REDUCING PACLITAXEL-INDUCED PERIPHERAL NEUROTOXICITY VIA LIPOSOMAL DRUG TARGETING

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Paclitaxel (PTX) is a highly effective chemotherapeutic agent widely used in breast cancer treatment, but its clinical application is significantly limited by peripheral neurotoxicity. Innovative drug delivery systems are needed to selectively release PTX at the tumor site while minimizing neuronal damage. In this proof-of-concept study, we developed and characterized PTX-loaded liposomes functionalized with a metalloproteinase-sensitive lipopeptide (MSLP), exploiting the overexpression of metalloproteinases in the tumor microenvironment to achieve site-specific drug release.

Liposomes were prepared via thin-film hydration followed by extrusion, resulting in four formulations: PTX-loaded liposomes (LipoPTX), metalloproteinase-sensitive functionalized PTX liposomes (MSLP-LipoPTX), and unloaded liposomes (functionalized or not). Antitumor activity was evaluated in MCF-7 breast cancer cells using the MTT assay. Neurotoxicity was assessed both *in vitro*, using primary cultures of adult mouse sensory neurons, and *in vivo*, in transgenic zebrafish embryos (Tg(isl2b:GFP)^{zb7}), analyzing morphological, behavioral, and molecular endpoints.

Our results demonstrated that both LipoPTX and MSLP-LipoPTX preserved the anticancer activity of free PTX while significantly reducing its neurotoxic effects. In sensory neuron cultures, liposomal formulations induced only mild neurite shortening compared with free PTX. In zebrafish embryos, treatment with LipoPTX and MSLP-LipoPTX was associated with lower mortality, fewer caudal fin abnormalities, and improved responsiveness to mechanical stimuli.

Overall, these findings suggest that functionalized liposomes can effectively deliver PTX while mitigating peripheral neurotoxicity in both *in vitro* and *in vivo* models. This strategy offers a promising approach to enhance the therapeutic index of PTX and supports further investigations in zebrafish xenograft models of human breast cancer to validate its translational potential.