Modified antimetabolites-loaded lipid nanocapsules to enhance antitumor immunity

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Résumé en anglais	Introduction : Myeloidderived suppressor cells (MDSCs) are critical players of tumor-induced immunosuppression in mouse models and cancer patients. They accumulate in the spleen and cancers of tumorbearing hosts where they suppress Tcell activation, proliferation and cytotoxic function [1]. Previous studies demonstrated that some anticancer agents, in addition to their cytotoxic effects on tumor cells, were able to affect MDSCs. This occurs for antimetabolites like 5fluorouracile (5FU) and Gemcitabine (Gem) [2]. In this work, the potential activity of novel lipophilic 5FU and Gem derivatives encapsulated into lipid nanocapsules (LNCs) to target monocytic (M-)MDSC subset and tumor cells (pancreatic B6KPC3) was assessed. The aim was to study the immunogenic and anticancer properties of innovative nanosystems. Methods: Gem and 5FU were modified to obtain monolauroylderivatives (GemC12 and 5FUC12). The derivatives were purified by chromatography on silica column and characterized by nuclear magnetic resonance. Blank and loadedLNCs were prepared using the phase inversion process [3]. Physicochemical characterization (size, dispersity, zeta potential and encapsulation efficiency) was performed. To study the in vitro induction of MMDSCs, the immunosuppressive activity and internalization assays of GemC12loaded LNCs, mouse bone marrow cells cultured in presence of GMCSF and IL6 were used. To investigate the efficacy of 5FUC12loaded LNCs, B6KPC3 cells were employed. Finally, as a preliminary in vivo study, the biodistribution of fluorescentloaded LNCs (i.v. or s.c.) using tumor-bearing mice (EG7OVA subcutaneous model) was evaluated. Results: Lipophilic derivatives, 5FUC12 and GemC12, were synthetized. The yield of the products recovered was 60% and 40% for 5FUC12 and GemC12, respectively. Blank, 5FUC12 and GemC12loaded LNCs showed an average size of 60 nm, dispersity index below 0.1 and neutral surface charge. The encapsulation efficiency of drugs was close to 100%. In vitro and in vivo studies highlighted that GemC12loaded LNCs were internalized and depleted selectively MMDSCs. Using K6PC3, we demonstrated that 5-FUC12loaded LNCs exerted a toxic effect comparable to the commercial 5FUsolution. In vivo studies following i.v. or s.c. administration of fluorescentloaded LNCs showed that LNCs reached peripheral tissues. As compared with i.v., following s.c. injection, fluorescent signal increased with time in the spleen, suggesting a slow LNCs absorption. Conclusions : In the present study, lipophilic 5FUC12 and GemC12loaded LNC were obtained. GemC12 loaded LNCs were able to target MMDSCs in vivo and in vitro. Besides, 5FUC12loaded LNCs showed efficacy as anticancer drug in a pancreatic cell line. Further in vitro and in vivo therapeutic evaluations would disclose the full potential of these novel LNCs.
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