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pH-sensitive and pluronic-modified pullulan nanogels for greatly improved antitumor in vivo

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ABSTRACT

It remains a crucial challenge to achieve efficient cellular uptake in tumor cells for nanoscale drug delivery systems. This work described that two multi-functional pullulan nanogels were prepared by co-polymerization between methacrylated pullulan (Pullulan-M) and different crosslink agents, an acid-labile ortho ester-modified pluronic (L61-MOE) or non-acid-sensitive methacrylated pluronic (L61-M). The prepared nanogels showed a regular spherical structure with the size about 200 nm measured by dynamic light scattering and transmission electron microscopy (TEM). Doxorubicin as a model drug was successfully encapsulated into nanogels. As expected, Pul-L61-MOE showed pH-dependent DOX release, and 25% of DOX was released at pH 7.4 while 84.48% of DOX was released at pH 5.0. In vitro cellular uptake and MTT results indicated that pH-sensitive nanogels (Pul-L61-MOE) displayed higher cellular internalization and cytotoxicity than acid-insensitive nanogels (Pul-L61-M) and free DOX. Flow cytometry assay suggested these nanogels remarkably increased intracellular reactive oxygen species (ROS) level and induced more cell apoptosis by the function of pluronic. Finally, in vivo antitumor results indicated that the multi-functional nanogels exhibit supreme antitumor efficiency, and the tumor growth inhibition (TGI) was 83.37%. Therefore, the pH-sensitive pullulan nanogels can be potential nano-carriers for drug delivery in tumor treatment.

1. Introduction

Chemotherapy with various cytotoxic agents is still a routine strategy for clinical cancer treatment [1]. Chemotherapeutic efficacy is usually compromised due to some drawbacks including the poor solubility, low stability, nonspecific drug distribution and low drug accumulation in tumor sites [2–4]. Nano-drug delivery systems (NDDS) such as nanoparticles, liposomes, micelles, vesicles and nanogels can enhance the drug stability, prolong blood circulation and improve drug accumulation at tumor site by the enhanced permeability and retention effect (EPR), resulting in preferable anti-tumor effects [5–8]. However, the clinical application of NDDS is still limited by the occurrence of multidrug resistance (MDR) during the treatment [9]. It is demonstrated that the activated MDR can significantly reduce drug accumulation in tumor cells due to a superfamily of ATP binding cassette proteins, such as the P-glycoprotein (P-gp) and MDR-associated proteins (MRPs), eventually leading to the failure of chemotherapy [10–13]. Although various small molecular weight MDR inhibitors (such as verapamil and cyclosporin A) have been used to overcome MDR, the non-specific biodistribution during the circulation may cause severe side effects [14]. Thus, there is an urgent demand to develop an optimal NDDS with tumor-targeting ability and controlled drug release to deliver high concentration of MDR inhibitors and chemotherapeutics to MDR tumor cells simultaneously.

Pluronic is an amphiphilic triblock copolymers composed of hydrophilic poly (ethylene oxide) (PEO) blocks and hydrophobic poly (propylene oxide) (PPO) blocks (PEO-PPO-PEO). As a nonionic surfactant, these copolymers can self-assemble into micelles for anti-tumor drug delivery [15]. Furthermore, it is demonstrated that these copolymers can effectively increase intracellular drug accumulation by blocking drug efflux transporters including P-gp and MRPs, and reducing ATP levels in MDR tumor cells [16,17]. On the other hand, low hydrophile lipophilic balance (HLB) pluronic can target mitochondria and induce reactive oxygen species (ROS) generation, resulting in significant cytotoxicity by amplifying the oxidative stress [1,18,19]. Although pluronic copolymers-based NDDS have been used for anticancer drug delivery to overcome MDR effect, some defects need to be solved [20,21]. The low micellization and solubilization ability to hydrophobic drugs of pluronic copolymers makes it necessary to use high dose and may cause toxicity. The poor dilution stability in blood stream of pluronic self-assembled micelles due to their relatively high critical micelle concentration (CMC) values may cause premature and nonspecific drug release in vivo [1,22]. Therefore, a reasonable and appropriate

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