

Molecular Mechanisms of Tendon Healing and their Potential Clinical Applications: A Review of Recent Developments

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ABSTRACT

Tendon injuries are frequent and responsible for substantial morbidity both in sports and in the workplace. Tendon injuries possess an elevated morbidity percentage and is challenging to accomplish a satisfying prognosis with currently accessible management methods. Contemporary strategies utilized for tendon healing constantly result in the formation of fibrovascular scar tissue, which substantially affects the biomechanics of the healed tendon. Furthermore, the related functional deficit declines over time with an augmented injury repetition risk. Tendinopathies are aching, impairing conditions that affect 25% of adults all over the world. In this article a narrative review of the literature on known general molecular mechanisms of tendon healing and their potential clinical applications has been performed. Based on experimental and in vitro studies, the most important new possible therapeutic options for tendon healing include asperosaponin VI, hyaluronic acid, substance P inhibitor, tetranectin, platelet-rich plasma (PRP), platelet-derived growth factor, promethazine, milk fat globulin

protein E8, SS-31 (elamipretide), tamoxifen, kartogenin (KGN)-PRP gel, and percutaneous electrolysis. Based on clinical studies, the most important new possible therapeutic options for tendon healing include acellular dermal matrix (ADM), sodium hyaluronate, augmentation with resorbable type I bovine collagen implant, and microfragmented adipose tissue (M-FATS). Although much progress has been made in understanding the molecular mechanisms of tendon healing, much remains to be understood about them. It is hoped that future research may help to fully or better understand these mechanisms, which will be very important to find new therapies to help improve the healing capacity of tendon injuries.

Key words: Tendon healing; Molecular mechanisms; Clinical applications

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INTRODUCTION

Tendon injuries can be incapacitating, and that tendon pathology has turned into notably important only in the last few years, mainly for two reasons: (a) The dissemination of competitive sports at a high level; (b) Different strategy to tendon injuries since there is better information on the physiopathology and molecular configuration of tendons^[1].

Tendon is a dense connective tissue that transfers mechanical forces from skeletal muscle to bone^[2]. Tendons are essential for the function of the musculoskeletal system both to confer stability and to allow movement; however, little is known about the molecular mechanisms involved with tendon development and tendon cell differentiation^[3,4].

Tendon injuries are common and are responsible for substantial morbidity both in sportspeople and in the general population^[5]. Tendons are regularly put through mechanical stresses and these initiate intricate mechanisms in response which affect their structure during their healing response. Whilst the importance of mechanical stresses has long

been understood for tendon function and repair, the precise mechanisms of mechanotransduction in tendon cells are unclear and the clarification of these mechanisms is a key objective in the science of tendon healing^[6]. A quarter of adults worldwide have experienced a tendinopathy^[7]. However, in spite of this, with currently accessible management methods full functional healing is difficult to achieve. Contemporary strategies utilized for tendon healing result in the formation of fibrovascular scar tissue, which substantially affects the biomechanics of the healed tendon; this is particularly important in multiply injured tendons where these structural abnormalities become cumulative^[8]. It is unlikely that these will improve without better understanding of the cells and molecular pathways that drive tendon regeneration^[9].

The purpose of this article is to perform a narrative review of the literature about recent developments in the molecular mechanisms of tendon healing and the possibility of using this knowledge for promoting tendon healing in clinical practice. On 28 February 2023 I searched in PubMed using “tendon healing AND molecular mechanisms” as keywords and found 155 results. Then I searched in PubMed using “tendon healing AND clinical applications” as keywords and found 183 results. I finally reviewed 61 because I considered that they were directly related to the title of this article.

MOLECULAR MECHANISMS OF TENDON HEALING: RECENT DEVELOPMENTS

In tendon injury, mesenchymal stem cells (MSCs) can improve tendon healing by secreting their own protein

In a controlled rat tendon injury model published in 2017, Lee et al studied whether MSCs could differentiate into the tenogenic lineage and secrete their own proteins. They found that in tendon injury MSCs can improve tendon healing by secreting their own protein and have potential as a treatment alternative in human tendinopathy^[10].

