European Cells and Materials Vol.53 2025 (pages 65–81) DOI: 10.22203/eCM.v053a06 ISSN 1473-2262

Review

VASCULAR DYNAMICS IN TENDON HEALTH AND PATHOLOGY: EXPLORING MECHANISMS AND THERAPEUTIC OPPORTUNITIES

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Abstract

Tendons are bradytrophic tissues, characterized by a dense extracellular matrix in their core, low cellularity, and limited vascularization under healthy conditions. Upon sustaining injury or undergoing degenerative changes, matrix quality decreases and generally a hypervascular, fibrotic scar tissue forms. The significance of angiogenesis in this context remains a topic of ongoing debate and investigation. This review focuses on the vasculature of healthy tendon tissue and the angiogenic mechanisms involved in tendinopathy, with a particular emphasis on Achilles tendon tendinopathy. Furthermore, this narrative review discusses the ongoing controversy surrounding the potential benefits of either promoting or limiting vascular supply in tendon healing.

Keywords: Tendon vasculature, Achilles tendinopathy, VEGF, angiogenesis.

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Introduction

Tendons are highly specialized connective tissues storing energy and transmitting force from muscles to bones. The mechanical strength is attributed to the tendon's hierarchical structure, composed primarily of highly aligned type I collagen fibers, along with other extracellular matrix (ECM) components such as elastin, fibronectin, and proteoglycans [1]. This abundant matrix is mainly built up and maintained by tendon fibroblasts, commonly referred to as tenocytes. In addition, tendons harbour sub-populations of multipotent tendon stromal progenitor cells (TSPCs) and a heterogeneous group of tendon resident cells, including macrophages, T cells, endothelial and mural cells [2–6]. The overall cellular content of healthy tendon is estimated to be around 5–10 % [7]. In line with the low cellularity, also vascular supply in healthy tendon is generally sparse. However, following injury or due to tissue degeneration, vascular ingrowth occurs, accompanied by a loss of structural integrity, hyperproliferation, and a shift in matrix composition [8].

Tendinopathy is a prevalent and multifactorial condition that can affect various tendons throughout the body. Due to its high clinical relevance, this review will mainly focus on tendinopathy of the Achilles tendon. While Achilles tendinopathy (AT) is much more common among athletes, it also affects the general population, with an incidence rate of 2 % [9,10]. Clinically, AT is characterized by symptoms such as swelling and tendon thickening, pain, and impaired function, frequently related to mechanical loading, with many cases proving resistant to full recovery [11].

Historically, "tendinitis" was the dominant term used, based on the assumption that inflammation was the primary underlying cause. Other terms such as "tenosynovitis" (inflammation of the tendon sheath) and "tendinosis" (degenerative changes within the tendon) were also frequently used. However, these terms are now discouraged as they imply specific pathological processes that are most likely not consistently present or clinically distinguishable in patients with Achilles tendinopathy. Instead, the term tendinopathy is now preferred, as it more accurately encompasses the spectrum of tendon disorders, including both degenerative and reactive changes, without attributing them to a specific underlying cause or pathology [11–13]. The pathophysiology of AT is primarily characterized by an impaired or failed healing response, leading to degenerative alterations in the tendon matrix that impair its mechani-

cal strength and function. These pathological changes include disorganization of collagen fibers, an accumulation of proteoglycan-rich ground substance, and the formation of new, abnormal blood vessels (neovascularization), all of which contribute to the tendon's reduced ability to withstand load and to recover from injury [14].

The biological processes responsible for maintaining low vascularization in healthy tendons, as well as those that trigger vascular ingrowth following injury remain largely unclear. Further, whether vascular ingrowth represents a causative factor or a secondary response to tendon degeneration remains a matter of debate.

This review provides an overview of current knowledge on tendon vascularization, including the mechanisms regulating vascular homeostasis in both healthy and pathological conditions, particularly in tendinopathic tendons. We also explore the potential of targeting tendon vascularization as a therapeutic strategy and highlight the ongoing debate surrounding the benefits of pro- vs. anti-angiogenic interventions in tendon healing, seeking to clarify the in part conflicting evidence reported in the literature.

Vasculature in Healthy Tendons

Anatomy of Tendon Vascularization and Tendon Blood Flow

Early anatomic literature described tendons to be "virtually dead during life" [15] or only being "non-viable cables" [16]. However, as early as 1872, Ludwig and Schweigger-Seidl demonstrated the presence of a vascular network in dog tendons by dye injection [17]. Over the last decades, our understanding of the complexity of tendon tissue has greatly advanced. It is now widely accepted that, although tendons are relatively hypovascular, they contain intrinsic vasculature playing an important role in maintaining tissue homeostasis under healthy conditions.

Generally, blood vessels enter tendons from three distinct origins: from the musculo-tendinous junction (the insertion of the tendon to the muscle), from the tendon-to-bone insertion site (enthesis), and from a loose areolar gliding tissue surrounding extra-articular tendons without a synovial sheath called "paratenon" [7,16,18,19]. The vascular supply to tendons varies considerably in both pattern and density. For example, the Achilles tendon is supplied by the peroneal artery at the mid-portion and from the posterior tibial artery in the proximal and distal sections [18,20]. In contrast, the patellar ligament is nourished by three distinct arteries and an anastomotic arch originating from the Hoffa fat pad [21]. The composition of the vascular network also varies depending on whether the tendon is embedded within synovial tissue. In 1953, Brockis [22] demonstrated that in intrasynovial digital flexor tendons, blood vessels enter the tendon at only a few specific sites. In contrast, in areas such as the distal palm and forearm, where the tendon is surrounded by paratenon tissue, blood vessels penetrate the tendon more frequently [22]. These two classifications of tendons later came to be known as "vascular tendons" and "avascular tendons." Together, while tendons are clearly not merely "non-viable cables," they are generally poorly vascularized. In particular, the avascular superficial zones of sheathed tendons primarily rely on nutrient diffusion from the surrounding synovial sheath for their nourishment.

As tendons are physically extended by mechanical load, also vasculature must be compliant to being stretched. In the endotenon tissue (a loose areolar intratendineous tissue surrounding individual fascicles) of vascularized tendons, vessels form "curves". Upon loading of the tendon the vessels are stretched accordingly [22]. A clinically highly relevant and anatomically well described example for the role of tendon vasculature is the rotator cuff, a group of four muscles and their tendons stabilizing the glenohumeral joint of the shoulder. Despite the relatively similar function of these four tendons, the supraspinatus tendon is unique in terms of its vascular bed. In this tendon, 1 cm proximal from the insertion to the humeral head an avascular zone, referred to as the "critical zone," has been described. It remains a matter of debate whether hypovascularity in this region contributes to its susceptibility to rupture and impaired healing, particularly given the pronounced vascular ingrowth observed in conditions such as impingement syndrome [23]. A subsequent study demonstrated the presence of a vascular bed in healthy rotator cuff tendons and it was postulated that the positioning of the arm influences the degree of blood vessel filling [24]. Relatively avascular zones have also been described for other tendons, i.e., the Achilles tendon [25]. In particular, the midportion of the tendon, located approximately 4 cm proximal to the calcaneal insertion, has been identified as a hypovascular region, corresponding to the area supplied by the peroneal artery [20]. This region—the isthmus of the tendon—is also known as the "watershed area" in the Achilles tendon, endures the highest mechanical loads and is the most common site of tendon rupture [26]. It is particularly prone to inflammation, which can lead to painful, chronic tendinopathy [1] and, in severe cases, tendon rupture [27].

