Colon cancer treatment: use of magnetoliposomes associated to LGR5

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Abstract

The lack of specificity of conventional chemotherapy is one of the main problems to be solved in cancer therapy. Biomimetic magnetoliposomes [1] are successful chemotherapy controlled-release systems, hyperthermia, and active targeting agents by functionalization of their surface with monoclonal antibodies. The membrane receptor Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) [2] stands out as colorectal cancer (CRC) biomarker and appears to be related to treatment resistance and the development of metastasis [3]. The purpose of this study was to evaluate the effectiveness and safety of LGR5-targeted biomimetic magnetoliposomes loaded with oxaliplatin (OXA) or 5-fluorouracil (5-FU) in the selective therapy of CRC and their possible application in hyperthermia. Synthesis, characterization and determination of heating capacity of magnetoliposomes transporting OXA or 5-FU (with and without LGR5 functionalization) were conducted. *In vitro* antitumoral activity was assayed in multiple colorectal cell lines at different times of exposition. Besides this, cell internalization was studied by Prussian Blue staining, flow cytometry and fluorescence microscopy. *In vivo* acute toxicity of magnetoliposomes were performed to evaluate iron-related toxicity. OXA and 5-FU loaded magnetoliposomes functionalized with LGR5 antibody showed higher cellular uptake than non-targeted nanoformulation with a reduction of the percentage of proliferation in colon cancer cell lines up to 3.2-fold of the IC_{50} value compared to that of free drug. The differences between non-targeted and targeted nanoformulations were more evident after short exposure times (4 and 8 hours). Interestingly, assays in the MC38 transduced cells with reduced LGR5 expression (MC38-L(-)), showed lower cell internalization of LGR5-targeted magnetoliposomes compared to non-transduced MC38 cell line. In addition, magnetoliposomes showed an *in vitro* favorable heating response under magnetic excitation and great iron-related biocompatibility data *in vivo*. Drug-loaded magnetoliposomes functionalized with anti-LGR5 antibodies could be a promising CRC treatment strategy for LGR5+ targeted chemotherapy, magnetic hyperthermia, and both in combination.

References

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Figures

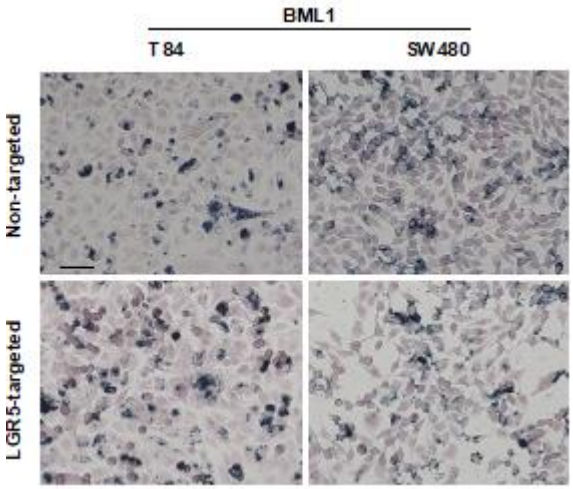

Figure 1. Internalization of magnetoliposomes with and without LGR5 functionalization at 24 hours of exposition in T84 and SW480 cell lines.

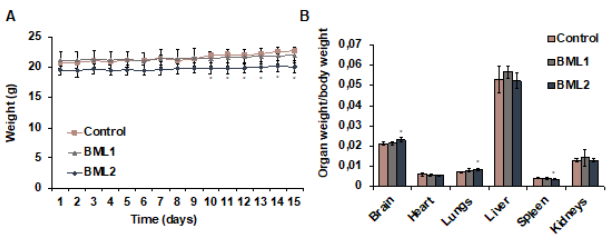

Figure 2. Acute toxicity of Fe in mice treated with blank magnetoliposomes BML1 and BML2 (A) Graphic representation of the weight variation in mice along the experiment. Data are presented as mean ± SD (n = 16). (B) Graphic representation the weight of the organs from sacrificed mice treated with BML1 and BML2.