

Contribution of insulin-like growth factor-1 to tendon repair (Review)

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Abstract. Tendinopathy is a common musculoskeletal disorder that markedly diminishes both physical performance and overall quality of life across age groups, imposing considerable socio-economic burdens. Insulin-like growth factor-1 (IGF-1) functions as a protective cytokine with significant involvement in multiple pathological conditions, including tendinopathy. The present review integrated current evidence on the role of IGF-1 in tendon repair. IGF-1 actively participates in every phase of tendon repair, making it a central driver of the injury response. When administered for tendon repair, IGF-1 binds to IGF-1R on target cell membranes, initiating sequential phosphorylation cascades that transmit signals from the membrane to the nucleus, while IGFBPs finely modulate this process. These intricate signaling pathways ultimately yield beneficial effects such as reduced inflammation, enhanced cell proliferation and migration and increased collagen synthesis, thereby promoting restoration of tendon structure and integrity. IGF-1 has emerged as one of the most promising growth factors in tendon regenerative strategies. Nevertheless, clarification of critical parameters such as administration dosage and timing remains necessary to optimize its therapeutic value and to fully delineate its contribution to tendon repair.

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1. Introduction

Musculoskeletal disorders account for a substantial proportion of healthcare costs across a number of nations, exerting extensive effects on public health and individual functioning (1,2). Nearly one-third of the global population suffers from musculoskeletal disorders and 30-50% of these clinical visits are related to tendons (3). Tendons, as a special type of connective tissues, exhibit adaptive capacity in response to mechanical loading and injury (4), while serving as essential conduits for force transmission between muscle and bone (5). Inadequate adaptation to mechanical loading is widely considered the principal driver of tendinopathy (6). Characteristic features of tendinopathy include degenerative alterations in tendon mechanics and cytoarchitecture (7). This condition affects individuals irrespective of age or socioeconomic background, restricting physical performance and diminishing overall quality of life (1,8). While the low metabolic rate of the tendon may reduce the risk of ischemia and necrosis amid elevated local tension (9), it can also make the repair of the tendon a lengthy event.

In general, early damage to the tendon matrix triggers a healing response. However, the intrinsic capacity for regeneration remains limited due to the inherently sparse cellularity of the tendon, restricted vascular supply and structural complexity, particularly at junctional regions. Consequently, matrix injury tends to accumulate progressively, rendering subsequent repair more challenging (10). Current therapeutic strategies for tendinopathy are broadly categorized into conservative and surgical approaches. As surgical procedures are often associated with complications, conservative modalities, such as physiotherapy, local injections, pharmacologic agents and exercise-based regimens, are more frequently adopted in clinical practice (11). Within these non-surgical options, growth factors have been intensively investigated for their capacity to enhance tendon repair (12). Functioning as peptide mediators, they regulate essential processes including cell proliferation, differentiation, migration and extracellular matrix (ECM) remodeling in response to tendon injury. Owing to these biological functions, growth factors are regarded as promising candidates

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for accelerating tendon regeneration (13,14). Among them, insulin-like growth factor-1 (IGF-1) has attracted particular attention as an effective regulator of tendon metabolism and a potential therapeutic agent for improving tendon repair (13).

IGF-1 serves as a central mediator in tendon repair, exerting regulatory effects across multiple phases of the healing cascade (15,16). Beyond its hepatic synthesis and systemic release, IGF-1 is also produced locally in tendons and ligaments, where it contributes directly to tissue remodeling (17). Its synthesis is regulated by multiple factors, with the hormonal environment and nutritional status being particularly influential (18). Research indicates that IGF-1 expression is not solely dependent on growth hormone (GH) but is also modulated by factors such as thyroid hormones, sex hormones and nutritional status (19,20). Disturbances in these regulatory factors can markedly impair IGF-1 synthesis. For instance, reduced IGF-1 concentrations are observed in hypothyroid patients compared with healthy controls (21). Hypothyroidism is also associated with tendon damage, characterized by decreased collagen synthesis and the degeneration of connective tissue (22). As a potent stimulator of mitosis and protein synthesis in various cell types, IGF-1 not only promotes tendon cell mitosis but also stimulates the production of ECM components, including collagen and proteoglycans (23,24). Consequently, exogenous IGF-1 supplementation may have a more profound impact on tissue repair in such patients. Research suggests that androgens may enhance the effects of GH in peripheral tissues, potentially explaining why men often show an improved response to recombinant human GH (rhGH) therapy compared with young women (25). Additionally, estrogen appears to support tendon healing by stimulating type I collagen formation (26), indicating that IGF-1 therapy may also provide therapeutic benefit in hypogonadal states. Nevertheless, the mechanisms by which hormones influence GH-induced IGF-1 secretion and their subsequent effects on tendon repair are complex and warrant further investigation to support more personalized treatment strategies (21,27).

The anti-inflammatory effects of IGF-1 have attracted considerable attention (13,28). It is considered to facilitate tendon regeneration by mitigating inflammation, reducing scar tissue formation and preventing adhesions (28). In addition, its potent chemotactic properties are regarded as indispensable for effective tissue repair (29,30). Owing to these positive effects, IGF-1 is administered either alone or in combination with other growth factors to enhance tissue healing and improve therapeutic efficacy. While the effectiveness of IGF-1 in promoting tendon healing is supported by numerous studies (13,15,16,28), the underlying mechanisms remain inadequately understood. The present review clarified the roles and mechanisms of IGF-1 in tendon repair, evaluated strategies to enhance its therapeutic use and outlined priorities for future research.

Search strategy. i) Search site: Articles are from PubMed (pubmed.ncbi.nlm.nih.gov/), a database of papers on biomedical science. ii) Database: MEDLINE (<https://www.webofscience.com/wos/medline/basic-search>). iii) Key words: Insulin-like growth factor-1, IGF-1, tendon injury, tendinopathy, tendon repair iv) Boolean algorithm: ('insulin-like growth factor-1' OR 'IGF-1') AND ('tendon' OR 'tendinopathy' OR 'tendon

repair'). v) Retrieval timeframe: Selected journals published 1988-2025. vi) Inclusion and exclusion criteria: Articles were included if the topic was related to Insulin-like growth factor-1 and tendon and the article type was a review or an experimental paper. The search process is shown in Fig. 1.

2. Preclinical experimental studies of IGF-1 in tendon repair

Numerous studies have highlighted the critical role of IGF-1 in tendon repair (13,31,32).

Rieber, Caliarì and Herchenhan, through *in vitro* studies, investigated the effects of IGF-1 on tendon repair. Rieber *et al* (12) examined the stimulatory effect of IGF-1 on collagen production in rabbit Achilles tendon cells. After supplementing the cells with IGF-1 for 3 days in culture, the authors observed a dose-dependent increase in collagen I gene expression at 0, 0.1 and 1 ng/ml. Similarly, Caliarì and Harley (33) isolated equine tendon cells from the superficial finger flexor tendons of horses and in culture, they found that 10 and 100 ng/ml IGF-1 led to a 2- to 3-fold increase in type I collagen gene expression. Herchenhan *et al* (34) investigated the effect of IGF-1 on tendon constructs in a 3D cell culture model, revealing that IGF-1 promoted collagen expression and formation in human tendon cell-derived constructs. Additionally, IGF-1 accelerated the onset of collagen synthesis, which may positively influence fibroblast proliferation. These findings highlight the significance of growth factors in tendon development and regeneration.

