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Review

Mechanobiology of tendon

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Abstract

Tendons are able to respond to mechanical forces by altering their structure, composition, and mechanical properties—a process called tissue mechanical adaptation. The fact that mechanical adaptation is effected by cells in tendons is clearly understood; however, how cells sense mechanical forces and convert them into biochemical signals that ultimately lead to tendon adaptive physiological or pathological changes is not well understood. Mechanobiology is an interdisciplinary study that can enhance our understanding of mechanotransduction mechanisms at the tissue, cellular, and molecular levels. The purpose of this article is to provide an overview of tendon mechanobiology. The discussion begins with the mechanical forces acting on tendons in vivo, tendon structure and composition, and its mechanical properties. Then the tendon's response to exercise, disuse, and overuse are presented, followed by a discussion of tendon healing and the role of mechanical loading and fibroblast contraction in tissue healing. Next, mechanobiological responses of tendon fibroblasts to repetitive mechanical loading conditions are presented, and major cellular mechanotransduction mechanisms are briefly reviewed. Finally, future research directions in tendon mechanobiology research are discussed.

Keywords: Tendon; Mechanobiology; Mechanical adaptation; Tendon fibroblasts; Mechanotransduction

Contents

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1. Introduction

Tendons are mechanically responsible for transmitting muscle forces to bone, and in doing so, permit locomotion and enhance joint stability. Moreover, tendons are a living tissue and respond to mechanical forces by changing their metabolism as well as their structural and mechanical properties. For example, tendons exhibit increased cross-sectional area and tensile strength, and tendon fibroblasts increase the production of collagen type I in response to appropriate physical training (Suominen et al., 1980; Michna and Hartmann, 1989; Langberg et al., 2001; Tipton et al., 1975). However, inappropriate physical training leads to tendon overuse injuries, or tendinopathy (Khan and Maffuli, 1998; Maffulli et al., 1998), and excessive repetitive stretching of human patellar tendon fibroblasts (HPTFs) increases the production of inflammatory mediators, such as prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) (Li et al., 2004; Wang et al., 2001).

The ability of connective tissues like tendons to alter their structure in response to mechanical loading is referred to as tissue mechanical adaptation. There is little doubt that the adaptation is effected by cells in tissues. However, the mechanotransduction mechanisms by which cells sense mechanical forces and convert them into the biochemical signals that ultimately lead to tissue adaptive physiological or pathological changes are still not completely understood. Mechanobiology, the interdisciplinary study of changes in tissue structure and function, will play an important role in our understanding of mechanotransduction mechanisms at the cellular and molecular levels.

The goal of this review is to provide an overview of tendon mechanobiology. First, we will describe the mechanical forces acting on tendons in vivo, tendon structure and composition, and mechanical properties. We will then review the tendon's response to training (or exercise), disuse, and overuse. This will be followed by introducing tendon healing and the roles of mechanical loading and fibroblast contraction in tissue healing. Next, we will review the mechanobiological responses of tendon fibroblasts to repetitive mechanical loading conditions. Finally, we will briefly review the major mechanotransduction mechanisms proposed in the literature and discuss future directions in tendon mechanobiology research.

2. Tendon forces in vivo

Forces generated in muscles are transmitted to bone through tendons, which makes joint and limb movement possible. To do this effectively, tendons must bear large forces. In humans, it has been estimated that the peak force transmitted through the Achilles tendon during running was 9 kN, which is equivalent to 12.5 times the body weight (Komi, 1990; Komi et al., 1992). In human hand flexor tendons (Schuind et al., 1992), it was shown that the intratendinous force of the tendon depends on whether the force was generated passively or actively, and on whether the position of the joint was in flexion or extension. During passive mobilization of the wrist, the flexor tendon force was found to range between 1 and 6 N, and up to 9 N during similar mobilization of the fingers. During a 35 N tip-pinch, the tendon force measured up to 12 N whereas during active, unresisted finger motion, the tendon force reached about 35 N.

In vivo tendon forces in animals have also been measured. Using an implantable force transducer (IFT) in a goat, it was found that during standing, the PT force was, on average, 207 N, whereas the PT force reached a maximum 800 N during walking and 1000 N during trotting (Korvick et al., 1996). In rabbits, the peak force bore by the flexor tendon increased with physical activity. For the most vigorous activity (inclined hopping), tendon forces reached, on average, 30% of the tendon's ultimate failure load (Malaviya et al., 1998).

Several factors affect the mechanical forces on tendons during normal locomotion. First, different tendons in the body are subjected to different levels of mechanical loads. For example, the Achilles tendon withstands higher tensile forces than those of the tibialis anterior (Maganaris, 2002; Maganaris and Paul, 2002). Second, both the level of muscle contraction and the tendon's relative size influence mechanical forces on a tendon. In general, the greater the cross-sectional area of a muscle, the higher force it produces and the larger stress a tendon undergoes (e.g., patellar tendon vs. hamstrings tendons) (Kellis, 1998). Third, different activities induce different levels of forces, even on the same tendon (Korvick et al., 1996; Malaviya et al., 1998). Similarly, varying the rate and frequency of mechanical loading result in different levels of tendon forces (Finni et al., 1998; Kyrolainen et al., 2003).

