International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Liver-Targeting and pH-Sensitive Sulfated Hyaluronic Acid Mixed Micelles for Hepatoma Therapy

This article was published in the following Dove Press journal:
International Journal of Nanomedicine

Zhi-peng Li[1,*]
Gui-xiang Tian[1,*]
Hong Jiang[1,*]
Rui-yan Pan[2]
Bo Lian[1]
Min Wang[1]
Zhi-qin Gao[1]
Bo Zhang[2]
Jing-liang Wu[1]

[1]School of Bioscience and Technology, Weifang Medical University, Weifang, Shandong, People's Republic of China; [2]School of Pharmacy, Weifang Medical University, Weifang, Shandong, People's Republic of China

*These authors contributed equally to this work

Background: The tumor-targeting ability and pH-sensitive properties of intelligent drug delivery systems are crucial for effective drug delivery and anti-tumor therapy.

Methods: In this study, sHA-DOX/HA-GA mixed micelles were designed with the following properties: sulfated hyaluronic acid (sHA) was synthesized to block cell migration by inhibiting HAase; sHA-DOX conjugates were synthesized via pH-sensitive hydrazone bond to realize DOX-sensitive release. The introduction of HA-GA conjugate could improve active-targeting ability and cellular uptake.

Results: The results showed that the mixed micelles possessed a nearly spherical shape, nanoscale particle size (217.70±0.89 nm), narrow size distribution (PDI=0.07±0.04), negative zeta potential (−31.87±0.61 mV) and pH-dependent DOX release. In addition, the sHA-DOX /HA-GA micelles exhibited concentration-dependent cytotoxicities against liver carcinoma cells (HepG2) and HeLa cells, and were shown to be effectively taken up by HepG2 cells by confocal microscopy analysis. Furthermore, the in vivo anti-tumor study showed that mixed micelles had a superior anti-tumor effect compared to that of free DOX. Further evidence obtained from the hematoxylin–eosin staining and immunohistochemistry analysis also demonstrated that sHA-DOX/HA-GA exhibited stronger tumor inhibition and lower systemic toxicity than free DOX.

Conclusion: The sHA-DOX/HA-GA mixed micelles could be a potential drug delivery system for anti-hepatoma therapy.

Keywords: hyaluronic acid, glycyrrhetinic acid, hepatoma-targeting, pH-sensitive, micelles, anti-tumor therapy

Introduction

Liver cancer is one of the most common malignancies, with steadily increasing incidence globally. It has become the fourth leading cause of cancer-related deaths.[1,2] Traditional chemotherapy is one of the main treatment approaches used for cancer therapy.[3,4] Typical anti-cancer drugs, such as paclitaxel (PTX), doxorubicin (DOX), cisplatin (Pt), exhibit remarkable tumor inhibition, but these anti-cancer drugs are restricted in clinical applications due to their strong systemic toxicities, short half-times, non-specific targeting and vulnerability to multi-drug resistance (MDR).[5–8]

To overcome these limitations, intelligent drug delivery systems based on nano-scaled polymeric carriers, such as alginate micelles, hyaluronic acid micelles, and polyethylene glycol-phosphatidylethanolamine (PEG-PE) micelles, have been widely applied in anti-cancer therapy.[9–11] Hyaluronic acid (HA), a kind of nonsulfated glycosaminoglycan consisting of alternating units of D-glucuronic acid and N-acetyl-D-glucosamine, can serve as drug-loaded carriers due to many advantages, such as

Correspondence: Bo Zhang
School of Pharmacy, Weifang Medical University, Weifang, Shandong 261053, People's Republic of China
Email bozh315@163.com

Jing-liang Wu
School of Bioscience and Technology, Weifang Medical University, Weifang, Shandong 261053, People's Republic of China
Tel +86 536 846 2541
Email jlwu2008@163.com

http://doi.org/10.2147/IJN.S214528