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Chemotherapy for gastric cancer by finely tailoring anti-Her2 anchored dual targeting immunomicelles

Wei Li [a,b,*,1], He Zhao [a,1], Weizhu Qian [a,b,1], Huafei Li [a], Li Zhang [a], Zengwei Ye [a], Ge Zhang [a], Mao Xia [a], Jinfeng Li [a], Jie Gao [a,b], Bohua Li [a,b,c], Geng Kou [a,b,c], Jianxin Dai [a,b,c], Hao Wang [a,b,c], Yajun Guo [a,b,c,*]

[a] International Joint Cancer Institute, The Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, PR China
[b] National Engineering Research Center for Antibody Medicine, State Key Laboratory of Antibody Medicine and Targeting Therapy and Shanghai Key Laboratory of Cell Engineering, 399 Libing Road, Shanghai 201203, PR China
[c] PLA General Hospital Cancer Center, PLA Graduate School of Medicine, Beijing 100853, PR China

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ABSTRACT

Micelles with high *in vivo* serum stability and intratumor accumulation post intravenous (*i.v.*) injection are highly desired for promoting chemotherapy. Herein, we finely synthesized and tailored well-defined anti-Her2 antibody Fab fragment conjugated immunomicelles (FCIMs), which showed interesting dual targeting function. The thermosensitive poly(N-isopropylacrylamide-*co*-N,N-dimethylacrylamide)$_{118}$ (PID_{118}) shell with volume phase transition temperature (VPTT: 39 °C) and the anchored anti-Her2 Fab moiety contributed to the passive and active targeting, respectively. The doxorubicin (DOX) loading capacity of such FCIMs was successfully increased about 2 times by physically enhanced hydrophobicity of inner reservoir without structural deformation. The cellular uptake and intracellular accumulation of DOX by temperature regulated passive and antibody navigated active targeting was 4 times of Doxil. The cytotoxicity assay against Her2 overexpression gastric cancer cells (N87s) showed that the IC50 of the FCIMs was ~9 times lower than that of Doxil under cooperatively targeting by Fab at $T >$ VPTT. FCIMs showed high serum stability by increasing the corona PID_{118} chain density (S_{corona}/N_{agg}). *In vivo* tissue distribution was evaluated in Balb/c nude mice bearing gastric cancer. As observed by the IVIS® imaging system, the intratumor accumulation of such finely tailored FCIMs system was obviously promoted 24 h post *i.v.* administration. Due to the high stability and super-targeting, the *in vivo* xenografted gastric tumor growth was significantly inhibited with relative tumor volume <2 which was much smaller than ~5 of the control. Consequently, such finely tailored FCIMs with anti-Her2 active and temperature regulated passive dual tumor-targeting function show high potent in chemotherapy.

1. Introduction

Block copolymer micelles with well-defined core-corona structure provide a unique and powerful nanoplatform for drug delivery in chemotherapy for overcoming the traditional formulation's drawbacks such as the side toxicity, *in vivo* instability and the fast clearance in the circulation [1–5]. The hydrophobic core can provide a natural hydrophobic environment that allows easy encapsulation of poorly soluble anticancer drugs via the similar-to-similar interaction. On the other hand, the densely packed hydrophilic corona-forming chain can protect micellar system from the reticuloendothelial system (RES) by reducing the interaction with serum proteins and renal filtration [6–8]. Additionally, the size of polymeric micelles, 10–100 nm, can be easily regulated by varying the block compositions of the amphiphilic copolymer. The unique physiochemical properties and tunable size increased micelles preferentially accumulate in solid tumor through the enhanced permeability and retention (EPR) effects [9,10].

Despite many advantages of block copolymer micelles for *in vitro*/*vivo* applications, several challenges still exist for translating the micellar drug delivery system to clinical application. For example, the small micellar size of 10–100 nm limits the amount of drug that can be incorporated inside the core and the premature release prior to the micelle reaching its intended site of action. Although chemical conjugation strategies increased compatibility of drug in the micelle core, the aggregation number (N_{agg}) of polymer chains inside one micelle can not be changed at

* Corresponding authors. International Joint Cancer Institute, The Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, PR China. Tel./fax: +86 21 81870801.
E-mail addresses: liwei.dds@gmail.com (W. Li), yjguo@smmu.edu.cn (Y. Guo).
[1] The authors contributed equally.

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