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Flexor Tendon: Development, Healing, Adhesion Formation, and Contributing Growth Factors

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Summary:

Management of flexor tendon injuries of the hand remains a major clinical problem. Even with intricate repair, adhesion formation remains a common complication. Significant progress has been made to better understand the mechanisms of healing and adhesion formation. However, there has been slow progress in the clinical prevention and reversal of flexor tendon adhesions. The goal of this article is to discuss recent literature relating to tendon development, tendon healing, and adhesion formation to identify areas in need of further research. Additional research is needed to understand and compare the molecular, cellular, and genetic mechanisms involved in flexor tendon morphogenesis, postoperative healing, and mechanical loading. Such knowledge is critical to determine how to improve repair outcomes and identify new therapeutic strategies to promote tissue regeneration and prevent adhesion formation.

Tendon injuries to the hand and wrist constitute one of the most common disorders of the human body, affecting one in 2700 people each year.[1,2] These tendon injuries can result from trauma, chronic overuse, and/or age-related degeneration.[3] Injuries to tendons, tendon-bone junctions, and related tissues (such as ligaments) can occur in numerous areas of the body. Tendons are hypovascular compared to many other tissues.[3,4] Flexor tendons are covered by an intrasynovial sheath and have been thought to have a limited vascular supply compared with other tendons.[3,5] However, synovial fluid may compensate for the differences in vascular supply.[6–8] In addition, tendons overall are hypocellular and may lack sufficient cellularity for adequate healing.[3] Unfortunately, 30 percent of flexor tendon injuries result in adhesion formation, which can cause significant disability,[9–11] and the exact cause remains unknown.

Both nonoperatively and operatively managed flexor tendon injuries can be complicated by fibrotic adhesions that severely impair the function of the hand by disrupting the gliding mechanism.[11,12] Tendon adhesions to the fibro-osseous canal and surrounding tissues have been associated with a myriad of pathologic factors.[11] Many pharmacologic agents (such as hyaluronic acid, 5-fluorouracil, lubricin, and a variety of growth factors) and mechanical

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barriers have been investigated in the reduction of adhesion formation, but none has been proven useful in clinical settings.[13–16]

Our understanding of the formation of flexor tendon adhesions remains limited.[17] We will discuss what is currently known about limb tendon development, tendon healing, growth factors involved in tendon healing compared with those in tendon development, and the role they play in both repair and adhesion formation.

LIMB TENDON DEVELOPMENT

Limb tendons arise from the lateral plate mesoderm, which form secondary to bone morphogenetic protein-4 secretion provided by the ectoderm.[18] These same cells give rise to endoskeletal cartilage. Tenocytes themselves are distinct from other fibroblast-like cell types.[19] Mature tenocytes are spindle-shaped and can be identified in mouse embryos as early as embryonic day 13.5. Although tenocytes are noted to be sparse in mature tendon tissue—generally anchored to the collagen fibers they produce—changes in their structure and activity have been specifically linked with a variety of tendinopathies.[20]

Tendons are composed primarily of collagen type I, with the fibrils organized along the axis of the tendon. Collagen type I is made up of two a1 molecule chains (encoded by the gene *Col1a1*) and one a2 molecule chain (encoded by the gene *Col1a2*), which form a triple helix.[21] Although much remains to be fully understood, it is thought that most of the fibril assembly takes place during the prenatal period, whereas the tissue grows and matures postnatally.[21] This maturation process includes a dramatic increase in the elastic modulus.[22] In addition to collagens, small leucine-rich proteoglycans are important for tendon development and growth, particularly in terms of regulating the growth of collagens.[21]

The only known marker for a developing tendon is the transcription factor scleraxis. Scleraxis regulates *Col1a1* in mice and is known to play an important role in tendon development in chick and zebrafish as well. Tenocyte overexpression of scleraxis causes up-regulation of the gene tenomodulin (*Tnmd*), the protein product of which is specific to tendons and ligaments and is understood to be a marker of tendon formation.[23] Postnatally, scleraxis expression is restricted largely to the epitenon.[24] Two other transcription factors are known to guide tendon development in vertebrates: Mohawk (Mkx) and Early growth response 1 (Egr1). Mkx−/− mice show smaller tendons with defective collagen.[25] Egr1−/− mice also show collagen fibril defects; tendons from these animals are weaker than wild-type and have healing deficiencies after injury.[26]

A variety of other factors are known to be involved in intrasynovial (flexor) tendon development. These include cytokines, chemokines, and signaling molecules. Mechanical forces also play a role. Limb tendons initiate their development independent of muscles; however, muscles are required for subsequent tendon differentiation.[27]

