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ARTICLE

Active-targeting and acid-sensitive pluronic prodrug micelles for efficiently overcoming MDR in breast cancer

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Multidrug resistance (MDR) seriously hinders the therapeutic efficacy in clinical cancer treatment. Herein, we reported new polymeric prodrugs micelles with tumor-targeting and acid-sensitivity based on two different pluronic copolymers (F127 and P123) for enhancing tumor MDR reversal and chemotherapy efficiency in breast cancer. Hybrid micelles were composed of phenylboric acid (PBA)-modified F127 (active-targeting group) and doxorubicin (DOX)-grafted P123 (prodrugs group), which were named as FBP-CAD. FBP-CAD exhibited good stability in neutral environment, which accelerated drug release under mildly acidic condition by the cleavage of β-carboxylic amides bonds. In vitro studies demonstrated that FBP-CAD significantly increased cellular uptake and drug concentration in MCF-7/ADR cells through the homing ability of PBA and the anti-MDR effect of P123. In vivo testing further indicated that hybrid micelles facilitated drug accumulation at tumor sites as well as reduced side effects to normal organs. The synergistic effect of active-targeting and MDR-reversing lead to the highest tumor growth inhibition (TGI 78.2%). Thus, these multifunctional micelles provide a feasible approach in nanomedicines for resistant-cancer treatment.

Introduction

Breast cancer is a highly malignant tumor and the second leading cause of cancer death in females.[1,2] Although many efforts have been made and new chemotherapeutic agents have emerged in recent years, the efficacy of chemotherapy is often limited by the occurrence and development of multidrug resistance (MDR) during treatment.[3,4] Besides, tumor heterogeneity such as hypoxia, metabolic detoxification system, and drug sequestration in cytoplasmic vesicle can also induce drug resistance.[5] It is demonstrated that the activated MDR directly mediated the cross-resistance toward various anticancer agents with different structure and function (e.g., doxorubicin (DOX) and paclitaxel (PTX)) on the basis of a superfamily of ATP binding cassette (ABC) proteins, such as P-glycoprotein (P-gp), MDR-associated proteins (MRPs) and breast cancer resistance protein (BCRP), eventually leading to the failure of treatment.[6,7] Various small molecular MDR inhibitors (e.g., verapamil, cyclosporine and quinine) have been used to overcome MDR, however, the inherent toxicity of these inhibitors and/or the non-specific biodistribution during blood circulation further limit their applications in clinic.[8–10]

Recently, nanoparticles-mediated small molecule MDR inhibitors and chemotherapeutic agent combination therapy have attracted more and more attention because of their synergistic effect toward MDR-tumor.[11] For example, wu et. al. reported a nano-twin drug using DOX and vorinostat (SAHA) by the supramolecular self-assembly, which increased the acetylation degree of histone and terminated tumor cells growth, eventually led to MDR reversal.[12] Although these measures achieved some extent progress, it is still a challenge how to efficiently deliver drugs in vivo, control drugs release and perform MDR-inhibiting functions for clinical transformation. Besides, single reversal pathway might not completely overcome tumor MDR due to the complex resistance mechanisms as mentioned above.[13] Thus, it is desirable to design a safe and efficient nano drug delivery system (nDDS) to realize good therapeutic efficacy as well as high-efficiently reversing tumor MDR.

Pluronics-based nDDS have been considered to be promising strategy for solving these problems. Pluronic is an amphiphilic triblock copolymer composed of hydrophilic poly (ethylene oxide) (PEO) blocks and hydrophobic poly (propylene oxide) (PPO) blocks (PEO-PPO-PEO).[14] Typically, pluronic copolymers are capable of forming pores on bio-membrane, which can abolish drug

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