In vivo studies have also demonstrated the critical role of IGF-1 in tendon healing. Dahlgren *et al* (13) assessed the effects of intra-tendon IGF-1 injections on tendon healing in an equine flexor tendinitis model. The authors found that tendons treated with IGF-1 exhibited increased cell proliferation and collagen content, with a tendency for greater stiffness compared with the saline-treated control group. Furthermore, soft tissue swelling at the injury site was consistently reduced in the IGF-1-treated group, with this effect becoming apparent by the second day following treatment. These observations suggest that IGF-1 possesses anti-inflammatory properties when administered locally. These results further reinforce the potential of IGF-1 as a therapeutic agent for tendon healing.

Additionally, Tang *et al* (28) developed a rat Achilles tendon injury model and employed ultrasound-targeted microbubble destruction to transfect IGF-1 into tendon cells, investigating its role in promoting tendon regeneration. Pathological analysis revealed that IGF-1 accelerates Achilles tendon repair in rats by reducing inflammation and minimizing scar tissue formation at the injury site. The study also suggested that IGF-1 may enhance tendon regeneration by promoting the transformation of fine, disorganized type III collagen fibers into stronger, more mature type I collagen fibers. Biomechanical tests further supported these findings, confirming that IGF-1 promotes tendon healing both histologically and biomechanically. In another study, Disser *et al* (5) used a tamoxifen-induced Cre-recombinase system to conditionally delete the IGF-1 receptor (IGF-1R) in tendon cells. In comparison to control mice expressing IGF-1R, mice lacking IGF-1R in tendon cells showed reduced cell proliferation and tendon size. Moreover, the authors showed that IGF-1 stimulates cell proliferation

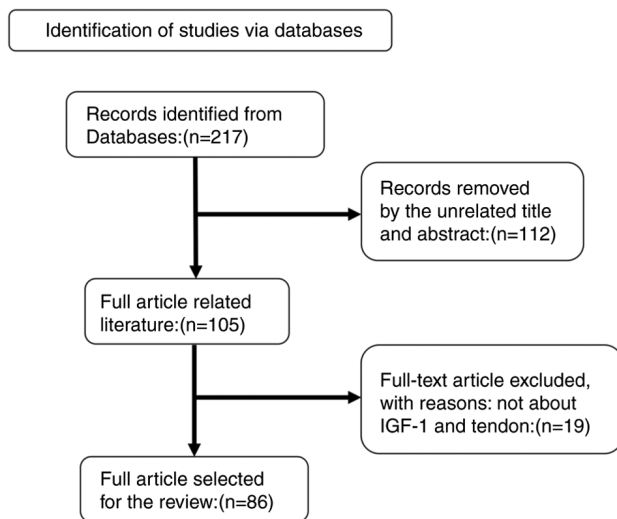


Figure 1. Article retrieval flow chart with inclusion and exclusion process. IGF-1, insulin-like growth factor-1.

and protein synthesis by activating the phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase (or protein kinase B, AKT) and extracellular regulated protein kinases (ERK) pathways. These findings provide mechanistic insights supporting the potential use of IGF-1 in treating tendinopathy.

In summary, studies highlight that IGF-1 promotes tendon repair by reducing inflammation, stimulating cell growth, enhancing collagen synthesis and improving the structural integrity of healed tendons. Table I summarizes the various mechanisms through which IGF-1 exerts these beneficial effects, as evidenced by multiple experimental studies.

3. The basis of IGF-1 efforts: IGF-1R

The biological functions of IGF-1 are primarily mediated through its binding to IGF-1R (35). Yang and Goldspink (36) demonstrated that IGF-1 promotes myoblast proliferation via the IGF-1R. As highlighted by Li *et al* (23), IGF-1 markedly stimulates tendon cell proliferation, with the effect being directly dose-dependent. Conversely, inhibiting IGF-1R activation not only hampers tendon cell proliferation but also results in reduced tendon size. IGF-1, a hormonal protein synthesized by the liver in response to GH stimulation in response to GH (37), is also directly released from skeletal muscle tissue through autocrine and paracrine mechanisms. Upon binding to its receptor, IGF-1 initiates a cascade of intracellular signaling events (38,39).

IGF-1R is a heteromeric tetrameric receptor in the trans-membrane receptor tyrosine kinase (RTK) family, consisting of two extracellular α -subunits and two transmembrane β -subunits and is widely expressed in human tissues (40). Its primary ligand is IGF-1, followed by IGF-2 and insulin (35). IGF-1, structurally similar to insulin except for its interaction with IGF-1R, can also bind the insulin receptor (IR) and vice versa (41). However, these ligands differ in their affinity for the receptor. IGF-1 binds IGF-1R with 10 times greater affinity than IR. As for insulin, on the other hand, the IGF-1R binding strength is ~ 100 times weaker than IR (42). Additionally, IGF-1 and insulin exhibit differences in tissue distribution and

internalization kinetics (41). Despite their structural similarities and shared signaling pathways, they activate downstream pathways to varying extents and through distinct mechanisms (31).

In cells that express both IGF-1R and IR, the receptors undergo heterodimerization (forming hybrid receptors) and homodimerization (42). In skeletal muscle tissue, IGF-1R and IR primarily exist as hybrid receptors. While these hybrid receptors can interact with both insulin and IGF-1, they show a preferential binding to IGF-1 (43). Upon binding IGF-1 to the α -subunit of IGF-1R, morphological changes occur in the β -subunit, which activates the receptor's caspase activity (44). This activation triggers phosphorylation of various receptors, including IR substrates (IRS) and Src homology collagen (SHC). Signaling molecules containing Src homology 2 (SH2) domains, such as SH2-containing protein tyrosine phosphatase 2 (SHP2/SYP), growth factor receptor-bound protein 2 (Grb2) and PI3K, can recognize phosphorylated tyrosine residues on these receptors (42). The interaction of these molecules activates critical downstream signaling pathways, notably the Ras-mitogen-activated protein kinase (MAPK) and PI3K pathways (45). In summary, IGF-1R serves as the primary mediator for the biological effects of IGF-1. Fig. 2 illustrates the signal transduction process following IGF-1 binding to its receptor, focusing on the key activities involved in tendon repair while omitting other mechanistic processes.

4. The important regulators of the IGF-1 system in tendon repair: IGFBPs

As the primary carriers of IGFs, insulin-like growth factor-binding proteins (IGFBPs) play a central role in mediating interactions between IGF ligands and their receptors (46). By binding to IGFBPs, IGF-1 markedly extend its half-life in circulation and prevent its binding to the IR, thereby allowing for more precise IGF-1 actions. This interaction greatly enhances the flexibility and multifunctionality of the IGF signaling system (47).

The IGFBP family comprises six highly conserved proteins encoded by the IGFBP-1 to IGFBP-6 genes, all sharing notable structural similarities (48). While the term 'IGFBP' has been extended to include various proteins with limited structural homology to the IGFBPs, such as mac25 (IGFBP-7), the consensus is that only the six proteins with a strong affinity for IGFs should be referred to as IGFBPs (49). IGFBPs typically consist of 200-300 amino acids and feature a conserved structure. This structure features a highly cysteine-dense N-terminal domain that remains remarkably consistent among the IGFBP family and across different species (50). Additionally, there is a linker domain with a variable sequence, followed by a cysteine-rich C-terminal domain that has been similarly preserved throughout evolution. The N-terminal and C-terminal domains both adopt a globular structure, stabilized by disulfide bonds between conserved cysteine residues, which are critical for establishing the IGF-binding site (51). By contrast, the central linker domain lacks a defined structure and serves as a bridge, contributing to the functional diversity of each binding protein (52).

IGFBPs are widely expressed in most tissues and regulate circulating IGF-1 concentrations through both overlapping

Table I. Biological responses manifested by IGF-1 in different experiments.