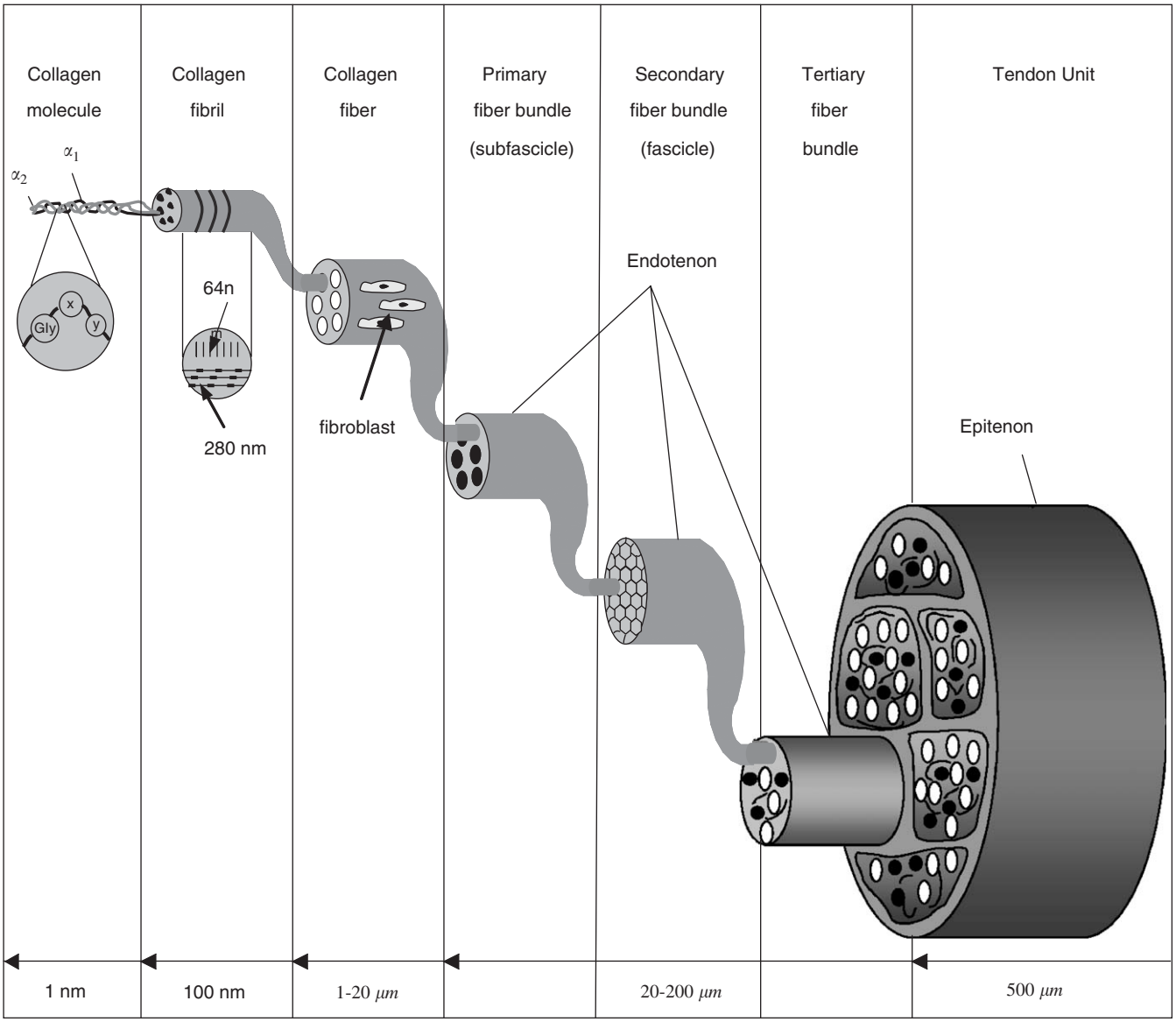

Fig. 1. A schematic of a multi-unit hierarchical structure of the tendon (modified from Silver et al., 2003).

3. Tendon structure, composition, and mechanical properties

3.1. Tendon structure

The tendon has a multi-unit hierarchical structure composed of collagen molecules, fibrils, fiber bundles, fascicles and tendon units that run parallel to the tendon's long axis (Fig. 1). The fibril is the smallest tendon structural unit; it consists largely of rod-like collagen molecules aligned end-to-end in a quarter-staggered array. Fibril diameters vary from 10 to 500 nm, depending on species, age, and sample location. Young animals have uniformly small fibrils, whereas mature animals typically have small and large fibrils, whose diameters are distributed in a bimodal fashion (Moore and De Beaux, 1987; Parry et al., 1982).

Fibers form the next level of tendon structure. Fibers are composed of collagen fibrils and are bound by endotenons (Kastelic et al., 1978), a thin layer of connective tissue that contains blood vessels, lymphatics and nerves (Kastelic et al., 1978; Ochiai et al., 1979). Fiber bundles form fascicles, and bundles of fascicles are enclosed by the epitenon, which is a fine, loose connective-tissue sheath containing the vascular, lymphatic, and nerve supply to the tendon (Kastelic et al., 1978).

It is known that tendons are also surrounded by a third layer of connective tissue called the paratenon (synovial sheath in some sites). The epitenon and paratenon make up the so-called peritendon, which

reduce friction with the adjacent tissue (Schatzker and Branemark, 1969).

This type of hierarchical structure aligns fiber bundles with the long axis of the tendon and affords the tendon's tensile strength. This structure appears as a "crimp pattern" when longitudinal sections of the tendon are viewed in a polarized microscope (Stouffer et al., 1985; Whittaker and Canham, 1991).

Tendons connect bone and muscles at their ends. The tendon–bone junction is called the enthesis. There are two types of enthesis: the fibrous enthesis, and the fibrocartilaginous enthesis. At the fibrous enthesis the tendon attaches to the periosteum during childhood or to the bone itself during adulthood, whereas at the fibrocartilaginous enthesis, a transitional zone of hyaline fibrocartilage, which distributes mechanical loads, is present (Benjamin et al., 1986, 2002). The enthesis can bear tensile, compressive and shear forces, and it is estimated that the tensile forces at this site may be four times that of the tendon midsubstance (McGonagle et al., 2003). These forces may lead to histopathological changes of fibrocartilage at the tendon–bone junction, which, in addition to the accumulation of proteoglycans in tendon enthesis, are implicated in enthesopathy (McGonagle et al., 2003; Thomopoulos et al., 2003).

The myotendinous junction transfers muscular forces to the tendon and enhances muscle growth (Benjamin and Ralphs, 1996). At this junction, the tendon's collagen fibrils are inserted into deep recesses formed by myofibroblasts, which allow tensile forces generated by contractile proteins (actin and myosin) of muscle fibers to be transmitted to tendon collagen fibers (Michna, 1983; Tidball, 1991, 1984. This structure also reduces tension on tendons during muscle contraction. However, the myotendinous junction is also the weakest point of the muscle-tendon unit (Garrett, 1990; Jarvinen et al., 1991).

3.2. Tendon composition

Tendons consist of collagens, proteoglycans, glycoproteins, water and cells. Tendons are rich in collagens, with the most abundant tendon component being type I collagen, which constitutes about 60% of the dry mass of the tendon and about 95% of the total collagen (Evans and Barbenel, 1975; Riley et al., 1994a). The remaining 5% consists of types III and V collagens. In normal tendons, type III collagen is mainly located in the endotenon and epitenon (Duance et al., 1977). However, it is also found in aging tendons and at the insertion sites of highly stressed tendons such as the supraspinatus (Fan et al., 1997). Type III collagen forms smaller, less organized fibrils (Lapiere et al., 1977), which may result in decreased mechanical strength. Type V collage is intercalated into the core of type I collagen fibrils and regulate fibril growth (Birk et al., 1990).

Other collagens, including types II, VI, IX, X, and XI, are present in trace quantities in tendons (Fukuta et al., 1998). These collagens are mainly found at the bone insertion site of fibrocartilage, where they strengthen the connection by reducing stress concentration at the hard tissue interface (Fukuta et al., 1998; Waggett et al., 1998).

The basic structural unit of collagen is tropocollagen, which is a long, thin protein produced inside a cell (e.g., fibroblast) and secreted into extracellular matrix as procollagen. According to the Trelstad–Birk model (Birk and Trelstad, 1986; Birk et al., 1989; Trelstad et al., 1982), it was assumed that only uncleaved procollagen was transferred from compartments inside the cell to compartments outside the cell—plasma membrane recesses, where collagen morphogenesis is completed. However, a recent study showed that procollagen can be converted to collagen within the cell, and that fibril formation can occur in closed intracellular carriers (Canty et al., 2004).

Collagens in the matrix are cross-linked (Bailey and Light, 1985; Eyre et al., 1984). The cross-linking increases the Young's modulus of the tendon and reduces its strain at failure(Thompson and Czernuszka, 1995). The enzyme, lysyl oxidase, is involved in cross-linking adjacent amino acids. The best-characterized cross-links are lysylpyridinoline (LP) and hydroxylysylpyridinoline (HP). LP crosslinks exist in only small quantities in soft connective tissues and are restricted to bone connections (Bailey et al., 1998; Knott and Bailey, 1998). The amount of HP present in different tissues is related to the tissue's mechanical function. For example, hyaline cartilage and intervertebral discs contain the highest HP concentration, with about two HP cross-links per collagen molecule (Eyre et al., 1984). Note, however, collagen cross-linking occurs also by non-enzymic glycation, when reducing sugars, such as pentose derived from circulation, bind irreversibly to matrix proteins (Bailey et al., 1998).

