Histol Histopathol (2013) 28: 1537-1546
DOI: 10.14670/HH-28.1537

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

Tendinopathy and its treatment with platelet-rich plasma (PRP)

Dapeng Jiang and James H-C. Wang
MechanoBiology Laboratory, Department of Orthopaedic Surgery,
University of Pittsburgh School of Medicine, BST,Pittsburgh, PA, USA

Summary. This article has two goals. First, it reviews studies on tendinopathy in the literature while highlighting the following points: a) tendinopathy refers to a spectrum of tendon disorders with multiple facets of "tissue phenotypes," and b) mechanical loading is a major factor that contributes to the development of tendinopathy by inducing the aberrant differentiation of tendon stem/progenitor cells into non-tenocyte cell lineages. Second, the current treatments of tendinopathy with platelet-rich plasma (PRP) are briefly described, issues related to PRP treatment in clinics are highlighted, and the needs for basic science research on clinical usage of PRP for tendinopathy treatment are discussed.

Key words: Tendinopathy, Tenocytes, Tendon stem cells, Platelet-rich plasma

Introduction

The major function of tendons is to transmit muscular forces to bone, thus enabling body movements. Tendons consist predominantly of collagen and small amounts of matrix components such as proteoglycans. In tendons, tenocytes are the major resident cells that are responsible for the maintenance and repair of tendons. Recently, a new type of tendon cells, referred to as tendon stem/progenitor cells (TSCs), was identified in human and animal tendons (Bi et al., 2007; Rui et al., 2010; Zhang and Wang, 2010a). These adult stem cells are capable of self-renewal and differentiation into multiple cell types, including adipocytes, chondrocytes, and osteocytes, in addition to tenocytes (Zhang and Wang, 2010a).

Because tendons such as patellar and Achilles tendons are constantly subject to large loads, they are frequently injured. Tendinopathy, a chronic tendon injury, is particularly common in recreational and competitive athletes. With an increase in sports participation in recent years, the incidence of tendinopathy has also risen. In elite athletes, the prevalence of tendinopathy can be as high as 45% (Knobloch et al., 2008).

Once injured, tendons are repaired slowly, which is generally attributed to poor vascularization, low oxygen consumption, low metabolic rate in tendons, and excessive loads on tendons (Amiel et al., 1984).

To date, it remains a significant challenge to restore the normal structure and function to injured tendons in the areas of orthopaedic surgery and sports medicine (Almekinders et al., 2003; Krapf et al., 2012; Longo et al., 2009). Thus, there is an urgent need to better understand the mechanisms of tendinopathy and improve its treatment.

Research in tendon biology in recent years has provided considerable new information about the pathogenesis of tendinopathy. In addition, platelet-rich plasma (PRP) has emerged as a promising treatment option for tendinopathy and is being widely used in clinics. However, the efficacy of PRP treatment for tendinopathy is highly controversial, and current clinical practices using PRP are far ahead of the basic science studies on PRP treatments. This review will discuss recent advancements in the study of tendinopathy and PRP treatments for it. Future research to improve PRP treatment for tendinopathy is also suggested.

Histopathological features of tendinopathy

On gross inspection, a tendinopathic tendon is gray or brown, in contrast to the glistening appearance of a normal tendon. Tendinopathic tendons are also soft, thin, and amorphous to the naked eye (Khan et al., 1999). On ultrasonographic images, tendinopathic tendons appear to be thickening with edema (Longo et al., 2009).

Histopathologically, increased vascularity and randomly oriented vessels can be seen in tendons with

Offprint requests to: James H-C. Wang, PhD, 210 Lothrop Street, BST, E1640, Pittsburgh, PA 15213, USA. e-mail: wanghc@pitt.edu

tendinopathic symptoms. Such hyper-vascularity might elicit pain and alter the mechanical properties of tendons. Microscopy also revealed presence of discontinuous and disorganized collagen fibers that lack reflectivity under polarized light (Silva et al., 2011). This is in contrast to the hierarchical arrangement of tightly-packed, parallel bundles of collagen fibers in normal tendons. Interstitial gaps representing microtears were also more intense in degenerative tendinopathy or tendinosis (Silva et al., 2011). These collagen microtears may also be surrounded by erythrocytes, fibrin, and fibronectin deposits (Longo et al., 2009).

In addition, accumulations of lipid cells, mucoid patches between fragile collagen fibers, and tissue calcification are commonly seen in degenerative tendinopathic tendons (Kannus and Jozsa, 1991; Khan et al., 1999; Cetti et al., 2003; Buck et al., 2009). These findings suggest that tendinopathy may result from a combination of micro-traumatic injuries, regeneration, and chronic degeneration, supporting the argument that tendinopathy is a spectrum of tendon disorders resulting from multiple etiologic factors. The argument that tendinopathy is a spectrum of tendon disorder implies that tendinopathy can "locate" anywhere between two extreme "conditions:" healthy/normal tendon and abnormal tendon. Therefore, in theory there are "infinite" numbers of tendinopathy conditions. This may be one of the most important reasons why tendinopathy cannot be treated effectively with any one individual treatment.

In addition to the histo-morphological changes in tendinopathic tendons described above, an imbalance in the synthesis and degradation of the tendon matrix in tendinopathy eventually leads to structural deterioration and degeneration of tendons. For example, degenerated tendons may exhibit a significant decrease in the total collagen content and an increased proportion of type III collagen relative to type I collagen (Birch et al., 1998). These collagenous changes may accumulate with age and substantially weaken tendon structure. Further, matrix metalloproteinases (MMPs) and their inhibitors are also important for the turnover of tendon proteins during regeneration. These are capable of cleaving type I collagen molecules in the extracellular environment and changes in their expression could lead to the alteration of tendon homeostasis. Elevated levels of MMPs 1, 9, 19, and 25 were found in degenerated tendons, whereas the tissue inhibitor of MMP-3 was lower in tendinopathic tendons (Jones et al., 2006). Therefore, these degenerative enzymes and their inhibitors may also be involved in the development of tendinopathy (Riley, 2005; Jones et al., 2006).

Many studies have reported the absence of inflammatory cells in tendinopathic tendons (Alfredson and Lorentzon, 2002; Khan et al., 2002; Silva et al., 2011). However, acute inflammation at the site of rupture was detected in all 60 case studies with spontaneously ruptured Achilles tendons, and the presence of neutrophils was also confirmed with immuno-histochemical staining (Cetti et al., 2003). In addition, the numbers of B-lymphocytes, T-lymphocytes, and macrophages were significantly higher in Achilles tendon samples with tendinopathy (Schubert et al., 2005).

