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cRGDyK modified pH responsive nanoparticles for specific intracellular delivery of doxorubicin

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ABSTRACT

Stimuli-responsive nanocarriers attract wide attention because of the unique differences in microenvironment between solid tumors and normal tissues. Herein, we reported a novel cRGDyK peptide modified pH-sensitive nanoparticle system based on poly(ethylene glycol)-poly(2,4,6-trimethoxy benzylidene-pentaerythritol carbonate) (PEG-PTMBPEC) diblock copolymer, which was expected to destroy tumor angiogenesis and kill tumor cells simultaneously. Doxorubicin (DOX)-loaded nanoparticles (NPs) were characterized to have a uniform size distribution, high entrapment efficiency, good stability in plasma as well as a pH dependent drug release pattern. Blank NPs were non-toxic to both tumor cells and normal cells, while DOX-loaded cRGDyK peptide modified NPs (cRGDyK-NPs) exhibited the pronounced cytotoxicity against B16 cells and human umbilical vein endothelial cells (HUVEC) overexpressing $\alpha_v\beta_3$ integrin receptors. Cellular uptake studies revealed that the highly efficient uptake of cRGDyK-NPs was attributed to the receptor-mediated endocytosis and acidic-triggered drug release. Importantly, cRGDyK-NPs could dramatically reduce the systemic toxicity of DOX and exert excellent tumor killing activity *in vivo*. The cRGDyK modified pH-sensitive nanocarrier is a promising vehicle for intracellular drug delivery to $\alpha_v\beta_3$ integrin receptor overexpressed tumor cells and neovascular cells.

Statement of Significance

Slow intracellular drug release and poor tumor targeting capacity are still the critical barriers of polymeric nanoparticles (NPs) for the treatment efficiency of chemotherapy. In the present study, we designed cRGDyK peptide modified poly(ethylene glycol)-poly(2,4,6-trimethoxybenzylidene-pentaery thritol carbonate) (cRGDyK-PEG-PTMBPEC) NPs with active targeting and fast pH-triggered drug release. Doxorubicin (DOX)-loaded cRGDyK-PEG-PTMBPEC NPs exhibited pronounced cytotoxicity and enhanced cellular uptake against B16 cells and human umbilical vein endothelial cells overexpressing $\alpha v\beta 3$ integrin receptors. Moreover, the active targeted pH-sensitive NPs can enhance the antitumor activity and reduce the systematic toxicity of DOX *in vivo*.

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1. Introduction

Numerous lines of evidence from clinical and preclinical studies have illustrated that the treatment efficiency of chemotherapy in malignant tumors is limited due to the poor physiochemical properties, low stability and short circulating half-time. Moreover, it has high toxicity to normal tissues and is inadequately located in tumor sites [1,2]. Recently, nanoparticles (NPs) such as liposomes, micelles, silica NPs and carbon nanotubes have attracted much attention to solve these problems [3–5] owing to their ability to efficiently encapsulate the anticancer drugs and selectivity accumulate in tumors by the well-known enhanced permeability and retention effect (EPR) [6–8].

However, most of the NPs have the relatively slow drug release and the intracellular drug concentration could fail to promptly