Transcription factors

The transcription factor scleraxis (*Scx*) is a precise marker of both precursor and mature tenocytes. Some studies have shown a crucial role of (*Scx*) in a progenitor-cell lineage in tendon healing of adult mouse. These progenitor cells could constitute goals in approaches to promote tendon repair^[2,3].

Small extracellular vesicles with long non-coding RNA (LncRNA) H19 “overload”

Tao et al confirmed a somewhat dependable approach for enrichment of LncRNAs into extracellular vesicles (EVs), offering new clues for modularized EVs-based treatments, and modularized EVs represented a potential option for tendon regeneration^[11]. Hayashi et al have shown that early passaged MSC-EVs facilitate Achilles tendon healing compared with senescent MSC-EVs. In this study EVs from conditioned medium of human bone marrow MSCs at passage 5 (P5) and passage 12 (P12) were examined utilizing mouse Achilles tendon rupture model and lectin microarray. P5 MSC-EVs expedited Achilles tendon healing compared with P12 MSC-EVs^[12].

The role of YAP/TAZ in tendon cells

Xu et al encountered that irisin facilitates the proliferation and tenogenic differentiation of rat tendon-derived stem/progenitor cells (TSPCs) in vitro by activating Yes-associated protein 1 (YAP) / Tafazzin (TAZ), and the process was associated with a ubiquitin-proteasome proteolytic pathway. Therefore, irisin and drugs targeting YAP/TAZ might be promising therapeutic alternatives for tendinopathy^[13].

NEW POSSIBLE THERAPEUTIC OPTIONS FOR TENDON HEALING

Experimental and in vitro studies

Based on experimental and in vitro studies, the most important new possible therapeutic options for tendon healing include asperosaponin VI, hyaluronic acid, substance P inhibitor, tetranectin, PRP, platelet-derived growth factor, promethazine, milk fat globulin protein E8, SS-31 (elamipretide), tamoxifen, kartogenin (KGN)-PRP gel, and percutaneous electrolysis. It is hoped that as the science develops, we can improve the treatment of these common but difficult to treat injuries. Table 1 summarizes the most recent data on possible treatments that could improve tendon healing from experimental and in vitro studies^[14-51].

Clinical studies

Based on clinical studies, the most important new possible therapeutic options for tendon healing include acellular dermal matrix (ADM), sodium hyaluronate, augmentation with resorbable type I bovine collagen implant, and microfragmented adipose tissue (M-FATS). Table 2 summarizes the most recent information on possible treatments that could improve tendon healing from clinical studies^[52-61].

CONCLUSIONS

This article has reviewed the existing knowledge on the molecular mechanisms of tendon healing and their use for new treatments to effectively improve tendon healing. Based on experimental and in vitro studies, the most important new possible therapeutic options for tendon healing include asperosaponin VI, hyaluronic acid, substance P inhibitor, tetranectin, PRP, platelet-derived growth factor, promethazine, milk fat globulin protein E8, SS-31 (elamipretide), tamoxifen, kartogenin (KGN)-PRP gel, and percutaneous electrolysis. It is hoped that as the science develops, we can improve the treatment of these common but difficult to treat injuries. Based on clinical studies, the most important new possible therapeutic options for tendon healing include acellular dermal matrix (ADM), sodium hyaluronate, augmentation with resorbable type I bovine collagen implant, and microfragmented adipose tissue (M-FATS). Whilst much progress has been made in recent years, there still remains much to be understood about the molecular mechanisms of tendon healing. It is hoped that as the science develops, we can improve the treatment of these common but difficult to treat injuries.

Table 1 Experimental and in vitro studies: possible treatments that could improve tendon healing.

AUTHORS [REFERENCE]	YEAR	FINDINGS
Hudgens et al [20]	2016	PRP contains many growth factors and cytokines that trigger several cellular signaling cascades, but it had been had to establish exactly which signaling pathways and cellular responses were triggered following PRP treatment.
Andia et al [19]	2018	PRP can be utilized in the treatment of tendinopathy due to its prospect to rebalance inflammation, and because PRP contains tendoinductive factors that can drive the fate of stem cells.
Kobayashi et al [21]	2020	Local application of PRP could improve the tissue-healing process both directly via action on localized cells and indirectly through the recruitment of reparative cells via the blood flow.

