Surface-functionalization with NFL peptide of Lipid NanoCapsules LNC: preferential entry into human glioblastoma cells

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Résumé en anglais	Glioblastoma (GBM) is one of the most fatal brain cancers with median survival of only 14.6 months. Hence, more efficacious therapies are necessary. Ferrocifen (FcTriOH) is an organometallic antitumor compound, selectively active on cancer cells [1]. However, this metallocomplexe is highly insoluble in water, requiring a formulation stage before being in vivo administered. Lipid nanocapsules (LNC), prepared via a solvent free process of emulsion phase inversion, could be a suitable vehicle for FcTriOH [2]. Moreover, NFL peptide is able to enter massively into glioblastoma cells, and poorly in healthy neurons and astrocytes (NHA) [3]. Indeed, the aim of the study was to evaluate the effect of the surface-functionalizing NFL concentrations on LNC uptake in U87MG human GBM cells. Moreover, FcTriOH was encapsulated in LNC and their in vitro efficacy on U87MG cells was evaluated. Finally, in vivo antitumor effect was evaluated in ectopic and orthotopic murine U87MG tumor models. Fluorescent LNC (F1), LNC with 0.86% w/w and LNC with 2.58% w/w surface-adsorbed NFL (F2 and F3 respectively) were prepared and characterized. FACS analysis revealed that cellular uptake of F3 into U87MG cells was 31.5 and 1.6-folds higher after 6 h compared to F1 and F2 respectively. Moreover, uptake of F3 was significantly higher in the GBM cells compared to NHA, whereas F1 was internalized preferentially in NHA. Uptake of F3 in U87MG cells was energy dependent. Macropinocytosis was possibly the major uptake pathway, followed by clathrin-dependent endocytosis. Then, FcTriOH loaded LNCs have been successfully prepared with a drug loading of 2.4 % and an encapsulation efficacy of 99 %. MTS assay on U87MG cells revealed an IC50 of 0.46 µM for F3-FcTriOH (free FcTriOH: IC50 = 1.31 µM). Preliminary in vivo experiments on subcutaneous U87MG tumor bearing nude mice showed significantly reduced relative tumor volume after two intravenous injections of F1-FcTriOH and F3-FcTriOH compared to saline. Moreover, intracranial administration of F3/F3-FcTriOH in orthotopic U87MG tumor bearing mice revealed 2 to 3-folds higher apparent diffusion coefficients (ADC) near the injection site in diffusion tensor imaging, compared to F1/F1-FcTriOH. Although dose adjustment will be necessary to avoid toxic effects, the results are promising as therapy induced increased ADC values could indicate possible cell necrosis/lysis. References [1] Laine A.L. et al. (2014), Nanomedicine, 10, pp.1667-1677. [2] Heurtault B. et al. (2003), EJPS, 8, pp. 55-61. [3] Balzeau J. et al. (2013), Biomaterials, 34, pp.3381-3389.
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