

Paul W. Ackermann

---

### 23.1 Introduction

Optimization of tendon healing is a complex process, which requires a perfect understanding of the sequences of the repair process and the close interaction between blood-derived cells (e.g., platelets, leukocytes, monocytes, and lymphocytes) and tissue-derived cells (e.g., macrophages, fibroblasts, myofibroblasts, endothelial cells, mast cells, and stem cells). The

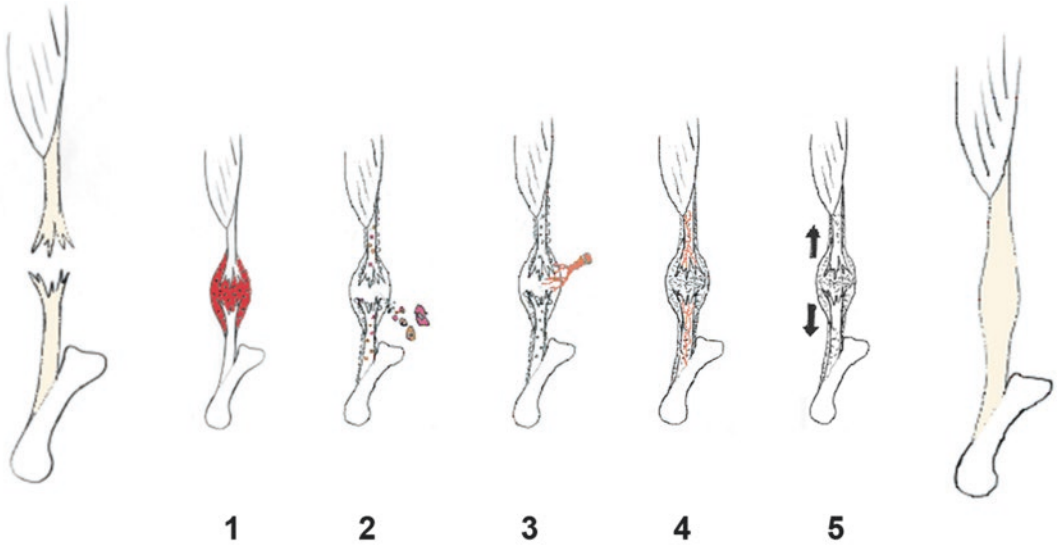
direct aim of the healing process is to achieve tissue integrity, homeostasis, and load-bearing capability.

The repair process can be subdivided into five important overlapping sequences: (1) induction, (2) production, (3) orchestration, (4) conduction, and (5) modification (Fig. 23.1). Biological enhancement of the healing process with novel procedures can be performed by interaction in different stages of the healing process [1].

---

P.W. Ackermann  
Karolinska Institutet, Department of Molecular  
Medicine and Surgery, SE-17176 Stockholm, Sweden

Department of Orthopaedics and Sports Medicine,  
Karolinska University Hospital,  
SE-17176 Stockholm, Sweden  
e-mail: [paul.ackermann@karolinska.se](mailto:paul.ackermann@karolinska.se)



**Fig. 23.1** Tendon repair overview. (1) Induction, (2) production, (3) orchestration, (4) conduction, and (5) modification of the healing process (Reproduced with permission from Ackermann [1])

## 23.2 Induction of the Healing Process

After tendon injury, the wound site is infiltrated with blood-derived cells, which contribute to ending of the bleeding process, clean up tissue debris, and direct further traffic by release of inflammatory mediators, e.g., cytokines, nitric oxide, and growth factors (GF). This is the initiation of the inflammatory healing phase.

### 23.2.1 Platelets

One of the most important blood-derived cells is platelets, which release a wide variety of growth factors at the site of tendon injury. Many of these growth factors have been demonstrated to promote repair in various soft tissue models. Thus, blood-derived cells, e.g., platelets, and the subsequently released growth factors are essential for the initiation of the healing process [2].

#### 23.2.1.1 Can Platelet-Rich Plasma (PRP) Speed Up Tendon Healing?

Platelet-rich plasma (PRP) is derived from centrifugation of whole blood; it is the cellular component of plasma that settles after centrifugation. PRP contains numerous growth factors such as platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor (IGF)-1, and fibroblast growth factor, which each individually has demonstrated important regulatory effects on tendon repair. Thus, PRP is believed to be able to enhance tendon healing.

In deficient healing conditions without bleeding, such as Achilles tendon disorders, e.g., tendinopathy, platelet-rich plasma (PRP) injections have become a very popular treatment alternative [3]. Thus, experimental studies have found positive effects in tendinopathy and tendon healing, possibly by PRP influencing neovascularization, collagen production, and fibroblast proliferation in the early phase of tendon healing [4–6]. However, at present the most effective dose of different growth factors in various PRP preparations and optimal treatment intervals for

enhancement of tendon repair are not even known for experimental tendon injuries.

