

## Cellular Response of the Tendon Sheath in Tendon Injury: Experimental Research in New Zealand Rabbits

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### Abstract

**Purpose:** We aimed to investigate the synovial sheath cell migration in response to flexor tendon injury under direct visualization.

**Methods:** We used New Zealand rabbits based on an animal model described in previous studies, which we modified in order to create conditions similar to real tendon injury and healing. We used a special paint marker (1,1'-dioctadecyl-1-3,3,3'-tetramethylindocarbocyanine-percolate-Dil) of the sheath cells. The Flexor Digitorum Profundus first was sectioned through a distal skin incision and pulled outside the sheath through a proximal skin incision. Then the sheath was labeled. A second intrasynovial full thickness cross-section of the flexor was done and repaired by Kessler and running type suture. We harvested the tendons day 1, 3, 5, 7, 14 and 28 after tendon injury. Tendon sections were prepared with cryotomy and tested by infrared microscope. To evaluate our results, we divided the migration of synovial sheath cells in four phases: 1<sup>st</sup> phase) no or sporadic migration to the surface of the tendon, 2<sup>nd</sup> phase) massive migration to the surface of the tendon, 3<sup>rd</sup> phase) migration just below the surface of the tendon, and 4<sup>th</sup> phase) migration in the endotenon. For each day's group the percentage of tendon sections in each phase of migration was determined.

**Results:** According to our findings the second phase of migration of cells was 85% reached on the 3<sup>rd</sup> day, the third phase 66.6% reached on the seventh day and the fourth phase 50% reached on the fourteenth day after flexor tendon injury.

**Conclusions:** This study confirms that the synovial sheath cells migrate first into the surface and later into the core of the healing tendon.

**keywords:** Synovial sheath cells; Neutrophils; Tendon injury

### Introduction

The tendons are units of musculoskeletal tissue that transmit force from muscle to bone. The normal tendon consists of soft and fibrous connective tissue that is composed of densely packed collagen fiber bundles aligned parallel to the longitudinal tendon axis and surrounded by tendon sheath, also consisting of extracellular matrix components. Collagen constitutes 75% of the dry tendon weight and its main function is to withstand and transmit large forces between muscle and bone.

In most cases of tendon laceration or rupture, surgical intervention is required to direct the natural process of healing. Tendon repair is a slow process that takes place in three overlapping stages. The initial stage of repair involves the inflammatory phase. Erythrocytes and inflammatory cells, especially neutrophils, enter the area of the lesion. In the first twenty-four hours, monocytes and macrophages arrive and a phagocytosis process of the necrotic material is taking place. Angiogenic factors are released during this phase and initiate the formation of a vascular network [1]. Tenocytes migrate to the damaged area and synthesize collagen type III [2]. The second stage called proliferative phase involves the continued recruitment of fibroblasts and their rapid proliferation at the wound site which are responsible for the synthesis of collagens, proteoglycans and other components of the extracellular matrix. At this point the extracellular matrix is largely composed of type III collagen [2]. At the end of the proliferative stage,

the repair tissue is highly cellular and contains relatively large amounts of water and an abundance of extracellular matrix components. The third stage called remodeling stage begins 6-8 weeks after injury and is characterized by a decrease in cellular, matrix and type III collagen synthesis and an increase in type I collagen synthesis. The remodeling phase can be divided into a consolidation and a maturation stage [3]. The consolidation stage starts from the sixth week and lasts until the tenth week. During this period, the repair tissue changes from cellular to fibrous. Cellular metabolism remains high at this stage. Tenocytes and collagen fibers are aligned with the direction of the stress forces [4]. More collagen type I is produced during this phase [5]. After the tenth week the maturation stage starts. At this stage the fibrous tissue is gradually replaced with scar-like tendon tissue [6]. This process takes

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about a year, during which the cellular metabolism gradually decreases [7].

