0214 Advanced treatment for arthritic diseases based on the capture and inactivation of interleukin-6 by biofunctionalized polymeric nanoparticles

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Arthritic diseases, such as osteoarthritis and rheumatoid arthritis, are associated with synovium inflammation (synovitis). Several pro-inflammatory cytokines, especially tumor necrosis factor-α (TNF-α) and interleukins (IL), are important mediators of inflammation and articular cartilage destruction, supporting a potential possibility of anticytokine therapy in these diseases. IL-6 is one of the key regulators of the inflammatory response. Thus, human monoclonal antibodies against IL-6 may prevent its action, and consequently reduce inflammation after intra-articular (IA) injection. Indeed, several clinical trials have already demonstrated positive outcomes over disease progression. Although these treatments are very attractive, they are associated with limited efficacy because of the rapid clearance of antibodies by the synovium. A solution to overcome this problem is using nanoparticles (NPs) as a substrate to protect and extend the action of the antibodies. Natural-derived polymers, like chitosan (Ch) and hyaluronic acid (HA), are biocompatible and biodegradable polysaccharides, being HA a natural component of the extracellular matrix of articular cartilage. Therefore, biodegradable polymeric NPs represent a good candidate for IA administration.

In the present work we propose natural biodegradable polymeric NPs biofunctionalized with immobilized antibodies that selectively capture and inactivate the pro-inflammatory cytokine IL-6, reducing synovium inflammation. Ch-HA NPs were successfully prepared by polyelectrolyte complexation and further stabilized through carbodiimide chemistry (ethyl(dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS)). The particle size and zeta potential of the NPs were optimized. Stable NPs with 121.8 ± 2.4 of particle diameter, 0.11 ± 0.01 of polydispersity index and +25.12 ± 1.86 mV of zeta potential were produced with 0.25 mg/mL of initial polymers concentrations, at pH 5 and with 50/200 mM of EDC/NHS concentration. The anti-IL-6 antibody was immobilized at the surface of Ch-HA NPs. After determining the maximum antibody immobilization ability (7 µg/mL), the capacity to capture the recombinant IL-6 was evaluated. The efficacy was around 94-97%. Biological assays demonstrated not only the cytocompatibility of the produced NPs with human articular chondrocytes (hACs) (Fig 1) and human macrophages, but also the benefits of the capture and inactivation of IL-6 after stimulation with monocyte-derived macrophage conditioned medium. In conclusion, it is foreseeable that these NPs will overcome the limitations of the abovementioned treatments, since such NPs will increase the therapeutic efficacy due to their subcellular size, non-toxicity and high stability, being a promising approach for the local and sustained treatment of arthritic diseases.

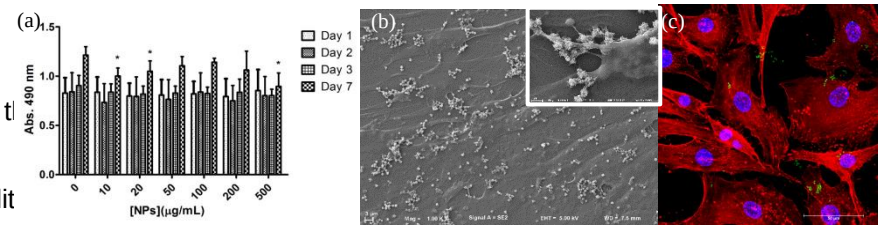

Fig 1. performance of t with NPs (a) cell viabilit (b) SEM micrographs, and (c) confocal microscopy with NPs at 50 µg/mL.