**Summary.** Tendons are the structures that attach muscles to bones and transmit mechanical forces. Tendon cells are composed of mature tenocytes and a rare population of tendon stem cells. Both cell types ensure homeostasis and repair of tendon extracellular matrix to guarantee its specific mechanical properties. Moreover, tendon cells seem to present a marked potential for trans-differentiation, predominantly into the chondrocyte and osteoblast lineages. In this review article, we first present chronic tendon pathologies associated with abnormal ossification, such as spondyloarthritis and calcifying tendinopathy, and discuss how tendon cell differentiation and trans-differentiation may participate in these diseases. We moreover present the factors known to influence tendon cell differentiation and trans-differentiation, with a particular emphasis on extracellular environment, mechanical stimulation and several soluble factors that can tip the balance toward one or another lineage. A better understanding of the neglected tendon cell biology may be extremely useful to understand the pathological mechanisms of spondyloarthritis and calcifying tendinopathy.

**Key words:** Tenocytes, Tendon stem cells, Transdifferentiation, Pathological ossification

**Introduction**

Tendons attach muscles to bones and their essential role is transferring contraction forces. This function explains why tendon physiology and pathology are highly dependent on mechanical stress. As connective tissues, tendons are mainly composed of an organized extracellular matrix (ECM), which confers to the tissue its mechanical properties: high strength and good flexibility and elasticity. In tendons, the ECM represents approximately 95% of the tissue volume, with type I collagen fibers accounting for 95% of all ECM components. Collagen fibers are organized in bundles that are arranged parallel to the forces exerted on the tendon (Fig. 1). This axial alignment is essential for tendon-specific mechanical features [for a review more focused on tendon structure and biomechanics, please read (Wang et al., 2012; Weinreb et al., 2014)].

Overall, the tendon is a poorly cellularized tissue (Tozer and Duprez, 2005). Tendon cells are fibroblast-like cells, which present an elongated morphology. They are stuck between the collagen bundles and align along the long axis of the tendon. The mature differentiated resident cells of tendons are called tenocytes. Tenocytes are the dominant contributors to tendon homeostasis and repair, which is to say the dominant contributors to tendon ECM remodeling. In addition, tendons contain a unique cell population of progenitor cells referred to as tendon stem cells (TSCs).

**Distinct types of tendon pathologies**

Tendon injuries can result from an acute trauma or from a chronic degenerative process (Sharma and
Maffulli, 2005). Acute tendon injury causes disruption of tendon ECM continuity and thus dramatic loss of mechanical force transmission between muscle and bone. Chronic tendon diseases are classified in two types: inflammatory enthesitis and tendinopathies (Weinreb et al., 2014).

- Entheses are the sites of insertion of tendon or ligament to bone through a fibrocartilaginous connection (Fig. 2). Inflammatory enthesitis deals with an inflammation in this area and it is a characteristic of spondyloarthritis.
- Tendinopathy was traditionally named tendinitis. This term recovers any painful state arising in or around tendons due to mechanical, degenerative or overuse disease. Degeneration and disorganization of the tendon structure may lead to full thickness tear.

**Tendon pathologies associated with excessive ossification**

Enthesophytes: spondyloarthritic ossification

In spondyloarthritis, inflammation first develops in entheses. This severe inflammation (enthesitis) is followed at late stages by an abnormal ossification spreading from the underlying bone to the tendon or ligament. These excessive ossifications are the so-called enthesophytes. The orthotopic new bone formation at enthesis in the pathological context of spondyloarthritis is relatively similar to the normal age-related process of tendon ossification. Bony spur initiation and development involve both endochondral and intramembranous ossifications. However, enthesophytes look less well-organized and structures called cartilage metaplasia can appear in tendons and/or bones (Benjamin et al., 2009; Lories and Schett, 2012). Very small spurs are seen in patients with early spondyloarthritis and in normal subjects, whereas large spurs are characteristic of patients with late spondyloarthritis (McGonagle et al., 2008).

**Calcifying tendinopathy**

Calcifying tendinopathy (or calcific tendinitis) is a subset of tendinopathy characterized by the presence of calcifications inside tendons. This abnormal ossification deteriorates tendon structure and worsens the clinical symptoms. New bone formation in the pathological context of calcifying tendinopathy is also suggested to resemble endochondral ossification. Fibrocartilage structures emerge in the diseased tendon, and progress toward calcification (Uhthoff et al., 1976; Fenwick et al., 2002).

