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Glutathione-responsive self-delivery nanoparticles assembled by curcumin dimer for enhanced intracellular drug delivery

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ABSTRACT

Poor water solubility, short half-life, and low drug efficacy posed a challenge for clinical application of curcumin (CUR). In this work, a kind of CUR prodrug was synthesized by coupling two CUR molecules with a monothioether linker for glutathione (GSH)-responsive drug delivery. The synthesized CUR prodrug (CUR-S-CUR dimer) could self-assemble into the homogeneous spherical nanoparticles (NPs) in aqueous solution followed by surface functionalization of trace amounts of DSPE-PEG. These CUR-S-CUR@PEG NPs exhibited a small particle size of ~100 nm, high CUR-loading content of ~78 wt%, and good colloid stability. Moreover, the CUR-S-CUR@PEG NPs demonstrated much more efficient cellular uptake and intracellular/nuclear drug delivery compared with free CUR, indicating the advantages of small molecular prodrug assembly. In addition, the GSH with high concentration in tumor cells could trigger the disassembly of CUR-S-CUR@PEG NPs. Furthermore, the cytotoxicity assays indicated that the CUR-S-CUR@PEG NPs exhibited the comparable inhibition effect of tumor cell proliferation with free CUR due to sustained drug release. Therefore, these stimuli-responsive CUR-S-CUR@PEG NPs might have promising potential for highly efficient intracellular drug delivery and controlled drug release in cancer therapy.

1. Introduction

An increasing research on curcumin (CUR) has been reported in recent decades due to its antioxidant and anti-inflammatory abilities (Aggarwal et al., 2003; Aggarwal and Sung, 2009). CUR was a potential drug for different kinds of diseases including cancer, that came of its capacity to interact with a nuclear transcription factor NF-kβ and protein kinase C, eventually causing apoptosis (Aggarwal and Shishodia, 2006; Sharma et al., 2005; Tomita et al., 2006). Recently, CUR has attracted tremendous interest and been widely used in cancer therapy because of its extensive spectrum of antitumor efficiency against breast, cervical, melanoma carcinomas and low toxicity to normal tissues/cells. Nevertheless, it still suffered from the limitations including low aqueous solubility, rapid metabolism, fast elimination, and low bioavailability (Requejo-Aguilar et al., 2017; Sarika et al., 2015).

To overcome the above-mentioned problem and thus enhance the therapeutic efficacy of CUR, different methods have been extensively studied like physical encapsulation of CUR in liposomes or micelles, self-assembly through the complexation of CUR and cyclodextrin, and self-assembly of polymer-CUR conjugates (Bisht et al., 2007; Manju and Sreenivasan, 2011a,b, 2012). It was worthy mentioning that most of the strategies devoted to forming nanoscale formulation, which could increase water solubility of drug, protect drugs from degradation, retain a long blood circulation time, and allow easy entry into tumor tissues because of enhanced permeability and retention (EPR) effect (Dey and Sreenivasan, 2014; Maeda, 2010). Thus self-assembly based nanoscale formulations remarkably improved the delivery properties of drugs *in vivo* and *in vitro*. However, the loading efficiency was not satisfying, because the addition of extra carrier materials could induce the potential toxicity and the problem of excretion, metabolism, and degradation (Pei et al., 2017b). Thus a simple nanoparticle (NP) formulation with high CUR-loading content was urgently in need.

