ORIGINAL RESEARCH

Doxycycline-Embedded Nanofibrous Membranes Help Promote Healing of Tendon Rupture

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Background: Despite recent advancements in surgical techniques, the repair of tendon rupture remains a challenge for surgeons. The purpose of this study was to develop novel doxycycline-loaded biodegradable nanofibrous membranes and evaluate their efficacy for the repair of Achilles tendon rupture in a rat model.

Materials and Methods: The drug-loaded nanofibers were prepared using the electrospinning process and drug release from the prepared membranes was investigated both in vitro and in vivo. Furthermore, the safety and efficacy of the drug-loaded nanofibrous membranes were evaluated in rats that underwent tendon surgeries. An animal behavior cage was employed to monitor the post-surgery activity of the animals.

Results: The experimental results demonstrated that poly(D,L-lactide-co-glycolide) (PLGA) nanofibers released effective concentrations of doxycycline for more than 40 days post-surgery, and the systemic plasma drug concentration was low. Rats receiving implantation of doxycycline-loaded nanofibers also showed greater activities and stronger tendons post-operation.

Conclusion: Nanofibers loaded with doxycycline may have great potential in the repair of Achilles tendon rupture.

Keywords: doxycycline, tendon, nanofibrous membrane

Introduction

The Achilles tendon is the strongest and largest tendon in human body. Acute Achilles tendon rupture is one of the most commonly seen injuries around ankle joints and can cause severe disability, especially in athletes. The incidence rate of Achilles tendon rupture ranges from 11 to 37 per 10,000 people.[1–3] The mechanism of Achilles tendon injuries can be predominantly attributed to a contracted gastro-cnemius-soleus complex against forced dorsiflexion of ankle. Furthermore, Achilles tendon rupture can occur not only through a single traumatic event, but also via tendon degeneration, poor vascularity, and corticosteroid/fluoroquinolone use.[1,4–6] Treatment options include surgical repair or conservative treatment, although there is no consensus on these treatment options, and re-rupture is the main concern for acute Achilles tendon injuries. It has previously been reported that the re-rupture rate ranged from 1.7% to 8.0% in a surgically treated group,[7–10] whereas this rate ranged from up to 4.0% to 20.8%[7–11] in patients treated conservatively.

Matrix metalloproteinase (MMP) is an enzyme that involves degradation and remodeling of extracellular matrix (ECM) and plays an important role in the tendon repair process.[12–17] Inhibition of matrix metalloproteinase (MMP) has been the treatment of choice for tendinopathy.[18–21] Systemic daily

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administration of doxycycline orally has been demonstrated to improve collagen fibril organization through inhibition of local MMP activity, which accelerates matrix remodeling, increases equilibrium modulus, and decreases creep strain of surgically repaired Achilles tendons in rats.[20–22] Common side effects of doxycycline include esophageal erosion, heartburn, nausea, vomiting, diarrhea, and gastritis.[23] This may reflect patients' inability to tolerate the high systemic drug concentrations required to achieve adequate exposure of the drug at the target site. Local drug delivery may potentially provide the advantage of achieving high and sustained local concentrations with a low systemic dose, thus minimizing systemic side effects.

The purpose of our study was to evaluate the efficacy of novel doxycycline-loaded biodegradable membranes that provide sustained-release drug at the target site. We hypothesized that doxycycline-loaded biodegradable membrane would enhance the healing process and improve the biomechanical properties of surgically repaired Achilles tendons. To the best knowledge of the authors, no one has ever analyzed the effect of local slow-released doxycycline in surgically repaired Achilles tendons.

Poly(D,L-lactide-co-glycolide) (PLGA) polymers were selected as the delivery vehicles, mainly due to their excellent biocompatibility, controllable biodegradability, tunable degradation rates, mechanical properties, and thermal processibility.[24] Biodegradable doxycycline-loaded nanofibrous membranes were fabricated using the electrospinning technique, which is a fiber production process that adopts electric force to draw charged threads of polymer solutions up to fiber diameters in the order of some hundred nanometers. The technique can also be used to generate nanofiber assemblies for mimicking the special fiber organizations in musculoskeletal tissues. Nanofibrous scaffolds can provide the required mechanical properties that minimize the risk of re-rupture associated with the movement of the tendon gap defect following surgical repair.[25] After electrospinning technique, the extent of drug release from the prepared membranes was measured both in vitro and in vivo. Furthermore, animal models of rats that underwent tendon repair surgeries were used to evaluate the efficacy and safety of the drug-loaded nanofibrous membranes. Animal activities post-operation was also compared by employing an animal behavior cage (ABC) developed by our group.

Materials and Methods
Preparation of Doxycycline-Incorporated Nanofibrous Membranes

The polymeric materials included PLGA polymer (lactide/ glycolide: 50/50, molecular weight Mw=33,000 Da) (Sigma-Aldrich, MO, U.S.A.). Doxycycline and hexafluoroisopropanol (HFIP) were also acquired from Sigma-Aldrich.

To manufacture the nanofibrous membranes, PLGA and doxycycline were primarily dissolved in HFIP at concentrations of 30% (w/v) and 7.5% (w/v) respectively.[26,27] Electrospinning of the PLGA/doxycycline solution was performed on a lab-made setup consisting of a syringe and needle (the internal diameter is 0.42 mm), a ground collection plate, and a high voltage supply. The flow rate of the solution was 0.1 mL/h, while the applied voltage was 15 kV. The solution was gathered by the collection plate distanced 15 cm from the syringe in a nonwoven form. All procedures were performed at a temperature of 26°C and a relative humidity of 64%.

Characterization of Electrospun Nanofibrous Membranes

To quantify the doxycycline-incorporated nanofibers, we used a field emission scanning electron microscope (FE-SEM) (JSM – 7500F, Joel, Japan). The diameter compositions of nanofibers were obtained by characterizing the micro-images of 50 arbitrarily picked fibers for each specimen.

The spectra of electrospun nanofibrous membranes were characterized using a Fourier Transform Infrared (FTIR) spectrometry. We used Nicolet iS5 spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) at a resolution of 4 cm^{-1} and 32 scans to perform FTIR analysis. Nanofibrous membranes were pressed as KBr discs, and spectra were analyzed over the 400–4000 cm^{-1} range.

