

## Review Article

## Research on Plantar Fasciitis

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### Abstract

The plantar fascia is a ligament connecting the heel bone to the toes and is constantly subjected to mechanical loads during daily activities. Despite being one of the most common foot diseases in orthopedics, the mechanism of plantar fasciitis remains largely unknown and there is no effective treatment. The structure of human plantar fascia is different from that of other animals because humans are bipeds; thus, there is no suitable animal model. In this review, we summarize the current research on the structural components of human plantar fascia, discuss its cellular properties, and introduce treatment approaches for plantar fasciitis. Finally, we conclude by sharing our perspective on existing challenges and future directions for new treatments.

### Introduction

The Plantar Fascia (PF) is a flat band of ligament-like tissue that connects the calcaneus to the metatarsals. Sustaining the body weight during daily activities, PF is constantly subjected to mechanical loading [1]. During activities like walking and running, the mechanical load on PF can be several folds the body weight [2]. PF is easily injured in its functional capacity. Plantar fasciitis is commonly found among the physically active population and affects more than 3 million people in the United States every year [3]. However, there is no effective treatment because its pathogenesis is largely unknown [4]. While PF has been extensively studied biomechanically, little has been done at the structural and cellular levels because of the structural differences between the human PF and that of other animals such as mice, rats,

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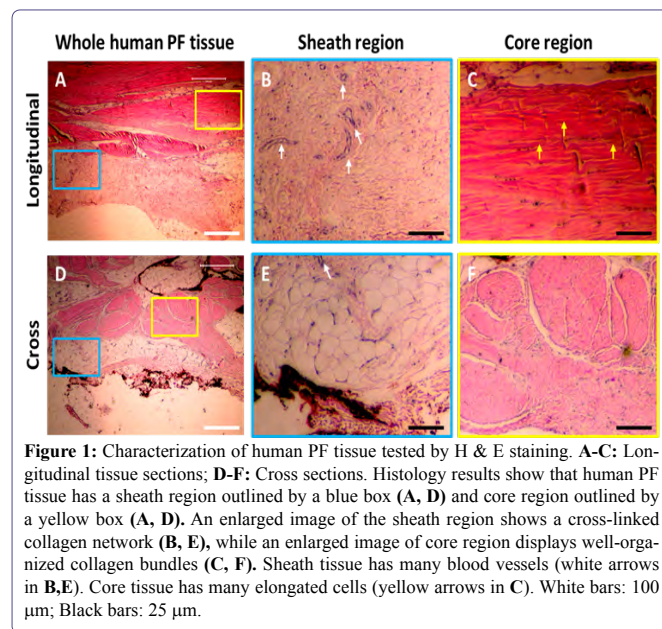
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rabbits, goats, and birds. More important reason is that humans are bipeds [5]. This review covers the current research on plantar fasciitis including the structure of PF, the cellular and molecular mechanisms of pathogenesis, the role of mechanical loading, clinical approaches to treatment, and areas in need of future investigation.