Authors, year	Research object type	Models establish	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Disser <i>et al.</i> , 2019	<i>In vitro</i>	Mice plantaris tendons	IGF-1:100 ng/ml	1, 2, 6, 24 h	Proliferation marker Ki67↑ Protein synthesis↑	IGF-1 promotes cell proliferation and protein synthesis.	(5)
Rieber <i>et al.</i> , 2023	<i>In vitro</i>	Rabbit tenocytes	IGF-1:1 ng/ml	3 days	Ki67↑ Tenomodulin expression↑ Type I collagen↑	IGF-1 stimulates cell proliferation and matrix synthesis at the site of tendon injury.	(12)
Dahlgren <i>et al.</i> , 2002	Horses aged 2-6 years	Flexor digitorum	rh IGF-1:2 µg	Treated tendons were injected superficialis tendon with rhIGF-1 every other day for 10 injections starting 3 days following the collagenase injection	Cell proliferation↑ Collagen content↑ Soft tissue swelling↓ Mechanical properties↑ PI3K/AKT↑ERK↑	IGF-1 leads to increased cell proliferation, improved ultrasound healing of lesions, increased collagen content, reduced soft tissue swelling and improved mechanical properties.	(13)
Hansen <i>et al.</i> , 2013	Twelve healthy men	IGF-1 was injected into the patellar tendon	1 mg IGF-1 per day	Two injections of IGF-1 both 3 h and 24 h before the measurements of tendon collagen fractional synthesis rate	Tendon collagen fractional synthesis rate↑ PINP↑	Topical administration of IGF-1 directly promotes tendon collagen synthesis within and around human tendon tissue.	(17)
Hagerty <i>et al.</i> , 2012	<i>In vitro</i>	Human ACL cell	IGF-1:300 ng/ml	10, 12 and 14 days	Collagen content↑ Collagen dissolution↓	IGF-1 increases collagen synthesis and further increases collagen content by reducing collagen degradation.	(140)
Laplante and Sabatini, 2012	<i>In vitro</i>	Equine flexor tendon cells	IGF-1:100 ng/ml	7 days	Cell proliferation↑ Matrix synthesis↑	IGF-1 markedly increased cell number and matrix synthesis <i>in vitro</i> .	(132)
Saxton and Sabatini, 2017	<i>In vitro</i>	Human fibroblasts and tenocytes	IGF-1:10, 50 and 100 ng/ml	3 days	Cell proliferation↑	Cell proliferation was accelerated.	(137)
Dahlgren <i>et al.</i> , 2005	<i>In vitro</i>	Equine tendon fibroblasts	IGF-1:250 ng/ml	10 days	Collagen synthesis↑ DNA content↑	IGF-1 stimulated an anabolic response in tendon. Collagen synthesis and glycosaminoglycan and DNA content of explants were all increased.	(141)
Durgam <i>et al.</i> , 2012	Male Sprague-Dawley rats	MCL rupture and repair	Inject 0.5 ml IGF-1 twice daily	3 weeks	Mechanical properties↑ Type I collagen↑ Matrix tissue expression↑	The addition of IGF-1 markedly increases the expression of matrix tissue and type I collagen.	(142)

Table I. Continued.

Authors, year	Research object type	Models establish	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Holz <i>et al.</i> , 2005	<i>In vitro</i>	Rat tenocytes	IGF-: 10, 50 and 100 ng/ml	72 hs	Collagen production↑ Tenomodulin expression↑ Aggrecan↑	Lower concentrations of IGF-1 (10 ng/ml) markedly increased collagen deposition and tenocytes treated with all concentrations of IGF-1 had markedly higher gene expression levels of tenomodulin.	(133)
Frank <i>et al.</i> , 1999	<i>In vitro</i>	Equine tenocytes	IGF-1:10, 50 and 200 ng/ml	7 days	Tenocyte migration↑ Tenocyte number↑ Metabolic activity↑	IGF-1 induces a significant increase in tendon cell migration and leads to a dose-dependent increase in the number and metabolic activity of tendon cells.	(139)
Musson <i>et al.</i> , 2017	<i>In vitro</i>	Rabbit deep flexor tendon	rh IGF-1:50 ng/ml	3 weeks	Proteoglycan↑ Matrix synthesis↑	rh IGF-1 may be used as a defined growth-promoting factor serum-free media and may be of importance in tendon healing.	(143)

IGF-1, insulin-like growth factor-1; ↑, significant increase; ↓, significant decrease; ACL, anterior cruciate ligament; MCL, medial collateral ligament; PINP, Type I procollagen N-terminal propeptide.

and distinct mechanisms, thus influencing IGF-1 activity and signaling (53). IGFBP-1 is primarily produced in the liver and kidneys and plays key a role in metabolic and reproductive processes. It also regulates the extent to which IGF-1 can infiltrate tissues, as the IGFBP-1-IGF-1 complex can migrate from the vascular compartments to tissues (54). Few studies have reported that IGFBP-1 is produced locally in tendons or connective tissues and some have even indicated that expression of all remaining IGFBPs except IGFBP-1 can be shown in equine tendons (51,53,55). However, research by Olesen *et al* (56) showed that IGFBP-1 concentrations increase in human peritendinous tissues following exercise. This elevation could influence tendon healing processes. The phosphorylation state of IGFBP-1 plays a pivotal role in modulating the ability of IGF-1 to stimulate cell proliferation. Slight phosphorylation of IGFBP-1 enhances its ability to promote cell division by facilitating the interaction of IGF-1 with its receptor, while extensive phosphorylation of IGFBP-1 binds to IGF-1, preventing it from engaging with the receptor and inhibiting proliferation (45). The predominant binding protein in healthy tendons, which also responds most markedly to injury, is IGFBP-2 (55). As is well known, IGFBP-2 can interact with a receptor known as receptor protein tyrosine phosphatase β , initiating a signaling cascade. This process results in the suppression of Phosphatase and tensin homolog phosphatase activity, thereby augmenting the stimulatory effect of IGF-1 on the AKT pathway activation (57). IGFBP-3, which binds ~80% of circulating IGF-1, plays a critical role in IGF regulation (58). It often forms a ternary complex with IGF and the glycoprotein acid labile subunit, a complex that markedly extends the half-life of IGF, thus maintaining a persistent reservoir of IGF (59). IGFBP-4 is considered to play a critical role in connective tissue and may influence the effects of IGF-1 in tendons, as it is produced by fibroblasts (60). Wang *et al* (61) demonstrated that IGFBP-4 enhances the expression of tendon-associated and proliferative markers. The authors found that adding IGFBP-4 helped retain IGF-1 in the postoperative tendon, boosting protein synthesis through the IGF-1/AKT signaling pathway and effectively promoting tendon healing. Similarly, Olesen *et al* (62) suggested that local elevation of IGFBP-4 amplifies the anabolic effects of IGF-1, thereby improving tendon strength. As with IGFBP-4, IGFBP-5 is also expressed in connective tissues (60). IGFBP-5 acts as a stable binding site for IGF and promotes the interaction between IGF ligands and their receptors, especially when its affinity for IGF is reduced (46). Compared with other binding proteins, IGFBP-6 has the highest mRNA expression in tendons (56). Although IGFBP-6 has a higher binding affinity for IGF-2 than for IGF-1, it serves as a reliable marker of tendon phenotype, enabling the assessment of tendon physiology and guiding permissive cell differentiation toward functional tendon cells. These functions represent biological roles of IGFBP-6 that are independent of IGF activity (63).