The role of vasculature in tendon development, as well as the mechanisms guiding vascular formation in this context, remains poorly understood. Vascular pruning is a crucial biological process observed during the maturation of tendons, involving the regression of excessive vasculature to enhance tissue efficiency and specialization. In fetal tendons, angiogenesis is marked by the presence of vascular endothelial growth factor (VEGF) and its receptors, which are prominently expressed in early development. A study by Petersen *et al*. [28] shows that VEGF expression decreases in avascular zones of tendons exposed to compressive forces, such as gliding tendons, while regions subjected to tensile forces retain higher vascular density. This suggests a mechanical influence on vascular remodeling. Furthermore, pruning generally aligns vascular density

Table 1. Promotion vs. reduction of angiogenesis to improve tendon healing.

Intervention	Type of study	Main finding	Citation
Pro-angiogenic	Randomized controlled clinical trial	ESWT extracorporeal shockwave therapy is more effective than traditional conservative treatments in the management chronic patellar tendinopathy.	[101]
Pro-angiogenic	Preclinical study in horses	ESWT promotes angiogenesis after collagenase-induced tendinopathy, although it does not affect ultrasonographic appearance.	[89]
Pro-angiogenic	Preclinical study in rabbits	ESWT promotes angiogenesis and levels of eNOS and VEGF in healthy tendon- to bone junction.	[90]
Pro-angiogenic	Preclinical study in rats	Injection of VEGF in patella tendon defects reduces adipocyte accumulation in aged animals. Moderate improvement of histological scores.	[91]
Pro-angiogenic	Meta-analysis of RCTs in humans	PRP is effective in treating epicondylitis in humans, with sustaineds long term effects.	[87]
Pro-angiogenic	Randomized double-blinded prospective study	Injection of PRP improves midportion Achilles tendinopathy pain scores and reduced tendon thickness, but does not affect vascularization.	[88]
Pro- and antiangiogenic	Preclinical study in rats	Both VEGF and a VEGF inhibitor (B20) result in a trending improvement of mechanical properties in injured rat Achilles tendons.	[92]
Pro- and antiangiogenic	Preclinical study in rats	B20 leads to impaired tendon biomechanics when applied 3-6 days after Achilles tendon injury; no improvement after VEGF treatment.	[93]
Pro- and antiangiogenic	Preclinical study in rats using human cells	Human cells transduced to either produce VEGF or the VEGF inhibitor sFLT1 were added to autologous ACL grafts. VEGF-transduced cells significantly improve Biomechanical properties at 4 weeks post injury compared to no cell treatment.	[100]
Anti-angiogenic	Randomized controlled clinical trial	Heavy slow resistance training leads to a reduction of blood vessels and pain in midportion Achilles tendinopathy.	[102]
Anti-angiogenic	Randomized controlled clinical trial	Eccentric training decreases paratendon capillary blood flow and preserves paratendon oxygen saturation in chronic Achilles tendinopathy.	[95]
Anti-angiogenic	Randomized controlled, single-blind trial	Eccentric decline squat training and heavy slow resistance training are superior to corticosteroid injections in regard to pain and structural improvement of patellar tendinopathy and result in reduced tissue vascularization.	[94]
Anti-angiogenic	Randomized prospective clinical study	Good clinical outcomes after eccentric training are associated with normalized tendon structure and absence of neovascularization.	[96]
Anti-angiogenic	Clinical pilot study	Polidocanol sclerotherapy targeting neovessels in the supraspinatus tendon and/or bursa wall may reduce shoulder pain during loading in patients with impingement syndrome.	[99]

Table 1. Continued.

Intervention	Type of study	Main finding	Citation
Anti-angiogenic	Retrospective clinical study	Sclerosing injections as a promising alternative to surgery for treatment of chronic midportion Achilles tendinopathy, effectively reducing pain in most patients.	[97]
Anti-angiogenic	Randomized controlled clinical trial	Polidocanol sclerosing injections targeting neovessels in chronic patellar tendinopathy outperform lidocaine/epinephrine injections in pain and function scores at 4-month follow-up.	[98]
Anti-angiogenic	Preclinical study in rats	Injection of the antiangiogenic antibody Bevacizumab 3 and 7 days after Achilles tenotomy in rats improves structural and biomechanical tendon properties.	[86]

VEGF, vascular endothelial growth factor; PRP, platelet-rich plasma; ESWT, extracorporeal shock wave therapy; sFLT1, soluble fms-like tyrosine kinase-1; ACL, anterior cruciate ligament; eNOS, endothelial nitric oxide synthetase; RCTs, randomized controlled trials.

with oxygen demands, as e.g., hyperoxia-induced pruning in retinal vasculature demonstrates. This pruning generally ceases with the recruitment of pericytes, which stabilize endothelial structures, yielding a mature vascular network [29]. Insights from brain and cardiac tissue studies further illustrate that pruning eliminates redundant vessels based on low perfusion, enhancing overall flow efficiency. These findings suggest, that similarly in tendon vascular pruning ensures optimal perfusion and structural specialization critical for functional demands in mature tendons [30]. Along these lines, a histomorphometric study of the musculus flexor digitalis superficialis tendon and the cranial cruciate ligament of immature sheep (1–40 weeks post-natal) shows a significant decline in both cellularity and vascular supply in tendon and ligament as they mature [31]. However, the signals that trigger vascular regression and the underlying mechanisms remain largely unknown [32].

In line with their sparse vascularization, tendons exhibit low blood flow at rest. However, in healthy individuals, acute exercise leads to a transient increase in tendon perfusion without triggering proangiogenic signaling [29]. In contrast, tendinopathic tendons not only show a markedly greater increase in blood flow following exercise but also display enhanced neovascularization, suggesting an altered vascular response under pathological conditions [30]. Overall, the maintenance of low vascularity can either be achieved by low expression of pro-angiogenic factors, or by the presence of factors actively inhibiting angiogenesis. Among the latter, only endostatin—a 20 kDa cleavage fragment of collagen XVIII with potent anti-angiogenic activity—has been identified in tendon tissue, with highest expression levels observed in embryonic tendon. In tendon cell cultures, hydrostatic pressure was found to promote expression of endostatin and to inhibit endothelial cell growth. In tendons, endostatin may ensure a balance between vascularization and avascularity, particularly in zones subjected to different mechanical loads. Its presence could help explain the restricted vascular supply observed in certain tendon regions, especially those exposed to high compressive and shearing forces, where vascularization is less favourable [33]. However, it is likely that additional, yet unidentified mechanisms also contribute to the sparsely vascularized state of tendon tissue (Fig. 1).

