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Cyclic stretch induces decorin expression via yes-associated protein in tenocytes: A possible mechanism for hyperplasia in masticatory muscle tendon-aponeurosis hyperplasia

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ABSTRACT

Objective: Masticatory muscle tendon-aponeurosis hyperplasia (MMTAH) is a disease which exhibits limiting mouth opening caused by hyperplasia of the tendon and aponeurosis of bilateral masticatory muscles. Although it is unclear whether hyperplasticity of tendons in MMTAH is due to cyclic stretch, we hypothesize that cyclic stretch is the main cause of force on MMTAH. In this study, we examined decorin expression in the masticatory muscle tendon of MMTAH patients. We also examined decorin (Dcn) expression of tenocytes on which stretch forces are loaded to explore whether stretch forces affect yes-associated protein (YAP) signaling and whether Dcn expression is regulated by YAP.

Methods: Quantitative reverse-transcription polymerase chain reaction, immunoblot analysis and immunohistochemistry were performed in tendons of patients having MMTAH. Mechanical loading experiment for TT-D6 tendon fibroblastic cells using RNA interference technique was conducted.

Results: We found that Dcn expression is increased in tendons of MMTAH patients. We also showed that cyclic stretch force increases decorin expression in TT-D6 tendon fibroblastic cells and that Dcn expression is regulated via YAP in TT-D6 tendon fibroblastic cells acted upon by cyclic stretch.

Conclusions: Our results, for the first time, demonstrated that cyclic stretch induces decorin expression via YAP in tenocytes and Dcn is upregulated in tendons of MMTAH, suggesting that tendons of MMTAH were subjected to cyclic stretch conditions.

1. Introduction

Masticatory muscle tendon-aponeurosis hyperplasia (MMTAH) is a disease caused by hyperplasia of the tendon and aponeurosis in bilateral masticatory muscles, which exhibits limiting mouth opening in the affected individuals, [1]. Although the etiology of MMTAH still remains unclear, bilateral juvenile onset and parafunctional habits suggest that environmental and genetic factors may be involved in the progression of this disease. Although the tendons and aponeuroses of MMTAH patients appear to be physiologically normal, microstructural observation by electron microscopy reveal mineralized nodules and silicon along with calcium and phosphorus deposits in the tendon tissues. However, such findings are not exhibited by patients with facial deformities [2]. Through proteomic analysis, we have also

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demonstrated that fibrinogen fragment D and β-crystallin A4 were up-regulated and myosin light chain 4 was down-regulated in patients with MMTAH compared to patients with facial deformities [3].

Mechanical overloading increases muscle and tendon volumes [4]. It has been observed that tendon and muscle volumes of MMTAH patients are clinically higher than those of normal individuals, indicating that excessive mechanical loading is involved in the onset or development of MMTAH. Excessive mechanical loading on muscle and tendon of such patients is in the form of stretching or compression force. However, the main cause of such force in MMTAH still remains unclear. The effects of mechanical forces on skeletal muscles and tendons has been well-investigated [5–7]. Yes-associated protein (YAP) has been identified as a sensor of mechanical activity and mediates cellular and transcriptional responses downstream to mechanical forces [8]. Accumulated evidence demonstrated that cyclic stretch activates YAP nuclear translocation [9,10]. Codelia et al. demonstrated that induction of YAP by cyclic stretch is associated with Jak/Stat signaling-dependent pathway [11].

Tendons are composed of tenocytes and extracellular matrix which includes collagen fibrils and proteoglycan. Proteoglycans play a critical role in collagen regulation and also tendon function [12]. Proteoglycans of tendons are classified into two groups, small leucine-rich proteoglycans having a small core protein and large-sized proteoglycans having a large core protein. The former includes decorin, biglycan, fibromodulin, and lumican; the latter includes aggrecan and versican. Decorin (Dcn), which is the most abundant small leucine-rich proteoglycan present in tendons, is essential for proper collagen fibrillogenesis [13].

We previously reported that collagen 6 A protein is up-regulated in the masticatory muscle tendon of patients with MMTAH [14]. However, it has not been reported whether proteoglycan production of tendons of such patients is affected. Intriguingly, it is observed that Dcn is upregulated in lamina cribrosa cells with stretch load [15] while it is downregulated in vascular smooth muscle cells with stretch load [16].