As important regulators of IGF activity, IGFBPs markedly enhance the flexibility and versatility of IGF signaling (53,64). IGFBPs also display IGF-independent activities, substantially expanding their functional and research scope. While much progress has been made, further investigation is needed to improve our understanding of how these interactions influence

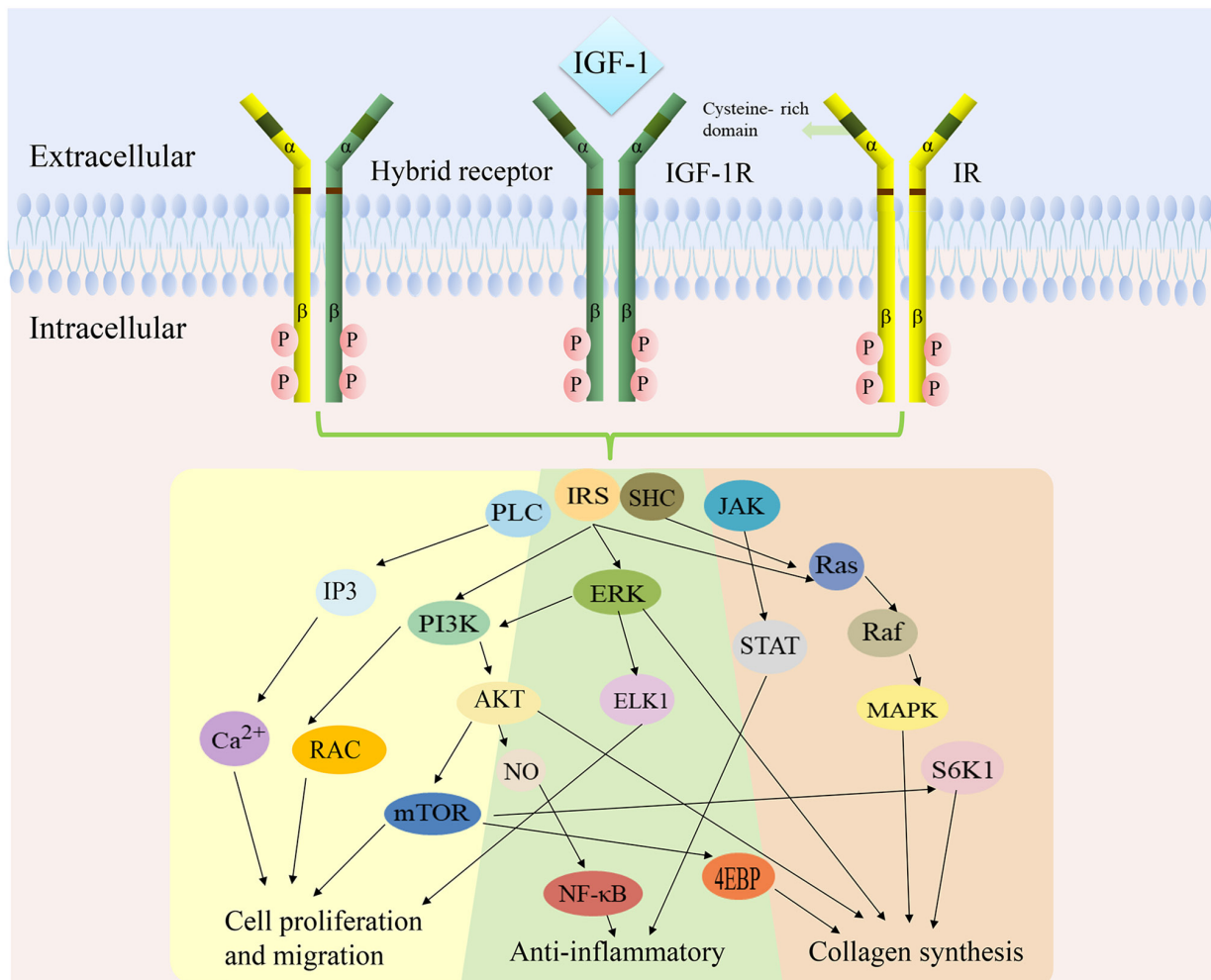


Figure 2. A streamlined representation of the signaling action of IGF-1 upon binding to its receptor has been made, showing mainly the relevant activities involved in tendon repair and omitting other mechanistic processes. IGF-1R and IR primarily exist in the form of mixed receptors in skeletal muscle tissue. The biological function of IGF-1 is mainly produced by binding to IGF-1R. When IGF-1 specifically binds to the α subunit of IGF-1R, it leads to morphological changes in its β subunit, thereby activating receptor casein activity. The activated receptors trigger phosphorylation of several specific receptors, including IRS and SHC. Some signaling molecules containing the SH2 domain can recognize phosphorylated tyrosine residues in these receptors. These combinations lead to the activation of downstream signaling pathways such as PI3K/AKT, ERK, JAK, PLC and ras mitogen activated protease. IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IR, insulin receptor; IRS, IR substrates; SHC, Src homology collagen; SH2, Src homology 2; PI3K/AKT, phosphatidylinositol 3-kinase/serine/threonine kinase (or protein kinase B); ERK, extracellular regulated protein kinases; JAK, Janus kinase; PLC, phospholipase C; IP3, inositol triphosphate; Ca^{2+} , calcium; mTOR, mammalian target of rapamycin; 4EBP, eIF4E binding protein; S6K1, p70S6 kinase 1; NO, nitric oxide; NF- κ B, nuclear factor- κ B; STAT, signal transducers and activators of transcription; MAPK, the Ras-mitogen-activated protein kinase.

growth and metabolism within the organism (48,50). Fig. 3 illustrates the structural domains of IGF-BPs and their varying effects on IGF-1 during tendon repair.

5. The mechanisms of IGF-1 in tendon repair

Tendon repair is a complex process, involving three overlapping and successive stages: inflammation, proliferation and remodeling (65). The inflammatory phase typically occurs within the first hour following injury, during which blood collects and clots at the site, releasing pro-inflammatory growth factors. These factors attract macrophages, neutrophils and other inflammatory cells to the injury site, where they play a pivotal role in pathogen clearance and initial healing. This cellular activity sets the stage for the subsequent proliferative phase (9). During this phase, fibroblasts can be recruited from tendon sheaths and tendons, proliferating in response to the growth factors at the injury site. These cells begin synthesizing

ECM components, such as collagen. The remodeling phase begins ~four weeks after injury, during which type III collagen is gradually replaced by type I collagen. Collagen fibers are reorganized to form cross-links, ultimately leading to a more structured ECM (66). It is important to note that even when regenerative healing predominates, the process remains slow, often taking more than three to six months and ultimately does not lead to full functional recovery and strength (12).

One effective approach to enhancing tendon repair involves the direct application of growth factors to the injury site. IGF-1, being active throughout various stages of the healing process, has emerged as a key player in tendon repair (15). When IGF-1 is administered, it triggers a cascade of phosphorylation events by binding to IGF-1R on the target cell membrane, thereby transmitting signals from the membrane to the nucleus. This process is regulated by IGF-BPs. The resulting signaling pathways promote inflammation suppression, cell proliferation and collagen synthesis, accelerating tendon tissue repair (51,67,68).