Compared to other sparsely vascularized tissues, anti-angiogenic mechanisms in tendons remain largely underexplored. While the cornea has been extensively studied for its strict regulation of vascular ingrowth to maintain transparency, tendons also exhibit tightly controlled vascularization. Gaining insight into the underlying mechanisms may reveal novel therapeutic targets for tendon pathologies [34].

The Blood-Tendon Barrier

This chapter explores the composition of tendon blood vessels, highlighting how their vascular permeability may play a critical role in regulating and maintaining an environment required for tendon function. The degree of tissue supply with nutrients, oxygen or even pharmacologic molecules is not only depending on the abundance of blood vessels perfusing the tissue, but also on vessel permeability. In the liver, blood capillaries are commonly discontinuous, facilitating free passage even of large molecules, whereas fenestrated capillaries of organs like the kidney mainly allow passage of fluids and small molecules [35]. Particularly in testes and the brain, capillary endothelial cells are connected by tight junctions, complex structures that are crucial in maintaining selective cellular barriers—the blood-testis and the blood-brain barrier. They effectively limit the paracellular flux of molecules and ions, allowing the maintenance of unique microenvironments within these tissues [36]. In healthy tendon, a comparable selective barrier has been described. In both mouse and human tendons, the tight junction associated markers Occludin (OCLN),

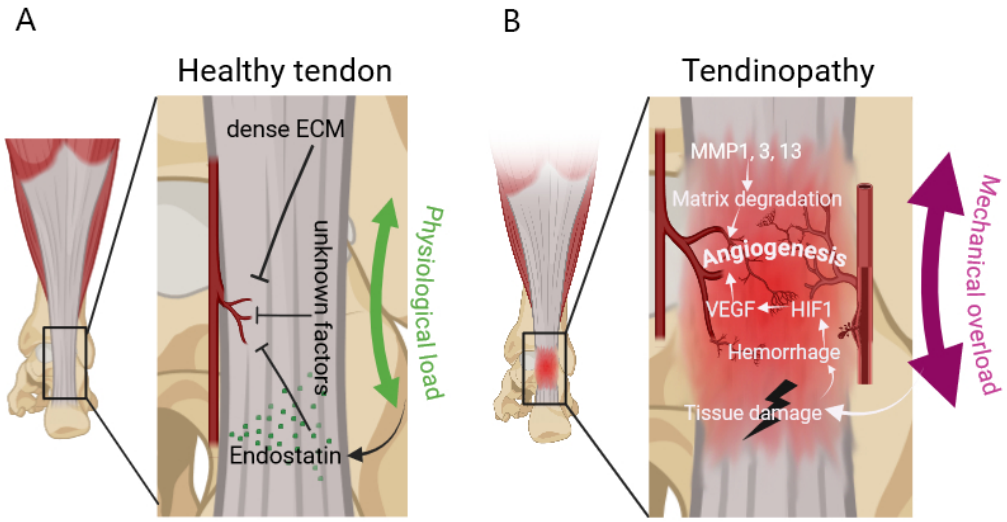

Fig. 1. Proposed mechanisms underlying angiogenesis in healthy and diseased tendon. (**A**) In healthy adult tendons tenocytes produce the antiangiogenic factor endostatin in response to physiological mechanical load, thus limiting neo-angiogenesis. Additionally, other yet unidentified factors may contribute to the maintenance of this sparsely vascularized state. (**B**) In diseased tendons, hypoxia-inducible factor-1 alpha (HIF-1α) is produced by tendon cells in response to stimuli such as mechanical overload, inflammation and/or hypoxia. Among its various downstream effects, HIF-1α promotes the expression of VEGF, thereby promoting neoangiogenesis. Haemorrhage caused by vascular injury also elevates HIF-1α levels and promotes the production of matrix metalloproteinases (MMPs), which degrade the extracellular matrix and weaken the tendon structure that in turn facilitate additional vascular ingrowth. While further pro-angiogenic mechanisms are likely involved, they remain to be described (Created in BioRender.com https://biorender.com/w06v233). VEGF, vascular endothelial growth factor; ECM, extracellular matrix.

Claudin 3 (CLDN3) and Claudin 5 (CLDN5) are expressed. In Achilles tendon, electron microscopy revealed a non-fenestrated type of capillaries. Perfusion experiments with labelled dextran demonstrated that the capillaries, particularly in the epi- and endotenon, are impermeable for molecules >10 kD. In contrast, smaller molecules such as 300 Da dextran, were observed to leak into the surrounding tissue [37]. This suggests that while tendon capillary barriers effectively block the passage of larger macromolecules, they may permit the diffusion of smaller molecules under certain conditions, potentially through paracellular pathways or localized disruptions in barrier function.

The molecular factors regulating the expression of the transmembrane barrier proteins are unknown in tendon. In the brain, molecular pathways like Wnt/β-Catenin signaling or Notch signalling regulate the expression of these tight junction proteins [38]. However, these junctions are highly complex, with their main functional components being redundant. In the mouse brain, a complete knock out of occluding for example does not cause a complete breakdown of the barrier, suggesting other proteins to functionally compensate [39]. In addition to the formation of transmembrane multi-protein complexes, the blood-brain barrier is also induced and stabilized by neighbouring cells, particularly pericytes and astrocytes [40]. Pericytes have been described to be present on tendon vessels [4,41], however, their impact on the tightness of tendon vessels remains unknown.

Variations in capillary permeability between different tendons and within specific regions of individual tendons remain unexplored. Additionally, the role of this barrier in diseased tendons and following injury has yet to be thoroughly investigated. If and how the tightness of this barrier changes after injury or in tendinopathy and if it restores upon tendon healing is still unclear. Also the role of the barrier for drug delivery to the tendon is elusive. A potentially relevant factor to modulate endothelial barrier function is hypoxia. For example, it has been shown that hypoxia reduces the expression of Claudin 5 protein, resulting in a loss of barrier function in retinal microvascular endothelial cells [42]. In addition, reactive oxygen species (ROS), which are also produced in tendons under stress, are well known to disrupt tight junction structures in brain capillaries, in part through the induction of matrix metalloproteinases (MMPs). Finally, in the gut inflammation was shown to increase intestinal permeability in a nuclear factor kappa B (NF-κB) p65 dependent manner [43]. NF-κB signaling was shown to be critically involved in tendon inflammation, scar formation, and fibrosis [44]. Thus, exploring the tendon barrier's potential as a pharmacologic target could provide novel strategies to enhance tendon healing by optimizing systemic drug delivery.

