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Controlled delivery of recombinant adeno-associated virus serotype 2 using pH-sensitive poly(ethylene glycol)-poly-L-histidine hydrogels

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ABSTRACT

Loading of viral vectors in synthetic polymers is a promising strategy for overcoming hurdles associated with viral gene delivery. For enhanced gene expression at a specific site, gene transfer by using hydrogels represents a versatile approach. In this study, adeno-associated virus serotype 2 containing the green fluorescent protein gene (rAAV2-GFP) were loaded into poly(ethylene glycol) (PEG) hydrogels, with and without incorporation of poly-L-hisditine (polyHis). Inclusion of polyHis created pH responsive hydrogels in a physiological range of tissues, containing the damaged vasculature and activated phagocytosis. The fraction of polyHis used controlled the degree of swelling, water uptake and subsequent degradation of the hydrogels and release rate of rAAV2-GFP. The swelling ratio of the PEG-polyHis hydrogels increased inversely with environment pH. As pH declined from 7.4 to 6.0, PEG-polyHis hydrogel swelling ratio and degradation rate increased 875% and 135%, respectively. As a result, release and transduction efficiency of the rAAV2-GFP from PEG-polyHis hydrogel in human HT-1080 fibrosarcoma cells increased significantly compared to a PEG hydrogel. Transduction rate can be controlled by the hydrogels' polyHis concentration and is sensitive to localized decreases in pH consistent with inflammation. This is relevant to optimizing parameters for wound care and regenerative medicine applications.

1. Introduction

Non-viral vectors have broad application in gene delivery due to low immunogenicity, ability to accommodate and deliver large-size genetic material, and potential for modification of surface physico–chemical properties relating to biological interaction [1–4]. However, the relatively low efficiency of gene expression of non-viral vectors, in comparison to viral vectors, compromises gene delivery efficacy. Alternatively, recombinant adeno-associated virus (rAAV) is a powerful transgenic vehicle for delivering genetic molecules. The advantages of rAAV include the relative ease of producing high titers, ability to transfect dividing and non-dividing cells with high efficiency, great genome stability, low levels of viral genome integration, and extensive characterization of virus biology [5]. In human clinical trials, rAAV carrying specific genomic material has shown promising results for gene therapy [6,7]. However, non-specificity and insufficient efficacy in up-regulating expression remain as issues needing resolution. Delivery of genes away from their targets can lead to undesirable results, such as loss of efficiency, ectopic gene expression, and/or risk eliciting a severe immune response.

Recently, several studies have indicated that the combination of viral vectors with biomaterial matrices either through encapsulation within scaffolds or immobilization onto a matrix surface could enhance gene expression [8–11]. Promising results using combined tissue engineering and viral gene therapy in healing cutaneous wounds and bone grafts have been reported [12–14]. In addition, layer-by-layer coating of viral vectors with biomaterials can be employed to modulate virus tropism or reduce inflammatory and

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