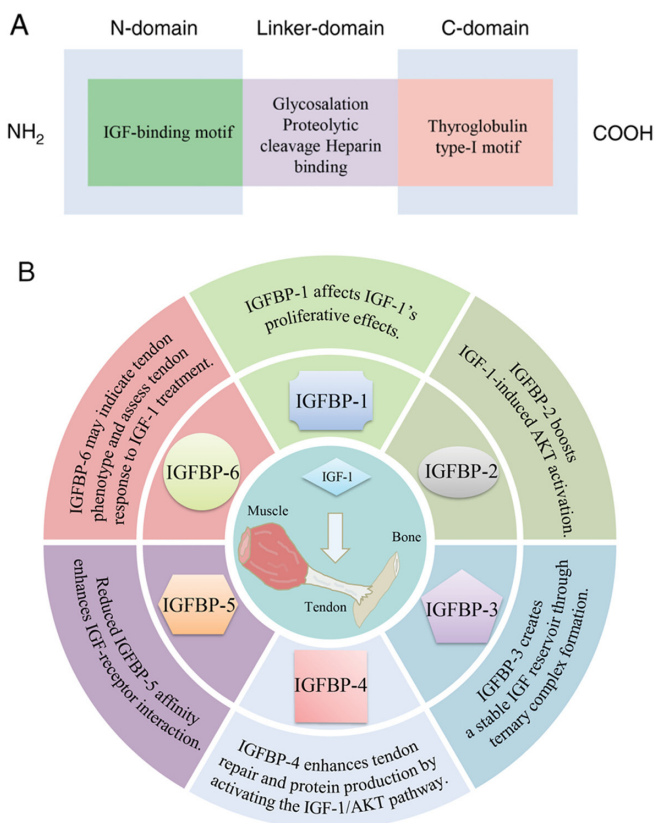


Figure 3. The important regulatory role of IGFBPs in the IGF-1 system for tendon repair. (A) The structural domains of IGFBPs. IGFBP contains conserved N-terminal and C-terminal structural domains, as well as variable junction domains between them; the N domain contains the IGF-binding motif and the C domain contains the thyroglobulin type I repeat sequence. (B) The different effects of IGFBPs on IGF-1 during tendon repair. IGF-1, insulin-like growth factor-1; IGFBPs, insulin-like growth factor-binding proteins.

These findings highlight the critical role of IGF-1 in biological healing. Fig. 4 illustrates the mechanism by which IGF-1 promotes tendon repair, focusing on the key activities involved in this process and omitting other less relevant mechanistic details.

IGF-1 modulates the inflammatory process. Modulating the inflammatory response is critical for initiating tendon repair (11). Reducing inflammation promotes ECM remodeling, enhances tendon regeneration and minimizes scarring and adhesions, thereby aiding the resolution of tendinopathies (28). Studies have demonstrated that IGF-1 plays an anti-inflammatory role in tendon injury healing (9,69). Dahlgren *et al* (13) provided further evidence of the anti-inflammatory effects of IGF-1 by injecting 2 μ g rh IGF-1 into the flexor tendons of horse forelimbs. The study revealed a significant reduction in soft tissue swelling at the injury site in the IGF-1-treated group compared with the control group, with improvements being most noticeable the day following treatment. Zhang *et al* (70) also investigated the potential of IGF-1 to reduce inflammation by examining the expression levels of inflammation related proteins. Their results showed a decrease in the levels of pro-inflammatory factors (TNF- α , IL-1 β and NLRP3), while anti-inflammatory factors (IL-4 and IL-10) were markedly elevated. Additionally, immunofluorescence

analysis revealed a marked reduction in the fluorescence intensity of the pro-inflammatory cytokine IL-6, accompanied by a notable increase in the anti-inflammatory cytokine IL-10. These findings collectively suggest that IGF-1 effectively inhibits inflammation.

The mechanisms underlying the anti-inflammatory effects of IGF-1 remain incompletely understood, but IGF-1 appears to curb inflammation by skewing macrophages toward an M2 phenotype and increasing IL-10 and transforming growth factor- β (TGF- β) production (71). Macrophages play a pivotal role in the effective debridement and repair of injured tendons (72). They exist in two phenotypes: M1 and M2 (73). M1 macrophages have pro-inflammatory properties and contribute to the initial immune response by clearing necrotic tissue. Subsequently, M2 macrophages, which exhibit anti-inflammatory and repair characteristics, release growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), IGF-1 and TGF- β to promote tissue repair (74). This may enable IGF-1 to function via a negative feedback loop. As a major product of the inflammatory cascade, high levels of IGF-1 likely modulate the early inflammatory response by downregulating inflammatory genes in the involved cells, rather than inhibiting the migration of inflammatory cells to the injury site, leading to suppression of the initial inflammatory cascade (75). Additionally, increased IGF-1 secretion stimulates the release of the anti-inflammatory cytokine IL-4, further reducing the inflammatory response (76). This effect may also be linked to macrophages, as IL-4 is critical for inducing macrophage polarization to the anti-inflammatory phenotype (77). Like macrophages, neutrophils, which are among the first cells to arrive at the injury site, exhibit distinct phenotypes. These can be classified at least into pro-inflammatory N1 neutrophils and reparative N2 neutrophils (78). Research by Nederlof *et al* (79) suggests that IGF-1 can also modulate neutrophil function by enhancing the phosphorylation of STAT6, polarizing neutrophils towards the anti-inflammatory N2 phenotype through activation of the atypical downstream Janus kinase (JAK)-STAT pathway, thereby promoting an anti-inflammatory response.

Additionally, IGF-1 can mediate anti-inflammatory effects through the PI3K pathway (80,81). Notably, PI3K has been shown to inhibit the activation of nuclear factor- κ B (NF- κ B) (82). NF- κ B participates in all stages of tendon repair, including inflammation, angiogenesis, cell proliferation and tissue adhesion formation (83). During the inflammatory phase, NF- κ B is a central player in the immune response. Its activation triggers the upregulation of pro-inflammatory genes such as cytokines, chemokines and adhesion molecules, which help clear necrotic tissue and facilitate healing (84). However, if the inflammatory response remains uncontrolled in the early stages of tendon healing, it can lead to an excess of pro-inflammatory cytokines and over-deposition of ECM due to prolonged inflammatory signaling, resulting in excessive fibrotic repair (85). This can lead to the formation of dense fibrous adhesions between the tendon and surrounding tissues, a condition commonly associated with chronic tendon injuries (86). Inhibiting NF- κ B activity is thus considered beneficial for promoting anti-inflammatory effects, thereby accelerating tendon repair (87). Notably, nitric oxide (NO) may be involved in this process. As it has been demonstrated