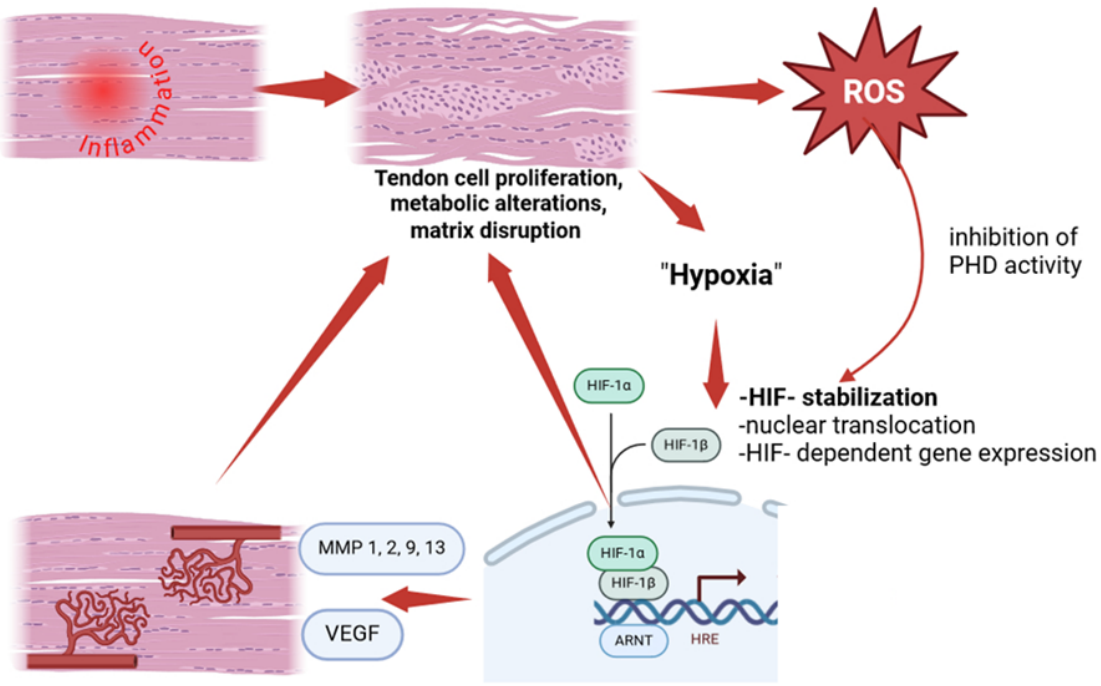

Fig. 2. HIF1-dependent mechanisms in tendon degeneration. Inflammation, either local or systemic, induces pathologic tendon cell proliferation and disruption of tendon matrix components. Moreover, reactive oxygen species (ROS) are formed, leading to cellular stress responses. Hypoxia due to altered cellular oxygen consumption leads to stabilization and nuclear translocation of HIF-1α, inducing transcription of proangiogenic and matrix degrading factors such as MMPs and VEGF. ROS also directly mediate HIF-1α stabilization by inhibition of PHD activity. By induction of aberrant tendon neovascularization, this signalling pathway further fuels tendon degeneration. However, HIF-1α also induces a tendinopathic phenotype independent from angiogenic processes (Created in BioRender.com https://biorender.com/bbchden). PHD, prolyl hydroxylase; ARNT, aryl hydrocarbon receptor nuclear translocator; HRE, hypoxia responsive element.

Lymphatic Drainage of Tendons

The lymphatic system of intact tendons has received very little attention. Early literature reports lymphatic vessels to be associated with blood vessels in calf tendons as demonstrated by injection of India ink [15]. However, it is widely acknowledged that identifying lymph vessels solely by morphologic parameters is challenging and prone to error. Even with immunohistochemistry, differentiating between blood vessels and lymphatic vessels can be difficult. To ensure accurate identification of lymphatic vessels, it is recommended to use a minimum of three lymph-associated markers such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), vascular endothelial growth factor receptor 3 (VEGFR3) and podoplanin (PDPN) [45].

In healthy tissue, lymph vessels are responsible for tissue drainage and immunosurveillance. The role of lymphatic vessels in tendon disease has widely been neglected so far. To our knowledge, there is no published work systematically addressing lymphatic drainage in common tendon disorders such as tendinopathy, calcific tendinitis, or chronic tendon inflammation due to mechanical overuse. Intact rat Achilles tendons have been shown to lack lymphatic vessels, but following injury, lymph vessel ingrowth is evident by two weeks post-injury [46]. This response may be partially attributed to interleukin (IL)-17A, a well-established inflammatory mediator in early tendinopathy [47], which also acts as an angiogenic factor, promoting both pathological angiogenesis and lymphangiogenesis. Notably, IL-17-induced lymphangiogenesis has been observed in animal models of chronic dry eye disease (DED), where it plays a significant role in disease progression [48]. Furthermore, a preclinical study suggests that lymphangiogenesis may be crucial for tendon healing, as inhibition of this process via VEGF receptor 3 inhibitor SAR131675 has been shown to impair both the structural and biomechanical recovery of rotator cuff tendons following injury [49]. Collectively, these findings underscore the complexity of lymphatic involvement in tendon healing, highlighting the dual potential of lymphatic vessels in either contributing to pathological conditions or facilitating tissue regeneration, a balance that remains to be fully understood.

In other fibrous tissues such as the skin, lymphangiogenesis is induced by inflammation following injury, which can be actively blocked by anti-inflammatory drugs such as dexamethasone. In healthy skin, lymph vessels are present, but remain quiescent until activation by pathologic stimuli

[50]. The delivery of lymphangiogenic factors to the skin was shown to reduce acute skin inflammation via promotion of lymph flow from the skin and reduction of edema formation in a mouse model [51]. Along these lines, in chronic venous leg ulcers in humans, lymphatic drainage was found to be impaired, potentially contributing to the delayed healing [52]. This healing delay is likely to occur due to increased tissue pressure resulting from insufficient tissue drainage. In tendon, intratendinous pressure is increasingly being recognized as a contributing factor to tendinopathy and the associated pain [53]. Glycosaminoglycans (GAGs), known for their high water-binding properties, accumulate in tendinopathic tissue, leading to swelling and elevated intratendinous pressure. This increase in pressure exerts excessive compressive loads on tendon-resident cells, potentially resulting in maladaptive responses and accelerating the progression of tendinopathy [54]. Thus, while speculative, by addressing both mechanical stress and fluid retention through enhancing lymphatic drainage function may prevent the excessive compression that drives tendinopathy progression, thereby improving outcomes and alleviating pain [55].

Lymphatic drainage of tendons after injury and in tendinopathy is a promising, yet underexplored area of research. Given the growing recognition of intratendinous pressure as a potential contributor to tendon pathologies, this topic warrants greater attention in both basic and clinical research [56].

Vasculature and Hypoxia in Achilles Tendinopathy

Neovascularization is a major hallmark commonly observed in AT and studies have shown that increased blood flow in the tendon is correlated with pain levels in patients suffering from tendinopathy [57,58]. Further, Alfredson *et al*., 2003 [27,59] proposed that the formation of new blood vessels is accompanied by ingrowth of sensory nerves, which may explain the chronic pain experienced by individuals with AT.

