Colloids and Surfaces B: Biointerfaces 170 (2018) 330–340

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Full length article

Paclitaxel delivered by CD44 receptor-targeting and endosomal pH sensitive dual functionalized hyaluronic acid micelles for multidrug resistance reversion

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ARTICLE INFO

Keywords:
Paclitaxel
CD44 receptor-targeting
Endosomal pH sensitive hyaluronic acid micelles
Multidrug resistance reversion

ABSTRACT

The drug efflux mediated by P-glycoprotein (P-gp) transporter is a major factor responsible for multidrug resistance (MDR) of paclitaxel (PTX). The efficient intracellular PTX delivery is a promising strategy for overcoming the MDR of tumor cells. A CD44 receptor targeting and endosome-pH sensitive dual functionalized hyaluronic acid-deoxycholic acid-histidine (HA-DOCA-His) micellar formulation was developed to overcome MDR, and a CD44 receptor targeting hyaluronic acid-deoxycholic acid (HA-DOCA) micelles was used as a comparison. Compared with Taxol solution and HA-DOCA micelles, the cytotoxicity of PTX loaded in HA-DOCA-His micelles against drug-resistant tumor cells was improved significantly and possessed superior MDR-overcoming performance; this phenomenon is due to the increased intracellular PTX delivery by CD44 receptor-mediated endocytosis pathway and endosome-pH sensitivity-mediated PTX triggering release. Upon pharmacokinetic study, PTX/HA-DOCA-His micelles demonstrated longer blood circulation time, larger AUC, decreased V_d and CL than the Taxol solution. More importantly, PTX/HA-DOCA-His micelles were more effective in tumor growth inhibition in MCF-7/Adr tumor-bearing mice compared with PTX/HA-DOCA micelles and Taxol solution. Dual targeting strategy-functionalized HA-DOCA-His micelles demonstrated excellent MDR-reversing ability for therapeutic efficacy and improvement on MDR tumors, thereby providing an effective targeting strategy for PTX delivery of nano-drug delivery system in MDR cancer chemotherapy.

1. Introduction

The development of multidrug resistance (MDR) is one of major clinical problems that limit the chemotherapy efficacy of paclitaxel (PTX) [1]. The drug efflux mediated by P-glycoprotein (P-gp) transporter is a major reason for PTX resistance, which hampers chemotherapeutic treatments with the conventional formulation of Taxol solution [2]. This situation provides a strong incentive to develop MDR-reversing strategies that either evade drug efflux or suppress the function of MDR-related transporters [3].

Given the developments in nanotechnology, nano-drug delivery systems have become considerably promising in overcoming MDR and improving the chemotherapeutical efficacy for enhancing intracellular drug delivery and circumventing drug efflux via the distinct P-gp-escaping endocytosis pathway [4–7]. To date, polymeric micelle-based nano drug delivery systems have exhibited high potential for bypassing P-gp mediated efflux via the endocytosis pathway, and have shown improved antitumor therapeutic efficacy by tumor tissue targeted accumulation-mediated enhanced permeability and retention (EPR) effect [8–10].

High intracellular entry efficiency is a primary determinant for the MDR-overcoming efficiency of nanocarriers. Polymeric micelles can be conjugated with ligands or antibodies for active targeting, thereby aiding efficient intracellular uptake and improving drug retention in MDR tumor cells via receptor-mediated endocytosis, while avoiding P-gp-mediated drug efflux [11]. Hyaluronic acid (HA)-based micelles can be used as active tumor-targeted carriers for efficient intracellular drug delivery because of its CD44 receptor specific binding property [12,13].

Despite CD44 receptor-targeted HA micelles being capable of delivering the incorporated drugs into the cytoplasm of cancer cells with

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[1] The two authors contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to final version of the manuscript.

https://doi.org/10.1016/j.colsurfb.2018.06.024
Received 14 February 2018; Received in revised form 5 May 2018; Accepted 15 June 2018
Available online 18 June 2018
0927-7765/

high intracellular entry efficiency by evading P-gp-mediated efflux, the encapsulation of drugs in the endosome after endocytosis is a major barrier during intracellular transport [14,15]. Inefficient drug release during intracellular transport leads to decreased effective drug concentration in MDR tumor cells. Therefore, the accumulation enhancement of cytotoxic drugs in the MDR cells by receptor-mediated endocytosis can only attain a limited MDR reversion effect. Thus, in general, an ideal drug delivery nanosystem for overcoming MDR is further required to release drugs into the cytoplasm rapidly and thoroughly, thereby leading to a sufficiently high intracellular drug concentration to exceed drug efflux and threshold concentration that inhibits the proliferation of drug-resistant cancer cells and kills them [16].

Increasing, pH-responsive intracellular targeting has been investigated as a pathway to trigger the release of anticancer drugs after the micelle has been taken up by cells; this approach is competitive and favorable for MDR reversion [17–21]. Therefore, developmenting multiple-targeting nanosystems that combines receptor targeting with pH-responsive targeting strategies should be considered a better option in overcoming MDR and in enhancing tumor-specific drug delivery; moreover, these effects are indispensable in facilitating successful chemotherapy [16,22–25].