Two distinct models have been proposed to explain the mechanism of tendon healing [8-10]. Intrinsic healing entails the proliferation and migration of cells from epitenon into the injury site [11,12]. During extrinsic healing fibroblasts and inflammatory cells invade the healing site from the periphery or external tissue in order to initiate and later promote repair and regeneration. This process involves the initial formation of adhesions. Intrinsic healing gives better biomechanical results, unlike the extrinsic healing in which the scar tissue adhesions between the tendon and the sheath can cause fixed contracture [13]. In most cases both mechanisms are involved in the healing process that is dependent on several factors including tendon location, extent of trauma and postoperative motion.

The healing of injured is achieved mainly by the epitenon cells [14]. Endotenon cells contribute to the healing process by producing larger and more mature collagen fibers [15]. Different types of collagen produced by different cell types are involved in the healing of the tendon at different phases. Collagen is initially synthesized by epitenon and later by endotenon cells [16-19]. The involvement of each cell type in collagen synthesis can be affected by the type of wound, the anatomical location of the lesion, the existence of synovial tendon sheaths, and the stress developed by the movement of the repaired tendon [20].

During tendon repair several biological factors such as Metallo Proteinases (MMPs) [21], growth factors and cytokines [22,23] are involved in the activation and regulation of the cellular response. These factors bind to specific receptors that are present on the cellular surface and activate specific signaling events within the cell. The release of these factors is stimulated by cells that are located at the site of injury [24]. Other substances that can affect the healing process are nitric acid [25], the substance P and the Calcitonin Gene-Related Peptide (CGRP) [26,27].

Numerous studies of tendon healing have been performed either on transected tendons of animal models or ruptured human tendons in cadavers. However, the conditions under which healing and cellular response of both the cells of the injured tendon and the cells of neighboring tissues take place, have not been fully elucidated.

## Purpose

The aim of this study was to investigate the synovial sheath cell

migration in response to flexor tendon injury by selective cell labeling and direct observation. Previous studies have investigated the fibroblast migration from the synovial sheath to the injury site, using animal models. The tendon was injured by a longitudinal incision causing partial tendon tear, after having previously marked the sheath cells with a special dye [28]. We adopted a similar methodology, but we performed complete tendon intersection and sutured the tendon trying to reproduce realistic conditions of tendon healing.

