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# Reconstituted high density lipoprotein mediated targeted co-delivery of HZ08 and Paclitaxel enhances the efficacy of Paclitaxel in multidrug-resistant MCF-7 breast cancer cells

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In the past decades, reconstituted high density lipoprotein (rHDL) has been successfully developed as a drug carrier since the enhanced HDL-lipids uptake is demonstrated in several human cancers. In this paper, rHDL for the first time was utilized to co-encapsulate two hydrophobic drugs: An anticancer drug, paclitaxel (PTX), and a new reversal agent for P-gp (P-glycoprotein)-mediated multidrug resistance (MDR) of cancer, N-cyano-1-[(3,4-dimethoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxy-N′-octyl-2(1H)-isoquinoline-carboximidamide (HZ08). We proposed this drug co-delivery strategy to reverse PTX resistance. The study aimed to develop a biomimetic nanovector, reconstituted high density lipoprotein (rHDL), mediating targeted PTX-HZ08 delivery for cancer therapy. Using sodium cholate dialysis method, we successfully formulated dual-agent co-delivering rHDL nanoparticles (PTX-HZ08-rHDL NPs) with a typical spherical morphology, well-distributed size (~100 nm), high drug encapsulation efficiency (approximately 90%), sustained drug release properties and exceptional stability even after storage for 1 month or incubation in 10% fetal bovine serum (FBS) DMEM for up to 2 days. Results demonstrated that PTX-HZ08-rHDL NPs significantly enhanced anticancer efficacy *in vitro*, including higher cytotoxicity and better ability to induce cell apoptosis against both PTX-sensitive and resistant MCF-7 human breast cancer cell lines (MCF-7 and MCF-7/PTX cells). Mechanism studies demonstrated that these improvements could be correlated with increased cellular uptake of PTX mediated by scavenger receptor class B type-I (SR-BI) as well as prolonged intracellular retention of PTX due to the HZ08 mediated drug-efflux inhibition. In addition, *in vivo* investigation showed that the PTX-HZ08-rHDL NPs were substantially safer, have higher tumor-targeted capacity and have stronger antitumor activity than the corresponding dosage of paclitaxel injection. These findings suggested that rHDL NPs could be an ideal tumor-targeted nanovector for simultaneous transfer of insoluble anticancer drug and drug resistance reversal agents. The PTX-HZ08-rHDL NPs co-delivery system might be a new promising strategy to overcome tumor drug resistance.

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