SELF-ASSEMBLED POLYMER DRUG CONJUGATES OF GEMCITABINE AND CAMPTOTHECIN FOR COMBINATIONAL THERAPEUTICS

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ABSTRACT

Pancreatic cancer is associated with very low survival rates and poor prognosis, due to the lack of afficient therapeutic modalities and diagnostic tools. Tumor targeted combinational drug delivery therapies have been proposed as a promising potent approachto maximiza therapeutic efficiency through drug synergism and enhanced tumor accumulation [1-3]. The aim of this work was the development of thermoresponsive diblock copolymers consisting of a camptothecin/gemcitabine rich block and a second thermoresponsive protein repellent block, prepared by reversible addition fragmentation transfer (RAFT) polymerization. The PDC monomer precursors were synthesized by standard carbodiimide coupling and were characterized with analytical techniques, such as ^{1}H NMR, and IR. The PDCs were synthesized by copolymerization either with a poly(ethylene glycol) macroinitiator or with a thermoresponsive oligo(ethylene glycol methacrylate) chain transfer agent to form self-assembled micellar nanoconstructs. The resulting PDCs were characterized by gel permeation chromatography (GPC), and dynamic light scattering (DLS). It was shown that the PDCs had high drug loading rates (>50%) and could elicit controlled drug release owing to the insertion of hydrolyzable linkers. Preliminary in vitro studies against pancreatic cancer cells (MiaPaCa-2) showed promising cytotoxicity retults exceeding the potency of the parent drug molecules. The use of a thermal stimulus within the mild hyperthermia window (i.e. 42C^{o}) was found to further enhance the cytotoxic potency of the nanomedicines.

KEYWORDS: polymer drug conjugates, gemcitabine, camptothecin, combinational delivery, thermoresponsive polymers, nanomedicines

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