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Propoxylation of cationic polymers provides a novel approach to controllable modulation of their cellular toxicity and interaction with nucleic acids

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ABSTRACT

An effective chemical approach to modulation of biological interactions of cationic polymers was proposed and tested using polyethyleneimine (PEI) as a drug carrier. Branched 25 kDa PEI was modified in the reaction with propylene oxide (PO) to produce a series of propoxylated PEIs with NH groups grafted by single or oligomer PO units. Clear relationships between the propoxylation degree and biological effects, such as interaction with plasmid DNA, hemolytic, cytotoxic, and pro-apoptotic activities were revealed for PEIs modified upon PO/NH molar ratio of 0.5, 0.75, 1.0 and 3.0. The partial modification of available cationic centers up to 100% is predominantly accompanied by a significant gradual reduction in polycation adverse effects, while ability of complex formation with plasmid DNA is being preserved. Grafted PEI with 0.75 PO/NH ratio provides better protection from nuclease degradation and transfection activity compared with other modified PEIs. Revealed relationships contribute to the development of safe polymeric systems with controllable physicochemical properties and biological interactions.

1. Introduction

Synthetic cationic polymers are important polymeric systems which have been intensively studied as components of biomedical materials and drug formulations. Cationic polymers exhibit relatively strong interactions with anionic membrane constituents, nucleic acids and other macromolecules, which may result in beneficial antimicrobial effect [1,2] and promotion of cellular uptake [3], or undesirable (cyto-)toxicity [4].

Cationic polymers have been used as cell adhesives [5], controlled release systems [6,7], and oral drug formulations [8,9]. Non-viral gene delivery is one of the most promising applications of cationic polymers, which covers the direct gene therapy of multiple disease, modification of biomedical materials as well as cell biology research [10,11].

Basic amino acids and their derivatives have been utilized to produce biodegradable linear homopeptides and dendrimeric poly(amidoamine) peptides with a good ability for binding, condensation and cellular translocation of nucleic acids [10–14]. Among synthetic cationic carriers, polyethylenimines (PEIs) are considered as the 'gold standard' characterized by a high cationic charge, controllable structure, and robust synthesis techniques [15,16].

Toxicity issues of PEIs and other polycations have been reported previously in experimental studies [17–22] and reviews [3,16]. High membrane-damaging and hemolytic action of the polycations remains the main obstacle to their use as therapeutic gene carriers [4]. Adverse effects of cationic polymers are especially critical in vivo, compromising their therapeutic potential [23].

An appropriate chemical structure of cationic polymers should be developed to reduce side interactions, toxic outcome and improve pharmacokinetics of polymeric complexes with a substance delivered. Grafting of polymer backbone with small molecules and oligomers is a primary approach to improving biocompatibility of polycations, optimizing their cellular transport, and increasing selectivity. Attachment of saccharides, e.g. by cross-linking of PEI fragments with mannitol diacrilate to stimulate caveolae-mediated endocytosis [24], grafting of PEG molecules [19,25,26], and some combinative modifications [11,27] were recently proposed. Labeling of biodegradable PEI derivative with pyridoxal phosphate for specific gene delivery into cancer cells was reported [28]. Similarly, PEI–pullulan–folic acid conjugate has been recently developed for targeted delivery of plasmid DNA and short interfering RNA into folate receptor-overexpressing cells [29].

Among above approaches, PEGylation is the most accepted technology to modulate bio-interactions of macromolecular drugs and polymers [15,20,26,30]. In particular, structure-activity relationships of PEI modified with different PEG molecules of ~0.5–20 kDa were examined in [19,25]. The PEGylation allows for non-specific attenuation of side

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