pH-Sensitive Polypeptide Conjugated with Carborane Clusters and Cyanine for NIR Bioimaging and Multi-Therapies

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Abstract: A novel pH-sensitive carborane and cyanine dye conjugated polypeptide and its micelles has been designed and synthesized for potential near infrared fluorescence imaging-guided boron neutron capture therapy (BNCT). The amphiphilic polymer we synthesized with tertiary amine as functional group could self-assemble to micelle nanoparticles at neutral pH, and responsive to acidic solution for the disassembly of the micelles for drug release. The tertiary amine sensitive induced process was observed via dynamic light scattering (DLS) and transmission electron microscopy (TEM). The efficiency of cell killing ability is studied by MTT assays and fluorescence microscope measurement, indicating a new intelligent system for potential NIR imaging-guided therapy.

Keywords: pH-sensitive, carborane, tertiary amine, imaging-guided, boron neutron capture therapy.

1. Introduction

Boron neutron capture therapy (BNCT) is a form of radiotherapy which provides a way to selectively destroy malignant cancer cells while at the same time spare normal cells.1,3 It is based upon 10B to yield high energy particles (He, 163 keV μm⁻¹, and ⁷Li, 210 keV μm⁻¹) after giving thermal neutron irradiation.4 The ¹⁰B has a large thermal neutron cross section of 3838 barns, which could efficiently capture thermal neutrons to generate the secondary radiations. The high energy transfer (LET) range is limited to a diameter of 5-9 μm so the cytotoxicity is largely confined to one cell range where ¹⁰B agent is located.5 The selective distribution of the ¹⁰B-compounds to tumors allows pinpoint treatments, while avoiding damage to healthy tissues without distribution of ¹⁰B-compounds. Theoretically BNCT provides a selective damage of cancer cells while sparing normal ones if the BNCT agent could be transported specifically into tumor cells.6 The ¹⁰B-compounds used for cancer BNCT are non-radioactive and safe, which is different from some other radioactive isotopes induced radiotherapeutic.7

So far, ¹⁰B-compounds of sodium boronophenylalanine (BPA) and borocaptate (BSH) have been widely used for BNCT, presenting potential for clinical cancer treatment.8 However, these ¹⁰B-compounds present limited tumor targeting ability and retention to achieve abundant ¹⁰B-level and high tumor-to-healthy tissue selectivity. The carboranes have a high content of ¹⁰B atoms (75 wt%), which make them ideal ¹⁰B agents for BNCT.9,11 Nevertheless, effective tumor BNCT in vivo still needs prolonged circulation in the bloodstream which the small molecules cannot realize. Carborane-containing nanocarriers can efficiently and homogeneously deliver the ¹⁰B-compounds across tumor tissues to access all cancer cells. And carboranes have been conjugated to some hydrophilic polymeric segments to form amphiphilic dendrimers,12 liposomes,13 polyethylene glycol derivatives,14,15 etc. These polymeric boron agents have been shown to enhance the accumulation of ¹⁰B in tumor tissues via the enhanced permeability and retention (EPR) effect and then the therapeutic efficacy has been highly improved comparing with small molecules.16-18

Here, we have designed and synthesized a novel pH-sensitive polypeptide conjugated with carborane and cyanine probe for NIR imaging-guided therapeutic (Figure 1). Modified m-carborane was polymerized via reversible addition fragmentation reversible addition-fragmentation chain transfer (RAFT) polymerization.19 Poly-oligo (ethylene glycol) methacrylate (POEGMA) was used as the hydrophilic segment and poly(b-benzyl-L-aspartate) (PBLA) via ring opening polymerization (ROP) as the functional hydrophobic part were attached.20 After ammonolysis with N,N-diisopropylethylamine (DIEA) for pH responsive, cyanine was attached to the triblock polymer to make a near infrared fluorescence probe. The whole polymer has a narrow polymer dispersity index (PDI) with suitable size after self-assembling to micelles which also showed applicable optical properties for bioimaging. MTT and cellular uptake experiments with HepG2, HeLa, and HL7702 cell lines were also carried out to study the biocompatibility and cell
fluorescence imaging ability of the copolymer, respectively. The results indicate that these pH-sensitive biodegradable micelles are potential useful tools for precisely imaging-guided therapy.

2. Experimental

2.1. Reagents and characterization

All reagents mentioned were bought from Aladdin Corporation.