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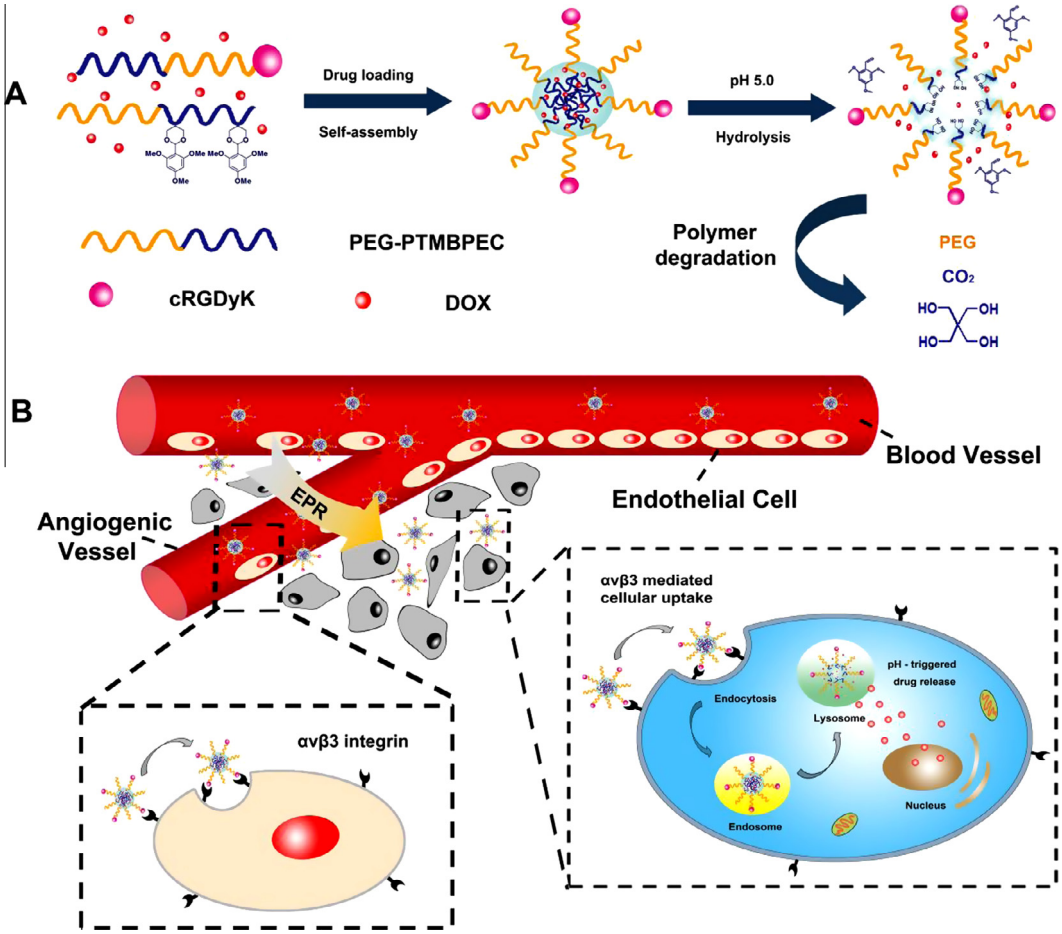
reach the effective therapeutic concentration, which will probably lead to the development of multidrug resistance (MDR). Hence, the quick drug release is the critical barrier for the treatment efficiency of chemotherapy [9,10]. The drug delivery systems sensitive to stimulus have been widely utilized to overcome this obstacle [11–13]. Among all the applied stimuli, sensitivity to pH is a particularly appealing stimulus due to the mildly acidic pH encountered in tumor and inflammatory tissues as well as in the intracellular compartments such as endosomes and lysosomes [14]. Generally speaking, this drug delivery system can be divided into two main approaches. One is the combination of the drug and the hydrophobic section based on the acid-sensitive chemical bond, such as hydrazine and acetal [5]. The other relies on the transition of copolymers in response to the pH changes, leading to the destabilization of the NPs [15,16].

In previous works, we have reported polymersomes and micelles based on the diblock copolymer of poly(ethylene glycol)-poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate) (PEG-PTMBPEC) [17–19]. PEG was conjugated to control the particle morphology and prolong the circulation time by reducing non-specific interactions *in vivo* [20,21]. The particles were responsible for mild pH changes because of the hydrolysis of trimethoxybenzylidene acetals. Importantly, the particles exhibited low cytotoxicity since the polymer could degrade to the non-toxic PEG, CO_2 and pentaerythritol, which will contribute to the high injection dose to exert good antitumor effect. Furthermore, clathrin-mediated endocytosis is present and inherently active in all mammalian cells, and the nanocarriers can eventually be delivered to the acidic endolysosomes through this pathway [22]. Therefore, the pH-sensitive NPs can perform a fast drug release after being taken up by tumor cells through the clathrin-mediated endocytosis. As we all know, only when anticancer drugs arrive at their intracellular target sites and reach optimum therapeutic threshold concentration they can exhibit an efficient killing effect. Therefore, this delivery system can also facilitate the subcellular distribution of anticancer drugs.

Although the NPs based on PEG-PTMBPEC copolymer had shown low cytotoxicity and fast pH-triggered drug release, they arrived at the tumor tissues just relying on the EPR-mediated passive targeting which might cause low drug accumulation into the cells. Therefore, we hypothesized that the efficiency of the PEG-PTMBPEC NPs could be significantly improved by combining with active targeted delivery strategy. Receptor-medicated endocytosis of NPs with ligand modification could be obviously higher than the non-modified one [23–25]. It has been reported that RGD (arginine–glycine–aspartic acid) short peptide can specifically bind with integrin $\alpha_v\beta_3$ receptors which are overexpressed on various tumor cells as well as angiogenic endothelium and RGD plays an important role in regulating tumor growth, metastasis and tumor angiogenesis [26–28]. This makes it become an attractive ligand for active targeted delivery of anticancer drugs to tumor cells and neovascular cells [29–32].

Doxorubicin (DOX) is a well-known anticancer drug, but its application is limited owing to the cardiotoxicity side effect [33]. Therefore, the active targeted pH-sensitive NPs based on the cRGDyK-PEG-PTMBPEC copolymers were constructed to enhance antitumor toxicity and reduce the systematic toxicity of DOX. Schematic illustration of the NPs is shown in Scheme 1. It will be



Scheme 1. (A) Self-assembly and disassembly processes of the cRGDyK modified pH-sensitive NPs. (B) Illustration of the uptake of cRGDyK modified pH-sensitive NPs into tumor cells and angiogenic endothelium cells via integrin receptor-mediated endocytosis.

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