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Review Article

Biological and Mechanical Factors and Epigenetic Regulation Involved in Tendon Healing

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Tendons are an important part of the musculoskeletal system. Connecting muscles to bones, tendons convert force into movement. Tendon injury can be acute or chronic. Noticeably, tendon healing requires a long time span and includes inflammation, proliferation, and remodeling processes. The mismatch between endogenous and exogenous healing may lead to adhesion causing further negative effects. Management of tendon injuries and complications such as subsequent adhesion formation are still challenges for clinicians. Due to numerous factors, tendon healing is a complex process. This review introduces the role of various biological and mechanical factors and epigenetic regulation processes involved in tendon healing.

1. Introduction

Tendons are the connective tissue that links muscles to bones. They are highly resistant to mechanical loads. Tendons transmit, distribute, and regulate the force applied by muscles to connective structure and anchor muscles [1, 2].

Mature tendons are comprised of tightly packed collagen fibers of different sizes. Tendon cells are distributed between fibers and synthesize a lot of extracellular matrices (ECMs), composed mostly of collagen and proteoglycan, which lubricates and assembles collagen fibers [3]. Despite having a high tensile strength and the ability to endure the powerful forces, produced by skeletal muscle contractions, tendons are susceptible to acute or chronic injury [4]. There are several biological causes of tendon injury including trauma, chronic overuse, aging, inflammation, and genetic factors [5–8]. Physical factors such as acute mechanical loads often lead to tendon tears. Clinical symptoms of chronic tendon injury or tendinopathy include pain, decreased muscle strength, and decreased physical activity [9].

Tendon injuries are common causes for seeking medical attention and account for 30% of all musculoskeletal symptoms [10]. Since connective tissue is different from other highly vascularized tissues, its sparse vascular network and low cellular metabolic rate lead to poor intrinsic healing of tendon resulting in restricted tendon regeneration potential. The healing of injured tendons needs a long time [11–13]. To make matters worse, complications often linger on even after a long recovery period. Noticeably, the formation of tendon adhesions remains the leading cause of disability in all instances of complications. When tendons are injured, they often form disordered scar tissue that does not heal well. Such restrictive adhesions within the synovial sheath of the tendon can impair function, increase the rerupture risk, and severely hinder tendon healing [14–16].

Inflammation, proliferation, and remodeling are three overlapping stages of tendon healing. The intrinsic tendon cells from inside the tendon along with the external and peripheral fibroblasts cooperate during the healing process [17]. Inflammation is the first stage of tendon healing and it involves inflammatory cells and the invasion of exogenous fibroblasts to the injury site. During the inflammation stage, a large number of cytokines are secreted by inflammatory cells. These cytokines stimulate cell migration and neovascularization. The second stage is the repair process during which numerous regenerative activities are carried out under the guidance of tenocytes and macrophages. These activities include fibroblast proliferation, excessive

ECM synthesis, tendon stem/progenitor cell (TSPC) activation, and tendon differentiation. Finally, new collagens reassemble to form healing tissue, with type I collagen playing a leading role [18].

Stem cells possess the ability to expand and differentiate into various cell lines. Stem cells also participate in tendon regeneration by regulating inflammation and promoting scar tissue regeneration. Tendon stem/progenitor cells (TSPCs) are an ideal cell type as the largest number of tendon-related markers is noticed during TSPC expression. Noticeably, elderly people possess fewer TSPCs than those in younger adults, which may explain the high incidence of tendinopathy in the elderly population. Importantly, both in vitro as well as animal studies have reported that TSPCs do differentiate into tendon cells [9].

Recent studies have reported that tendon adhesion is caused by an imbalance between endogenous healing pathways led by tenocytes and fibroblast-led exogenous healing pathways [19, 20]. The proliferation and differentiation of tendon cells primarily support endogenous healing by preventing tendon adhesion. However, exogenous healing involves the proliferation of fibroblasts around the tendon leading to growth at the broken end of the tendon which eventually leads to scar tissue formation. Often, fibroblast activity causes aggregation of collagen and fibrin around the site of injury causing adhesions, which in turn, reduce the affected joint's range of motion. Therefore, tendon adhesion is inevitable in cases where exogenous healing is more prominent than endogenous healing. Other causes for the formation of tendon adhesion include the destruction of the blood supply, loss of integrity of the tendon, and the inflammatory reaction of the tissue around the tendon. Moreover, fibrin leakage exacerbated by inflammatory exudates further worsens adhesion [16, 18].

