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Polymer vectors *via* controlled/living radical polymerization for gene delivery

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ABSTRACT

The design of efficient gene delivery vectors is a challenging task in gene therapy. Recent progress in living/controlled radical polymerizations (LRPs), in particular atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization providing a means for the design and synthesis of new polymeric gene vectors with well-defined compositions, architectures and functionalities is reviewed here. Polymeric gene vectors with different architectures, including homopolymers, block copolymers, graft copolymers, and star-shaped polymers, are conveniently prepared *via* ATRP and RAFT polymerization. The corresponding synthesis strategies are described in detail. The recent research activities indicate that ATRP and RAFT polymerization have become essential tools for the design and synthesis of advanced, noble and novel gene carriers.

Abbreviations: AFM, atomic force microscopy; AGET, activator generated by electron transfer; APMA, 3-aminopropyl methacrylamide; ATRP, atom transfer radical polymerization; BBL, *a*-bromo-*r*-butyrolactone; BIBB, 2-bromoisobutyrate bromide; BMA, butyl methacrylate; BMPA, 2-bromo-2-methylpropionic acid; Boc, *tert*-butoxycarbonyl; Boc-AEAEMA, *N*,*N*′-di-(*tert*-butoxycarbonyl)-2-(2-aminoethylamino)ethyl methacrylate; Boc-AEMA, *N*-*tert*-butoxycarbonyl-aminoethyl methacrylate; Boc-EDA, *N*-*tert*-butoxycarbonyl-ethylenediamine; BPN, 2-bromopropionitrile; BTBP, 1,4-bis(2-(thiobenzoylthio)prop-2-yl)benzene; CD, cyclodextrin; CDI, 1,1′-carbonyldiimidazole; CNTs, carbon nanotubes; CPADP, 4-cyanopentanic acid dithiobenzoate; CS, chitosan; CTA, chain transfer agent; CTP, 4-cyanopentanoic acid dithiobenzoate; LRP, living radical polymerization; DCT, dodecyl cyanovaleric trithiocarbonate; DEAEMA, 2-(diethylamino)ethyl methacrylate; DETA, diethylenetriamine; DMAEMA, 2-dimethylaminoethyl methacrylate; DMAPMAA, *N*-(3-(dimethylamino)propyl) methacrylamide; DPAEMA, 2-(diisopropylamino)ethyl methacrylate; DSC, *N*,*N*′-disuccinimidyl carbonate; DTT, dithiothreitol; EBiB, ethyl 2-bromoisobutyrate; EDA, ethyldiamine; EDC, *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride; EEP, 2-ethoxy-2-oxo-1,3,2-dioxaphospholane; FA, folic acid; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GAPMA, 3-gluconamidopropyl methacrylamide; GMA, glycidyl methacrylate; HAEAPMA, (2-hydroxy-3-(2-aminoethyl)amino)propyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; HMTETA, 1,1,4,7,10,10-hexamethyltriethylenetetramine; HPC, hydroxypropyl cellulose; HPMA, *N*-(2-hydroxypropyl)methacrylamide; LAEMA, 2-lactobionamidoethyl methacrylamide; LCST, lower critical solution temperature; MAS, methacryloxysuccinimide; MBP, methyl a-bromophenylacetate; MeDMA, (2-(methacryloyloxy)ethyl) trimethyl ammonium chloride; MPC, 2-methacryloyloxyethyl phosphorylcholine; MPA, 3-mercaptopropionic acid; NBPS, *N*-(2-bromo-2-methylpropionyloxy) succinimide; NHS, *N*-hydroxysuccinimide; NIPAAm, *N*-isopropylacrylamide; NMRP, nitroxide mediated free radical polymerization; OEGMA, oligo(ethylene glycol) methacrylate; PAA, poly(acrylic acid); PAAM, polyamidoamine; PBAC, poly(*N*,*N*-bis(acryloyl) cystamine); PC, phosphorylcholine; PCL, poly(*ε*-caprolactone); PDI, polydispersity index; PDMAEMA, poly(2-(dimethylamino)ethyl methacrylate); PEI, polyethylenimine; PEG, poly(ethylene glycol); PEGMA, poly(ethylene glycol) methacrylate; PGMA, poly(glycidyl methacrylate); PGOHMA, polyglycerol methacrylate; PIC, polyion complex; PLL, poly(L-lysine); PMDETA, *N*,*N*,*N*,*N*,*N*-pentamethyldiethylenetriamine; PNAs, peptide nucleic acids; PNIPAAm, poly(*N*-isopropylacrylamide); PPO, poly(propylene oxide); POEGMA, poly(oligo(ethylene glycol) methacrylate); PPE, polyphosphoester; PSMA, poly(styrene-*alt*-maleic anhydride); PTPA, 2-((2-phenyl-1-thioxoethyl)-thio)propanoic acid; RAFT, reversible addition-fragmentation chain transfer; ROP, ring-opening polymerization; SCL, shell cross-linked; SE, spectroscopic ellipsometry; siRNA, small interfering ribonucleic acid; SPDP, *N*-succinimidyl 3-(2-pyridyldithio)-propionate; St, styrene; tBA, *tert*-butyl(meth)acrylate; TEM, transmission electron microscopy; TETA, triethylenetetramine; TsCl, *p*-toluenesulfonyl chloride.

