Delivery strategy and timing shape macrophage responses to glucocorticoid-loaded PLGA nanoparticles

N. Esteban-Pérez[1,2*], S. Del Sol-Fernández[1], R. Martín-Rapún[1,2] and J. Martínez de la Fuente[1,2]

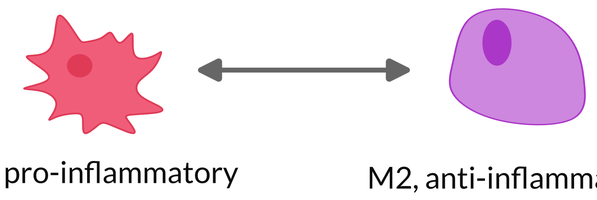
[1]Instituto de Nanociencia y Materiales de Aragón (INMA), CSIC-Universidad de Zaragoza, 50009, Zaragoza, Spain
[2]Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), 28029 Madrid, Spain

The problem

Glucocorticoids (GCs) such as hydrocortisone (HC) and dexamethasone (DEX) are widely used as anti-inflammatory drugs. However, chronic GC therapy is associated with severe effects, highlighting the need for improved delivery strategies

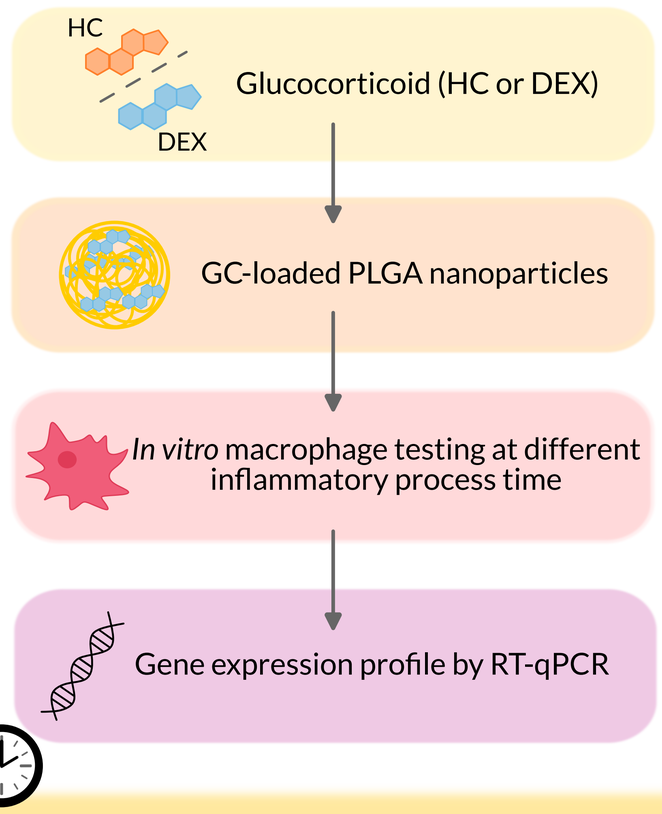
Poly(lactic-co-glycolic acid) is a biocompatible and biodegradable polymer widely used for drug delivery. Enable sustained release, potentially lowering systemic toxicity

