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A nanomedicine-based curcumin and doxorubicin combination treatment of glioblastoma with scFv-targeted micelles: In vitro evaluation in 2D and 3D tumor models

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Overcoming chemotherapy-induced resistance caused by activation of PI3K/Akt and NF-κB pathways is crucial for successful glioblastoma therapy. We developed an all-in-one nanomedicine formulation for co-delivery of a chemotherapeutic agent (topoisomerase II inhibitor, doxorubicin) and a multidrug resistance modulator (NF-κB inhibitor, curcumin) for treatment of glioblastoma due to their synergism. Both agents were incorporated into PEG-PE-based polymeric micelles. The glucose transporter-1 (GLUT1) is overexpressed in many tumors including glioblastoma. The micellar system was decorated with GLUT1 antibody single chain fragment variable (scFv) as the ligand to promote blood brain barrier transport and glioblastoma targeting. The combination treatment was synergistic (combination index, CI of 0.73) against U87MG glioblastoma cells. This synergism was improved by micellar encapsulation (CI: 0.63) and further so with GLUT1 targeting (CI: 0.46). Compared to non-targeted micelles, GLUT1 scFv surface modification increased the association of micelles (>20%, $P<0.01$) and the nuclear localization of doxorubicin (~3-fold) in U87MG cells, which also translated into enhanced cytotoxicity by more than 30%. The increased caspase 3/7 activation by targeted micelles indicates successful apoptosis enhancement by combinatory treatment. Moreover, GLUT1 targeted micelles resulted in deeper penetration into the 3D spheroid model. The increased efficacy of combination nanoformulations on the spheroids compared to a single agent loaded, or to non-targeted formulations, reinforces the rationale for selection of this combination and successful utilization of GLUT1 scFv as a targeting agent for glioblastoma treatment.