Oliva et al [16]	2021	In <i>in vitro</i> and preclinical research, HA has demonstrated physical-chemical properties that are useful to contribute to tendon healing. Besides, in clinical reports, HA has been utilized with encouraging outcomes in different tendinopathies.
Han et al [23]	2022	Exosome-delivered BMP-2 and PLA promoted tendon bone healing in rotator cuff tears via Smad/RUNX2 pathway.
Xu et al [24]	2022	IPFP MSCs-derived exosomes accelerated tendon-bone healing and intra-articular graft remodeling after ACLR, which may have resulted from the immunomodulation of macrophage polarization.
Li et al [25]	2022	BMSC-Exos promoted M1 macrophage to M2 macrophage polarization via miR-23a-3p, diminished the early inflammatory reaction at the tendon-bone interface, and promoted early healing after ACLR.
Wang et al [26]	2022	Local administration of <i>in situ</i> -forming ASC-Exos effectively facilitated the healing of bursal-side partial-thickness rotator cuff tears.
Cai et al [27]	2022	A self-healing hydrogel antiadhesion barrier with MMP-2-responsive drug release behavior was highly effective for reducing inflammation and inhibiting tendon adhesion.
Uyar et al [28]	2022	The tensile breaking force of the repaired tendons was similar to healthy controls after the application of MSCs and PRP following tendon repair.
Dietrich-Zagonel et al [29]	2022	Dexamethasone treatment at the right time point (days 7-11) and dose (0.1 mg/kg) substantially ameliorated the material properties of the healing Achilles tendon. Dexamethasone treatment was dose- and time-dependent, and positive effects were detected even in a partly unloaded condition.
Sakaguchi et al [30]	2022	IWR-1 and promethazine suppressed Wnt/ β -catenin signaling and improved the histological abnormalities of healing tendons. IWR-1, however, compromised the biomechanical properties of healing tendons, whereas promethazine improved them.
Geng et al [31]	2022	MFG-E8 promoted tendon-bone healing histologically and biomechanically, probably by the regulation of inflammatory processes via macrophage efferocytosis and M2 macrophages polarisation.
Zukawa et al [32]	2022	HD-AM prevented peritendinous adhesion macroscopically, pathologically, and mechanically without impairing the sutured tendon.
Chen et al [33]	2022	These authors developed a functionalized anti-adhesive membrane that promotes nascent tendon matrix remodeling and improves the regenerative immune microenvironment.
Wang et al [34]	2022	In flexor tendon injury, the wrapping of a Him-MFM relieved pathological responses, protected tenocytes <i>in situ</i> , and restored hierarchically arranged collagen fibers covered with basement membrane, and was structurally and functionally comparable to mature tendons.
Fakhraci et al [35]	2022	The engineered electrospun NFMs could withstand forces of 33 and 19 N before and after 1000 pull cycles that are sufficient during tendon healing process. The bonding of chitosan fibers over PCL nanofibers allowed for production of NFMs with appropriate mechanical integrity and degradation rate.
Izumi et al [36]	2022	Mucoid degeneration in injured Achilles tendons might result from the upregulated expression of genes implicated the synthesis of sulfate proteoglycans and can be inhibited by reduction of glucose utilization. Inhibition of glucose use improved structural recovery of injured Achilles tendons.
Liu et al [22]	2022	Biomechanical studies demonstrated an increase of tendon stiffness, maximum load and maximum stress with treatment of PDGF-loaded microneedles.
Chen et al [37]	2022	PDGF-BB has a positive effect on tendon healing by enhancing inflammatory responses, speeding up angiogenesis, stimulating tendon cell proliferation, increasing collagen synthesis and increasing the biomechanics of the repaired tendon.
Wang et al [38]	2022	PLGA-PDGF-AA promoted regeneration after tendon injury and serves as a potential adjuvant material for surgical tendon injury repair.