When these inflammatory cells become activated at the site of tendon injury, they may release toxic, non-specific, reactive oxygen species and proteolytic enzymes (Diegelmann and Evans, 2004; Martin and Leibovich, 2005) and, as a result, damage tissues. Moreover, higher levels of COX-2 and prostaglandin E2 (PGE_2) were also found in tendon tissues and cells harvested from tendinopathic tendons (Fu et al., 2002). COX (COX-1 and COX-2) is responsible for the increased PGE_2 production in tendon fibroblasts after cyclic mechanical stretching (Wang et al., 2003). As a major mediator of acute inflammation, injection of PGE_2 into a healthy tendon can induce degenerative changes within the animal tendon (Khan et al., 2005); thus, high levels of PGE_2 production in tendons under excessive mechanical loading conditions may represent a critical step in the development of tendinopathy (Zhang and Wang, 2010d).

Currently, the mechanisms which lead to the clinical symptoms (e.g. pain) of tendinopathy are not completely clear. Several studies also suggest the involvement of neuro-chemical mediators in causing tendinopathy (Bjur et al., 2008a,b; Scott et al., 2008; Danielson, 2009). This hypothesis is based on findings that show the production of neuronal signaling molecules in tendon cells obtained from patients with tendinopathy. In particular, previous studies have shown that chronic tendinopathy results in a significant increase in substance P (SP) positive nerve fibers (Andersson et al., 2008; Backman et al., 2011). SP can stimulate angiogenesis and tenocyte proliferation during the tendon healing process (Burssens et al., 2005). In addition, higher levels of the neurotransmitter glutamate were present in subjects with chronic painful Achilles tendons (Lian et al., 2006). Thus, both SP and glutamate might be related to pain sensation in tendinopathic tendons. Further research is necessary to determine whether there is a causative relationship between these neuro-chemical mediators and tendinopathy.

The mechanisms for the development of tendinopathy

Several theories regarding the developmental mechanisms of tendinopathy have been advocated (Fenwick et al., 2002; Bjur et al., 2008a; Danielson, 2009; Wang et al., 2006). For example, the vascular insufficiency theory considers that degeneration or rupture of tendons is associated with hypo-vascularity within certain tendons (Fenwick et al., 2002). Such decrease in circulation can be caused by multiple factors including aging, vascular diseases, or trauma, leading to the disintegration of collagen bundles (Fenwick et al., 2002; Riley, 2004). Since tendons, in general, are

sparsely vascularized tissues, hypoxia may be a potential factor leading to tendon degeneration and subsequent injury (Birch et al., 1997). This theory provides a good explanation for why certain types of tendons, such as Achilles tendons, posterior tibial tendons, and rotator cuff tendons, are particularly vulnerable to the occurrence of tendinopathy because of their low vascular make-up in specific areas (Cofield, 1985; Frey et al., 1990; Ahmed et al., 1998).

Perhaps the most accepted theory for the pathogenesis of tendinopathy is mechanical strain theory, where mechanical loading is linked to tendinopathy in a cause-effect relationship. The strength of this theory is that it explains why athletes have such a high incidence of tendinopathy: they are simply subjected to excessive mechanical loading. Animal model studies showed that repetitive mechanical loading of tendons causes tendon inflammation and destruction via mechanical damage and biochemical mediators (Barbe et al., 2003; Wang et al., 2006). Tendons lose their wavy configuration when they are stretched more than 2% and can be stretched up to 4% before microscopic collagen fiber ruptures appear. Stretching to 8% results in macroscopic tears, and complete tendon rupture occurs at approximately 12% strain (Butler et al., 1978; Ker, 1981). However, damage to the tendon can occur by cumulative micro-trauma even if it is repetitively loaded with a small mechanical strain (Nakama et al., 2005). Tendon micro-trauma can also result from a non-uniform stress occurring within a tendon. While tendons are mainly subjected to tensile loads, compressive and shear forces also act on some tendons or some part of tendons (Almekinders et al., 2003; Wang et al., 2006). Repetitive compressive overloading can produce overuse injuries in compressed tendons representing an additional mechanism that causes tendon injury.

Mechanical loading not only produces mechanical damages to tendon matrices, but also can cause abnormal biological responses in tendon cells, thus leading to patho-physiological changes in tendons. Therefore, the mechanical strain theory may be properly referred to as the mechanobiological theory of tendinopathy. There is abundant evidence to support this theory. For example, the stimulation of repetitive tendon overloading can lead to altered MMP expression and apoptosis in tenocytes, followed by tendon degeneration (Lyman et al., 2004; Lavagnino and Arnozky 2005; Lavagnino et al., 2005, 2006). MMPs production may weaken the tendon and put more of the extracellular matrix at risk for further damage during subsequent loading. Strikingly, even when mechanical loading is no longer present, its effects remain as tenocytes isolated from the site of tendinopathy produce abnormally higher amounts of collagen type III (Maffulli et al., 2000). Also, because significantly higher numbers of apoptotic cells were found in ruptured rotator cuff specimens (Yuan et al., 2002) and tendinopathic Achilles tendons (Pearce et al., 2009), it has been suggested that short-term mechanical loading with a high strain may cause tendon cells to undergo apoptosis and contribute to tendon degeneration (Scott et al., 2005). Mechanical stretching of tendon fibroblasts have been shown to result in the activation of c-Jun N-terminal kinase (JNK), which in turn initiates the apoptotic cascade (Skutek et al., 2003) that may cause degeneration often seen in tendinopathic tendons (Yuan et al., 2002).

In addition, repetitive mechanical loading of human tenocytes *in vitro* increases the production of PGE_2 and leukotriene B_4 (LTB_4) (Li et al., 2004; Lavagnino and Lyman). High levels of PGE_2 can induce profound degenerative changes in the tendon matrix and lead to the formation of non-tendinous tissues in the tendon (Khan et al., 2005; Zhang and Wang, 2010d). On the other hand, over-production of leukotrienes, including LTB_4, induces neutrophil infiltration and activation, resulting in tissue swelling, as seen in tendons with tendinopathy (Denzlinger, 1996).