Although many *in vitro* and *in vivo* studies suggest potentially beneficial effects of using PRP in Achilles tendon pathology, there are only a few well-conducted randomized controlled clinical trials, which show a very limited evidence of clinical advantage. Thus, at present, there are unknown variables, e.g., delivery system, local environment, receptor activation, and tendon loading, which have to be mastered before growth factor delivery therapies, e.g., PRP, can become clinically effective.

Platelet-rich plasma injection for treating tendon problems, such as tendinopathy, is a relatively new treatment method, and current evidence recommends against its clinical use and instead suggests the use of PRP in clinical studies. There is a lack of clinical RCT studies, and the majority of the studies show little or no evidence for PRP injections as treatment for tendinopathy [6]. A prospective study by De Vos et al. showed in patients with Achilles tendinopathy no more effectiveness with PRP injections compared with saline injections (placebo), while both groups also underwent an eccentric exercise program [6].

Recently, a publication in *Lancet* by Alsousou et al. examined tendon tissue biopsy samples from 20 patients with ruptured Achilles tendon by means of ultrasound-guided needle biopsies from the healing area of the Achilles tendon 6 weeks after treatment with PRP or placebo controls [7]. The study by Alsousou et al. demonstrated immunohistologically that locally applied PRP enhanced the maturity of the healing tendon tissues by promoting better collagen I deposition, decreased cellularity, less vascularity, and higher glycosaminoglycan content when compared with control samples. However, further work is required to determine the long-term clinical effects of the use of PRP injections.

#### 23.2.1.2 Platelet-Rich Fibrin (PRF)

Platelet-rich fibrin (PRF) and leukocyte- and platelet-rich fibrin (L-PRF) are matrices, which consist of bioactive components of whole blood that include platelet activation and fibrin

polymerization [8]. The L-PRF matrix is produced by a standard centrifugation procedure in less than 20 min. As opposed to PRP, L-PRF does not dissolve so quickly during the first hours after application [9]. Moreover, due to the primary fibrin polymerization, the stable matrix encapsulates growth factors, which allows a continuous slow release of growth factors for up to 28 days [9]. The leukocytes additionally produce a significant amount of growth factors that are known to promote healing [10].

One experimental study on Achilles tendon healing suggested that rats treated with PRF compared to those treated with PRP showed a better cellular organization when compared at 28 days after treatment [11]. Fibrin glue has been known since the 1980s for augmenting repair of the human Achilles tendon. Some authors have suggested that the use of fibrin glue could be an alternative to the traditional suture repair of ruptured Achilles tendon. However, still there are not sufficient scientific evidences to support clinical use of PRF or fibrin glue to enhance Achilles tendon healing as compared standard procedures [12].

---

### 23.3 Stimulation of Callus Production

Tissue-derived cells are attracted and transformed into myofibroblasts at the healing site by inflammatory mediators released from the blood clot. The myofibroblasts subsequently activate production of tendon callus [13]. In that way, granulation tissue, i.e., extracellular matrix and collagen type III, is formed from the tissue-derived cells that normally reside in the extrinsic peritendinous tissues and the intrinsic tissue of the epitenon and endotenon. During the first week, collagen synthesis commences and reaches its maximum by week four – the reparative, collagen-forming phase. The glycoprotein, fibronectin, acts as a chemotactic agent for fibroblasts, which are the predominant cell type for production of type III collagen. The fibroblasts respond to mechanical loading by increased production of collagen.

The tissue- and blood-derived cells that infiltrate the wound area moreover release a cascade of mediators (growth factors, cytokines, bone morphogenetic proteins (BMPs), and neuropeptides). Supplements of these factors have in numerous experimental studies demonstrated promising results for optimization of the repair process. Growth factors (GF) typically have a very short half-life in the tissues, therefore the development of a number of different methods of prolonged GF release such as GF-saturated sponges, scaffolds, and lately GF-coated sutures.

#### 23.3.1 Insulin-Like Growth Factor (IGF)

IGF promotes cell proliferation and collagen synthesis and decreases swelling in healing tendons [14]. Experimental studies have shown higher Achilles tendon function scores and accelerated recovery in rats after IGF administration [15, 16].

#### 23.3.2 Transforming Growth Factor- $\beta$ (TGF- $\beta$ )

TGF- $\beta$  is profuse in healing and scar formation. Its fetal isoforms (TGF- $\beta$ 2 and 3) promote healing without scar tissue formation. This might be suggesting that inhibition of TGF- $\beta$ 1 and exogenous administration of  $\beta$ 2 and 3 would promote healing in the absence of excessive scar tissue formation. Experimental studies have shown that TGF- $\beta$ 1 administration and suppression of  $\beta$ 2 and 3 results in increased cross-sectional area but lower failure load, i.e., mechanically inferior tissue quality [17].

