properties (Williams, 1986; Ahmed et al., 1998; Chen et al., 2009). Only around 5% of the normal tendon tissue volume is represented by resident cells in tendon, the tenocytes (Tozer & Duprez, 2005; Meller et al., 2009) (Fig. 1). Tenocytes produce and remodel this abundant, but strictly organized tendon ECM (Riley et al., 2002). It consists mainly of parallel running collagen fibrils whereby the tenocytes, which are embedded between these ECM fibre bundles, show a uniaxial alignment in rows (Fig. 1b) (Ippolito et al., 1980; Meller et al., 2009). Approximately 95% of the whole collagen in traction tendons, which are tendons, where the direction of pull is in line with the direction of the muscle, is type I (50–80% of tendon dry weight) (Riley et al., 1994), with types III and V also present in small amounts (Waggett et al., 1998; Ottani et al., 2002; Sharma & Maffulli, 2005; Benjamin et al., 2008). Type II collagen can be found in the gliding areas of tendons (Koch & Tillmann, 1995; Petersen et al., 2004a). Gliding tendons such as the *Musculus tibialis posterior* tendon change their direction by turning around a bony or fibrous pulley ("hypomochlion"). In this region, the tendon is subjected to intermittent compressive and shear forces and contains avascular fibrocartilage. The tendon ECM also contains 1–2% of dry weight elastic fibers which are an important prerequisite for the elastic modulus of tendon. At all segmental variations in the microstructure, ECM synthesis and cell proliferation could be observed in tendons (Abrahamsson et al., 1989). Hence, the elastin content mediates tendon elasticity

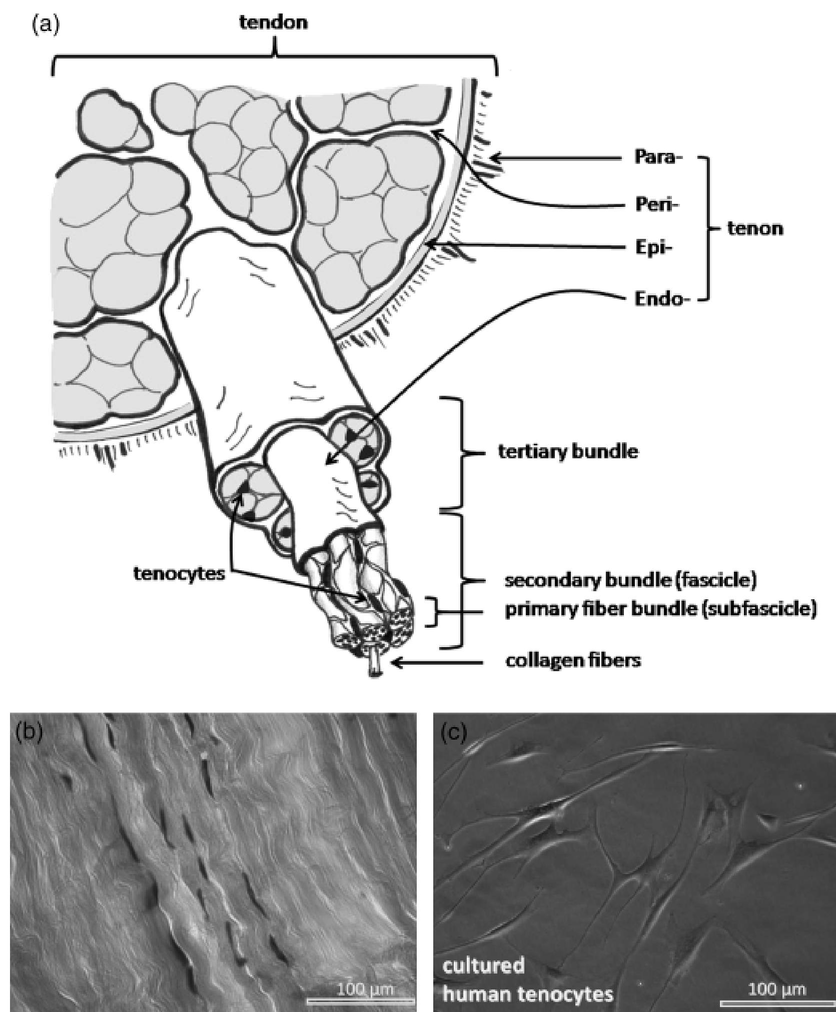

Fig. 1. (a–c) Tendon structure and tenocytes. (a) Schematic picture of tendon organization. (b) Hematoxylin Eosin staining of human hamstring tendon (*Musculus semitendinosus*). Tendon is a hypocellular and -vascular tissue containing only few cells, that are aligned in rows between extracellular tendon matrix fiber bundles. (c) Isolated and cultured human hamstring tendon-derived tenocytes (first passage) are spindle shaped with multiple long cytoplasmic processes forming cell–cell contacts. (b, c) scale bars 100 µm.

whereby increasing elastin amounts mostly go hand in hand with reduced ECM stiffness. In contrast, type I collagen is mainly responsible for tendon stiffness. Obviously, both components (type I collagen and elastin) are differently regulated in tendon by cytokines (Qi et al., 2006a; John et al., 2010). While collagen provides the tissue with its tensile strength, proteoglycans play a role in tissue hydration and regulate collagen integrity (Rees et al., 2009). It is well known that deposition and expression of ECM components such as collagens and proteoglycans can be regulated by pro-inflammatory cytokines in connective tissue cells (Seguin et al., 2005; Qi et al., 2006a; Thampatty et al., 2007; John et al., 2010). In tendon disorders such as tendopathy as well as *post* tendon injury, a shift of the proteoglycan deposition has been observed (Lo et al., 2005; Rees et al., 2009; Samiric et al., 2009; Lui et al., 2010). Hence, the question arises whether the proteoglycan disequilibrium emerges from an altered cytokine expression.