The tensile strength of electrospun nanofibrous scaffolds was measured with a Lloyd tensiometer (AMETEK, Berwyn, PA, USA) that was equipped with a 100 N load cell, in accordance with the ASTM D638 standard. A strip cut from the membrane that had dimensions of 10 mm by 50 mm was held between two clamps that were separated by 3 cm. During the tests, the membrane was pulled by the top clamp at a rate of 60 mm/minthrough a distance of 10 cm before the clamp was returned to its starting point. The force and elongation before the membrane was broken

were recorded. Measurements were made five times on each membrane.

A contact angle measuring apparatus (First Ten Angstroms, Portsmouth, VA, USA) was used to assess the water contact angles of the scaffolds that have a dimension of 1 cm × 1 cm (N= 5).

Evaluation of Doxycycline Levels in vitro

The amount doxycycline released from the drug-incorporated membranes was evaluated. Specimens with an approximate size of 2.0 × 3.0 mm and weight of 1 g were cut from the electrospun membrane and then kept in glass tubes. In each tube, 1 mL of buffered solution (0.15 mol/L, pH 7.4) was added to the specimen. Then, tubes were maintained at 37°C for 24 hrs. Then, the eluent was collected for analysis with another 1 mL of fresh-buffered solution added into each tube. Every 24 hrs, the procedure was repeated, until the specimen was fully dissolved. The experiment was performed in triplicate (N=3). The doxycycline levels in the eluents were quantified using a high-performance liquid chromatography (HPLC) assay on a Hitachi L-2200R system (Hitachi Inc., Tokyo, Japan).

In vivo Animal-Related Procedure

Eighteen Sprague Dawley (SD) rats, weighing 250±25 g each, were enrolled for the in vivo study. All animal-related procedures received institutional approval of Chang Gung University (CGU 107-168), and all of the animals were cared for under the supervision of a licensed veterinarian in a manner that was consistent with the regulations of the Department of Health and Welfare, Taiwan.

The rats were sedated under general anesthesia in an anesthesia chamber (40cm × 20cm × 28cm, transparent acrylic box), with isoflurane (Aesica-Queenborough, Queenborough, Kent, UK) by a vaporizer (Matrix, USA). Isoflurane inhalation was used throughout the entire surgical procedure to maintain anesthesia. Before the surgical procedure, the rat received a local injection over right leg with 0.5 mL 2% Xylestesin-A containing epinephrine at a concentration of 1:100,000. As shown in Figure 1, a 3 cm longitudinal skin incision lateral to Achilles tendon was made over right leg of each rat using a #15 blade. The Achilles tendon was exposed by dissecting the surrounding soft tissue. The mid-portion of Achilles tendon was then cut via scalpel and sutured end-to-end with a 5-0 Dexon suture (Johnson & Johnson, USA), and the 18 rats were randomly separated into two groups. In the test group, the repaired Achilles tendon was surrounded with
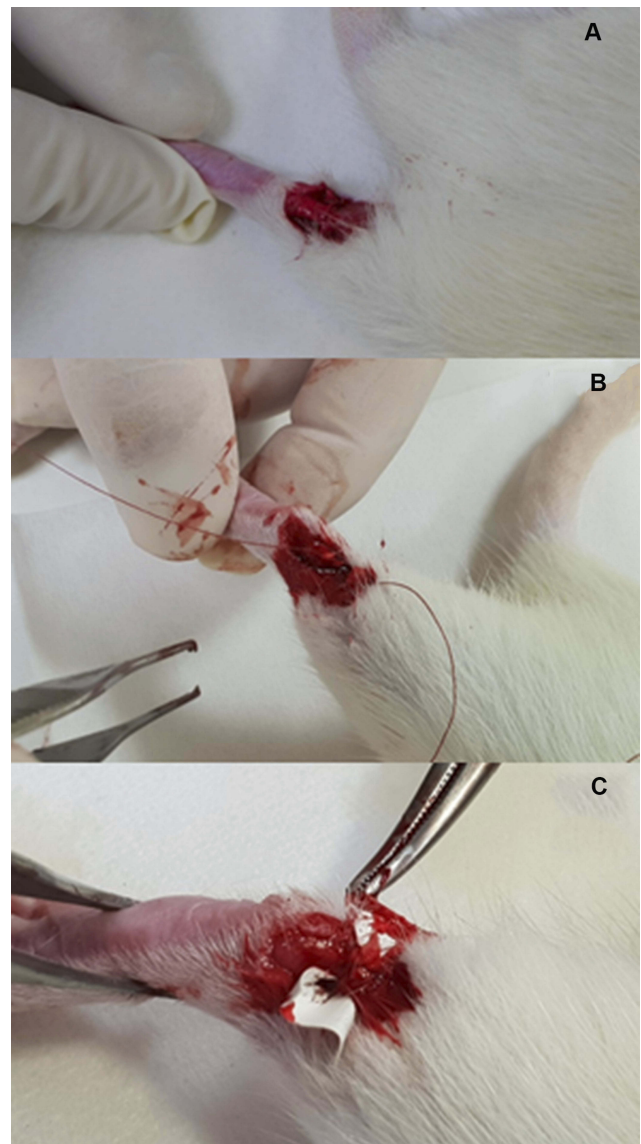

Figure 1 (**A**) Exposing the Achilles tendon, (**B**) suturing the tendon with sutures, and (**C**) enveloping the tendon with doxycycline-loaded nanofibrous membrane.

biodegradable nanofibrous membrane and suture fixation with 5-0 suture, and the wound was closed with 3-0 Nylon suture (Johnson & Johnson, USA). In the control group, the repaired tendon was not covered with nanofibrous membrane.