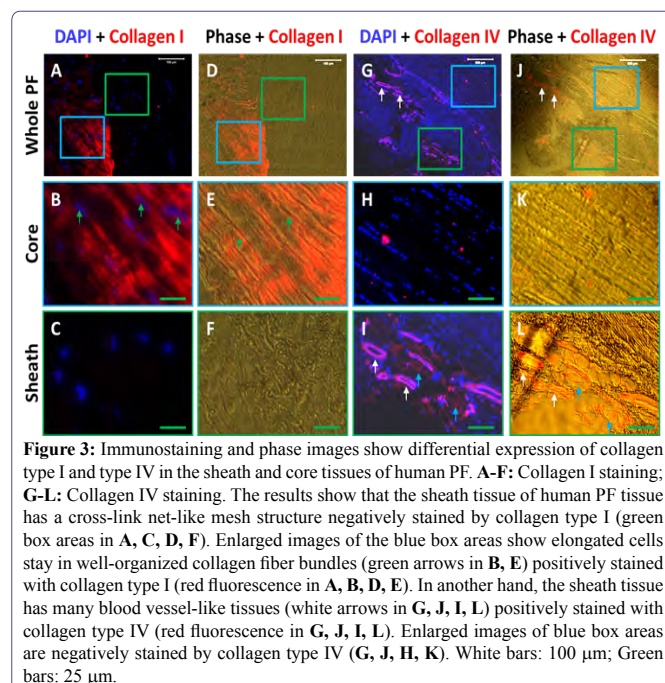
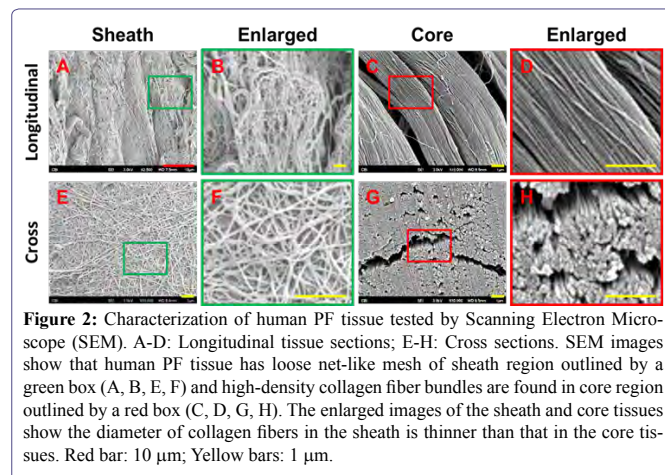
### Structural Components of the Plantar Fascia

Anatomical studies of human plantar fascia have been done by several groups [6,7]. Human PF is a pearly white, glistening layer of fibrous bundles measuring a few millimeters in thickness. The ligament-like tissue firmly joins the plantar muscles and skin [7]. On average, the widths of PF are 2 and 6 cm at the proximal and distal ends, respectively. Its length is 12 cm from the medial tuberculum to the metatarsophalangeal joint [6,7].

Structural details of human PF have been published recently [1]. Our results showed that human PF consists of two different kinds of tissues: on the outside is a loose mesh-like “sheath” (PF-S) that surrounds the inner “core” made of dense and tight collagen bundles (Figure 1). Scanning Electron Microscope (SEM) images showed that the diameter of collagen fibers in the sheath is thinner than those in the core ( $61.3 \pm 8.5$  nm vs.  $89.5 \pm 9.2$  nm) (Figure 2).

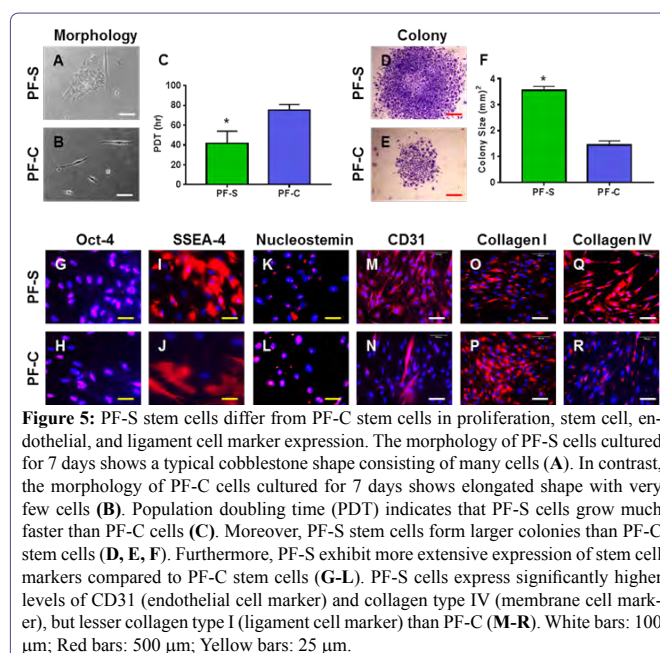
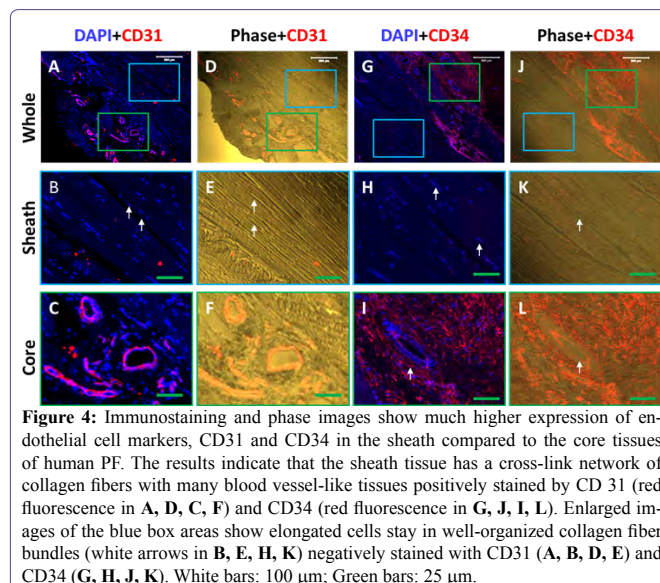