On the cellular level, pathological conditions drive morphological changes of tendon fibroblasts, which adopt a more rounded and proliferative phenotype. This shift is indicative of increased metabolic and synthetic activity, and is accompanied by the expression of fibroblast activation markers such as cluster of differentiation (CD)90, PDPN, CD248, fibroblast activating protein (FAP), and CD106 [60,61]. Further, advances in single-cell and single-nuclei RNA sequencing have revealed that fibroblasts in Achilles tendon tissues, both human and murine, are heterogeneous and consist of distinct sub-populations [5,41,62]. In a study on tendon samples from both tendinopathic and ruptured human Achilles tendons, both groups showed a complex inflammatory signature accompanied by significantly increased vasculature, particularly in the ruptured stumps [60,63]. In a tendinopathy animal model in New Zealand white rabbits, repetitive, pathological loading of the flexor digitorum profundus tendon lead to significant upregulation of VEGF and CTGF (connective tissue growth factor), indicating that overload triggers a pro-angiogenic response [64]. In many tissues, hypoxia acts as a powerful trigger for angiogenesis, particularly in response to injury. The main molecular cascade responsible for this pro-angiogenic response is the stabilization of hypoxia-inducible factor-1 alpha (HIF-1α), a key transcription factor driving the expression of VEGF [65]. Along these lines, elevated levels of HIF-1α were demonstrated in human samples of torn supraspinatus tendons [66]. Additionally, evidence of hypoxic damage was identified at various stages of disease progression, including mild impingement, as well as partial, small, medium, and large rotator cuff tears [67].

Oxygen tension in healthy and diseased tendons remains an understudied area. An unresolved question is why healthy tendons do not attract neovessels, despite the presumably low oxygen supply. One hypothesis is that tendinopathy induces a metabolic shift in tendon cells, increasing cellular oxygen consumption and leading to local hypoxia and ROS production. This may activate the HIF-1α-VEGF axis, which influences downstream targets that contribute to tendon homeostasis, repair, and adaptation. This axis has wide-reaching implications for tendon homeostasis and adaptation. One critical target is the regulation of matrix metalloproteinases (MMPs), which play a pivotal role in remodeling the extracellular matrix (ECM). This dynamic restructuring is essential during tendon repair and adaptation to mechanical stress. For example, in human subscapularis tendon samples, hypoxia and HIF signaling upregulate pro-inflammatory cytokines, such as interleukin-6 (IL-6) and IL-8 as well as promote apoptosis [66]. In a rat model of collagenase induced tendon injury, inhibition of HIF-1α, resulted in reduced levels of IL-6. MMP3, MMP9 and MMP13, indicating a direct effect of HIF1 on these proteins in tendon defects [68]. Another important molecular mechanism driven by HIF-1α, is the excessive production of ROS. HIF-1α promotes a shift in mitochondrial respiration by upregulating pyruvate dehydrogenase kinase 1 (PDK1), which inhibits pyruvate dehydrogenase (PDH) (see Fig. 2). This reduces the entry of pyruvate into the tricarboxylic acid (TCA) cycle and decreases electron flow in the electron transport chain (ETC). HIF-1α also influences antioxidant defenses, potentially by influencing the expression of genes involved in glutathione metabolism or antioxidant enzyme systems. Lower glutathione levels, for instance, reduce the cell's ability to detoxify ROS, amplifying oxidative stress. In recent work it was convincingly shown that HIF-1α signaling not only causes a tendinopathic phenotype via inducing VEGF mediated angiogenesis, but also by VEGF independent mechanisms through a maladaptive tissue response to chronic overload [69]. Moreover, hypoxia-induced IL-6, can activate inflammatory pathways mediated by NF-

κB, which further enhances ROS production through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzymes, creating a destructive feedback loop [70]. Together, the interplay of hypoxia, inflammation, and oxidative stress creates a pathological microenvironment that perpetuates damage while attempting repair. Understanding these molecular pathways will provide important insights into tendinopathy progression and might reveal therapeutic targets to restore tendon tissue homeostasis.

Interplay between Vasculature, Inflammation and Mechanical Stimulation

Mechanical loading is a fundamental requirement for maintaining homeostasis across most musculoskeletal tissues. For instance, immobilization leads to significant physiological changes resulting in, e.g., loss of bone density or cartilage degradation [71,72]. Similarly, tendons require optimal mechanical input to sustain their structural integrity and to prevent tendon-resident cells from pathological activation. Notably, both excessive and insufficient loading disrupt tendon homeostasis. Supraphysiological and repetitive loading causes extracellular matrix (ECM) damage, exceeding the repair capacity of tendon cells and leading to degenerative changes [8]. Conversely, underloading inhibits matrix turnover by tenocytes, weakening the ECM and triggering a degenerative cascade similar to that seen in overload injuries. Tissue damage further exacerbates this cycle by reducing mechanical stimuli not only at the site of injury but also in proximal and distal regions, driving maladaptive responses such as heterotopic ossification via activation of the Wnt-β-catenin pathway, as demonstrated in a rabbit tendon underloading model [73]. Therefore, a lack of physiological mechanical input, combined with localized damage, may set the stage for pathological angiogenesis. Pathological loading also results in alteration of the local mechanical environment, promoting an inflammatory response mediated by both systemic and tendon-resident mechanisms. For instance, an *ex vivo* study of murine unloaded tail tendon fascicles demonstrated upregulation of inflammatory markers such as IL-1β and NFκB2 alongside vascular markers (Wnt7b, HIF-1α), but only in the presence of serum [74], suggesting that local bleeding after local tendon injury *in vivo* might exacerbate this response.

Tendon cells possess an inherent capacity to mount an inflammatory response, independent of immune cell infiltration. When subjected to pathological stimulation, these cells can autonomously upregulate the expression of inflammatory cytokines, demonstrating their ability to drive local inflammation without relying on the invasion of immune cells [75]. Recent findings have also identified "tenophages," a tendon-resident cell population with macrophage-like properties that may play a surveillance role in initiating or driving local tendon inflammation. These cells express proinflammatory mediators such as fractalkine (FKN), its receptor C-X3-C motif chemokine receptor 1 (CX3CR1), and epiregulin, linking local inflammation and repair processes [76]. Additionally, it has been reported that the inflammatory response in tendinopathy is modulated by Toll-like receptor (TLR) pathways, particularly TLR4, which is implicated in sensing and responding to ECM damage [77]. Systemic inflammation further compounds this interplay. Chronic inflammatory conditions such as rheumatoid arthritis, diabetes, and smoking are well-established risk factors for tendinopathy, potentially priming tendons for maladaptive responses to mechanical stress [78]. Interestingly, allergic responses, such as grass pollen allergy, have also been implicated in tendon impairment, emphasizing the complex interplay between systemic and localized inflammatory processes [79]. This highlights how systemic and localized mechanisms may synergistically drive the progression of tendinopathy.

In summary, pathological matrix remodeling, inflammation, and hypervascularization are interdependent mechanisms that may reinforce one another, contributing to a self-perpetuating cycle of tendinopathy.