Zhang et al [39]	2022	Mitochondrial dysfunction appeared to play a role in the development of tendinopathy, and SS-31 (elamipretide), as a mitochondrial protective agent, might be a therapeutic drug in the treatment of tendinopathy.
Zhang et al [40]	2022	In a supraspinatus tendinopathy model the mitochondrial protectant SS-31(elamipretide) improved mitochondrial function, promoting tendon healing, especially when combined with removal of subacromial impingement.
Kim et al [41]	2022	A vitamin D (Vit D) delivery system with cross-linked HA hydrogel (Gel) and Tween 80 (T80), Vit D@Gel/T80, could be a new regeneration technique for the treatment of tendinopathy. Vit D@Gel/T80 diminished TNF- α induced damage to human tenocytes <i>in vitro</i> . In an animal study, the Vit D@Gel/T80 injected group demonstrated tendon restoration features. This Vit D@Gel/T80 system may be a local injection material in the treatment for tendinopathy.
Kayiran et al [42]	2022	A recent study achieved less peritendinous adhesion with the local administration of tamoxifen when compared to systemic administration of tamoxifen.
Tong et al [43]	2022	Lymphangiogenesis played a positive role in rotator cuff healing, and targeting the lymphatic drainage at healing site could be a new therapeutic method to promote rotator cuff injury repair.
Uno et al [44]	2022	A model of degenerative rotator cuff tears demonstrated that rotator cuff repair combined with BM-PRF enhanced tendon-bone continuity and augmented the VEGF-positive cells at 4 weeks and obtained preferable tendon-bone maturation at 12 weeks.
Freedman et al [45]	2022	A tough hydrogel with an adhesive side and high drug-loading capacity was biocompatible, strongly adhered to patellar, supraspinatus and Achilles tendons of live rats, boosted healing and reduced scar formation in a rat model of Achilles-tendon rupture.
Mohindra et al [46]	2022	These authors suggested that matrikines (extracellular matrix fragments) can improve the outcomes post-injury by assisting with tendon healing.
Rocha et al [47]	2022	Wet-spun fibrous structures based on biopolymers, more specifically PHA, PCL and polyethylenes, are extensively used due to their exceptional properties, such as the ability to mimic the native tissue, their biodegradability and biocompatibility, and good mechanical properties.
Zhang et al [48]	2022	After ACLR, injection of kartogenin-PRP gel substantially diminished the inflammatory response and inhibited AKT/PI3K/NF- κ B activation in cartilage tissue, which promoted tendon-bone healing.
Yoon et al [49]	2022	At 8 weeks after rotator cuff repair, the graphene oxide /alginate scaffold improved tendon-to-bone healing without causing any signs of toxicity.
Yamaura et al [50]	2022	Augmentation therapy utilizing tilapia scale-derived type I collagen scaffolds promoted angiogenesis and fibrocartilage regeneration at the enthesis and provided higher mechanical strength than controls.
Bai et al [51]	2022	A bioprinted living tissue construct with layer-specific, GFs-loaded μ S had the unique capability to reduce fibrovascular scar tissue formation and simultaneously facilitate enthesis tissue remodeling.
Wang et al [14]	2022	The effects of asperosaponin VI on injured tendons principally involve eliminating inflammation, reestablishing balance to extracellular matrix collagen metabolism and inducing tendon cell proliferation.
Peñin-Franch et al [15]	2022	Percutaneous electrolysis (galvanic current) activates the NLRP3 inflammasome and induces an inflammatory reaction that triggers a collagen-mediated regeneration of the tendon.
Ko et al [17]	2022	In a collagenase-induced rat model of tendinopathy SPI promoted tendon healing. Therefore, SPI seemed to be a promising agent for the treatment of tendinopathy in humans.
Hanaka et al [18]	2022	Utilizing the patella tendon injury model in tetranectin-null mice, it was found that tetranectin promoted tendon healing at the inflammatory stage after a tendon injury. Therefore, tetranectin could be a good candidate for enhancing tendon healing after injury in clinical practice.