The sheath and core differ on cellular and protein composition as well. PF-S has less type I collagen and more type IV collagen (Figure 3) when compared to PF-C [1]. Some blood vessel-like tissues are also found in sheath with positively stains for CD31 and CD34 (Figure 4) [1]. In addition, the sheath contains elastic fibers and hyaluronans shown by Gieson stain and Alcian blue [7].



## Characterization of Human PF Cells

Few studies to date focus on biological properties of the cells in PF [1]. There are several different cell populations in human PF. The cells isolated from sheath tissue (PF-S cells) have a cobblestone-like shape, while the cells isolated from core tissue (PF-C cells) maintain an elongated shape (Figures 5A, 5B). Proliferation testing indicates that PF-S cells grow faster (Figure 5C), produce larger colonies and higher cell numbers than PF-C cells (Figures 5D-5F) [1]. PF-S cells express markers for stem cell (e.g. nucleostemin, Oct-4 and SSEA-4) and vascular cell (e.g. CD31 and CD34) and produce collagen IV (Figure 5G, 5I, 5K, 5M, 5O, 5Q). On the other hand, PF-C cells resemble fibroblasts and produce collagen I (Figure 5P). These findings indicate that PF-S cells maintain their “stemness” better than PF-C cells [1]. Studying PF on the cellular level provides the basic scientific data to help understand the mechanisms for developing plantar fasciitis.



## Biomechanics of the Plantar Fascia

The biomechanical features of the plantar fascia have been well studied [6,8,9]. Traditionally, human joint kinematics is analyzed using a link-segment model [10]. However, this approach cannot be adapted to the intrinsic foot structures [11]. Using improved camera and computer technology, multi-segment foot models have been developed [12]. The biomechanical behavior of the medial, middle and lateral PF regions has been investigated [13]. The elastic modulus is the greatest at the lateral PF component (1560 MPa), followed by the middle (1100MPa), middle-lateral (714 MPa), and medial (701 MPa). A biomechanical model has been used to calculate the load bearing characteristics of the plantar fascia and determine the effect

of cutting the plantar fascia on the stiffness of the foot. With a load of 683 N applied to the foot, the model predicts a 17% increase in vertical displacement and a 15% increase in horizontal elongation when the plantar fascia was cut, compared to when the plantar fascia was intact [14].