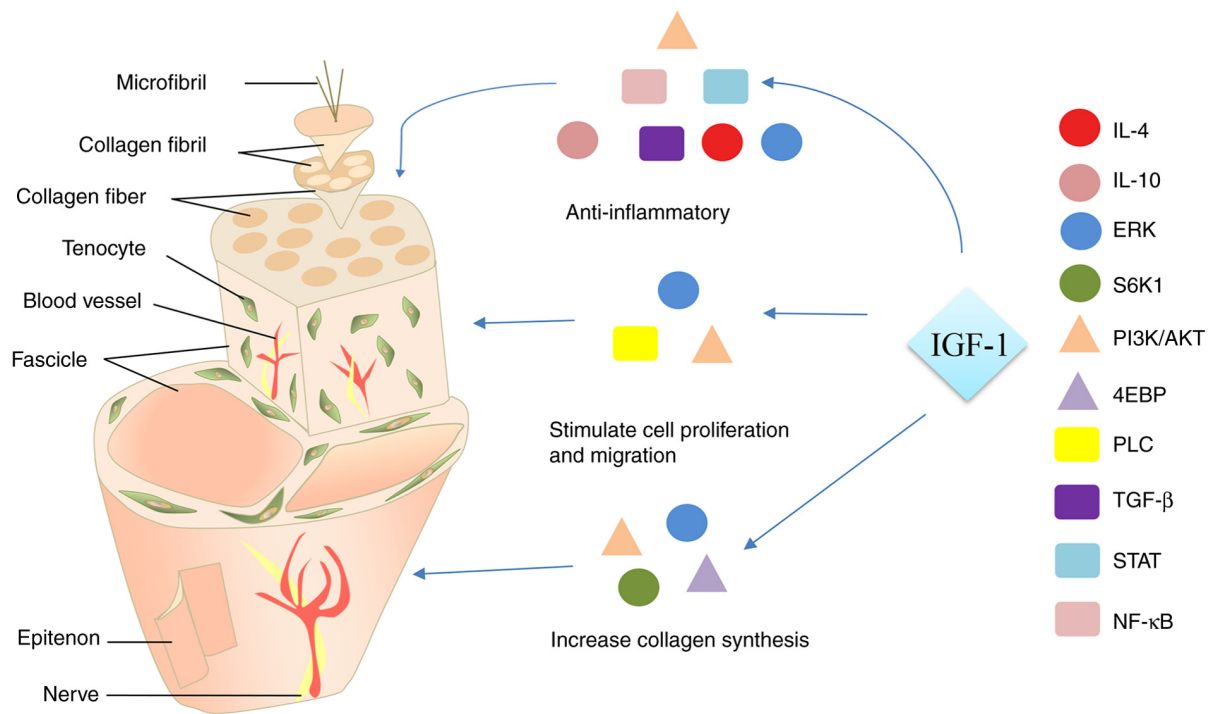


Figure 4. The mechanisms of IGF-1 in tendon repair. IGF-1 acts on the molecular structure of tendons by regulating related signal transduction. IGF-1 participates in tendon repair by regulating important factors such as IL-4, IL-10, TGF- β , key proteins such as S6K1 and 4EBP, as well as important signaling pathways such as ERK, PI3K/AKT, NF- κ B and PLC. They play important roles in the anti-inflammatory, cell proliferation, and matrix remodeling processes of tendon repair. IGF-1, insulin-like growth factor-1; IL-4, interleukin-4; IL-10, Interleukin-10; ERK, extracellular regulated protein kinases; S6K1, p70S6 kinase 1; PI3K/AKT, phosphatidylinositol 3-kinase/serine/threonine kinase (or protein kinase B); 4EBP, eIF4E binding protein; PLC, phospholipase C; TGF- β , transforming growth factor- β ; STAT, signal transducer and activator of transcription; NF- κ B, nuclear factor- κ B.

that IGF-1 can release NO via the PI3K/AKT pathway to assist in reducing inflammation and moderate concentrations of NO (estimated to be <50 nM) are formidable inhibitors of NF- κ B activation (81,88). Conversely, when NO levels fall below physiological levels, its inhibitory effect on NF- κ B diminishes (89). Therefore, the PI3K-related pathway is likely a key mechanism underlying the anti-inflammatory therapeutic effects of IGF-1, ultimately improving tendon healing outcomes.

In addition, IGF-1 can exert anti-inflammatory effects by down-regulating Toll-like receptor 4 (TLR4) signaling (80). TLR4, a pattern recognition receptor, plays a pivotal role in detecting pathogens and is integral to both innate and adaptive immunity (90,91). Notably, targeting TLR4 for treatment holds promise for safely alleviating inflammation without impairing the innate immune response (92). TLR4 is essential in regulating the inflammatory process (93). Myeloid differentiation factor 88 (MyD88) was the first adaptor protein discovered to be compatible with the TLR signaling pathway and its activation is the major cause of TLR4-promoted inflammatory factor production (94,95). As a key protein in transmitting upstream information and inducing disease, MyD88 consists of an N-terminal structural domain and a C-terminal kinase structural domain (94,96). The kinase structure at the C-terminus of MyD88 can recognize a kinase structure that associates with TLR4, whereas the N-terminus combines with TNF receptor-associated factor 6 (TRAF6) (97). The binding of MyD88 to TRAF6 triggers NF- κ B release and rapid nuclear translocation, initiating the expression of signaling transcripts and activating the inflammatory transcriptional program. This promotes the production of pro-inflammatory cytokines such

as TNF- α , IL-1 β and IL-6. Jin *et al* (98) demonstrated that inhibiting the TLR4/MyD88/NF- κ B signaling pathway markedly reduces inflammation. Furthermore, Lee (80) suggested that IGF-1 inhibits TLR4 through the PI3K/AKT signaling pathway. In the authors' experiments, the inhibitory effect of IGF-1 on TLR4 was diminished when a PI3K/AKT-specific inhibitor was used, indicating that PI3K/AKT signaling modulates IGF-1's action on TLR4. The study also found that IGF-1 most effectively inhibited TLR4 at a concentration of 200 ng/ml. Together, these findings suggest that the anti-inflammatory effects of IGF-1 are at least partially mediated by TLR4.

Moreover, IGF-1 also plays an anti-inflammatory role through the estrogen receptor (ER), particularly ER- α (99). In ER- α -deficient mice, the anti-inflammatory effects of IGF-1 were markedly reduced (100). Estrogen is known for its regulatory functions in various connective tissues and its receptors are essential for the normal tendon function (101,102). It has been shown that ER- α can be activated in a ligand-independent manner in response to several stimuli, including IGF-1 (103). Chen *et al* (104) demonstrated that ER- α can be activated by the IGF-1R-mitogen-activated protein/extracellular signal-regulated kinase (MEK)-ERK1/2 pathway, which is also ligand independent. This suggests that IGF-1 may induce the activation of protein kinase Raf through the activation of IGF-1R, which in turn induces the phosphorylation of MEK-ERK1/2 and finally activates ER- α to achieve anti-inflammatory effects.

IGF-1 stimulates tendon cell proliferation and cell migration. Fibroblast proliferation is essential for tendon healing. Under

normal conditions, tendon fibroblasts maintain a balance between the degradation and production of ECM molecules. However, this balance is disrupted following tendon injury. Since the upregulation of individual cell metabolism may not be sufficient to heal the injury, the number of fibroblasts must be increased through cell division and/or migration into the tendon parenchyma (13). IGF-1 is known to be a potent stimulator of mitosis in various cell types, promoting both cell migration and regulating the cell cycle to encourage cell proliferation (7,24,105). Previous *in vitro* and *in vivo* studies have demonstrated that IGF-1 enhances cell proliferation and migration during tendon healing (5,23,31).

The PI3K pathway is closely linked to cell proliferation and migration (106). The PI3K/AKT/mammalian target of rapamycin (mTOR) is regarded as one of the pathways for IGF-1-inspired cell proliferation (31). Activation of the IGF-1 receptor's tyrosine kinase domain by IGF-1 initiates IRS phosphorylation, which triggers the PI3K signaling cascade. This activation converts intramembrane phosphatidylinositol-(4,5) diphosphate (PIP2) into phosphatidylinositol-(3,4,5) triphosphate (PIP3) (107). PIP3 activates phosphatidylinositol-dependent protein kinase (PDK), which then recruits AKT to the plasma membrane. Once localized to the membrane, PDK phosphorylates AKT at Thr308 and Ser473 (108). AKT is then released into the cytoplasm, where it activates mTOR to transmit mitotic signals (109). This signaling cascade upregulates the translation of key cell cycle regulatory proteins, including cyclin-dependent protein kinases (CDKs) and cell cycle proteins, accelerating the cell cycle and promoting cell proliferation (110,111). In addition, p110 α as one of the catalytic subunits of PI3K has been reported to specifically affect cell migration and proliferation independent of AKT. Researchers also identified other downstream effectors of PI3Kp110 α signaling, such as Rac, which are involved in promoting cell migration (112). Furthermore, studies suggest that PI3K interacts with members of the Rho GTPase family, which modulate the cytoskeleton and intercellular junctions, thereby influencing collective cell migration (113). These findings highlight the potential of PI3K in regulating cell migration. On the other hand, a study by Li *et al* (30) emphasized the importance of the PI3K/AKT pathway in IGF-1-induced cell migration. Pathway-specific inhibitors (LY294002 and wortmannin) were shown to reduce IGF-1-induced cell migration. Additionally, as pathways simultaneously activated by IGF-1, the PI3K/AKT and ERK pathways appear to regulate cell proliferation in a coordinated manner (5).