While tenocytes are the main resident cells in tendons, TSCs represent a new type of tendon cells in human and animal tendons (Bi et al., 2007; Rui et al., 2010; Zhang and Wang, 2010a; Mienaltowski et al., 2013). TSCs can self-renew and differentiate into tenocytes under normal physiological conditions (Zhang and Wang, 2010a); therefore, these tendon cells play a vital role in the maintenance of healthy tendons and the repair of injured tendons. TSCs also respond to mechanical loading in a loading magnitude-dependent manner: under low mechanical loading, TSCs differentiate towards tenocytes, whereas under high mechanical loading, in addition to differentiating into tenocytes, they also differentiate into non-tenocytes, as evidenced by the upregulation of genes associated with adipocytes, chondrocytes, and osteoblasts. These cells are responsible for lipid accumulation, mucoid degeneration, and ectopic ossification *in vivo*, respectively. Therefore, TSCs may be responsible for the development of degenerative tendinopathy as a result of aberrant differentiation in response to excessive mechanical loading placed on tendons (Zhang and Wang, 2010b,d). Moreover, one mediator that is responsible for the TSC-based mechanism for tendinopathy may be PGE_2, as high levels of PGE_2 are produced when high mechanical loading is placed on tendons triggering TSC differentiation into non-tenocytes (Zhang and Wang, 2010d). *In vivo* animal model studies have also demonstrated the high expression of cartilage-associated genes in rat supraspinatous tendons after intensive mechanical loading (Archambault et al., 2007). Moreover, accumulations of proteoglycans and "round tenocytes" are detected in chronically-loaded tendons (Scott et al., 2007); a likely explanation for these findings is that under chronic mechanical loading conditions, TSCs differentiate into active chondrocytes that are round and produce abundant proteoglycans in the loaded tendons. The intracellular signaling mechanisms leading to this non-tenocyte differentiation of TSCs may involve the

Wnt5a-RhoA pathway (Shi et al., 2012).

It should be pointed out that many intrinsic factors, including genetics, gender, and age, may also contribute to the development of tendinopathy. One of the major intrinsic factors may be genetic characteristics. Individuals with the blood type O appeared to have an increased risk of tendon rupture (Kujala et al., 1992) suggesting a genetic linkage between the ABO blood groups and the molecular structure of the tissue in Achilles tendons. One study suggested that the COL5A1 BstUI restriction fragment length polymorphism is associated with chronic Achilles tendinopathy (Mokone et al., 2006). Also, persons expressing variants of the tenascin-C gene with 12 and/or 14 guanine-thymine repeats appear to have a 6-fold higher risk of developing Achilles tendon injuries (Mokone et al., 2005). Gender is also a contributor to tendinopathy, and it was found that tendinopathies are more prevalent in men than in women (Cook et al., 2000). These findings suggest that some persons could be genetically predisposed to the development of tendinopathy. In addition, age has been considered as another factor that may predispose athletes to tendon lesions, and the prevalence of tendinopathy seems to increase with age in the general population (Maffulli and Kader, 2002).

Treatment of tendinopathy with platelet-rich plasma (PRP)

Tendinopathy is difficult to manage; even when early diagnosis is combined with appropriate management, rehabilitation of tendinopathy takes months (Maffulli and Longo, 2008b). Conservative or physical therapies are generally accepted as the first line approach for managing tendinopathy (de Jonge et al., 2010; Schofer et al., 2009). Shock wave treatment is reported to be an effective method to treat Achilles tendinopathy (Fridman et al., 2008), and the effectiveness of eccentric training on chronic Achilles tendinopathy has been shown in clinical studies (Verrall et al., 2011). However, many of the therapeutic treatment options lack a rigorous scientific justification (Longo et al., 2009; Maffulli and Longo, 2008b).Therefore, it is difficult to select the best evidence-based management because few randomized prospective, placebo-controlled trials exist (Maffulli and Longo, 2008a).

Non-steroid anti-inflammatory drugs (NSAIDs) are frequently used to treat tendinopathy although they reduce only the symptoms associated with tendinopathy such as tendon inflammation and associated pain. The administration of NSAIDs may in fact have a detrimental effect on the healing of tendons (Ferry et al., 2007). In addition, these drugs may have serious side effects, such as dyspepsia, abdominal discomfort, and even life-threatening gastric/duodenal bleeding and perforation (Wolfe et al., 1999). Therefore, the clinical use of NSAIDs is limited.

Corticosteroid injections are commonly used in the treatment of chronic tendon lesions. These are also used to reduce inflammation and pain in patients with tendinopathies. Inflammation is a vital component of the healing response and therefore, inhibiting this process may inhibit healing and reduce the tensile strength of tissues (Wong et al., 1996). Dexamethasone injection has been shown to cause aberrant differentiation of TSCs into non-tenocytes and result in the formation of non-tendinous tissues in tendons (Zhang et al., 2012). Therefore, in clinics dexamethasone should be used with caution for the treatment of tendon injury.

In recent years, PRP therapy has emerged as a promising treatment option for tendinopathy and has been widely used in orthopaedic/sports medicine. PRP is prepared from the patient's own blood and centrifuged to achieve a high concentration of platelets in a small volume of plasma. It is then injected at the site of injury or implanted as a gel during surgery. Platelets in PRP contain growth factors that are essential for the repair of injured tissues. Most of these growth factors, including PDGF, TGF-ß1, VEGF, and HGF, are also involved in tendon healing (Molloy et al., 2003; Hsu and Chang, 2004; Wang, 2006). Moreover, the growth factors/cytokines in PRP, which are in normal ratios and coordinated in spatial and temporal releases, can stimulate the expression of the matrix molecules and promote angiogenesis in healing tendons (Schnabel et al., 2007; de Mos et al., 2008). PRP also acts as a scaffold (or fibrin gel) on which cells can adhere and begin the process of repair (Foster et al., 2009). Finally, as a product from autologous blood, PRP has the minimal risk of disease transmission and antigenic reaction.

Because of these advantages, PRP has been widely used in clinics to treat injured tendons and ligaments and other musculoskeletal injuries. Many studies showed that PRP enhances the recovery of athletes with acute or chronic tendinopathy (Sanchez et al., 2007; Kon et al., 2009, 2011; Monto, 2012). After PRP treatment of Achilles tendon injuries, the recovery time before athletes could return to sporting activities also shortened (Sanchez et al., 2007). In general, after failure of previous conservative treatments multiple PRP injections are needed for the treatment of chronic tendinopathy (Filardo et al., 2010). In addition, PRP can reduce pain during the immediate post-operative period (Gaweda et al., 2010; de Almeida et al., 2012). Patients with chronic elbow tendinosis reported significantly reduced pain after treatment with PRP compared to before treatment (Mishra and Pavelko, 2006). A single injection of autologous PRP was able to reduce pain and increase function more significantly than corticosteroid injection in chronic lateral epicondylitis, and the improvements were sustained over a 2-year follow-up time (Gosens et al., 2011). These pain reduction mechanisms activated by PRP may be related to the fact that platelets can modulate tissue inflammation (Asfaha et al., 2007). Indeed, a recent *in vitro* study suggested the anti-inflammatory properties of PRP (El-Sharkawy et al., 2007). It was reported that PRP could diminish the

inflammatory effects of interleukin-1 beta (IL-1ß) on human osteoarthritic chondrocytes by inhibiting nuclear factor kappa-B activation (van Buul et al., 2011). Another study also linked the anti-inflammatory role of PRP to the presence of HGF in PRP preparations (Bendinelli et al., 2010). Taken together, it can be concluded that PRP offers an alternative treatment option for tendinopathy in patients who did not improve using conservative treatments.

