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Intracellular delivery of VEGF165 encoding gene therapeutic using trifunctional copolymers of ethylene oxide and propylene oxide

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ABSTRACT

New type of copolymers of propylene oxide and ethylene oxide was assessed for promoting delivery of plasmid DNA based gene therapeutics. Lipid-like trifunctional copolymers (TFCs), with both random or diblock structures and relatively low hydrophilic–lipophilic balance, were studied and compared with linear Pluronic™ L61. Structure-dependent relationships for micelle-forming, cytotoxic and hemolytic properties of these copolymers were revealed. The TFC with the mean number of propylene oxide and ethylene oxide units of 83.5 and 24.2, respectively, exhibited relatively low adverse effects in vitro. The latter TFC interacted with plasmid DNA–polyethyleneimine complexes and improved their intracellular delivery. Furthermore, this TFC efficiently promoted the transfection of dermal fibroblasts with VEGF165-encoding Neovasculgen® plasmid DNA, which has been clinically used for the therapeutic angiogenesis. Our findings demonstrated for the first time that TFCs are promising for the polymer-mediated delivery of gene therapeutics.

1. Introduction

Gene therapeutics are promising biologics which have been engineered to treat a host of monogenic and complex diseases including neurodegenerative, cardiovascular and cancer ones [1]. The main engineering platforms for gene therapeutics include synthetic oligonucleotides, viruses and plasmid DNAs (pDNA) [1,2], the two latter types are considered 'pro-drugs' that allow for a template-directed synthesis of a desired peptide within the cell. Compared to viruses, pDNA has a great advantage in clinical application due to its intrinsic safety, low cost and vector capacity. However, pDNA itself suffers from its poor intracellular penetration and stability [3].

Several pDNAs encoding bioactive peptides have been developed and studied as potential drugs in different applications, e.g. for: therapeutic angiogenesis, regeneration of peripheral nerves and bones (see review [4]), cancer treatment [5], and DNA vaccination [6]. However, the improvement of intrinsically low pDNA transfection efficiency remains relevant and unresolved biomedical task. The common approach exploits various cationic lipids and polymers, both of synthetic and natural origin, which bind to, condense and neutralize nucleic acids, thereby improving their stability and cellular pharmacokinetics [2,4].

While cationic carriers of pDNA exhibit a relatively high efficiency in vitro, their gene therapy applications are strictly restricted, due to membrane-damaging and cytotoxic properties of polycations [2,7]. To overcome this problem, new polymeric systems that deliver pDNA, both alone and combined with polycations, have been proposed.

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