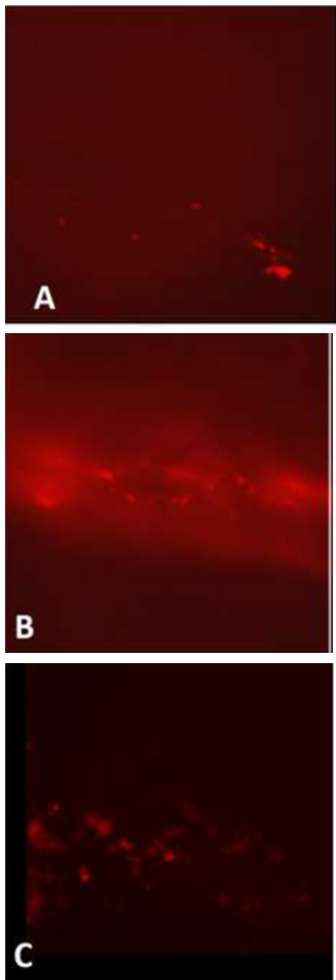
## Material and Methods

Thirty six New Zealand rabbits were used for this study with the approval of the ethics committee. General anesthesia was induced by intramuscular injection of fentanyl-fluanisone (Hypnorm, Jensen Pharmaceutical Ltd.). Then the rabbit was prepared by shaving its front limbs and washing it thoroughly with a solution of povidone iodine 10% (Betadine, Lavipharm Hellas AE). Then local anesthetic (lidocaine hydrochloride 2%) was injected in the areas of skin incision. Two small transverse skin incisions of 1-1.5 cm were performed, one above the ankle (proximal incision) and the other below the ankle of the front leg (distal incision). Through the distal skin incision the Flexor Digitorum Superficialis (FDS) was moved to the side in order to approach the Flexor Digitorum Profundus (FDP). The FDP was transected at two different levels, the first, at the level of the distal skin incision and the second at the level of the proximal skin incision. After the first transection (at the level of the distal skin incision) the FDP was dragged outside its sheath from the proximal skin incision and protected inside gauze soaked with saline. A gauze impregnated with a special dye, 1,1'-diocetadecyl-3,3',3'-tetramethylindocarbocyanine percolate (Dil) (Molecular Probes Inc., Eugene, OR) was introduced in the empty tendon-sheath and left there for 5 minutes. This is a fluorescent lipophilic membrane tracer dye. Previous studies have shown that a 5 minutes period allows for a good uptake of the Dil<sup>®</sup>. After removing the gauze a diligent washing of the sheath with saline 0.9% was done. The washing was repeated at least 5 times with 5 ml saline boluses to ensure no diffusion of the dye in other tissues. Then a second cross-section at the middle of the intrasynovial part of the FDP was performed. The tendon was repaired using a Kessler's type suture with nylon 4/0 and running suturing with prolene 6/0. The FDP was dragged back into the sheath and the distal incision was repaired at the same way. Eventually, the wound was closed with nylon 3/0 (Figure 1). The exact same procedure was performed at the opposite side, but without intersection of the intrasynovial part of the FDP (i.e. without the proximal tendon incision). This side served as a control. This process was done in all rabbits and then they were freed without any type of cast-immobilization of the limbs.

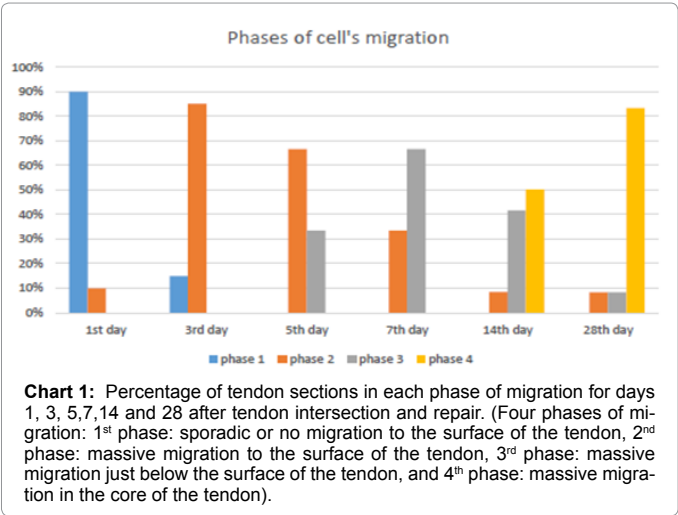
The animals were divided into 6 groups (6 animals for each group) in order to study the histologic samples of the flexors in 1, 3, 5, 7, 14 and 28 days after the initial procedure. The rabbits were killed with an overdose of fentanyl-fluanisone (Hypnodorm, Jansen) administered intramuscularly. In each group the FDP was removed and snap-frozen within a cry-vial in liquid nitrogen and stored at -80°C. The FDPs were then sectioned at 8 µm thickness using a cryostat with a tungsten blade with 4 representative sections cut from each tendon. Four sections were assessed from each flexor, with 6 animals being assessed for each time period, hence a total of 144 sections were analyzed in this study. The sections obtained were visualized under light and ultraviolet microscopy. Fluorescent Dil-dyed cells were visualized under ultraviolet light with a terta methyl rhodamine iso thiocyanate filter. The images of the sections were taken using a digital camera connected to a computer and saved as a JPGS files. To evaluate the results, we divided the migration of cells in four phases: 1<sup>st</sup> phase) no or sporadic



**Figure 1:** The arrows show the two skin incisions (distal on the left and proximal on the right). The proximal part of the flexor is sutured, and the tendon is going to place into the synovial sheath for the distal suturing. The synovial sheath for the distal suturing. The synovial sheath is already labeled with Dil dye.



