P19

# The efficacy of sustained releasable PDGF-microsphere for the treatment of rotator cuff tendinopathy

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## Introduction

Degeneration as well as healing of the rotator cuff can be occurred in three stages: (1) inflammatory phase, (2) repairing phase and (3) remodeling phase. Platelet-derived growth factor (PDGF) plays a significant role in promoting chemotaxis, cell proliferation, extracellular matrix (ECM) production, surface integrin expression, and revascularization in fibroblasts. Previous studies demonstrated that PDGF treatment improved the biochemical, structural, and biomechanical properties in animal of tendon or ligament healing. In this study, porous microspheres (PMSs) were fabricated by a fluidic device. To impregnate PDGF on PMSs, heparin-dopamine (Hep-DOPA) was anchored on PMSs. PDGF was impregnated on Hep-PMSs. The effects of PDGF/Hep-PMSs were demonstrated by tissue amelioration in collagenase-induced rotator cuff rabbit model after local injection of PDGF/Hep-PMSs.

## Methods

To create collagenase-induced rotator cuff tendinitis in rabbits, rabbits undergone anesthesia with isoflurane. Under anesthetization, 50 μL of collagenase type I [50 mg/mL dissolved in PBS (pH 7.4)] was injected into near the supraspinatus tendon. Rabbits were euthanized at 4th weeks after injections of PMSs, PDGF/PMSs, PDGF/Hep-PMSs, and PDGF solution for further analysis. Experimental groups were divided into six treatment groups: (I) control (no treatment), (II) Col (I) (collagenase treatment), (III) Col (I) + PMSs, (IV) Col (I) + PDGF, (V) Col (I) + PDGF/PMSs, and (VI) Col (I) + PDGF/Hep-PMSs. To demonstrate the anti-inflammatory effects after each group injection, pro-inflammatory cytokines (MMP-3, MMP-13, COX-2, IL-1, IL-6, and TNF-α) and anti-inflammatory cytokines (IL-4, IL-10, and IL-13) were measured at 4th weeks after injection of each group and PDGF. To confirm the tendon healing of rotator cuff tendinitis after PDGF/PMSs injection, collagen contents on rotator cuff were measured by hydroxyproline assay kit. For histological evaluations, the specimens isolated from rabbit were fixed. The sliced tissue samples were stained with Masson's trichrome to confirm the rotator cuff healing.

## Results

In the tendons injected with PDGF as a positive control, some collagen fibers could be showed. Moreover, collagen fibers seemed to be better organized in the PDGF/PMSs-injected tendons compared with PMSs. Furthermore, collagen fibers were neater and much more aligned in the PDGF/Hep-PMSs-injected tendons. PDGF/Hep-PMSs not only markedly decreased mRNA levels of pro-inflammatory cytokines (MMP-3, MMP-13, COX-2, IL-1, IL-6, and TNF-α) but also significantly increased mRNA levels of anti-inflammatory

cytokines (IL-4, IL-10, and IL-13) in tendon tissues. PDGF/Hep-PMSs also provide improved tendon amelioration by increasing the collagen content.

**Conclusion**

PDGF-impregnated Hep-PMSs are a promising therapeutic injectable material to control the degenerative tendon disorder and the pain associated with it.
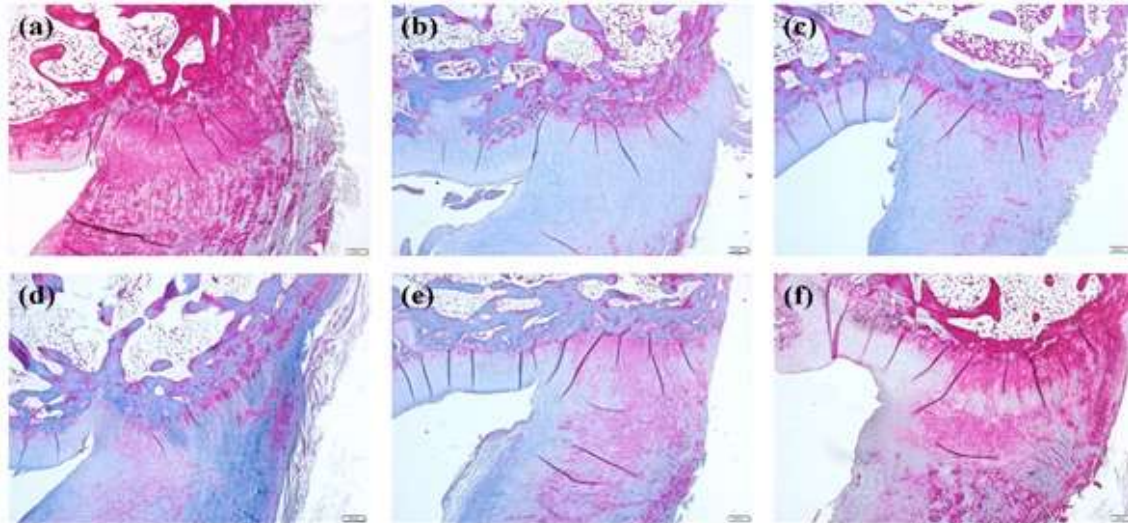