Besides collagens, tendons also contain proteoglycans in small quantities. The proteoglycan content varies with the site of the tendon and depends on the mechanical loading conditions (e.g., tension vs. compression) of the tendon (Berenson et al., 1996; Riley et al., 1994b). For example, in compression-bearing regions of bovine flexor digitorum profundus tendons, the proteoglycan content is 3.5% of the tendon dry weight (Vogel and Koob, 1989). In contrast, in a tension-bearing bovine flexor tendon, the amount of proteoglycans makes up about 0.2–0.5% of the tendon's dry weight (Koob and Vogel, 1987). There are many proteoglycans, including aggrecan and decorin (Vogel and Heinegard, 1985). Aggrecan holds water within the fibrocartilage and resists compression (Vogel and Koob, 1989). Decorin, a small leucine-rich proteoglycan, is located on the surface of the middle portions of collagen fibrils (Graham et al., 2000) and is thought to facilitate fibrillar slippage during mechanical deformation (Pins et al., 1997).

There are several glycoproteins present in the extracellular matrix of the tendon. These include tenascin-C and fibronectin. Tenascin-C contributes to the mechanical stability of the extracellular matrix through its interaction with collagen fibrils (Elefteriou et al., 2001). Fibronectin is located on the surface of collagens, and its synthesis increases to facilitate wound healing (Jozsa et al., 1989a; Williams et al., 1984). Additionally, tendons contain elastin, which composes about 2% of the dry weight of the tendon (Jozsa et al., 1989b). The elastic fibers, which comprise elastin and microfibrillar proteins, may contribute to the recovery of the crimp configuration of the collagen fibers after stretching (Butler et al., 1978).

Although endothelial cells, synovial cells and chondrocytes are present in tendons, fibroblasts (tenoblasts and tenocytes) are the dominant cell type. Tendon fibroblasts align in rows between collagen fiber bundles. Fibroblasts are responsible for synthesizing extracellular matrix proteins (e.g., collagens, fibronectin, and proteoglycans), producing an organized collagen matrix, and remodeling it during tendon healing. Tendon fibroblasts communicate via gap junctions with connexins 32 and 43 (McNeilly et al., 1996). In vitro, mechanical stretching of tendon fibroblasts has been shown to increase the expression levels of junctional components (N-cadherin and vinculin), and the stress fiber component (tropomyosin) (Ralphs et al., 2002).

3.3. Tendon mechanical properties

Tendons are subjected to dynamic mechanical forces in vivo, and hence tendons have fiber patterns and viscoelastic characteristics that contribute to the unique mechanical behavior of the tendon. A typical tendon stress–strain curve has an initial toe region, where the tendon is strained up to 2% (Fig. 2). This toe region represents the stretching-out of the "crimp-pattern" of a tendon. The angle and length of the "crimp pattern" depend on the type of tendon and the sample site within the tendon (Wilmink et al., 1992), where differences in the "crimp pattern" affect the tendon's mechanical properties. For example, fibers with a small crimp angle fail before those with a larger crimp angle (Wilmink et al., 1992).

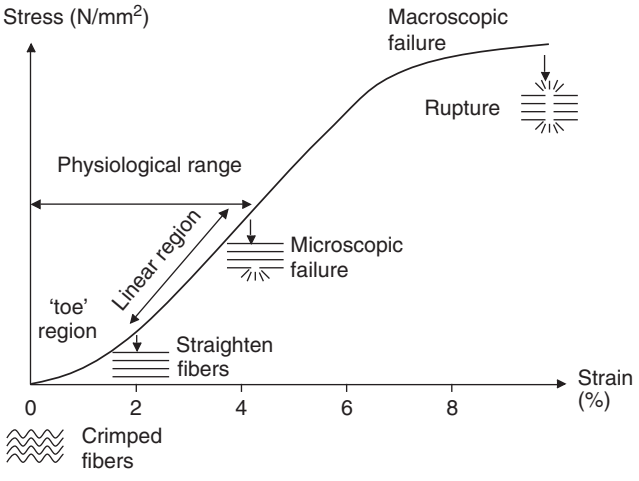

Fig. 2. Tendon stress–strain curve.

In the linear region of the stress–strain curve, where the tendon is stretched less than 4%, collagen fibers lose their crimp pattern. The slope of this linear region is referred to as the Young's module of the tendon. If the tendon is stretched over 4%, microscopic tearing of tendon fibers occurs. Beyond 8–10% strain, macroscopic failure occurs. And further stretch causes tendon rupture (Butler et al., 1978). It should be noted that these values of tendon strains may be under-estimated. Using a modern testing technique, a recent study has shown that avian flexor tendons can be elastically stretched up to 14% (Devkota and Weinhold, 2003).

In vitro mechanical properties of the tendon are determined by mechanical testing. A study by Johnson et al. (1994) found that the ultimate tensile strength of the human patellar tendon for younger donors (29–50) was 64.7 ± 15.0 MPa, whereas it was 53.6 ± 10.0 MPa for older donors (64–93). The strain at failure for the young and old groups was $14 \pm 6\%$ and $15 \pm 5\%$, respectively. The values of the Young's modulus were found to be 660 ± 266 MPa and 504 ± 222 MPa for the young and old tendons, respectively.

A study by Maganaris and Paul (1999) estimated the in vivo structural and mechanical properties of the human tibialis anterior (TA) tendon. It was determined that the tendon stiffness and Young's modulus at maximum isometric load were 161 N/mm and 1200 MPa, respectively.

Like other soft tissues including ligaments and skin, tendons are viscoelastic and sensitive to different strain rates. The viscoelastic behavior of the tendon likely results from collagen, water, and interactions between collagenous proteins and non-collagenous proteins (e.g., proteoglycans). The viscoelasticity of a material is defined by stress-relaxation, creep, and hysteresis (Butler et al., 1978). Because of their viscoelasticity, tendons are more deformable at low strain rates. Therefore, the tendons absorb more energy, but are less effective in transferring loads. At high strain rates, tendons become less deformable with a high degree of stiffness and are more effective in moving large loads (Jozsa and Kannus, 1997).

4. Tendon response to mechanical loading

4.1. Training and mobilization effects on tendons

Tendons change structure in response to the functional demands on them. In rabbits that exercised for 40

weeks, the ultimate load and energy absorbed at failure of the rabbit peroneus brevis tendon were higher than those of rabbits without exercise (Viidik, 1967, 1969). Also, running exercise for 12 months increased the strength of the tendon insertion site in swine (Woo et al., 1981). In mice exercised on a treadmill for 1 week, the number and size of collagen fibrils, and cross-sectional area of the digital flexor tendons increased compared to those of sedentary mice (Michna, 1984; Michna and Hartmann, 1989).

Furthermore, training also induces biochemical changes in tendons. For example, after strenuous endurance training for 8 weeks, collagen deposition in the Achilles tendon in roosters increased by 46%, and the collagen contained 50% fewer pyridinoline cross-links (Curwin et al., 1988). These results suggest that strenuous endurance training increases collagen turnover but decreases collagen maturation in tendons. According to Hansson's study (Hansson et al., 1988), exercise stimulates tenocytes in the rat Achilles tendon to increase the expression of insulin-like growth factor-I (IGF-I). IGF-I is a potent stimulus of collagen synthesis and cell proliferation (Simmons et al., 2002; Svegliati-Baroni et al., 1999). As such, the IGF-I may serve as a protein marker for remodeling activities of the tendon.

Using microdialysis techniques, the effect of physical training on human subjects has also been determined. It was found that training increases the turnover of type I collagen in the peritendinous Achilles' region (Langberg et al., 2001). This study also showed that physical training promotes both the synthesis and degradation of collagen. The anabolic processes, however, dominated, which results in a net synthesis of type I collagen in tendon-related tissue. It still remains to be determined whether human activity levels affect the diameter of collagen fibrils and/or the cross-sectional area of the tendon (Magnusson et al., 2003).

