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Dual-functional liposomes based on pH-responsive cell-penetrating peptide and hyaluronic acid for tumor-targeted anticancer drug delivery

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ABSTRACT

Dual-functional liposomes with pH-responsive cell-penetrating peptide (CPP) and active targeting hyaluronic acid (HA) were fabricated for tumor-targeted drug delivery. A series of synthetic tumor pH-triggered CPPs rich in arginines and histidines were screened by comparing tumor cellular uptake efficiency at pH 6.4 with at pH 7.4, and R6H4 (RRRRRRHHHH) was obtained with the optimal pH-response. To construct R6H4-modified liposomes (R6H4-L), stearyl R6H4 was anchored into liposomes due to hydrophobic interaction. HA was utilized to shield positive charge of R6H4-L to assemble HA-coated R6H4-L (HA-R6H4-L) by electrostatic effect for protecting the liposomes from the attack of plasma proteins. The rapid degradation of HA by hyaluronidase (HAase) was demonstrated by the viscosity and zeta potential detection, allowing the R6H4 exposure of HA-R6H4-L at HAase-rich tumor microenvironment as the protection by HA switches off and cell-penetrating ability of R6H4 turns on. After HAase treatment, paclitaxel-loaded HA-R6H4-L (PTX/HA-R6H4-L) presented a remarkably stronger cytotoxicity toward the hepatic cancer (HepG2) cells at pH 6.4 relative to at pH 7.4, and additionally coumarin 6-loaded HA-R6H4-L (C6/HA-R6H4-L) showed efficient intracellular trafficking including endosomal/lysosomal escape and cytoplasmic liberation by confocal laser scanning microscopy (CLSM). In vivo imaging suggested the reduced accumulation of near infrared dye 15 (NIRD15)-loaded HA-R6H4-L (NIRD/HA-R6H4-L) at the tumor site, when mice were pre-treated with an excess of free HA, indicating the active tumor targeting of HA. Indeed, PTX/HA-R6H4-L had the strongest antitumor efficacy against murine hepatic carcinoma (Heps) tumor xenograft models in vivo. These findings demonstrate the feasibility of using tumor pH-sensitive CPPs and active targeting HA to extend the applications of liposomal nanocarriers to efficient anticancer drug delivery.

1. Introduction

Cell-penetrating peptides (CPPs), facilitating the cellular uptake of various cargos without causing any cellular injury, have been widely investigated in the fields of gene and drug delivery for cancer therapy [1–3]. Hereinto, octaarginine (R8), an arginine homopolymers derived from the basic domain of HIV-1 TAT protein, has been extensively used [4–6] as a result of its shortest possible peptide sequence still able to penetrate the plasma membrane [7]. Constant efforts have been devoted to exploit a variety of CPPs based on the template of oligoarginine for improved cellular uptake efficiency [8–10]. However, CPPs with effective tumor targeting are still lacking and remain highly desirable, which present more accumulations in tumor cells but less in normal cells.

In the light of this, the pH gradient between the tumor milieu and physiological environment [11] draws more attention to designing pH-responsive CPPs for tumor-targeted drug delivery, which can be used to conjugate drugs or modify nanocarriers. Histidine, a unique amino acid, is able to protonate for positive charge at the acidic tumor microenvironment instead of predominantly no charge at the physiological condition [12,13]. This feature of histidine has been used to design various pH-dependent peptides [13–15]. Zhang et al. replaced all the lysines of TK (AGYLLGKINLKKLAKL(Aib)KKIL-NH_2) with histidines

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