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A linear-dendritic cationic vector for efficient DNA grasp and delivery

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ABSTRACT

This paper presents an attempt to design an efficient and biocompatible cationic gene vector via structural optimization that favors the efficient utilization of amine groups for DNA condensation. To this end, a linear-dendritic block copolymer of methoxyl-poly(ethylene glycol)-dendritic polyglycerol-graft-tris(2-aminoethyl)amine (mPEG-DPG-*g*-TAEA) was prepared with specially designed multiple functions including strong DNA affinity, endosomal buffering and expected serum-tolerance. Based on the transfection in serum-free and serum-conditioned media, the influences of the polymer structures including the degree of polymerization of DPG and TAEA substitution degree were explored. As compared to polyethylenimine (M_w = 5 kDa) (PEI5k) with similar molecular weight and higher amine density, mPEG-DPG-*g*-TAEA displayed comparably high DNA affinity due to the special linear-dendritic architecture. Consequently, at very low N/P ratio, mPEG-DPG-*g*-TAEA vectors could mediate efficient in vitro luciferase expression at levels that are comparable with or even superior to the commercially available Lipofectamine™ 2000, while being apparently higher than PEI5k. The designed vectors exhibit considerably higher cell biocompatibility and better resistance against bovine serum albumin adsorption than PEI5k. The stability of the complexes on coincubation with heparin was found to be largely dependent on the polymer structure. As concluded from the comparative transfection study in the absence/presence of chloroquine, it is likely that the polycation itself could produce endosomal buffering. This linear-dendritic vector shows promising potential for the application of gene delivery.

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1. Introduction

Gene therapy has gained significant attention as a potential strategy for treating genetic disorders, as well as an alternative to traditional chemotherapy used for cancer treatment [1,2]. Appropriate vectors that can protect DNA from degradation prior to completion of the function while circumventing both in vitro and in vivo biological barriers during the transgene process are currently considered to be an important factor for achieving desirable therapy performance [3,4]. Over the last decade, increasing interest from researchers has been directed at nonviral polycation vectors in light of their prominent advantages, including large payload, high tolerance towards gene sizes and low immunogenic risk as compared to viral vectors [5–9].

Hyperbranched polyethylenimine (PEI) is the most investigated polycation vector so far due to its high transfection efficiency towards most cell lines [10,11]. The pertinent studies offer valuable information for the rational design of potentially applicable gene carriers. For instance, among three kinds of amine groups of PEI, it is suggested that the primary amine groups are more powerful for efficient payload of DNA [12,13]. The secondary and tertiary amine groups contribute much to the endosomal escape of DNA/PEI complexes, thus avoiding the premature degradation of DNA in the lysosome, which is usually called the "proton sponge" effect [14,15].

Based on these understandings about PEI, many polycations have been proposed and designed for gene delivery. Nevertheless, the toxicity issue still poses challenges mainly due to the damage to the cell membrane caused by a high charge density of polycations. Another hurdle is the serious side-effect caused by contamination with negatively charged blood components [16,17], including the particle aggregation/sediment, premature DNA release and ingestion, etc. This effect is assumed to be associated with the strong electrostatic attraction from polycations. Those drawbacks also eventually cause substantially reduced transfection efficacy.

Due to the three-dimensional (3-D) shape of PEI, some of its amine groups might be exposed on the complexes' surface and inevitably not combine with DNA. That would lead to high surface potentials and more PEI being required for DNA condensation, which is disadvantageous in terms of safety. At least partly for this

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