Post-Operative Activity Test

After the surgery, general activity level was recorded daily by housing each rat in a lab-developed animal behavior cage (ABC) for 1 week, after which the rats were sent back to their original cages for animal care. As shown in Figure 2, the dimensions of the cage were 50 cm × 50 cm × 50 cm. The movement of the rats was monitored and recorded by nine
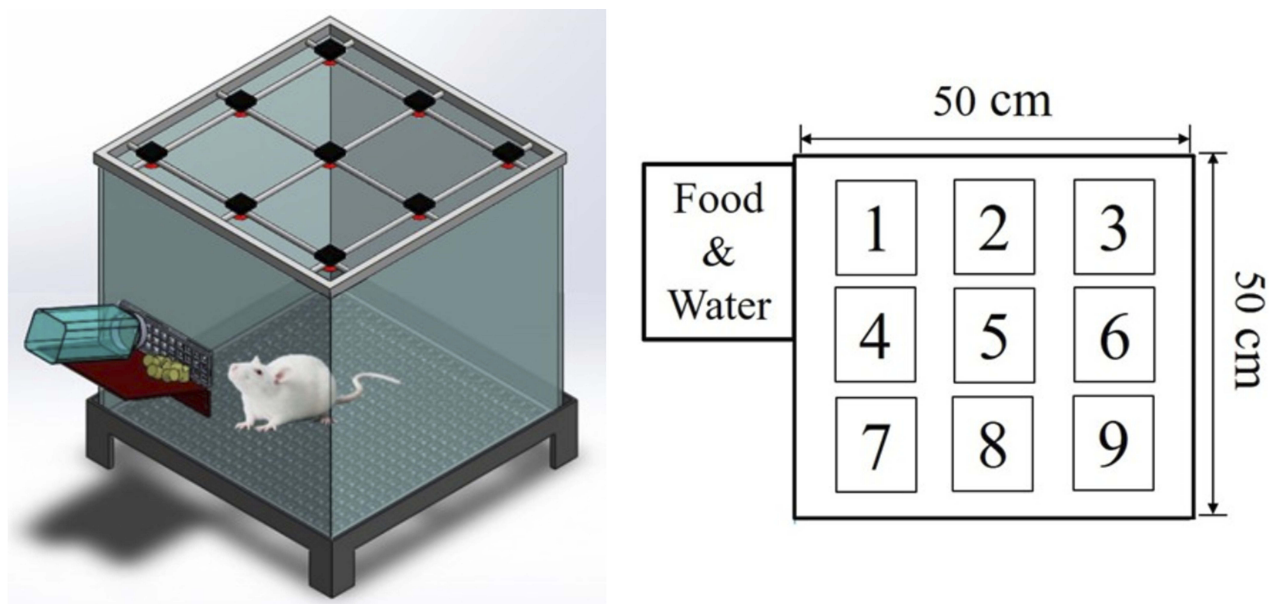
Figure 2 Schematic of the animal behavior cage.

diffusion-scan type photoelectric switch sensors with self-contained amplifiers (HP100-A1, Azbil Corp., Tokyo, Japan). The cage was sub-divided into nine symmetric areas, each with one sensor placed at the top of the cage with 16.7 cm between each sensor. Each sensor has the ability to scan up to 1 m of distance. As the rat moves, the corresponding "arriving" sensor will be triggered by activity and start recording the movement. The total triggered count was recorded on a personal computer equipped with an acquisition interface, with the entire monitoring process lasting 7 days.

Analysis of in vivo Levels of Doxycycline

In each group, the rats were divided into three sub-groups (N=3) and euthanized at 1.5 weeks, 3 weeks, and 6 weeks. At each time point, 1 mL of blood was sampled following the injection of 1 mL lidocaine to euthanize the rats. Meanwhile, tiny tissue near the membranes was also sampled. The levels of doxycycline in tissue and in blood were characterized by the HPLC assay. An additional six rats undergoing Achilles tendon repair with doxycycline-loaded nanofibrous membrane were euthanized on days 1 and 3 (three in each day). Through skin incision, Achilles tendon was also dissected and sampled. In each sub-group, one Achilles tendon sample was sent for histologic analysis and the other two tendon samples were sent for biomechanical analysis.

Biomechanical Test

The biomechanical properties of retrieved tendons were assessed with a Lloyd tensiometer (AMETEK, USA) equipped with a 100 N load cell, in a manner consistent with the ASTM D638 standard. Before testing, tendon was wrapped with gauze and immersed in normal saline solution in order to simulate the in vivo condition. During measurement, the repaired Achilles tendon was pulled by the top clamp at a rate of 60 mm/minute for a 10 cm distance before the clamp was returned to its starting point.

Histological Analysis

The harvested tendon for histological assay was fixed in 10% formalin and embedded in paraffin. The embedded tendon was cut into 4 μm frontal section and stained by hematoxylin and eosin (H&E) staining. An independent examiner completed the histologic interpretation at ×10 and ×20 magnification.

Statistical Analysis

The statistical analysis between groups was evaluated by a paired sample t-test using commercially available SPSS software (Version 12.0; SPSS Inc, Chicago, IL, USA). Data are expressed as mean ± SD (standard deviation), and the threshold for significance was established at a p-value of less than 0.05.

Results

Characterization of Electrospun Nanofibers

Doxycycline-embedded nanofibers were prepared using the electrospinning technique. Figure 3 shows the SEM images of the doxycycline-embedded and pure PLGA nanofibers, as well as the fiber size distributions. The calculated diameters were 1.07±0.73 μm and 104±25.8 nm for pure PLGA nanofibers and doxycycline-embedded nanofibers, respectively. The fiber diameter decreased significantly upon the addition of doxycycline.

Figure 4 shows the FTIR spectra of pure PLGA nanofibers versus doxycycline-embedded PLGA nanofibers. In the spectra of the drug-loaded nanofibers, a new vibration peak at 3400 cm^{-1} was observed and can be attributed to the N–H bonds of doxycycline. In contrast, the vibration at 1725 cm^{-1} (C=O bond) was increased upon drug loading. Furthermore, the absorbance peak at around 1300 cm^{-1} might be a result of the increase in C–O bonds in doxycycline.[23,24] The FTIR spectra analysis verified that the drugs were incorporated into the PLGA matrices successfully.

We observed that the water contact angles of pure PLGA and doxycycline-embedded nanofibers in Figure 5 were 138.3 ±3.5° and 85.6±5.2°, respectively. Furthermore, the addition of doxycycline increased the hydrophilicity of PLGA nanofibers.

The tensile test results in Figure 6 suggest that the maximum tensile strength and the elongation at the break of the pure PLGA and doxycycline-embedded nanofibers were 1.74±0.10 MPa (136.14%) and 4.90±1.18 MPa (94.39%), respectively. Moreover, the mechanical strength of the nanofibers increased with the incorporation of drugs, whereas the elongation at the break decreased.