PRP, platelet-rich plasma; HA, hyaluronic acid; BMP-2, bone morphogenetic protein-2; PLA, polylactic acid; IPFP MSCs, infrapatellar fat pad mesenchymal stem cells; ACLR, anterior cruciate ligament reconstruction; BMSC-Exos, bone marrow stromal cell-derived exosomes; ASC-Exos, adipose stem cell-derived exosomes; MMP-2, matrix metalloproteinase-2; MSCs, mesenchymal stem cells; MFG-E8, milk fat globulin protein E8; HD-AM, hyperdry amniotic membrane; Him-MFM, hedging immune strategy based microfibrillar membrane; NFMs, nanofibrillar membranes; PCL, polycaprolactone; PDGF, platelet-derived growth factor; PLGA-PDGF-AA, PDGF-AA-modified poly(lactide-co-glycolide) acid (PLGA); BM-PRF, bone marrow-derived platelet-rich fibrin; TNF- α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; PHA, polyhydroxyalkanoates; GFs, growth factors; SPI, substance P inhibitor.

Table 2 Clinical studies on possible treatments that could improve tendon healing.

AUTHORS [REFERENCE]	YEAR	FINDINGS
Hurley et al [52]	2019	The utilization of PRP in rotator cuff repair improved healing percentages, pain levels, and functional results. However, PRF had no benefit in improving tendon healing percentages or functional results.
Schwitzgubel et al [53]	2019	PRP injections within interstitial supraspinatus tears did not ameliorate tendon healing or clinical results compared with saline injections and were associated with more complications.
Yang et al [54]	2020	This systematic review indicated the effectiveness of PRP when applied to the bone-tendon interface during arthroscopic rotator cuff repair.
Hurley et al [55]	2021	LP-PRP diminished the percentage of retear and/or incomplete tendon healing after arthroscopic rotator cuff repair and ameliorated patient-reported outcomes as compared with a control. However, it was still unclear whether LP-PRP improved the tendon healing percentage when compared with LR-PRP.
Martel et al [56]	2022	This study demonstrated a trend to ameliorate tendon healing after RC repair with vitamin C supplementation.
Lee et al [57]	2022	The beneficial impact of acellular dermal matrix after tendon repair was confirmed by ameliorated postoperative functional result at flexor zones III, IV, and V, preventing peritendinous adhesions and acting effectively as an anti-adhesive barrier.
Zhang et al [58]	2022	Through the analysis of filtered multi-relational data mining image data, it was encountered that the application of biomaterials had a positive effect on promoting the stable healing of tendon. A multilevel model was utilized to assess the actual impact of several commonly used biomaterials in repairing tendon injury and adhesion. The outcomes demonstrated that sodium hyaluronate had the best repair effect on tendon injury.
Camacho-Chacon et al [59]	2022	This prospective study analyzed 30 patients with partial or complete rotator cuff tears who experienced arthroscopic repair and augmentation with a resorbable type I bovine collagen implant. Biopsies of tissue formed from bioinductive type I bovine collagen implants demonstrated, 6 months after surgery, the generation of a neotendon indistinguishable from the native one. Histology and MRI, showed complete integration of the implant and absence of inflammatory or foreign body reactions. The clinical parameters, thickness and MRI signal of the tendon ameliorated substantially at 6 months, regardless of the type and size of the tear, and remained unchanged until 12 months (case series, level IV of evidence).
Ferracini et al [60]	2022	After complete Achilles tendon tear, 8 patients experienced open suture repair in conjunction with perilesional application of a preparation of M-FATS rich in MSCs. The combined application of derived M-FATS for tendon rupture was safe and presented new possibilities for enhanced healing (case control study, level III of evidence).
Boksh et al [61]	2022	A systematic review and meta-analysis found that PRP injections for acute Achilles tendon ruptures do not improve medium to long-run biomechanical and clinical results.

PRP, platelet-rich plasma; PRF, platelet-rich fibrin; LP-PRP, leukocyte-poor PRP; LR-PRP, leukocyte-rich PRP; MRI, magnetic resonance imaging; M-FATS, microfragmented adipose tissue; MSCs, mesenchymal stem cells.

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