#### 23.3.3 Bone Morphogenetic Proteins (BMPs)

BMPs were discovered by their ability to induce formation of bone and cartilage. In Achilles tendon healing, a local injection of each of BMP-12, BMP-13, or BMP-14 into the hematoma 6 hours after Achilles tendon transection leads to approximately 30% increase in total strength after

1 week in the rat [18]. In the rabbit, similar effects have been observed at 2 weeks [19]. BMP-12 has also been demonstrated to induce tenogenic differentiation of adipose-derived stromal cells [20].

### 23.3.4 Neuropeptides

In addition to growth factors, specific neuromediators, so-called neuropeptides that are released by ingrowing nerve fibers during tendon repair, have essential effects on the healing process (Fig. 23.3) [21–24]. Nerve sprouting and growth within the tendon proper is followed by a time-dependent expression of neuropeptides during the tendon healing process [24]. During inflammatory and early proliferative healing, mainly sensory neuropeptides (e.g., substance P) are released (Fig. 23.4) [24]. Subsequently, after the healing process is finished, sprouting nerve fibers within the tendon proper retract to the surrounding structures, i.e., the paratenon and surrounding loose connective tissue. Presumably, nerve retraction is also essential for healing progression.

Injections of substance P in physiological concentrations to the healing Achilles tendon have proved to enhance fibroblast aggregation, collagen production, and organization and to increase tensile strength more than 100% compared with controls [25–27]. Moreover, supplement with substance P enhanced nerve retraction.

### 23.3.5 Stem Cells

Since optimal delivery of growth factors as yet has been of limited clinical success, molecular

approaches have been developed. Mesenchymal stem cells (MSC) [28], bone marrow stem cells (BMSC) [29], and genetically modified cells that synthesize and deliver the desired growth factor in a temporally and spatially orchestrated manner to the wound site would be a powerful means to overcome the limitations of various delivery systems [30].

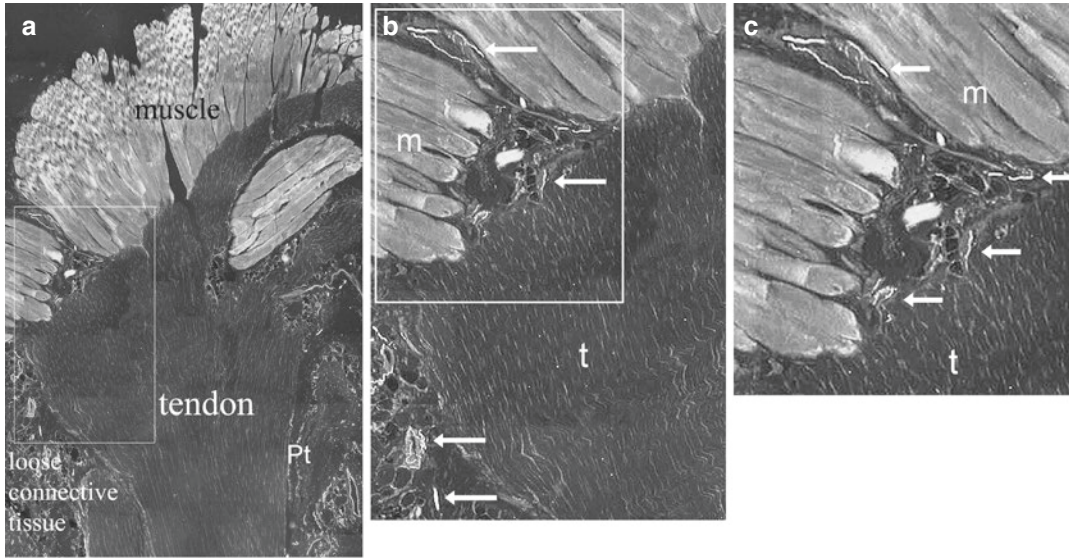
Since tendon healing and tendinopathy often involves a component of failed healing, the rationale of supplementing the healing process with stem cells is an interesting and lucrative approach. Some experimental studies have shown beneficial effects on the repair process with stem cell injections; however, much regarding the type of therapy still needs to be further investigated.