In vitro and in vivo Release Profiles of PLGA/Doxycycline Nanofibrous Membrane

The daily and accumulated release profiles of doxycycline from the nanofibrous membranes in vitro are shown
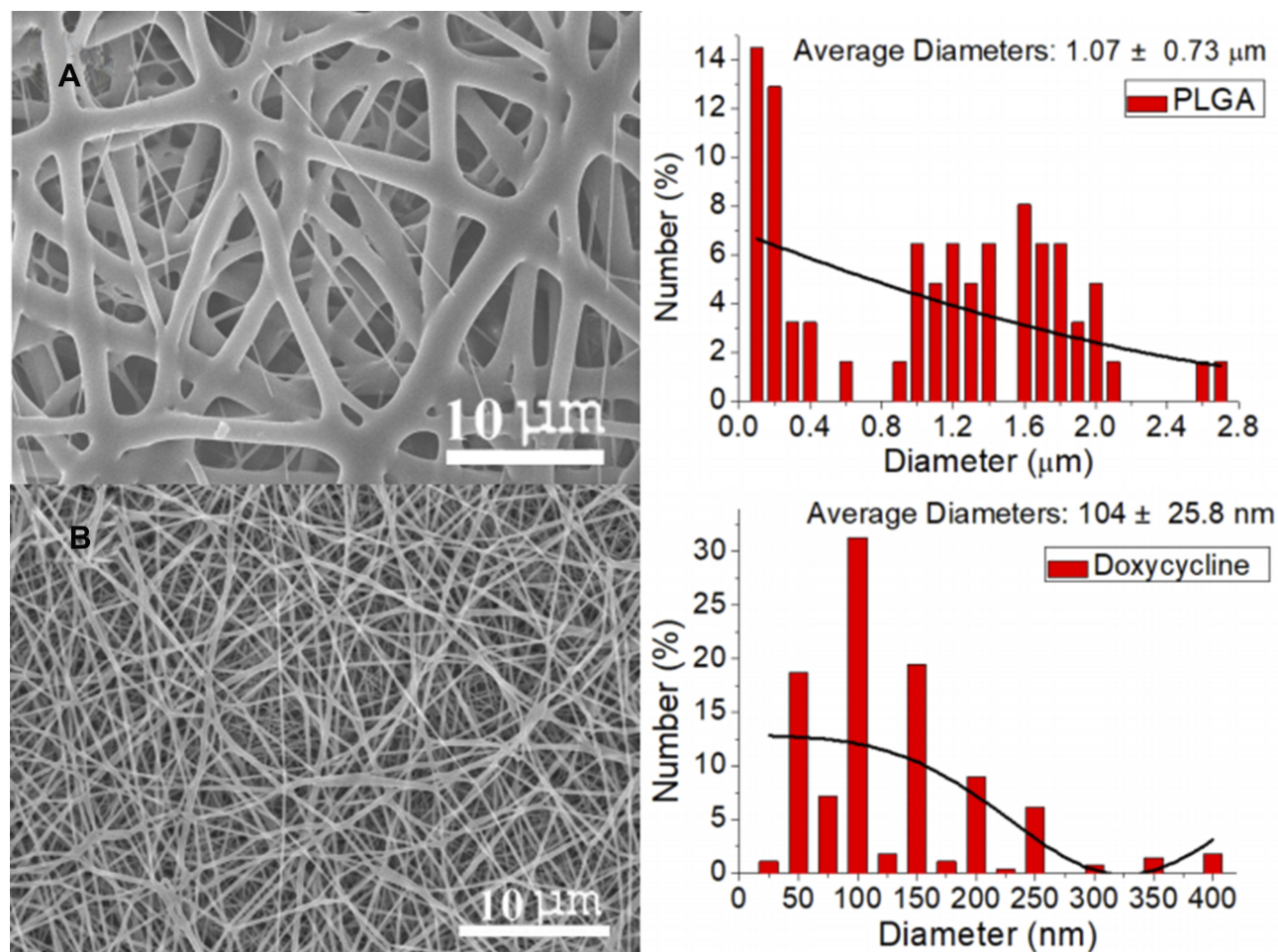

Figure 3 SEM images and fiber diameter distribution of electrospun (**A**) pure PLGA nanofibers and (**B**) doxycycline-loaded PLGA nanofibers.
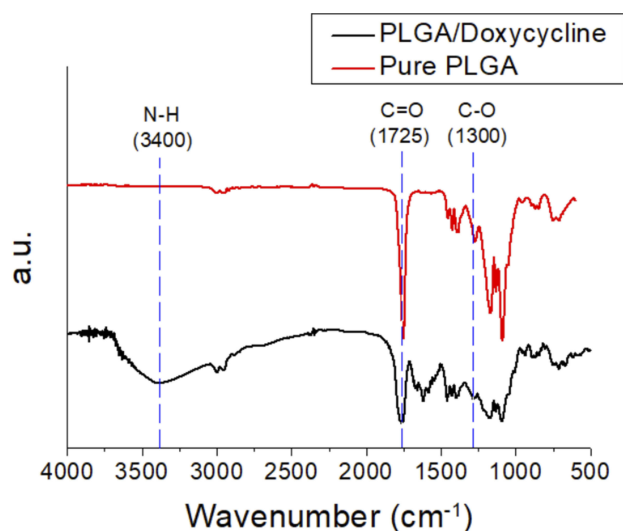
Figure 4 FTIR spectra of pure PLGA and drug-loaded PLGA nanofibers.

in Figure 7. The daily doxycycline release curve showed a high concentration released on day 1, and a second peak was observed on day 13 (Figure 7A). Meanwhile, the cumulative release profiles suggested that 21.1% of the doxycycline was released on day 1 and 58.3% was eluted on day 13 (Figure 7B). At 42 days (6 weeks), the accumulated released of doxycycline reached 69.6%. Overall, the PLGA/doxycycline nanofibrous membranes could provide sustained drug release for more than 40 days in vitro.

Figure 8 shows the in vivo release patterns of doxycycline in tissue near the nanofibers. A burst release was observed at day 1. After that, the doxycycline level decreased gradually with time. On the other hand, the release profile in blood exhibited similar pattern, but with much lower concentrations.