4.2. Disuse and immobilization effects on tendons

There have been few studies to determine the effects of tendon disuse and immobilization. Therefore, our knowledge of their effects on the tendon is limited. Also, the effect of disuse and immobilization on tendons is much slower and less dramatic than on skeletal muscles because they have a much slower metabolism and vascularity (Maffulli and King, 1992). In general, however, immobilization decreases the total weight of the tendon, stiffness, and tensile strength (Amiel et al., 1982; Tipton et al., 1975, 1986; Woo et al., 1982).

Joint immobilization has commonly been used as a model of disuse. In rabbits, after immobilization of the knee joint for 4 weeks, the ultimate load and stiffness of healing Achilles tendons decreased compared to control tendons. Also, immobilization caused the formation of irregular and uneven collagen fibers, dilated veins and capillaries (Yasuda et al., 2000). Stress deprivation due to immobilization was thought to be responsible for the degenerative changes in tendons (Yasuda and Hayashi, 1999). Indeed, stress deprivation by stress shielding for 3 weeks markedly decreased the Young's modulus and tensile strength of the rabbit patellar tendon (Yamamoto et al., 1993).

Using tissue culture approaches, the effect of stress deprivation and mechanical loading on the histologic and mechanical properties of the canine flexor digitorum profundus tendon was investigated (Hannafin et al., 1995). It was found that stress deprivation for 8 weeks resulted in significant changes in cell shape, cell number, and collagen fiber alignment, and decreased the Young's modulus. However, in vitro cyclic tensile loading of tendons for 4 weeks increased the Young's modulus (93% of the control) compared with that of the stress-deprived tendons (68% of the control). In addition, tendons subjected to cyclic mechanical loading maintained normal histologic patterns. In another study (Nabeshima et al., 1996), the application of a 4% strain to rabbit patellar tendons in culture was shown to protect against degradation by bacterial collagenase.

4.3. Tendon overuse injuries

Tendon overuse injuries, which are collectively referred to as tendinopathy (Khan et al., 2002), affect millions of people in occupational and athletic settings (Almekinders and Temple, 1998). Despite this, there are few studies on non-traumatic, overuse tendon injuries. The term "overuse" implies a repetitive stretching of a tendon and results in the inability of the tendon to endure further tension (Jozsa and Kannus, 1997). Although tendinopathy is likely caused by intrinsic or extrinsic factors or in combination (Kjaer, 2004; Riley, 2004), excessive mechanical loading is considered a major causation factor. It is believed that small, repetitive strains, which are below the failure threshold of the tendon, cause tendon microinjuries and subsequently tendon inflammation. Tendon inflammation due to the production of PGE_2 and LTB_4 in response to repetitive mechanical loading may contribute to the development of tendon degeneration (Khan and Maffuli, 1998). The evidence that supports this hypothesis is that elevated PGE_2 levels were found in the human tendon after repetitive mechanical loading (Langberg et al., 1999). Furthermore, tissue damage, such as tendon injuries due to repetitive mechanical loading, can result in production of abundant LTB_4 and subsequent neutrophil infiltration and activation. For example, mechanical trauma in an anesthetized rat induces a large increase in the production of leukotrienes (Denzlinger et al., 1985). The presence of abundant leukotrienes in injured tissues is sufficient to induce tissue edema, which is seen in tendons with

tendinopathy (Backman et al., 1990). In addition, in vitro studies have shown that repetitive mechanical loading of human tendon fibroblasts increases the production of PGE_2 (Almekinders et al., 1993; Wang et al., 2003) and LTB_4 (Li et al., 2004). Finally, peritendinous injection of prostaglandin-E_1 in the area surrounding the rat Achilles' tendon leads to degeneration as well as inflammation around and within the tendon (Sullo et al., 2001). We have also shown that injection of PGE_2 into the mid-substance of the tendon induces profound degenerative changes in the tendon matrix (Khan et al., 2005). Interestingly, a previous study using microdialysis techniques found that the level of PGE_2 in the Achilles tendon of human subjects exhibiting symptoms of tendinopathy was not significantly higher than that of healthy subjects (Alfredson et al., 1999). Possible explanations for this result include: (1) small sample size (four patients with chronic Achilles tendinosis) with large variations, so that statistical significance could not be declared; and (2) inflammation occurs in the early stages of tendinopathy and when tendons become degenerative, inflammation has largely disappeared; therefore, there are no markedly high levels of inflammatory mediators such as PGE_2 present in tendons.

In addition, the tendon–bone junction (i.e., enthesis) is susceptible to tendon overuse injury, or enthesopathy. The features of enthesopathy include: the insertion site of tendons become metabolically active, the extracellular matrix composition is altered, collagen bundles loosen, lipids accumulate, and microcalcification may occur (Jarvinen et al., 1997; Thomopoulos et al., 2002, 2003).

Injury to the paratenon either due to trauma or excessive loading causes inflammation in the paratenon and results in so-called paratenonitis or peritendinitis, which features edema, swelling, hyperemia of the tenosynovium, infiltration of lymphocytes, and proliferation of blood vessels (Jarvinen et al., 1997). Many studies showed that inflammation and metabolic activity of the paratenon proceed in parallel with those of the tendon substance. Using microdialysis techniques, it was found that acute exercise causes changes in tendon metabolism and increases the inflammatory reaction in the paratenon (Langberg et al., 1999), and that peritendinous changes reflect changes within the tendon as well (Langberg et al., 2002).

Besides non-pharmaceutical therapies, such as controlled immobilization, physical therapy, stretching, application of electrical and magnetic fields, non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat tendinopathy. These drugs, however, only provide symptomatic relief. Effective treatment strategies that stimulate a healing response of the diseased tendon need to be developed. In order to achieve this, the molecular mechanisms for the development of tendinopathy must be understood first.

5. Tendon healing, mechanical loading effects, and fibroblast contraction

5.1. Tendon healing processes

Tendon healing can be largely divided into three overlapping phases: the inflammatory, repairing, and remodeling phases (Frank et al., 1994; Woo et al., 1999). In the initial inflammatory phase, which lasts about 24 h, erythrocytes, platelets, and inflammatory cells (e.g., neutrophils, monocytes, and macrophages) migrate to the wound site and clean the site of necrotic materials by phagocytosis. In the mean time, these cells release vasoactive and chemotactic factors, which recruit tendon fibroblasts to begin collagen synthesis and deposition. A few days after the injury, the repairing phase begins. In this phase, which lasts a few weeks, tendon fibroblasts synthesize abundant collagen and other ECM components such as proteoglycans and deposit them to the wound site. During the repairing phase, water content and glycosaminoglycan concentration remain high. After about 6 weeks, the remodeling phase starts. This phase is characterized by decreased cellularity and decreased collagen and glycosaminoglycan synthesis. During this period, the repaired tissue changes to fibrous tissue, which again changes to scar-like tendon tissue after 10 weeks. During the later remodeling phase, covalent bonding between collagen fibers increases, which results in repaired tissue with higher stiffness and tensile strength. Also, both the metabolism of tenocytes and tendon vascularity decline.

During tissue healing, growth factors play an important role. There are five growth factors whose activities have been well-characterized in tendon healing (Molloy et al., 2003): IGF-I, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta (TGF-β). Following tendon injuries, all these factors are markedly up-regulated and are active during the healing process. IGF-I is highly expressed during the early inflammatory phase and promotes the proliferation and migration of tendon fibroblasts and subsequently increases collagen and proteoglycan production (Abrahamsson and Lohmander, 1996; Murphy and Nixon, 1997). In injured rat Achilles tendons, intratendinous injection of IGF-I accelerates functional recovery (Kurtz et al., 1999).