Five clinical trials have reported the use of stem cells for the promotion of tendon repair (chronic tendinopathy, three; rotator cuff tear, two) with initially promising results. There are two clinical studies reporting the safety of using allogeneic stem cells for the promotion of tendon repair. Injection of allogeneic stem cells for the treatment of chronic lateral epicondylitis was reported to be safe and effectively improved elbow pain, performance, and structural defects after 1 year in a small, uncontrolled trial of 12 patients [31]. Ultrasound-guided injection of allogeneic human placenta-derived mesenchymal stromal cells was also reported to be safe in six patients with refractory Achilles tendinopathy at 4 weeks after administration. However, still the sample sizes in the clinical studies are small and mostly there were no control groups.

### 23.4 Orchestration of Callus Formation

During initiation of matrix production, the healing tendon proper, which normally is practically devoid

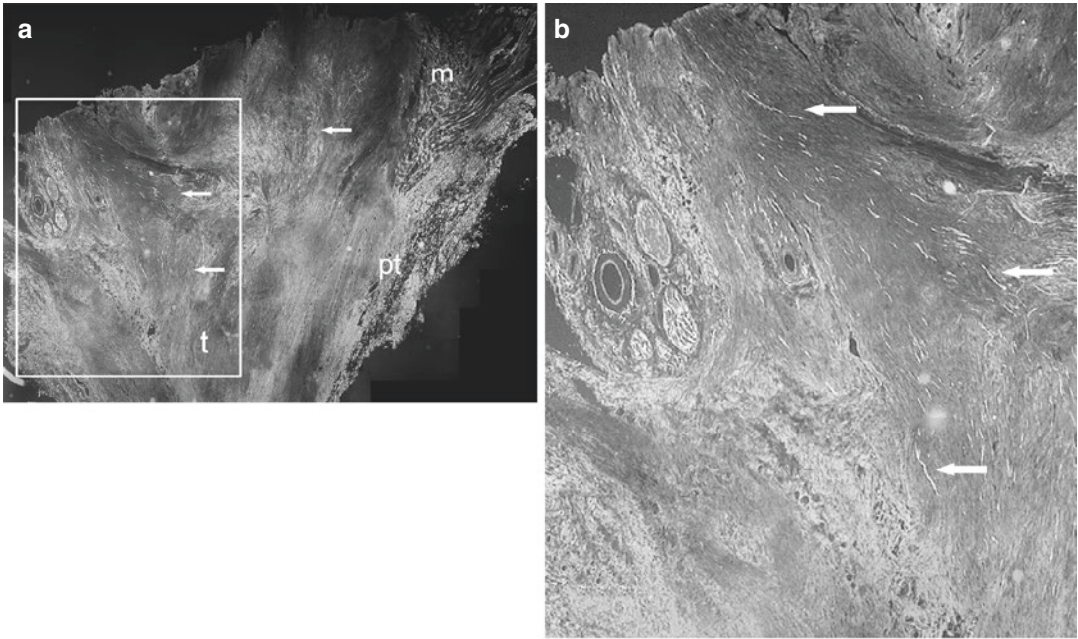
of nerves and vessels (Fig. 23.2), is successively infiltrated by new nerves and vessels providing a “highway” for the delivery of essential neurovascular mediators that orchestrate and enhance the repair process (Fig. 23.3) [13, 21, 23, 24].



**Fig. 23.2** (a–c). Healthy tendon neurovascular anatomy. Tendon proper (intrafascicular matrix) practically devoid of nerves and blood vessels. Overview micrographs of longitudinal sections through the Achilles tendon. Incubation with antisera to the general nerve marker PGP 9.5. Micrographs depict the proximal half of the Achilles tendon at increasing magnification in figures (a–c). *Arrows* denote varicosities and nerve terminals. The typical

vascular localization of autonomic neuropeptides is depicted in the *lower left* (b), whereas the free nerve endings are a typical localization of sensory neuropeptides (c). The immunoreactivity is seen in the paratenon (interfascicular matrix) and surrounding loose connective tissue, whereas the proper tendinous tissue, notably, is almost devoid of nerve fibers (*pt* = paratenon) (Reproduced with permission from Ackermann et al. [23])