Currently, conservative and surgical treatments are the two primary methods for treating tendon and ligament injuries. While the conservative treatment involves daily rest, drug administration, or ice administration, the surgical treatment has a restorative effect [21, 22]. Despite significant advances in surgical and rehabilitation methods, functional recovery remains limited when dealing with cases involving gap formation, adhesion, and rupture. Consequently, the regenerative capacity of tendon is insufficient to fully return to the preinjury condition [23]. Thus, researchers have been trying to improve tendon repair methods which have led to the development of advanced tendon healing methods such as gene therapy, stem cell therapy, platelet-rich plasma (PRP) therapy, growth factors, drugs, and tissue engineering [9].

In this review, the effects of biological and mechanical factors and epigenetic regulation on tendon healing are discussed. Further, we examine the relationships between biological, mechanical, and epigenetic factors to provide theoretical support to more effectively address the tendon-healing process (Figure 1 and Table 1).

2. Biological Mediation of Tendon Healing

Tendon injury can lead to a series of biological changes in the body, and these complex changes are related to the signaling pathways involved in each process.

Oxygen and lactic acid levels strictly regulate the regenerative activity of the healing tendon. Macrophages indirectly promote collagen formation by releasing large amounts of lactate [24]. Additionally, hypoxic conditions and elevated lactate concentrations stimulate angiogenesis [25]. These physiological changes may be related to the effect of oxygen on some biological factors, such as transformational growth factor-beta (TGF-β) [24].

Matrix metalloproteinases (MMPs) are enzymes that depend on zinc to function and participate in tendon healing [26, 27]. While MMP-9 and MMP-13 contribute to the degradation of the ECM several days after tendon injury, MMP-3, MMP-4, and MMP-14 are involved in matrix degradation and matrix remodeling throughout the healing process [28, 29].

Growth and transcription factors as well as some proteins have an important impact on tendon healing, and researchers have investigated these factors with some good results over the last 15 years [9]. According to recent advances, tissue engineering and gene therapy in tendon therapy often involve these factors. For example, 3D printing technology was used to implant tendons loaded with TGF-β1 gene silencing plasmids having sustained release and good biocompatibility with chicken tendon injury models [30].

2.1. Growth Factors

2.1.1. Transforming Growth Factor-Beta (TGF-β) Signaling. There are currently three main subtypes of TGF-β that participate in many cellular pathways [31]. TGF-β1 is considered to take part in initial inflammatory responses, angiogenesis, collagen synthesis, and fibrosis or excessive scarring during tendon healing [32–34]. Meanwhile, TGF-β2 and TGF-β3 are considered to be indispensable factors for tendon development and can induce the differentiation of tendon stem cells [35, 36]. These TGF-β ligands mainly mediate biological responses through the intracellular Smad2/3 pathway [33, 37–39]. Additionally, in terms of gene expression levels, the application of TGF-β3 to tendon cells can increase the level of Smad7 and reduce the level of Smad3, thereby reducing exogenous scarring and tendon adhesion, thereby promoting tendon repair [40]. Similarly, another study demonstrated that suppression of Smad3 may play a role in rotator cuff repair [41].

However, the role of TGF-β is also controversial. It can promote the differentiation of fibroblasts, but at high concentrations, TGF-β cannot play this role and may even induce apoptosis [42]. Exogenous transmission of TGF-β has long been a therapeutic approach studied in vitro and in vivo. TGF-β1 is thought to cause excessive scarring. TGF-β1 upregulation has been linked to the rising deposition of fibronectin and type I and III collagen, confirming that tendon repair through scar tissue is the basis of tendon adhesion formation [43–45]. In vitro, TGF-β1 treatment of tenocytes enhanced ECM and decreased matrix remodeling MMPs, which suggests that it may stimulate the development of adhesions [46]. Bone marrow mesenchymal stem cells transfected with TGF-β1 cDNA significantly improved the biomechanical properties of rabbit Achilles tendon injury [47]. Studies have shown that TGF-β1 inhibition

