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Nanodiamond-based drug delivery system for the modulation of macrophage behavior

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Abstract

Chronic inflammation occurs when the body's natural innate immune response is disrupted, resulting in the progression of several diseases, including autoimmune disorders such as rheumatoid arthritis. In rheumatoid arthritis, primary innate immune cells, called macrophages, overproduce inflammatory cytokines and chemokines, leading to the destruction of cartilage and bone tissue, and, consequently, chronic pain. Current treatments for the disease include delivering anti-inflammatory drugs, like dexamethasone (Dex) to macrophages, which have many negative off-target effects, including reduced drug potency and immunosuppression. To limit such side effects, drug-incorporated nano- and microparticles have been investigated as drug delivery carriers to selectively target macrophages via phagocytosis, because of their roles as highly effective phagocytes in the body. Nanodiamond (ND) is uniquely suited to serve as a platform to deliver Dex because of its rich surface chemistry, which allows for adsorption/desorption properties to be easily tuned, as well as their ability to form micron-sized aggregates, which enable optimal phagocytosis. In this thesis, different types of surface-modified nanodiamond (ND) were explored as platforms for the delivery of dexamethasone (Dex) to macrophages both *in vitro* and *in vivo*.

To first gain a more thorough understanding of the relationship between Dex adsorption and ND surface chemistry, the adsorption properties of other model drugs with different therapeutic applications and chemistries were also explored and compared. The results showed that octadecylamine-functionalized ND (ND-ODA) showed superior adsorption of Dex, compared to carboxylated ND (ND-COOH), likely due to a combination of hydrophobic bonding and electrostatic interactions. Furthermore, these results emphasized that ND surface chemistry can be tailored to promote different types of adsorption properties with drugs of different chemistries.

After selecting ND-ODA as the Dex delivery platform, the effects of free Dex, ND-ODA, and Dex-adsorbed ND-ODA (ND-ODA-Dex) on primary human macrophage gene expression and protein secretion was explored. Surprisingly, even in the absence of Dex, ND-ODA had strong anti-inflammatory effects and increased the expression of phagocytic receptors. Interestingly, the adsorption of Dex to ND-ODA further increased some anti-inflammatory effects, but abrogated the effect on phagocytic receptors, compared to its individual components.

Because of their proven anti-inflammatory effects in vitro, ND-ODA and ND-ODA-Dex were evaluated for their ability to target and treat macrophages in a murine model of rheumatoid arthritis. Free Dex, ND-ODA, and ND-ODA-Dex were injected locally into the arthritic joints of collagen type II-induced arthritic mice, and physical symptoms of inflammation were clinically scored over time. At the end of the study, the mice were sacrificed, and their arthritic limbs were analyzed for bone and collagen degradation, cell infiltration, and inflammatory protein expression. The ex vivo results correlated with the clinical scoring, which suggested that a low dose of ND-ODA and ND-ODA-DEX both had slight, but not significant anti-inflammatory effects.

Overall, the ability of ND-ODA to promote anti-inflammatory behavior in macrophages, even in the absence of loaded drugs, suggests its potential for use as an anti-inflammatory therapeutic to directly target macrophages through phagocytosis. Future studies should focus on discovering mechanism through which ND-ODA is anti-inflammatory, as this information holds potential to inform future immunomodulatory nano- and microparticle designs.