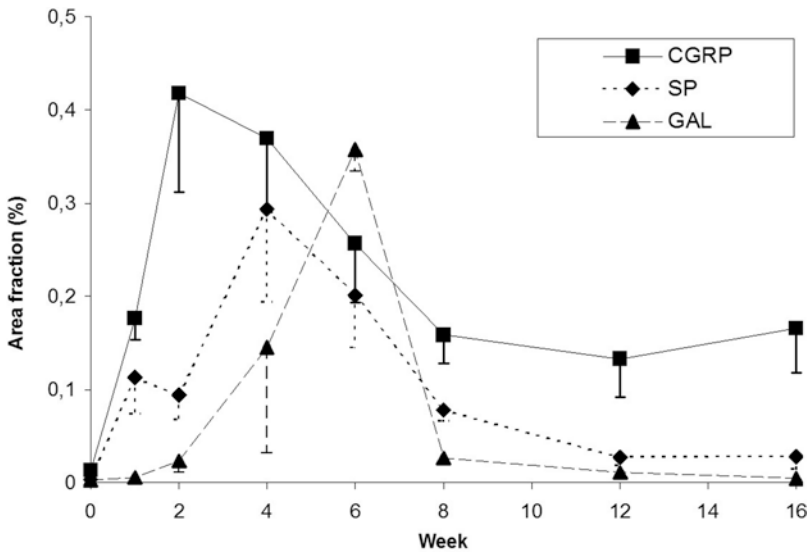
**Fig. 23.3** (a, b) Tendon healing anatomy. Overview micrographs of longitudinal sections through the Achilles tendon at 2 weeks post-injury (rupture). Incubation with antisera to a nerve growth marker, GAP-43. Micrographs depict the proximal half of the Achilles tendon at

increasing magnification in figures (a, b). *Arrows* denote varicosities and nerve terminals. The GAP-positive fibers, indicating wound reinnervation, are abundantly observed in the healing tendon tissue (Reproduced with permission from Ackermann et al. [23])

### 23.4.1 Neoinnervation and Neovascularization

New nerve ingrowth within the tendon proper, which normally is aneuronal, is followed by a time-dependent expression of neuropeptides during the tendon healing process (Fig. 23.4) [21, 23, 24]. During the inflammatory and early proliferative phase, i.e., 2–6 weeks after injury, there is a striking increased occurrence of sensory neuropeptides, substance P (SP), and calcitonin gene-related peptide (CGRP) in the healing tendon tissue. Thus, SP is known to enhance angiogenesis [32] and improves repair by homing stromal stem cells to the site of injury [33].

However, for healing to progress, the ingrown nerves and vessels have to retract, a process which is promoted by adequate mechanical stimuli. In case of tendinopathy, an increased number of vessels and sensory nerves with elevated SP levels have been observed within the proper tendon, indicating an unaccomplished healing process. Thus, signals that regulate nerve and blood vessel retraction are critical in the understanding of tendinopathy prevention. Factors that may regulate nerve retraction and are released at mechanical stimulus during tendon healing include IL-6 family members [34–36], neurotrophic factors [37], glutamate [38], and their receptors [39–42].



**Fig. 23.4** Tendon healing – neuropeptide expression. Area within tendon proper occupied by nerve fibers (%) immunoreactive to neuropeptides SP, CGRP, and GAL in

relation to the total healing area, over 16 weeks post-tendon injury (mean  $\pm$  SEM) (Reproduced with permission from [24])



## 23.5 Conduction of Cell and Tissue Ingrowth

A prerequisite for healing to commence is an existing and functioning tissue matrix into which cells, vessels, and nerves can grow in and where production of new granulation tissue can occur. If a tissue defect exists, the repair process will be prolonged or will not be able to take place at all. Hence, in conservative as well as in surgical treatment of patients with tendon injuries, it is an important principle to bring the disrupted tendon parts close together for regulation of fibril fusion and new tissue ingrowth. Small-sized defects can mostly be managed by autologous methods, i.e., repair by remaining tendon tissue, flap techniques, or tendon grafts. Larger defects do sometimes need free tendon grafts (e.g., semitendinosus tendon) and/or scaffolding techniques – either biogenic or synthetic (e.g., bioresorbable polymers) scaffolds. At present, autologous graft is still the gold standard, while the development of new biogenic or synthetic scaffolds is still under investigation [14].

---

## 23.6 Modification of the Healing Callus

### 23.6.1 Mobilization

Mobilization leading to mechanical tendon loading is the most well-known extrinsic factor adapted to regulate tendon protein synthesis and degradation [43]. One exercise bout in human tendons activates an initial increase in both the synthesis and degradation of collagen. The initial loss of collagen after loading is thus over time ensued by a net gain in collagen.

During the healing process, the mechanical loading is even more important for tendon tissue properties. Increasing mechanical loading activates myofibroblasts and fibroblasts to increase the production of collagen type I to increase the callus size and enhance the capacity to withstand high mechanical load. With loading of the tendon,

the orientation of fibroblasts and collagen changes to the longitudinal axis of the tendon by 4 weeks after injury. By 4 weeks, the mechanical strength of the repairing tendon increases, as there is consolidation and remodeling of the maturing granulation tissue under tension, and the collagen synthesis under load changes from type III to type I. Various factors influence the rate and quality of tendon healing. The most important is the mechanical tension across the repair which speeds realignment of collagen fibers, increases tensile strength, and minimizes deformation at the repair site [44]. Early mobilization accelerates the nerve plasticity, i.e., nerve regeneration, expression of neuromediators and their receptors, and nerve retraction (Figs. 23.2 and 23.3) [41, 45].

