INTRODUCTION

Osteoarthritis (OA) is the most prevalent joint disease and a common cause of pain, functional loss, and disability in older adults. It results from a combination of biomechanical factors and genetic predisposition, affecting the whole joint. In addition to macroscopic features, such as cartilage degradation, subchondral bone remodeling and osteophytes formation, joint capsule hypertrophy, OA is characterized by several cellular and molecular alterations resulting in a chronic low-grade inflammation. Nowadays, there is no treatment for curing this chronic disease by halting or reversing its progression. The only therapeutic options can provide transient relief from the symptoms and allow enhancing temporarily joint mobility and function and joint replacement continues to be ultimately the sole option.

A top-down approach was employed for synthesizing shape-defined PLGA microplates (µPLs)1,2 for the sustained release of anti-inflammatory molecules, dexamethasone (DEX) and matrix metalloproteinase 13 (MMP-13) RNA interference nanoparticles (siMMP-13-NPs). µPLs, square prisms of 20 x 10 x 10 μm size, were made out of 15 mg of PLGA (Fig. 1).

RESULTS

The anti-inflammatory activity of DEX-loaded µPLs was tested in vitro on LPS-stimulated chondrocytes (ATDC5). Results demonstrated that DEX-µPLs reduced the expression of pro-inflammatory cytokines at stimulated ATDC5 at both concentrations tested (Fig. 4).

At the same time, the therapeutic efficacy of an intra-articular injection of DEX-µPLs in a murine overload injury model was assessed. Results showed that a single injection of DEX-µPLs decreased the expression of IL-1β, TNF-α, IL-6 and MMP-13 by approximately half compared to free DEX at 4 weeks post-treatment. DEX-µPL treatment also reduced load-induced histological changes in the articular cartilage and synovial tissues relative to saline or free DEX treated knees (Fig. 4).

siMMP-13-NPs µPLS PRELIMINARY CHARACTERIZATION

Finally, siMMP-13-NPs were efficiently loaded inside µPLs. At the same time, gene silencing efficiency was obtained by siMMP13-NPs released from µPLs for the whole duration of the study (5 weeks), perturbing ~50% silencing after 4 weeks.

CONCLUSIONS

Top-down fabrication strategy allowed us to synthesize shape-defined µPLs ensuring a sustained drug release for several weeks, to alleviate pain, inflammation, and favor tissue regeneration, and mechanical support of the joint, to minimize wear, cartilage laceration and improper bone remodeling.