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Tumor vasculature targeting following co-delivery of heparin-taurocholate conjugate and suberoylanilide hydroxamic acid using cationic nanolipoplex

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ABSTRACT

The chemical conjugate of low molecular weight heparin with taurocholate (LHT7) was previously designed to offer anticancer activity while minimizing the anticoagulant activity. In the present study, we found that the systemic administration of LHT7 in nanolipoplex could substantially enhance tumor vasculature targeting and anticancer effects. Moreover, we found that co-delivery of LHT7 with suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, in nanolipoplex could provide synergistic antitumor effect. LHT7/SAHA nanolipoplex was formulated by encapsulating SAHA inside cationic liposomes, followed by complexation of negatively charged LHT7 onto the cationic surfaces of SAHA-loaded liposomes (SAHA-L). LHT7/SAHA nanolipoplex was positively charged with a mean diameter of 117.6 nm, and stable in serum. The nanolipoplex form of LHT7 could alter its pharmacokinetics and biodistribution. Compared to the free form of LHT7, LHT7 in the nanolipoplex showed 1.9-fold higher mean residence time, and higher tumor vasculature accumulation after its intravenous administration. LHT7/SAHA nanolipoplex showed highest antitumor efficacy in SCC-bearing mice, compared to LHT7, SAHA-L and sequential co-administration of LHT7 and SAHA-L. Consistent with the enhanced antitumor effect, the reduction of abnormal vessels in the tumor site was also the highest in the LHT7/SAHA nanolipoplex-treated group. These results suggested the potential of LHT7/SAHA nanolipoplex for enhanced tumor vasculature targeting, and the importance of nanolipoplex-mediated co-delivery with a histone deacetylase inhibitor for maximal anticancer effect.

1. Introduction

Heparin, widely used as an anticoagulant drug, has been studied as an anticancer drug [1] for its inhibition effect on cancer cell proliferation, adhesion, angiogenesis, migration and invasion [2]. However, heparin anticoagulant activity causes adverse effects such as bleeding, which limits its expanded applications. In the previous study, Lee et al. reported a low molecular weight heparin (LMWH)-derived angiogenesis inhibitor with a low anticoagulant activity but with high antiangiogenic efficacy [3]. Moreover, the newly developed angiogenesis inhibitor, namely LMWH-taurocholate conjugate (LHT7), would be a promising agent owing to its wide range of inhibition effects on several angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor, and platelet-derived endothelial cell growth factor [3]. Considering that the kinds of angiogenic factors that are released from the tumor tend to increase as tumor progresses, multi-targeting antiangiogenic drugs such as LHT7 would be preferred to inhibit tumoral angiogenesis [4,5].

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