### 23.6.2 Immobilization

Mechanical stimuli promote tendon repair, while immobilization is detrimental for healing (Fig. 23.5). In a rat model with plaster cast immobilization of the hind limb after Achilles tendon rupture, the ultimate tensile strength was reduced 80% at 2 weeks post-rupture compared with a freely mobilized group [46]. Moreover, in the same model of hind limb immobilized rats, mRNA expression of essential sensory neuropeptide receptors (NK-1, RAMP), growth factors (BDNF, bFGF), and extracellular matrix molecules (collagen type I and III, versican, decorin, biglycan) were all downregulated at 2 weeks post-rupture [37, 41]. In the same studies, it was demonstrated that a shorter period of immobilization, i.e., 1 week, did not affect mRNA expression of the abovementioned molecules. These reports support the notion that prolonged immobilization post-injury hampers the healing process by compromising the up-regulation of repair gene expression in the healing tendon. Moreover, the data also suggest that endogenous, as well as exogenously given, growth factors PRP-therapies may not be effective until mechanical stimulation is initiated, since their receptors are not up-regulated [37].

### 23.6.3 Mechanical Stimulation During Immobilization

One novel method of applying mechanical stimulation to an immobilized tendon could be applied by using adjuvant intermittent pneumatic compression (IPC). IPC, which clinically is adapted to prevent thrombosis and increase blood circulation [47], has experimentally proven positive effects on wound and fracture healing [46, 48], although the mechanisms are still largely unknown. Recently,

however, IPC was demonstrated to enhance neurovascular ingrowth in a tendon repair model such as to increase the expression of sensory neuropeptides by up to 100% [49]. In the same model, IPC was able during immobilization to improve maximum force by 65%, energy 168%, organized collagen diameter 50%, and collagen III occurrence 150% compared with immobilization only [46] (Fig. 23.5). Whether IPC can reverse the negative effects of immobilization in patients still needs to be further explored.

Group	Intact <sup>a</sup>		Mobilization		Immobilization		Immobilization + IPC treatment	
	Mean ± SEM	Mean ± SEM	Mean ± SEM	<i>p</i> -Level <sup>c</sup>	Mean ± SEM	<i>p</i> -Level <sup>c</sup>		
Max force (N)	43.0 ± 4.2	46.9 ± 3	9.5 ± 1.4	<0.001	15.7 ± 2.4	<0.001		
Energy (J)	82.9 ± 4.2	99 ± 13.5	25 ± 9.7	0.005	67 ± 12.5	0.109		
Stiffness (N/mm)	13.1 ± 1.2	16.6 ± 1	3.8 ± 0.4	<0.001	5 ± 0.6	<0.001		
Length (mm)	8.9 ± 0.4	14.7 ± 0.9	11.4 ± 1	0.025	14.3 ± 0.5	0.567		
Cross area (mm <sup>2</sup> )	3.0 ± 0.5	16.2 ± 1.9	8.6 ± 0.5	0.013	11.3 ± 1.6	0.050		
Stress (N/mm <sup>2</sup> )	17.5 ± 3.9	3.3 ± 0.3	1.1 ± 0.2	0.002	1.5 ± 0.2	0.001		
Organized collagen (%)	100	53 ± 3.1	27 ± 3.5	0.004	40 ± 2.5	0.017		
Collagen III-LI (%)	NA <sup>b</sup>	5.9 ± 1.9	1.0 ± 0.1	0.004	2.5 ± 0.5	0.052		

**Fig. 23.5** Biomechanical healing properties during mobilization/immobilization. At 2 weeks post-tendon rupture, maximum force at failure of freely mobilized rats already reached the values of “normal” uninjured. Compared to mobilization, 2 weeks of immobilization

caused significantly lower values ( $p \leq 0.05$ ) for all parameters. IPC treatment, however, seems to counteract the effects of immobilization (Reproduced with permission from Schizas et al. [46])

### Conclusion

Several novel and modified versions of old therapies rapidly become available for the use of enhancing tendon repair. Although novel tissue engineering and tissue regenerative techniques addressing tendon repair seem promising, these are not yet ready for routine clinical use. Such methods include molecular approaches by which PRP, PRF, and fibrin glue, including stem cells, synthesize growth factors, or other mediators needed for progression of failed healing.

Having this said, I also want to clearly state that – the future lies in biological augmentation of tendon healing – once the correct indications are there, the correct formulations are understood, and the adjuvant treatments during the different healing phases are correctly applied.