In normal tendon, the local proteoglycan distribution differs between the midsubstance (tensile region) of tendon where decorin is more prominent and the fibrocartilaginous enthesis region with a higher aggrecan content in tendon (Abrahamsson et al., 1989; Waggett et al., 1998; Rigozzi et al., 2009) and also under pathological and altered biomechanical conditions (Smith et al., 2008; Samiric et al., 2009). Fibronectin is an ECM glycoprotein, which is produced by tenocytes mediating their adherence to the ECM (Tillander et al., 2002). It is upregulated in tendon healing (Tillander et al., 2002). Furthermore, the glycoprotein cartilage oligomeric matrix protein is a typical component of tendon ECM and scleraxis is a differentiation-associated transcription factor in tendon (Schweitzer et al., 2001). Tendon is surrounded by the para- and epitenon and subdivided by the peritenon (Strocchi et al., 1985; Kannus, 2000). Fascicles of tendon are enclosed by the endotenon (Kannus, 2000). These connective tissue sheaths (Fig. 1a) provide both a frictionless gliding of tendon fascicles during motion and a flexible connection to the environmental tissue (Rowe, 1985). These connective sheaths also play a major role in tendon healing (Wojciak & Crossan, 1993). Endotenon contains small nerves and blood vessels. Some tendons are surrounded by a protective and nutritive tenosynovium (Lundborg & Myrhage, 1977; Sharma & Maffulli, 2005). The tenosynovium is intimately involved in the healing response after rupture (Takasugi et al., 1976; Ikeda et al., 2010). Healing can occur intrinsically, by proliferation of epitenon and endotenon tenocytes, or extrinsically, by invasion of cells from the surrounding sheath and synovium (Lundborg et al., 1985; Siddiqi et al., 1992; Sharma & Maffulli, 2005).

Tendon-resident cells

Most intrinsic cells in tendon are tenocytes, which are highly specialized fibroblasts with a mostly heterochromatic elongated nucleus (Chuen et al., 2004) (Fig. 1b and c). Other small cell populations of ubiquitous fibroblasts can be observed in tendon residing in the epi-, peri- and endotenon; some endothelial cells derived from few microvessels in tendon are also present, as well as synovial fibroblasts covering the tenosynovium. Fibro-chondrocytes can be found as small cell populations in the tendon, particularly in the gliding area of gliding tendons (Benjamin & Ralphs, 1998; Petersen et al., 2002; Petersen et al., 2003b; Petersen et al., 2004a) or in the center of special traction tendons such as the Achilles tendon (Zantop et al., 2003), especially in regions that react to biomechanical loading. These cells can be found in higher amounts in the bone attachment enthesis region, which usually contains fibrocartilage (Benjamin & Ralphs, 1998; Sharma & Maffulli, 2005).

In order to assess the real capacity and sensitivity of the highly specialized intrinsic tendon-specific cells, the tenocytes, isolated and cultured tenocytes (Fig. 1c) are a versatile *in vitro* model. Tenocytes can be identified by scleraxis gene expression (Schweitzer et al., 2001). Tenomodulin and tenascin C have also been suggested as tendon marker proteins (Docheva et al., 2005; Shukunami et al., 2006; Jelinsky et al., 2010). Both markers are also expressed by other cell types to some degree (Saiki et al., 2009; Jelinsky et al., 2010). However, under inflammatory conditions as observed during tendinitis or after tendon rupture, the presence of major populations of immigrated cells such as neutrophils and macrophages derived from the blood or the surrounding tissue can be observed in tendon. These cells phagocyte, opsonize, and hence, remove ECM fragments of the damaged tissue, but might also release various cytokines and growth factors affecting tendon homeostasis.

Immigrated blood-derived cells in damaged tendon and tendon healing

Wojciak and Crossan demonstrated the presence of inflammatory cells during tendon healing in a rat tendon rupture model: an infiltration of the synovial tendon sheath and epitenon with lymphocytes and macrophages was discernable (Wojciak & Crossan, 1993). Adhesion formation during tendon healing was also influenced by the interaction of leukocytes with epitenon and tenosynovial cells, which correlated strongly with an increased transforming growth factor (TGF)β1-mediated fibronectin production by the epitenon cells (Wojciak & Crossan, 1993; Wojciak & Crossan, 1994). In response to tendon

rupture, bleeding occurs, leading to a ruptured hematoma, which is characteristic for the first so-called "hemorrhagic healing phase". The blood coagulation is followed by growth factor and cytokine release e.g. by aggregating platelets. These factors chemotactically attract leukocytes (neutrophils, lymphocytes and macrophages) to immigrate into the injured tissue (Chbinou & Frenette, 2004; Sharma & Maffulli, 2005) and to produce cytokines and growth factors (e.g. TGFβ1, insulin-like growth factor [IGF]-I, basic fibroblast growth factor [bFGF], platelet-derived growth factor [PDGF], growth and differentiation factor [GDF]). However, an enhanced IL-1β expression was evident in ruptured tendon (Berglund et al., 2007) and TNFα also seems to be involved in healing processes at this time, as analyzed in a rat Achilles tendon healing model (Eliasson et al., 2009). Additionally, complement split products resulting from the damaged tissue might also act as chemoattractants for neutrophils as reported for other tissues (Amsterdam et al., 1995; Morgan, 2000). Polymorph nuclear cells (PMNs, e.g. neutrophils) dominate on days 1–3 of tendon healing, and subsequently, macrophages prevail (Chbinou & Frenette, 2004). Peripheral blood-derived macrophages express the ED1 antigen, macrophages immigrating from the peritendinous tissue into the defect appear later with a maximum on the 28th day *post* rupture and express the ED2 antigen. They possibly have an anabolic function in tendon healing (Massimino et al., 1997). ED1-macrophages remove cell debris and necrotic tissue by phagocytosis representing the second so-called "inflammatory healing phase", which lasts 24–48 h, whereas later ED2-macrophages become resident cells enhancing the cell proliferation (Massimino et al., 1997; Chbinou & Frenette, 2004). The presence of these heterogenic leukocyte subpopulations underlines the fact that different subclasses of leukocytes exhibit complementary functions during tissue healing. Under the influence of growth factors (Chang et al., 1997; Chen et al., 2008), the tendon fibroblasts start proliferation and produce an immature neomatrix, which differs from mature tendon matrix e.g. by the predominance of type III compared with type I collagen (Loiselle et al., 2009), as a typical feature of the third, the "proliferation healing phase" (Loiselle et al., 2009). Furthermore, vascular ingrowth can be observed (Petersen et al., 2003a ,d). A cell-rich granulation tissue is the result (fourth phase of healing: "granulation phase") (James et al., 2008). The tendon ECM is later reorganized by a remodeling process, which starts around 5–8 weeks *post* injury (Loiselle et al., 2009). The cellularity decreases, matrix synthesis is reduced and shifts towards an increased type I vs type III collagen deposition (Loiselle et al., 2009). Cells become aligned according to the direction of tension in this fourth phase of tendon healing called the "remodeling phase" (James et al., 2008).