Animal Activity

The total activity counts for the control and doxycycline-treated groups over 7 days post-operation are shown in Figure 9. The total triggered counts recorded from the photoelectric switch sensors in doxycycline-treated and control groups were 12,977±10,223 and 9220±708, respectively. The total number of triggered counts was significantly greater in the doxycycline group than in the control group (P<0.05). Therefore, rats that underwent Achilles tendon repair with doxycycline-loaded biodegradable nanofibrous membrane demonstrated higher activity levels than those who received Achilles tendon repair alone.

Biomechanical Study

The rats were euthanized at 1.5, 3, and 6 weeks after surgery. Repaired tendons were cut from the musculotendinous junction proximally and bony insertion sites distally, and sent for biomechanical testing. In addition, healthy and normal tendons from the left leg were obtained for comparison. At 1.5 weeks (Figure 10A), the maximum strength levels of the tendons in both doxycycline and control groups were lower than those of the healthy tendons (P<0.01).

At 3 weeks (Figure 10B), the doxycycline group exhibited maximum tendon strength levels that were comparable with the healthy tendon group. The control group, which did not receive doxycycline-loaded nanofibrous membranes, had inferior maximum strengths compared to other two groups (P<0.05).

At 6 weeks (Figure 10C) post-operation, all three groups showed comparable tendon strengths (nonsignificant, P>0.05), while the doxycycline group exhibited a slightly larger value compared to the other groups. In conclusion, doxycycline-loaded nanofibrous membrane can significantly improve tendon healing at 3 weeks, and to a lesser extent at 6 weeks, post-surgery.

Histology Study

There was no obvious difference between two groups in tendon cell organization and cellularity at 3 weeks post-surgery. However, there was only mild inflammation with a few mononuclear inflammatory cells noted (Figure 11A). On the contrary, severe inflammation was observed in the control group (Figure 11B).

Discussion

Achilles tendon rupture commonly occurs in athletes and individuals performing leisure activities. The spectrum of Achilles tendon injuries varies from tendonitis to partial tear and eventually complete rupture. Treatment options for an Achilles tendon rupture range from non-operative brace protection to surgical repair. The different treatment choices to each patient are dependent on their age, general medical condition, and desired function of activity. Non-surgical treatment includes initial brace or cast protection for months, then followed by gentle passive range of motion rehabilitation and muscle strengthening. For those with young age or high functional demand, surgery is indicated. Most surgical procedures are primary repair of the ruptured Achilles tendon. A curved or straight longitudinal skin incision is made medial to the Achilles
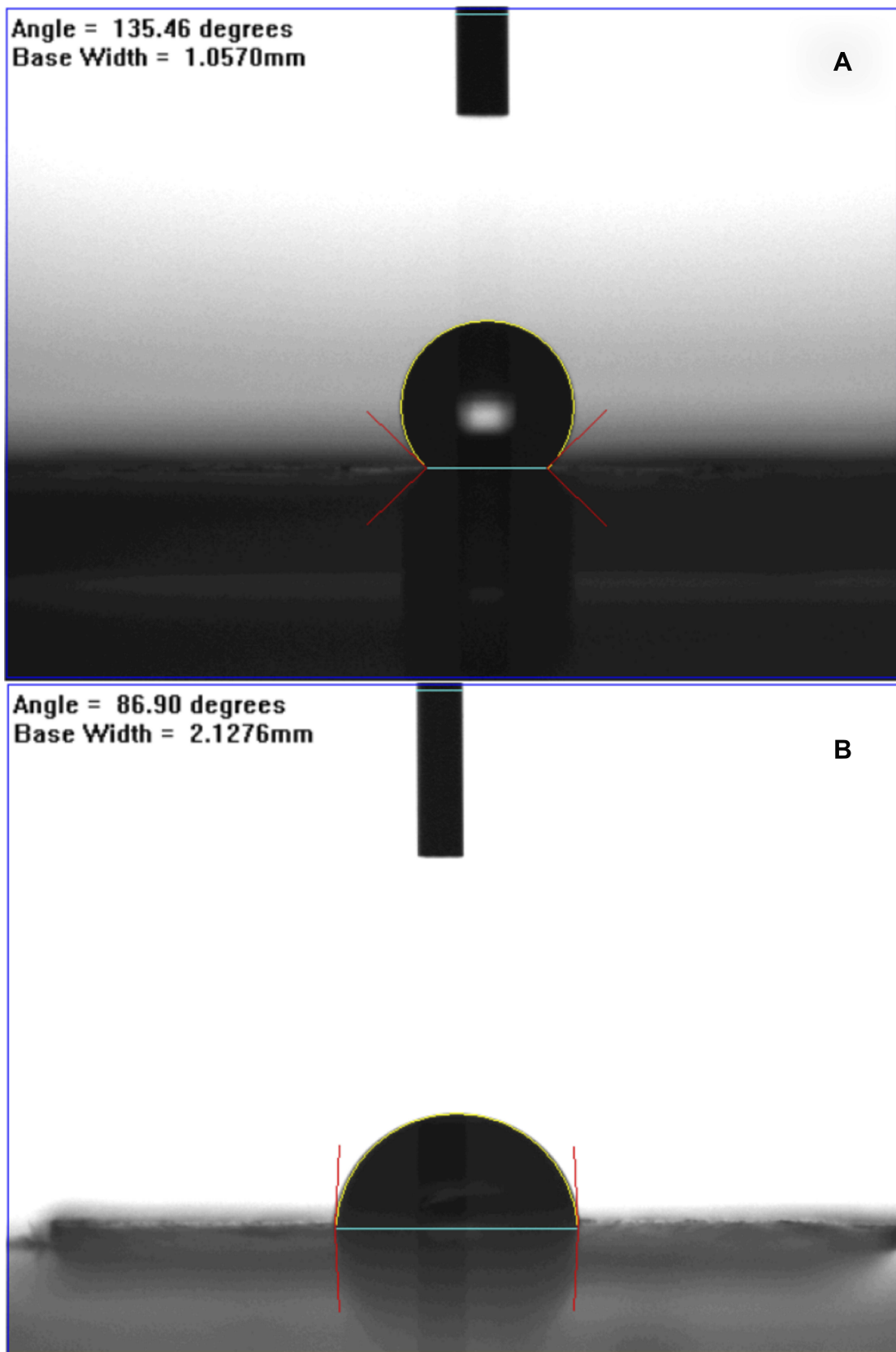
Angle = 135.46 degrees
Base Width = 1.0570mm