**Pathological behavior of tendon cells**

Increasing evidence indicates that the abnormal ossification of the diseased tendon in calcifying tendinopathy or the diseased enthesis in spondyloarthritis is due to a pathological behavior of tendon cells (Rui et al., 2011b; Lories and Schett, 2012). Both tenocytes and TSCs may be involved in this pathological process. Tenocytes may be responsible for tendon matrix degeneration and degradative events and TSCs may present aberrant functions due to modifications of their microenvironment (Clegg et al., 2007; Lui and Chan, 2011). Several studies reported an altered fate of tendon cells in distinct pathological contexts. For instance, an
overuse protocol showed in adult rats that excessive mechanical stimulation increases gene expression of cartilage markers in tendon cells (Archambault et al., 2007). A collagenase-induced tendon injury model was also used to show that TSCs express more chondrocyte and osteoblast markers and less tenocyte markers, compared to healthy TSCs. Moreover, upon stimulation, the trans-differentiation potential of degenerative TSCs toward chondrogenic and osteogenic lineage appears enhanced (Rui et al., 2013a). Analysis of tissue from human Achilles tendon lesions has also featured an up-regulation of cartilage matrix and marker genes (de Mos et al., 2009).

As discussed below, tendon cells are known to be highly mechanosensitive. Yet, it seems that cyclic strain has no effect on tendon cells isolated from patients with tendinopathy. Thus, degenerative tendon cells present an altered response to mechanical stress (Choi et al., 2014). This aberrant mechanosensitivity may be due to dysregulation in cell-matrix interactions and/or aberrant actin cytoskeleton organization (Kohler et al., 2013).

Growth factors likely involved in tendon cell pathological behavior

Mediators of pathological behavior of tendon cells have essentially been studied by Lui and colleagues in the model of tendon ossification induced by injection of collagenase into the patellar tendon of rats. Bone morphogenetic proteins (BMPs) have proven to be highly implicated. BMPs are a subfamily belonging to the transforming growth factor (TGF)-β superfamily. The BMP family includes 20 members, which are active as secreted homo- or hetero-dimers. They are particularly well-known for their ability to induce ectopic formation of bone and cartilage. Immunohistochemical staining proved the presence of BMP-2 but also -4 and -7 in ossifying tendons. BMP-2 was especially located around chondrocyte-like cells (Lui et al., 2009; Yee et al., 2011). At the cellular level, higher expression of BMP ligands and specific receptors (BMPRs) has been detected in degenerative TSCs than in healthy ones. Signal transduction through BMPRs results in phosphorylation of downstream Smad pathway targets. Accordingly, upon stimulation, diseased TSC showed enhanced BMP-Smad sensitivity (Lui and Wong, 2013). Moreover, clinical data corroborate the putative role of BMP signaling in tendon pathology associated with abnormal ossification. BMP-2 and -6 precursors have indeed been found in synovial tissue biopsies and activation of the BMP pathway has been detected in enthesis biopsies from spondyloarthritic patients (Lories et al., 2003, 2005). Furthermore, differential expression of BMP-2, -4, -6 and -7 has been shown in patients with degeneration or calcific tendinopathy of the rotator cuff (Neuwirth et al., 2006; Oliva et al., 2011).

Alongside the TGF-β superfamily, Wnt proteins are also preponderant regulators of tissue development and maintenance. The Wnt family includes 19 secreted lipid-modified signaling glycoproteins, whose downstream pathways can be canonical (involving the protein β-catenin) or non-canonical. Of interest, activation of the canonical Wnt pathway has also been shown in the rat ossifying tendon model (with an increased expression of Wnt-3a and β-catenin) and in some patients with patellar tendinopathy (Lui et al., 2013).

Two cell populations in tendon: tenocytes and tendon stem cells (TSCs)

Understanding tendon cell biology and contribution of tenocytes and TSCs to tissue homeostasis and repair should help to understand the development of tendon pathologies.