Fibroblast growth factors (FGFs) and the transforming growth factor (TGF)-β family are known to promote tendon commitment of limb mesodermal cells and act downstream of mechanical forces to regulate tendon differentiation during chick limb development. TGF-β2 was noted to be tenogenic for tendon progenitor cells at all stages of development in vitro,[28]

whereas FGF4 lacked tenogenicity for tendon progenitor cells in vitro. However, FGF4 is believed to induce and maintain scleraxis expression during tendon development.[29] Bone morphogenetic protein-12 signaling, by means of Smad 1/5/8, guides the expression of scleraxis, Tnmd, Col1, and tenascin-C in tendon progenitor cells in vitro. This effect was found to be positively regulated by connective tissue growth factor.[30]

Although vascularity is limited in mature tendons, vascular endothelial growth factor (VEGF) signaling is important during tendon development in human tissue—specifically, within developing tendons under traction—and gliding tendons maintain an avascular zone even from the fetal period.[31] Nearly all of the 23 known matrix metalloproteinases and the 19 disintegrin and metalloproteinase with thrombospondin motif proteins can be identified in adult tendon specimens. These are involved in regulation of the tendon extracellular matrix and establishment of the muscle-tendon junction.[32] Some of the specific extracellular matrix proteins, such as fibronectin and laminin-a1, are also known to be involved in interactions at the muscle-tendon junction. Other factors known to be involved in tendon healing, which are also believed to play a role in tendon development, include insulin-like growth factor 1, platelet-derived growth factors (PDGFs), and interleukins such as interleukin-6 and interleukin-1β and their receptors.[33]

INTRASYNOVIAL TENDON HEALING PROCESS

Successful flexor tendon healing after complete laceration requires restoration of the baseline collagen fibers in the tendon and reestablishment of the tendon gliding within the sheath, which does not occur spontaneously, unlike in extrasynovial tendons.[34] Tendon healing is believed to involve both the extrinsic and intrinsic pathways and is composed of three phases: inflammatory (days 1 to 7), fibroblastic (days 3 to 14), and remodeling (beyond day 10).[12,35–38] The extrinsic mechanism proposes that cells not resident to the local injury niche, such as immune cells and fibroblasts, are directly involved in repair.[39] The intrinsic mechanism suggests that the cells involved in tendon repair are from within the tendon.[40] Immediately after an injury until approximately 3 to 7 days after injury, an acute inflammatory response is initiated, with both resident intrinsic cells from the epitenon and endotenon, and extrinsic cells from the surrounding peritendinous, recruited to and proliferated at the injury site.[12] The strength of the tendon during this phase is reliant almost entirely on the blood clot. If a surgical repair is performed, the surgical suture provides the majority of the mechanical strength of the tendon.[41,42] The strength of the tendon does not begin to increase until the fibroblastic phase is initiated at day 3. During the fibroblastic phase, the injury site becomes hypercellular as components of the extracellular matrix are deposited. Initial deposition of collagen type III occurs in a disorganized fashion and is then reorganized into longitudinal structures. The collagen type III is subsequently replaced with collagen type I during the remodeling phase. Over the span of the ensuing 2 months, the tendon tissue matures, and the prevailing tension forces cause the fibers to reorient longitudinally. Unfortunately, the repaired tendon will never achieve its full uninjured strength[43,44]; it has been reported that an injured tendon heals to approximately 40 to 70 percent of a normal uninjured tendon’s strength.[45–47]

FACTORS INVOLVED IN FLEXOR TENDON ADHESIONS

A great deal of research has been devoted to understanding the formation and prevention of tendon adhesion after injury and/or surgical repair.[12] Adhesions are most commonly seen in healing intrasynovial flexor tendons.[33] Through the use of animal studies, we have identified some of the critical aspects of tendon healing and adhesion formation. In addition to the extent of initial injury and quality of subsequent surgical repair, mechanical loading is critical to the reduction of adhesions.[34,48–54] Mechanical loading up-regulates the expression of collagen type III mRNA expression in tenocytes and increases the concentration of growth factors, resulting in cell proliferation and differentiation, and matrix formation at the injury site.[48] However, for tendon repair rehabilitation to be beneficial, it must protect the repair from excessive forces and also allow for enough mechanical loading to help prevent development of adhesions with some loading. Excessive loading may not only rupture the repair but also impair healing.[55] Prolonged immobilization will also result in adhesion formation.[35,56] Wong et al. developed a mouse model in which the flexor tendons were immobilized through the creation of a proximal tenotomy to the injury site, which greatly increased the likelihood of adhesion formation.[35] They also found that adhesions not only are caused by resident (local) cells but also are a result of cells in the surrounding tissue that had trauma. These cells appear to develop an excessive amount of collagen.