A

Angle = 86.90 degrees
Base Width = 2.1276mm

B

Figure 5 Water contact angle of (**A**) pure PLGA nanofibers (138.3±3.5°) and (**B**) doxycycline-loaded PLAG nanofibers (85.6±5.2°).
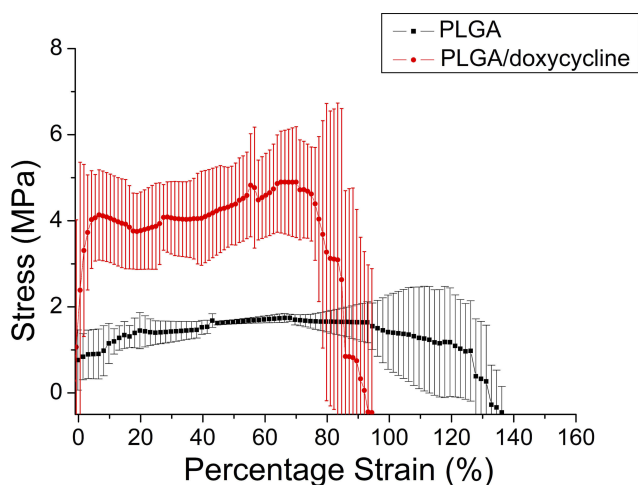
Figure 6 Tensile test results of PLGA nanofibers and doxycycline-loaded PLGA nanofibers (maximum strengths: PLGA nanofibers 1.74±0.10 MPa, doxycycline-loaded PLGA nanofibers 4.89±1.18 MPa).
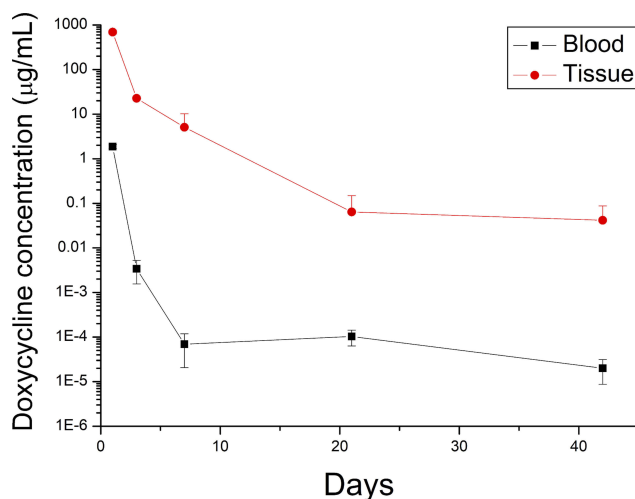

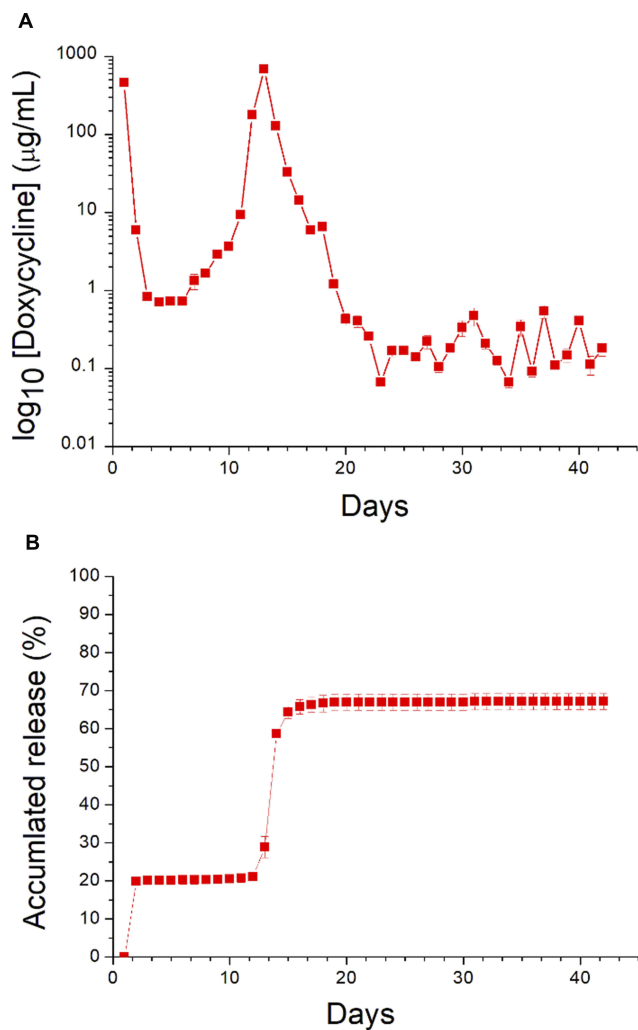**Figure 8** In vivo release profiles of doxycycline in tissue and in blood.

Figure 7 In vitro (**A**) daily and (**B**) accumulated release of doxycycline from the nanofibers.

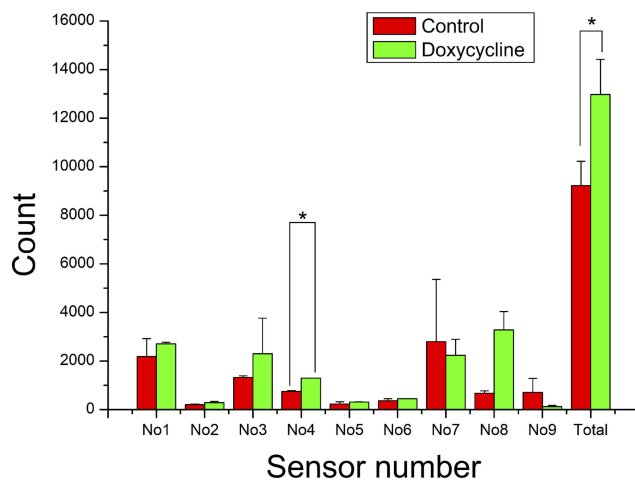**Figure 9** Activity counts of the rats (*P<0.05).

tendon. Deep dissection into the subcutaneous tissue gently and identify both ends of the ruptured tendon. Clamps are used to approximate each ends together then primary repair of the tendon is performed by suturing two ends of the tendon together using a variety of different stitching techniques. In addition to the traditional open surgery, a minimal invasive technique has also been used to reduce the risk of complications during wound healing. The type of surgery and repair techniques used will depend on the surgeon, the type of rupture, and tissue quality.