Tendon stem cells

TSCs have recently been identified and characterized (Bi et al., 2007). They possess stem cell characteristics of clonogenicity, multipotency and self-renewal. First identified in human and mouse tendons, TSCs have been isolated from rat and rabbit tendons since then (Rui et al., 2010; Zhang and Wang, 2010b). This unique population may represent 1 to 3% of the tendon cells. Among mouse tendon-derived cells, the percentage of colony-forming cells has been recorded around 3%, and that of slow-cycling cells around 6%. Comparably, the percentage of TSCs within rat tendon-derived cells has been estimated at around 1-2%. The multi-differentiation potential of TSCs includes differentiation into tenocytes, adipocytes, chondrocytes and osteoblasts. Their osteogenic, chondrogenic and adipogenic multipotent differentiation capacity appears to be greater than that of bone marrow stromal cells (Bi et al., 2007; Tan et al., 2012). Upon osteogenic stimulation, faster accumulation of calcium and a higher number of nodules have been observed, together with higher expression of osteogenic markers. Upon chondrogenic induction in pellet culture, type II collagen and glycosaminoglycan deposition and chondrogenic marker expression is also increased. Adipogenic conditions induce adipocyte marker expression and more lipid droplets have been observed in TSC than in bone marrow stromal cells. The tenogenic capacity of TSC seems to vary depending on their position within the tissue. TSC are mostly located in the peritendinous zone and the tendon-bone junction, but also in the tendon core (Tan et al., 2013). Tendon core-derived progenitors show a higher tenogenic potential than progenitors from the peritendinous tissue; they express greater levels of tenogenic markers and produce a more tendon-like ECM (Mienaltowski et al., 2014).

Tenocytes

Tendon-specific mechanical properties rely on an ECM free from defect. The influence of tenocytes on tissue tensile properties is negligible (Hammer et al., 2014) but their role is to maintain ECM integrity.
Tenocytes produce large amounts of ECM, in particular type I collagen (Fig. 3), which is the major component of the tendon ECM (about 75% of tendon dry weight). Type I collagen is a heterotrimer helical molecule consisting of two α-1 chains and one α-2 chain. Of note, replacement of the α-2 chain by an α-1 chain, which occurs in the case of osteogenesis imperfecta, results in reduced mechanical strength of the tendons (Chang et al., 2012). Type I collagen fibers are organized with other minor types of collagens, such as the fibrillar type III collagen. Other matrix proteins are also produced by tenocytes, in particular elastin, which forms extensible cross-linked chains that provide elasticity to the ECM, and tenasin C, which is a homohexameric glycoprotein that modulates cell adhesion to the ECM. Tenocytes also produce various proteoglycans, including decorin, which binds to collagen fibers and may affect the collagen fibrillation. In addition, tenocytes are characterized by expression of tenomodulin (Tnmd), also known as tendin. Tenomodulin is a transmembrane glycoprotein belonging to the chondromodulin-1 family that is strongly expressed in tendons and ligaments (Brandau et al., 2001). Tnmd-deficient mice (Docheva et al., 2005) show a decrease in tenocyte proliferation that leads to a reduced tenocyte density. The amount of ECM proteins is not affected, but collagen fibril diameter is abnormal. Therefore, tenomodulin appears crucial for tendon physiology as it seems to regulate tenocyte proliferation and collagen fibrillation (Docheva et al., 2005). Expression of tenocyte specific markers is under the control of one important transcription factor: scleraxis (Scx). This basic helix-loop-helix (bHLH) transcription factor requires dimerization with another bHLH protein for efficient DNA binding to the E-box consensus sequence (Cserjesi et al., 1995). Its expression can be used as a marker of progenitors and mature cells of all tendon tissues (Schweitzer et al., 2001). Scx was shown to regulate in particular the transcription of Collα1 and Collα2, coding type I collagen α-1 and α-2 chains (Léjard et al., 2007; Bagchi and Czubryt, 2012). Scleraxis thus appears to be involved in the transcriptional regulation of key ECM components specifically in tendon cells. Scx-deficient mice (Murchison et al., 2007) show severe defects in tendons associated with reduced and disorganized ECM, revealing that scleraxis is crucial for tendon differentiation, especially in force-transmitting tendons, by opposition to muscle-anchoring tendons.

