International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Hypoxia-responsive ionizable liposome delivery siRNA for glioma therapy

This article was published in the following Dove Press journal:
International Journal of Nanomedicine
8 February 2017
Number of times this article has been viewed

Hong-Mei Liu[1,2,*]
Ya-Fei Zhang[1,2,*]
Yan-Dong Xie[1,2]
Yi-Fan Cai[1,2]
Bai-Yang Li[1,2]
Wen Li[3]
Ling-Yu Zeng[4]
Yu-Ling Li[4]
Ru-Tong Yu[1,2]

[1]Department of Neurosurgery, Brain Hospital, Affiliated Hospital of Xuzhou Medical University, [2]Department of Neurosurgery, Institute of Nervous System Diseases, Xuzhou Medical University, [3]Department of Hematology, Affiliated Hospital of Xuzhou Medical University, [4]Department of Chemistry, School of Chemistry and Chemical Engineering, Jiangsu Normal University, Xuzhou, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hong-Mei Liu; Ru-Tong Yu
Institute of Nervous System Diseases, Xuzhou Medical University, No 84, West of Huaihai Road, Xuzhou 221002, Jiangsu, People's Republic of China
Tel +86 516 8580 2008
Email liuhongmei816@sina.com; yu.rutong@163.com

Abstract: Here, we report the hypoxia-responsive ionizable liposomes to deliver small interference RNA (siRNA) anticancer drugs, which can selectively enhance cellular uptake of the siRNA under hypoxic and low-pH conditions to cure glioma. For this purpose, malate dehydrogenase lipid molecules were synthesized, which contain nitroimidazole groups that impart hypoxia sensitivity and specificity as hydrophobic tails, and tertiary amines as hydrophilic head groups. These malate dehydrogenase molecules, together with DSPE-PEG2000 and cholesterol, were self-assembled into O′[1],O[1]-(3-(dimethylamino)propane-1,2-diyl) 16-bis(2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl) di(hexadecanedioate) liposomes (MLP) to encapsulate siRNA through electrostatic interaction. Our study showed that the MLP could deliver polo-like kinase 1 siRNA (siPLK1) into glioma cells and effectively enhance the cellular uptake of MLP/siPLK1 because of increased positive charges induced by hypoxia and low pH. Moreover, MLP/siPLK1 was shown to be very effective in inhibiting the growth of glioma cells both in vitro and in vivo. Therefore, the MLP is a promising siRNA delivery system for tumor therapy.

Keywords: hypoxia responsive, cellular uptake, siRNA delivery, ionizable liposome, hypoxic conditions

Introduction

Gene silencing through RNA interference (RNAi) has been demonstrated as a great potential therapeutic agent for cancer treatment.[1,2] Accumulating evidences have suggested that small interference RNAs (siRNAs), a class of small regulatory RNAs that recognize and degrade the complementary target messenger RNAs (mRNAs) in a sequence-specific manner at a post-transcriptional level, are linked to cancer formation and progression.[3] Recently, RNAi-based gene silencing approaches have been demonstrated in humans, and hold promise for cancer treatment.[4,5] Nevertheless, due to poor stability of siRNA in physiological conditions and its inability to cross cellular membranes, the in vivo delivery of siRNA holds a great challenge and remains a crucial issue for its therapeutic success.[6] Many kinds of nanosized cationic delivery systems have been developed for siRNAs delivery through electrostatic interaction, such as cationic polymers[7–9] and cationic lipids,[10,11] among which cationic lipids are the most widely used for systemic delivery of RNAi therapeutics in vivo. However, the toxicity is still an obstacle to the application of cationic lipids in siRNA delivery. The toxicity of cationic lipids is mainly determined by their cationic nature.[12,13] The positive zeta potential of nanoparticles (NPs) is required for binding siRNAs and their uptake by tumor cells. Therefore, designing a liposome with high siRNA loading capacity, high transfection efficiency, and low cytotoxicity is of great significance for therapeutic gene delivery, which remains highly challenging.

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/IJN.S125286