Complications following Achilles tendon rupture are not uncommon. Among them, re-rupture of tendon is most widely seen. Re-rupture rate of the Achilles tendon after surgical repair is around 1.7–5.6%.[28] Wound dehiscence and infection are also commonly seen complications after
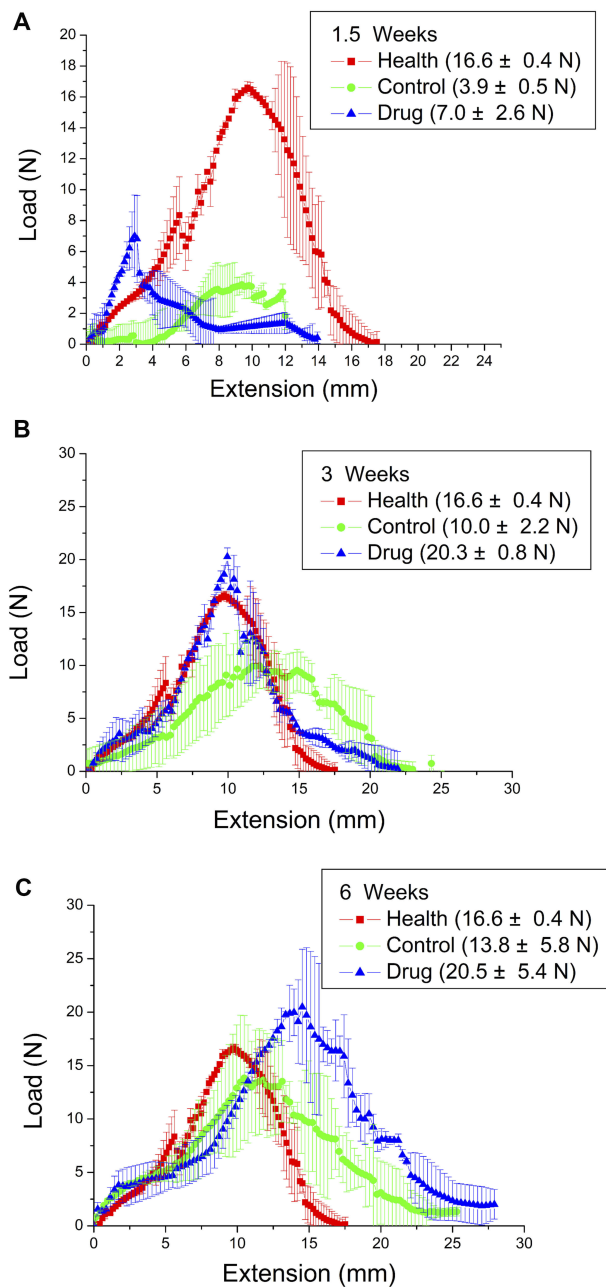
Figure 10 Mechanical strength of tendons at (**A**) 1.5, (**B**) 3, and (**C**) 6 weeks post-surgery.

Figure 11 H&E stain of Achilles tendon in the (**A**) doxycycline group and (**B**) control group, at 3 weeks post-surgery (scale bar: 250 μm).

surgical intervention. Surgical treatment of Achilles tendon ruptures is reported to have lower rates of re-rupture compared to non-operative treatment, despite the risk of adverse events such as wound dehiscence and infections.[29]

The risk of wound-related complications, such as infection or dehiscence of wound, can be minimized through minimal invasive technique or even arthroscopic surgery.[28] In contrast, the issue of poor tendon healing and re-rupture is difficult to address. Sufficient initial mechanical stability of repaired tendon can be achieved through various suture
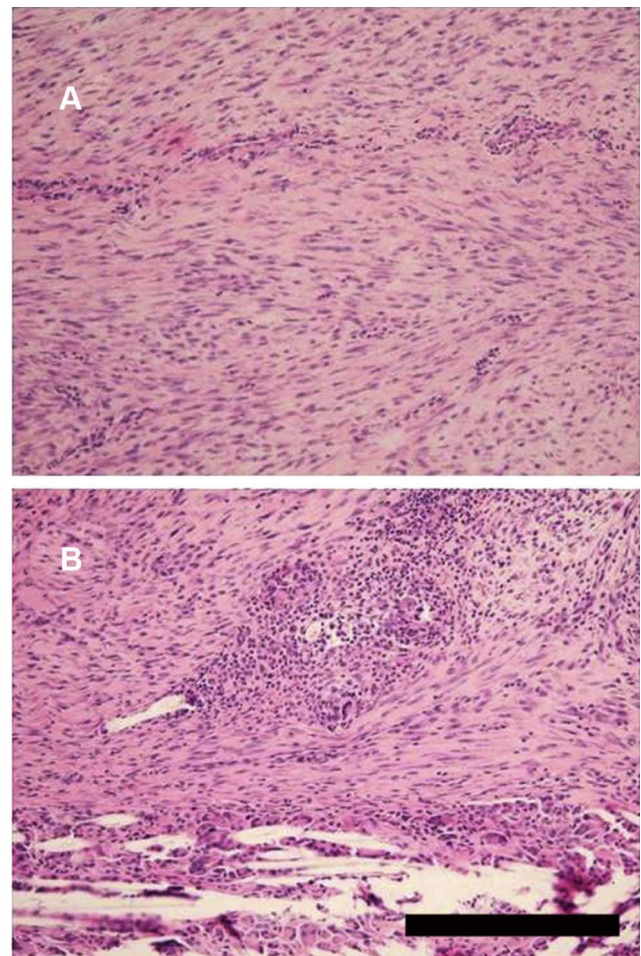
techniques. Due to the relatively deficient vascularity around the Achilles tendon, poor tendon healing may result in tendon re-rupture. Various agents have been proposed and employed to improve tendon healing, including platelet-rich-plasma (PRP),[29] mesenchymal stem cells,[30,31] simvastatin[32] and doxycycline.[21]