Although it is unclear whether hyperplastic tendons in MMTAH is due to cyclic stretch, we hypothesize that cyclic stretch is the main cause of force on the masticatory muscle tendon. In this study, we examined Dcn expression in the tendon of MMTAH patients and also examined Dcn expression of tenocytes on which stretch forces are loaded. Furthermore, we explored whether stretch forces affect YAP signaling and whether Dcn expression is regulated by YAP.

2. Materials and methods

2.1. Subjects

Tissue specimens from the temporal muscles and tendons of two patients with MMTAH (both MMTAH-1 and MMTAH-2 were 45-year-old women), and two patients with facial deformity (FD) [FD-1 and FD-2 were 19- and 26-year-old women respectively] whose tendon tissues showed no signs of hyperplasia were obtained at surgery. No subject had any other underlying disease and FD patients had normal mouth opening. They were treated and followed up at Saitama Medical University Hospital. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (approval number 717-III) of Saitama Medical University Hospital. All participants provided their written informed consent to participate in this study and were free to withdraw from the study at any time.

2.2. Antibodies

We used anti-rabbit YAP polyclonal antibody (#4912; Cell Signaling, Massachusetts, USA), anti-rabbit Dcn polyclonal antibody (ab175404; Abcam, Cambridge, MA, USA), anti-rabbit α-tubulin polyclonal antibody (PM054; MBL, Nagoya, Japan), and anti-mouse Histone H1 monoclonal antibody (D209-3; MBL). Anti-rabbit IgG horseradish peroxidase (HRP)-linked antibody (#7074; Cell Signaling) and anti-mouse IgG HRP-linked antibody (#7076; Cell Signaling) were used as secondary antibodies.

2.3. Cell culture

TT-D6 tendon fibroblastic cells were cultured in α-minimum Eagle's medium (α-MEM; WAKO, Osaka, Japan) supplemented with 1% penicillin/streptomycin and 10% fetal bovine serum (FBS), at 33 °C in a 5% CO_2 atmosphere [17].

Tissue specimens were washed with phosphate-buffered saline (PBS), cut into small pieces with scissors, and digested for 90 min with collagenase type I (3 mg/mL; WAKO) and dispase II (4 mg/mL; WAKO) in PBS at 37 °C. After centrifugation, cell pellets were resuspended in the following culture medium: α-MEM supplemented with 2 mM glutamine, 1% penicillin/streptomycin and 20% FBS. Cells were then filtered with a cell strainer (70 μm; BD Falcon, San Jose, California) and plated. Adherent cells were cultured at 37 °C in a 5% CO_2 atmosphere [18].

2.4. Reverse-transcription quantitative polymerase chain reaction (RT-qPCR)

Tissue specimens stocked in liquid nitrogen were cut into small pieces with scissors. The harvested cells were rinsed with ice-cold PBS. QIAZOL (QIAGEN, Hilden, Germany) was added to these samples and total RNA extracted. qPCR was conducted by TaqMan-based detection using THUNDERBIRD probe qPCR Mix (Toyobo, Osaka, Japan). TaqMan Gene Expression Assay kits (Thermo Fisher Scientific) for mouse Dcn (Mm00514535_m1), mouse GAPDH (Mm99999915_g1), human Dcn (Hs00754870_s1), and human 18S (Hs99999901_s1) were used.

2.5. Immunoblot analysis

Tissue specimens stocked in liquid nitrogen were cut into small pieces and lysed with 1% Triton X-100 containing ProteoGuard™ EDTA-Free Protease Inhibitor Cocktail (TaKaRa). The harvested cells were rinsed with ice-cold PBS and then their cytoplasmic and nuclear proteins were extracted with NE-PER Nuclear and Cytoplasmic Extraction Reagents (Thermo Fisher Scientific) according to the manufacturer's instructions.

The lysates were incubated on ice for 20 min and then centrifuged at 15,000 × *g* for 5 min at 4 °C. Equal amounts of proteins were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis with 10% polyacrylamide gels containing 0.1% sodium dodecyl sulfate at 40 mA for 120 min using an electrophoresis apparatus (ATTO, Tokyo, Japan) and then electro-blotted onto Immobilon PVDF membranes (Merck Millipore, Burlington, MA, USA) at 100 V, 120 min using a tank system (Cleaver scientific, Warwickshire, UK). After blocking of non-specific binding by soaking the filters in non-fat dry milk (9999S; Cell Signaling), the desired proteins were immuno-detected with their respective antibodies. The membrane was developed using Clarity Western ECL Substrate (Bio-Rad) according to the manufacturer's instructions. The bands were visualized using a Chemi-Doc XRS system (Bio-Rad). Semi-quantification of identified bands was performed by densitometry with the Image J program. Cytoplasm Dcn and YAP were normalized by α-tubulin. Nuclear Dcn and YAP were normalized by Histone H1.

