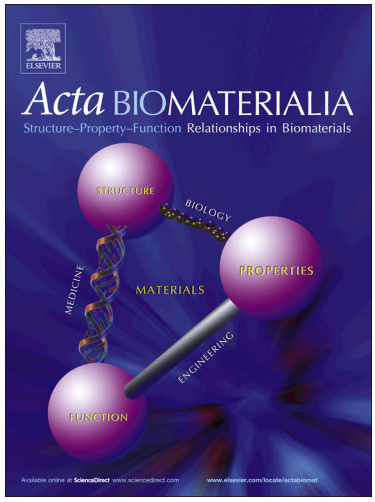

Full length article

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Targeting Tumor Hypoxia with Stimulus-Responsive Nanocarriers in Overcoming Drug Resistance and Monitoring Anticancer Efficacy

Zhiqi Xie[a,#], Wangwei Guo[a,#], Ningning Guo[a], Mingyi Huangfu[a], Huina Liu[a], Mengting Lin[a], WenHong Xu[b], Jiejian Chen[b], TianTian Wang[a], Qichun Wei[b], Min Han[a,*], Jianqing Gao[a,*]

[a] College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P.R.China.

[b] Department of Radiation Oncology, Key Laboratory of Cancer Prevention and Intervention, the Second Affiliated Hospital, Zhejiang University, College of Medicine, Hangzhou, 310058 China.

[#] These two authors contributed equally.

[*] Corresponding Author：Min Han, E-mail: hanmin@zju.edu.cn；JianQing Gao, E-mail: gaojianqing@zju.edu.cn

ABSTRACT

Although existing nanomedicines have focused on the tumor microenvironment with the goal of improving the effectiveness of conventional chemotherapy, the penetration of a tumor's core still represents a formidable barrier for existing drug delivery systems. Therefore, a novel multifunctional hypoxia-induced size-shrinkable nanoparticle has been designed to increase the penetration of drugs, nucleic acids, or probes into tumors. This cooperative strategy relies on three aspects: (i) the responsiveness of nanoparticles to hypoxia, which shrink when triggered by low oxygen concentrations; (ii) the core of a nanoparticle involves an internal cavity and strong positive charges on the surface to deliver both doxorubicin and siRNA; and (iii) a reactive oxygen species (ROS) probe is incorporated in the nanoparticle to monitor its preliminary therapeutic response in real time, which is expected to realize the enhanced efficacy together with the ability to self-monitor the anticancer activity. A more effective inhibition of tumor growth was observed in tumor-bearing zebrafish, demonstrating the feasibility of this cooperative strategy for in vivo applications. This research highlights a promising value in delivering drugs, nucleic acids, or probes to a tumor's core for cancer imaging and treatment.

KEYWORDS: hypoxia-sensitive, size-shrinkable nanomedicine, penetration, reporter

1. Introduction

The effectiveness of conventional chemotherapy remains problematic, and increasing attention has recently been given to the tumor microenvironment (TME), which is characterized by abnormal vasculature, complex stromal cells, dense extracellular matrix (ECM), and increased interstitial fluid pressure (IFP). TME constitutes a barrier that restricts penetration and the spatial distribution of drugs throughout solid tumors, and it further contributes to the poor response of tumors to chemotherapy.[1] Although the barrier may sometimes be circumvented by normalization of blood vasculature through antiangiogenic agents such as the VEGF inhibitor bevacizumab, the FDA-approved antiangiogenic monoclonal antibody (mAb), capable of reverting abnormal structure of tumor vessels toward a more normal phenotype, has been applied in the treatment of metastatic colorectal cancer.[2, 3] It remains uncertain how to optimize scheduling for combining antiangiogenic agents with cytotoxic treatment.

Additionally, the diffusion of nanomedicine, which can penetrate the tumor tissue only at approximately a 3- to 5-cell diameter scale, is even more limited owing to its larger size than conventional chemotherapeutic compounds.[4, 5] Enhancement of the intratumoral penetrating efficiency of nanoparticles is thought to improve