Intra-articular controlled release of anti-inflammatory siRNA with biodegradable polymer microparticles ameliorates temporomandibular joint inflammation

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1. Introduction

Temporomandibular joint (TMJ) disorders are a common and heterogeneous group of diseases that cause painful, progressive joint degeneration that restricts daily activities, including talking and chewing [1]. In severe TMJ degeneration, oral medications are often insufficient for pain relief, and thus intra-articular injections of corticosteroids or hyaluronic acid are necessary to treat pain. However, these intra-articular injections are complicated by rapid clearance of injected agents, which necessitates frequent injections that carry a high risk of iatrogenic injury [1,2]. These limitations have motivated research into the development of novel therapeutics, including sustained release delivery systems, to alleviate severe TMJ pain.

Recently, inflammatory cell signaling via the immunoglobulin type G (IgG) cell-surface Fc receptor (FcγRIII, also known as CD16) has been implicated as a significant factor in painful TMJ inflammation [3]. Silencing of FcγRIII signaling via intra-articular injection of a solution of small interfering RNA (siRNA) targeting FcγRIII, using poly(ethyleneimine) (PEI) as a transfecting agent, showed promising results in a rat model of TMJ inflammation for 2 days [3]. However, as with the corticosteroid injections currently used in humans, a major challenge for intra-articular delivery of siRNA is the lack of a method for intra-articular sustained release [4,5].

Motivated by these results, we have been developing an intra-articular controlled release system for the rat TMJ based on biodegradable poly(3-lactic-co-glycolic acid) (PLGA) microparticles (MPs). Several studies have demonstrated that PLGA MPs are effective for in vitro controlled release of siRNA [6–8], including sustained release of polyplexes consisting of siRNA together with the transfecting agent PEI [8], but few in vivo studies of siRNA release from PLGA MPs exist in the literature. One report has described the efficacy of PLGA-based MPs in delivering siRNA to treat tumors in vivo [7]. We have previously shown that non-drug-loaded PLGA MPs are biocompatible in vivo in the rat TMJ [9].

In a continued effort to develop an intra-articular controlled release system for the rat TMJ, this work reports the in vivo thera-