**Tenogenic differentiation**

Like other musculoskeletal cells such as myoblasts, chondrocytes and osteoblasts, during embryonic development, tenocytes derive from mesodermal progenitor cells (Tozer and Duprez, 2005). Cell orientation toward the tendon lineage goes along with a persistent expression of the master gene scleraxis and an increasing expression of tenomodulin at the late stages (Schweitzer et al., 2001; Docheva et al., 2005). In addition to scleraxis, another transcription factor called mohawk (Mkx) has recently been shown to be a critical regulator of tenogenic differentiation (Ito et al., 2010). Tendons of Mkx-deficient mice show defects in collagen fibrillation (Ito et al., 2010; Liu et al., 2010), suggesting that mohawk, like scleraxis, is involved in tendon ECM regulation. The more we learn about physiological tenogenic differentiation, the better we will know how to treat tendon pathologies. Any means that could enhance tenogenic differentiation is of particular interest in the context of tendon tissue engineering. Indeed, cell therapy in tendon disease is a current hot spot of the field (Ho et al., 2014).

**Soluble differentiation factors**

Several studies have highlighted the capacity of tendon tissue or tenocytes to orientate stem cell differentiation toward the tenogenic lineage. For instance, indirect co-cultures of bone marrow mesenchymal stem cells (MSCs) with tendon tissue fragments have tenogenic effects (Lovati et al., 2012). Similarly, direct co-culture of MSCs with primary tenocytes upregulates tenocyte markers including type I collagen, tenomodulin and scleraxis (Schneider et al., 2011). Furthermore, numerous intercellular contacts between MSCs and tenocytes have been reported suggesting an extensive exchange of soluble factors. Among soluble tenogenic factors, particular attention was paid to the growth and differentiation factor (GDF) family. GDFs are members of TGF-β superfamily proteins, such as the previously mentioned BMPs. GDF proteins (GDF-1 to GDF-15) are active as secreted homodimers that are particularly involved in development. GDF-5 was in particular shown to promote differentiation of TSCs towards tenocytes, by up-regulating ECM proteins such as type I collagen or

![Image](image_url)

**Fig. 3.** Immunofluorescence staining of type I collagen in cultured tendon cells from new-born mouse tail tendons. Nucleus was stained by Hoechst (in blue). All tendon cells are producing type I collagen (in green).
decorin, and tendon specific markers such as scleraxis and tenomodulin, in particular (Holladay et al., 2015; Mienaltowski et al., 2014). These tenogenic effects of GDF-5 are also observed on bone-marrow derived MSCs, adipose tissue-derived stem cells or periodontal ligament cells (Tan et al., 2012; Raabe et al., 2013; Xia et al., 2013). However, GDF-5 is known to affect various other skeletal tissues such as intervertebral disk, cartilage and bone (Mikic, 2004). In some in vitro studies, GDF-5 seemed to reduce adipogenic, chondrogenic and osteogenic pathways along with favoring tenogenic differentiation (Tan et al., 2012a,b; Xia et al., 2013; Holladay et al., 2015).

Similarly, GDF-7 (also called BMP-12) was shown to activate tendon transcription factors including scleraxis and mohawk and tendon markers including tenomodulin and decorin in bone marrow MSCs (Violini et al., 2009; Otabe et al., 2015). GDF-7 has tenogenic effects on adipose tissue- derived stem cells comparable to those of GDF-5 (Raabe et al., 2013; Shen et al., 2013). However, GDF-7-induced orientation toward tenocytes lineage seems less frank than that induced by GDF-5 because some chondrogenic and osteogenic markers seem also to be upregulated by GDF-7 (Shen et al., 2013).

**Extracellular three-dimensional environment**

Because in situ tenocytes are embedded in a highly specific ECM, the role of tendon matrix components and/or structural organization on tenogenic differentiation is likely crucial. Indeed, tendon-derived decellularized ECM promotes tenogenic differentiation in TSCs while inhibiting osteogenesis (Yin et al., 2013). The tenogenic potential of tendon matrix components on adipose tissue stem cells has been assessed by Yang and colleagues: the addition of urea-extracted fraction of tendon ECM, which contains critical tendon ECM components, to a collagen gel, increases tenogenic markers tenomodulin, scleraxis and tenascin C, while reducing osteogenic markers (Yang et al., 2013).

The structural organization of the extracellular environment is also significant for tenogenic differentiation. Tissue-engineered scaffolds should be shaped as dense and aligned fibers to mimic tendon ECM collagen network. Indeed, a synthetic matrix composed of aligned collagen threads has been shown to enhance tenogenic differentiation of MSCs and adipose tissue-derived stem cells, compared to randomly oriented collagen, without osteogenic trans- differentiation (Kishore et al., 2012; Cheng et al., 2014).