2.6. Mechanical loading experiment

Cells were seeded at 30 × 10^4 cells/well in a BioFlex 6-well plate (Flexcell International Corporation, Hillsborough, NC, USA). After 12 h of seeding, the cells were subjected to cyclic sinusoidal equi-biaxial

tensile strain (from 0% to 20% amplitude at 1.0 Hz) for the indicated times using the Flexcell FX-3000™ Tension System (Flexcell International Corporation) according to the manufacturer's instruction. Each reaction was performed in triplicate on three individual samples.

2.7. Small interfering RNA (siRNA) transfection

Silencer™ Select pre-designed siRNA for yes-associated protein 1 (s76159) as siYAP, and Silencer™ Select Negative Control No. 1 siRNA as si-control (si-CTR) were purchased from Life Technologies. They were transfected with ScreenFect A (WAKO) according to the manufacturer's instructions into TT-D6 tendon fibroblastic cells. Results are representative of more than four individual experiments.

2.8. Immunohistochemistry

For histological staining, fixed tissues were embedded in paraffin, and sectioned in 5-μm slices. They were processed for immunohistochemical procedures using anti-rabbit Dcn polyclonal antibody (ab175404; Abcam) as a primary antibody and observed under an upright microscope. We also performed hematoxylin and eosin staining.

2.9. Statistical analysis

Comparisons between two groups were analyzed using Student's t-tests, and comparisons among three groups were analyzed using one-way analysis of variance (ANOVA) and Bonferroni–Dunn methods (statistical significance at $p < 0.05$). All values are presented as the mean ± S.E.M. Results are representative examples of more than three independent sets of experiments

3. Results

3.1. Dcn expression is increased in tendons of MMTAH patients

We first examined whether tendons of MMTAH patients express Dcn mRNA using qPCR. Tendons of MMTAH patients significantly increased Dcn mRNA compared to that of FD patients (Fig. 1A). Protein levels were also estimated in FD-1 and MMTAH-1 patients. Immunoblot analysis revealed that Dcn protein level in tendons of MMTAH patients was dramatically increased in comparison with that of FD patients (Fig. 1B). We next examined the distribution of Dcn protein in temporal tendons using immunohistochemistry (Fig. 1C). Dcn protein was broadly expressed in temporal tendons of MMTAH-2 patients compared to that of FD-2 patients. These results suggest that Dcn expression is increased in tendons of MMTAH patients.

3.2. Cyclic stretch force increases Dcn expression in tenocytes

We hypothesize that loaded cyclic stretch exhibits the condition of MMTAH tendon and aponeurosis. As cyclic stretch affects Dcn expression in various cells, we investigated the expression of Dcn mRNA in tendon cells with loaded cyclic stretch. qPCR analysis revealed that Dcn mRNA expression was increased at 24 h and 48 h in cyclically stretched tenocytes (Fig. 2A). We also showed that protein expression of Dcn was increased in cyclic stretched tenocytes at 48 h (Fig. 2B).

Next, we explored whether cyclic stretch affects YAP expression at protein level. YAP, which is located in cytoplasm under the static condition, accumulates into the nucleus after cyclic stretch at 48 h [9,11]. We found that YAP is not detected in TT-D6 cells under static condition. However, YAP protein in cytoplasm fraction (Cyt) was drastically increased and YAP protein in nuclear fraction (Nuc) was increased in TT-D6 cells under stretched condition (Fig. 2B). These results suggest that cyclic stretch force increases Dcn and YAP expression in tenocytes.