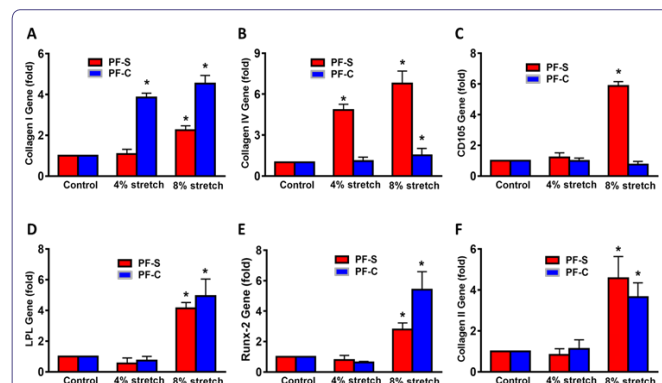
Similarly, a computational model for analysis of the structural behavior of the human foot during standing has been used to investigate the biomechanical effects of releasing the plantar fascia [15]. This model has been successfully validated by comparing its resultant ground reactions with foot-ground pressure measurements and its predicted displacements with those observed in radiological tests. Total fascia release causes extensive arch deformation during standing, exceeding normal deformation by more than 2.5 mm [15]. Simultaneously, the tension stress carried by the long plantar ligaments increases to more than 200% of the normal average stress [15]. These findings indicate that the plantar fascia plays an important role in the foot load-bearing ability, and plantar fascia release must be very carefully considered [16]. More mechanical studies have corroborated that operative procedures may pose a risk to arch stability and clinically may produce dorsolateral midfoot pain [17,18].

One clinical application of quantitative biomechanical measurements is the evaluation of the running patient [19]. Running injuries can be characterized by kinematic data including stride figures, angle-time graphs, and angle-angle diagrams for the sagittal plane motion of the hip, knee, and ankle joints [19].

A recent study has found that forefoot strike may overload the plantar fascia and impose higher risk of plantar fasciitis by comparing the foot arch deformation and PF tension between different foot strike techniques in running using computational models [9]. Forefoot strike increases stress on the plantar connective tissue by 18.28-200.11% and PF tensile force by 18.71-109.10%. These findings suggest that forefoot strike runners are more vulnerable to plantar fasciitis [9].

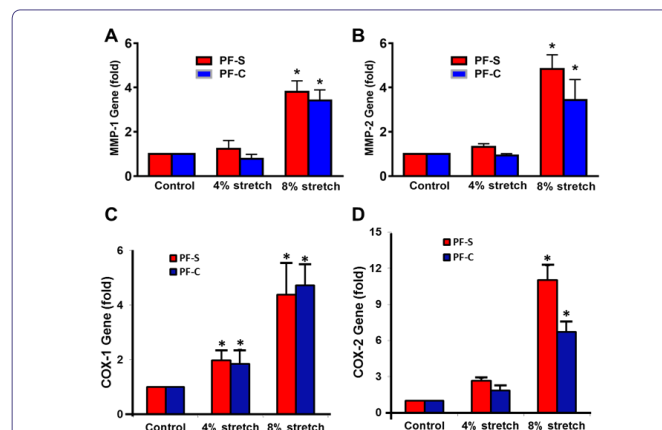
Since plantar fascia maintains the foot arch structure and absorbs dynamic foot contact loading during human locomotion, excessive stretching, repetitive and abnormal stress can induce plantar fascia injury. A study has shown that mechanical overloading on plantar fascia during daily walking could make fascia more stressed and might cause acute or even chronic inflammation [20]. However, the effect of mechanical overloading on cellular changes is not well studied. We have investigated the mechanobiological responses of human PF stem cells using an *in vitro* cell stretching model [1]. The results have shown that Moderate Mechanical Stimulation (MMS) at 4% stretching did not enhance collagen I expression in PF-S cells but did increase it significantly in PF-C cells (Figure 6A). Moreover, Intensive Mechanical Stimulation (IMS) at 8% stretching enhances collagen I expression in both types of PF stem cells (Figure 6A). Furthermore, MMS induces collagen IV expression significantly in PF-S stem cells (Figure 6B), but not in PF-C stem cells (Figure 6B). IMS increases the expression of collagen IV in both PF-S and PF-C cells with higher expression in PF-S stem cells compared to PF-C cells and un-stretched control cells (Figure 6B). MMS does not increase angiogenesis gene CD105 expression in both PF-S and PF-C cells, but IMS increases CD105 expression in PF-S cells (Figure 6C). MMS does not enhance non-ligament-related gene expression including lipoprotein lipase (LPL) for adipocytes (Figure 6D), Runx-2 for osteocytes (Figure 6E), and collagen II for chondrocytes (Figure 6F) in both PF-S and PF-C stem cells. However, IMS increases all

three non-ligament-related genes in both PF-S and PF-C stem cells [1].