**Mechanical stimulation**

Tendons are subjected to high mechanical stress and tenocytes are surrounded by a mechanoactive environment. Cyclic stretching has been shown to promote tenogenic differentiation of bone marrow MSCs, with an increase in tenogenic marker expression and tendon ECM deposition (type I collagen and tenascin C, in particular) (Kuo and Tuan, 2008; Morita et al., 2013; Nam et al., 2015). This differentiation was efficiently induced by 8 to 10% uniaxial stretching stimuli and seemed associated with cell orientation angle and cumulative elongation load on the cells (Morita et al., 2013; Nam et al., 2015). RhoA/ROCK, cytoskeletal organization and focal adhesion kinase appears to be part of the signaling pathways that drive mechanical stretch-induced tenogenic differentiation of MSC (Xu et al., 2011, 2012). Furthermore, dynamic stretching seems required to preserve tenocyte phenotype over time. In MSC culture, mechanical stress is necessary to sustain expression of the tenocyte marker scleraxis (Kuo and Tuan, 2008). Similarly, in the absence of mechanical stress, allogeneic tenocytes seeded in tendon scaffolds fail to preserve ECM homeostasis, whereas under cyclic strain, they maintain the construct’s tensile properties (Whitlock et al., 2013).

**Combined strategies for tendon tissue engineering**

Now that various tenogenic factors are identified, new approaches currently test different combinations of them to further optimize tenogenic differentiation (Fig. 4). The main objective of these studies is to develop functional constructs for tendon tissue engineering. For
instance, tendon ECM-mimicking scaffolds can be associated with mechanical stimulation to enhance MSC differentiation toward tenocyte lineage (Teh et al., 2013; Yang et al., 2013; Czaplewski et al., 2014). Dynamic culture conditions can favor the intensity and onset of differentiation markers, accelerate tendon matrix deposition and improve tensile properties of the constructs. Mechanical forces and three dimensional environments can be further combined with soluble factors to synergistically enhance stem cell tenogenic differentiation (Raabe et al., 2013; Barsby et al., 2014).

**Trans-differentiation potential of tendon cells**

As discussed above, several tendon pathologies are associated with abnormal ossification. Studying chondro- or osteogenic trans-differentiation of tendon cells may provide new tools to address cellular events in pathological context. The multipotency of TSCs has been proven for tenogenic, adipogenic, chondrogenic and osteogenic lineages (Bi et al., 2007; Rui et al., 2010; Zhang and Wang, 2010b; Tan et al., 2012a,b). In addition, mature tenocytes also show an intrinsic trans-differentiation potential and can turn into adipocytes, chondrocytes or osteoblasts (de Mos et al., 2007). Thus, supplemental studies were conducted to isolate the molecular mechanisms that can favor tendon cell trans-differentiation in one or another cell lineage.

**Proximity of tenogenic and chondrogenic lineages during development**

During embryonic development, tendon morphogenesis is strongly associated with chondrogenesis. Even if considered as a tendon marker, scleraxis seems to have multiple roles during mouse embryogenesis, and is described as a regulator of gene expression in mesoderm formation and chondrogenesis (Cserjesi et al., 1995; Brown et al., 1999). The balance between sox9 and scleraxis, key transcription factors of chondrocytes and tenocytes respectively, appears to be tightly regulated during the coordination of tendon and skeleton development (Asou et al., 2002). A unique pool of progenitor cells expressing both sox9 and scleraxis has been characterized. These cells can give rise to both chondrocytes and tenocytes and are expected to contribute to the establishment of the junction between cartilage and tendon (Blitz et al., 2013; Sugimoto et al., 2013). Indeed, inactivation of sox9 in those cells causes defects in tendon-bone structure formation. TGF-β

![Fig. 5. Balance between tenogenic differentiation and chondro- or osteogenic trans-differentiation. Extracellular environment, mechanical stimulation and various soluble factors from GDF, BMP and Wnt families can tip the equilibrium toward one or another lineage. Cellular switch from physiological tenogenesis to pathological chondro- or osteogenesis may lead to abnormal ossification.](image-url)
Tendon cells in tendon pathologies

superfamily proteins seem especially involved in regulating the balance between sox9 and scleraxis and therefore in the shift between chondrogenesis and tenogenesis. TGF-β ligands have been shown to regulate the emergence of bone attachment structures from sox9- and sex-positive cells (Blitz et al., 2013). Similarly, TGF-β ligands (including TGF-β1 and 2) down-regulate sox9 and up-regulate scleraxis and tenomodulin in micromass cultures of mesenchymal cells (Lorda-Diez et al., 2009).

