Secretory phospholipase A2 responsive liposomes exhibit a potent anti-neoplastic effect in vitro, but induce unforeseen severe toxicity in vivo - DTU Orbit (13/04/2019)

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The clinical use of liposomal drug delivery vehicles is often hindered by insufficient drug release. Here we present the rational design of liposomes optimized for secretory phospholipase A2 (sPLA2) triggered drug release, and test their utility in vitro and in vivo. We hypothesized that by adjusting the level of cholesterol in anionic, unsaturated liposomes we could tune the enzyme specificity based on membrane fluidity, thus obtaining liposomes with an improved therapeutic outcome and reduced side effects. Cholesterol is generally important as a component in the membranes of liposome drug delivery systems due to its stabilizing effects in vivo. The incorporation of cholesterol in sPLA2 sensitive liposomes has not previously been possible due to reduced sPLA2 activity. However, in the present work we solved this challenge by optimizing membrane fluidity. In vitro release studies revealed enzyme specific drug release. Treatment of two different cancer cell lines with liposomal oxaliplatin revealed efficient growth inhibition compared to that of clinically used stealth liposomes. The in vivo therapeutic effect was evaluated in nude NMRI mice using the sPLA2 secreting mammary carcinoma cell line MT-3. Three days after first treatment all mice having received the novel sPLA2 sensitive liposome formulation were euthanized due to severe systemic toxicity. Thus the present study demonstrates that great caution should be implemented when utilizing sPLA2 sensitive liposomes and that the real utility can only be disclosed in vivo. The present studies have clinical implications, as sPLA2 sensitive formulations are currently undergoing clinical trials (LiPlaCis®).

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