A facile preparation of novel multifunctional vectors by non-covalent bonds for co-delivery of doxorubicin and gene

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A R T I C L E   I N F O

Article history:
Received 30 March 2011
Received in revised form 20 September 2011
Accepted 3 November 2011
Available online 11 November 2011

Keywords:
Transfection efficiency
Multifunctional
Electrostatic interaction
Avidin–biotin
Co-delivery

A B S T R A C T

In this study, novel multifunctional ternary complexes of biotinylated transferrin–avidin–biotin–poly(ethylene glycol)–poly(l-glutamate acid)/poly(2-(2-aminoethylamino) ethyl methacrylate)/doxorubicin–poly(l-aspartic acid)/pDNA (TAB/PIC–D/pDNA complexes) were prepared based on polyion complex micelles (PIC) and the avidin–biotin system, which aimed to target co-delivery of anti-cancer doxorubicin and gene. Cytotoxicity studies revealed that PIC–D could have anti-tumor effect on HeLa cells and HepG2 cells; TAB coating could increase the biocompatibility of PIC–D/pDNA complexes and the targeting delivery efficiency of doxorubicin. TAB/PIC–D/pDNA complexes possessed higher transfection efficiency than the unmodified complexes in serum, and transferrin could enhance luciferase expression in HeLa cells and HepG2 cells. Furthermore, confocal laser scanning microscopy showed that doxorubicin and gene could be delivered into HepG2 cells simultaneously by TAB/PIC–D/pDNA complexes. The formation of the ternary complexes provides a facile approach to constructing a multifunctional delivery system for targeted co-delivery of anticancer drugs and gene.

A R T I C L E   S T R U C T U R E

1. Introduction

Recently, combined delivery of drug and gene has emerged as an exciting method of treating cancer which possesses a synergistic effect of overcoming drug resistance or enhancing gene transfection efficiency [1–3]. One of the most critical challenges for highly efficient delivery is the design and development of a delivery system with multiple functionality. For example, a shielding component can prolong the circulation time of nanoparticles in the blood [4–6]; targeting moieties on the surface of a nano-system loading gene/drug can increase the specific binding between nanoparticles and targeted cells [7–9]; some other functional components can increase the biocompatibility of the nanoparticles or enhance the ability of nanoparticles to escape from endosomes [10–12]. Owing to the difficulty of synthesizing delivery carriers that meet all the requirements, construction of a highly efficient vector with multiple functionality via a non-covalent bond has drawn increasing attention.

To date, polymeric micelles made from amphiphilic block copolymers have been used for solubilization, stabilization and delivery of poorly water-soluble drugs that are loaded in the hydrophobic core of polymeric micelles [13]. When hydrophilic segments of amphiphilic block copolymers are cationic, these polymeric micelles can further bind negatively charged macromolecules via electrostatic interaction to form polyion complex micelles (PIC) [3,14]. Cheng also prepared positively charged PIC by protamine sulfate and doxorubicin-conjugated poly(l-aspartic acid) (PASP) as a vector for combined delivery of drug and gene [15]. The formation of PIC is thought a promising way to co-deliver DNA and drugs into various cell lines. More interestingly, the existence of the surface charge allows further decoration of PIC with oppositely charged macromolecules, which provides a new approach to constructing multifunctional vectors [16,17]. For example, Leroux [18], reported that using negative poly(ethylene glycol)–block–poly(propyl methacrylate–comethacrylic acid) (PEG–b–P(PrMA–co–MAA)) to modify the positively charged poly(amidoamine) (PAMAM) dendrimer–nucleic acid core could form pH-responsive PIC as gene vectors, and these PIC could greatly increase transfection efficiency and decrease cytotoxicity.

Avidin is a glycoprotein with four subunits which can each bind a biotin. A major distinguishing feature of the avidin–biotin system is its extraordinarily high affinity. Because of its high affinity, the avidin–biotin system has been employed as a linker and broadly applied to biomedical studies [19,20]. Transferrin, which is a typically monomeric glycoprotein, has been widely used as a target ligand, owing to the over-expression of its respective receptor on many cancer cells [21,22]. Pei, reported that transferrin modified stealth nanoparticles (transferrin–PEG–NP) encapsulating poly(ethylene) glycol–hydroxypropothecin conjugate (PEG–HCPT) could show higher tumor accumulation [23]; Gabrielson and Pack [24] reported that modified 25 kDa branched