### References

- Ackermann PW. Healing and repair mechanisms. London: DJO Publications; 2014.
- Broughton 2nd G, Janis JE, Attinger CE. Wound healing: an overview. *Plast Reconstr Surg*. 2006; 117(7 Suppl):1e-S–32e-S.
- Andia I, Sanchez M, Maffulli N. Tendon healing and platelet-rich plasma therapies. *Expert Opin Biol Ther*. 10(10):1415–26.
- Kaux JF, Drion PV, Colige A, et al. Effects of platelet-rich plasma (PRP) on the healing of Achilles tendons of rats. *Wound Repair Regen*. 2012;20(5):748–56.
- Lyras DN, Kazakos K, Verettas D, et al. The influence of platelet-rich plasma on angiogenesis during the early phase of tendon healing. *Foot Ankle Int*. 2009;30(11):1101–6.
- Paoloni J, De Vos RJ, Hamilton B, et al. Platelet-rich plasma treatment for ligament and tendon injuries. *Clin J Sport Med*. 2011;21(1):37–45.
- Alsousou J, Thompson M, Harrison P, et al. Effect of platelet-rich plasma on healing tissues in acute ruptured Achilles tendon: a human immunohistochemistry study. *Lancet*. 2015;385 Suppl 1:S19.
- Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101(3):e37–44.
- Zumstein MA, Berger S, Schober M, et al. Leukocyte- and platelet-rich fibrin (L-PRF) for long-term delivery of growth factor in rotator cuff repair: review, preliminary results and future directions. *Curr Pharm Biotechnol*. 2012;13(7):1196–206.
- Dohan Ehrenfest DM, de Peppo GM, Doglioli P, et al. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies. *Growth Factors*. 2009;27(1):63–9.
- Dietrich F, Duré G L, P Klein C, et al. Platelet-rich fibrin promotes an accelerated healing of Achilles tendon when compared to platelet-rich plasma in rat. *World J Plast Surg*. 2015;4(2):101–9.
- Knobe M, Gradl G, Klos K, et al. Is percutaneous suturing superior to open fibrin gluing in acute Achilles tendon rupture? *Int Orthop*. 2015;39(3):535–42.
- Martin P. Wound healing—aiming for perfect skin regeneration. *Science (New York)*. 1997;276(5309):75–81.
- Longo UG, Lamberti A, Maffulli N, et al. Tissue engineered biological augmentation for tendon healing: a systematic review. *Br Med Bull*. 2011;98:31–59.
- Tang Y, Leng Q, Xiang X, et al. Use of ultrasound-targeted microbubble destruction to transfect IGF-1 cDNA to enhance the regeneration of rat wounded Achilles tendon in vivo. *Gene Ther*. 2015;22(8):610–8.
- Kurtz CA, Loebig TG, Anderson DD, et al. Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. *Am J Sports Med*. 1999;27(3):363–9.
- Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. *Sports Med*. 2003;33(5):381–94.
- Forslund C, Rueger D, Aspenberg P. A comparative dose-response study of cartilage-derived morphogenetic protein (CDMP)-1, -2 and -3 for tendon healing in rats. *J Orthop Res*. 2003;21(4):617–21.
- Forslund C, Aspenberg P. Improved healing of transected rabbit Achilles tendon after a single injection of cartilage-derived morphogenetic protein-2. *Am J Sports Med*. 2003;31(4):555–9.
- Shen H, Gelberman RH, Silva MJ, et al. BMP12 induces tenogenic differentiation of adipose-derived stromal cells. *PLoS One*. 2013;8(10):e77613.
- Ackermann PW, Franklin SL, Dean BJ, et al. Neuronal pathways in tendon healing and tendinopathy—update. *Front Biosci*. 2014;19:1251–78.
- Ackermann PW. Neuronal regulation of tendon homeostasis. *Int J Exp Pathol*. 2013;94:271–86.
- Ackermann PW, Ahmed M, Kreicbergs A. Early nerve regeneration after achilles tendon rupture—a prerequisite for healing? A study in the rat. *J Orthop Res*. 2002;20(4):849–56.
- Ackermann PW, Li J, Lundeberg T, et al. Neuronal plasticity in relation to nociception and healing of rat achilles tendon. *J Orthop Res*. 2003;21(3):432–41.
- Burssens P, Steyaert A, Forsyth R, et al. Exogenously administered substance P and neutral endopeptidase inhibitors stimulate fibroblast proliferation, angiogenesis

