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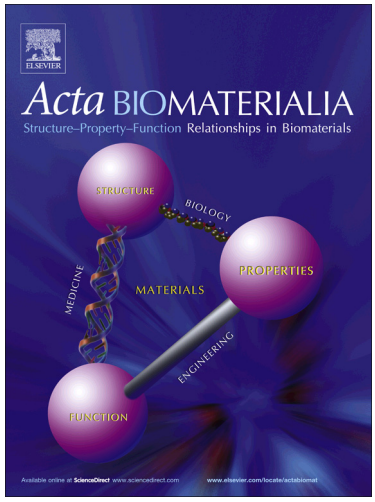

Full length article

A targeted nanoplatform co-delivering chemotherapeutic and antiangiogenic drugs as a tool to reverse multidrug resistance in breast cancer

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A targeted nanoplatform co-delivering chemotherapeutic and antiangiogenic drugs as a tool to reverse multidrug resistance in breast cancer

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Abstract

Several obstacles are currently impeding the successful treatment of breast cancer, namely impaired drug accumulation into the tumor site, toxicity to normal cells and narrow therapeutic index of chemotherapy, multidrug resistance (MDR) and the metastatic spread of cancer cells through the blood and lymphatic vessels. In this regard, we designed a novel multifunctional nano-sized drug delivery system based on LyP-1 peptide-modified low-molecular-weight heparin-quercetin conjugate (PLQ). This nanosystem was developed for targeted co-delivery of multiple anticancer drugs to p32-overexpressing tumor cells and peritumoral lymphatic vessels, using LyP-1 peptide as active targeting ligand, with the aim to achieve a targeted combinatorial chemo/angiostatic therapy and MDR reversal. The cellular uptake of PLQ nanoparticles by p32-overexpressing breast cancer cells was significantly higher than nonfunctionalized nanoparticles. Besides, the anti-angiogenic activity of PLQ nanoparticles was proven by the effective inhibition of the bFGF-induced neovascularization in subcutaneous Matrigel plugs. More importantly, PLQ/GA nanoparticles with better targeting ability toward p32-positive tumors, displayed a high antitumor outcome by inhibition of tumor cells proliferation and angiogenesis. Immunohistochemistry and western blot assay showed that PLQ/GA nanoparticles significantly disrupted the lymphatic formation of tumor, and inhibited the P-glycoprotein (P-gp) expression in MCF-7 tumor cells, respectively. In conclusion, PLQ/GA nanoparticles provide a synergistic strategy for effective targeted co-delivery of chemotherapeutic and antiangiogenic agents and reversing MDR and metastasis in breast cancer.

Statement of Significance

Herein, we successfully developed a novel amphiphilic nanomaterial, LyP-1-LMWH-Qu (PLQ) conjugate, consisting of a tumor-targeting moiety LyP-1, a hydrophobic quercetin (a