Pro- and anti-inflammatory cytokines in cultured tenocytes and tendon

Tenocyte isolation for *in vitro* studies can be performed easily using explant cultures or enzymatic digestion of the tendon ECM to release the tenocytes (Schulze-Tanzil et al., 2004) (Fig. 1b). Tenocytes expanded in monolayer culture proliferate slowly and can display an unstable phenotype with increasing culture time reflecting the tendency to dedifferentiate (Bernard-Beaubois et al., 1997; Yao et al., 2006; Almarza et al., 2008). For long-term tenocyte cultivation, three-dimensional culture conditions provide a more suitable basis (Schulze-Tanzil et al., 2004; Stoll et al., 2010). Cultured tenocytes are a versatile system to study particular cytokine effects on tenocyte homeostasis (Tsuzaki et al., 2003b; John et al., 2010). Sources for cytokine release are the tenocytes and particularly in tendinitis and tendon rupture immigrated blood-derived inflammatory cells such as neutrophils and macrophages (Tsuzaki et al., 2003b; Chbinou & Frenette, 2004).

Endogenous expression of various cytokines such as TNFα, IL-1β, IL-6, IL-10, VEGF and TGFβ has been demonstrated in tenocytes (Pufe et al., 2001; Tsuzaki et al., 2003b; Tohyama et al., 2007; John et al., 2010). However, we were not able to show interferon (IFN)γ gene expression in tenocytes (own unpublished results). IL-1β was up-regulated in ruptured tendon (Berglund et al., 2007). Heat stress, which might occur during prolonged tendon exercise and overuse, induced TNFα but not IL-1β expression in equine tendon fibroblasts (Hosaka et al., 2006). An increased amount of pro-inflammatory cytokines such as IL-1α, IL-1β, TNFα and IFNγ was demonstrated in inflamed native equine tendon (Hosaka et al., 2002). Mechanical factors influence tendon cytokine profile. Adequate physiological mechanical stimuli are important for the maintenance of tendon homeostasis. Cyclic strain induced VEGF expression in tenocytes (Petersen et al., 2004b). Stress deprivation lead to an over-expression of pro-inflammatory cytokines such as IL-1β and TNFα and other cytokines such as TGFβ in the patellar tendon with mechanical deterioration of the tendon (Uchida et al., 2005).

Role of IL-1β and TNFα in tendon and tenocytes

Tenocytes expressed the IL-1RI as a precondition for sensibility against IL-1β. The type II receptor for IL-1β – a decoy receptor, was barely detectable

(Tsuzaki et al., 2003b). In human tenocyte cultures, the pro-inflammatory cytokine IL-1β induced inflammatory and catabolic mediators such as cyclo-oxygenase (COX)-2, prostaglandin (PG)E2 and various matrix metalloproteinases (MMPs), which accelerate the degradation of tendon ECM and hence the loss of the biomechanical resistance and durability of tendon (Corps et al., 2002; Archambault et al., 2002a; Tsuzaki et al., 2003b; Corps et al., 2004; Yang et al., 2005; Thampatty et al., 2007) (Table 1; Fig. 2a). COX-1 was constitutively expressed by tenocytes and not regulated by IL-1β (Tsuzaki et al., 2003b). In equine superficial digital flexor tendons, TNFα was found as a key factor in degeneration (Hosaka et al., 2004). It was up-regulated in inflamed equine tendon and also expressed in scar-formed tendon (Hosaka et al., 2005a ,b). TNFR1 and -R2 co-localized on the same tenocyte and were up-regulated by TNFα in equine tenocytes. TNFR-associated factor (TRAF)2 was also detected in tendon (Hosaka et al., 2004). TNFα stimulated tenocytes to produce further pro- and anti-inflammatory cytokines such as IL-1β, TNFα, IL-6 and IL-10 and matrix degradative enzymes such as MMP1. Hence, tenocytes can be highly activated by TNFα (John et al., 2010). Interestingly, Tohyama et al. (2007) reported that extrinsic fibroblasts that immigrate from outside into the healing tissue were less sensitive to pro-inflammatory cytokines such as IL-1β compared with tenocytes. These cytokines suppressed ECM synthesis such as that of type I collagen (Qi et al., 2006a; John et al., 2010). However, the expression of other ECM components such as elastin was up-regulated by TNFα (John et al., 2010). A similar effect was reported by Qi et al. (2006a) in response to tenocyte IL-1β-treatment hypothesizing a role in "constructive remodeling" in tendon for this cytokine. IL-1β increased the elastic modulus in tendon by differentially regulating the expression of major tendon matrix proteins, type I collagen (its expression was suppressed by IL-1β, which led to reduced stiffness) and elastin (its expression was amplified, which might augment tendon elasticity) (Qi et al., 2006a). Additionally, exogenous VEGF applications decreased the stiffness of grafted ligaments (Yoshikawa et al., 2006; Tohyama et al., 2009). TNFα expression was lower in loaded compared with unloaded tendon repair callus during healing, which underlines the important influence of mechanobiology on healing (Eliasson et al., 2009). Moreover, IL-1β regulated tenocytes cytoskeletal polymerization, and hence, cell stiffness, which was an important precondition for the cell adaptiveness to mechanical loading in tendon (Qi et al., 2006b). A disruption of cytoskeletal actin filaments leading to a more stellate cell shape and down-regulation of actin in IL-1β-treated tenocytes was observed whereby cytoskeletal tubulin was up-regulated (Qi et al., 2006b). Taken together, IL-1β impaired the Young's modulus in human tenocytes, which may help the cells to survive higher mechanical loading as observed in damaged tendon (Qi et al., 2006a). Cytoskeletal alterations toward a more stellate shape and loss of F-actin fibers were also visible in tenocytes treated with TNFα (John et al., 2010).