**Figure 2:** (A). Ultraviolet photomicrographs of longitudinal tendon frozen sections taken at sequential time intervals after the procedure. On the 3rd day labeled cells are present upper the tendon surface. (B). Ultraviolet photomicrographs of longitudinal tendon frozen sections taken at sequential time intervals after the procedure. On the 7th day labeled cells are up and below the tendon surface. (C). Ultraviolet photomicrographs of longitudinal tendon frozen sections taken at sequential time intervals after the procedure. On the 28th day labeled cells are in all tendon body



migration to the surface of the tendon, 2<sup>nd</sup> phase) massive migration to the surface of the tendon, 3<sup>rd</sup> phase) migration just below the surface of the tendon, and 4<sup>th</sup> phase) migration in the endotenon. For each day group the percentage of tendon sections in each phase of migration was determined.

## Results

We repeated the process in another 3 rabbits, in order to have the same number of rabbits in each group, because in two, the distal suturing failed and in one, autocanibalism due to infection of the wound was observed.

On the first day after tendon injury, in 90% of the sections the cells were in the first phase of migration and in 10% in the second phase of migration. On the third day post injury we observed a massive collection of fibrocytes on the surface of the tendon (85% of sections were in the 2<sup>nd</sup> phase and 15% were in the 1<sup>st</sup> phase). On the fifth day post injury sporadic migrations just below the surface of the tendon was observed (66.6% were in 2<sup>nd</sup> phase and 33.4% in the 3<sup>rd</sup> phase). On the seventh day post injury massive migration just beneath the surface of the tendon was observed (66.6% were in the 3<sup>rd</sup> phase and 33.4% in the 2<sup>nd</sup> phase). After the fourteenth day post injury a massive collection of fibroblasts in the endotenon was observed (Figure 2). On the fourteenth day post injury 50% were in the 4<sup>th</sup> phase, 41.6% were in the 2<sup>nd</sup> phase and 8.4% were in the 3<sup>rd</sup> phase. On the twenty-eighth day post injury 83.4% were in the 4<sup>th</sup> phase, 8.3% were in the 3<sup>rd</sup> phase and 8.3% were in the 2<sup>nd</sup> phase. According to the staging of migration of cells, the second phase was reached in the third day, the third phase in the seventh day and the fourth phase in the fourteenth day after the flexor tendon injury (Chart 1).

On the contralateral limbs, which were used as control, we noticed that on the first day after the flexor tendon injury 90% of sections were in the 1<sup>st</sup> phase of migration and 10% in the 2<sup>nd</sup> phase. On the third day 80% were in the 1<sup>st</sup> phase and 20% were in the 2<sup>nd</sup> phase. On the fifth day 50% were in the 1<sup>st</sup> phase and a 50% were in the 2<sup>nd</sup> phase and remained the same for the rest of the groups (7<sup>th</sup>, 14<sup>th</sup> and 28<sup>th</sup> day group). On the control sections we did not observe any 3<sup>rd</sup> or 4<sup>th</sup> phase of migration (Table 1).

## Statistical Analysis

Simple linear regression analysis was used to check the correlation between the number of days after the tendon injury and the phase of the

INJURED TENDONS				
	1 <sup>st</sup> phase	2 <sup>nd</sup> phase	3 <sup>rd</sup> phase	4 <sup>th</sup> phase
1 <sup>st</sup> day	90%	10%		
3 <sup>rd</sup> day	15%	85%		
5 <sup>th</sup> day		66.6%	33.4%	
7 <sup>th</sup> day		33.4%	66.6%	
14 <sup>th</sup> day		8.4%	41.6%	50%
28 <sup>th</sup> day		8.3%	8.3%	83%
CONTROL				
1 <sup>st</sup> day	90%	10%		
3 <sup>rd</sup> day	80%	20%		
5 <sup>th</sup> day	50%	50%		
7 <sup>th</sup> day	50%	50%		
14 <sup>th</sup> day	50%	50%		
28 <sup>th</sup> day	50%	50%		

**Table 1:** Percentage of tendon sections for each day group in each phase of migration.



cells migration using the software of SPSS 16.0. Based on that analysis we estimated that the  $r$  square equaled 0.568 and the  $b_1$  equaled 5.749 for  $p=0.00$ . That means there is a weak but statistically significant correlation between the number of days after surgery and the phase of cell migration.