Masson's trichrome staining 5 weeks after collagenase [Col (I)] injection into tendon tissues, and 4 weeks after injection of PMSs, PDGF, PDGF/PMSs, and PDGF/Hep-PMSs. Groups were divided into six treatment groups: (a) control (no treatment), (b) Col (I) (collagenase treatment), (c) Col (I) + PMSs, (d) Col (I) + PDGF, (e) Col (I) + PDGF/PMSs, and (f) Col (I) + PDGF/Hep-PMSs.
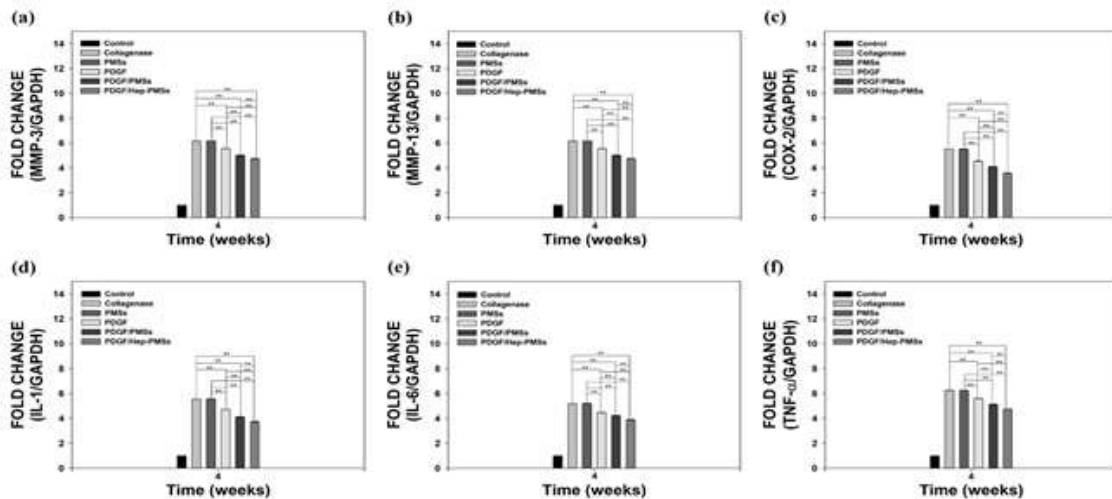


The relative mRNA levels of pro-inflammatory cytokines, including: : (a) MMP-3, (b) MMP-13, (c) COX-2, (d) IL-1, (e) IL-6 and (d) TNF-α in tendon tissues from a collagenase-induced rotator cuff tendinitis rabbit model in each group at 4th weeks after injections of PMSs, PDGF, PDGF/PMSs, and PDGF/Hep-PMSs. Each mRNA expression level was determined using real time-PCR analysis. Error bars represent the means ± SDs (n = 5). (*P < 0.05 and **P < 0.01).
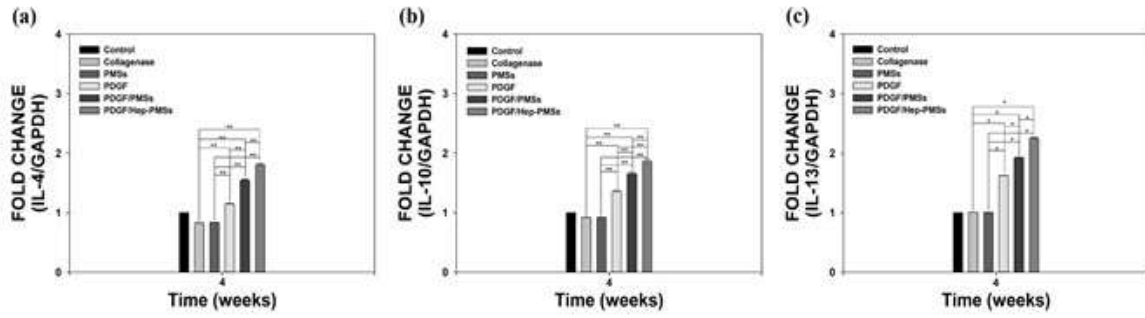
The relative mRNA levels of pro-inflammatory cytokines, including: (a) IL-4, (b) IL-10, and (c) IL-13 in tendon tissues from a collagenase-induced rotator cuff tendinitis rabbit model in each group at 4th weeks after injections of PMSs, PDGF, PDGF/PMSs, and PDGF/Hep-PMSs. Each mRNA expression level was determined using real time-PCR analysis. Error bars represent the means ± SDs (n = 5). (*$P < 0.05$ and **$P < 0.01$).