Modulation of Macrophage Phenotype Using Nanoparticle-Delivered Gene Therapy for Treatment of Inflammatory Diseases

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Chronic inflammation contributes to the pathogenesis of seven of the ten leading causes of mortality in the U.S. However, current anti-inflammatory drugs are oftentimes ineffective and/or cytotoxic, so I aimed to develop a new therapy against chronic inflammation that targets macrophages. Classically activated (M1) macrophages normally release proinflammatory cytokines that trigger the inflammatory pathway, but when exposed to interleukins (IL) 4 and 10, they polarize to an alternatively activated, anti-inflammatory (M2) state. In this project, I designed a novel gene therapy system that delivers IL4 and IL10 cytokines in the form of plasmid genes to macrophages using a hyaluronic acid-polyethylenimine (HAPEI) vector. The engineered nanocomplexes were characterized using dynamic light scattering analysis and TEM imaging, which showed that the nanoparticles were approximately 160 nm in diameter and stable in an aqueous solution. Gel retardation studies proved that HAPEI encapsulated 100% of the plasmid and would be an effective vector, which was visually confirmed using confocal imaging. Moreover, macrophages exposed to this gene therapy system overexpressed IL4 up to 120X and IL10 up to 400X. In a form of autocrine and paracrine signaling, this increased IL4 and IL10 production also caused macrophages to upregulate expression of M2 markers and downregulate expression of M1 markers ($p<0.01$). These results indicate that HAPEI nanoparticles containing IL4 and IL10 genes can successfully polarize macrophages from a proinflammatory to an anti-inflammatory phenotype and thus can be used as a therapeutic against chronic inflammation.

Awards Won:
Third Award of $1,000