To solve the above-mentioned shortcomings, pure nanodrugs based

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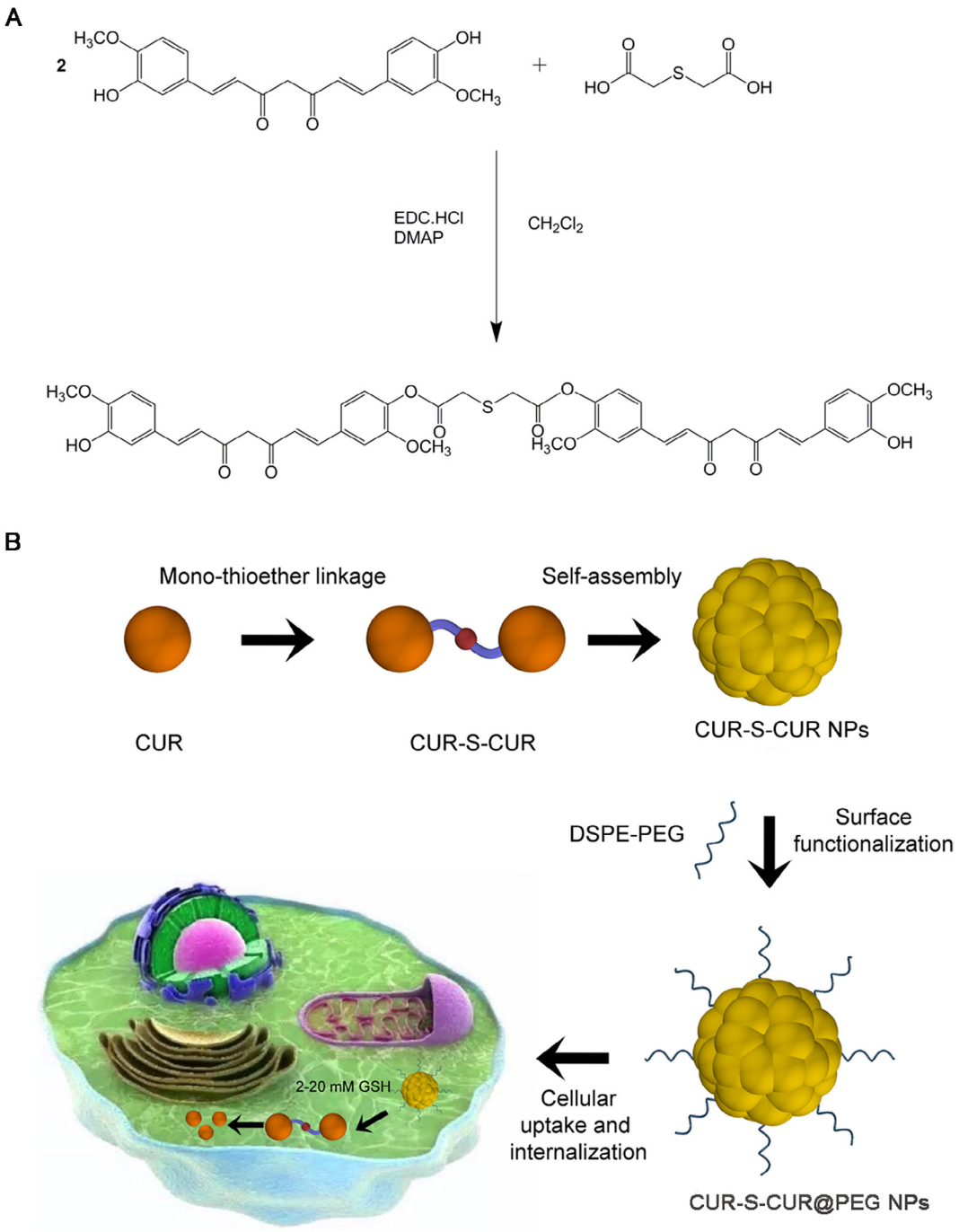

Scheme 1. (A) The synthesis route of CUR-S-CUR prodrug. The CUR-S-CUR prodrug conjugate was synthesized via esterification between the carboxyl group of 2′2-thiodiacetic acid and the hydroxyl group of curcumin. (B) The self-assembly of CUR-S-CUR prodrug followed by surface functionalization of trace amounts of DSPE-PEG and the endocytosis of CUR-S-CUR@PEG NPs by cancer cells.

on drug or prodrug building blocks prepared by the nanoprecipitation method were studied recently. On the one hand, this kind of one-component nanomedicine with high drug-loading capacity could achieve accumulation at the tumor site by passive targeting mechanism, on the other hand, the simply optimized molecular structure could help control drug loading and drug release of nanodrugs (Han et al., 2016; Su et al., 2015; Wang et al., 2014). At present, CUR-based nanodrugs without excess addition of carrier materials have barely been reported.

For anticancer drug delivery, the drug-drug conjugates were synthesized through a liable linker, which would fracture to release anticancer drug resulted from enzyme, pH value or glutathione (GSH) in tumor cells. It was well known that through regulating metabolism and activating types of enzymes, GSH could contribute to the growth of tumor cells in which GSH concentration was much higher than that in normal cells (Lee et al., 1989; Yin et al., 2013). There have been many studies on design of redox-sensitive nanosystems exploiting the high GSH concentration in tumor cells (Han et al., 2016; Huang et al., 2016; Li et al., 2016; Luo et al., 2016a; Luo et al., 2016b; Pei et al., 2017b; Tang et al., 2016). Sun and He et al. developed a novel prodrug nanosystem showing excellent GSH responsive ability, which was self-assembled by paclitaxel (PTX)-oleic acid (OA) conjugate through a mono-thioether linker (Luo et al., 2016a). Xie and Pei et al. Reported PTX dimer nanosystems containing a disulfide or mono-thioether linker to achieve GSH responsiveness (Pei et al., 2017a; Pei et al., 2017b). In