Aging has also been found to be associated with impaired healing in flexor tendons in addition to patella and rotator cuff tendons.[57–59] Ackerman et al. found that, at baseline, tendons in older mice have a decrease in cell density. It is unknown what proportion of adult cells within the tendon are tendon progenitor cells or stem cells. However, it is likely that the number of tendon progenitor cells decreases in proportion to the age-related decrease in cell density. In addition, as cells age within a tendon, they lose their rounded morphology, taking on a more elongated shape. The number of organelles within the cells also decreases.[57,60,61] Collagen synthesis and collagenolytic activity diminish with age.[62] This results in an altered composition and alignment of collagen fibrils in the aging population, whereas collagen fibrils of the young tendon are largely homogenous and arranged in parallel.[57] Interestingly, after flexor tendon injury, there is a decrease in the amount of extracellular matrix deposition in older mouse tendons, and the mechanical strength is diminished.[57,63] Despite significant research on tendon healing strength, there has been minimal investigation into flexor tendon adhesions with aging; it is also unknown whether there are any differences in how aging effects intrasynovial compared to extrasynovial tendons.

RECAPITULATION OF TENDON DEVELOPMENT PROCESSES IN TENDON HEALING

Tendon healing is a complex process controlled by a variety of regulatory growth factors. Many of the same processes and regulators involved in tendon development are involved in tendon healing.[33,64] Growth factors, including TGF-β, bFGF, VEGF, and PDGF, have been studied extensively in a variety of tendon healing models both in vivo and in vitro (Table 1).[1–127]

TGF-β

TGF-β has three main isoforms and is involved in a myriad of cellular pathways.[65] Within tendon healing, it is known to be involved in the initial inflammatory response, collagen synthesis, angiogenesis, and fibrosis/excessive scar formation.[66–73] TGF-β1 is expressed by tenocytes, infiltrating fibroblasts, and inflammatory cells[72,73] and is thought to be associated with the pathogenesis of excessive scar tissue formation. Interestingly, when TGF-β1 signaling is disrupted either by means of antibody or miRNA after flexor tendon injury, range of motion of the digit improves; however, the mechanical strength of the tendon decreases.[57,73,74] TGF-β2 and TGF-β3 are thought to be essential for tendon formation and are potent inducers of the tendon progenitors.[28,75] When TGF-β signaling is disrupted during chick development, almost all tendons and ligaments are absent.[75,76] Mechanical cues are important in the initiation of TGF-β and FGF signaling in utero. Both TGF-β/SMAD2/3 and FGF/ERK MAPK signaling pathways are decreased in tendons under immobilization conditions in developing chicks. The application of FGF4 or TGF-β2 ligands prevents scleraxis down-regulation in immobilized developing chick limbs.[27]

Exogenous delivery of TGF-β has been long studied as a treatment, both in vivo and in vitro. TGF-β1 has been thought to lead to excessive scar formation. The treatment of tenocytes in vitro with TGF-β1 promotes extracellular matrix synthesis (up-regulation seen in biglycan, collagen V, collagen XII, plasminogen activator inhibitor-1, scleraxis, and Mohawk) and down-regulates matrix remodeling matrix metalloproteinases,[77] which is suggestive of how it may facilitate adhesion formation. The mechanical strength of injured rabbits' Achilles tendons that received bone marrow–derived mesenchymal stem cells transfected with TGF-β1 cDNA was significantly increased.[78] Despite evidence that disrupting TGF-β1 reduces the extent of scarring, mechanical strength of the tendon and repair site decrease,[56,73,74] suggesting that complete blockade of TGF-β1 is not optimally therapeutic.

Unlike with TGF-β1, ectopic delivery of TGF-β3 has demonstrated some promising results. TGF-β3 promoted the tenogenic differentiation of stem cells in co-culture.[79] Jiang et al. found that the addition of TGF-β3 to tenocytes can significantly down-regulate the expression of Smad3 and up-regulate the expression of Smad7 at the gene and protein levels, which may minimize scarring.[80] Exogenous delivery of TGF-β3 after Achilles tendon injuries in rats has improved the structural and mechanical properties of the tendon.[81] Further evaluation into the specific isoforms' role in tendon healing is required to evaluate their possible therapeutic application in flexor tendon injuries.