**Figure 6:** Mechanical loading induces differential gene expression in PF-S stem cells and PF-C stem cells. Moderate mechanical stimulation (MMS) at 4% stretching does not alter collagen expression in PF-S stem cells, but MMS significantly increases collagen I expression in PF-C stem cells (A). However, intensive mechanical stimulation (IMS) at 8% stretching enhances collagen I expression in both types of stem cells (A). In contrast, MMS induces collagen IV expression significantly in PF-S stem cells, but not in PF-C stem cells (B). IMS increases the expression of collagen IV in both PF-S and PF-C stem cells with higher expression in PF-S stem cells compared to PF-C cells and un-stretched control cells (B). Moreover, MMS does not increase angiogenesis marker, CD105 expression in both PF-S and PF-C stem cells, but IMS increases CD105 expression in PF-S stem cells (C). MMS does not enhance non-ligament-related gene expression including LPL for adipocytes (D), Runx-2 for osteocytes (E), and collagen II for chondrocytes (F) in both PF-S and PF-C stem cells. However, IMS increases all three non-ligament-related genes in both PF-S and PF-C stem cells.

The study has demonstrated that mechanical overloading increases matrix degradative enzymes of MMP-1 (Figure 7A) and MMP-2 (Figure 7B) in both of PF-S and PF-C stem cells (Figure 7A, 7B). Furthermore, mechanical overloading also enhances inflammatory marker genes of COX-1 (Figure 7C) and COX-2 (Figure 7D) in both of PF-S and PF-C stem cells [1]. These findings indicated that stem cells play an important role in the development of plantar fasciitis.



**Figure 7:** Mechanical loading induces differential gene expression on matrix degradative enzymes (MMP-1, MMP-2) and inflammatory markers (COX-1, COX-2) in PF-S stem cells and PF-C stem cells. Moderate mechanical stimulation (MMS) at 4% stretching does not alter the expression of MMP-1 (A) and MMP-2 (B) in PF-S and PF-C stem cells, but Intensive Mechanical Stimulation (IMS) at 8% stretching enhances the expression of MMP-1 (A) and MMP-2 in both types of stem cells (B). Moreover, MMS slightly increases inflammatory marker expression of COX-1 (C), and COX-2 (D) in both PF-S and PF-C stem cells. However, IMS significantly enhances inflammatory gene expression including COX-1 (C), and COX-2 (D) in both PF-S and PF-C stem cells.

More studies have indicated that in response to mechanical stimulation cells would release bioactive signal molecules such as interleukins (IL), adhesion kinases and many others. It has been found that mechanical loading of human tendon results in a marked interstitial increase in concentration of various growth factors, and some growth factors such as IGF-1 [21], transforming growth factor (TGF- $\beta$  [22], PDGF [23], IL-1 $\beta$  [24], and IL-6 [25]) can stimulate the synthesis of collagen. However, the signals triggering the plantar fascia stem cells in response to mechanical loading, and the subsequent expression and synthesis of specific extracellular matrix proteins, as well as its coupling to the mechanical function of the PF tissue are only partly described.

## Plantar Fasciitis Treatments

Plantar fasciitis is the most common cause of chronic pain beneath the heel in adults. About 10% of people develop plantar fasciitis during their lifetime [3]. However, the etiology of plantar fasciitis is not well understood [26,27]. Traditionally, clinicians have thought that mechanical overload plays a major role in the development of plantar fasciitis but the mechanism itself remains unclear [28]. The collagen degeneration seen in plantar fasciitis is similar to the chronic necrosis of tendinosis, featuring loss of collagen continuity and increases in ground substance and vascularity [29]. Some researchers have shown that when PF is exposed to abnormal levels of stress bilaterally, such as during an unaccustomed activity, with prolonged standing or by wearing inappropriate footwear, micro-damage to the PF accumulates and overtime degenerative change ensues [30,31].