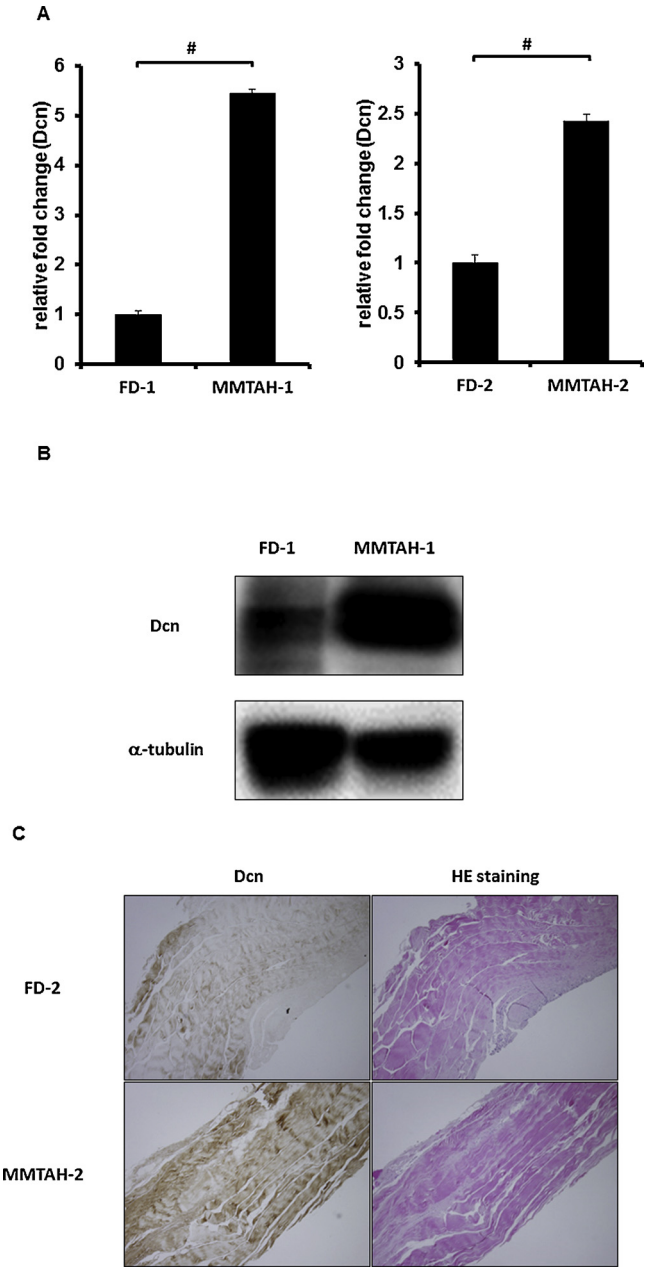


Fig. 1. Decorin expression in tendons of MMTAH and FD patient.
(A) Expression of Dcn mRNA in tendons of MMTAH and FD patients, as estimated by quantitative RT-PCR (qPCR). 18S was used as a loading control. (B) Protein expression of Dcn in tendons of MMTAH-1 and FD-1 patients, as estimated by immunoblot analysis. α-tubulin was used as a loading control. (C) Comparison between immunohistochemically stained temporal tendon of FD-2 and temporal tendon of MMTAH-2 with anti-Dcn antibody (left panel). HE staining is shown in the right panel. Each image was observed under 4x magnification. #, $p < 0.05$. Data are expressed as the means ± S.E.M.

3.3. Dcn expression is regulated via YAP in tenocytes forced by cyclic stretch

Finally, to examine whether Dcn expression is regulated via YAP during cyclic stretch, we conducted knockdown experiment by RNA interference. Cyclic stretch was performed in TT-D6 cells transfected siRNA for YAP. Decrease in YAP expression was validated by western blotting (Fig. 3A). We showed that knockdown of YAP resulted in reduction of Dcn expression (Fig. 3A). According to semi-quantitative analysis for protein expression, both cytoplasm and nuclear of Dcn