Role of the immunoregulatory cytokines IL-6 and IL-10 in tendon

Immunoregulatory and anti-inflammatory cytokines might play a role in tendon healing. Increased IL-6 production and signal transducer and activator of transcription (STAT3) phosphorylation was found in ruptured rotator cuff tendon (Nakama et al., 2006a). IL-6 is a multifunctional Th2 cytokine, which exhibits immunoregulatory functions in tissues and obviously plays an essential role in tendon healing (Skutek et al., 2001; Lin et al., 2005; Lin et al., 2006). Mechanical properties of healing tendons in

Table 1. Cytokines and VEGF, which play a role in tendon rupture, healing and inflammation and their known effects on tendon derived cells

Cytokine	Effects in tendon/on tenocytes	References
IL-1β	ECM degradation (MMPs), induction of inflammatory mediators (IL-1β, TNFα, IL-6, COX-2, PGE2), suppression of type I collagen, induction of elastin, cytoskeletal changes	Archambault et al. (2002a ,b), Corps et al. (2002), Tsuzaki et al. (2003a ,b), Corps et al. (2004), Yang et al. (2005), Qi et al. (2006a ,b), Thampatty et al. (2007)
TNFα	ECM degradation (MMPs), induction of cytokines (IL-1β, TNFα, IL-6, IL-10), suppression of type I collagen, induction of elastin, SOCS1, pro- and anti-apoptotic effects, cytoskeletal changes	Archambault et al. (2002), Machner et al. (2003); Tsuzaki et al. (2003a ,b), Hosaka et al. (2005a ,b), Thampatty et al. (2007), John et al. (2010)
IL-6	STAT3 phosphorylation, VEGF expression, supports tendon healing, induction of SOCS3 and of IL-10	Wei et al. (2003), Lin et al. (2006), Nakama et al. (2006a), John et al. (2010)
IL-10	IL-10R1 induction	John et al. (2010)
VEGF	Neo-angiogenesis, remodeling (MMP expression)	Pufe et al. (2001), Petersen et al. (2004b); Pufe et al. (2005), Nakama et al. (2006b)
TGFβ1	Fibronectin expression, tendon scar formation	Wojciak & Crossan (1993), Wojciak & Crossan (1994)

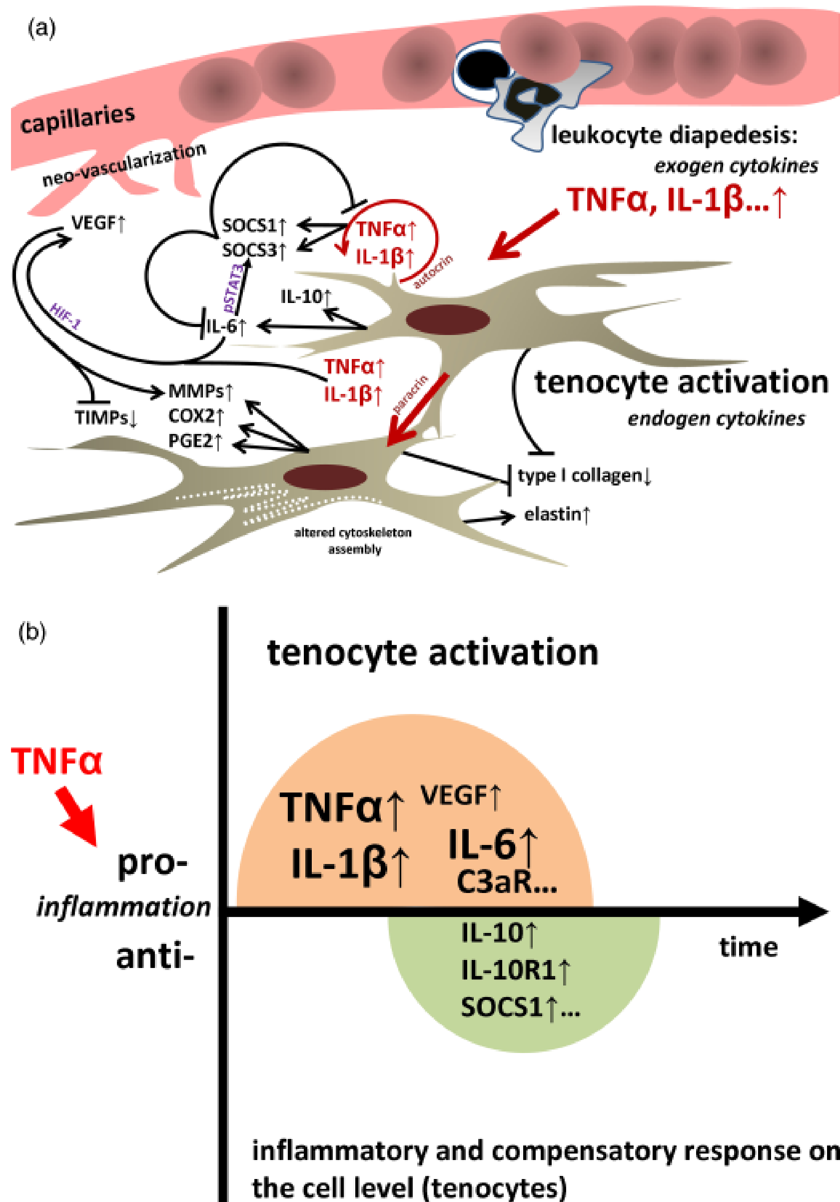

Fig. 2. (a–b) Interplay of cytokines: effects on tenocytes. (a) Exogenic pro-inflammatory cytokines such as TNFα and IL-1β lead to an autoamplification loop in tenocytes activating them in an autocrine and paracrine manner. TNFα and IL-1β induce pro-inflammatory cytokine expression, expression of inflammatory mediators (COX-2, PGE2), degradative enzymes (MMPs), neoangiogenesis (VEGF), suppression of type I collagen expression and induction of cytokine inhibitors (SOCS1, SOCS3). (b) the cytokine and inhibitor induction in tenocytes shows some time dependency revealing an early inflammatory and a subsequent immunoregulatory response. HIF-1, hypoxia inducible factor-1; TIMPs, tissue inhibitors of matrix-metalloproteinases; pSTAT3, phosphorylated STAT3; SOCS, suppressor of cytokine signaling.