Marcrophages are key regulators of the immune system and highly plastic



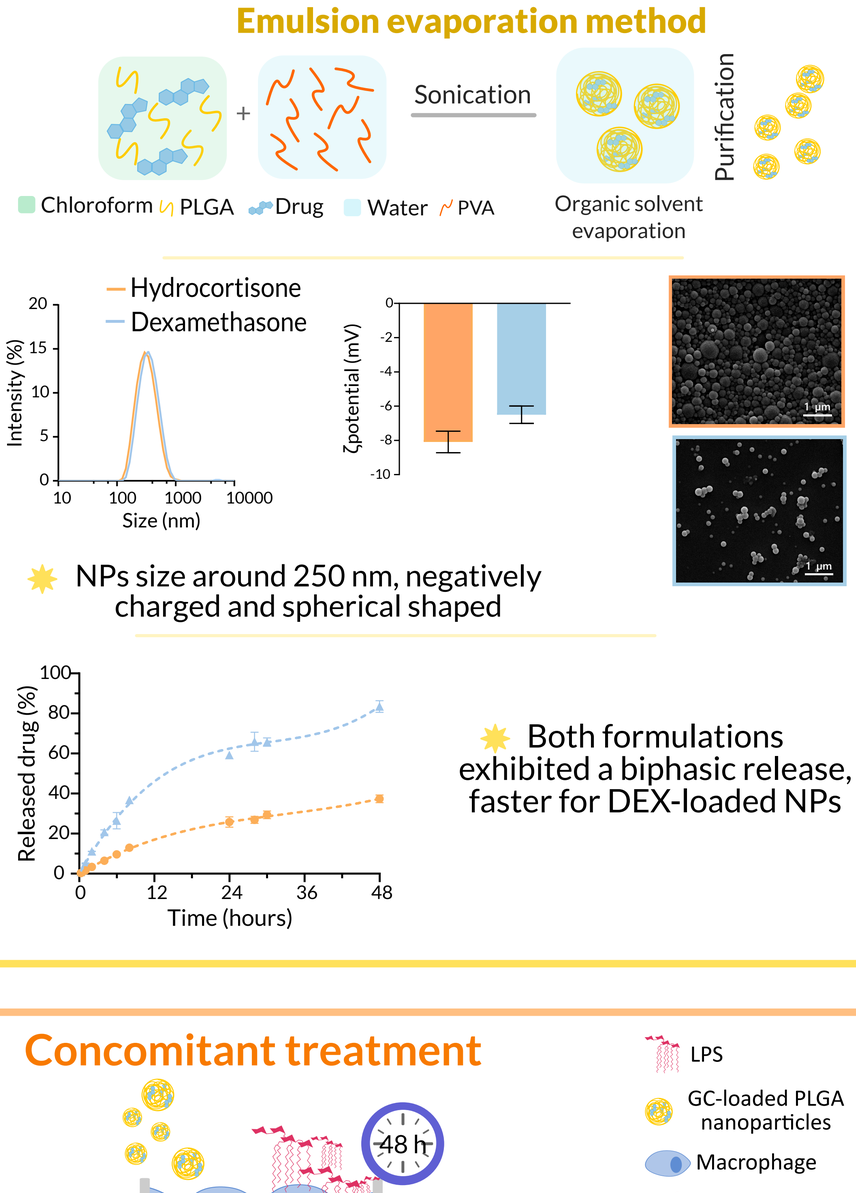
M1/M2 imbalance contributes to chronic inflammation

Our approach



Does treatment timing shape nanoparticle-mediated macrophage responses?

Nanoparticle Characterization

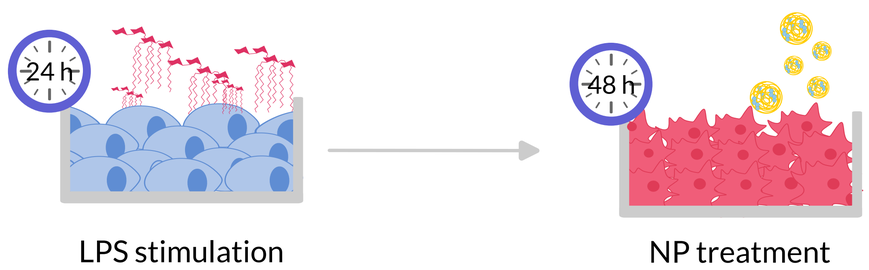


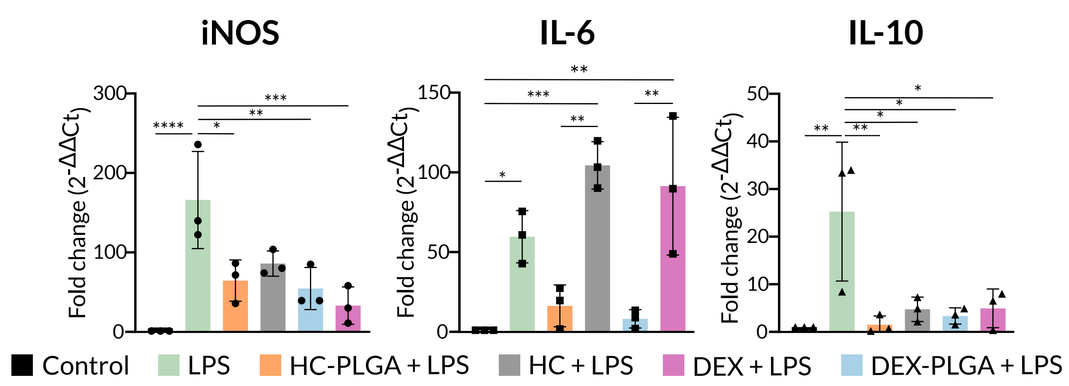
NPs size around 250 nm, negatively charged and spherical shaped