However, the use of PRP for the treatment of tendinopathy is highly controversial. Some argue that the evidence to support the use of PRP injections for the treatment of chronic tendinopathy is limited (de Vos et al., 2010b; Park et al., 2012). This conclusion was drawn based on a double-blind, block-randomized, placebo-controlled trial on the clinical use of a PRP injection (de Vos et al., 2010b). A systematic review analyzed a large number of studies on the use of autologous growth factors, including PRP, and found no significant improvement in tendon function in patients with chronic tendinopathy compared to control groups (de Vos et al., 2010a). Another systematic review also found evidence that PRP is effective in the treatment of Achilles tendon ruptures, but demonstrated no beneficial effect on Achilles tendinopathy (Sadoghi et al., 2013).

This situation indicates a pressing need to determine the efficacy of PRP treatment on tendinopathy through basic science studies (Wang, 2006), especially given that clinical practices of PRP treatment are far ahead of its basic supporting science studies (Engebretsen et al., 2010; Del Buono et al., 2011). It also illustrates the complexity of human subject studies where many factors, including age, gender, disease history, and treatment history, can influence the clinical outcomes of PRP treatment. Also, human subject studies are limited by unavoidable subjective evaluation of PRP treatment effects, such as pain and functional scores from patients (de Jonge et al., 2011; de Vos et al., 2010b, 2011). These limitations of human subject studies for PRP may be best addressed by studying outcomes of this treatment on well-defined animal models of tendinopathy.

There are three major issues in the current use of PRP treatment for tendinopathy, which urgently need to be addressed in clinics. The first is the compositional variation of PRP preparations (Weibrich et al., 2005). In addition to enriched platelets, PRP preparations in general contain concentrated white blood cells (WBCs). These cells become activated at the site of injury and provide an antibiotic effect by releasing toxic, non-specific, reactive oxygen species and proteolytic enzymes (Diegelmann and Evans, 2004; Martin and Leibovich, 2005). This reaction could result in an inevitable damage to tissues. While the specific effects of WBCs-rich PRP on injured tissues have not been defined, delivery of concentrated WBCs along with PRP to the site of injury may hinder the healing response or amplify the release of catabolic, pro-inflammatory mediators such as IL-1ß and TNF-α (McCarrel and Fortier, 2009). Treatment of tendons with concentrated WBCs has also been shown to cause early tissue inflammation, fibrosis, and disrupted fiber structure (Dragoo et al., 2012), most likely because, in opposition to platelets, WBCs cause catabolic biological effects (Sundman et al., 2011). Thus, concentrated WBCs in PRP preparations represent a condition of abundant neutrophils in tendinopathic tendons, which are typically in a sterile condition. Moreover, these neutrophils interact with platelets to induce a hyperactive leukotactic response of circulating neutrophils toward the injury site; this results in even more of these cells present at the tendon's injury site (Andia et al., 2010), leading to the activation of oxidative and enzymatic processes that can worsen tendon tissue damage.

The second issue in PRP treatment for tendinopathy is that the dosage is not optimized. In most studies and clinical treatments of human subjects, the dosages of PRP used for injection were not even measured. Our *in vitro* study has shown that the effects of PRP treatment on TSCs are dosage-dependent (Zhang and Wang, 2010c). Also, PRP effects on tissue healing are largely due to growth factors released by the activated platelets (Marx et al., 1998), and the effects of growth factors on tissue healing are typically concentration-dependent (Batten et al., 1996).

The third issue in clinical PRP treatment is that the same PRP treatment regimen, mainly in the form of PRP injections, is applied to all "cases" of tendinopathy. As we have argued in this article, tendinopathy is not a single tendon disorder; rather, it is a spectrum of tendon disorders. Therefore, we believe that the “one-size-fits-all” approach, or PRP injections alone, may not work for all cases of tendinopathies, which can range from early stage, which is mainly inflammatory with damage to tendon matrices (Nakama et al., 2005), to advanced stage, which is mainly degenerative, with extensive formation of fatty tissues, cartilage-like tissues, and bone-like tissues (calcification), either alone or in combination with tendon lesions (Kannus and Jozsa, 1991). It is suggested that at the early stages, PRP can be effective, as it can exert anti-inflammatory action on affected tendons, as well as induce TSCs to differentiate into active tenocytes (Zhang and Wang, 2010c). PRP can also stimulate tenocytes to repair damaged tendon matrices; when applied to tendinopathic tendons at advanced stages (chronic tendinopathy), PRP may not be effective because, after all, PRP can only stimulate tendon cells (TSCs and tenocytes) to repair damaged tendon tissues. In the severely-degenerated tendon lesions characteristic of chronic tendinopathy, these resident cells are few in number, non-existent, or inactive. Consequently, the damaged and degenerated tendon matrices cannot be properly repaired. Under such circumstances, implantation of PRP gels may be a better option to optimize tendon healing (Chaudhury et al., 2013; de Almeida et al., 2012). Additionally, a recent study showed that non-activated PRP promotes angiogenesis more effectively than activated PRP (Pietramaggiori et al., 2010). Moreover, PRP activation

by collagen can induce the sustained release of growth factors (Harrison et al., 2011). Because of this, use of non-activated PRP may produce a better clinical outcome in the management of tendinopathy.

Concluding remarks

Tendinopathy is highly prevalent in both occupational and athletic settings. Despite its prevalence, the precise pathogenic mechanisms of tendinopathy remain poorly understood, and treatment of tendinopathy is difficult for both physicians and patients alike. Thus, there is an urgent need to better understand the mechanisms of tendinopathy in order to improve its treatment.

As briefly presented in this review, several theories have been proposed to explain the pathogenic mechanisms responsible for the development of tendinopathy. This situation reflects the complexity of tendinopathy, particularly regarding its multiple etiological factors and resulting diverse histopathological changes in affected tendons. Therefore, it is suggested that tendinopathy is not a single tendon disorder caused by a single factor; rather, it is likely a spectrum of tendon disorders resulting from multiple etiologic factors, which may be mechanical, neurological, genetic, or a combination of these.