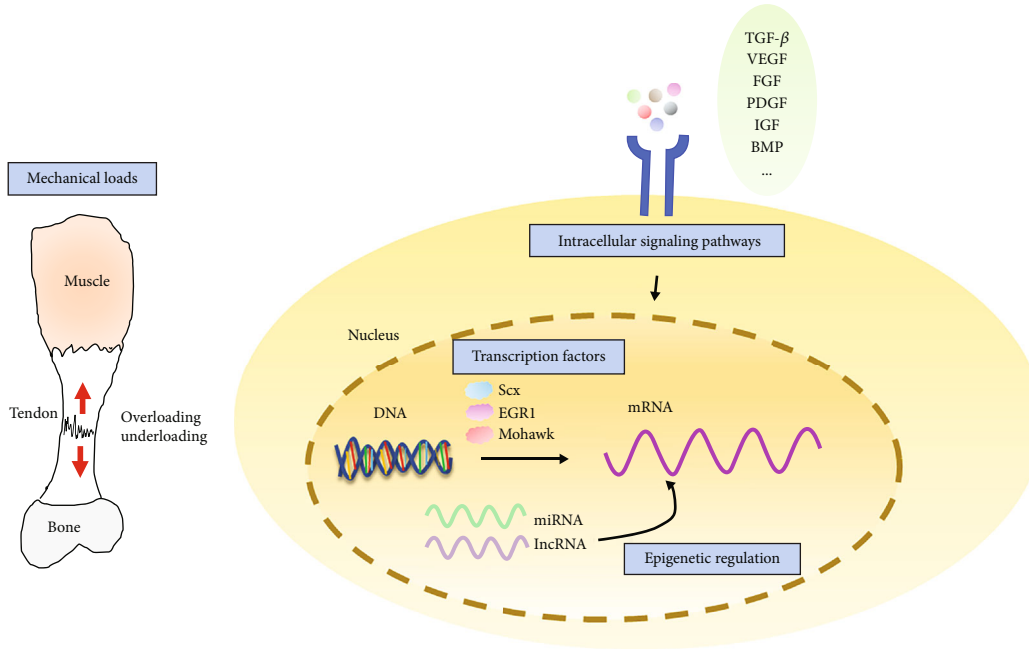

Figure 1: Biological and mechanical factors and epigenetic regulation involved in tendon healing. EGR1: early growth response 1; Scx: scleraxis; TGF-β: transformational growth factor-beta; VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; PDGF: platelet-derived growth factor; IGF: insulin-like growth factor; miRNA: microRNA; lncRNA: long noncoding RNA.

Table 1: Influencing factors in tendon healing process.

Factor		Effects on tendon healing	
Mechanical factors	Overloading	Helps the middle tendon repair but inhibits healing at the enthesis.	[139, 177–179]
	Underloading	Inhibits the middle tendon repair but helps healing at the enthesis.	[177–180]
Transcription factors	Scx, EGR1, and Mohawk	Promote tendon repair and regeneration and provide conditions conducive to cell differentiation.	[2]
Signaling	TGF-β	Involved in initial inflammatory responses, collagen synthesis, and angiogenesis.	[79]
	VEGF	Promotes angiogenesis and fibroblast proliferation and activates the synthesis of other growth factors.	[79]
	FGF	Involved in inflammation, angiogenesis, cell proliferation, and collagen synthesis.	[79]
	PDGF	Promotes angiogenesis, ECM synthesis, tenoblast migration, and differentiation.	[79]
	IGF	Promotes collagen synthesis in fibroblasts and ECM synthesis.	[79]
	BMP	Improves molecular, organizational, and mechanical properties of healing tendon.	[181–184]
Epigenetic regulation	miRNA and lncRNA	Guide tendon stem cell differentiation and tissue regeneration, promote tendon healing, and reduce adhesion.	[161–163]

EGR1: early growth response 1; Scx: scleraxis; TGF-β: transformational growth factor-beta; VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; PDGF: platelet-derived growth factor; ECM: extracellular matrix; IGF: insulin-like growth factor; BMP: bone morphogenetic protein.

can decrease the degree of scar formation, but the biomechanical power of tendon repaired sites is reduced. Unlike TGF-β1, ectopic delivery of TGF-β3 has shown excellent promise. TGF-β3 promoted tendinous differentiation of stem cells in coculture [48]. Extrinsic delivery of TGF-β3 improved the tendon structure and mechanical properties after Achilles tendon injury in rats [49].

Due to these conflicting roles that TGF-β signaling plays in tendon scar formation, the direct effect of TGF-β signaling in tendon regeneration is unclear. There are many studies that try to address this ambiguity. For example, Kaji et al. [50] compared tendon healing with and without TGF-β and found that scleraxis- (Scx-) tenocyte proliferation and subsequent tenoblast recruitment and functional recovery

depended on a TGF-β signal whereas Scx+tenocyte early proliferation did not [50].