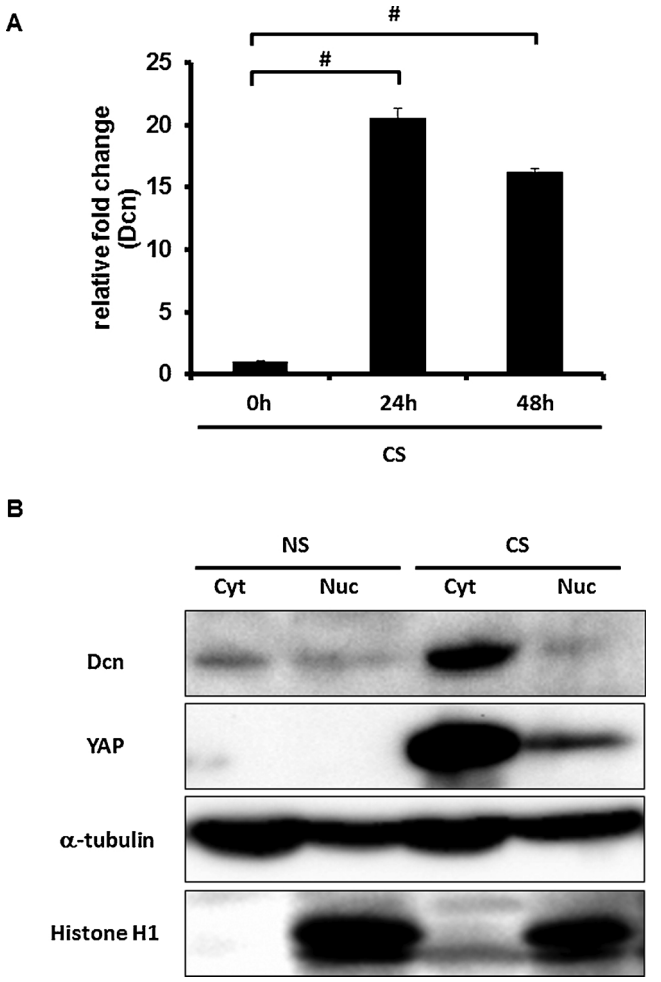
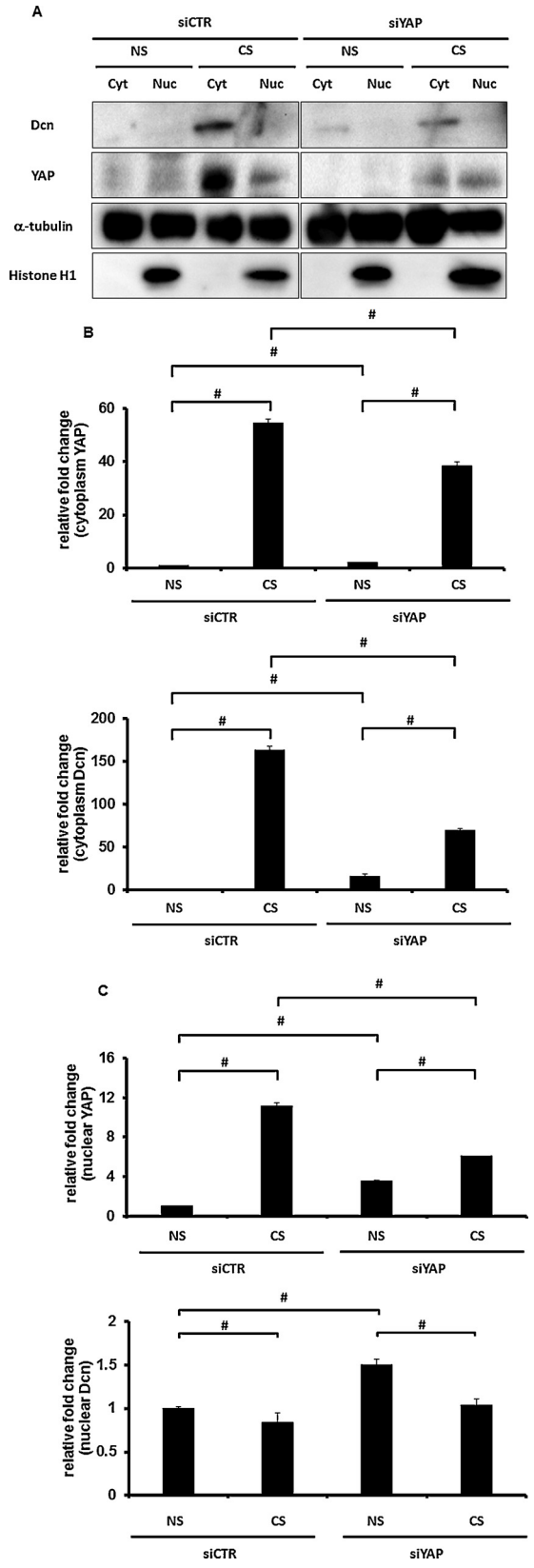


Fig. 2. Decorin and YAP upregulation in murine tenocytes under cyclic stretch. (A) Expression of Dcn mRNA in TT-D6 cells loaded with cyclic stretch, as estimated by qPCR. GAPDH was used as a loading control. (B) Protein expression of Dcn and YAP in TT-D6 cells loaded with cyclic stretch, as estimated by immunoblot analysis. α-tubulin was used as a loading control of cytoplasm fraction and Histone H1 was used as a loading control of nuclear fraction. NS, non stretch; CS, cyclic stretch; Cyt, cytoplasm; Nuc, nuclear; #, $p < 0.05$. Data are expressed as the means ± S.E.M.

expression was significantly reduced (Fig. 3B and C). These results suggest that Dcn expression is regulated via YAP.

