MICROSCOPIC SHAPE-DEFINED POLYMERIC DEPOTS FOR PROLONGED AND LOCALIZED DELIVERY OF DEXAMETHASONE AND SIRNA NANOPARTICLES IN POST-TRAUMATIC OSTEOARTHRITIS

Martina Di Francesco [1], Sean K. Bedingfield[2], Valentina Di Francesco [1], Juan M. Colazo[2], Fang Yu[2], Daniele Di Mascolo, Craig Duvall[2], Paolo Decuzzi[1]

[1] Laboratory of Nanotechnology for Precision Medicine, Italian Institute of Technology – Genoa (IT). [2] Department of Biomedical Engineering, Vanderbilt University, Nashville, TN 37235, United States.

Background: 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.

Methods: Within this context, a top-down approach was employed for synthetizing shape-defined poly (D,L-lactide-co-glycolide) (PLGA) microPlates (μPLs) for local and sustained release of anti-inflammatory molecules, such as Dexamethasone (DEX) and matrix metalloproteinase 13 (MMP-13) RNA interference nanoparticles (siMMP13-NPs). Both formulations were physico-chemical and pharmacological characterized. Their therapeutic efficacy was assessed in a mechanically-induced OA mouse model (PTOA).

Results: μPLs (square prims of 20 ×10 μm size), made out of 15 mg of PLGA, exhibited a an apparent Young's modulus of ~ 3 MPa value of about of 3.1 ± 0.9 Pa, similar to that of cartilage. Also, they showed a high damping capability ($\tan\delta = 0.3$). Indeed, under confined conditions mimicking the joint capsule, this resulting formulation was able to guarantee a continuous drug release for several months, with ~20% of DEX released in 1 month. 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 on stimulated ATDC5 at both concentrations tested. At the same time, the therapeutic efficacy of an intraarticular 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. At the same time, gene silencing efficiency was obtained by siMMP13-NPs released from μPLs for the whole duration of the study (5 weeks), preserving 50% silencing after 4 weeks.

Conclusions: Top-down fabrication strategy allowed us to synthetize shaped-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