2.1.2. Vascular Endothelial Growth Factor (VEGF) Signaling. Angiogenesis is an early event in tendon healing that causes many cells, such as fibroblasts, to converge on the area of injury to assist in tendon healing. The newly formed blood vessels mainly remove waste, deliver oxygen and nutrients, and transport biological factors. This is also the role of neovascularization in tendon repair [51–54]. Additionally, dysplasia is understood to inhibit normal healing of tendons after injury and further impair tendon quality [55]. The proliferation of vascular endothelial cells and perivascular cells is conducive to neovascularization, and VEGF has also been shown to stimulate the self-renewal ability of these cells, assist in angiogenesis, and improve the permeability of the neovascularization wall [56–59]. Additionally, VEGF can stimulate fibroblast multiplication and promote leukocyte chemotaxis [60, 61].

Proteins in the VEGF family include VEGFA, VEGFB, VEGFC, VEGFD, placental growth factor (PLGF), VEGFE encoded by a virus, and VEGFF derived from snake venom. Binding to VEGF receptors (VEGFRs), VEGFA is a typical member of the family and the most effective stimulator of angiogenesis [56, 62].

The expression of VEGF changes following acute and chronic tendon injuries. Oxygenation, inflammation, mechanical stress, and nerve signaling can affect VEGF expression levels [63–66]. First, tissue hypoxia induced by tendon injury promotes hypoxia-inducible factor-1 (HIF-1) expression and in turn stimulates VEGF gene expression. Second, the synthesis of VEGF is also induced by the liberation of inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). In addition, due to the upregulation of nerve growth factor (NGF), nerve fibers in damaged tendons tended to grow endogenously. Finally, the use of tendons under long-term overstrength mechanical load can also lead to VEGF upregulation in tendon injury [67]. After acute injury, due to an almost complete cessation of blood supply to the tendon, the metabolic rate during healing is elevated, leading to tendon hypoxia [68]. The presence of inflammatory factors after acute tendon injury and inflammation in the damaged area can also promote the upregulation of VEGF [65, 69, 70].

The increase in VEGF can promote the generation of new blood vessels in the early phase of the repair process. Nutrients, surrounding cells, and growth factors are transported to damaged areas in the process of angiogenesis mediated by VEGF [58]. Further, neovascularization involves more pericytes, which surround tendon vasculature and have the ability to self-renew and regenerate and can transform into tendon stem cells, thus mediating tendon injury healing [16, 69–71]. Then, as the blood vessel formation and repair processes are gradually completed, oxygen supply to the damaged area may be improved, and inflammation and VEGF expression may decrease [72, 73]. The periodic changes in VEGF and neovascularization were regarded as indicators of the severity and recovery status of the injury [68, 72].

However, there is some controversy over VEGF's role in promoting tendon angiogenesis. In chronic tendon diseases, VEGF was elevated in the degenerate tendons compared with natural tendons [66, 68, 74], while tendons induce the growth of new blood vessels by secreting angiogenic growth factors; unfortunately, these new blood vessels are useless and do not provide the oxygen and nutrients needed to reverse hypoxia. Since tissue regeneration requires an adequate supply of oxygen and nutrients, the presence of neovascularization in tendinopathy can be considered a sign of persistent hypoxia and a failed attempt at tissue repair. Since hypoxia-induced new blood vessels are hyperpermeable, these new blood vessels do not provide the oxygen and nutrients needed for tissue maintenance and regeneration. Moreover, the high permeability also explains an apparent paradox as to why there is persistent hypoxia in areas of neovascularization [75]. Additionally, in chronic tendinopathy, the microrupture of tendon microvessels caused by chronic tendon load initiates a vascular remodeling cascade mediated by VEGF, leading to the activation of new vessels. Hence, there is evidence that VEGF-induced angiogenesis cannot play a positive role in tendon healing in degenerative tendon diseases and may also have a negative impact on mechanical capability [64, 68, 76]. This negative effect may result from the potential of VEGF to stimulate the expression of MMPs and inhibit the expression of tissue inhibitors of matrix metalloproteinases (TIMPs) in endothelial cells and fibroblasts [64, 66]. This in turn leads to the destruction of type I collagen, a crucial part of the ECM playing an important role in mechanical loading [76].

