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Basic Science

Fibrin-genipin annulus fibrosus sealant as a delivery system for anti-TNFα drug

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Abstract

BACKGROUND CONTEXT: Intervertebral discs (IVDs) are attractive targets for local drug delivery because they are avascular structures with limited transport. Painful IVDs are in a chronic inflammatory state. Although anti-inflammatories show poor performance in clinical trials, their efficacy treating IVD cells suggests that sustained, local drug delivery directly to painful IVDs may be beneficial.

PURPOSE: The purpose of this study was to determine if genipin cross-linked fibrin (FibGen) with collagen Type I hollow spheres (CHS) can serve as a drug-delivery carrier for infliximab, the anti-tumor necrosis factor α (TNFα) drug. Infliximab was chosen as a model drug because of the known role of TNFα in increasing downstream production of several pro-inflammatory cytokines and pain mediators. Genipin cross-linked fibrin was used as drug carrier because it is adhesive, injectable, and slowly degrading hydrogel with the potential to seal annulus fibrosus (AF) defects. CHS allow simple and nondamaging drug loading and could act as a drug reservoir to improve sustained delivery.

STUDY DESIGN/SETTING: This is a study of biomaterials and human AF cell culture to determine drug release kinetics and efficacy.

METHODS: Infliximab was delivered at low and high concentrations using FibGen with and without CHS. Gels were analyzed for structure, drug release kinetics, and efficacy treating human AF cells after release.

RESULTS: Fibrin showed rapid infliximab drug release but degraded quickly. CHS alone showed a sustained release profile, but the small spheres may not remain in a degenerated IVD with fissures. Genipin cross-linked fibrin showed steady and low levels of infliximab release that was increased when loaded with higher drug concentrations. Infliximab was bound in CHS when delivered within FibGen and was only released after enzymatic degradation. The infliximab released over 20 days retained its bioactivity as confirmed by the sustained reduction of interleukin (IL)-1β, IL-6, IL-8, and TNFα concentrations produced by AF cells.

FDA device/drug status: infliximab. Approved by the FDA for other indications; fibrin-genipin mixture. Fibrin is approved but the mixture of fibrin with genipin is investigational; collagen hollow spheres. investigational.

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The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

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CONCLUSIONS: Direct mixing of infliximab into FibGen was the simplest drug-loading protocol capable of sustained release. Results show feasibility of using drug-loaded FibGen for delivery of infliximab and, in the context with the literature, show potential to seal AF defects and partially restore IVD biomechanics. Future investigations are required to determine if drug-loaded FibGen can effectively deliver drugs, seal AF defects, and promote IVD repair or prevent further IVD degeneration in vivo.

Keywords: Intervertebral disc; Annulus fibrosus repair; Biomaterials; Anti-inflammatory drug; Drug delivery; Spinal injection

Introduction

Regenerative repair of degenerated intervertebral discs (IVDs) is a clinical challenge because of the large spinal loading that must be resisted immediately after repair and the chronic inflammatory environment of injured and degenerated IVDs [1–3]. Intervertebral discs have limited self-repair capabilities after traumatic injuries or degenerative damage, and unrepaired ruptures can lead to accelerated IVD degeneration that is implicated as a source of low back pain [1,2,4]. The patterns of IVD pathology are distinct between degenerative disc disease and IVD herniation [5] with few treatments available for either condition. Herniated IVDs are more amenable to IVD repair as they often involve annulus fibrosus (AF) injury in an otherwise ''healthy'' IVD [1]. Tears and fissures of the AF can progress to herniations that interact mechanically and chemically with spinal nerves and tissues to induce painful conditions [1,6–9]. Microdiscectomy surgery to remove the prolapsed tissue responsible for painful conditions is effective at resolving acute pain from herniation [10]. However, herniation with or without microdiscectomy likely leads to accelerated IVD degeneration [11], which may be because of increased inflammation and altered biomechanics associated with the unrepaired AF defects [2,12,13]. Repair of the AF is required to restore the IVD structure and normal function; yet, effective IVD repair strategies remain an unmet clinical need [1,2,14,15]. We believe that microdiscectomy procedures can be improved with the development of effective strategies that are capable of repairing the AF, sealing the IVD, and providing local delivery of therapeutic drugs directly to the IVD. Determining the repair capacity of injured human AF requires the development of novel biomaterials and effective repair strategies to be tested using animal models and clinical studies. This study focuses on biomaterial development for drug delivery.

Pro-inflammatory cytokines have an important role in all aspects of IVD disease including pain and are a relevant therapeutic target [3,16]. Tumor necrosis factor α (TNFα) and IL-1β increase with severity of disease [17,18], and TNFα upregulates pain-related proteins [19]. TNFα is prominently implicated in injured and diseased human IVDs because it increases downstream production of pro-inflammatory cytokines (IL-1β, IL-6, and IL-8) and propagates matrix-degrading enzymes and pain mediators [19–22].

Anti-inflammatory cytokines exhibited strong potential to ameliorate structural damage and mitigate neuropathic pain in cell, organ culture, and animal models but have not provided consistent results in human clinical trials directed at alleviating the symptoms of back or radicular pain associated with IVD pathologies [3]. In human trials, a TNFα-blocking agent was intravenously injected to treat disc herniation–induced sciatica; yet, there was no improvement in conditions compared with placebo treatment [23,24]. In contrast, local delivery of anti-TNFα drug for sciatica via epidural administration or subcutaneous injection was effective in reducing pain with no observed adverse side effects [25] and also reduced the long-term need for surgery [26]. In another study, epidural delivery of anti-TNFα was less effective than epidural steroidal treatments in improving pain in a multicenter trial, although no statistically significant differences were detected and the authors noted that it was impossible to conclude whether a TNFα inhibitor delivered for longer times or at higher doses could have been more effective [27]. In an in vivo experimental study in rats, lumbar disc puncture through the AF induced pain-associated behavioral changes, which were decreased with local infliximab delivery to the IVD [28]. Systemic drug administration for back pain is often not effective, which is likely because of the poor transport environment inhibiting delivery of drugs into the IVDs or because of rapid absorption from the epidural space [4,16,29]. Therefore, local drug delivery to the IVD may offer more promise. We believe that the mixed results in clinical trials are related to the lack of sustained delivery of drugs at appropriate dose to the painful IVD and may also be associated with assessments of pain alone without evaluation of IVD degeneration and the inherent causes of that pain.

Local delivery of anti-inflammatories to the IVD shows some promise; yet, few technologies are available for such delivery. Interleukin-1 receptor antagonist delivery to agarose-based engineered nucleus pulposus constructs in vitro was able to inhibit degradation from IL-1β, with decreased messenger RNA expression and activity of catabolic enzymes and pro-inflammatory cytokines, improved