Chondrogenic trans-differentiation

Concerning chondrogenic trans-differentiation of tendon cells, particular attention was paid to the BMP family of growth factors. For instance, injection of BMP-7 into rat Achilles tendon induces trans-differentiation of tendon cells towards chondrocyte-like cells and changes the surrounding ECM composition with an enrichment in cartilage-specific proteins, i.e. glycosaminoglycan and type II collagen (Ozeki et al., 2013). In response to BMP-2, tenogenic marker expression is decreased in TSCs, whereas chondrogenic orientation is enhanced, as shown by an increase in glycosaminoglycan deposition (Rui et al., 2013). Tendon cells grown in pellet culture in chondrogenic medium have the same differentiation potential as MSCs (Funakoshi and Spector, 2010). Overall, tenocytes proved to have a strong potential for conversion into chondrocytes.

Osteogenic trans-differentiation

Osteogenic trans-differentiation seems to be greatly influenced by the extracellular three dimensional environment. As tendon decellularized ECM can turn TSC toward tenogenic lineage, bone decellularized ECM can strongly turn them toward osteogenic cells (Yin et al., 2013). Interestingly, alteration of TSC niche-associated ECM by genetic inactivation of two small proteoglycans led to tendon malformation and abnormal ossification (Bi et al., 2007). In these mice, TSCs switched from tenogenesis to osteogenesis through an ectopic activation of BMP signaling. Lots of cytokines and growth factors are stored within the ECM and the authors suggested that modifications in its composition may possibly perturb the differentiation cocktail delivered onto TSC.

Moreover, TSCs can also be induced to trans-differentiate into osteogenic lineage by specific mechanical stretching (Zhang and Wang, 2010a; Shi et al., 2012). Stretch-induced osteogenic response of TSC may be partly mediated by Wnt-5a and by BMP-2. An up-regulation of BMP-2 was observed in stretched TSCs and addition of BMP-2 on cultured TSCs increases osteogenic trans-differentiation, leading to characteristic mineralization (Rui et al., 2011a). The strong osteogenic potential of BMP-2 on tendon cells has been demonstrated several times. For example, over-expression of BMP-2 in tenocytes is sufficient to induce the osteogenic mineralization process (Murray et al., 2010). Similarly, mineralization is induced by addition of BMP-2 in TSC cultures (Rui et al., 2012). BMP-2-mediated osteogenic trans-differentiation of TSCs was also observed in response to prostaglandin E2, suggesting that BMP-Smad pathway may be activated by inflammatory disorders (Zhang and Wang, 2012; Liu et al., 2013). Alternatively, increased mineralization and expression of osteogenic markers have also been observed in TSCs in response to Wnt signaling activation by Wnt-3a (Lui et al., 2013).

Finally, tendon cell capacity to trans-differentiate into the osteogenic lineage seems as strong as into the chondrogenic lineage. Therefore, we can conclude a strong chondro- and osteogenic potential, which could be partly explained by a high sensitivity to BMP signals, as a consequence of high expression levels of BMP receptors (Rui et al., 2012).

Conclusion

The tenocyte phenotype must be tightly regulated to preserve tissue homeostasis and to maintain tendon-specific mechanical properties. Control of tenogenic differentiation of both mature differentiated tenocytes and TSCs appears essential in tendon development and remodeling but also in the repair process. Tendon cells proved to have a strong potential for chondro- or osteogenic trans-differentiation, and the balance between tenogenesis and chondro- or osteogenesis seems tenuous. A set of factors, including the three dimensional environment, mechanical stress, GDF, BMP and Wnt signaling have been shown to participate in this equilibrium (Fig. 5). Different tendon pathologies, including spondyloarthritis and calcifying tendinopathy, cause cartilage metaplasia, which further degenerates into abnormal ossifications. These ectopic calcifications in the tendon core or in enthesis lead to dramatic loss of force transmission between muscle and bone and thus to significant disability for the patients. A better understanding of tendon cell biology therefore deserves investigation.

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