knock-out mice were inferior compared with normal controls (Lin et al., 2006). IL-6 was highly up-regulated by both prototype pro-inflammatory cytokines TNFα and IL-1β in tenocytes (Tsuzaki et al., 2003b; John et al., 2010). As reported in other cell types, IL-6 and the anti-inflammatory cytokine IL-10 induce the activation of the STAT3 signaling pathway, which is implicated in cell proliferation and survival (Ahmed & Ivashkiv, 2000; Tanuma et al., 2001; Nishimoto & Kishimoto, 2006). IL-6 exerts its biological functions mainly through Janus tyrosine kinases (JAKs) and STAT factors. Stimulating cells with IL-6 induces receptor oligomerization and causes the local aggregation, and consequent activation, of associated JAKs (Nakama et al., 2006a). JAKs, activated by tyrosine-phosphorylation activate STATs, which subsequently translocate to the cell nucleus to modulate gene expression. Tendon healing was impaired in IL-6 knock-out mice underlining an essential role of IL-6 in tendon healing (Lin et al., 2006). IL-6 was also up-regulated in tendon and peritendineous tissue during tendon exercise. Accord-

ingly, cyclic mechanical stretching enhanced the secretion of IL-6 in human tendon fibroblasts (Skutek et al., 2001). Despite this, IL-6 did not induce its own expression or that of TNFα or IL-1β, however, it had a slight but significant stimulatory effect on IL-10 gene expression (John et al., 2010). IL-6 also promotes blood vessel proliferation by VEGF-dependent angiogenesis via the STAT3 pathway in other cell types (Wei et al., 2003). IL-6 might play a role in the proliferation phase of tendon healing via STAT3 activation by stimulation of cell proliferation and thus supporting survival. IL-4, IL-13 and IL-10 are typical anti-inflammatory Th2 cytokines, whereby IL-10 is the most effective one. IL-10 not only plays a major role in immune cells but also has been demonstrated to be produced by and to affect connective tissue cells such as fibroblasts and chondrocytes (Iannone et al., 2001; Yamamoto et al., 2001; Moroguchi et al., 2004; John et al., 2007a; Muller et al., 2008; Schulze-Tanzil et al., 2009). We could recently show IL-10 expression in tenocytes, which was up-regulated by TNFα and also that the IL-10-specific IL-10R1 was expressed and up-regulated by pro-inflammatory cytokines such as TNFα (John et al., 2010). In IL-4 knock-out mice, an up-regulated IL-10 and IL-13 expression correlated with even superior healing properties compared with the control mice indicating that these cytokines might compensate for the lack of IL-4 (Lin et al., 2006). Ricchetti et al. (2008) reported some time-dependent effects of IL-10 on the biomechanics of healing tendons when using an IL-10 overexpression model in the mice. However, the role of IL-10 in tendons remains still unclear; it is probable that co-stimuli are necessary for full effects. In other fibroblastic cell types, IL-10 seemed to be involved in ECM remodeling because an up-regulation of elastin, decorin as well as MMPs and down-regulation of type I collagen expression by IL-10 have been shown (Reitamo et al., 1994a ,b; Yamamoto et al., 2001; Moroguchi et al., 2004). Another research group reported recently that tenocytes are sensitive to the other so-far known anti-inflammatory cytokines IL-4 and IL-13. Both cytokines stimulated tenocyte proliferation (Courneya et al., 2010).

Cytokine inhibitors and time dependencies in cytokine regulation

Studies comparing the regulation of cytokines und other inflammatory factors in a time-dependent manner are scarce up to now. Tsuzaki et al. (2003b) found MMP and COX-2 expression after 16 h of cytokine stimulation. Induction of TNFα expression by TNFα could be observed at 6 and 24 h, but it was higher at 6 h. In contrast, gene expression of IL-6 in response to TNFα was superior at 24 compared with 6 h. The IL-10 gene expression induced by TNFα was only evident after a 24-hour observation period (John et al., 2010; Fig. 2b). A TNFα-mediated expression of the C3aR anaphylatoxine receptor on tenocytes was higher at 24 compared with 6 h (unpublished own results). Many cytokines utilize the JAK-STAT signal transduction pathway to mediate most part of their key physiological and pathological actions. Suppressors of cytokine signaling (SOCS)1 and SOCS3 are cytokine inhibitors of the STAT signaling pathways and exhibit negative feedback loops (Tan & Rabkin, 2005; Qin et al., 2008). SOCS1 and SOCS3 were expressed by tenocytes and both were up-regulated by TNFα. SOCS3 was additionally induced by IL-6 in tenocytes (John et al., 2010). Hence, SOCS3 might time-dependently limit the IL-6 effects in tendon. Indicating an important function for IL-6 in neo-angiogenesis during tendon healing, Nakama et al. (2006a) detected the expression of IL-6, the IL-6 receptor and phosphorylated STAT3 in ruptured rotator cuff tendon, mainly in proliferative vessels, and to a lesser extent, in the tenocytes.

VEGF in tendon and interrelation with pro-inflammatory cytokines

The angiogenic factor VEGF, which was firstly described as an endothelial cell mitogen and critical for neo-vascularization, is nearly completely down-regulated in healthy tendons. It is expressed during embryogenesis and only in a few sites in the adult body, such as in the lung (Fehrenbach et al., 2003). However, its expression also reoccurs during various disease states in the tendon as well as during tendon healing (Zhang et al., 2003; Petersen et al., 2003a). Interestingly, a neo-angiogenesis could be observed in Achilles tendon disorders (Ohberg et al., 2001). Sclerosing these vessels using sclerosing agents leads to an improved healing of the disordered Achilles tendon (Willberg et al., 2008).

