Self-Assembling Chimeric Polypeptides as Drug-Carrying Nanoparticles for Anti-Cancer Chemotherapy

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Chemotherapy is often limited by unfavorable pharmacokinetics and pharmacodynamics that result in dose-limiting cytotoxicity. Therefore, self-assembling nanoparticles have been of particular interest to address these limitations by altering the physicochemical properties of payloads. Motivated by current challenges, I designed and recombinantly synthesized amphiphilic chimeric polypeptides (CPs) capable of versatile payload conjugation and spontaneous assembly into monodisperse micelles. These CPs consisted of a hydrophilic elastin-like polypeptide that enabled non-chromatographic polypeptide purification, an aspartic acid linker, a short Cys-rich segment for drug conjugation, and a hydrophobic domain that promoted the spontaneous formation of CP nanoparticles. Additionally, bio-orthogonal conjugation of chemotherapeutics onto CPs through short acid-labile chemical linkers enabled controlled pH-mediated release of conjugated chemotherapeutics and enhanced self-assembly. Doxorubicin (Dox) was conjugated onto CPs to determine the effectiveness of pH-mediated release and the effects of payload conjugation on CP morphology. Results indicated that CP and Dox-CP nanoparticles had critical aggregation concentrations of 3.24 and 0.58 μM and hydrodynamic radii of 57.09 and 72.86 nm, respectively. Both CP and Dox-CP possessed transition temperatures of ~48 °C. Dox-CP also released 76.8% of conjugated chemotherapeutics after 24 hours in late endosome pH and was effective against triple-negative breast cancer cells. These favorable characteristics and the independent self-assembly of the designed CP will enable targeted chemotherapeutic delivery regardless of payload hydrophobicity.

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