Currently, there are two options for treating plantar fasciitis. First option is non-operative, including rest, weight loss, ice packs, deep massage, shoe inserts [29], heel cups [32], night splint, anti-inflammatory drugs [33], extracorporeal shock wave therapy [34], and plantar fascia stretching exercises [35]. Second is surgery [36].

Rest is one of the most commonly used treatments for plantar fasciitis. However, only 25% of patients experience effective improvement after resting, suggesting that it does not conduce healing [37].

Stretching is another important approach [38]. Studies on the effects of stretching have yielded conflicting results [39]. One study has reported successful improvements in heel pain in 83% of patients [37]. In another study, a two-week stretching program has failed to provide statistically significant benefit in foot pain, foot function, or general foot health [40]. Some improvements on stretch reflex activity and clinical outcomes have been shown with counter-strain [41]. In a pilot study using static progressive stretch brace to treat pain and functional limitations in the patients with plantar fasciitis, the brace has become a viable alternative to stretching exercises [42]. A systematic review paper has shown that stretching improved both pain and function subjectively, but when compared to other interventions, including sham treatment, no statistically significant benefit was observed [39].

Medications including Nonsteroidals Anti-Inflammatory Drugs (NSAIDs) and steroids are also used for plantar fasciitis. Although NSAIDs may increase pain relief and decrease disability in patients with plantar fasciitis [32], they confer substantial side effects including gastrointestinal bleeding, gastric pain and renal damage [43].

Steroid injection is a common treatments for plantar fasciitis, with a success rate for pain relief of more than 70% [44,45]. In a study of 65 patients treated with corticosteroid versus a placebo, the subjective pain scores in the corticosteroid group has been significantly higher than the placebo group at 6 weeks and the effect can persist for up to 12 weeks [46]. However, others warn that steroid treatment may cause plantar fascia rupture [47].

Platelet Rich Plasma (PRP) is an autologous blood product in which the platelets have been concentrated. In the recent years, PRP has been used to promote wound healing since it is rich in cytokines, growth factors, chemokines, and fibrin scaffolds [48]. The normal concentrations of platelets in whole blood are  $1.5 \times 10^5$  platelets/ml to  $3.5 \times 10^5$  platelets/ml, while the concentration of platelets in PRP at least is  $1 \times 10^6$ /ml [49]. The use of PRP as a supplement of cell culture media has consistently shown to potentiate stem cell proliferation, migration, and differentiation [50]. *In vivo*, platelets are activated at the site of injury where they participate in haemostasis, promoting tissue repair, including revascularization [51]. Although PRP has been used in surgery for 3 decades, there has been a recent interest in the use of PRP for the treatment of tendon and ligament injuries [49]. A clinical study has been performed in 50 patients with plantar fasciitis by PRP injection treatment. The results showed that mean pain severity improvement was 45% at 6 months with almost two in three patients reporting satisfaction with the treatment [52]. Similar outcomes with patient satisfaction rates of 79-96% have been reported [53,54]. The clinical findings indicated that PRP is a safe alternative with the potential to decrease the pain in plantar fasciitis [53]. A systematic review has demonstrated statistically significant improvements in terms of FAAM score (Foot and Ankle Ability Measure), Foot-SANE (Foot-Single Assessment Numeric Evaluation), SF-12-v2 (Short Form 12 item Health Survey version 2) after 32 weeks for 22 patients with chronic plantar fasciitis receiving a single PRP injection [55]. A meta-analysis shows that PRP treatment has better long-term efficacy in relieving pain than steroid injections [56,57].