Targeting Tendon Vasculature: A Potential Therapeutic Strategy for Treating Tendinopathy and Tendon Rupture

This chapter explores the potential role of tendon vascularization as a therapeutic target for enhancing or accelerating tendon healing following injury or during recovery from tendinopathy. Notably, studies offer contrasting perspectives: while some support the stimulation of angiogenesis as beneficial for tendon repair, other suggest that inhibiting vessel formation—or even actively promoting vessel regression—may also contribute to improved healing outcomes.

In most tissues, such as bone or skin, a high degree of revascularization following injury is widely recognized as essential for healing. Adequate blood supply is crucial for delivering oxygen and nutrients, removing waste products, and supporting the recruitment of immune cells and other healing factors to the injury site. Thus, most therapeutic strategies in these tissues aim to enhance angiogenesis to promote tissue regeneration and repair. For example in bone healing, where angiogenesis plays a critical role in the coupling of osteogenesis and vascular invasion, promoting proper bone remodelling [80]. Similarly, in skin wound healing, angiogenesis is integral to the formation of granulation tissue and the subsequent re-epithelialization of the wound bed [81]. In contrast, the role of angiogenesis in tendon healing is still a matter of debate [32]. Enhancing angiogenesis may be beneficial in tendon repair by promoting better oxygenation and nutrient delivery to the healing tendon (see further below). For instance, increased vascularization has been observed during the early phases of tendon healing, suggesting it could play a positive role in the initial repair process. On the other hand, excessive angiogenesis has been linked to adverse outcomes in tendon healing,

such as fibrosis and scar formation, which can impair tendon function. Although extensively studied across various pathologies, the complex relationship between excessive angiogenesis and tissue fibrosis remains controversial. For example, in idiopathic lung fibrosis, there is conflicting evidence on the ability of lung homogenates to induce new vessel formation *in vitro* and a variety of angiogenesis-related factors seem to be deregulated in this disease [82]. In chronic fibrotic liver disease, angiogenesis is closely linked to the fibrotic progression. Hypoxia, hypoxia-inducible factors, and a range of signals released by various liver cells collectively regulate the pro-fibrotic and pro-angiogenic functions of hepatic myofibroblasts [83]. Interestingly, in a mouse liver fibrosis model, distinct regional changes in vascularization have been observed during fibrotic progression, with a decrease in portal vessels, increased sinusoid capillarization, and an increase in central vessels. Lin *et al*. [84] demonstrated that selectively modulating angiogenesis through combined pro- and anti-angiogenic approaches influenced these vascular changes: inhibiting sinusoid capillarization via adeno-associated virus serotype 9 (AAV9)-leukocyte cell-derived chemotaxin 2 (LECT2)-short hairpin RNA (shRNA) treatment stimulated portal angiogenesis, while targeting VEGF/VEGFR signaling with Bevacizumab, a humanized anti-VEGF antibody, reduced central vessel formation and decreased sinusoid capillarization, ultimately enhancing the therapeutic effect on liver fibrosis. These findings highlight the complexity of angiogenesis modulation as a therapeutic strategy and suggest that a balanced regulation of pro- and anti-angiogenic effects is essential for effectively limiting liver fibrosis [84].

In tendons, impaired regression of immature, non-functional blood vessels can lead to excessive vascularization, which may promote fibrosis through sustained inflammatory responses. This, in turn, contributes to adhesion formation and tissue contraction, ultimately compromising tendon flexibility and mechanical strength [85]. One could argue that the optimal balance between angiogenesis and fibrosis is crucial, as an overly vascularized environment may lead to the deposition of disorganized collagen fibers, resulting in a mechanically weaker tendon [86]. This dichotomy raises important questions about whether promoting or inhibiting angiogenesis should be a target for therapeutic intervention in tendinopathy and tendon repair.

Pro-Angiogenic Strategies to Improve Tendon Healing

A number of human and animal studies show a beneficial effect of promoting angiogenesis for tendon healing. Several examples illustrating these beneficial effects are outlined below (Table 1, Ref. [86–102]).

Platelet Rich Plasma

The application of platelet-enriched plasma products has become a standard treatment in various musculoskeletal diseases such as osteoarthritis, but also in tendinopathy [103]. For this treatment, autologous platelets are concentrated by centrifugation of freshly drawn venous blood samples and immediately reinjected to the diseased site. These preparations contain a high concentration of a large variety of growth factors, such as transforming growth factor beta (TGF-β), platelet derived growth factor (PDGF) and also VEGF [104]. However, VEGF concentrations strongly vary depending on platelet yield, preparation method and patient heterogeneity [105]. While the level of evidence varies across studies, a recent meta-analysis (Level of evidence 2) demonstrated effectiveness of platelet-rich plasma (PRP) in treatment of lateral epicondylitis, particularly in achieving long-term ($\geq$6 months) functional improvement and sustained pain relief [87]. In contrast, in Achilles tendinopathy evidence is less convincing, with several randomized controlled trials (RCTs) reporting no beneficial effects [106–108]. Data on the effects of PRP on tendon vascularization in humans remain limited. No effect on neovascularization was observed in a 1 year follow up study comparing PRP injections with placebo in 54 patients [109]. A randomized, double-blinded prospective study of 60 patients with mid-portion Achilles tendinopathy found no significant difference in tendon blood flow over a period of 24 weeks between those treated with PRP and those that had received a placebo. However, PRP was more effective than the placebo in increasing tendon thickness and reducing pain scores [88]. Similarly, a double-blind, randomized, placebo-controlled clinical trial involving 54 patients demonstrated that PRP injections had no impact on tendon vascularization, but also not on tendon structure after 24 weeks [110]. In contrast, animal studies demonstrated a positive correlation between the injection of PRP after injury and the degree of vascularization. For example, Bosch *et al*. [111] observed neovascularization in surgically created equine superficial digital flexor tendon lesions up to 23 weeks after injury, attributing this observation to the beneficial effects of PRP in promoting tendon healing. Overall, PRP shows potential in the treatment of certain types of tendinopathy; however, its specific effects on tendon vascularization remain unclear.

Extracorporeal Shock Wave Therapy

One widely used treatment strategy employed for both skin- and tendon regeneration is extracorporeal shock wave therapy (ESWT). In skin, ESWT has been shown to strongly induce VEGF, significantly improving healing outcomes by enhancing angiogenesis, a the key factor in skin regeneration [112]. Similarly, ESWT is a well-established treatment for various tendinopathic conditions, with strong evidence supporting its ability to reduce pain and enhance tendon function, particularly in plantar fasciitis [113]. In addition, ESWT has demonstrated high effectiveness in treating lateral epicondylitis [114], yielding outcomes comparable to those of surgical intervention [115]. However, these studies did not explicitly focus on tendon

vascularization, thus the effect of ESWT on tendon vascularity remains unclear. Numerous studies using animal models, such as horses, dogs, and rats, have reported increased vascularization of tendons following ESWT application, suggesting its role in enhancing blood supply to injured tendons [89,116,117]. On a molecular level, Wang *et al*. [90] demonstrated an increase of VEGF after ESWT at the healthy tendon-to-bone junction in rabbits after treatment for up to 12 weeks, resulting in increased vascular perfusion. In summary, ESWT is a widely used and effective treatment for tendinopathy, demonstrating significant benefits in pain relief and functional recovery. However, the exact contribution of a vascular response to ESWT's therapeutic effects remains unclear. It is still uncertain whether its benefits are primarily driven by modulating tendon vascularization or other mechanisms, such as modulating inflammation or providing beneficial mechanical stimulation.