- and collagen organization during Achilles tendon healing. *Foot Ankle Int.* 2005;26(10):832–9.
26. Carlsson O, Schizas N, Li J, et al. Substance P injections enhance tissue proliferation and regulate sensory nerve ingrowth in rat tendon repair. *Scand J Med Sci Sports.* 2011;21(4):562–9.
  27. Steyaert AE, Burssens PJ, Vercruyse CW, et al. The effects of substance P on the biomechanic properties of ruptured rat Achilles' tendon. *Arch Phys Med Rehabil.* 2006;87(2):254–8.
  28. Nourissat G, Diop A, Maurel N, et al. Mesenchymal stem cell therapy regenerates the native bone-tendon junction after surgical repair in a degenerative rat model. *PLoS One.* 2010;5(8):e12248.
  29. Okamoto N, Kushida T, Oe K, et al. Treating Achilles tendon rupture in rats with bone-marrow-cell transplantation therapy. *J Bone Joint Surg Am.* 2010;92(17):2776–84.
  30. Ackermann PW, Salo PT, Hart DA. Gene therapy. In: Van Dijk N, Karlsson J, Maffulli N, editors. *Achilles tendinopathy current concept.* London: DJO Publications; 2010. p. 165–75.
  31. Lee SY, Kim W, Lim C, et al. Treatment of lateral epicondylitis by using allogeneic adipose-derived mesenchymal stem cells: a Pilot Study. *Stem Cells.* 2015;33(10):2995–3005.
  32. Haegerstrand A, Dalsgaard CJ, Jonzon B, et al. Calcitonin gene-related peptide stimulates proliferation of human endothelial cells. *Proc Natl Acad Sci U S A.* 1990;87(9):3299–303.
  33. Hong HS, Lee J, Lee E, et al. A new role of substance P as an injury-inducible messenger for mobilization of CD29(+) stromal-like cells. *Nat Med.* 2009;15(4):425–35.
  34. Legerlotz K, Jones ER, Screen HR, et al. Increased expression of IL-6 family members in tendon pathology. *Rheumatology.* 2012;51(7):1161–5.
  35. Ackermann PW, Domeij-Arverud E, Leclerc P, et al. Anti-inflammatory cytokine profile in early human tendon repair. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(8):1801–6.
  36. Andersen MB, Pingel J, Kjaer M, et al. Interleukin-6: a growth factor stimulating collagen synthesis in human tendon. *J Appl Physiol.* 2011;110(6):1549–54.
  37. Bring D, Reno C, Renstrom P, et al. Prolonged immobilization compromises up-regulation of repair genes after tendon rupture in a rat model. *Scand J Med Sci Sports.* 2010;20(3):411–7.
  38. Greve K, Domeij-Arverud E, Labruto F, et al. Metabolic activity in early tendon repair can be enhanced by intermittent pneumatic compression. *Scand J Med Sci Sports.* 2012;22(4):e55–63.
  39. Schizas N, Lian O, Frihagen F, et al. Coexistence of up-regulated NMDA receptor 1 and glutamate on nerves, vessels and transformed tenocytes in tendinopathy. *Scand J Med Sci Sports.* 2010;20(2):208–15.
  40. Schizas N, Weiss R, Lian O, et al. Glutamate receptors in tendinopathic patients. *J Orthop Res.* 2012;30(9):1447–52.
  41. Bring DKI, Reno C, Renstrom P, et al. Joint immobilization reduces the expression of sensory neuropeptide receptors and impairs healing after tendon rupture in a rat model. *J Orthop Res.* 2009;27(2):274–80.
  42. Hou ST, Jiang SX, Smith RA. Permissive and repulsive cues and signalling pathways of axonal outgrowth and regeneration. *Int Rev Cell Mol Biol.* 2008;267:125–81.
  43. Magnusson SP, Langberg H, Kjaer M. The pathogenesis of tendinopathy: balancing the response to loading. *Nat Rev Rheumatol.* 2010;6(5):262–8.
  44. Gelberman RH, Manske PR, Akeson WH, et al. Flexor tendon repair. *J Orthop Res.* 1986;4(1):119–28.
  45. Bring DKI, Kreicbergs A, Renstrom PAFH, et al. Physical activity modulates nerve plasticity and stimulates repair after Achilles tendon rupture. *J Orthop Res.* 2007;25(2):164–72.
  46. Schizas N, Li J, Andersson T, et al. Compression therapy promotes proliferative repair during rat Achilles tendon immobilization. *J Orthop Res.* 2010;28(7):852–8.
  47. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. *Cochrane Database Syst Rev.* 2008;4:CD005258.
  48. Khanna A, Gougoulias N, Maffulli N. Intermittent pneumatic compression in fracture and soft-tissue injuries healing. *Br Med Bull.* 2008;88(1):147–56.
  49. Dahl J, Li J, Bring DK, et al. Intermittent pneumatic compression enhances neurovascular ingrowth and tissue proliferation during connective tissue healing: a study in the rat. *J Orthop Res.* 2007;25(9):1185–92.