## Discussion

The use of dye Dil to mark flexor fibroblasts has been described by McNeilly et al. [29], where the studied cell response to mechanical loading. This type of fluorescent membrane label has the most appropriate characteristics to study the cells migration: lack of leakage from cells, cellular specificity, and sufficient longevity. Once attached to cells the dye is not passed to other cells. This dye, later, was used by Jones et al. [30] to study the migration of fibroblasts from the epitenon and by Harrison et al. [28] who studied the migration of fibroblasts from the synovial sheath with an animal model of partial intersection of the flexor. We adopted the same methodology as the previous two studies to study the behavior of cells in the sheath during healing after complete intersection suturing of the flexor, i.e. as often happens in reality.

This study confirms that there is migration of cells from the synovial sheath in the core of the flexor tendon during the healing process. On the first day after the injury no significant migration is noted. On the third post-injury day a significant cell migration on the tendon surface was noted. In the first 3 days of the flexor injury, there is intense enzymatic activity in epitenon and after two weeks, there is intense enzymatic activity in endotenon [31]. This schedule coincides with that of the migration of fibroblasts from the synovial sheath. But we do not know if this intense enzymatic activity is of the migrated fibroblast or if the fibroblast just stimulates the cells of the endotenon. On the seventh day a massive collection of fibroblast under the tendon surface was observed. After the fourteenth postoperative day a big number of fluorescent cells diffused in the core of the tendon were noted. Khan et al. [32] found differences in composition and type of collagen derived from fibroblasts of the sheath and epitenon. The participation of the fibroblasts of the synovial sheath in healing process of the injured flexor is associated with adhesions [33]. Berglund et al. [34] observed significantly increase of the levels of collagen I mRNA in the tendon sheath at 12 and 24 days after injury in contrast with the unvaried levels in injured tendons compared with the uninjured tendons. The same authors observed differences of type III mRNA levels and growth factors between synovial sheath cells and tendon cells. What is the rule of the synovial sheath cells in the tendon healing? A previous study has revealed many differences between synovial sheath cells and tendon cells regarding the type of collagen they produce and their association with the formation of adhesions. In our model control we observed that despite there is no migration from the sheath to the core of the tendon in uninjured tendons there is a migration to the tendon surface. If that observation is not because of dye diffusion could mean that there is a turnover of the synovial sheath cells between sheath and tendon surface. Considering that early mobilization prevent the formation of adhesions a hypothesis can be done. The synovial sheath is very active cells and in case of injury they migrate and stimulate the tendon cells to repair faster the lesion and to permit an earlier mobilization preventing the formation of adhesions. But if mobilization does not happen this faster collagen production create adhesions. A comparative study of the healing time between intrasynovial and extra synovial tendon injury should be done. An interesting study of Oryan et al. [35] showed a very slow healing in an extra synovial injured tendon (superficial digital flexor tendon of the hind leg of rabbit).

The statistical analysis revealed that there is synovial sheath migration in the injured tendon but there is a weak correlation between the day after injury and the phase of cells migration. That weak correlation could be explained because of the variability of the migration's phases observed during the days after the tendon injury. Despite the majority of the cells were in the 4<sup>th</sup> phase of migration at the fourteenth day after surgery (50%) and at the twenty-eighth day (83.4%) contemporaneously others phases of cell's migration observed.

It is important to understand the biology of healing of the injured tendon to find strategies that can stimulate healing and also prevents the formation of adhesions. Further investigation is required however, to better understand the factors or variables that control healing in these different tissues. Flexor tendon healing is a complex process. Immobilization decreases the risk of tendon rupture but help the adhesion formation. The opposite happen in early mobilization. The ideal would be to find the way to stimulate a faster tendon repair and mobilize before adhesion formation.

In conclusion, we, also, purpose this animal model for the comparative studies of different methods of suturing the tendon, to study whether how it can affect the cellular response and the development of adhesions.

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