Vascular Endothelial Growth Factor (VEGF)

VEGF as a therapeutic intervention has only been explored in animal models within the context of acute tendon injuries, with findings that remain partially contradictory. The direct administration of VEGF to a patellar defect in aged rats immediately after surgery resulted in improved mechanical properties and histological scores. Additionally, it reduced adipocyte accumulation and was associated with increased vascularization [91]. In a study on injured Achilles tendons in aged rats, administration of VEGF lead to increased vascular supply at 14 days post-injury. Interestingly, both VEGF and B20, a VEGF-antagonizing antibody, lead to a trending improvement of maximum load and elastic modulus of the repair tissue. However, only VEGF had a positive impact on viscoelastic properties, which is vital for absorbing shock, storing energy, and ensuring smooth, flexible motion [92]. The same authors observed functional impairment in the biomechanical properties of healing Achilles tendons in young rats treated with B20. However, administration of VEGF did not enhance tendon function, despite a clear improvement in tendon blood supply has been reported [93]. To date, the VEGF pathway has not been directly targeted in human clinical trials. Although some animal models suggest that VEGF administration may enhance tendon repair following injury, further research is necessary to elucidate its therapeutic efficacy and underlying mechanisms in clinical contexts.

Anti-Angiogenic Strategies to Improve Tendon Recovery

Heavy Slow Restistance Training and Eccentric Loading

Heavy slow resistance training (HSRT) and eccentric loading are among the most evidence-based treatments for Achilles tendinopathy, with strong evidence for their effectiveness in reducing pain and improving functional outcomes. HSR training, which involves controlled, progressive resistance exercises, enhances tendon adaptation by promoting collagen synthesis and tendon remodeling while normalizing intratendinous blood flow. Research comparing HSR to eccentric training indicates that both modalities significantly reduce tendon pain and improve function [94]. However, HSRT may provide superior mechanical adaptations, as it elicits greater increases in tendon stiffness and collagen turnover. Additionally, studies show that both training approaches reduce vascularization within the tendon, as measured by Doppler ultrasonography, suggesting that they effectively modulate pathological neovascularization [94,95,118] (Table 1). Similarly, Ohberg and Alfredson reported a strong correlation between favorable clinical outcomes following eccentric loading therapy and the regression of neovessels within the tendon [96]. Potentially, this is due to the load-induced mechanical stress placed on tendons during these exercises, which may reduce blood flow and result in decreased vascularity as part of the adaptive response. Additionally, decreased inflammation due to controlled mechanical loading might contribute to the reduction in blood vessels, as vascular growth often correlates with inflammatory responses. However, despite the clear therapeutic benefits of these interventions, the precise cellular and molecular mechanisms driving vascular dynamics remain elusive. While it is understood that mechanotransduction plays a key role in tendon adaptation, the specific pathways through which loading exercises drive vascular remodeling in tendinopathy are not fully explored. Future research should focus on unraveling these mechanisms to optimize exercise-based therapies and enhance treatment efficacy for individuals with chronic tendon disorders.

Sclerosing Therapy

Similar to the effects observed with physiotherapeutic interventions, direct reduction of tendon blood vessels in tendinopathy by injection of a sclerosing agent have been demonstrated to result in a clinical benefit for various types of tendinopathy [97–99,119,120]. Sclerosing therapy can significantly alleviate pain and improve functional outcomes in patients with chronic tendinopathies, particularly in cases of Achilles tendinopathy, with studies reporting significant reductions in pain scores and high levels of patient satisfaction [121,122]. The injection of polidocanol not only leads to pain reduction, but also to endothelial cell death, causing a loss of microvessels, thus reducing tissue perfusion. However, the efficacy of this promising method remains inconclusive due to the limited number of large-scale randomized clinical trials supporting its use [122].

Inhibition of VEGF-Signalling

Some preclinical studies, including our own, have shown beneficial effects of controlled reduction of angiogenesis on tendon healing [86,123,124]. It has been shown that the anti-VEGF monoclonal antibody, Bevacizumab, promotes tenogenic differentiation and maturation of tendon stem/progenitor cells (TSPCs) *in vitro*, suggesting that reducing VEGF signaling may enhance tendon matrix orga-

nization and function [123]. *In vivo* studies further demonstrated that Bevacizumab injections in rat Achilles tendon repair models resulted in reduced angiogenesis, improved matrix organization, and enhanced biomechanical properties, including increased stiffness and maximum load capacity [86]. Similarly, in a collagenase injection model of tendinopathy in rats, Bevacizumab showed beneficial effects on joint mobilization and tendon size [124]. Additionally, ultrasound-based evaluations confirmed dose-dependent vascular alterations following anti-VEGF treatment, highlighting the need to optimize dosage and timing for maximal therapeutic benefit [125]. Overall, while reducing pathological vessels can alleviate symptoms, it remains unclear whether this approach addresses the underlying degenerative changes within the tendon matrix itself.

In contrast, anti-angiogenic treatment using VEGF scavenger soluble fms-like tyrosine kinase-1 (sFLT1) transduced cluster of differentiation 34 positive cells ($CD34^+$) cells did not yield positive effects on rat anterior cruciate ligament (ACL) graft maturation and quality. In this study, human ACL-derived $CD34^+$ cells were genetically modified to either secrete VEGF or sFLT1 and were subsequently applied as cell sheets wrapped around autologous tendon grafts. While VEGF expression showed a modest improvement in biomechanical properties, sFLT1 transduction negated the beneficial effects of the cell sheet on graft maturation [100]. However, this model does not clarify whether excessive angiogenesis occurs in untreated grafts, potentially leading to tissue impairment.

While preclinical findings suggest that controlling angiogenesis may facilitate tendon healing, further research is required to refine treatment protocols and assess the long-term effects of VEGF inhibition, potentially paving the way for future human studies.

Blood Flow Restriction Training

Several well-designed studies on blood flow restriction (BFR) training support the hypothesis that reducing blood flow has beneficial effects on tendon adaption in health and disease. This type of training was originally developed to improve muscle strength at low training intensities by restricting blood flow to the trained limb by application of an elastic cuff or a tourniquet [126,127]. Most likely BFR training induces localized hypoxia, which potentially stimulates anabolic signaling and extracellular matrix remodeling in muskuoskeletal tissue. In healthy tendon, low intensity BFR training has been shown to significantly increase tendon cross sectional area and to be superior to high resistance training without BFR [128,129].