FGF2

FGF2 is a single-chain polypeptide belonging to the heparin-binding growth factor family that facilitates numerous mitogenic and angiogenic activities.[82,83] Within tendon healing, FGF2 has been found to be associated with inflammation, neovascularization/angiogenesis, cellular proliferation, and collagen synthesis.[3,38,66,84–86] Despite FGF2 not being directly investigated in tendon formation, several other factors within the FGF family have been investigated with regard to their effects on tendon development. FGF4 and FGF8 are both expressed on muscle and tendon boundary regions during limb development.[87] This suggests that the FGF signaling pathway may play a role in the muscle and tendon interactions that

facilitate tendon development.[87] Brent and Tabin demonstrated that FGF signaling may induce the formation of a tendon progenitor population that expressed scleraxis during somite development.[29] However, Brown et al. reported that FGF4 did not increase scleraxis expression in mouse limbs in both early and late developmental stages in vitro.[28,88] Rather, it had negative effects on scleraxis and *Col1a1* gene expression in vitro.[28,88]

The effects of exogenous FGF delivery after tendon injury are controversial. Ectopic FGF2 has been shown to increase cell proliferation and promote neovascularization within tendon repairs; however, improvements in mechanical strength remain equivocal.[3,89] Tang et al. demonstrated improvements in tensile strength in injured chick flexor tendons treated with FGF2.[90] However, Thomopoulos et al. did not find improvements in mechanical or functional properties with exogenous delivery of FGF2 by means of a fibrin-heparin–based delivery system to dog flexor tendon injuries.[85]

VEGF

The VEGF family consists of several isoforms that bind to three tyrosine kinase receptors, but their bioavailability for each receptor depends on the isoform.[91] VEGF levels are elevated during tendon development. The VEGF present in human fetal tendons is thought to be responsible for the differentiation of vascular and avascular zones within tendons.[31] VEGF levels then decrease to low concentrations within healthy (homeostatic) adult Achilles tendons.[92] The presence of minimally elevated VEGF in adults is suggestive of a chronic overuse tendon injury.[93] Within tendon healing, it has been well established that VEGF is up-regulated very early in the healing process and is involved in angiogenesis.[42,94,95] VEGF promotes neovascularization by means of the stimulation of matrix metalloproteinases to possibly degrade connective tissues to facilitate angiogenesis.[92]

Ectopic VEGF delivery improves tensile strength of injured Achilles tendons.[96] However, it has also been found by Wang et al. that VEGF does not significantly up-regulate collagen gene expression.[97] Therefore, it may not necessarily be the most important factor in collagen synthesis in intrasynovial tendon healing; however, it clearly plays an important role in angiogenesis in tendon healing and in the formation of tendon.

PDGF

PDGF is a 30-kDa dimer, and its family comprises four different polypeptide chains.[98] PDGF plays a role in the migration and proliferation of the tenocytes, fibroblasts, and mesenchymal stem cells responsible for tissue homeostasis.[99] PDGF expression is up-regulated shortly after tendon injury and helps to stimulate the production of other growth factors.[82] PDGF signaling may be essential to tendon homeostasis. Sugg et al. demonstrated that the inhibition of PDGF signaling prevented the normal growth response in tendon tissue to a mechanical stimulus in adult mice.[100] Little is known regarding its role in tendon development. Exogenous delivery of PDGF improves both morphologic and biomechanical properties in numerous animal and tendon models, suggesting the PDGF may help augment tendon healing.[101–105]

There appear to be common growth factors and gene expression patterns between tendon development and repair. Further investigation is required to better understand the roles that

growth factors, cytokines, chemokines, and/or other signaling molecules play in both tendon development and healing. Despite a wealth of knowledge regarding what factors play a role in tendon healing, a better understanding of how tendons develop would likely provide additional insights toward improving tendon repair after injury (Table 1).

CONCLUSIONS

Further exploring the similarity and differences in gene expression between tendon morphogenesis and repair may elucidate novel strategies to improve perioperative and postoperative flexor tendon injury management. In addition, understanding the molecular mechanisms dependent on mechanical loading involved in flexor tendon healing without adhesion formation is also critical in learning how to best improve repair outcomes. Fundamental and translational studies will help us decipher which growth factors, cytokines, chemokines, and/or other signaling molecules are most crucial in the prevention of adhesion formations.

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Table 1.

