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Tumor Microenvironment-Responsive Dual Drug Dimer-Loaded PEGylated Bilirubin Nanoparticles for Improved Drug Delivery and Enhanced Immune-Chemotherapy of Breast Cancer

*Xiaotong Yang, Chuan Hu, Fan Tong, Rui Liu, Yang Zhou, Lin Qin, Liang Ouyang, and Huile Gao**

The application of combinational therapy makes up for the limitation of monotherapy and achieves superior treatment against cancer. However, the combinational therapy remains restricted by the poor tumor-specific delivery and the abscopal effect. Herein, reactive oxygen species (ROS)-responsive PEGylated bilirubin nanoparticles (BRNPs) are developed to encapsulate two glutathione-activatable drugs, including dimer-7-ethyl-10-hydroxycamptothecin (d-SN38) and dimer-lonidamine (d-LND). Dimerization of the drugs significantly increases the drug loading capacity and the encapsulation efficiency of nanoparticles. With the assistance of iRGD peptide (cRGDKGPDC), the cellular uptake of BRNPs is more than double when compared with the control. In response to high levels of intracellular ROS, d-SN38 and d-LND are rapidly released from nanoparticles (SL@BRNPs). Furthermore, the pharmacodynamic experiments verify combining SL@BRNPs with anti-PD-L1 antibody greatly inhibits the primary tumor of breast cancer, improves CD8+ T cells levels, and CD8+ T cells/Tregs ratios in the tumor. Additionally, it shows high immune memory effect and can prevent the growth of lung metastasis. Taken together, the strategy pioneers a new way for the rational design of nanoassemblies through the combination of activatable drug dimers and stimuli-responsive drug release, and a successful application of novel drug delivery systems in combination with the immune checkpoint blockade antibody.

1. Introduction

The application of chemotherapy is limited by the low tumor selectivity and severe side effect. The development of the nanotechnology-based drug delivery systems (NDDSs) elevates the tumor accumulation and reduces the distribution in normal tissue.[1–4] However, one practical problem lies in the irresponsiveness of NDDSs towards the tumor microenvironment, which results in insufficient intratumoral drug release and more off-target exposure.[5–7] Thus, bilirubin, an endogenous hydrophobic antioxidant, can react with overproduced reactive oxygen species (ROS) inside tumors,[8] turn into hydrophilic biliverdin and lead to on-demand drug release.[9] Unlike free bilirubin, the introduction of hydrophilic poly (ethylene glycol) (PEG) is seized upon as a solution to make hydrophobic one well-dispersed in water and dramatically prolong the blood circulation.[10] Besides, the intermolecular aromatic planar rings help to facilitate the packing between bilirubin itself and drugs with similar structure through the π–π stacking and hydrophobic interactions, thus leading to superb loading efficiency and capacity.[11–13]

Of note, typically when amphiphilic copolymers encapsulate small and hydrophobic drugs, it is found out lower drug loading and encapsulation efficiency of nanoparticles.[14] This outcome may be largely attributed to the formation of large drug aggregates, through long-range-ordered drug molecule packing. The drug dimer design has emerged as one of the most potential strategies to prevent the formation of large particles. In addition, compared to free drug, dimeric prodrug should have increased intermolecular hydrophobic interactions because of increased surface area and an augmented tendency for prodrug aggregation.[15–19] Therefore, two disulfide-linked dimeric prodrugs, including dimer-7-ethyl-10-hydroxycamptothecin (d-SN38) and dimer-lonidamine (d-LND), were successfully fabricated. Furthermore, the dimeric prodrugs could respond to the high glutathione (GSH) level of the tumor, to

X. Yang, C. Hu, F. Tong, R. Liu, Y. Zhou, L. Qin, Prof. H. Gao
Key Laboratory of Drug Targeting and Drug Delivery System
of the Education Ministry
Sichuan Engineering Laboratory for Plant-Sourced Drug
and Sichuan Research Center for Drug Precision Industrial Technology
West China School of Pharmacy Sichuan University
No. 17, Block 3, Southern Renmin Road, Chengdu 610041, P. R. China
E-mail: gaohuile@scu.edu.cn
L. Ouyang
State Key Laboratory of Biotherapy and Cancer Center
West China Hospital, and Collaborative Innovation Center of Biotherapy
Sichuan University
Chengdu 610041, China
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.201901896.

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