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PII: S0168-3659(16)30448-5
DOI: doi: 10.1016/j.jconrel.2016.07.014
Reference: COREL 8371

To appear in: *Journal of Controlled Release*

Received date: 6 February 2016
Revised date: 20 June 2016
Accepted date: 9 July 2016

Please cite this article as: Dan Wang, Jijun Fu, Yujie Shi, Dong Peng, Lan Yuan, Bing He, Wenbing Dai, Hua Zhang, Xueqing Wang, Jie Tian, Qiang Zhang, The modulation of tumor vessel permeability by thalidomide and its impacts on different types of targeted drug delivery systems in a sarcoma mouse model, *Journal of Controlled Release* (2016), doi: 10.1016/j.jconrel.2016.07.014

The modulation of tumor vessel permeability by thalidomide and its impacts on different types of targeted drug delivery systems in a sarcoma mouse model

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Abstract: The transport of nanocarriers is supposed to be based on EPR effect which is affected by diverse factors, so the modulation of EPR effect seems very significant for nanocarriers including targeted drug delivery systems (TDDSs). Besides, it is extremely unclear how the EPR effect impacts the fate of different types of TDDSs. To make the most advantage of EPR effect for TDDSs, it is definitely necessary to clarify these key issues. Here, we construct and characterize various TDDSs, including sterically-stabilized liposomes (SSL), RGD functionalized SSL (RGD-SSL) and novel 7PEP functionalized SSL (7PEP-SSL), loaded with doxorubicin (DOX), DIR or DID. Here, we modulate the permeability of tumor vessels by thalidomide (THD) in a sarcoma-bearing EPR mouse model via monitoring endogenous deoxygenated hemoglobin in circulation, and then we confirm the effect of THD on tumor vessel permeability by vessel density, vessel maturity, VEGF expression and so on. Importantly, we investigate and find the impacts of EPR effect on the antitumor efficacy, in vivo distribution and intratumoral microdistribution of the three TDDSs. Interestingly, the EPR effects affect different TDDSs differently. The elevated EPR effect enhances the tumor accumulation of SSL and RGD-SSL but fails to increase their efficacy. The RGD-SSL exhibits the best efficacy with the least fluctuation, demonstrating the advantage of angiogenesis targeted systems. 7PEP-SSL seems the biggest beneficiary of EPR effect, suggesting the significance of EPR modulation for cells targeted systems. Generally, this study demonstrates the feasibility of modulating EPR effect bidirectionally by THD as well as the impacts of EPR effect on different type of testing TDDSs based on this animal model. It certainly provides novel insight into the design and potential use of TDDSs.

Key words: Targeted drug delivery systems; animal model of EPR effect; tumor vessel permeability; thalidomide; antitumor efficacy; distribution

1. Introduction

Tumor blood vessels, characterized by its hyper-permeable feature and less maturated than normal vessels, are aligned defective endothelial cells resulting in wide fenestrations. The existence of fenestrations permits extravasation of large molecules or nanoparticles from tumor vessels into cancer interstitium. On the other hand, long retention of these macromolecules or nanoparticles in tumor tissues is found after intravenous administration due to impaired tumor lymphatic drainage [1]. Above mentioned pathophysiological features are defined as enhanced permeability and retention (EPR) effect [2]. The concept of EPR effect has been considered as the main reason of the favorable distribution of different nanomedicines in malignant tissues [3,4]. In fact, several nano-sized therapeutic agents have been successfully translationed to clinic [5-7], such as Abraxane, Genexol-PM and Opaxio and so on. However, there is still no breakthrough for active targeted drug delivery systems (TDDSs) such as the receptor- or antibody-mediated nanocarriers.

The in vivo transportation of TDDSs is supposed to be based on EPR effect first and then the following interaction with target cells. On the one hand, it is generally believed that EPR effect is affected by diverse factors such as tumor type, tumor microenvironment, the state of cancer growth as well as some exogenous agents [8-11]. So the modulation of EPR effect seems very significant for the nanocarriers like TDDSs. On the other hand, although many reports have declared the demonstration of EPR effect in animal [12,13] and even in human [14], the significance of EPR effect for nanomedicines or TDDSs seems controversial. In fact, it is still unclear currently how the EPR effect, or the permeability of tumor vessel, impacts the fate of nanomedicines, especially, the antitumor efficacy and drug distribution of different types of