Emerging evidence suggests that this relatively novel method is also effective in improving tendon quality, as indicated by increases in cross-sectional area, reduced hypoechogenicity, enhanced tendon strength, and decreased pain in patients recovering from tendon rupture or undergoing treatment for tendinopathy [130]. For example, low load resistance training with blood flow restriction showed to be significantly more effective than low load resistance training alone in treating lateral elbow tendinopathy, resulting in reduction of pain intensity, patient-rated tennis elbow evaluation (PRTEE) score, pain-free grip strength, and global rating of change [131]. However, overall only very few randomized controlled trials are available on BFRT in treatment of tendinopathy. Nevertheless, BFR-training potentially has a positive impact on healthy and diseased tendons, indicating that controlled restriction of tendon blood flow may support tendon homeostasis.

Challenges, Knowledge Gaps, and Future Directions

A major limitation of current studies investigating the VEGF pathway in tendon angiogenesis—whether through upregulation or inhibition using agents such as Bevacizumab or sFLT1—is the dual role of VEGF, which affects not only vascular-associated cells but also tendon cells directly. Bevacizumab recent findings indicate that tendon cells express several VEGF receptors, with VEGFR3 activation increasing the expression of matrix metalloproteinases (MMP1 and MMP3), which can impair extracellular matrix integrity [102]. In a recent study on lymphatic vessels in rotator cuff healing, these direct effects on tendon cells were not considered [49], raising the possibility that both pro- and anti-angiogenic treatments may influence tendon repair through mechanisms beyond vascular modulation. Other interventions, such as ESWT, also affect tendon cells independently of vascular changes, as seen in reduced MMP and IL-6 expression in human cells isolated from Achilles tendinopathic tissue [132] and increased GAG synthesis in superficial digital flexor tendons of ponies within hours of treatment [133]. Furthermore, ESWT triggers adenosine triphosphate (ATP) release, activating purinergic signaling pathways which are known to promote tissue repair [134,135].

The role of vascularization in tendon healing presents a complex dichotomy—while early angiogenesis supports oxygen and nutrient delivery crucial for repair, excessive neovascularization has been linked to fibrosis and impaired tendon function. The key to optimizing tendon healing likely lies in finely tuning angiogenic responses, but the precise mechanisms governing these effects remain elusive. As evidence grows that vascularity is a key therapeutic target, a personalized approach based on healing phase and patient-specific factors might also be key for effective treatment of tendinopathy or improve healing after tendon rupture.

Future research should focus on delineating the effects of neovessels on tissue inflammation and extracellular matrix remodeling. Advanced genetic mouse models that tightly regulate angiogenesis could provide insights into these interactions. Additionally, there is a lack of tendinopathy-specific animal models, as commonly used

collagenase or cytokine injection models fail to mimic the natural disease etiology [136]. Small animal models most likely not fully replicate human tendon pathology due to differences in physiological load, aging, regenerative capacity, and genetic variability. Large animal models, such as racehorses, present challenges in terms of sample size requirements and variability in breed, sex, and age. Finally, surgical tendon injury models, while widely available, may not accurately reflect the pathomechanisms of tendinopathy.

Oxygen availability in healthy and diseased tendons remains an underexplored factor with significant implications for angiogenesis. Systematic studies measuring oxygen tension in both animal and human tendons are needed to establish a foundation for mechanistic research, particularly for *in vitro* studies. The role of lymphatic vessels in tendon disease represents another promising yet underexplored area of research, warranting detailed analysis of human tendinopathy biopsies using advanced lymphatic vessel identification protocols [45]. Controlling lymphatic ingrowth after injury in animal models could further uncover mechanisms underlying tendon fibrosis and failed healing.

Given the contradictory findings on pro- and anti-angiogenic interventions in tendon repair, future studies should systematically examine the effects of VEGF and its inhibitors across different time points and various dosages in preclinical tendon defect models. Such studies might help identifying potential biphasic effects that could account for the reported discrepancies. Addressing the interconnectivity between vascular, cellular, and mechanical factors will require innovative experimental designs that integrate vascular modulation with cellular and mechanical interventions. Despite the complexity of such studies, a multidisciplinary approach holds the greatest promise for advancing our understanding of tendon healing and optimizing therapeutic strategies.

Conclusions

Future research should aim to refine our understanding of the molecular and biomechanical mechanisms governing tendon vascularization, particularly in relation to hypoxia, inflammation, and extracellular matrix remodeling. Advanced animal models, imaging techniques, and biomolecular studies will be essential in determining the optimal balance between angiogenesis and vascular regression for tendon healing. Additionally, personalized treatment approaches that consider patient-specific factors, such as disease stage and activity level, may enhance clinical outcomes. By addressing these knowledge gaps, the field can move towards more precise, evidence-based therapeutic strategies that effectively target vascular dynamics in tendon healing, ultimately improving treatment options for patients suffering from tendinopathy and tendon injuries.

List of Abbreviations

ACL, anterior cruciate ligament; AT, Achilles tendinopathy; BFR, blood flow restriction; $CD34^{+}$, cluster of differentiation 34 positive cells; CTGF, connective tissue growth factor; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthetase; ESWT, extracorporeal shock wave therapy; FAP, fibroblast activating protein; GAG, glycosaminoglycan; HIF-1α, hypoxia-inducible factor-1 alpha; HSRT, heavy slow resistance training; IL-6, interleukin-6; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; PDPN, podoplanin; PHD, prolyl hydroxylase; PRP, platelet-rich plasma; ROS, reactive oxygen species; sFLT1, soluble fms-like tyrosine kinase-1; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; TSPCs, tendon stromal progenitor cells; VEGF, vascular endothelial growth factor; OCLN, Occludin; CLDN3, Claudin 3; CLDN5, Claudin 5; MMPs, matrix metalloproteinases; DED, dry eye disease; PDK1, pyruvate dehydrogenase kinase 1; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; ETC, electron transport chain; NOX, NADPH oxidase; FKN, fractalkine; PDGF, platelet derived growth factor; PRTEE, patient-rated tennis elbow evaluation; RCTs, randomized controlled trials; ARNT, aryl hydrocarbon receptor nuclear translocator; HRE, hypoxia responsive element; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; VEGFR3, vascular endothelial growth factor receptor 3; CD, cluster of differentiation; CX3CR1, C-X3-C motif chemokine receptor 1; AAV9, adeno-associated virus serotype 9; LECT2, leukocyte cell-derived chemotaxin 2; shRNA, short hairpin RNA; ATP, adenosine triphosphate; NADPH, nicotinamide adenine dinucleotide phosphate.

Availability of Data and Materials

Not applicable.

Author Contributions

HT and AT contributed to the design of this work. HT and AT contributed to the interpretation of data. HT drafted the work. HT and AT revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

Not applicable.

Funding

This research was funded by "Good Fibration - Targeting Fibrosis to Enhance Regeneration" (#20102/F2400948-FPR; Land Salzburg/WISS2025) and FMS_B_116.23-KNMS (PMU Research and Innovation Fund).

Conflict of Interest

The authors declare no conflict of interest.

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Editor's note: The Scientific Editor responsible for this paper was Kaili Lin.

Received: 4th October 2024; **Accepted**: 2nd July 2025; **Published**: 31st October 2025