PDGF is produced shortly after tendon injury and stimulates the production of other growth factors. In fibroblast culture from avian flexor tendons, PDGF-BB, a PDGF isoform, stimulated mitogenic responses in a dose-dependent manner (Banes et al., 1995). Tissue explant studies have also shown that tendons increase DNA synthesis in response to PDGF-BB (Abrahamsson and Lohmander, 1996).

TGF-β is active during the inflammatory and repair phases of tendon healing. There are three mammalian TGF-β isoforms, TGF-β1, TGF-β2, and TGF-β3, all of which have been extensively studied in the wound healing process (Moulin et al., 2001). In wound tissues, TGF-β1 aids in extracellular matrix deposition (Chen et al., 1993; Shah et al., 1999). Its over-expression, however, results in tissue fibrosis (Shah et al., 1999). TGF-β2 functions similarly to TGF-β1; however, TGF-β3 has been shown to improve tissue scarring (Ferguson and O'Kane, 2004; Shah et al., 1995).

TGF-β plays a major role in the repair of injured tendons. TGF-β1 mRNA expression increases a short time after tendon injury. In a rabbit zone II flexor tendon wound healing model, TGF-β1 was activated in the tendon wound environment as evidenced by mRNA up-regulation (Chang et al., 1997). In this tendon wound healing model, it was found that TGF-β receptors are up-regulated after injury and that the peak levels of TGF-β receptor expression occurred at day 14 and decreased at day 56 post-injury. In addition, the highest TGF-β receptor expression was located at the tendon sheath and epitenon (Ngo et al., 2001), whereas minimal receptor expression was observed in non-injured tendons.

VEGF stimulates endothelial cell proliferation, enhances angiogenesis, and also increases capillary permeability (Ferrara, 1999). In a canine flexor tendon repair model (Bidder et al., 2000; Boyer et al., 2001), high levels of expression of VEGF mRNA expression were detected at the repair site 7 days post-surgery, but the peak expression levels were found to occur at 10 days after surgery. bFGF regulates cellular migration and proliferation and also promotes angiogenesis. Treatment of rat patellar tendon fibroblasts with bFGF increases proliferation (Chan et al., 1997, 2000) and collagen gene expression (Tang et al., 2003).

Bone morphogenetic proteins (BMPs), a subgroup of TGF-β superfamily, induce bone and cartilage formation by influencing tissue differentiation (Chen et al., 2004; Reddi, 2003). For example, injection of cells containing BMP-12 gene into nude mice thigh muscles induced formation of tendon and cartilage-like tissue (Lou et al., 1999). BMPs also affect tendon healing. Both BMP-13 and BMP-14 were shown to increase the amount of tendon callus in transected rat Achilles tendon, thereby increasing the strength of the healing tendon (Aspenberg and Forslund, 2000). However, induction of bone or tendon-like tissue by BMP-13 depends on the mechanical environment at the site where it is applied (Forslund and Aspenberg, 2003). The addition of recombinant BMP-12 to human tendon fibroblast cultures increased proliferation and gene expression of procollagen-type I and III, but decreased gene expression of decorin (Fu et al., 2003).

During tendon healing, all three nitric oxide synthase (NOS) isoforms are expressed with differential expression patterns during three phases of tendon healing (Lin et al., 2001). NOS inhibition decreased the cross-sectional area and ultimate tensile strength of the Achilles tendon (Murrell et al., 1997). Furthermore, stimulation of nitric oxide synthase in endothelial cells mediates VEGF-induced vasodilation (Yang et al., 1996).

In a rat flexor tendon laceration model, the expression of type I collagen gene decreased initially and then returned gradually to the initial level by day 28, whereas the expression levels of types III, V, and XII collagen genes were increased after surgery. Furthermore, the expression levels of MMP-9 and MMP-13 peaked between days 7 and 14, whereas MMP-2, MMP-3, and MMP-14 levels increased after surgery and remained at high levels until day 28. These findings suggest that MMP-9 and MMP-13 participate only in collagen degradation, whereas MMP-2, MMP-3, and MMP-14 participate in both collagen degradation and remodeling (Oshiro et al., 2003).

It should be noted that except degenerative tendons (tendinosis), injured tendons tend to heal; however, the healing tendon does not reach the biochemical and mechanical properties of the tendon prior to injury (Leadbetter, 1992). Also, injury to the osteotendinous junction (OTJ) leads to bone loss at the junction and impaired function due to the weak tendon–bone interface (Devkota and Weinhold, 2003). Such an OTJ injury requires a long time to heal and results in inferior mechanical properties (Boyer et al., 2003; St Pierre et al., 1995; Thomopoulos et al., 2002).

Tendons are often used as autografts for the reconstruction of a ruptured ACL, PCL or other knee ligaments (Dunn et al., 1995; Tom and Rodeo, 2002). Therefore, understanding of tendon-to-bone healing is essential for successful knee ligament reconstruction. In a canine model, a long digital extensor tendon was transplanted into a bone tunnel in the proximal tibial metaphysis, and the histological and biomechanical characteristics of the tendon–bone interface were evaluated. It was found that a fibrous tissue layer formed between the tendon and the bone, and the strength of the interface increased progressively at 12 and 26 weeks. In addition, the progressive increase in strength correlated with the degree of bone ingrowth, mineralization, and maturation of the healing tissue (Rodeo et al., 1993). The same group also showed that application of recombinant human BMP-2 enhanced bone ingrowth into a tendon graft placed into a bone tunnel (Rodeo et al., 1999), and that treatment with bone-derived proteins (a mixture of various proteins) increased the tensile strength of the tendon graft by 65% (Anderson et al., 2001).

5.2. The effect of mechanical loading on tendon healing

While training and stretching during the inflammatory phase should be avoided to minimize disruption of

the healing process, controlled mobilization after the inflammatory phase (about 1 week after injury) enhances the quality of healing tendons. In canine flexor digitorum profundus tendons injured by surgical laceration, active mobilization increased the tendon's ultimate strength compared to those of immobilized tendons (61.6 and 41 N, respectively) (Wada et al., 2001). Additionally, early mobilization of the injured canine flexor tendons restored the gliding surfaces of the tendons, increased tensile strength, and improved excursion properties (Gelberman et al., 1986). In general, experimental and clinical evaluations of injured tendons treated postoperatively with early mobilization increase the tendon's tensile strength and reduce adhesions over the immobilized controls (Amiel et al., 1982; Gelberman et al., 1986; Jozsa and Kannus, 1997).

Interestingly, application of mechanical loading to a tendon with chronic tendinopathy has been shown to relieve symptoms (Alfredson et al., 1998). It is suggested that mechanical loading enhances tendon repair and remodeling by stimulating fibroblast activities (e.g., increased collage synthesis) (Kannus, 1997). It is also suggested that soft tissue mobilization promotes the healing of rat Achilles tendon after collagenase induced injury through fibroblast proliferation and collagen realignment (Davidson et al., 1997).

5.3. The role of fibroblast contraction in tissue healing

Injured tendons usually heal (Carlstedt et al., 1986), but the healing often results in scar tissue formation. It is known that fibroblasts during healing generate and exert force on the extracellular matrix. This force is referred to as fibroblast contraction, which is essential for wound closure during tissue healing (Grinnell, 1994). Excessive cell contraction, however, may lead to tissue scarring. On the other hand, inhibiting fibroblast contraction results in impaired wound healing (Coleman et al., 1998; Nedelec et al., 2000). Thus, an optimal level of fibroblast contraction is desirable to facilitate wound closure while minimizing scar tissue formation.

