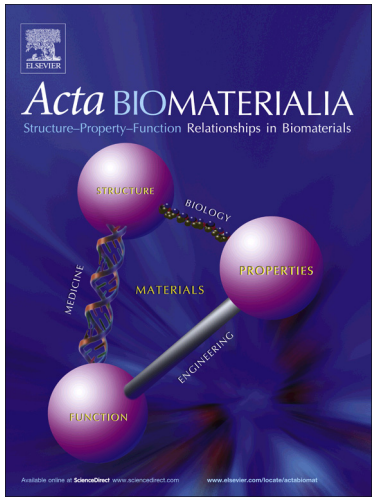

Full length article

Multilayer Photodynamic Therapy for Highly Effective and Safe Cancer Treatment

Ling Yang, Shaojuan Zhang, Xiaoxi Ling, Pin Shao, Ningyang Jia, Mingfeng Bai

PII: S1742-7061(17)30174-5
DOI: http://dx.doi.org/10.1016/j.actbio.2017.03.012
Reference: ACTBIO 4780

To appear in: *Acta Biomaterialia*

Received Date: 1 October 2016
Revised Date: 20 February 2017
Accepted Date: 8 March 2017

Please cite this article as: Yang, L., Zhang, S., Ling, X., Shao, P., Jia, N., Bai, M., Multilayer Photodynamic Therapy for Highly Effective and Safe Cancer Treatment, *Acta Biomaterialia* (2017), doi: http://dx.doi.org/10.1016/j.actbio.2017.03.012

Multilayer Photodynamic Therapy for Highly Effective and Safe Cancer Treatment

Ling Yang[a, 1], Shaojuan Zhang[b, 1], Xiaoxi Ling[b], Pin Shao[b], Ningyang Jia[*, c], and Mingfeng Bai[*, b, d, e, f]

[a] Department of Cellular and Genetic Medicine, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China
[b] Department of Radiology, University of Pittsburgh, 100 Technology Drive, Pittsburgh, PA 15219, USA
[c] Department of Radiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China
[d] Department of Medicine, University of Pittsburgh, 3501 Fifth Ave, Pittsburgh, PA 15213, USA
[e] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA 15261, USA
[f] University of Pittsburgh Cancer Institute, Pittsburgh, PA 15232, USA
[1] These authors contributed equally to this work.

[*] To whom Correspondence should be addressed
Mingfeng Bai
Postal Address: Molecular Imaging Lab, Department of Medicine, University of Pittsburgh
3501 Fifth Ave, Suite 10020, Pittsburgh, PA 15213
Telephone: +1-412-624-2565
Email: baim@upmc.edu

Abstract

Recent efforts to develop tumor-targeted photodynamic therapy (PDT) photosensitizers (PSs) have greatly advanced the potential of PDT in cancer therapy, although complete eradication of tumor cells by PDT alone remains challenging. As a way to improve PDT efficacy, we report a new combinatory PDT therapy technique that specifically targets multilayers of cells. Simply mixing different PDT PSs, even those that target distinct receptors (this may still lead to similar cell-killing pathways), may not achieve ideal therapeutic outcomes. Instead, significantly improved outcomes likely require synergistic therapies that target various cellular pathways. In this study, we target two proteins upregulated in cancers: the cannabinoid CB2 receptor (CB_2R, a G-protein coupled receptor) and translocator protein (TSPO, a mitochondria membrane receptor). We found that the CB_2R-targeted PS, IR700DX-mbc94, triggered necrotic cell death upon light irradiation, whereas PDT with the TSPO-targeted IR700DX-6T agent led to apoptotic cell death. Both PSs significantly inhibited tumor growth *in vivo* in a target-specific manner. As expected, the combined CB_2R- and TSPO-PDT resulted in enhanced cell killing efficacy and tumor inhibition with lower drug dose. The median survival time of animals with multilayer PDT treatment was extended by as much as 2.8-fold over single PDT treatment. Overall, multilayer PDT provides new opportunities to treat cancers with high efficacy and low side effects.

Keywords: Photodynamic therapy, CB2 receptor, TSPO, synergistic, combination therapy.

1. Introduction

Photodynamic therapy (PDT) offers a minimally invasive, effective and highly controllable therapeutic strategy, and has become popular as an alternative or additional approach to conventional cancer treatments, such as chemotherapy and surgery [1, 2]. During the process of PDT, a light-sensitive photosensitizer (PS) is activated by light irradiation at a specific wavelength to produce reactive oxygen species (ROS), such as singlet oxygen and free radical, which consequently lead to cell death [3]. PDT has been clinically approved to treat several types of cancers, such as esophageal and non-small cell lung cancer, as well as precancerous changes of Barrett's esophagus and skin (actinic keratosis). Moreover, many clinical trials are currently