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Synthetic nano-low density lipoprotein as targeted drug delivery vehicle for glioblastoma multiforme

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Abstract

The low density lipoprotein (LDL) receptor has been shown to be upregulated in GBM tumor cells and is therefore a potential molecular target for the delivery of therapeutic agents. A synthetic nano-LDL (nLDL) particle was developed and tested to determine its utility as a drug delivery vehicle targeted to GBM tumors. nLDL particles were constructed by combining a synthetic peptide containing a lipid binding motif and the LDL receptor (LDLR) binding domain of apolipoprotein B-100 with a lipid emulsion consisting of phosphatidyl choline, triolein, and cholesteryl oleate. Composition analysis, fast protein liquid chromatography, and electron microscopy revealed that nLDL was highly reproducible and intermediate in size between high density lipoprotein and LDL particles (10.5 ± 2.8 nm diameter). The binding and uptake of fluorescently labeled nLDL particles was assessed using fluorescence microscopy. Uptake of nLDL was time dependent, exhibiting saturation at approximately 3 h, and concentration dependent, exhibiting saturation at concentrations greater than $5 \mu\text{M}$ peptide. Using Lysotracker as a cellular marker, nLDL co-localized with lysosomes. nLDL binding was eliminated by blocking LDLRs with suramin and nLDL inhibited binding of plasma LDL to LDLRs. Collectively these data strongly suggest that the synthetic nano-LDLs described here are taken up by LDLR and can serve as a drug delivery vehicle for targeting GBM tumors via the LDLR.

Keywords: Low density lipoprotein; Low density lipoprotein receptor; Glioblastoma multiforme; Lipid emulsion; Peptide; Nano-low density lipoprotein



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