

## Current Concepts in Tendon Bioengineering

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### Introduction

Due to their specific morphologic structure, tendons are the soft tissue with the highest tensile strength, needed to transfer muscle power to the skeletal system. In case of tendon injury, such as traumatic tendon tears, chronic overuse of tendons, or degenerative tendinopathy, function and motion are impaired. However, repaired tendon tissue rarely achieves functionality equal to that of the pre-injured state, whereas final tear resistance may be reduced by up to 30% [1-3]. The fact that tendons often tear upon an underlying tendinopathy as a precondition, is considered rather rarely for research and treatment of patients with acute tendon injuries [4]. For optimal treatment, enhanced understanding of tendon physiology, degenerative pathology, and healing processes in ruptured tendons is necessary. Due to their similar structure, healing of ligaments is usually compared and subsumed to tendon healing.

For a preferably comprehensive survey, literature was systematically reviewed for English peer-reviewed journals on tendon healing and tendon bioengineering including cytokine modulation, autologous sources of growth factors, biomaterials, gene therapy, and cell-based therapy [5]. This article shall highlight the most important findings and main concepts in tendon bioengineering.

Aiming for optimized and accelerated tendon healing, several approaches in tendon engineering have been described to improve and accelerate the slow process of tendon healing, which runs through different stages of haemorrhage, inflammation, proliferation, and remodelling and can be classified as follows:

### Collagen Recycling

Apart from the classical stages of tendon healing by collagen de novo synthesis via weak collagen type III, a collagen type I recycling process from adjacent tendon tissue has been reported [6]. This fact could explain the observed post-operative rupture of flexor tendons next to the site of previous repair [7]. Based on the recycling theory, we have found significantly improved healing in tendons treated with a type I collagen scaffold [8].

### Mechanical Load

Tenocytes are able to respond to mechanical stress, which helps to structure the maturing tendon during development or the healing tendon during remodeling. Mechanical load leads to an up-regulation of type III collagen mRNA expression and increased growth factor concentrations inducing cell proliferation, differentiation, and matrix formation in tendon tissue [9,10]. Mechanical stimulation is beneficial for proper organization of collagen fibers and prevention of adhesions in healing tendons. However, mechanical under- or overstimulation can induce lipid accumulation, mucoid formation, and tissue calcification, all of them being markers of tendinopathy increasing the risk of re-rupture or micro-tears [11]. The misconfiguration of load within in one tendon – higher load to the superficial than to the deep layer due to greater distance to the central axis of rotation – is meant to cause stress shielding of tendons leading to tendinopathy. If conservative treatment fails in these cases, the superficial layer can be incised to equally load the deep and superficial portion [12].

### Cytokine Modulation of Tendon Healing

The expression of a variety of natural growth factors is induced at multiple stages throughout natural tendon healing [13-16] leading to increased cellularity and tissue volume [17]. The following growth factors have turned out to play an important role in tendon healing [18-20]:

- Basic fibroblast growth factor (BFGF),
- Bone morphogenetic protein (BMP),
- Connective tissue growth factor (CTGF),
- Insulin-like growth factor (IGF-1),
- Platelet-derived growth factor (PDGF),
- Transforming growth factor beta (TGFβ),
- Vascular endothelial growth factor (VEGF).

However, combinations of growth factors seem more potent than individual growth factors delivered singly [21]. Thus concentrates of multiple autologous growth factors, such as those contained within platelet rich plasma (PRP) or autologous conditioned serum (ACS) have been tested for tendon healing and showed up to 30% increased tendon strength [22-25]. In clinical studies, PRP was shown to reduce

pain in patellar tendinopathy [26], to have a positive effect on donor site healing in the harvested patellar tendon for ACL-reconstruction [27], and to accelerate remodeling of ACL-graft itself [28].

In surgical repair of Achilles tendons no improvement of tendon healing was found for PRP treated patients [29]. In chronic Achilles tendinopathy, PRP and saline groups showed no differences regarding pain or activity level [30]. There is evidence in the literature for and against efficacy of PRP in chronic lateral epicondylar tendinopathy, the so-called tennis elbow [31,32]. However, PRP is a variable, poorly characterized cocktail of growth factors and other substances, which could explain the contrary findings for PRP in tendon treatment. So far no clear growth factor formula has been found for routine use in clinics either as an autologous blood product or as recombinant growth factors.

## Biomaterials in Tendon Healing

To bridge a defunct or missing tendon part, scaffolds potentially in combination with biological active substances or cells have been described in the literature [33-36]. However, none of these scaffolds could be used routinely in clinics yet. Auto- and allografts remain the gold standard to augment healing sites, even though availability is restricted and complications may arise making new biomaterials desirably.

## Gene Therapy

Short half-life and quick clearance are issues of delivering growth factors to the healing site. For a potential longer and constant growth factor release transfer of genetic material (DNA) to cells has been studied. Thereby the cells incorporate the genetic material and produce the desired growth factors over a substantial period of time. Improved tendon healing was found in animal models for gene transfer of BMP12, PDGF, TGF $\beta$ , and VEGF [37-40].

## Cell-Based Therapy

Stem cells are subject of interest and research aiming for new tendon tissue formation. Improved tendon healing in acute tears or tendinopathy has been described using stem cells in laboratory studies [41-48]. Though results may be promising, use of these cells is ethically problematic and far away from routine clinical use.

## Summary

Results of tendon treatment in daily practice are inconsistent. The current knowledge on new attempts in tendon engineering is mainly based on laboratory studies and clinical approaches are still experimental. Aiming for regenerated tendon tissue comparable to healthy tendon, underlying degenerations, i.e. tendinopathy means a great challenge in treatment. A quick increase of type I collagen seems to be important and can be supported by an external collagen supply.

Knowing that physical over- or under-stimulation can have adverse effects, the appropriate amount and timing of mechanical load to the healing tendon are challenging and have to be defined. However, an early activation of the corresponding muscle and joint seem to be reasonably.

As intrinsic tendon healing is guided by growth factors, one promising goal is to find the right composition of growth factors, which could be contained within autologous blood products. Direct injections of growth factors could be easier than carrier based approaches. However, time of release vs. overflow loss and half-life has to be taken into account as tendon healing still takes rather months than weeks. Complex approaches using gene or cell based therapy hold great promise but research and development in this direction has barely just begun.

Focusing on growth factors in a defined composition and possibly added to a collagen type I scaffold could promise a realistic approach for patients with tendon defects or severe tendinopathy in the near future.

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