Therapeutic Efficacy and Tribological Performance of Shape-Defined MicroPlates in Osteoarthritis

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ABSTRACT INTRODUCTION: Osteoarthritis (OA) is the most common form of arthritis and chronic degenerative joint disease. It is characterized by subchondral bone sclerosis, synovial membrane inflammation, and progressive cartilage degradation. All these alterations result in chronic pain, functional loss, and, eventually, permanent disability [1]. Currently, there is no disease-modifying drug available to reverse the progression of the OA, and conventional therapies provide only a temporary relief from the symptoms. Intra-articular injections of both small and macromolecules are commonly prescribed to alleviate symptoms, but their efficacy is severely impaired by their rapid clearance from the joint space. In this context, the development of drug delivery systems that can act as biomaterial deposits represents a promising strategy for OA management. Following this line of thought, the authors applied a top-down approach to develop shape-defined poly(D,L-lactide-co-glycolide) microPLates (PLGA μPL) for the intra-articular delivery of the anti-inflammatory molecule dexamethasone (DEX) and matrix metalloproteinase 13 (MMP-13) RNA interference nanoparticles (siNPs). Since MMP13 is upregulated in OA and degrades the cartilage structural protein type II collagen, its inhibition may be an effective and broadly useful disease-modifying OA drug [2,3].

METHODS: A thorough characterization of the physical-chemical and mechanical properties of μPL was conducted. The therapeutic efficacy was assessed in a post-traumatic osteoarthritis murine model, whereas the tribological behavior was investigated using a customized two-axis tribometer, where the microparticles were suspended within artificial synovial fluid and squeezed between two rigid surfaces (Teflon on glass) during sliding.

RESULTS SECTION: μPL presented a well-defined square shape with a 20 μm edge length and a 10 μm height, and a stiffness of 3.1 ± 0.9 MPa (Figure 1a). Both μPL formulations (DEX-μPL and siNP-μPL) provided a sustained release over a period of 30 days in a confined environment, biomimicking the synovial cavity. In vivo, a single injection of DEX-μPL decreased the expression of IL-1β, TNF-α, IL-6 and MMP-13 approximately by half compared to free DEX at 4 weeks post-treatment (Figure 1b). Also, siNP-μPL reduced MMP13 gene expression and protein production (Figure 1c), and alleviated articular cartilage degradation/fibrillation, meniscal deterioration, synovial hyperplasia, osteophytes, and pro-inflammatory gene expression. Finally, tribological studies showed that the friction coefficient (static and dynamic) was not significantly affected by the microparticles’ presence at low concentrations. Under these conditions, μPL could protect the surface of the articular cartilage, acting as cushions.

DISCUSSION: PLGA μPL realized the controlled and sustained delivery of different therapeutic molecules involved in the treatment of OA, including DEX and siRNA against MMP13. In a post-traumatic OA model, the intra-articular injection of μPL reduced the MMP13 gene expression and ameliorated local inflammation for at least 1 month. This work continues to motivate the development of microparticles for OA treatment and management.

SIGNIFICANCE/CLINICAL RELEVANCE: μPL were demonstrated for the sustained delivery of a variety of disease-modifying OA drugs, for conventional anti-inflammatory intervention as well as RNA therapy. One single intra-articular deposition of μPL was sufficient to ameliorate key OA markers for at least 1 month, including cartilage degradation, synovial hyperplasia, osteophyte formations, and inflammation.


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Figure 1. a. False-color SEM image of a μPL (red) deposited and not internalized over a layer of ATDC5 cells; b. In vitro expression of IL-1β, TNF-α, IL-6, and MMP-13 measured by TaqMan®PCR (for each treatment groups n = 6, while for the healthy group n = 4); c. MMP13 gene expression in combined cartilage and synovium over time after a single siMMP13-μPL treatment in mouse PTOA model.