Matrix metalloproteinases (MMP) have been reported to play an important role in tendon healing process.[16,33,34] Increased MMP activity is associated with deterioration of collagen quality after tendon rupture.[35–37] Doxycycline is considered as the most potent MMP inhibitor among tetracyclines group and has various clinical applications.[38–41] Several previous studies had demonstrated the effect of doxycycline in enhancing Achilles tendon repair. In 2007, Pasternak et al[42] showed that improved suture-holding capacity occurs in rats with Achilles tendon sutures who have been administered systemic doxycycline (100 mg/kg/day). Furthermore, the authors also demonstrated that sutures

coated with doxycycline had improved suture-holding capacity at 3 days after surgery. Nguyen et al[21] used oral administration of 10 mg/kg doxycycline in a rat model of Achilles tendon laceration. The authors concluded that oral administration of doxycycline accelerates matrix remodeling and enhances biomechanical properties of surgical repaired Achilles tendon. The enhancements were observed most significantly at 3 to 6 weeks after operation.

However, the exact mechanism of doxycycline in the healing process of Achilles tendon remains controversial. A negative effect of doxycycline on Achilles tendon healing was also reported by Pasternak et al.[43] In their study, the Achilles tendon was transected and left unrepaired. They found significantly decreased mechanical strength at 5, 8, and 14 days after transection of Achilles tendon in rats when doxycycline was given orally at the dosage of 130 mg/kg body weight/day. The biomechanical tests were performed until 2 weeks after surgery; however, no data were available later than 2 weeks post-operation.

Biodegradable polymers can be applied for the delivery of drugs in a controlled and targeted manner. We adopted the PLGA as the material for scaffolding and the delivery vehicle for doxycycline. PLGA is one of the most characterized biodegradable copolymers that decomposes to non-toxic products (H_2O and CO_2) during the degradation process. In the development of devices for controlled delivery of proteins, small molecules, and other macromolecules, PLGA has been studied extensively.[44] Local drug therapy with pharmaceuticals incorporated within the implants possess the benefit of delivering high concentration of drug directly to the target site with extremely low drug concentration systemically, thus minimizing associated side effects. Additionally, the highly porous scaffold is able to accommodate mammalian cells and guide their growth and tissue regeneration in three dimensions. The incorporation of doxycycline increased the hydrophilicity of PLGA nanofibers, which in turn help promote the healing of tendons. It has been reported[45] that human skin fibroblasts showed significantly higher proliferation on electrospun PLGA fiber matrices possessing fiber size in the range of 350–1100 nm. Despite the diameter of the doxycycline-incorporated nanofibers in this study (range of 80–130 nm) is less than the reported optimum value, the electrospun nanofibrous scaffolds show good capability in promoting tendon healing.

This study exploited doxycycline-embedded nanofibrous membranes that provide local and sustainable release of drugs to the target site for tendon repair. The results presented here highlight that the doxycycline-embedded nanofibrous membranes exhibit a three-stage drug-release process in vitro, namely a primary blast at day 1, steady release thereafter until day 12, at which point a second peak was observed, followed a steadily diminishing release for more than 40 days. In general, drug release from a pharmaceutical-embedded biodegradable device can be divided into three phases, including a burst liberation, a diffusion-dominated elution, and a degradation-dominated release. After the electrospinning process, most drugs are dispersed into the volume of the PLGA/doxycycline membranes. However, a few pharmaceutical compounds located on the surface of nanofibers may result in initial burst release of medication. Following the initial burst, the drug-release profiles were mainly dominated by diffusion. A relatively constant slow elution of doxycycline was thus observed. Finally, the drug-loaded nanofibers swell due to the water absorption during elution, leading to disruption of the polymer matrix to form openings for doxycycline release. Consistent with this, a second peak was observed at day 12. From day 12 onwards, the liberation rate of doxycycline decelerated gradually.

The in vivo release profile differed from that of in vitro release, and we observed a burst of liberation followed by a gradually diminishing release profile. This might be due to the fact that in vivo metabolism is slower than that in the glass tube. Meanwhile, the levels of drug in the blood remained much lower, which in turn resulted in minimal side effects. Most importantly, our in vivo analysis demonstrated that the biodegradable drug-embedded nanofibers resulted in sustained liberation of doxycycline for more than 40 days, which would be advantageous for promoting tendon healing.

Both the animal activity and the mechanical strength tests suggested that rats who received doxycycline-embedded nanofibrous membranes showed superior outcome than the control rats. Additionally, the nanofibers significantly enhanced the biomechanical strength of tendons at 3 weeks post-surgery in a rat model with Achilles tendon laceration. In other words, doxycycline embedded nanofibrous membranes improved tendon healing most significantly at mid-term and this result is similar to oral administration of doxycycline.[21] This also highlights that doxycycline, when administered locally, promotes healing of the Achilles tendon.

Several limitations existed in our study. First, we did not examine the dose-dependent effects of various doxycycline concentrations loaded onto nanofibrous membranes and further studies will be needed to elucidate these effects. Second, Achilles tendon rupture in humans

mainly results from repetitive micro-trauma to the tendon. Moreover, the quality of tendon cell differs from that of the Achilles tendons surgically excised in our experiment. Third, there were only control group and doxycycline loaded with PLGA nanofibrous membrane group. There was no pure PLGA group proving that there is no effect on tendon healing of PLGA. Future studies may be needed to further clarify the mechanism and role of doxycycline in the repair of Achilles tendon rupture.

Conclusion

In this work, we fabricated biodegradable doxycycline-embedded nanofibrous membranes and evaluated their efficacy in Achilles tendon repair, utilizing PLGA as the delivery vehicle. The in vitro release patterns of doxycycline were evaluated by HPLC. A rat model of Achilles tendon rupture was created and used for the in vivo efficacy assessment of drug-eluting nanofibers. The empirical results revealed that PLGA nanofibers eluted effective concentrations of doxycycline for more than 40 days post-surgery and the systemic drug concentration in plasma was low. Rats receiving implantation of doxycycline-loaded nanofibers were more active and had stronger tendons post-operation. Nanofibers loaded with doxycycline, therefore, display great potential for the repair of Achilles tendon rupture.

Acknowledgements

Disclosure

The authors declare that there are no conflicts of interest in this work.

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