2.1.3. Fibroblast Growth Factor (FGF) Signaling. FGFs are polypeptide growth factors widely expressed in developing and adult tissues. There are seven members of the FGF gene family in humans; among which, FGF2 was one of the earliest members discovered [77]. As a single-chain peptide that binds to heparin, FGF2 stimulates mitosis and neovascularization [58, 78]. The expression level of FGF2 was greatly increased after tendon injury, and thus, it could be an important aid in tendon repair. FGF2 has been found to play a role in inflammation, angiogenesis, cell proliferation, and collagen synthesis during tendon healing [79–81].

In a rabbit model of acute rotator cuff tear, endogenous FGF2 is secreted by tendon sheath and ligament cells [82]. Further, elevated FGF2 levels occur at an early stage of tissue healing, which leads to many positive effects, including cell proliferation and migration, neovascularization, and collagen synthesis. Consequently, from ligament therapy, exogenous FGF2 is speculated to cooperate with endogenous FGF2 at an early stage of tendon healing. This cooperative effect can facilitate cell multiplication, ECM formation, and ECM remodeling; thus, significantly shortening tendon healing time [83].

FGF2 has been shown to induce upregulation of type I or III collagen mRNA, which is critical in maintaining the mechanical properties of ligaments and tendons. Therefore, possibly, the ultimate improvement in function is associated with the mRNA level upregulation of collagen that is intrinsic to the process [79, 84].

2.1.4. Platelet-Derived Growth Factor (PDGF) Signaling. The PDGF family has four subtypes, including PDGF-BB [85]. The impassability of the PDGF signaling pathway limits the effect of mechanical stimulation on tendon tissue growth in adult mice, which may be why PDGF signaling is critical to tendon homeostasis [86]. In many animal models, exogenous application of PDGF is beneficial for the morphology and mechanics of tendon healing, demonstrating that PDGF can aid tendon regeneration [87–91].

Importantly, the PDGF-BB dimer can bind to a wide range of surface binding proteins. Therefore, PDGF-BB is the universal isomer of PDGF and has been widely studied [13]. The role of PDGF in tendon healing is multifaceted. Following thrombosis, platelets release a variety of growth factors, which interact with one another. Moreover, tendon cells and fibroblasts are drawn to damage sites by PDGF, and there, they start the production of ECM components [92]. PDGF also promotes tendon healing by promoting neovascularization, stimulating tendon cell migration to the wound area, and increasing tendon cell differentiation [13]. Additionally, PDGF contributes to the chemotaxis and proliferation of white blood cells that are capable of the decomposition and clearance of tissue fragments. PDGF promotes tendon cell proliferation, collagen synthesis, and neovascularization, contributing to early tendon repair, which is beneficial to tendon morphology and function in the regeneration process [13].

2.1.5. Bone Morphogenetic Protein (BMP) Signaling. BMPs are multifunctional growth factors belonging to the TGF-β superfamily and were originally found to be inducers of bone and chondrogenesis [93]. Further, many members of this large population are known to be important in the formation of organs and tissues before birth [94, 95].

Several laboratories have demonstrated that three types of BMP (BMPs 12-14), named after growth and differentiation factor (GDF) 5-7 in mice and rats, can be inducers of tendon tissue in vivo [96–98]. Specifically, BMP-14 improved tendon healing in mice [99–101] and induced bone marrow mesenchymal stem cells to differentiate into tendons based on increased genes that encode tendon markers such as Scx, tenascin, and type I collagen [102]. BMP-13 may be an effective stimulus for ectopic tendon formation [103]. BMP-12 is also a cell differentiation agent for tendon healing and development in vivo and in vitro through gene transfer or following in vitro exposure [104–106].

Further, BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9 are of great importance in cartilage osteogenesis and are collectively referred to as chondrogenic BMP [107]. Not only does BMP contribute to the creation and development of cartilage but also of tendons. Recent studies suggest that BMP-2 facilitates the differentiation of bone, fat, and cartilage tissues but downregulates the expression of tenogenic markers in tendon-derived stem cells (TDSCs). This process may be related to the chondrogenesis, fat infiltration, and ossification present in tendinopathy [108, 109]. Specifically, due to a reduced supply of TDSCs for tendon development, BMP-2-induced differentiation of TDSCs into nontenocytes may prevent tendon repair. Further, some inhibitors, such as BMP receptor blockers, have the power to stop the chondrogenic pathway and guarantee the differentiation of tenocytes. The effectiveness, dose, and adverse effects of these inhibitors in the management of tenosynovial illness, however, require additional research [9].