Cell contraction involves the actin cytoskeleton (Kolodney and Wysolmerski, 1992). When actin polymerization was blocked, cell contraction was inhibited (Kitamura et al., 1991). The interaction between actin and myosin generates cell contraction (Takayama and Mizumachi, 2001), and the contractile forces transmit through actin filaments to integrins and to the extracellular matrix (Chrzanowska-Wodnicka and Burridge, 1996).

Most cell contraction studies focus on skin fibroblasts (Coleman et al., 1998; Coulomb et al., 1984; Eastwood et al., 1994). Interestingly, fetal skin fibroblasts were found to be less contractile than adult skin fibroblasts in vitro (Coleman et al., 1998). Fetal and adult skin have markedly different healing properties: fetal wounds heal without scar formation, whereas adult wounds heal with scar formation (Adzick and Lorenz, 1994; Nedelec et al., 2000). Therefore, the distinct contractile forces associated with fetal and adult skin fibroblasts suggest that fibroblast contraction may play an important role in tissue scarring. Previous studies showed that calf patellar and rabbit flexor tendon fibroblasts deformed fibroblast-populated collagen gels (FPCGs) (Khan et al., 1998, 1997; Torres et al., 2000), and that endotenon and synovial fibroblasts exhibited different levels of contraction (Khan et al., 1998, 1997). Using a cell force monitor system, contractile forces of tendon and skin fibroblasts were measured over time. It was found that tendon and skin fibroblasts exhibited different patterns of contraction, where tendon fibroblasts produced a lower maximum contraction force than skin fibroblasts (Eastwood et al., 1996). Recent studies from our laboratory demonstrated that HPTFs in collagen gels produced an average contraction of 0.2 nN/cell (Campbell et al., 2003), and that TGF-β1 and TGF-β3 differentially regulated the tendon fibroblast contraction (Campbell et al., 2004).

In healing tissues, myofibroblasts are thought to play a major role in tissue contraction. These cells have phenotypic characteristics of both fibroblasts and smooth muscle cells, including the formation of stress fibers parallel with the long axis of the cell (Burridge, 1981; Gabbiani et al., 1971). Alpha-smooth muscle actin (α-SMA) is a specific marker for myofibroblasts (Darby et al., 1990; Gabbiani, 1998). It is known that TGF-β1 induces differentiation of fibroblasts into myofibroblasts by upregulation of α-SMA expression (Desmouliere et al., 1993). For example, addition of TGF-β1 to fibroblast cultures induced high levels of α-SMA expression and resulted in the formation of α-SMA-containing stress fibers (Evans et al., 2003; Kurosaka et al., 1998). Fibroblasts grown in cross-linked collagen-glycosaminoglycan matrices expressed α-SMA (Torres et al., 2000), which indicated that these fibroblasts had differentiated into myofibroblasts.

Myofibroblasts generate large contraction forces within granulation tissue during wound healing (Gabbiani et al., 1972) and also produce excessive collagen in fibrotic diseases (Zhang et al., 1994). In addition to TGF-β1, mechanical loading also influences myofibroblast differentiation. Increased tension on granulation tissue in rats increases the formation of stress fibers and the expression levels of α-SMA and ED-A fibronectin (Hinz et al., 2001; Serini et al., 1998), which are two protein markers of myofibroblasts.

6. Tendon fibroblast response to mechanical loading

6.1. The effects of mechanical loading on cells

As discussed in the preceding sections, tendons respond to altered mechanical loading conditions by

changing their structure, composition, and mechanical properties. Fibroblasts within the tendons, which are their dominant cell type, are responsible for these changes by altering the expression of ECM proteins (Banes et al., 1999; Benjamin and Ralphs, 2000; Kjaer, 2004).

Because experimental conditions can be tightly controlled, in vitro model systems are often used to study responses of tendon fibroblasts to repetitive mechanical loading. Using a biaxial stretching system, cyclic stretching was found to cause fibroblasts at the surface edges to orient perpendicular to the radial stretching direction (Breen, 2000), which is the direction with minimal surface deformations (Wang et al., 1995; Wang and Grood, 2000). In addition, cyclic stretching was found to increase PGE_2 and LTB_4 production by human finger flexor tendon fibroblasts (Almekinders et al., 1993, 1995).

Our laboratory has developed a novel in vitro model system to study the mechanobiological responses of HPTFs (Wang et al., 2003). In this system, the alignment, shape, and repetitive uniaxial stretching conditions of human tendon fibroblasts mimic those occurring in vivo. Using this system, it was found that in serum-free conditions, cyclic stretching of HPTFs at 4% and 8% substrate strains only slightly increased proliferation compared to non-stretched fibroblasts. Also, cyclic stretching increased gene expression and protein production of collagen type I and TGF-β1, where the increase was dependent on stretching magnitude. Furthermore, TGF-β1 was found to mediate at least in part stretching-induced collagen type I production under cyclic stretching conditions (Yang et al., 2004). In addition, cyclic stretching of HPTFs increased the cyclooxygenase (COX) expression levels as well as PGE_2 and LTB_4 production (Li et al., 2004; Wang et al., 2003). The stretching-induced COX expression levels were found to depend on both stretching magnitude and frequency, while the levels of PGE_2 and LTB_4 production by stretched HPTFs are inversely related. In a similar study with HPTFs, it was shown that the production of procollagen peptides for collagen types I and III, and fibronectin increased, with the level of increase depending on both stretching magnitude and duration (Bosch et al., 2002).

In addition, cyclic stretching of tendon cells has been shown to activate the c-Jun N-terminal kinase (JNK), a stress-activated protein kinase (Arnoczky et al., 2002). The activation of JNK was induced immediately and peaked at 30 min and then returned to base-line levels by 2 h. In another study (Lavagnino et al., 2003), 1% cyclic stretching was found to decrease MMP-1 mRNA expression levels, whereas 3% or 6% completely inhibited the gene expression.

Previous studies have also investigated the expression of ECM proteins in fibroblasts embedded in collagen gels under stretched and relaxed conditions. The fibroblasts in the collagen adopted a synthetic phenotype characterized by their ability to synthesize matrix proteins and inhibit matrix degradation (Kessler et al., 2001). Compared with stretched fibroblasts, fibroblasts in relaxed collagen gels decreased both the collagen type I mRNA expression and protein levels (Eckes et al., 1993; Hatamochi et al., 1989). Other studies also showed that fibroblasts in relaxed collagen gels increased the synthesis of MMP-1 (Lambert et al., 1992; Mauch et al., 1989) and that fibroblasts in stressed gels increased the production of tenascin-C and collagen XII compared to the cells on floating or non-stressed gels (Chiquet-Ehrismann et al., 1994; Chiquet et al., 1996). These results suggest that tension exerted on the ECM by fibroblasts may be required to maintain tissue structure and function (Langholz et al., 1995).