The positive extensive clinical experience with PRP in different medical areas has prompted researchers to explore clinical opportunities for optimized PRP therapies [58]. Clinically, when nonoperative treatment for chronic plantar fasciitis fails, often a corticosteroid injection is given. Corticosteroid injection gives temporary pain reduction but no healing [59]. A study has been done in 115 patients with chronic plantar fasciitis treated either with PRP injection or corticosteroid injection. The treatment of patients with chronic plantar fasciitis with PRP seems to reduce pain and increase function more as compared with the effect of corticosteroid injection [59].

Overall, these results indicated that PRP has a great potential in clinical applications. Nevertheless, more scientific research with well design studies and large samples sized will have to conclude PRP effectiveness before it is more widely covered [50].

Extracorporeal shock wave therapy has been used to treat various musculoskeletal disorders including plantar fasciitis. Shock waves promote angiogenesis of PF leading to tissue regeneration [60]. Although laser irradiation is also used to treat plantar fasciitis, its efficacy is questionable [61]. Ultrasound is a high frequency sound wave used to treat injured tendons and ligaments. When comparing different modalities, high-intensity focused extracorporeal shock wave has superior pain-relieving effects at 2 to 4 months, while ultrasound-

guided pulsed radiofrequency treatment and intracorporeal pneumatic shock therapy have superior effects at 6 to 12 months. Only radial extracorporeal shock wave therapy induced significant pain reduction compared to placebo at 0 to 6 weeks [62].

When conservative treatment and time fail, surgical intervention may be necessary. In a case report, surgery is used as an adjunct for a patient with plantar fasciitis, who has remained pain free and returned to running at 10 months after the procedure [63]. Open plantar fascia release is the most traditional operative method. However, surgery has several drawbacks, including large wound, longer postoperative recovery time, and potential occurrence of complex regional pain syndrome. Although plantar fascia release under arthroscopy can minimize the wound, the postoperative satisfaction rate remains haphazard at 50-95% [64,65]. In order to reduce the risk of skin healing problems, nerve disturbance, infection and persistent pain associated with a prolonged recovery time, new surgical procedures are under development [66].

Although most patients respond well to conservative treatments and/or surgery, some still experience on-going pain after exhausting all available options. Newer experimental treatments involve human placental membrane and other types of point-care allografts, which are now commercially available. A successful case has been reported in a patient with chronic plantar fasciitis for whom both conservative therapies and surgery failed. After the implantation of viable intact cryopreserved human placental membrane, the patient has regained function and resumed working full time [67].

## Conclusion and Future Directions

Enhancing plantar fasciitis healing remains one of the greatest challenges in orthopedic research. The quality of existing publications on plantar fasciitis is weak due to the lack of a suitable animal model. Although plantar fasciitis is the most common disease in orthopedics (10% life time prevalence), its cellular molecular mechanism is largely unknown. In recent years, the importance of adult stem cells in tissue regeneration and degeneration has been noted and better understanding of the pathogenesis of plantar fasciitis at the cellular level is to be desired. To date, only one paper has studied the cellular structure and composition of human PF [1].

Advances in stem cell-based therapeutic approaches have shown great potential for tissue repair and regeneration. However, there is no research articles focused on stem cell based therapy for plantar fasciitis. Although some clinical medical doctors have anecdotally injected autologous bone marrow stem cells (BMSCs) to treat plantar fasciitis (Blutail Medical Group; <https://www.blutailmedicalgroup.com/services/plantar-fasciitis>), clinical data regarding its efficacy is limited.