Both formulations exhibited a biphasic release, faster for DEX-loaded NPs

Timing matters

Treatment after LPS-stimulation

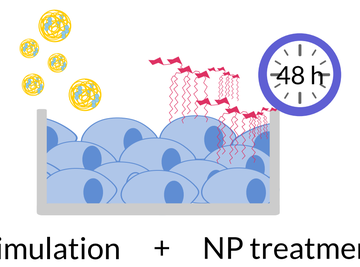


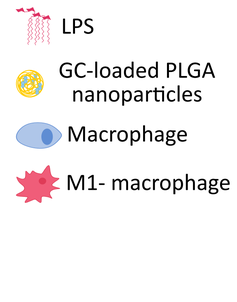


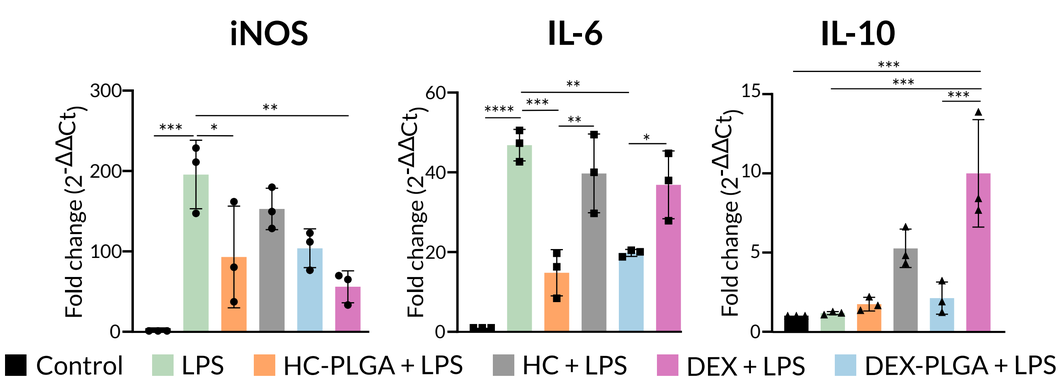
One-way ANOVA followed by Tukey's multiple comparison test (*p < 0.05, **p<0.01, ***p<0.001,****p<0.0001). n=3

- GC treatment reduced inflammatory markers in pre-activated macrophages
- IL-6 expression was better reduced by GC-loaded PLGA nanoparticles than free drugs
- IL-10 overexpression was only observed in M1 cells without treatment

Concomitant treatment







One-way ANOVA followed by Tukey's multiple comparison test (*p < 0.05, **p<0.01, ***p<0.001,****p<0.0001). n=3

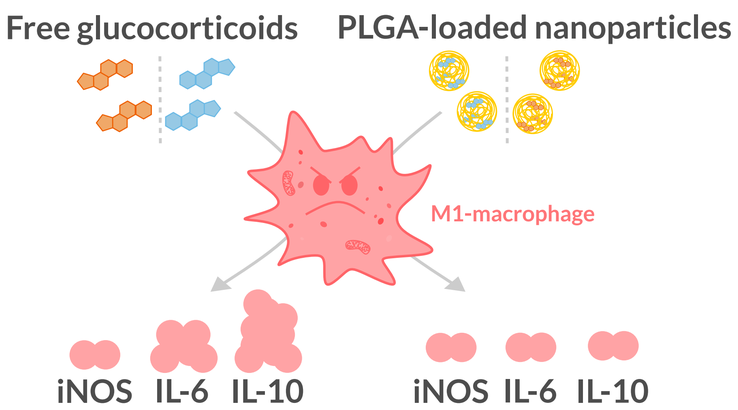
- GC treatment reduced NO and iNOS expression during M1 polarization
- GC-loaded NPs better prevented IL-6 overexpression than free drugs
- IL-10 induction was observed mainly with free drugs, suggesting delivery-dependent immune regulation

Different outcomes depending on the *in vitro* treatment timing

Conclusions

- HC- and DEX- loaded PLGA nanoparticles (~250 nm) showed sustained drug release over 48 h
- Both nanoparticles effectively reduced iNOS expression in M1-polarized macrophages
- GC-loaded nanoparticles were more effective than free drugs in preventing IL-6 overexpression
- IL-10 regulation depended on treatment timing suggesting differential immune regulatory mechanisms
- PLGA nanoparticles enable controlled GC delivery and improved modulation of inflammatory responses

Take home message



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