Stimuli-responsive fluorescent supramolecular polymers based on pillarenes for controlled drug release

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Tremendous effort has been dedicated to the targeted delivery and controlled release of drugs for degenerative disease treatments, in particular cancer therapy [1]. Considering the difficulties in the formulation and delivery of poorly water-soluble drug molecules, different types of vehicles, such as mesoporous silica nanocarriers, microemulsions, organogels, vesicles, micelles, and dendrimers, have been designed and constructed to achieve sustained drug release. Semisolid supramolecular organogels, constructed through the reversible host-guest interactions, allow the immobilization of liquid and solid components, thus provide the rigidity and functionality of the microstructures for drug loading and the stimuli-responsiveness for on-demand drug release [1,2].

We have designed and synthesized a tetraphenylethene (TPE)-bridged pillarene [3] tetramer (TPE-TP5) [4] and a 9,10-distyrylanthracene (DSA)-bridged pillarene dimer (DSA-DP5), both of which have been demonstrated to possess an obvious fluorescence emission enhancement upon addition of a neutral guest linker G since supramolecular polymers have been constructed through host-guest complexation between TPE-TP5 (or DSA-DP5) and G (Fig. 1). Fluorescent supramolecular gels have been successfully obtained at suitable host/guest concentrations. These supramolecular gels can be used as novel drug delivery systems. Drugs can be loaded within the matrix when the supramolecular gel is fabricated and released when used as novel drug delivery systems. Drugs can be loaded within the suitable host/guest concentrations. These supramolecular gels can be used as novel drug delivery systems. Drugs can be loaded within the

**Fig. 1.** Schematic representation of a supramolecular gel for the loading and temperature-controlled release of drugs.

**Keywords:** controlled drug release, fluorescence, supramolecular gel, pillarene, stimuli-responsive

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**References**

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Nucleolin targeting AS1411 aptamer modified pH-sensitive micelles: A dual-functional strategy for paclitaxel delivery

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Targeted drug delivery coupled with rapid drug release in cytoplasm is a powerful strategy to enhance efficacy and reduce off-target effects of anti-cancer drugs. Herein, we developed a dual-functional mixed micellar drug delivery system consisting of a biocompatible pH-responsive copolymer, d-α-tocopheryl polyethylene glycol 1000-block-poly-(l-lysino- amino ester) (TPGS-b-PBAE or TP) [1], and AS1411 DNA aptamers (Apt) [2] that recognize the over-expressed nucleolin located on plasma membrane of cancer cells. TP was synthesized by condensation polymerization of diacrylate and piperazine in the presence of TPGS-diacrylate macromonomer. Anti-cancer drug paclitaxel (PTX) was encapsulated in the Apt-TP micelles. The resulting PTX/Apt-TP micelles were uniformly round with particle size and zeta potential at 116.3 ± 12.4 nm and −26.2 ± 4.2 mV, respectively. The PTX/Apt-TP micelles were stable at pH 7.4 and dissociated in a weak acidic environment (pH 5.5) and quickly released the encapsulated PTX. Compared with non-Apt modified micelles, the uptake of Apt-modified micelles in SKOV3 ovarian cancer cells was significantly higher, whereas no remarkable difference in cellular uptake was observed by using Apt or non-Apt modified micelles in normal cells (Fig. 1). The enhanced transmembrane ability of PTX through Apt-nucleolin interaction was confirmed by pretreatment with endostatin, a nucleolin inhibitor. With a synergistic effect of cancer cell recognition and pH-sensitive drug release, we observed a significant higher cytotoxicity against SKOV3 cells by PTX/Apt-TP micelles compared with free PTX. The IC_{50} of PTX/Apt-TP micelles was about 10-fold lower than that of free PTX.

The potent cytotoxicity of PTX/Apt-TP micelles was manifested as increased cell apoptosis, cell arrest in the G2/M phase, and tubulin polymerization. More importantly, continuous intravenous administration of PTX/Apt-TP micelles significantly reduced the growth of tumor tissue and the representative toxicity of myelosuppression of

**Fig. 1.** Intracellular uptake observation of Cy5-loaded micelles in SKOV-3 cells.