Post tendon surgery, an enhanced VEGF expression was detected (Boyer et al., 2001). VEGF was up-regulated by hypoxia, pro-inflammatory cytokines and IL-6, growth factors (e.g. PDGF), mechanical loading and was elevated in fetal, ruptured and degenerated adult tendons (Pufe et al., 2001; Petersen et al., 2003c; Petersen et al., 2004b; Pufe et al., 2005; Nakama et al., 2006b). Hypoxia and PDGF had a synergistic effect on VEGF expression (Petersen et al., 2003c). Inhibition of the cytokines IL-1β and TNFα effectively reduced VEGF production in tenosynovial samples (Jain et al., 2002). VEGF was chemotactic for monocytes and was a procoagulant (Petersen et al., 2003c). We could show the

expression of VEGF by tenocytes and a culture system-dependent regulation of VEGF in tenocytes (Stoll et al., 2010). Five distinct VEGF isoforms can be observed as a result of alternative splicing (with 121, 145, 165, 189, 205 isoforms in humans), whereby the splicing variants 120 and 164, which correspond with human 121 and 165 isoforms were found during tendon healing in sheep (Petersen et al., 2003a). Hypoxia induced an increase in the production of VEGF by *ex vivo* tenosynovial lining cells and impaired IL-10 expression in the tenosynovium (Jain et al., 2002; Sivakumar et al., 2008). Tenosynovial hypoxia could result in tendon rupture, which is frequently observed in rheumatoid arthritis (RA) patients (Sivakumar et al., 2008). Hypoxia inducible factor 1 is a transcription factor involved in VEGF up-regulation in tendon (Petersen et al., 2003c). On the contrary, endostatin, a fragment of type XVIII collagen and an antagonist of VEGF, impaired VEGF up-regulation (Pufe et al., 2003; Pufe et al., 2005). Secretion of matrix-degrading MMPs facilitated angiogenesis and VEGF stimulated *vice versa* MMP expression in tendon. Hence, increased MMP levels might induce ECM degradation and remodeling and weaken tendons' biomechanical resistance (Petersen et al., 2003c; Pufe et al., 2005).

MMPs and Tissue inhibitor of matrix-metalloproteinases (TIMPs): regulation of ECM homeostasis by cytokines

MMPs are the key players in physiological and pathological tendon ECM remodeling (Smith et al., 2008). MMPs are zinc-dependent endopeptidases with a particular specificity for degradation of various extracellular tendon matrix components. The balance between MMPs and their natural inhibitors, TIMPs, regulates normal tendon remodeling. These enzymes are strictly regulated on the gene and protein expression level by specific inhibitors (TIMPs) and require activation (Clegg et al., 2007). Stromelysins such as MMP3 cleave proteoglycans, which surround and embed the collagen fibers in the tendon ECM (Imai et al., 1997). Subsequently, the collagen bundles might be more accessible for cleavage by collagenases such as MMP1 and MMP13, which both can cleave type I collagen (Nagase et al., 2006). However, this stromelysin-mediated proteoglycan cleavage might not play a major role *in vivo* where aggrecanases are more important. Aggrecanases such as aggrecanases-1 and –2, which are also called a disintegrin and metalloproteinase with thrombospondin motif (ADAM-TS)4 and –5, specifically degrade aggrecan. ADAM-TS4 also cleaves fibronectin, which plays a pivotal role in tendon repair and the main tendon matrix proteoglycan, decorin (Jones et al., 2006). ADAM-TS activity can be inhibited by TIMP3 (Jones et al., 2006). Increased MMP13 expression was found in rotator cuff tendon tears (Lo et al., 2004) as well as in a rabbit model of flexor tendon injury (Berglund et al., 2007). Meanwhile various MMPs, among them MMP1, -2, -3, -7, -9, -10, -13, -19, -23, -25 and ADAM-TS1, -8, -12, have been demonstrated in tendon (Tsuzaki et al., 2003b; Pufe et al., 2005; Jones et al., 2006; Qi et al., 2006a). Additionally, the natural MMP-inhibitors TIMP1–4 have been detected in tendon (Jones et al., 2006). The expression profile differed clearly between healthy, degenerative and ruptured tendons with lower levels of MMPs3, -10, TIMP3 and higher levels of ADAM12, MMP23 in painful compared with normal tendons. Lower levels of MMPs3, -7, TIMPs2, -3 and -4 and higher levels of ADAMs8, -12, MMPs1, -9, -19 and -25, and TIMP1 were evident in ruptured compared with normal tendons (Lo et al., 2004; Jones et al., 2006). MMP1 showed the greatest difference between ruptured and normal tendons suggesting a high level of collagen degradation by this enzyme (Jones et al., 2006). MMP19 cleaves nidogen 1, whose fragments are inhibitors of angiogenesis (Jones et al., 2006). An increase in MMPs and the resulting degradation of the ECM has also been implicated in the pathogenesis of tendinopathy (Arnoczky et al., 2007b). MMPs were up-regulated by TNFα, IL-1β and VEGF in tendon (Archambault et al., 2002a; Tsuzaki et al., 2003b; Thampatty et al., 2007; John et al., 2010). Cytokine IL-1β-mediated up-regulation of MMPs could be enhanced by tenotoxic agents such as ciprofloxacin (Corps et al., 2002) and could be inhibited by dietary phytochemicals such as epigallocatechin gallate, probably by inhibiting the stress-activated protein kinase/c-Jun NH_2-terminal kinase (JNK/SAP) pathway (Corps et al., 2004). Heat stress of equine tenocytes as well as treatment with TNFα and IL-1β induced MMP9 expression (Hosaka et al., 2006). The increase in MMPs (MMP1 and MMP3 expression) was more pronounced when IL-1β was combined with a mechanostimulation (Archambault et al., 2002a). Additionally, fluid flow stress induced IL-1β gene expression (Archambault et al., 2002b). Stretching stimulated MMP expression in rabbit tenocytes (Archambault et al., 2002a). To sustain, mechanical forces require adequate adaption of the tendon ECM, and hence, ECM remodeling, triggered by the MMPs. These processes can be accompanied by neo-angiogenesis triggered by an enhanced VEGF expression in tendon. TIMPs, the tissue-specific MMP inhibitors were down-regulated by VEGF in tendon (Pufe et al., 2005). TIMP1 and -2 mRNA were also detected in human flexor tendon cells, but both factors were rather constitutively expressed as reported by Tsuzaki et al. (2003b). On the contrary,