In basic science research on tendons, one remarkable progress is the discovery of TSCs in recent years. This discovery is significant because it has implications for our ability to better understand the pathogenesis of tendinopathy and provides alternate options to treat the disease. Specifically, unlike tenocytes, the dominant resident cells in tendons, TSCs have multi-differential potential, meaning that in addition to differentiating into tenocytes under normal physiological conditions, they can undergo aberrant differentiation into non-tenocytes, including adipocytes, chondrocytes, and osteocytes (Zhang and Wang, 2010b). These aberrant differentiations may occur particularly during tendon injury such as excess or chronic mechanical load. This TSC-based mechanobiology theory of tendinopathy extends traditional mechanical strain theory of tendinopathy (Almekinders et al., 2002; Lyman et al., 2004), and can explain why tendinopathic tendons at advanced stages contain fatty, cartilage-like, and calcified tissues (Kannus and Jozsa, 1991).

In clinics, PRP has been widely used for the treatment of tendinopathy. The rationales for using PRP to treat tendinopathy seem obvious: a) it can serve as a reservoir of growth factors; b) it can be used as a natural conducive scaffold, c) it can potentially function as an anti-inflammatory "drug," and d) it can be obtained from an autologous source. As a result, PRP is expected to be an excellent tissue engineering therapy reagent for the repair or even regeneration of tendinopathic tendons over existing treatment strategies for tendon injuries. In spite of this, the efficacy of PRP treatment in enhancing the recovery of tendinopathic tendons has not been conclusively or consistently demonstrated in clinical trials. This situation highlights the inherent difficulty in conducting human subject studies, where many factors, including age, gender, disease and treatment history, and subjective evaluation of treatment effects, come into play. Thus, well-controlled basic science studies, particularly with animal models, that enable objective and comprehensive evaluation of PRP treatment effects should be pursued in order to better define the precise effects of PRP treatment on tendinopathy in clinics. Moreover, as discussed in this review, three major factors in PRP applications need to be urgently addressed in clinics: the optimal concentration of PRP for tendon repair; the role of white blood cells (WBCs) in the effects of PRP on tendon repair; and the consideration of disease stages of tendinopathy when the treatment is administrated in clinics. With more basic scientific research on the use of PRP to repair of injured tendons, the full promise of this new therapy for effective repair of injured tendons may be realized in the near future.

Acknowledgements. The funding support from NIH (AR049921, AR061395, and AR060920) for this work is gratefully acknowledged (JHW).

References

Ahmed I.M., Lagopoulos M., McConnell P., Soames R.W. and Sefton G.K. (1998). Blood supply of the Achilles tendon. J. Orthop. Res. 16, 591-596.

Alfredson H. and Lorentzon R. (2002). Chronic tendon pain: no signs of chemical inflammation but high concentrations of the neurotransmitter glutamate. Implications for treatment? Curr. Drug Targets 3, 43-54.

Almekinders L.C., Vellema J.H. and Weinhold P.S. (2002). Strain patterns in the patellar tendon and the implications for patellar tendinopathy. Knee Surg. Sports Traumatol. Arthrosc. 10, 2-5.

Almekinders L.C., Weinhold P.S. and Maffulli N. (2003). Compression etiology in tendinopathy. Clin. Sports Med. 22, 703-710.

Amiel D., Frank C., Harwood F., Fronek J. and Akeson W. (1984). Tendons and ligaments: a morphological and biochemical comparison. J. Orthop. Res. 1, 257-265.

Andersson G., Danielson P., Alfredson H. and Forsgren S. (2008). Presence of substance P and the neurokinin-1 receptor in tenocytes of the human Achilles tendon. Regul. Pept. 150, 81-87.

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

Archambault J.M., Jelinsky S.A., Lake S.P., Hill A.A., Glaser D.L. and Soslowsky L.J. (2007). Rat supraspinatus tendon expresses cartilage markers with overuse. J. Orthop. Res. 25, 617-624.

Asfaha S., Cenac N., Houle S., Altier C., Papez M.D., Nguyen C., Steinhoff M., Chapman K., Zamponi G.W. and Vergnolle N. (2007). Protease-activated receptor-4: a novel mechanism of inflammatory pain modulation. Br. J. Pharmacol. 150, 176-185.

Backman L.J., Andersson G., Wennstig G., Forsgren S. and Danielson P. (2011). Endogenous substance P production in the Achilles tendon increases with loading in an *in vivo* model of tendinopathy-peptidergic elevation preceding tendinosis-like tissue changes. J. Musculoskelet. Neuronal Interact. 11, 133-140.

Barbe M.F., Barr A.E., Gorzelany I., Amin M., Gaughan J.P. and Safadi F.F. (2003). Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. J. Orthop. Res. 21, 167-176.

Batten M.L., Hansen J.C. and Dahners L.E. (1996). Influence of dosage and timing of application of platelet-derived growth factor on early healing of the rat medial collateral ligament. J. Orthop. Res. 14, 736-741.

Bendinelli P., Matteucci E., Dogliotti G., Corsi M.M., Banfi G., Maroni P. and Desiderio M.A. (2010). Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-kappaB inhibition via HGF. J. Cell. Physiol. 225, 757-766.

Bi Y., Ehirchiou D., Kilts T.M., Inkson C.A., Embree M.C., Sonoyama W., Li L., Leet A.I., Seo B.M., Zhang L., Shi S. and Young M.F. (2007). Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat. Med. 13, 1219-1227.

Birch H.L., Rutter G.A. and Goodship A.E. (1997). Oxidative energy metabolism in equine tendon cells. Res. Vet. Sci. 62, 93-97.

Birch H.L., Bailey A.J. and Goodship A.E. (1998). Macroscopic 'degeneration' of equine superficial digital flexor tendon is accompanied by a change in extracellular matrix composition. Equine Vet. J. 30, 534-539.

Bjur D., Danielson P., Alfredson H. and Forsgren S. (2008a). Immunohistochemical and in situ hybridization observations favor a local catecholamine production in the human Achilles tendon. Histol. Histopathol. 23, 197-208.

Bjur D., Danielson P., Alfredson H. and Forsgren S. (2008b). Presence of a non-neuronal cholinergic system and occurrence of up- and down-regulation in expression of M2 muscarinic acetylcholine receptors: new aspects of importance regarding Achilles tendon tendinosis (tendinopathy). Cell Tissue Res. 331, 385-400.

Buck F.M., Grehn H., Hilbe M., Pfirrmann C.W., Manzanell S. and Hodler J. (2009). Degeneration of the long biceps tendon: comparison of MRI with gross anatomy and histology. Am. J. Roentgenol. 193, 1367-1375.

