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A Serum-Stable supramolecular drug carrier for chemotherapeutics fabricated by a Peptide-Photosensitizer conjugate

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ABSTRACT

Supramolecular assemblies fabricated by peptide-photosensitizer conjugates have attracted increasing attentions in recent years as drug carriers for chemotherapeutics (CTs). However, these assemblies have been known to suffer from disintegration by serum components leading to off-target drug release, and thereby impairing antitumor effects and causing systemic toxicities. To address this problem, this study reports a nano-architectural self-assembly peptide-photosensitizer carrier (NSPC) fabricated by conjugating a phthalocyanine derivative (MCPZnPc) and ε-poly-L-lysine (EPL). By engineering the core and peripheral interactions, MCPZnPC-EPL (M−E) NSPC firmly encapsulated multiple CTs, creating CT@M−E NSPCs that were highly stable against disintegration in serum. More importantly, CT@M−E NSPCs exhibited controlled release of CTs in tumor tissues. The antitumor effects of CTs were further promoted by the synergism with the reactivated photodynamic effect. Furthermore, M−E NSPC-encapsulation optimized CTs' biodistribution reducing adverse effects *in vivo*. This study provides a serum-stable supramolecular drug delivery system with photodynamic effect, which is applicable for a broad-range of CTs to promote antitumor effects and ameliorate adverse effects.

1. Introduction

Chemotherapy remains one of the main therapeutic modalities for most types of cancers. It involves the administration of cytotoxic drugs to inhibit mitosis or damage chromosomal DNA inducing the apoptosis of tumor cells [1]. However, by intervening with mitosis, chemotherapeutics (CTs) also cause undesirable off-target damages in healthy tissues containing cells with rapid divisions [2], e.g., causing myelosuppression due to attacking bone marrow cells [3]. Thus, pharmaceutical formulations are applied to enhance tumor-targeting properties and minimize off-target damages in healthy tissues. Clinically used drug delivery systems (DDSs) for CTs include: 1) polyethylene glycol (PEGylation), e.g., PEGylated doxorubicin; 2) liposomes, e.g., liposomal cytarabine (DepoCyt®), liposomal daunorubicin (DaunoXome®); and 3) recombinant albumin, e.g., albumin-encapsulated paclitaxel (Abraxane®) [4]. In a phase III clinical trial, compared to Taxol® (paclitaxel formulated with Cremophor EL), Abraxane® resulted in a higher overall response rate (33% vs. 19%), longer tumor progression time (23-week vs. 17-week), and reduced adverse effects, e.g., neutropenia (9% vs. 22%) and hypersensitivity reactions (4% vs. 12%) [5].

Peptide-based supramolecular assemblies have attracted increasing attentions because of their natural composition and fascinating functions, including optical, photodynamic, photothermal, and photocatalytic properties [6-8]. These supramolecular assemblies are constructed by the driving force of non-covalent intermolecular interactions, e.g., electrostatic, polar, van der Waals, or π-π interactions [9,10]. Supramolecular assemblies are also of great interests as DDSs for anticancer drugs [11,12], especially nano-architectural self-assembly peptide-photosensitizer conjugates (NSPCs) [13]. NSPCs are fabricated

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