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Cathepsin S-cleavable, multi-block HPMA copolymers for improved SPECT/CT imaging of pancreatic cancer

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Abstract

This work continues our efforts to improve the diagnostic and radiotherapeutic effectiveness of nanomedicine platforms by developing approaches to reduce the non-target accumulation of these agents. Herein, we developed multi-block HPMA copolymers with backbones that are susceptible to cleavage by cathepsin S, a protease that is abundantly expressed in tissues of the mononuclear phagocyte system (MPS). Specifically, a bis-thiol terminated HPMA telechelic copolymer containing 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was synthesized by reversible addition−fragmentation chain transfer (RAFT) polymerization. Three maleimide modified linkers with different sequences, including cathepsin S degradable oligopeptide, scramble oligopeptide and oligo ethylene glycol, were subsequently synthesized and used for the extension of the HPMA copolymers by thiol–maleimide click chemistry. All multi-block HPMA copolymers could be labeled by ^{177}Lu with high labeling efficiency and exhibited high serum stability. *In vitro* cleavage studies demonstrated highly selective and efficient cathepsin S mediated cleavage of the cathepsin S-susceptible multi-block HPMA copolymer. A modified multi-block HPMA copolymer series capable of Förster Resonance Energy Transfer (FRET) was utilized to investigate the rate of cleavage of the multi-block HPMA copolymers in monocyte-derived macrophages. Confocal imaging and flow cytometry studies revealed substantially higher rates of cleavage for the multi-block HPMA copolymers containing the cathepsin S-susceptible linker. The efficacy of the cathepsin S-cleavable multi-block HPMA copolymer was further examined using an in vivo model of pancreatic ductal adenocarcinoma. Based on the biodistribution and SPECT/CT studies, the copolymer extended with the cathepsin S susceptible linker exhibited significantly faster clearance and lower non-target retention without compromising tumor targeting. Overall, these results indicate that exploitation of the cathepsin S activity in MPS tissues can be utilized to substantially lower non-target accumulation, suggesting this is a promising approach for the development of diagnostic and radiotherapeutic nanomedicine platforms.

1. Introduction

In 2015, pancreatic cancer was estimated to be the 11th and 8th most commonly diagnosed cancer for men and women in the United States, respectively. At the same time, it is estimated to account as the 4th leading cause of cancer related death for both men and women [1]. Pancreatic ductal adenocarcinoma (PDAC), which constitutes over 90% of pancreatic cancers in humans, is a devastating and virtually unexceptionally lethal malignancy [2]. Due