Burssens P., Steyaert A., Forsyth R., van Ovost E.J., Depaepe Y. and Verdonk R. (2005). Exogenously administered substance P and neutral endopeptidase inhibitors stimulate fibroblast proliferation, angiogenesis and collagen organization during Achilles tendon healing. Foot Ankle Int. 26, 832-839.

Butler D.L., Grood E.S., Noyes F.R. and Zernicke R.F. (1978). Biomechanics of ligaments and tendons. Exerc. Sport Sci. Rev. 6, 125-181.

Cetti R., Junge J. and Vyberg M. (2003). Spontaneous rupture of the Achilles tendon is preceded by widespread and bilateral tendon damage and ipsilateral inflammation: a clinical and histopathologic study of 60 patients. Acta Orthop. Scand. 74, 78-84.

Chaudhury S., de La Lama M., Adler R.S., Gulotta L.V., Skonieczki B., Chang A., Moley P., Cordasco F., Hannafin J. and Fealy S. (2013). Platelet-rich plasma for the treatment of lateral epicondylitis: sonographic assessment of tendon morphology and vascularity (pilot study). Skeletal Radiol. 42:91-97.

Cofield R.H. (1985). Rotator cuff disease of the shoulder. J. Bone Joint Surg. Am. 67, 974-979.

Cook J.L., Khan K.M., Kiss Z.S. and Griffiths L. (2000). Patellar tendinopathy in junior basketball players: a controlled clinical and ultrasonographic study of 268 patellar tendons in players aged 14-18 years. Scand. J. Med. Sci. Sports 10, 216-220.

Danielson P. (2009). Reviving the "biochemical" hypothesis for tendinopathy: new findings suggest the involvement of locally produced signal substances. Br. J. Sports Med. 43, 265-268.

de Almeida A.M., Demange M.K., Sobrado M.F., Rodrigues M.B., Pedrinelli A. and Hernandez A.J. (2012). Patellar tendon healing with platelet-rich plasma: a prospective randomized controlled trial. Am. J. Sports Med. 40, 1282-1288.

de Jonge S., de Vos R.J., Van Schie H.T., Verhaar J.A., Weir A. and Tol J.L. (2010). One-year follow-up of a randomised controlled trial on added splinting to eccentric exercises in chronic midportion Achilles tendinopathy. Br. J. Sports Med. 44, 673-677.

de Jonge S., de Vos R.J., Weir A., van Schie H.T., Bierma-Zeinstra S.M., Verhaar J.A., Weinans H. and Tol J.L. (2011). One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. Am. J. Sports Med. 39, 1623-1629.

de Mos M., van der Windt,A.E., Jahr H., van Schie H.T., Weinans H., Verhaar J.A. and van Osch G.J. (2008). Can platelet-rich plasma enhance tendon repair? A cell culture study. Am. J. Sports Med. 36, 1171-1178.

de Vos R.J., van Veldhoven P.L., Moen M.H., Weir A., Tol J.L. and Maffulli N. (2010a). Autologous growth factor injections in chronic tendinopathy: a systematic review. Br. Med. Bull. 95, 63-77.

de Vos R.J., Weir A., van Schie H.T., Bierma-Zeinstra S.M., Verhaar J.A., Weinans H. and Tol J.L. (2010b). Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA 303, 144-149.

de Vos R.J., Weir A., Tol J.L., Verhaar J.A., Weinans H. and van Schie H.T. (2011). No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. Br. J. Sports Med. 45, 387-392.

Del Buono A., Papalia R., Denaro V., Maccauro G. and Maffulli N. (2011). Platelet rich plasma and tendinopathy: state of the art. Int. J. Immunopathol. Pharmacol. 24, 79-83.

Denzlinger C. (1996). Biology and pathophysiology of leukotrienes. Crit. Rev. Oncol. Hematol. 23, 167-223.

Diegelmann R.F. and Evans M.C. (2004). Wound healing: an overview of acute, fibrotic and delayed healing. Front. Biosci. 9, 283-289.

Dragoo J.L., Braun H.J., Durham J.L., Ridley B.A., Odegaard J.I., Luong R. and Arnoczky S.P. (2012). Comparison of the acute inflammatory response of twocommercial platelet-rich plasma systems in healthy rabbit tendons. Am. J. Sports Med. 40, 1274-1281.

El-Sharkawy H., Kantarci A., Deady J., Hasturk H., Liu H., Alshahat M. and Van Dyke T.E. (2007). Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. J. Periodontol. 78, 661-669.

Engebretsen L., Steffen K., Alsousou J., Anitua E., Bachl N., Devilee R., Everts P., Hamilton B., Huard J., Jenoure P., Kelberine F., Kon E., Maffulli N., Matheson G., Mei-Dan O., Menetrey J., Philippon M., Randelli P., Schamasch P., Schwellnus M., Vernec A. and Verrall G. (2010). IOC consensus paper on the use of platelet-rich plasma in sports medicine. Br. J. Sports Med. 44, 1072-1081.

Fenwick S.A., Hazleman B.L. and Riley G.P. (2002). The vasculature and its role in the damaged and healing tendon. Arthritis Res. 4,

252-260.

Ferry S.T., Dahners L.E., Afshari H.M. and Weinhold P.S. (2007). The effects of common anti-inflammatory drugs on the healing rat patellar tendon. Am. J. Sports Med. 35, 1326-1333.

Filardo G., Kon E., Della Villa S., Vincentelli F., Fornasari P.M. and Marcacci M. (2010). Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int. Orthop. 34, 909-915.

Foster T.E., Puskas B.L., Mandelbaum B.R., Gerhardt M.B. and Rodeo S.A. (2009). Platelet-rich plasma: from basic science to clinical applications. Am. J. Sports Med. 37, 2259-2272.

Frey C., Shereff M. and Greenidge N. (1990). Vascularity of the posterior tibial tendon. J. Bone Joint Surg. Am. 72, 884-888.

Fridman R., Cain J.D., Weil L. Jr and Weil L. Sr (2008). Extracorporeal shockwave therapy for the treatment of Achilles tendinopathies: a prospective study. J. Am. Podiatr. Med. Assoc. 98, 466-468.

Fu S.C., Wang W., Pau H.M., Wong Y.P., Chan K.M. and Rolf C.G. (2002). Increased expression of transforming growth factor-beta1 in patellar tendinosis. Clin. Orthop. Relat. Res. 174-183.

