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Transfection of macrophages by collagen hollow spheres loaded with polyplexes: A step towards modulating inflammation ☆

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ABSTRACT

Macrophages are key orchestrators of inflammation as they secrete proteases and inflammatory cytokines. To date, therapies aimed at modulating macrophage phenotype have failed due to the short half-life of biomolecules in the body. Therefore, inhibition of inflammation by gene therapy constitutes a new hope.

In the present study, we have assessed collagen hollow spheres as a reservoir system for polyplexes in order to transfect human macrophages while preserving cell viability. Polyplexes were formed by complexing G-Luc plasmid with a poly(2-dimethylaminoethyl methacrylate) poly(ethylene glycol) based hyperbranched polymer. Several ratios of polymer/pDNA (5:1, 8:1, 10:1 w/w) complexes in two different sphere sizes (1.24 and 4.5 μm) were tested. Collagen hollow spheres were loaded with polyplexes up to 80 μg of pDNA per mg of microspheres. The release of polyplexes from the spheres was delayed and prolonged i.e. 20% of the initial amount released in 5 days. Following incubation with polyplex-loaded microspheres, macrophages were transfected (polyplex pDNA:polymer ratio 1:10 w/w). In addition, collagen hollow spheres maintained cell viability as more than 80% of cells were viable after 4 days in culture. In contrast, when used alone, polyplexes were seen to be toxic, while there was no transfection detected. Taken together, these results show that collagen hollow spheres may be used as a reservoir for controlled gene delivery to macrophages. Unlike existing gene delivery systems, this system allows for macrophage transfection with minimal toxicity. Hence, this system has a potential for the delivery of a therapeutic gene in order to modulate inflammation.

1. Introduction

Macrophages are key cells in the resolution of inflammation. During the inflammatory phase following injury, macrophages adopt a classically activated phenotype characterized by the secretion of reactive oxygen species, inflammatory cytokines and proteases [1,2]. Following exposure to biological signals such as interleukin (IL)-13, IL-4 or IL-10, macrophages progressively change their phenotype to adopt an alternatively activated phenotype. This phenotype promotes wound healing by the secretion of IL-10, VEGF and TGF-β1 to suppress the inflammatory response and promote matrix formation and stabilization [2]. In the case of many chronic inflammatory conditions, macrophages are locked in a pro-inflammatory phenotype [3].

With the aim of modulating inflammation, several trials based on the injection of growth factors have been performed. Unfortunately, owing to the short half-life and the rapid diffusion of biomolecules in vivo [4,5], these attempts have thus far proved unsuccessful. Hence, gene therapy in the form of the transfection of a gene encoding for a protein capable of modulating inflammation presents a new possibility to modulate the pro-inflammatory environment. Unfortunately macrophages, which are a non-dividing cell type, are difficult to transfect. Firstly, viral transfecting reagents cannot be used as they trigger an immune response [6]. Secondly, pDNA barely penetrates into the nucleus of non-dividing cells. Lastly, regular non-viral reagents reduce macrophage viability after transfection [7,8].

In gene therapy research, the utilization of cationic polymers has proven to have several advantages when compared to cationic lipids. Cationic polymers are more stable than lipids and complex a large amount of pDNA to form positively charged polyplexes. Unfortunately, however, they are toxic for macrophages [8]. To overcome this, polymeric hollow spheres made from natural polymers have been developed as a gene depot system [9]. These systems allow for the sustained release of polyplexes, which can

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