Redox-responsive nano-self assemblies for targeted cancer therapeutics

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Background: Despite significant advances in cancer therapeutics, it remains one of the leading causes of deaths due to poor response to available treatment modalities and drug resistance. Combination therapy has shown the potential to provide a synergistic therapeutic effect and to overcome drug resistance. However, smart delivery systems that can improve the bioavailability and the delivery of multiple hydrophobic anti-cancer drugs simultaneously at the tumor site without normal organ toxicity could be an effective strategy for cancer treatment.

Methods: Here, a PEGylated drug-drug conjugate (CUR-PEG-S-S-CPT) have been successfully synthesized by conjugating two hydrophobic anti-cancer molecules, curcumin and camptothecin through an ester and a redox-sensitive disulfide linkage (-S-S-), respectively, with the PEG chain, *via in situ* two-step reaction. This amphiphilic polymeric-dual drug conjugate was characterized in the presence and absence of the tannic acid (TA, a physical crosslinker) using various *in vitro* biophysical, analytical, and functional bioassays.

Results: The newly synthesized amphiphilic CUR-PEG-S-S-CPT polymer was found to spontaneously self-assembled in presence of tannic acid into anionic comparatively smaller sized stable nano-assemblies in water in comparison to parent conjugate, where the drug forms hydrophobic core of the particle with negative chirality and left-handed helical arrangement. TA, in addition to help forming stable nano-assemblies in water, it was able produce FRET pair in water between these two anticancer drugs. These nano-assemblies exhibited enhanced cellular uptake and antiproliferative effect in cancer cells (AsPC1 and SW480) in comparison to the individual drugs. Interestingly, our nanoassemblies showed preferential cleavage, breakdown and release of drugs in tumor-relevant redox environment leading to disappearance of the FRET signal, thus can be highly effective for targeted cancer treatment.

Conclusions: Our promising *in vitro* results with novel redox stimuli-responsive (CUR-PEG-S-S-CPT) conjugate system in presence of TA can be a highly useful advanced theranostic platform for effective cancer treatment/management.

Keywords: Combination therapy, nano-selfassemblies, FRET, redox stimuli, smart nanoparticle, theranostic.