6.2. *The interactions between mechanical loading and growth factors/cytokines*

In addition to the fact that mechanical loading induces gene expression and protein synthesis in fibroblasts, there are also interactions between mechanical loading and growth factors/cytokines. For example, tendon fibroblasts subjected to stretching in the presence of IL-1β produced a higher level of stromelysin proenzyme than treatment with IL-1β alone (Archambault et al., 2002). In human flexor digitorum profundus tendon cells, cyclic stretching induced the release of ATP, and the expression of IL-1β, cyclooxygenase-2 (COX-2), and matrix metalloproteinase-3 (MMP-3) genes. The released ATP decreased the stretching-induced expression of these genes (Tsuzaki et al., 2003). In bovine articular cartilage, IGF-I enhanced the synthesis of protein and proteoglycan, whereas static compression decreased their synthesis. Furthermore, the combination of both IGF-I treatment and static loading produced a decrease in synthesis after the initial 4 h, followed by an increase back to the initial levels at 24 h (Bonassar et al., 2001). One suggested mechanism by which static compression affects the action of IGF-I is that compression alters the transport of the IGF-I through the ECM. Also, both compression and IL-1α decreased the rate of proteoglycan synthesis; however, in the presence of IL-1 receptor antagonist, compressed cartilage explants increased proteoglycan synthesis (Murata et al., 2003).

7. Mechanotransduction

As described in previous sections, tendons have the ability to adapt to altered mechanical loading conditions by changing their structure and composition. Cells in the tendon are responsible for the tendon's adaptive response.

Tendon cells respond to mechanical forces by altering gene expression, protein synthesis, and cell phenotype. These early adaptive responses may proceed and initiate long-term tendon structure modifications and thus lead to changes in the tendon's mechanical properties.

These adaptive cellular responses also raise a critical question about mechanotransduction mechanisms: How do tendon cells sense mechanical forces and convert them into cascades of cellular and molecular events that eventually lead to changes in tendon structure? Herein, we will briefly review the mechanotransduction mechanisms, with a focus on several cellular components that are implicated in the transduction of mechanical forces. These cellular components include the extracellular matrix, cytoskeleton, integrins, G proteins, receptor tyrosine kinases (RTKs), mitogen-activated protein kinases (MAPKs), and stretching-activated ion channels. These components, however, are related in a cell either physically, functionally or both. Note that there are many excellent reviews in the literature that focus on different types of cells, including cardiac fibroblasts (MacKenna et al., 2000), cardiac myocytes (Sadoshima and Izumo, 1997), smooth muscle cells (Osol, 1995), endothelial cells (Davies, 1995; Resnick and Gimbrone, 1995), bone cells (Duncan and Turner, 1995), lung cells (Liu and Post, 2000), and dermal fibroblasts (Silver et al., 2003a). Interested readers should consult these references for an in-depth understanding of the topic of cellular mechanotransduction mechanisms.

Extracellular matrix—The extracellular matrix (ECM) is composed of cell-produced proteins and polysaccharides. ECMs act as scaffolds that define tissue shape and structure. They act as the substrate for cell adhesion, growth, and differentiation (Shadwick, 1990; Silver et al., 2003b). Previous studies have shown that mechanical loading increases ECM protein production by promoting release of growth factors, such as TGF-β1, bFGF, and PDGF (Skutek et al., 2001). TGF-β has been shown to mediate collagen secretion induced by mechanical loading (Kim et al., 2002; Yang et al., 2004). Mechanical loading of cells has also been shown to modulate ECM turnover by regulating the expression and activity of MMPs (Archambault et al., 2002; Tsuzaki et al., 2003; von Offenberg Sweeney et al., 2004). Finally, mechanical loading interacts with growth factors/cytokines to regulate ECM homeostasis in various tissues (Banes et al., 1995; Bonassar et al., 2000; Jin et al., 2003; Murata et al., 2003) (Fig. 3).

Mechanically, ECMs transmit mechanical loads, store and dissipate loading-induced elastic energy. Moreover, mechanical deformations in the ECM can transmit to the actin cytoskeleton and cause the remodeling of the actin cytoskeleton (Wang, 2000; Wang et al., 2001), which is known to control cell shape, affect cell motility, and mediate various cellular functions including DNA and protein syntheses (Janmey, 1991).

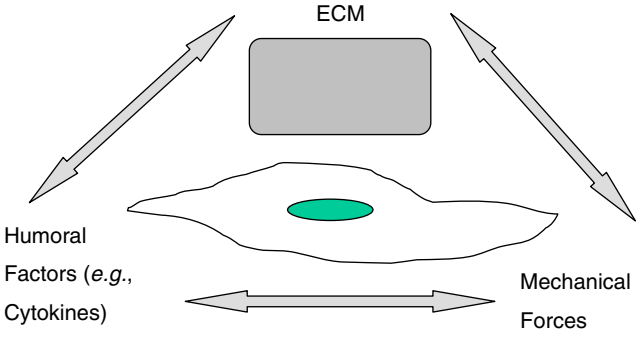

Fig. 3. A conceptual illustration of the relationship among the ECM, humoral factors, and mechanical forces.

Cytoskeleton—The cytoskeleton is composed of microfilaments, microtubules, and intermediate filaments and is thought to play a central role in mechanotransduction (Ingber, 1991). Microfilaments are actin polymers that bind and associate with a large number of proteins. In this organization, microfilaments form a continuous, dynamic connection between nearly all intra-cellular structures. The cytoskeleton responds to extracellular forces, participates in transmembrane signaling, and provides a network for organizing or translocating signaling molecules. According to tensegrity theory (Ingber, 1999, 1991), forces exerted by the extracellular matrix on a cell are in equilibrium with forces exerted by the cell, and these forces are transmitted via focal adhesion sites, integrins, cellular junctions, and the extracellular matrix. Mechanical forces applied to the cell surface have been shown to transmit directly to the cytoskeleton and cause changes in the cytoskeletal structure (Wang and Ingber, 1995). Therefore, changes to the cytoskeleton due to applied mechanical forces can initiate complex signal transduction cascades within the cell through the activation of integrins and the stimulation of G protein receptors, RTKs, and MAPKs.

Integrins—Integrins are transmembrane protein heterodimers composed of α and β subunits. They have three domains: an extracellular matrix domain, a single transmembrane domain, and a cytoplasmic domain (Hynes, 1992). The extracellular matrix domain of the integrin binds to substrates, whereas its cytoplasmic domain links various intracellular proteins that constitute the cytoskeleton and numerous kinases, such as focal adhesion kinase (FAK). Integrins therefore serve as a signaling interface between the extracellular matrix and the cell.

Integrins mediate mechanotransduction by "outside-in" and "inside-out" fashions. In the "outside-in" fashion, ligands in the extracellular matrix bind to integrins, which causes a signal transduction cascade resulting in cytoskeletal reorganization and changes in gene expression, protein synthesis, and cell differentiation. In the "inside-out" fashion, signals within a cell

propagate through integrins and regulate integrin–ligand binding affinity and cell adhesion (Hynes, 1992; Schwartz et al., 1995; Shyy and Chien, 1997). Mechanical forces stimulate the conformational activation of integrins in cells and increase cell binding to the extracellular matrix (Jalali et al., 2001). Furthermore, for stretch- or shear-induced mechanotransduction, formation of new integrin-ligand connections is required, because intracellular signaling induced by mechanical forces was inhibited when unoccupied extracellular matrix ligand sites were blocked with specific antibodies or RGD peptides (Jalali et al., 2001; Wilson et al., 1995).

Through $\alpha\beta$ pairing, integrins interact with extracellular matrix proteins, including fibronectin (ligand for $\alpha5\beta1$ and $\alpha v\beta3$), vitronectin (ligand for $\alpha v\beta3$), and laminin (ligand for $\alpha6\beta1$). Fibroblasts can bind to fibronectin in the ECM via integrin subunits $\alpha5\beta1$. The specific integrin–extracellular matrix interactions also determine how cells sense mechanical forces and their mechanobiological responses. For example, cyclic stretching of smooth muscle cells increased DNA synthesis when cells were grown on fibronectin, collagen, or vitronectin but not on elastin or laminin (Wilson et al., 1995).