In our previous report, a hyaluronic acid-deoxycholic acid-histidine (HA-DOCA-His) micelle integrating CD44 receptor-targeted drug delivery of HA and endosomal pH-triggered drug release property of His was developed for effective cytosolic delivery of PTX [13]. As shown in Fig. 1, the developed nanomicelles were accumulated in tumor tissues via EPR effect and then internalized into cells via CD44 receptor-mediated endocytosis, followed by endosomal-pH triggered drug release and endosomal escape into the cytoplasm, induced increased cellular uptake, pronounced highest PTX cytotoxicity, and improved antitumor efficacy.

Can the HA-DOCA-His micelles with dual functions truly solve problems, such as P-gp-related MDR of PTX? Based on this purpose, the in vitro MDR reversion and in vivo antitumor efficacy on MDR tumors of HA-DOCA-His micelles were focused on systemic evaluation, thereby providing additional insights on the active targeting and endosome pH-sensitive dual functional HA-DOCA-His micelles that possibly acts as prospective nanocarriers to overcome MDR of PTX.

The HA-DOCA-His micelles were expected to passively accumulate in the tumor tissue by EPR effect and to be internalized into the MCF-7/Adr cells via CD44 receptor-mediated endocytosis. After endocytosis, the micelles disassembled in the acidic endosomes because of His protonation, thereby resulting in the burst release of PTX. The His further facilitated the endo-lysosomal escape and the translocation of PTX to the cytosol, thereby achieving effective intracellular PTX delivery and MCF-7/Adr cell growth inhibition for MDR reversion.

The most important advantage of this pioneering design is that the

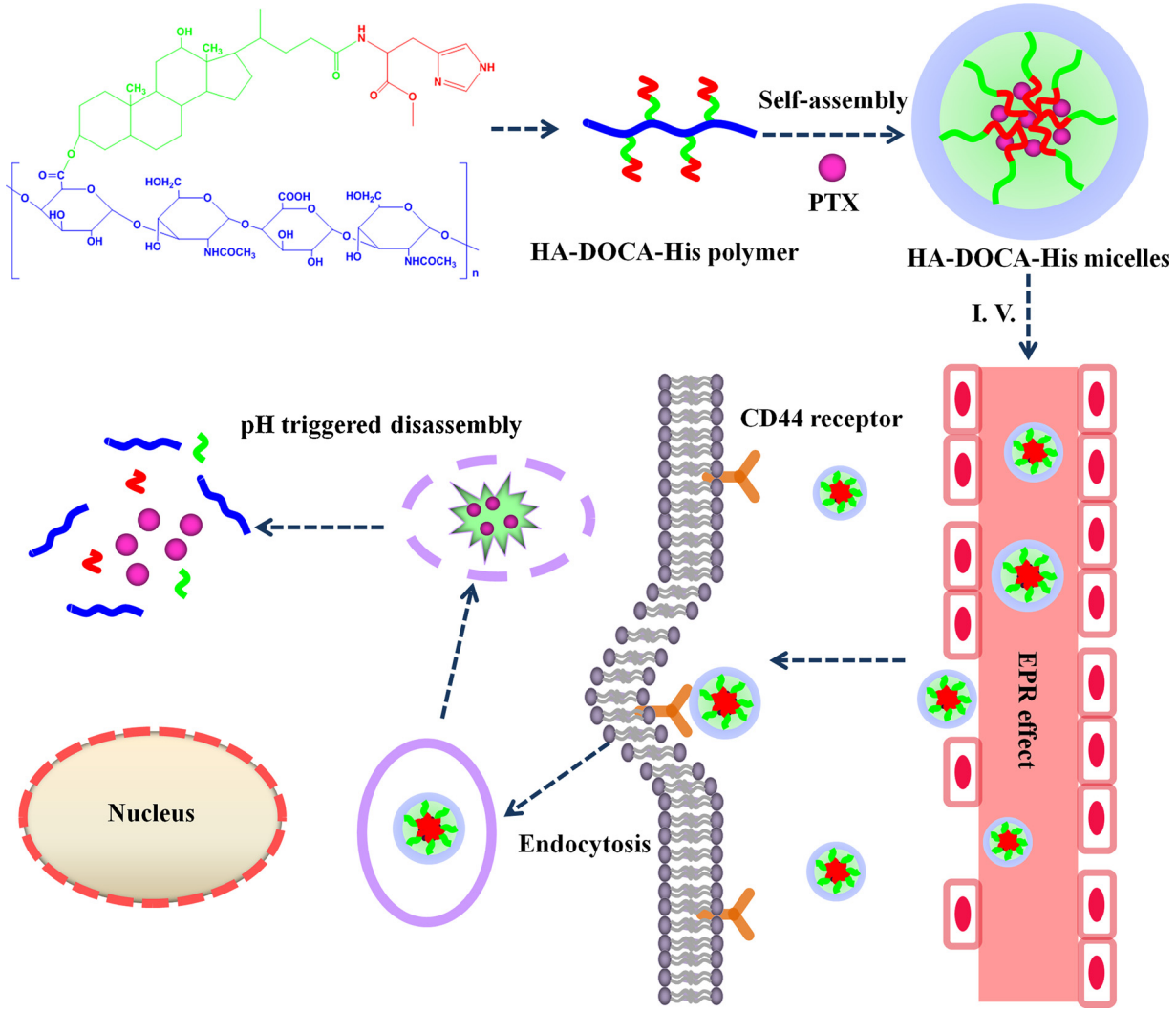

Fig. 1. Schematic illustration of the self-assembly, tumor tissue accumulation, tumor cells endocytosis and pH-sensitive intracellular PTX release of HA-DOCA-His micelles.