2.1.6. Insulin-Like Growth Factor (IGF) Signaling. The IGF family can be divided into two members: IGF-I and IGF-II, which are closely linked with insulin processes [110]. IGF-1 promotes collagen production in fibroblasts, which is associated with the mechanical load of the tendon. However, the relevant signaling pathways remain unclear [111–113]. Evidence also suggests that IGF-I indirectly promotes collagen synthesis via TGF-β1 [114, 115].

The liver secretes IGF influenced by GH (growth hormone). The main functions of IGF-1 include regulating the activity of GH and stimulating cell proliferation, including tenocyte formation [114, 116–118]. GH binds to IGF-1 binding proteins synthesized by the liver, mainly regulating the activity of IGF-1 [118–120]. Due to the increased release of GH from the pituitary gland, regular exercise results in a sustained increase in blood GH levels and IGF-1 levels, accompanied by increased IGF-1 mRNA expression in tendons [116]. However, the causal relationship between the upregulation of circulating GH/IGF-I and the stimulating effects of collagen synthesis in tendon healing remains to be elucidated [116]. Notably, GH is not seen to stimulate tendon healing in some studies using animal models [121, 122]. Crucially, the stimulating influence of IGF-I suggests that it can only play a local role, which cannot spread into a systemic effect. Similarly, studies have shown that load-induced IGF-I expression in skeletal muscle is unrelated to pituitary GH release [123, 124].

2.2. Transcription Factors and Relative Specific Proteins. In addition to the lack of tendon blood supply mentioned above, a common problem with tendon repair is that these regenerated tendons have poor histological characteristics and mechanical properties compared to normal tissue. Thus, the main problem of tendon differentiation is to find suitable conditions for stem cell differentiation. Transcription factors like Scx, early growth response 1 (EGR1), and Mohawk may offer promising solutions to these problems [125].

Scx plays a role as a transcription factor in tendon repair and regeneration. TGF-β signaling induces Scx expression in progenitor cells [126]. Normally, regeneration of damaged tendons requires that progenitor cells from the tissue surrounding the damaged area collect and bridge the defect. However, in Scx-deficient animals, progenitor cells move to the wound location but fail to correct for the deficit because ECM formation is impaired [126]. One study showed that Scx has an effect on human tendons during mechanical stimulation. After high physiological loading of the plantar tendon, the repair effect of Scx negative mice was inferior to that of the control group. Additionally, Scx-deficient mesenchymal stem cells have been reported to express fewer tendon-related genes than control cells [127]. Similarly, the

ability of CD146+ pericytes to differentiate into tenocytes decreased in Scx-negative mice [128].

Guerquin et al. [129] first demonstrated the importance of early growth response 1(EGR1) in tendon regeneration by finding that forced EGR1 expression converts MSC into tendon differentiation by activating Scx, Col1a1, Col1a2, and other tendon-related collagen and molecules. Like Scx, the tendency of EGR1-MSC to differentiate into osteogenic or adipogenic cell lines is also hindered [129]. In addition, EGR1 has been proven to promote fibrin-based mesenchymal stem cell-engineered tendon formation in vitro. These EGR1-engineered tendons had larger diameters and higher levels of Scx, Col1a1, and Col1a2 expression in vitro compared to the control group and promoted better repair after implantation into a rat Achilles tendon injury model. Therefore, EGR1 has good potential in tendon repair and regeneration [129].

3. Mechanical Stimulation in Tendon Healing

To explore how mechanical stimulation affects tendon healing, extensive studies have been conducted in animal models. Although stretching disrupts tendon healing at the early stage of the inflammatory phase, the injured tendon can move in a controlled manner after the inflammatory period (about 7 days after injury). Moreover, the maximum strength and deviation characteristics of the healed tendon were improved [130, 131]. Early activity of the flexor tendon following injury also contributes to recovering sliding ability in people, improving mechanical properties, and stimulating the injured tendon to return to a normal shape [132].

