Dual-action nanoplatform with a synergetic strategy to promote oxygen accumulation for enhanced photodynamic therapy against hypoxic tumors

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Journal: Acta Biomaterialia

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Date: 2022.10.14

一、簡述論文概要及重大發現

隨著不同的治療癌症方式的發展，光動力療法（PDT）成為臨床上應用最廣泛的治療方式之一，但腫瘤微環境的缺氧情況限制了 PDT 的療效，所以作者們設計了一種具有緩解缺氧的奈米藥物系統（SHRN），在 PDT 的基礎上緩解腫瘤缺氧。在 SHRN 奈米粒子加入產氧劑 MnO_2、耗氧抑製劑 atovaquone (ATO) 和光敏劑金絲桃素(HY)。MnO_2 會與腫瘤微環境中過量的 H_2O_2 進行反應以增加氧氣的產生，而 ATO 會抑制有氧呼吸鏈中的電子轉移以減少氧氣消耗。然後利用 HY 在充足的氧氣下產生 ROS 以增強 PDT 效應。且在經過體外和體內試驗證實後，SHRN 表現出強大的抗腫瘤效果。該系統可在缺氧腫瘤微環境中實施 PDT 療法提供替代策略。

二、對論文內容的提問

奈米粒子中的 MnO_2 是一種重金屬，且過去也發現 Mn 會造成一些疾病的發生，例如：神經性退化疾病，雖然論文中提到經過小鼠試驗後，對於小鼠並沒有產生毒性但因為實驗天數較短，無法得知長時間的 MnO_2 累積是否會對小鼠產生影響。

三、論文的缺點與評論

本研究中證明了產氧劑 MnO2、耗氧抑製劑 atovaquone (ATO) 和光敏劑金絲桃素(HY)奈米粒子的奈米載體 SHRN 可以標靶缺氧的癌細胞並通過解決缺氧的情況達到增加 PDT 的效果，此藥物載體的設計非常精巧，值得學習。

Acta Biomaterialia 146 (2022) 465–477

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

Full length article

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ARTICLE INFO

Article history:
Received 10 January 2022
Revised 1 April 2022
Accepted 20 April 2022
Available online 6 May 2022

Keywords:
Photodynamic therapy
Hypoxic tumor
Hypericin
Atovaquone
Manganese dioxide
Nanodrug delivery system

ABSTRACT

With the development of redox-related therapy modalities in cancer therapy, photodynamic therapy (PDT) has gradually become the most widely used type in the clinic. However, the hypoxic tumor microenvironment restricted the curative effect of PDT. Here, a strategic hypoxia relief nanodrug delivery system (SHRN) with a synergetic strategy was designed to alleviate tumor hypoxia on the basis of PDT. Specifically, the oxygen producer MnO_2, oxygen consumption inhibitor atovaquone (ATO) and photosensitizer hypericin (HY) were loaded in SHRN. MnO_2 reacted with excess H_2O_2 in the tumor microenvironment to increase oxygen generation, while ATO inhibited electron transfer in the aerobic respiratory chain to decrease oxygen consumption. Then, HY utilized this sufficient oxygen to produce ROS under irradiation to enhance the PDT effect. *In vitro* and *in vivo* assays confirmed that SHRN exhibits powerful and overall antitumor PDT effects. This formulation may provide an alternative strategy for the development of PDT effects in hypoxic tumor microenvironments.

Statement of significance

We constructed a strategic hypoxia relief nanodrug delivery system (SHRN) with a synergetic strategy to alleviate tumor hypoxia on the basis of photodynamic therapy (PDT). This work uniquely aimed at not only increased O_2 generation in hypoxic tumor microenvironment but also reduced O_2 consumption. Moreover, we designed a nanodrug delivery system to enhance the tumor permeability of SHRN. In vitro and in vivo assays all confirmed that SHRN exhibited powerful and overall antitumor effects. This formulation may provide an alternative strategy for the development of the PDT effect in hypoxic solid tumor.

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1. Introduction

Photodynamic therapy (PDT) is a redox-related cancer therapy modality that has been approved for clinical use in breast, lung, skin and esophageal cancers as a typical treatment pattern [1–4]. Compared with traditional therapies, PDT has the advantages of being noninvasive and having low toxicity, low drug resistance and so on [5]. PDT is made up of three basic components: photosensitizer, exciting light irradiation and tissue oxygen. A low-toxic photosensitizer transfers its excited state energy to tissue oxygen to generate a large amount of reactive oxygen species (ROS) when irradiated with excitation light. The generation of exogenous ROS can destroy the endogenous antioxidant system, break the tumor microenvironment homeostasis and leads to apoptosis and/or necrosis of tumor cells [6,7]. For PDT, the photosensitizer and light source can be selected readily according to the clinical needs. Therefore, the O_2 levels are deemed the critical factor affecting the PDT effect.

The rapid proliferation of tumor cells consumes a large amount of tissue oxygen, which constitutes an inherent characteristic in tumors [8]. The abnormal structure and function of tumor tissues limit O_2 delivery, resulting in a hypoxic microenvironment in solid tumor tissues compared with normal tissues. In addition, the O_2 pressure in some solid tumors is close to 0 mmHg, compared with 30 mmHg in normal tissues [9,10]. Moreover, tumor cells are far-

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https://doi.org/10.1016/j.actbio.2022.04.035
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