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Short-chain sphingolipids for enhanced cellular uptake of liposome-encapsulated amphiphilic anti-cancer drugs

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Short-chain sphingolipids, such as C_8-Glucosylceramide (C_8-GC) have been described to enhance the cellular uptake of amphiphilic drugs, in free form or when co-formulated in liposomes (1,2). The involved mechanism is currently unknown, but is hypothesized to induce domain or pore formation in the plasma membrane (3). The aim of this study is to further explore this specific drug uptake process by C_8-GC to enhance intracellular delivery of liposomal doxorubicin.

Liposomes, containing different percentages of incorporated C_8-GC were prepared and loaded with doxorubicin. Characterization was performed by measuring size, polydispersity index (pdi), phospholipid and doxorubicin content. In vitro anti-tumor activity was studied towards a panel of human tumor cell lines and normal cells: endothelial cells and fibroblasts.

Doxorubicin liposomes (Dox-L) enriched with 10 mol% C_8-GC presented less fluctuation in size and pdi than 15 mol% and efficiently retained their contents under culture conditions (10% serum). In all tumor cell lines tested C_8-GC-Dox-L exerted increased cytotoxicity, resulting in up to 20 fold lower IC_{50} values compared to standard Dox-L. This effect was not observed with endothelial cells and with fibroblasts it was much less pronounced.

In conclusion, 10 mol% C_8-GC-enriched Dox-L had optimal stability and showed enhanced cytotoxicity towards tumor cells and not towards normal cells. Based on these findings, modification of Dox-L formulations with 10 mol% of C_8-GC can be used to improve drug delivery to tumor cells.

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