Accepted Manuscript

Mitochondrial alkaline pH-responsive drug release mediated by Celastrol loaded glycolipid-like micelles for cancer therapy

Yanan Tan, Yun Zhu, Yue Zhao, Lijuan Wen, Tingting Meng, Xuan Liu, Xiqin Yang, Suhuan Dai, Hong Yuan, Fuqiang Hu

PII: S0142-9612(17)30500-8

DOI: 10.1016/j.biomaterials.2017.07.036

Reference: JBMT 18199

To appear in: *Biomaterials*

Received Date: 12 June 2017

Revised Date: 15 July 2017

Accepted Date: 30 July 2017

Please cite this article as: Tan Y, Zhu Y, Zhao Y, Wen L, Meng T, Liu X, Yang X, Dai S, Yuan H, Hu F, Mitochondrial alkaline pH-responsive drug release mediated by Celastrol loaded glycolipid-like micelles for cancer therapy, *Biomaterials* (2017), doi: 10.1016/j.biomaterials.2017.07.036.

Mitochondrial alkaline pH-responsive drug release mediated by Celastrol loaded glycolipid-like micelles for cancer therapy

Yanan Tan [a], Yun Zhu [a], Yue Zhao [a], Lijuan Wen [b], Tingting Meng [b], Xuan Liu [b], Xiqin Yang [b], Suhuan Dai [b], Hong Yuan [b], and Fuqiang Hu [a,b,]*

[a] Ocean College, Zhejiang University, 1 Zheda Road, Zhoushan 316021, People's Republic of China.

[b] College of Pharmaceutical Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, People's Republic of China.

*Corresponding Author: Prof. Fuqiang Hu

Tel/Fax: +86-571-88208439

E-mail: hufq@zju.edu.cn

Abstract

Mitochondria, crucial regulators of inducing tumor cells apoptosis, can be treated as the prime target for tumor therapy. The selective and responsive release of proapoptotic therapeutics into mitochondria may notably improve antitumor efficiency. Herein, (4-Carboxybutyl) triphenylphosphonium bromide (CTPP), a lipophilic cation, was conjugated with glucolipid-like conjugates (CSOSA) to produce mitochondria-targeted conjugates (CTPP-CSOSA). Loading with weakly acidic drug Celastrol (Cela), CTPP-CSOSA/Cela micelles could selectively respond to mitochondrial alkaline pH (pH 8.0), controlled by the weaker interaction between hydrophobic core of micelles and Cela with higher solubility at pH 8.0. However, there was a slow drug release behavior at pH 7.4 and pH 5.0. It illustrated that CTPP-CSOSA/Cela could realize mitochondrial fast drug release, and decrease drug leakage in the cytoplasm and lysosome. CTPP-CSOSA/Cela highly enhanced ROS levels, which further induced mitochondria membrane potential decreasing and more Cytochrome C releasing into cytoplasm, then promoted tumor cells apoptosis notably. *In vivo*, CTPP-CSOSA had an enhanced accumulation in tumor tissue, compared with CSOSA. Moreover, the tumor-inhibition rate of CTPP-CSOSA/Cela was 80.17%, which was significantly higher than CSOSA/Cela (58.35%) and Cela (54.89%). Thus,