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Super pH-sensitive multifunctional polymeric micelle for tumor pH_e specific TAT exposure and multidrug resistance

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Abstract

As an alternative to cell specific cancer targeting strategies (which are often afflicted with the heterogeneity of cancer cells as with most biological systems), a novel polymeric micelle constitute of two block copolymers of poly(L-lactic acid)-*b*-poly(ethylene glycol)-*b*-poly(L-histidine)-TAT (transactivator of transcription) and poly(L-histidine)-*b*-poly(ethylene glycol) was developed. The micelle formed via the dialysis method was approximately 95 nm in diameter and contained 15 wt.% of doxorubicin (DOX) by weight. The micelle surface hides TAT during circulation, which has the strong capability to translocate the micelle into cells, and exposes TAT at a slightly acidic tumor extracellular pH to facilitate the internalization process. The micelle core was engineered for disintegration in early endosomal pH of tumor cells, quickly releasing DOX. The ionization process of the block copolymers and ionized polymers assisted in disrupting the endosomal membrane. This processes permitted high DOX concentrations in the cytosol and its target site of the nucleus, thus increasing DOX potency in various wild and multidrug resistant (MDR) cell lines (3.8–8.8 times lower IC50 than free DOX, depending on cell line). When tested with the xenografted tumors of human ovarian tumor drug-resistant A2780/AD, human breast tumor drug-sensitive MCF-7, human lung tumor A549 and human epidermoid tumor KB in a nude mice model, all tumors significantly regressed in size by three bolus injections at a dose of DOX 10 mg equivalent/kg body per injection of DOX-loaded micelle at three day interval, while minimum weight loss was observed. This approach may replace the need for cell-specific antibodies or targeting ligands, thereby providing a general strategy for solid tumor targeting.

Keywords: Pop-up pH-sensitive polymeric micelle; Tumor pH; Triggering drug release; Multidrug resistance

Article Outline

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