stress deprivation of tendons leads to MMP induction (Arnoczky et al., 2007b). Tendinitis and tenosynovitis often arise as sequelae of arthritis such as RA: under these conditions, Jain et al. (2002), demonstrated that cytokine inhibition using a TNFα inhibitor could significantly reduce the amount of MMPs in tendon, and hence, tendon damage.

Tenocyte apoptosis and cytokines

The increased cell loss by apoptosis seriously affects the homeostasis of hypocellular tissues such as tendon, and hence, contributes to various tendon disorders. In the early phase of tendon healing (up to the third day in the inflammatory phase), an increased cell death rate was observed in tendon, which declined later. Cell death might be induced by pro-inflammatory cytokines and other catabolic factors (Wu et al., 2010). Stress deprivation, e.g. the absence of regular tension in tendon, also led to rat tenocytes apoptosis (Egerbacher et al., 2008). Prolonged elevated temperatures in tendon, which can occur during tendon overuse, raised the tenocyte death rate, whereby short periods of hyperthermia were found unproblematic and had no detrimental effects on equine tenocytes (Sharma & Maffulli, 2005; Hosaka et al., 2005b, 2006). Hosaka and colleagues, observed an enhanced expression of TNFα and caspase-3 activation in inflamed equine tendons indicating a pro-apoptotic effect of this cytokine. TNFα seemed to be involved in the occurrence of tendinitis and tendon degeneration (Hosaka et al., 2005a ,b). TNFα was able to induce apoptosis under particular conditions as reported for other connective tissue cell types (Fischer et al., 2000; Aizawa et al., 2001). Up to now, the direct effect of TNFα on tenocytes survival has been only partially investigated. However, Machner and colleagues reported, that TNFα had an inhibitory effect on pro-apoptotic Fas ligand expression in human tenocytes of tendons, which derived from the neighborhood of osteoarthritic joints. In tenocytes derived from healthy patients TNFα had no inhibitory effect on Fas expression (Machner et al., 2003). In human tenocyte cultures, the stimulation with TNFα alone was not sufficient to induce apoptosis (unpublished own results). Altogether, these facts indicate that environmental, also probably species-dependent conditions and particular co-stimuli, are necessary to provoke pro- or anti-apoptotic effects of TNFα in tendon.

Nitric oxide (NO)

NO is an important messenger molecule in physiological processes. However, it is also known to contribute to apoptosis in inflammatory cell types such as monocytes (Natal et al., 2008), or in connective tissue cells e.g. chondrocytes under inflammatory conditions such as osteoarthritis (Maneiro et al., 2005; Wu et al., 2007; Abramson, 2008). Elevated inducible nitric oxide synthase (NOS) expression seemed to be related to the increased apoptosis observed in Achilles tendinopathy (Pearce et al., 2009). On the contrary, NO generated by NOS is involved in tendon healing (Murrell, 2007). NO mediates angiogenesis *in vivo* and endothelial cell growth and migration *in vitro* (Ziche et al., 1994). Collagen synthesis and organization are improved by NO in healing tendons (Xia et al., 2006; Murrell, 2007). Accordingly, the synthesis of other ECM proteins is also enhanced by NOS such as decorin, biglycan, laminin and of the MMP10 as shown by the NOS overexpression in tenocytes (Molloy et al., 2006). The interrelation of cytokines with NOS activities and NO release is up to now only incompletely elucidated in tendon.

Mechanotransduction: influence on cytokine expression in tendon

Mechanoresponsiveness is a crucial feature of tendon. Adequate mechanostimuli play an essential role in tendon homeostasis, regular function, tenocyte survival and tendon healing (Arnoczky et al., 2007a; Egerbacher et al., 2008; Eliasson et al., 2009). Over-mechanostimulation of tendon and tenocytes leads to cytokine release such as IL-1β and VEGF (Tsuzaki et al., 2003a; Petersen et al., 2004b; Sun et al., 2008). IL-6 expression was induced during tendon exercise (Skutek et al., 2001; Kjaer et al., 2006). Stress deprivation and absence of mechanostimuli induced cytokine overexpression (particularly that of IL-1β, TNFα and TGFβ) and mechanical deterioration of the tissue (Uchida et al., 2005). Ruptured tendons revealed less TNFα expression when naturally loaded during the healing process compared with unloaded ruptured tendons in a rat Achilles tendon healing model (Eliasson et al., 2009). Natural loading improves tendon healing. However, the mechanotransduction pathways in tendon and their obvious interrelation with pro-inflammatory cytokines are mainly unclear. Whether the divergent mechanostimulation protocols used for cultured tenocytes or explants might fully allow the direct comparison with the *in vivo* conditions still remains questionable and further efforts should be undertaken to establish and characterize these *in vitro* tendon models.

Interrelation of complement and cytokines and their putative aspects in healing

Tissue trauma is well known to induce elevated complement activity as shown in other tissues.