IGF-1-mediated tenocyte proliferation requires ERK activation (5). ELK1, a transcription factor activated by ERK signaling, plays a pivotal role in driving the expression of genes essential for cell proliferation (114). Among its targets are Fos and Jun, which can orchestrate the expression of CDKs. These proteins are critical regulators of the cell cycle, ensuring orderly progression and proper cellular function (115). Disser *et al* (5) observed that blocking PI3K can inhibit the phosphorylation of ELK1. In other cellular contexts, the PI3K pathway has been shown to enhance ERK^{T202/Y204} phosphorylation (116). The results of Disser *et al* (5) suggested that a similar mechanism may exist in tendon cells. However, P-ERK^{T202/Y204} seems to inhibit AKT^{T308} phosphorylation through direct or targeted downstream processes of IRS1^{Y608}. IRS1^{Y608} is the primary site of interaction between IRS1 and the SH2 structural domain of

PI3K and phosphorylation of the S612 residue prevents phosphorylation of the Y608 residue (117). Notably, suppressing AKT activation eliminates IRS1^{S612} phosphorylation while increasing IRS1^{Y608}-phosphorylation. These results imply that the inhibition mediated by ERK causes AKT or downstream effector molecules to negatively modulate the PI3K pathway at IRS1 (5).

Furthermore, IGF-1 supports cell proliferation and migration via the phospholipase C (PLC) pathway (31). IGF-1 activates PLC through the phosphorylation of RTKs, leading to the hydrolysis of PIP2 to produce inositol triphosphate (IP3). When IP3 diffuses into the endoplasmic reticulum membrane and binds to the IP3 receptor of the calcium (Ca²⁺) channel; Ca²⁺ can be released from storage in the endoplasmic reticulum (ER) to flow into the cytoplasm (118,119). Ca²⁺ serves as a versatile second messenger involved in numerous physiological functions. Due to the close proximity of the ER to mitochondria, localized high concentrations of Ca²⁺ promote mitochondrial uptake, inducing conformational changes in regulatory factors like mitochondrial Ca²⁺ uptake proteins and enhancing cell motility, which supports cell migration (31,120). Notably, fluctuations in Ca²⁺ levels in the ER are critical for cell proliferation. The depletion of Ca²⁺ in the endoplasmic reticulum will induce the inflow of Ca²⁺ at the plasma membrane. This phenomenon is known as the store-operated calcium entries (SOCE) (119). SOCE is considered a more important factor for cell proliferation than external Ca²⁺ levels and channel function. Cell cycle arrest has been associated with a reduction in SOCE amplitude (121,122). Consequently, PLC-related pathways may play an essential role in IGF-1's promotion of cell proliferation and migration, contributing to the repair of injured tendons.

IGF-1 increases collagen synthesis. Natural and healthy tendon tissue is a well-circumscribed network of collagen fibers. As a functional matrix protein, the production of collagen aids in tissue repair and regeneration. Human tendon tissue can modulate collagen synthesis via IGF-1 in an autocrine/paracrine manner (4). During tendon healing, IGF-1 is highly expressed and exerts an anabolic effect on collagen production by tendon fibroblasts (67,75), particularly promoting the synthesis of type I collagen (34). Type I collagen synthesis is essential for tendon remodeling. The high abundance and parallel fiber arrangement of type I collagen provide tendons with both elasticity and resistance to distortion (123). Type I collagen synthesis improves fiber alignment, which enhances the mechanical properties of healing tendons and helps the ECM reorganize into a more organized structure (31,69,124). Langberg *et al* (125) confirmed that IGF-1 directly stimulates collagen synthesis in human connective tissue by measuring tendon tissue changes with stable isotopes and evaluating collagen synthesis around the tendon sheath using micro dialysis. Additionally, Disser *et al* (5) observed a twofold increase in protein synthesis rates in IGF-1-treated tendon cells using the SUNSET technique. Instead, the administration of anti-IGF-1 antibodies eliminated most of the mitogenic activity in the tendon tissue (126).

The activation of ERK is one of the dominant downstream signaling events involved in collagen I synthesis. Previous studies have shown that enhanced binding of IGF-1 to IGF-1R activates the ERK pathway, promoting collagen synthesis (127). When IGF-1 binds to the α subunit of IGF-1R, it triggers the

β -subunits of the receptor to exhibit intrinsic tyrosine kinase activity. This activation initiates a cascade of downstream signaling events, phosphorylating key proteins like PI3K and MAPK (128). In a study by Li *et al* (129), the MEK/ERK inhibitor U0126 markedly inhibited the ability of IGF-1 to increase collagen type I expression. The authors observed that IGF-1 increased *colla2* mRNA levels and type I collagen protein levels in a dose-dependent manner. Furthermore, IGF-1 markedly elevated the levels of phosphorylated IGF-1R and ERK1/2 in a time-dependent manner. However, MAP kinase inhibitors markedly suppressed IGF-1-promoted type I collagen expression. These findings suggest that IGF-1 promotes collagen I synthesis through the ERK-related pathway.

Similar to the ERK pathway, the PI3K-related pathway is also involved in the collagen synthesis process mediated by IGF-1. IGF-1 enhances the expression and accumulation of type I collagen genes through a PI3K-dependent mechanism (130). It has been proposed that IGF-1-induced collagen synthesis is linked to the activation of the PI3K/AKT/mTOR pathway (31). When IGF-1 activates the tyrosine kinase domain of IGF-1R, it catalyzes the phosphorylation of IRS, which in turn triggers the PI3K/AKT signaling pathway. This activation subsequently activates mTOR through mTOR Complex 1 (mTORC1). Then, two key effectors regulating mRNA translation, p70S6 kinase 1 (S6K1) and eIF4E binding protein (4EBP), will be phosphorylated, thereby promoting protein synthesis (131). mTOR, a serine/threonine protein kinase in the PI3K-associated kinase family, exists in two complexes: mTORC1 and mTORC2 (132). mTORC1 phosphorylates the hydrophobic motif site Thr389 of S6K1, allowing it to be further phosphorylated and activated by PDK1 (133). Activated S6K1 facilitates the initiation of mRNA translation by phosphorylating substrates such as eIF4B and promoting the degradation of PDCD4, an inhibitor of eIF4B (134). S6K1 also interacts with SKAR, a component of the exon junction complex, enhancing the translation efficiency of spliced mRNAs (135). Furthermore, mTORC1 phosphorylates 4EBP at multiple sites, causing its dissociation from eIF4E, thereby enabling 5'cap-dependent mRNA translation and facilitating protein synthesis (136). mTORC1 also regulates mTORC2 signaling, affecting multiple aspects such as cytoskeleton remodeling, cell proliferation and survival (137). The essential role of mTOR in tendon tissue has been confirmed in studies demonstrating that tendon-specific mTOR ablation leads to reduced type I collagen levels (132). Cong *et al* (138) showed that mTOR can promote type I collagen production in tendon tissue. When mTOR was inhibited using rapamycin, transmission electron microscopy analysis revealed a significant reduction in collagen fiber diameter, resulting in an ~60% decrease in tendon size. Reduced expression of type I collagen also occurred in rapamycin-treated cell slices and material properties were reduced by ~50%. These findings reveal the importance of mTOR in improving tendon structural integrity by promoting type I collagen production, offering a potential therapeutic target for IGF-1 in tendon repair applications.