The literature show that there are many challenging questions to be answered and both basic and translational studies are needed before stem cell based therapies can be recommended as a routine clinical treatment for plantar fasciitis. Plantar fasciitis is manifested as plantar fascia inflammation and degeneration, for which mechanical overloading is considered as the major causative factor [68]. However, the underlying cellular and molecular mechanisms remain unclear. Our previous studies have found that mechanical overloading plays an important role in the development of tendinopathy [69]. We have found that mechanical overloading induces tendinopathy

development by initiation of tendon inflammation via HMGB1, leading to eventual tendon degeneration [69]. However, whether HMGB1 mediates plantar fasciitis development due to mechanical overloading is largely unknown. Our previous studies have shown that mechanical overloading on the stem cells of tendon and plantar fascia produces abnormally high levels of Cyclooxygenase-2 (COX-2) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) [1,69]. Such an increase in PGE<sub>2</sub> and COX-2 levels not only elicits tendon/ligament inflammation, but also induces aberrant differentiation of tendon/ligament stem cells to non-tenocyte phenotypes. Within tendon/ligament, this inflammation and aberrant differentiation often lead to degeneration of tendon/ligament tissues characterized by hypercellularity, angiogenesis, and abnormal arrangement of collagen fibers [70,71]. These findings indicated that severe pain in plantar fasciitis may be mediated by the abnormal levels of proinflammatory mediators that are released under excessive mechanical loading. Thus, the future study should focus on the PF stem cells that response to mechanical overloading.

It is important to identify what cell populations (PF-S or/and PF-C stem cells) are involved in PF regeneration and degeneration. Our previous study has found that the stem cells isolated from the sheath of plantar fascia (PF-S cells) have more “stemness” than the stem cells isolated from the core of plantar fascia (PF-C cells). PF-S stem cells maintain “stemness” better than PF-C stem cells after long term culture. Both PF-S and PF-C cells are capable of differentiating into adipocytes, osteocytes and chondrocytes, but the extent of PF-S stem cell differentiation is significantly higher than that of PF-C stem cells [1]. The study on proliferation and differentiation of PF stem cells with various mechanical treatments can provide the first evidence for understanding the mechanisms of plantar fasciitis development.

Stem cells have multi-differentiation potential, can transdifferentiated into other types of cells, and have emerged as frontline regenerative medicine source in recent times, for reparation of tissues and organs anomalies occurring due to congenital defect, disease, and age associated effects [72]. It is believed that stem cells play a vital role in tissue regeneration and repair. Stem cell transplantation has been used to heal large bone defects, bad burns, spinal cord injuries, heart damage, worn joints, nerve damage, and Parkinson's disease. Recent advances in adult stem cell research offers a promising advanced alternative for stem cell transplantation [73]. An adult stem cell is thought to be an undifferentiated cell among differentiated cells in a tissue or organ. The adult stem cell can renew itself and can differentiate to some specialized cell type of the tissue or organ. If the differentiation of adult stem cells can be controlled, the adult stem cells may be a good stem cell source for autologous transplantation. Stem cells used in regenerative medicine include Embryonic Stem Cells (ESCs), Umbilical Cord Stem Cells (UCSCs), Bone Marrow Stem Cells (BMSCs), and some tissue and organ-derived adult stem/progenitor cells [74]. Currently, the most clinical stem cells used for wound healing and tissue regeneration were bone marrow stem cells (BMSCs) and adult stem cells. Although stem cells have been successfully used for tendon and ligament repair, which sources of stem cells (bone marrow stem cells or PF stem cells) care most promising or have the best potential to be used for plantar fasciitis remain unknown.

Further study should also identify what type of injury or disease in PF (such as plantar fascia rupture or chronic plantar fasciitis) requires the implantation of stem cells. The properties of the PF stem cells at

different stages of plantar fascia disorder are different. It is important to identify whether biologics such as stem cell-derived extracellular matrix replicate the therapeutic effect of stem cells. To address these issues, there is an urgent need to find a suitable animal model used for plantar fasciitis study. Mouse treadmill running model is a good approach for tendinopathy study [69]. Although the structure of human plantar fascia is different from that of other animals because humans are bipeds; the effect of mechanical overloading on plantar fasciitis may be investigated by mouse treadmill running model. Future study should focus on the mechanisms underlying the roles stem cells in PF degeneration and regeneration using cell culture model, and to establish standard methodologies and treatment protocols for plantar fasciitis.

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