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Article / Book Information

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種別(和文)	論文要旨
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（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Poly(*N*-isopropylacrylamide) (PNIPAAm) is the most extensively studied temperature-responsive polymer. Among thermosensitive poly(alkyl acrylamide) derivatives, PNIPAAm exhibits the sharpest phase transition at its lower critical solution temperature (LCST), transitioning from a hydrophilic coil conformation to a hydrophobic globule in aqueous solution. The LCST of PNIPAAm can be tailored by modification of the polymer structure: LCST can be altered to a higher or lower temperature via copolymerization with a hydrophilic or a hydrophobic monomer, respectively. Due to these unique characteristics, ionizable monomers, such as acrylic acid (AAc), are copolymerized with PNIPAAm to produce a pH-responsive LCST polymer (P(NIPAAm/AAc)). The charged state of the ionized pendent group enhances the hydrophilicity of the polymer structure, thereby increasing the LCST. Reversibly, when the ionic groups are deionized, the polymer's LCST decreases due to augmented hydrophobicity. Although copolymerization of NIPAAm with ionizable monomers has been exhaustively explored, designing a polymer structure that can exert sharp responsiveness to slight pH change remains a challenge. The major obstacle in this

ionization-dependent design is the gradual ionization profile of ionizable monomers at a broad pH range due to the electrostatic field produced by the polymers; consequently, LCST gradually changes across a wide pH range. Furthermore, excess introduction of the ionizable monomer can reduce or even eliminate phase transition behavior, because the aggregation force of the hydrophobic component in NIPAAm is offset by the increased hydration and disruption of the repetitive structure of the isopropylamide group that captures and releases hydrated water clusters during phase-transition. Considering the above-mentioned limitations, synthesis of a polymer that drastically decreases its LCST in response to a narrow pH change without compromising its thermal sensitivity may require a new design concept.

In this thesis, we proposed an ionization-independent approach for the synthesis of polymers that exert a sharp phase transition in response to a 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 a backbone consisting of NIPAAm and 2-aminoisoprpylacrylamide (AIPAAm) units, namely P(NIPAAm/AIPAAm). The AIPAAm structure is designed to allow the introduction of the primary amines into the PNIPAAm without disturbing the continuous structural similarity of the *N*-alkyl groups, which is essential for the sensitive hydration/dehydration transition. The hydrophilic and acid-sensitive moiety, 2-propionic-3-methylmaleic (PMM) amide is formed by reacting PMM anhydride to the amine in the AIPAAm unit, affording P(NIPAAm/AIPAAm-PMM). 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. 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. The sharp hydrophilic-to-hydrophobic transition of the polymer at a physiological temperature (37°C) *in vitro* could strikingly facilitated interaction with cultured cells. 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. This study, therefore, provides a novel polymer that offers delicate control of LCST and pH-responsiveness suitable for use in even fuzzy biological environments, and importantly, could be exploited further as a carrier for drug delivery in cancer treatment.

For photodynamic therapy (PDT), the physicochemical properties of photosensitizer (PS) play an important role on its biodistribution profile. In this thesis, hydrophilic photosensitizer (IRDye 700Dx) was conjugated to P(NIPAAm/AIPAAm-PMM). The 700DX-polymer conjugate successfully inherited the native character of P(NIPAAm/AIPAAm-PMM), permitting hydrophilic-to-hydrophobic phase transition in response to acidic pH. 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, isothermal hydrophilic-to-hydrophobic phase transition of the polymer enhanced polymer-cell interaction that led to enhanced 700Dx internalization, thereby augmenting its therapeutic photoactivity. In vivo study shows that the hydrophilic nature of the 700DX-conjugated polymer reduces unintended interaction with blood protein, averting skin phototoxicity unlike 700DX. Meanwhile, the hydrophobic character of PS-conjugated P(NIPAAm/AIPAAm-PMM at acidic condition permitted higher tumor retention compared to free-PS and PS-conjugated PNIPAAm, resulting in higher anti-tumor PDT efficacy. This character-switching strategy through isothermal hydrophilic-to-hydrophobic phase transition offers new strategy for effectively delivering low molecular 700DX to achieve enhanced photodynamic anti-tumor activity and simultaneously minimalize its side effect.