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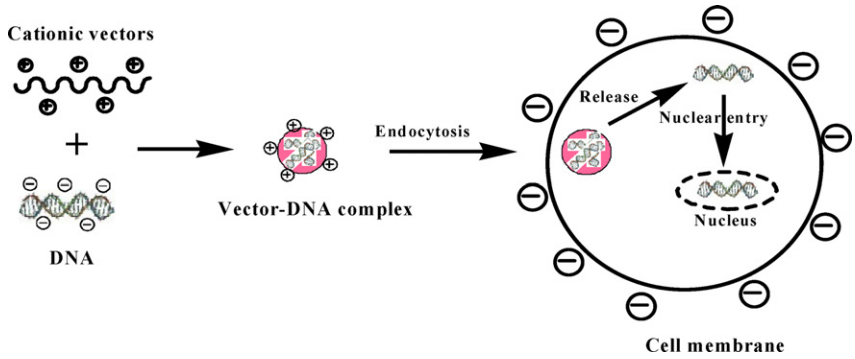
Contents

1. Introduction

Gene therapy shows much promise in therapies for various genetic diseases and cancers, viral infection, and cardiovascular disorders [1–9]. Gene delivery includes the delivery of both plasmid DNA (encoding therapeutic proteins) and RNA interference (RNAi) [4–11]. DNA delivery provides a corrective action by expressing suppressor proteins to suppress cancer growth or activate apoptosis, while RNAi delivery produces gene silencing to inhibit cellular protein expression or induce apoptosis. For efficient gene therapy, a gene carrier or vector is needed to escort negatively charged nucleic acids through cell membranes. The most challenging task in gene therapy is the design of gene delivery vectors with low cytotoxicity and high transfection efficiency. Two types of carriers are used in gene therapy, i.e., viral and non-viral vectors. Viral vectors (viruses) are effective delivery agents. However, there are numerous safety issues related with the use of viruses, such as immunogenicity and mutation of the host genome. In comparison with viral vectors, cationic polymers as the major type of non-viral gene delivery vectors show low host immunogenicity and high flexibility, and can be produced on a large scale [6–11]. Polymeric vectors as alternatives to viral vectors have received increasing attention for their potential applications in a broad variety of gene-mediated therapies.

A representative mechanism of cationic vector-based gene delivery is shown in Scheme 1. Cationic polymers are able to condense negatively charged nucleic acids into positively charged polyplexes amenable to translocation across negatively charged cell membranes. After cellular entry *via* endocytosis, the polymer/plasmid complexes can undergo dissociation *via* endosomal escape to release nucleic acid into the nucleus for gene expression. Such processes can also allow different types of released RNA to execute their biological functions inside cells [8,9]. A great number of polycations, including polyethylenimine (PEI), poly((2-dimethyl amino)ethyl methacrylate) (PDMAEMA), poly(L-lysine) (PLL) and polyamidoamine (PAAM), have been reported to be capable of delivering genes [2,4,6–8]. Among these cationic polymers, PEI homopolymers are



Scheme 1. Representative mechanism of cationic vector-based gene delivery.