6. Discussion

Tendon healing is a complex and prolonged event through three successive and overlapping phases. Compared with

healthy tendons, repaired tendons often exhibit lifelong structural and functional changes (139). Growth factors are widely used in tendon healing due to their critical role in the growth and remodeling of musculoskeletal tissues (140). As a protective growth factor with significant potential for biological enhancement, IGF-1 has been approved by the U.S. Food and Drug Administration for human use (67). Although IGF-1 is active throughout various stages of tendon healing, its protein concentrations are 40% lower during the early stages of tendon repair compared with healthy tendons. However, tissue concentrations of IGF-1 peak ~the fourth week after injury and remain elevated until ~the eighth week (141). Durgam *et al* (142) suggest that such findings might indicate a potential therapeutic advantage of IGF-1 supplementation during the early phases of tendon regeneration.

As a potent mitogen, IGF-1 is frequently studied for its role in regulating cell proliferation and protein synthesis. Nevertheless, due to species differences, IGF-1 exhibits varying effects in tendon-related experiments. In a number of species, including humans, equines, rabbits and mice, IGF-1 treatment visibly enhances cell proliferation. However, IGF-1 application in rats does not induce significant cell proliferation (143). Other experimental results show that IGF-1 promotes tendon regeneration in rats by fostering collagen production and reducing inflammation (28). Similar findings were observed in avian tendon studies, where IGF-1 alone did not markedly promote cell proliferation. However, tendon cells in avian species increased when treated with both IGF-1 and mechanical load (144). These imply that the effect of IGF-1 on cell proliferation is influenced by mechanical stimulation. IGF-1 is considered a key factor in the cellular response to mechanical stimuli across various cell types. Hansen *et al* (17) also highlighted that IGF-1 may regulate tendon collagen synthesis under mechanical loading. Therefore, combining IGF-1 treatment with appropriate mechanical loading could enhance its therapeutic potential in tendon injury treatment.

The effect of a single growth factor is often limited, while combination therapy frequently leads to improved outcomes. The pivotal role of IGF-1 in tendon healing has led to extensive research aimed at enhancing its effects. A common approach is to combine IGF-1 with other growth factors, which has demonstrated synergistic benefits in several studies (31,145-147). For instance, although combining IGF-1 with TGF β -3 did not stimulate proliferation of human tendon cells, it successfully maintained tendon cells in serum-free medium for up to two weeks. More importantly, this combination therapy restored the differentiation potential of poorly differentiated tendon cells and proved sufficient for human tendon regeneration. Their efficacy in promoting tendon regeneration was evident across various conditions, including both two-dimensional and three-dimensional environments, with or without silk scaffolds (145). In addition, Qiu *et al* (145) also made an important discovery: the combination of IGF-1, PDGF-BB and TGF β -3 accelerated collagen production in tendon cell cultures, a finding previously undocumented. Additionally, while IGF-1 alone is well-known for enhancing cell proliferation, combining it with PDGF-BB markedly amplified this effect in a dose-dependent manner. When both growth factors were used together, proliferation rates were markedly higher compared with when they were administered

separately. Specifically, the combined treatment resulted in a 114, 63 and 47% increase in the average absorbance of rabbit synovial sheath, superficial tendon and internal tendon cells, respectively. Furthermore, Costa *et al* (146) found that IGF-1 combined with PDGF-BB and b-FGF was distinctly more effective, increasing the mean absorbance of these tendon cell populations by 251, 98 and 106%, respectively. Raghavan *et al* (147) also confirmed that combining these three growth factors resulted in growth rates 2-3 times higher than the control group. However, because b-FGF can suppress tendon cell differentiation and collagen synthesis, Qiu *et al* (145) recommended discontinuing b-FGF in the second stage of culture to enhance further positive effects. The combination of multiple growth factors has shown significant therapeutic potential in tendon healing. Therefore, future research should focus on the synergistic effects of multiple growth factors, explore more potential mechanisms related to IGF-1 and optimize strategies for tendon repair.

Despite promising results in basic experiments and animal models, which suggest that IGF-1 can enhance tendon cell proliferation, migration, collagen synthesis and markedly improve tendon mechanical properties and healing speed, clinical trial data supporting its efficacy in human tendon repair is still relatively scarce. A number of studies have applied IGF-1 in clinical practice, but among the literature reviewed, only Olesen *et al* (148) used IGF-1 in human patients with tendinopathy. The study involved 40 athletes with unilateral patellar tendinopathy. They received injections of 0.1 ml of IGF-1 at a concentration of 10 mg/ml or saline at weeks 0, 1 and 2, followed by high-intensity slow resistance training immediately after the first injection. The results showed that at week 3, the IGF-1 group demonstrated superior clinical efficacy compared with the control group; however, by week 12, the IGF-1 group did not exhibit any additional therapeutic advantages. Therefore, Olesen *et al* (148) inferred that IGF-1 treatment may only produce a transient immediate clinical response and lacks long-term positive effects on clinical outcomes. The authors further concluded that, compared with high-intensity slow resistance training alone, the combination of IGF-1 injection and high-intensity slow resistance training did not further improve tendon healing and thus IGF-1 injection is not recommended as a supplementary treatment for patellar tendinopathy.

Previous studies have used human tendon cells for research and obtained positive results, yet the conclusions of Olesen *et al* (148) contradict these findings (34,147,149). They suggested that the negative results may have been caused by a failure to maintain their advantage through regular IGF-1 injections, but in fact, there may be a number of other reasons. The disparity between laboratory findings and clinical outcomes can be attributed to a variety of complex biological and clinical factors. Clinical patient populations vary greatly in terms of age, sex, genetics, lifestyle (diet, exercise), underlying conditions (diabetes, metabolic syndrome) and severity of tendon injuries. IGF-1 bioavailability and efficacy (150). More importantly, the intricate environment within the human body, featuring ischemia, oxidative stress and cytokine activity, is challenging to replicate in labs. Furthermore, systemic factors such as endocrine status (GH levels, glucocorticoid exposure), drug interactions (such as NSAIDs) and the tendons' inherent

low vascularization, which complicates local drug delivery, may further hinder IGF-1's clinical efficacy (151). The multifaceted variables undoubtedly pose numerous obstacles to the translation of basic research findings into clinical practice. Enhanced clinical studies are crucial for unlocking the application potential of IGF-1. Future research should emphasize refined patient categorization, improved dosing and multi-target combination therapies to overcome translational medicine hurdles.

7. Conclusions

IGF-1 contributes to tendon repair by modulating multiple phases of the healing process. Upon applying IGF-1 to repair tendons, it sparks a cascade of phosphorylation reactions by binding to the IGF-1R on the target cell's membrane, relaying messages from the outer cell layer straight to the nucleus. Simultaneously, the process is also regulated by IGF-BPs. These sophisticated signaling pathways can eventually inhibit local inflammation, promote cell proliferation and cell migration, increase collagen synthesis during tissue reconstruction and enhance the mechanical strength of the healing tendon, accelerating the restoration of tendon structural properties and tissue repair.

Given the short half-life of growth factors, numerous studies have focused on optimizing their delivery strategies (32,33,145). Drug delivery devices can reduce the rate of growth factor clearance, ensuring more sustained release over time and space, thereby enhancing therapeutic outcomes. However, to fully harness the therapeutic potential of growth factor administration for tendon healing, crucial issues such as the timing, dosage and method of delivery must be thoroughly examined. Addressing these factors will expand the applications of IGF-1 in tendon injury treatment. While the role of IGF-1 in musculoskeletal tissue development and remodeling is well-established, its precise biological pathways still require deeper investigation. Consequently, future research should focus on elucidating these mechanisms to optimize IGF-1's therapeutic efficacy in tendon repair.

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Authors' contributions

YC, YZ, SS and YH performed study conception and design. YC wrote the first draft of the manuscript. YZ and SS edited the manuscript. YC and YH were responsible for critical revisions of the article. YH contributed to the acquisition of funds. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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