Complement activation can lead to cell apoptosis. Complement activity is induced by apoptotic cells, ECM fragments and neoepitopes, which arise during tissue damage (Fishelson et al., 2001; Sjoberg et al., 2005). Key complement cleavage fragments are C3a and more downstream C5a, which bind to the so-called anaphylatoxine receptors C3aR and C5aR (CD88). Cells possess particular cell surface proteins, which protect them from tissue-intrinsic complement activity such as the complement regulatory proteins (CRPs) CD35 (CR1, complement receptor-1), CD46 (MCP, membrane co-factor protein), CD55 (decay accelerating factor: DAF) and CD59 (protectin). CD59 is the most downstream protein as it inhibits C9 polymerization and thereby the formation of the MAC and hence preventing complement-mediated lysis. Complement activity, which is up to now more thoroughly studied in other tissues, might also play a role in traumatic musculoskeletal tissue injury (Amsterdam et al., 1995; John et al., 2007b) and probably in tendon rupture. Up-regulation of complement activity by pro-inflammatory cytokines such as TNFα in other connective tissue cell types has already been reported by several authors (Davies et al., 1994; Onuma et al., 2002; Hyc et al., 2003). Regulation of CPRs and anaphylatoxine receptors in tendon tissues was demonstrated recently (unpublished own results) whereby TNFα induced the up-regulation of C3aR and IL-6 had an inhibitory effect on the expression of some CRPs. Hence, it can be hypothesized that distinct cytokines may well also modulate the sensitivity of tenocytes to complement-mediated cell lysis. Opsonization of damaged tissue fragments for phagocytosis by leukocytes by complement split fragments occurs in response to tendon rupture. The interrelation of cytokines, other factors and complement activity has to be studied in tendon more thoroughly to define its true role in tendon rupture and healing.

In vitro vs. *in vivo* studies using animal- and human-derived tenocytes to assess tendon healing

Tenocytes are essential for the full regeneration of injured tendons. Hence, cultured tenocytes are often used as a tool to study *in vitro* the specific effects of diverse cytokines, which might play a role during tendon healing (Tsuzaki et al., 2003b; Courneya et al., 2010; John et al., 2010). Up to now, many cytokine-mediated effects that might contribute to or interfere with tendon healing could only be demonstrated *in vitro*. An example is the stimulatory influence of the pro-inflammatory cytokines IL-1β and TNFα on tenocytes elastin gene expression, which has so far only been reported in cultured human tenocytes (Qi et al., 2006a; John et al., 2010), whereby it is still unclear whether increased amounts of functional elastin fibers can be formed *in vivo* in ruptured tendons in the presence of these cytokines. Several studies revealed some agreement between *in vivo* and *in vitro* results much regard to cytokine effects in tendon and cultured tenocytes as shown for the interrelation between the IL-1β and the MMP13 expression in the rat model (Sun et al., 2008). Additionally, VEGF was up-regulated by hypoxia and growth factors in cultured rat tenocytes (Pufe et al., 2001; Petersen et al., 2003c) and VEGF expression could also be observed in ruptured tendons or during tendon healing in animal-derived (sheep, dog and rat) (Boyer et al., 2001; Petersen et al., 2003a ,d) and human tendons (Pufe et al., 2001). Under these conditions, the presence of hypoxia and growth factors can be assumed.

Moreover, it was recently shown that the expression profile and proliferation capacity of cultured rat tenocytes derived from healthy control tissues differed from that of tenocytes isolated from ruptured tendons (Fu et al., 2008). Hence, Fu et al., suggested to prefer tenocytes isolated from healing tendons as a more realistic *in vitro* model to study tendon healing (Fu et al., 2008).

Differentiation-associated ECM components, and also other factors such as complement components were expressed to a lesser extend *in vitro* compared with native tendon tissue (Stoll et al., 2010). Mostly, unknown systemic factors regulate tenocyte expression profile, which are absent *in vitro*. Furthermore, it has to be considered that the majority of reported data are derived from studies with animal derived-tenocytes e.g. from the horse (Hosaka et al., 2004; Hosaka et al., 2006), rabbit (Bernard-Beaubois et al., 1997) or rat (Egerbacher et al., 2008; Eliasson et al., 2009). Results of the research studies using human (Tsuzaki et al., 2003b) and animal-derived tenocytes (Archambault et al., 2002a) seem to be mostly in agreement as shown for the interplay between IL-1β and MMPs. However, detailed analyses of species-dependent differences in the cytokine expression and regulation profiles as well as of tenocytes susceptibility to cytokines are still lacking.

In conclusion, it is only realistic to study the complex interaction among intrinsic tenocytes, extrinsic fibroblasts and blood-derived inflammatory cells via distinct cytokines in tendon healing using *in vivo* approaches. Hence, *in vitro* and *in vivo* studies should be intimately combined.

Conclusions

After tendon trauma, exogenous inflammatory cytokines are released at the tissue level from immigrated leukocytes, which induce a pro-inflammatory

response by activating the tenocytes as miscellaneous and sensitive players in the metabolically slow active tissue tendon (Tsuzaki et al., 2003b). At the cell level, these pro-inflammatory cytokines highly activate tenocytes to produce further pro-inflammatory mediators initiating auto- and paracrinic amplification loops. Subsequently and time-delayed, immunoregulatory mediators, cytokines and inhibitory factors are released by tenocytes representing an intrinsic counter-regulatory and compensatory response observable at the cell level. The release of degradative enzymes and the suppression of ECM synthesis are also evident; however, the production of some essential ECM components such as elastin and the angiogenic growth factor VEGF is up-regulated in tenocytes under the influence of pro-inflammatory cytokines. Additionally, cell stiffness is modulated by these cytokines. Together with mainly unknown costimuli, cytokines such as TNFα also seem to promote tenocyte apoptosis. These facts underline the putative multivalent function of pro-inflammatory cytokines in injured and healthy tendon. It is probable that pro-inflammatory cytokines are essential regulators of tendon healing simultaneously in a positive and negative manner acting as a regulatory link between several catabolic and anabolic systems. The application of cytokine inhibitors and anabolic cytokines e.g. by using gene therapeutic strategies has been proposed to support tendon healing. In this context, the dynamic and diverse involvement of multiple cytokines in overlapping phases of tendon healing, in mechanotransduction and in adaption of tendon to altered biomechanical conditions *post trauma* or tendon exercise has to be further considered. The knowledge should be used to further develop immunoregulatory strategies to improve tendon healing such as the use of anti-inflammatory cytokines (Courneya et al., 2010) or anti-angiogenesis agents such as bevacizumab (avastin) (Mizote et al., 2010; O'Neill et al., 2010).

Key words: tendon disorder, tenocyte, angiogenesis, healing.

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