Gaweda K., Tarczynska M. and Krzyzanowski W. (2010). Treatment of Achilles tendinopathy with platelet-rich plasma. Int. J. Sports Med. 31, 577-583.

Gosens T., Peerbooms J.C., van Laar W. and den Oudsten B.L. (2011). Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Am. J. Sports Med. 39, 1200-1208.

Harrison S., Vavken P., Kevy S., Jacobson M., Zurakowski D. and Murray M.M. (2011). Platelet activation by collagen provides sustained release of anabolic cytokines. Am. J. Sports Med. 39, 729-734.

Hsu C. and Chang J. (2004). Clinical implications of growth factors in flexor tendon wound healing. J. Hand Surg. Am. 29, 551-563.

Jones G.C., Corps A.N., Pennington C.J., Clark I.M., Edwards D.R., Bradley M.M., Hazleman, B.L. and Riley, G.P. (2006). Expression profiling of metalloproteinases and tissue inhibitors of metalloproteinases in normal and degenerate human achilles tendon. Arthritis Rheum. 54, 832-842.

Kannus P. and Jozsa L. (1991). Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J. Bone Joint Surg. Am. 73, 1507-1525.

Ker R.F. (1981). Dynamic tensile properties of the plantaris tendon of sheep (*Ovis aries*). J. Exp. Biol. 93, 283-302.

Khan K.M., Cook J.L., Bonar F., Harcourt P. and Astrom M. (1999). Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med. 27, 393-408.

Khan K.M., Cook J.L., Kannus P., Maffulli N. and Bonar S.F. (2002). Time to abandon the "tendinitis" myth. BMJ 324, 626-627.

Khan M.H., Li Z. and Wang J.H. (2005). Repeated exposure of tendon to prostaglandin-E2 leads to localized tendon degeneration. Clin. J. Sport Med. 15, 27-33.

Knobloch K., Yoon U. and Vogt P.M. (2008). Acute and overuse injuries correlated to hours of training in master running athletes. Foot Ankle Int. 29, 671-676.

Kon E., Filardo G., Delcogliano M., Presti M.L., Russo A., Bondi A., Di Martino A., Cenacchi A., Fornasari P.M. and Marcacci M. (2009). Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. Injury 40, 598-603.

Kon E., Filardo G., Di Martino A. and Marcacci M. (2011). Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use. Knee Surg. Sports Traumatol. Arthrosc. 19, 516-527.

Krapf D., Kaipel M. and Majewski M. (2012). Structural and biomechanical characteristics after early mobilization in an achilles tendon rupture model: operative versus nonoperative treatment. Orthopedics 35, e1383-1388.

Kujala U.M., Jarvinen M., Natri A., Lehto M., Nelimarkka O., Hurme M., Virta L. and Finne, J. (1992). ABO blood groups and musculoskeletal injuries. Injury 23, 131-133.

Lavagnino, M. and Arnoczky, S.P. (2005). In vitro alterations in cytoskeletal tensional homeostasis control gene expression in tendon cells. J. Orthop. Res. 23, 1211-1218.

Lavagnino M., Arnoczky S.P., Frank K. and Tian T. (2005). Collagen fibril diameter distribution does not reflect changes in the mechanical properties of in vitro stress-deprived tendons. J. Biomech. 38, 69-75.

Lavagnino M., Arnoczky S.P., Egerbacher M., Gardner K.L. and Burns M.E. (2006). Isolated fibrillar damage in tendons stimulates local collagenase mRNA expression and protein synthesis. J. Biomech. 39, 2355-2362.

Li Z., Yang G., Khan M., Stone D., Woo S.L. and Wang J.H. (2004). Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching. Am. J. Sports Med. 32, 435-440.

Lian O., Dahl J., Ackermann P.W., Frihagen F., Engebretsen L. and Bahr R. (2006). Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. Am. J. Sports Med. 34, 1801-1808.

Longo U.G., Ronga M. and Maffulli N. (2009). Achilles tendinopathy. Sports Med. Arthrosc. 17, 112-126.

Lyman J., Weinhold P.S. and Almekinders L.C. (2004). Strain behavior of the distal achilles tendon: implications for insertional achilles tendinopathy. Am. J. Sports Med. 32, 457-461.

Maffulli N. and Kader D. (2002). Tendinopathy of tendo achillis. J. Bone Joint Surg. Br. 84, 1-8.

Maffulli N. and Longo U.G. (2008a). Conservative management for tendinopathy: is there enough scientific evidence? Rheumatology (Oxford) 47, 390-391.

Maffulli N. and Longo U.G. (2008b). How do eccentric exercises work in tendinopathy? Rheumatology (Oxford) 47, 1444-1445.

Maffulli N., Ewen S.W., Waterston S.W., Reaper J. and Barrass V. (2000). Tenocytes from ruptured and tendinopathic achilles tendons produce greater quantities of type III collagen than tenocytes from normal achilles tendons. An in vitro model of human tendon healing. Am. J. Sports Med. 28, 499-505.

Martin P. and Leibovich S.J. (2005). Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol. 15, 599-607.

Marx R.E., Carlson E.R., Eichstaedt R.M., Schimmele S.R., Strauss J.E. and Georgeff K.R. (1998). Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 85, 638-646.

McCarrel T. and Fortier L. (2009). Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. J. Orthop. Res. 27, 1033-1042.

Mienaltowski M.J., Adams S.M. and Birk D.E. (2013). Regional differences in stem cell/progenitor cell populations from the mouse achilles tendon. Tissue Eng. Part A. 19, 199-210.

Mishra A. and Pavelko T. (2006). Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am. J. Sports Med. 34, 1774-

