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A mPEG-PLGA-*b*-PLL copolymer carrier for adriamycin and siRNA delivery

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ABSTRACT

A amphiphilic block copolymer composed of conventional monomethoxy (polyethylene glycol)-poly (D,L-lactide-*co*-glycolide)-poly (L-lysine) (mPEG-PLGA-*b*-PLL) was synthesized. The chemical structure of this copolymer and its precursors was confirmed by Fourier Transform Infrared Spectroscopy (FTIR), ^{1}H Nuclear Magnetic Resonance (^{1}H NMR) and Gel Permeation Chromatography (GPC). The copolymer was used to prepare nanoparticles (NPs) that were then loaded with either the anti-cancer drug adriamycin or small interfering RNA-negative (siRNA) using a double emulsion method. MTT assays used to study the in vitro cytotoxicity of mPEG-PLGA-*b*-PLL NPs showed that these particles were not toxic in huh-7 hepatic carcinoma cells. Confocal laser scanning microscopy (CLSM) and flow cytometer analysis results demonstrated efficient mPEG-PLGA-*b*-PLL NPs-mediated delivery of both adriamycin and siRNA into the cells. In vivo the targeting delivery of adriamycin or siRNA mediated by mPEG-PLGA-*b*-PLL NPs in the huh-7 hepatic carcinoma-bearing mice was evaluated using a fluorescence imaging system. The targeting delivery results and froze section analysis confirmed that drug or siRNA is deliver to tumor more efficiently by mPEG-PLGA-*b*-PLL NPs than free drug or Lipofectamine™2000. The high efficiency delivery of mPEG-PLGA-*b*-PLL NPs mainly due to the enhancement of cellular uptake. These results imply that mPEG-PLGA-*b*-PLL NPs have a great potential to be used as an effective carriers for adriamycin or siRNA.

1. Introduction

NPs have been widely evaluated as carriers for the delivery of drugs and genes because of their small size, sustained-release characteristics [1,2], ability to offer physical protection against RNase activity [3,4], and ability to deliver a drug or gene into tumors specifically [5–7].

Amphiphilic block copolymers, which consist of hydrophilic and hydrophobic segments, have attracted significant attention for their use with many different hydrophobic drugs or genes because of their ability to form NPs self-assembly in aqueous solutions. These NPs provide a core–shell structure in which the drug or gene in the core is surrounded by a hydrophilic outer shell that permits prolonged circulation in the blood and reduces uptake by the liver and spleen [8–11]. Moreover, by means of passive or active targeting mechanism, the polymeric NPs readily accumulate in tumor tissues and are then slow degraded, thereby allowing release of the drug or gene gradually [2,12–15]. Thus, various types of biodegradable polymers, such as polylactide (PLA) [16], poly(D,L-lactide-*co*-glycolide) (PLGA) [17], polycaprolactone (PCL) [18], and monomethoxy (polyethylene glycol)-poly(D,L-lactide-*co*-glycolide) (mPEG-PLGA) in particular, have been applied in drug or gene delivery [19–22]. However, the application of these aliphatic polyester NPs has been immensely restricted because of the scarcity of constituent functional groups.

Many different biodegradable aliphatic polyesters have been modified by incorporating natural amino acids in the polymer structure [23–25]. The functional side groups of the amino acids provide the ability to anchor drugs, targeting moieties and siRNA through covalent or ionic interactions [26,27]. Additionally, amino acid components provide safe building blocks for introducing functional side groups into biodegradable polymers, moreover, they are degraded by proteases or peptidases, thus enabling the modification of the degradation patterns of the polymers [28]. The poly(L-lysine) (PLL) cationic polypeptide has a targeted activity toward tumor cells because of its ability to bind to the cell membrane by electrostatic absorption to the negatively charged cell (e.g., malignant cell) surface [29–31], and when conjugated with aliphatic polyesters, it can be used as a specific delivery carrier for drugs, DNA and RNA [32,33].

Because of the potential benefits of using amphiphilic block copolymers with amino acid components for drug and siRNA delivery, we designed and synthesized a cationic block copolymer

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