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Development of stealth shell based on polycarboxybetaine structure tuned to selectively interact with cells in tumor extracellular acidic pH

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【Purpose and Methods】Polycarboxybetaines (PCBs) are in a class of polymers that have stable hydration layer as a result of strong electrostatic interaction with water. This hydration property suppresses nonspecific interactions of PCBs with biomacromolecules in blood, providing PCBs-coated nanoparticles (NPs) with prolonged blood circulation time, toward efficient accumulation in tumor based on enhanced permeation and retention effect. Meanwhile, extracellular pH in tumor tissue is weakly acidic (pH~6.5), compared to blood and normal tissue, due to tumor-specific metabolic activity (i.e., Warburg effect). This acidic condition in tumor motivates us to design a PCB with pH-responsiveness, and thus we developed poly-$_{L}$-glutamide (PGlu) with side chains having a carboxyethyl unit and one aminoethylene unit (EDA-Car) or two repeated aminoethylene units (DET-Car). PGlu(DET-Car) potentially behaves as polycation selectively in acidic tumor environment, leading to interaction with anionic extracellular matrix (ECM). In this study, fluorescence correlation spectroscopic (FCS) analysis and flow cytometric analysis (FCM) were performed to investigate the pH-responsive interaction of Cy3-PCBs with heparin (one of the components of ECM) and A549 (human lung carcinoma) cells, respectively.

【Results and Discussion】In FCS analysis, PGlu(DET-Car) interacted with heparin selectively at acidic pH (<6.5); the hydrodynamic diameter of PGlu(DET-Car) derivative increased by 20% compared to its original value. In addition, PGlu(EDA-Car) showed negligible interaction with heparin in the treated pH range (5.0-8.0), confirming the acidic pH-responsive behavior of PGlu(DET-Car). Moreover, results in FCM analysis showed acidic pH-responsive cellular uptake of PGlu(DET-Car) for cultured A549 cells. The cells treated with PGlu(DET-Car) at pH 7.4 showed comparable Cy3 fluorescence intensity with the cells treated with PGlu(EDA-Car) and non-treated cells, whereas 2-fold increase in the intensity was observed for the cells treated at pH 6.5, suggesting the interaction of PGlu(DET-Car) with ECM in tumor acidic pH for enhanced cellular uptake.