G Proteins—G proteins are another family of membrane proteins that are involved in mechanotransduction. G proteins consist of α, β, γ subunits, and they couple membrane receptors and induce intracellular signaling cascades. In cardiac fibroblasts, a single cycle of stretching activated G proteins (Gudi et al., 1998). Shear stresses also activate G proteins in endothelial cells (Gudi et al., 1996), where G protein activation was necessary for the induction of downstream signaling cascades such as ERK1/2 (Bao et al., 2001). Furthermore, it has been reported that the γ subunit of heterodimeric G proteins is present at integrin-rich focal adhesion sites and adjacent to F-actin stress fibers (Hansen et al., 1994). Because of their co-localization, G proteins and integrins may be simultaneously activated by mechanical forces. Therefore, G proteins could be indirectly involved in integrin-mediated signaling (Lehoux and Tedgui, 2003).

RTKs and MAPKs—RTKs are a class of cell membrane proteins that are phosphorylated when subjected to cyclic stretching or shear stress. In smooth muscle cells, for example, mechanical stretching induced phosphorylation of EGF receptors, and the phosphorylated EGF receptors participated in mechanotransduction, since stretching-induced protein synthesis was blocked when the cells were incubated with an EGF receptor antagonist (Iwasaki et al., 2000). The MAPK is downstream of the RTK and can travel into the nucleus and interact with transcription factors and promoters to alter gene expression as well as interact with the ribosomal S6 kinase (RSK) and initiate translation (Lehoux and Tedgui, 1998). The MAPK cascade comprises three different pathways: the extracellular signal-regulated kinase (ERK) 1 and 2, and stress-activated protein kinases (SAPK)/JNK. Previous studies have shown that mechanical forces, both in vitro and in vivo, activate MAPKs in vascular cells. For example, cyclic stretching of SMC activates ERK1/2 and JNK (Reusch et al., 1997), and acute hypertension transiently activates ERK1/2 and JNK in the arterial wall (Xu et al., 2000). Cyclic stretching has also been shown to activate JNK in patellar tendon fibroblasts (Arnoczky et al., 2002).

Stretching-activated ion channel—In addition to activation of signal proteins, mechanical forces also trigger stretch-activated ion channels (Sackin, 1995). Stretch-activated ionic channels are cation-specific, where their electric activities are detectable when open. The activation of these channels permit calcium (Ca^{2+}) and other ions (e.g., sodium and potassium) to influx followed by membrane depolarization (Sackin, 1995). Norepinephrine treatment of avian tendon cells increased the expression of functional adrenoceptors by increasing intracellular Ca^{2+} concentration (Wall et al., 2004). Cyclic stretching stimulated Ca^{2+} influx into osteoblastic cells (Vadiakas and Banes, 1992), and laminar fluid flow increased intracellular Ca^{2+} in human disc cells (Elfervig et al., 2001). In human gingival fibroblasts, application of forces with magnetic beads to integrins induced an immediate (<1 s) Ca^{2+} influx (Glogauer et al., 1997). Cyclic stretching of fetal rat lung cells induced a rapid Ca^{2+} via gadolinium-sensitive stretch-activated ion channels (Liu et al., 1994). Mechanical stretching-induced Ca^{2+} signal transmission appears to involve actin filaments, because actin polymerization inhibitor abolished Ca^{2+} responses (Diamond et al., 1994). Taken together, these studies suggest that calcium is an important mediator in cellular mechanotransduction.

8. Summary

Tendons are responsible for transmitting muscle-derived forces to bone and as a result, are subjected to dynamic mechanical loads. Although the effects of mechanical loading on tendons have been recognized for many years, little is known concerning the effects of mechanical forces on tendon cells and the mechanisms of mechanotransduction. During the last few decades, the rapid development of cell and molecular technologies has made it possible to investigate mechanobiological responses and mechanotransduction mechanisms. To this end, various culture systems have been developed to apply controlled mechanical forces/deformations to cells in culture. As a result, many cellular components, including integrins and membrane receptors, have been identified as mechano-transducers that

detect mechanical forces and mediate cascades of mechanotransduction events. The actin cytoskeleton plays a central role in mechanotransduction. It transmits and modulates the tension between the extracellular matrix, focal adhesion sites, and integrins. Subsequently this may lead to conformational changes in integrins, G proteins, and ionic composition, where these changes stimulate membrane receptors and induce complex biochemical cascades, including sequential phosphorylation of MAPKs, activation of transcription factors, subsequent gene expression, protein synthesis, and cell differentiation.

Future studies may proceed in several directions. First, it is necessary to identify the signaling pathways that lead to differential ECM gene expression and protein synthesis from different mechanical loading conditions. For example, appropriate mechanical loading from training results in positive changes in tendons, whereas excessive mechanical loading leads to tendon disorders such as tendon inflammation and degeneration.

Second, the interaction between mechanical forces and humoral factors needs to be investigated in tendons. There are few studies in this regard, but it is known that humoral factors (e.g., hormones, growth factors, and cytokines) in healing tendons are essential for inflammation, repair, and remodeling, as are the mechanical forces during tendon healing. With established cell culture models, the interaction between mechanical loading and humoral factors can be studied. For example, cyclic stretching of chondrocytes inhibits the inflammatory effects due to IL-1β treatment (Agarwal et al., 2001). Similarly, other factors, including cytokines, can be simultaneously tested on cultured cells under various mechanical loading conditions.

Third, studies that incorporate both culture and animal elements may be necessary to investigate mechanotransduction at the cell and tissue levels. In cell culture studies, one can readily control experimental conditions. However, it is difficult "if not impossible" to use cell culture to simulate the complexity of cell-to-cell and cell–matrix interactions as well as incorporate intercellular communication among different cell types. Also, in cell culture experiments, there are many variables that can influence cell phenotype and behavior. These include culture conditions, such as nutrients, growth factors, surface structure and chemistry of the culture substrate. Therefore, it is desirable to use tendon cultures to relate cell culture studies to those conducted at the tissue levels (Hannafin et al., 1995; Nabeshima et al., 1996). Furthermore, transgenic/knockout animal models can be used to study the contribution of a particular protein to tendon cell mechanobiology. This type of investigation will enhance our understanding of how mechanical forces influence tendon cell function in normal and diseased states.

Finally, mechanobiological approaches can be extended to study the responses of tissue-engineered constructs to enhance their in vitro and in vivo performance. Tissue engineering uses stem cells, growth factors, scaffolding materials, and their combinations to repair or regenerate injured connective tissues such as tendons (Butler et al., 2000; Guilak, 2002; Woo et al., 1999). However, little is known about how mechanical forces affect stem cell proliferation and differentiation, the remodeling of engineered tendon constructs, and the interaction between mechanical loading and humoral factors (e.g., hormones and growth factors). It has been shown that tendon cells in collagen gel constructs subjected to cyclic mechanical stretching exhibit a phenotype that is similar to that of native tendons, and that the collagen gel constructs are stronger than non-stretched counterparts (Garvin et al., 2003). Also, mechanical loading and humoral factor interact and result in synergistic effects (Agarwal et al., 2001; Archambault et al., 2002; Banes et al., 1995; Xu et al., 2000). Finally, tension exerted on the ECM may be required to maintain tissue structure and function (Langholz et al., 1995). Therefore, mechanical forces are an essential element for successful tissue engineering of tendon constructs, repair, or regeneration.

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