Growth Factors, Cytokines, Chemokines, and/or Other Signaling Molecules Involved in Tendon Development and Healing

	Role in Tendon Development	Role in Tendon Healing
TGF-βs	Tenogenesis[27,28,75,76,88]; up-regulation of SCX and Col1a1 expression[27]	Involved in initial inflammatory response[66,67]; repair site and sheath increase expression of TGF-β receptors after injury and repair[70]; collagen synthesis[66,68–71]; angiogenesis[66]; TGF-B1 expressed by tenocytes and infiltrating fibroblasts and inflammatory cells[72,73]; up-regulated initially after injury and elevated levels persist until at least 3 wk after injury[106]
VEGF	Angiogenesis[92]	Increased in early healing, neovascularization[42,94,95]; marker of chronic overuse[92,93]; up-regulation peaks at 10 days after injury[96]
IGF-1	Requires further investigation	Up-regulated expression in inflammatory cells[66]; stimulation of ECM synthesis[107]; involved in muscle hypertrophy[108]; up-regulated immediately after injury and peaks at 4–8 wk[109]
FGF2	Requires further investigation; FGF4 and FGF8 are expressed on muscle and tendon boundary regions during limb development[87]; equivocal evidence on ability to induce cells to express scleraxis during somite development[28,29,88]	Increased expression in inflammatory cells[66,84]; neovascularization[84]; proliferation[3,38,85,86]; collagen synthesis[3,38]; down-regulated after injury until at least 3 wk after injury[106]
PDGF	When inhibited suppresses mechanically cued tendon tissue growth[100]	Synthesis of ECM[68,110]; angiogenesis[66]; PDGF-B up-regulated persist for over 6 mo after tendon injury,[111] though has also been shown to be minimally expressed after injury[106]
CTGF	Requires further investigation	Exogenous and endogenous stem cell tenogenic differentiation[112]; increased expression in fibroblasts[113]; increased collagen type I deposition[113]; up-regulated gene expression persisting over 21 days after injury[106]
MMPs	MMP-1 involved in the processing of native collagen I, II, III, and X, which are also components of the tendon fibers[114]; MMP-2/MT3-MMP are involved in initiation of and progression of fibril growth, matrix assembly, and tendon development[115]	MMP-1 MMP-8, MMP-13, and MMP-18 degrade collagens, a critical component of the tendon ECM[116]; MMP-2 and MMP-9 cleave smaller collagen fragments and gelatin[116]; MMP-3, MMP-10, MMP-11, MMP-7, MMP-26, and MMP-12 degrade glycoproteins and proteoglycans[116]; MMP-9 and MMP-13 help degrade the ECM shortly after injury whereas MMP-3, MMP-4 and MMP-14 participate in both matrix degradation and matrix remodeling throughout the healing process[42,117–120]
TIMPs	Regulates MMPs; constant low TIMP-2 expression seen in tendon development[115]	MMP endogenous antagonists[117]; increased TIMP-1 mRNA expression in tendon and tendon sheath after acute injury[117]; TIMPs mRNA expression levels decrease in overuse tendon injuries[121]
ADAMTS	Removes the respective propeptides from procollagen, within the secretory pathway in tendon fibroblasts[122]	Lower mRNA 1 levels of ADAMTS-7, ADAMTS-13 seen in overuse injuries[123]; requires further investigation in acute injuries
IL-1β	Requires further investigation	Increased level of IL-1β mRNA expression in tendon[42] and tendon-sheath[117]; promotes inflammation and degradation of the ECM[118]; alters glucose metabolism in tendon progenitors[124]
IL-6	Requires further investigation	Inhibitory effect on fibroblast cellular proliferation[125]; increases proliferation capability and induced cell cycle of tendon-derived stem cells, but may inhibit their tenogenic differentiation (inhibited gene expression of inhibited gene expression of scleraxis, collagen I, tenomodulin, collagen III, early growth response protein 1 decorin, lumican, biglycan and fibromodulin)[126]
EGF	Requires further investigation	Increased expression on inflammatory cells[66]
TNFα	Requires further investigation	Increased level of mRNA expression in tendon after injury[42]
BMP-2	BMP-2 requires further investigation; BMP-4 secretion facilitates limb tendon formation[18]	Role within physiologic tendon healing requires further investigation; exogenous delivery augments bone ingrowth within tendon-to-bone junctions[127]

SCX, scleraxis; ECM, extracellular matrix; CTGF, connective tissue growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; EGF, epidermal growth factor; TNFα, tissue necrosis factor alpha; BMP-2, bone morphogenetic protein 2; IL, interleukin.