By stimulating tenoblast activity (e.g., fibroblast proliferation, collagen synthesis, and rearrangement), mechanical stimulation through controlled mobilization promotes tendon repair and remodeling, resulting in increased tendon diameter and tensile strength and less adhesion than fixed healing tendon [133, 134]. To stimulate tendon healing, this process is accompanied by fibroblast proliferation and collagen rearrangement [135]. Compared with the control group, artificial fixation after tendon injury may result in poor tendon healing, mainly reflected in its reduced tensile strength and strain adjustment at the fracture site [136]. Additionally, immobilization reduced the moisture content in the tendon, and the content of proteoglycan also decreased [137]. Nevertheless, the positive effect of mechanical loading on healing depends on the type of tendon and the location of its damage due to the improved effect of cast fixation [138]. Therefore, the effect of mechanical loads on tendon healing varies according to type and area [139]. Differences in results may be due to variations in the mechanical requirements for different tendon regions and for different tendon types [2].

Tenoblasts can mediate the effects of mechanical stimulation through gene, protein, and cellular adjustments. Tendons respond to movement and speed up the healing process through these mechanical force transduction mechanisms. Mechanical loading promotes ECM production by stimulating the release of growth factors through the mechanisms described above. In addition, ECM turnover can also be adjusted by MMP regulation [140, 141].

Mechanical forces applied to the cell surface also cause effects in cytoskeletal structure that initiate complex signal transduction cascades within cells by activating integrins and stimulating G-protein-coupled receptors, receptor tyrosine kinases, and mitogen-activated protein kinases [142]. While the mechanical factors that play a significant role in the biology of tendon healing are known, the process by which mechanical stimuli are converted into biochemical reactions is not well understood. Changes in the ECM, cytoskeleton, and related gene transcription can be caused by mechanical factors acting on cells [143]. The role of mechanical stimulation in molecular and cellular responses in tendon development, homeostasis, aging, and healing remains to be explored. According to previous studies, two signaling pathways related to mechanical factors, TGF-β–SMad2/3 and FGF-ERK/MAPK, play a role in tendon healing. However, thus far, there is no conclusive evidence to prove whether there is an exact relationship between mechanical load, tendon healing-related genes, related growth factors, and tendon collagen synthesis [143]. In addition, mechanical force can activate the TGF-β signaling pathway to stimulate the expression of transcription factor Scx in rat models. This signaling pathway is mediated by SMAD2/3 [40]. Enhanced phosphorylation of ERK/MAPK was observed in vitro tendon tensile tests [144]. Moreover, transcription factors EGR1 and EGR2 encoded by mechanically sensitive genes are reported to be involved in tendon development in chickens and mice [145, 146]. Noticeably, after 15 minutes of mechanical loading, elevated levels of EGR1 and EGR2 gene expression were reported in injured rat's Achilles tendon [147, 148]. Therefore, it can be inferred that the role of mechanical forces in tendon healing and development is likely mediated by certain biological factors. One possibility is that EGR1 and EGR2 transcription factors are involved in tendon differentiation. Furthermore, a study in adult mice reported that EGR1 directly acts on the regulatory areas of TGF-β2 gene to take control of TGF-β2 transcription [129]. Based on these observations, it can be hypothesized that mechanical force can drive the generation of growth factors related to tendon differentiation and ultimately promote tendon differentiation by inducing transcription of molecular sensors. We suggest that similar mechanical transduction processes drive the proliferation and differentiation of tenocytes during the development, stabilization, and repair of tenocytes.

4. Prospects of Epigenetic Regulation in Tendon Healing

Humans and other mammals undergo epigenetic regulation of gene expression. Epigenetic mechanisms associated with molecular pathology and disease management approaches are sufficiently well understood for certain diseases such as cancer, cardiovascular disease, diabetes, and neurological disorders. Inflammation is a well-established epigenetic regulatory biological process, and inflammation-associated genes have been described in detail. However, there exists insufficient evidence supporting the role of epigenetic regulation of gene expression in tendon tissue healing. Inflammation is a

common process of all tendinopathies associated with rotator cuff injury. Traditional treatment strategies have largely focused on dealing with pain and inflammation. However, since persistent disruption of ECM increases the risk of tendon injury recurrence, the possibility of epigenetic regulation of inflammatory genes and tendon repair-related gene expression cannot be ruled out [149].

