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Poly(*N*-isopropylacrylamide)-based polymer inducing isothermal hydrophilic-to-hydrophobic phase transition via detachment of hydrophilic acid-labile moiety for effective photodynamic therapy

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Introduction

Copolymerizing poly(N-isopropylacrylamide) (PNIPAAm) with ionizable monomers offers pH-responsive lower critical solution temperature (LCST) polymers. However, gradual ionization of comonomer limits LCST shift in response to narrow pH change[1]. Here, I developed ionization-independent LCST polymer that exerts remarkable LCST shift in response to slight pH change. The remarkable LCST shift is driven by the attachment and detachment of a hydrophilic moiety on the side chain. The polymer has PNIPAAm backbone with NIPAAm analogue units possessing amines termed as AIPAAm (2-aminoisopropylacrylamide) that are modified with hydrophilic acid-labile of 2-propionic-3-methylmaleic (PMM) amides (Figure 1a).

Methods

The pH-responsive polymer, P(NIPAAm/AIPAAm-PMM) was constructed by PMM anhydride to the amine group of P(NIPAAm/AIPAAm) that was synthesized by side chain modification of poly(acrylic acid). LCST was evaluated using an absorptiometer. Cellular uptake of fluorescently-labelled polymer was investigated in lung adenocarcinoma (A549) cells by flow cytometry. To examine tumor accumulation, polymer was intravenously injected to (BALB/c) mice bearing subcutaneous tumors, and the amount of the polymer in the tumor was quantified by measuring fluorescence.

Discussion

Because the PMM amide group contains two hydrophilic carboxyl groups, PMM amide formation augments the hydrophilicity of the polymer and increases the LCST. In addition, due to the double substitution of $-CH_3$ and $-C_2H_4CO_2H$ at its unsaturated carbon-carbon bond, the PMM amide can is cleaved in response to pH < 7.0[2]. As a result, even a slightly acidic environment (e.g., pH 6.8) could facilitate detachment of the PMM moiety and, consequently, lowered the LCST to that of the original P(NIPAAm/AIPAAm), thereby exerting sharp pH-responsive phase transition in an ionization-independent manner (Figure 1b). The sharp hydrophilic-to-hydrophobic transition of the polymer at a physiological temperature (37°C) *in vitro* could strikingly facilitated interaction with cultured cells (Figure 1c). The polymer also showed significantly higher accumulation within a solid tumor after systemic injection compared to conventional PNIPAAm, that can be attributed

to its conversion to a hydrophobic structure through the cleavage of the PMM group in the acidic cancer microenvironment and eventual interactions with the cells (Figure 1d).

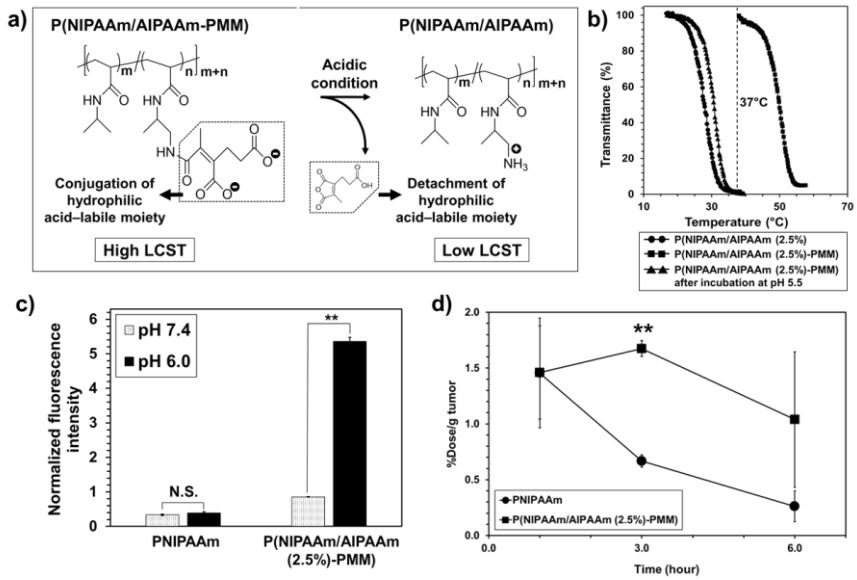

Figure 1. a) Chemical structure of the pH-responsive polymer. b) pH-responsiveness profile of the polymer. Result of c) cellular uptake study and d) tumor accumulation study (n=4, $p^{**} < 0.01$).

This character-switching strategy offers new approach for effectively delivering low molecular weight photosensitizer of 700DX. Endowing hydrophilic character at physiological condition, 700DX-conjugated P(NIPAAm/AIPAAm (2.5%)-PMM) minimalized the interaction with the normal cell, diminishing its phototoxicity. At acidic condition of cancer tissue, however, hydrophilic-to-hydrophobic phase transition of the polymer enhanced polymer-cell interaction that led to enhanced 700DX internalization, thereby augmenting its therapeutic photoactivity.

References

(1) Gao, X. et al., *J. Mater. Chem. B* **2013**, 1, 5578-5587.

(2) Maeda, Y. et al., *Macromol. Rapid Commun.* **2014**, 35, 1211-1215.

Journal Publication

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Conference Presentation

Muttaqien S. E., Nomoto, T., Takemoto, H., Matsui, M., Tomoda, K., and Nishiyama, N. Novel Design of pH-responsive Polymer for Targeting Acidic Microenvironment of Tumor. 256th American Chemical Society (ACS) National Meeting, August 19–23, 2018 (Boston, The USA).