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Paper Title:	CXCR4-Targeted Biomimetic Macrophage-Derived Hybrid Nanovesicle for Dual Delivery of Manganese and Doxorubicin to Enhance Cancer Therapy
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Abstract

Immune cell-derived membranes are at the forefront of cancer immunotherapy research due to their inherent immune-regulating properties and exceptional biocompatibility. By integrating these membranes with artificial liposomes encapsulating cancer-fighting agents, we have developed multifunctional hybrid vesicles. These vesicles not only enhance the immune response against cancer but also effectively deliver chemotherapeutic drugs, offering a powerful strategy for combination cancer therapies. In this study, we engineered a novel hybrid vesicle using macrophage-derived membranes designed for the co-delivery of anti-cancer drugs and the polarization of tumor-associated macrophages (TAMs) towards a tumor-fighting phenotype. Our system combines M1 macrophage vesicles with liposomes conjugated to a CXCR4-binding peptide and loaded with manganese and doxorubicin. These hybrid vesicles specifically target CXCR4-expressing tumor cells and reprogram TAMs to an aggressive M1 phenotype through the release of pro-inflammatory cytokines. The manganese and doxorubicin-loaded vesicles not only induce immunogenic cell death but also activate the STING signaling pathway, promoting dendritic cell maturation and significantly reducing tumor growth. In vivo studies using mice models of colon and breast cancer demonstrated that intravenous administration of these hybrid vesicles resulted in substantial tumor suppression at minimal doses, with no observed adverse effects. Furthermore, the vesicles induced an abscopal effect, effectively managing untreated tumors. Our findings introduce a promising approach for the simultaneous delivery of immunotherapy and chemotherapy using biomimetic hybrid nanovesicles, presenting a precise and effective method for dual therapeutic agent delivery.