1778.
Mokone G.G., Gajjar M., September A.V., Schwellnus M.P., Greenberg J., Noakes T.D. and Collins M. (2005). The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with achilles tendon injuries. Am. J. Sports Med. 33, 1016-1021.
Mokone G.G., Schwellnus M.P., Noakes T.D. and Collins M. (2006). The COL5A1 gene and Achilles tendon pathology. Scand. J. Med. Sci. Sports 16, 19-26.
Molloy T., Wang Y. and Murrell G. (2003). The roles of growth factors in tendon and ligament healing. Sports Med. 33, 381-394.
Monto R.R. (2012). Platelet rich plasma treatment for chronic Achilles tendinosis. Foot Ankle Int. 33, 379-385.
Nakama L.H., King K.B., Abrahamsson S. and Rempel D.M. (2005). Evidence of tendon microtears due to cyclical loading in an in vivo tendinopathy model. J. Orthop. Res. 23, 1199-1205.
Park Y.G., Han S.B., Song S.J., Kim T.J. and Ha C.W. (2012). Platelet-rich plasma therapy for knee joint problems: review of the literature, current practice and legal perspectives in Korea. Knee Surg. Relat. Res. 24, 70-78.
Pearce C.J., Ismail M. and Calder J.D. (2009). Is apoptosis the cause of noninsertional achilles tendinopathy? Am. J. Sports Med. 37, 2440-2444.
Pietramaggiori G., Scherer S.S., Mathews J.C., Gennaoui T., Lancerotto L., Ragno G., Valeri, C.R. and Orgill, D.P. (2010). Quiescent platelets stimulate angiogenesis and diabetic wound repair. J. Surg. Res. 160, 169-177.
Riley G. (2004). The pathogenesis of tendinopathy. A molecular perspective. Rheumatology (Oxford) 43, 131-142.
Riley G.P. (2005). Gene expression and matrix turnover in overused and damaged tendons. Scand. J. Med. Sci. Sports 15, 241-251.
Rui Y.F., Lui P.P., Li G., Fu S.C., Lee Y.W. and Chan K.M. (2010). Isolation and characterization of multipotent rat tendon-derived stem cells. Tissue Eng. Part A 16, 1549-1558.
Sadoghi P., Rosso C., Valderrabano V., Leithner A. and Vavken P. (2013). The role of platelets in the treatment of Achilles tendon injuries. J. Orthop. Res. 31, 111-118.
Sanchez,M., Anitua E., Azofra J., Andia I., Padilla S. and Mujika I. (2007). Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am. J. Sports Med. 35, 245-251.
Schnabel L.V., Mohammed H.O., Miller B.J., McDermott W.G., Jacobson M.S., Santangelo K.S. and Fortier L.A. (2007). Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. J. Orthop. Res. 25, 230-240.
Schofer M.D., Hinrichs F., Peterlein C.D., Arendt M. and Schmitt J. (2009). High- versus low-energy extracorporeal shock wave therapy of rotator cuff tendinopathy: a prospective, randomised, controlled study. Acta Orthop. Belg. 75, 452-458.
Schubert T.E., Weidler C., Lerch K., Hofstadter F. and Straub R.H. (2005). Achilles tendinosis is associated with sprouting of substance P positive nerve fibres. Ann. Rheum. Dis. 64, 1083-1086.
Scott A., Khan K.M., Heer J., Cook J.L., Lian O. and Duronio V. (2005). High strain mechanical loading rapidly induces tendon apoptosis: an ex vivo rat tibialis anterior model. Br. J. Sports Med. 39, e25.
Scott A., Cook J.L., Hart D.A., Walker D.C., Duronio V. and Khan K.M. (2007). Tenocyte responses to mechanical loading in vivo: a role for local insulin-like growth factor 1 signaling in early tendinosis in rats. Arthritis Rheum. 56, 871-881.
Scott A., Alfredson H. and Forsgren S. (2008). VGluT2 expression in painful Achilles and patellar tendinosis: evidence of local glutamate release by tenocytes. J. Orthop. Res. 26, 685-692.
Shi Y., Fu Y., Tong W., Geng Y., Lui P.P., Tang T., Zhang X. and Dai K. (2012). Uniaxial mechanical tension promoted osteogenic differentiation of rat tendon-derived stem cells (rTDSCs) via the Wnt5a-RhoA pathway. J. Cell. Biochem. 113, 3133-3142.
Silva R.D., Glazebrook M.A., Campos V.C. and Vasconcelos A.C. (2011). Achilles tendinosis: a morphometrical study in a rat model. Int. J. Clin. Exp. Pathol. 4, 683-691.
Skutek M., van Griensven M., Zeichen J., Brauer N. and Bosch U. (2003). Cyclic mechanical stretching of human patellar tendon fibroblasts: activation of JNK and modulation of apoptosis. Knee Surg. Sports Traumatol. Arthrosc. 11, 122-129.
Sundman E.A., Cole B.J. and Fortier L.A. (2011). Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am. J. Sports Med. 39, 2135-2140.
van Buul G.M., Koevoet W.L., Kops N., Bos P.K., Verhaar J.A., Weinans H., Bernsen M.R. and van Osch G.J. (2011). Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am. J. Sports Med. 39, 2362-2370.
Verrall G., Schofield S. and Brustad T. (2011). Chronic Achilles tendinopathy treated with eccentric stretching program. Foot Ankle Int. 32, 843-849.
Wang J.H. (2006). Mechanobiology of tendon. J. Biomech. 39, 1563-1582.
Wang J.H., Jia F., Yang G., Yang S., Campbell B.H., Stone D. and Woo S.L. (2003). Cyclic mechanical stretching of human tendon fibroblasts increases the production of prostaglandin E2 and levels of cyclooxygenase expression: a novel in vitro model study. Connect. Tissue Res. 44, 128-133.
Wang J.H., Iosifidis M.I. and Fu F.H. (2006). Biomechanical basis for tendinopathy. Clin. Orthop. Relat. Res. 443, 320-332.
Weibrich G., Kleis W.K., Hitzler W.E. and Hafner G. (2005). Comparison of the platelet concentrate collection system with the plasma-rich-in-growth-factors kit to produce platelet-rich plasma: a technical report. Int. J. Oral Maxillofac. Implants 20, 118-123.
Wolfe M.M., Lichtenstein D.R. and Singh G. (1999). Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N. Engl. J. Med. 340, 1888-1899.
Wong M.E., Hollinger J.O. and Pinero G.J. (1996). Integrated processes responsible for soft tissue healing. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 82, 475-492.
Yuan J., Murrell G.A., Wei A.Q. and Wang M.X. (2002). Apoptosis in rotator cuff tendonopathy. J. Orthop. Res. 20, 1372-1379.
Zhang J. and Wang J.H. (2010a). Characterization of differential properties of rabbit tendon stem cells and tenocytes. BMC Musculoskelet. Disord. 11, 10.
Zhang J. and Wang J.H. (2010b). Mechanobiological response of tendon stem cells: implications of tendon homeostasis and pathogenesis of tendinopathy. J. Orthop. Res. 28, 639-643.
Zhang J. and Wang J.H. (2010c). Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. Am. J. Sports Med. 38, 2477-2486.
Zhang J. and Wang J.H. (2010d). Production of PGE(2) increases in tendons subjected to repetitive mechanical loading and induces

differentiation of tendon stem cells into non-tenocytes. J. Orthop. Res. 28, 198-203.

Zhang J. and Wang J.H. (2012). BMP-2 mediates PGE(2) -induced reduction of proliferation and osteogenic differentiation of human tendon stem cells. J. Orthop. Res. 30, 47-52.

Accepted July 3, 2013