Till date, about 2600 mature microRNAs (miRNAs) have been discovered in humans, and they are reported to be involved in the regulation of more than 60% of the encoding genes [150]. A unique feature of miRNAs compared to short interfering RNAs (siRNAs) is that they usually bind to target mRNAs in a partially complementary manner, meaning that a single miRNA can regulate hundreds of target genes. Consequently, changes in miRNA expression can profoundly affect biological processes such as cell proliferation, migration, differentiation, and apoptosis. Although miRNA sometimes plays an enhancer role, [150, 151] it is primarily a gene-silencing agent. Crucially, miRNA expression is negatively correlated with the regenerative potential of damaged tissues. Fetal mice displaying skin healing patterns at different stages of development demonstrates the regulatory role of miRNA in tissue regeneration [152]. Compared with late scar formation, early embryonic skin scar healing is characterized by an overall inhibition of miRNA function [152]. In addition, downregulation of miRNAs leads to cell multiplication and tissue regeneration in liver transplant patients [153]. These findings suggest that selective inhibition of miRNA functions in specific damaged tissues may potentially relieve silencing of tissue repair and regeneration genes and may restore tissue regeneration potential [154]. miRNA participates in maintaining the homeostasis of the internal environment of cells. Involved in the development of tendinopathy, miRNA induces mRNA degradation and inhibits gene translation [144, 155–159]. A series of previous studies from our laboratory have established that miRNA regulates important factors in tendon healing, including bone morphogenetic protein- (BMP-) 2, BMP-7, interleukin- (IL-) 6, and collagen types I and III [53, 160]. In the differentiation and guidance of TDSCs, different miRNAs promote or inhibit TDSCs by targeting different genes [161–163]. In addition, miRNA also contributes to reducing adhesion of healing tendon and promoting tendon remodeling [164]. Treatments based on miRNA or miRNA inhibitors have considerable therapeutic potential in a variety of diseases, including cancer. Although miRNAs targeting multiple mRNAs involved in either same or different pathways offer a potential therapeutic choice, choosing which pathway to target requires careful evaluation, and consideration should be given to nonspecific targets [156].

In recent years, it was discovered that long noncoding RNAs (lncRNAs) widely transcribed from mammalian genomes have several biological functions [165, 166]. For example, lncRNAs are found to be crucial regulators of various biological activities and disease progression [167, 168]. Further, recent data suggest that lncRNAs regulate cellular differentiation and tissue regeneration [169–172]. lncRNA H19 is an imprinted gene [173] which was discovered more than 20 years ago. By now, it is well established that lncRNA H19 is located on human chromosome 11; however, its function is not fully understood. H19 is highly expressed in embryonic tissue that originates from the endoderm and mesoderm. However, after birth, it is uninhibited only in the skeletal muscle [174, 175]. Further, H19 is reported to be a new tendon differentiation activator of TDSCs. Furthermore, enhanced expression of H19 accelerated the differentiation of tendons induced by TGF-β1 in vitro and facilitated tendon proliferation in vivo [162]. In addition, lncRNA can also synergistically interact with miRNAs, and lncRNA X-inactive specific transcript (XIST) prevents the adhesion of healing tendons via miR-26a-5p/COX2 pathway and promotes tendon healing [176].

In addition to miRNA and lncRNA, the role of other epigenetic regulation mechanisms in tendon healing is currently being explored. It is suggested that understanding the DNA methylation patterns and histone modification mechanisms of tendon-specific inflammation genes will further our understanding of tendon pathology and may even lead to the development of novel treatment/management strategies [156].

5. Conclusion

As a complex human tissue, tendons have a unique structure and perform a specific mechanical function. Tendon repair after an injury is a complex process that may involve subsequent complications including adhesion formation. Multiple factors are involved in tendon healing such as mechanical and biochemical factors and epigenetic regulation. From a holistic point of view, the tendon-healing process should be stimulated by mechanical action from gene expression to a series of biochemical factors and finally the formation of proteins to perform biological functions.

While we have a good understanding of the framework of tendon healing, there are still several mechanisms including a few pathways mentioned above and certain mechanisms of epigenetic regulation that are still being explored. Noticeably, the latest research indicates that only epigenetically regulated miRNAs play a decisive role in promoting mechanical strength during tendon healing while simultaneously reducing the formation of adhesions. The role of VEGF remains unclear. Adhesion is the result of incoordination between intrinsic and extrinsic healing. Our review clearly points out that biochemical factors only promote healing by alleviating adhesions. Therefore, we advocate that to better understand the tendon-healing process, upstream epigenetic regulatory mechanisms should be identified by future studies. Hence, the exploration of epigenetic regulation is a promising direction in the field of tendon healing.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Z.J.L. wrote the initial manuscript, Q.Q.Y. participated in and revised the paper, and Y.L.Z. provided the initial idea of this study, designed the experiments, and revised the paper.

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