4. Discussion

The present study demonstrated that tendons of MMTAH express Dcn protein abundantly and cyclic stretch induces Dcn expression, suggesting that tendons of MMTAH undergo cyclic stretched conditions. Fibrotic tissues such as scar have not been observed in tendons and aponeurosis of MMTAH patients. This may be associated with excessive Dcn production. Scar formation results from disorders of the collagen metabolism [19]. Excessive collagen production is regulated by the TGF- β1 signaling [20]. As Dcn inhibits the function of TGF- β1 [21,22], Dcn can reduce scar formation via inhibiting TGF- β1 signaling [23]. According to our results, Dcn is increased in tendons of MMTAH patients and Dcn expression is up-regulated in cyclic-stretched tenocytes. It is conjectured that although a stretched tendon may produce the expression of TGF- β1 which promotes collagen type I production, Dcn up-regulation inhibits TGF- β1 function. Dcn is produced by fibroblast and essential for fibrogenesis [13]. As tendons derived from MMTAH express Dcn protein, we speculate that Dcn upregulation may increase normal fibers which constitute tendons and aponeuroses of MMTAH.



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Most of MMTAH patients have oral parafunction. Aberrant habits such as chewing several pieces of gum every day lead to oral parafunction, which in turn, may cause stretch overload on bilateral masticatory muscles. Our previous study showed that the β-crystallin A4

Fig. 3. Reduction of decorin by small interfering RNA mediated YAP knockdown.
(A) Protein expression of Dcn and YAP in TT-D6 cells transfected with small interfering RNA for YAP under cyclic stretch, as estimated by immunoblot analysis. α-tubulin was used as a loading control of cytoplasm fraction and Histone H1 was used as a loading control of nuclear fraction. (B) Semi-quantitative relative protein expression of Dcn and YAP against α-tubulin for cytoplasmic fraction, as estimated by Image J. (C) Semi-quantitative relative protein expression of Dcn and YAP against Histone H1 for nuclear fraction, as estimated by Image J. NS, non stretch; CS, cyclic stretch; Cyt, cytoplasm; Nuc, nuclear; siCTR, small interfering control; siYAP, small interfering YAP. #, $p < 0.05$. Data are expressed as the means ± S.E.M.

protein is expressed significantly in the temporal tendons of patients with MMTAH compared to those in patients with facial deformity [3]. Moreover, we showed that β-crystallin A4 levels were increased by stretch force in tenocytes, suggesting that this protein may be associated with the progression of MMTAH [24].

We found that YAP signaling plays a critical role in regulating the metabolism of proteoglycans. Chakraborty et al. demonstrated that agrin promotes oncogenesis through YAP-dependent transcription and is clinically relevant in human liver cancer [25]. Their finding is that proteoglycans affect YAP signaling. However, our results are novel because for the first time, the proteoglycan, decorin, on which this study is based, is demonstrated to be regulated by YAP-dependent pathway. Other pathways related to stretch force are also known to exist. Cyclic stretch increases the phosphorylation of p70 S6 kinase (p70S6K) via mammalian target of rapamycin (mTOR) and partially increases AMP-activated protein kinase (AMPK) signaling pathway in myoblasts [26,27]. On the other hand, the small heat shock protein HspB1 (hsp25/27) is phosphorylated in stretch-stimulated mouse fibroblasts via a p38 MAPK-dependent mechanism [28]. Other study demonstrated that mechanical stretch upregulates TGF-β1 expression, which is mediated by β1-integrin and c-Src and STAT3 activation in renal epithelial cells [29]. Moreover, Yang et al. reported that cyclic uniaxial stretching condition induces TGF-β1 production in human patellar tendon fibroblasts [30].

Other stimulant induces the expression of decorin and crystallin. Abidin et al. reported that decorin and crystallin are upregulated in cornea which is stimulated with retinoic acid [31]. Our present and previous data demonstrated that cyclic stretch induces the upregulation of decorin and crystallin in tenocytes [24]. We speculate that retinoic acid may induce the molecule which is activated by cyclic stretch.

This study has the following limitations. Firstly, the stretch system experiments in this study are not performed in vivo. Secondly, as we have used murine tenocytes, it is unclear whether the present results are applicable to human tenocytes. However, we believe that our study partially sheds light on the mechanisms of hyperplastic tendons in MMTAH. Further experiments are needed to elucidate the precise mechanisms of the disease onset.

Funding

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Conflict of interest

The authors have no conflicts of interest to declare.

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