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Targeted Gold Nanoparticles as Nanosonosensitizers: a new Challenge for the Sonodynamic Treatment of Cancer

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Abstract

Purpose: Sonodynamic therapy (SDT) is a therapeutic approach in which ultrasound irradiation is used to promote the generation of cytotoxic species via the excitation of particular chemical compounds (sonosensitizers). The aim of this study is to investigate cancer targeted gold nanoparticles (AuNPs) in their role as nanosonosensitizers to increase the acoustic cavitation effect, typically associated with sonodynamic therapy.

Experimental description: AuNPs have been produced via the reduction of tetrachlorauric acid with sodium citrate and decorated with 2 kDa mPEG-SH and 3.5 kDa folate-PEG-SH (FA-PEG-AuNPs), which acts as a targeting agent for the biorecognition of folate receptor expressing cancer cells. *In vitro* experiments were performed on human cell lines that express a folate receptor, i.e. epidermoid carcinoma KB and colon carcinoma HCT116, and that do not express a folate receptor, i.e. breast cancer MCF-7. Cell association has been investigated using atomic absorption spectrometry. FA-PEG-AuNP's ability to selectively kill cancer cells under US field exposure has been studied at 1.8 MHz and two different energy densities inside the cell tube; $8x10^{-6}$ J cm^{-2} for 5 minutes (US_n) and $8x10^{-5}$ J cm^{-2} for 5 minutes (US_t). The treatment's effect on cell growth has been investigated using a WST-1 proliferation assay, cell death and reactive oxygen species (ROS) production studied using flow cytometric analysis (FCA). Experiments have also been carried out with the free radical scavenger N-acetylcysteine (NAC) to assess the role of ROS in cancer cell death.

Results: FA-PEG-AuNPs selectively target folate receptor expressing cancer cells, KB and HCT116, and do not associate with MCF-7 cells that do not express folate receptors. A significant reduction in cancer cell growth was only observed in folate receptor expressing cells, KB and HCT116, upon incubation with FA-PEG-AuNPs and US treatment, as compared to control conditions, 72 hours from sonodynamic treatment. Moreover, FCA only showed a significant increase in necrotic cells in KB and HCT116 cells that had been treated with FA-PEG-AuNPs and US at the two different energy densities. A specific ROS production pattern was also observed after FA-PEG-AuNPs and US treatment at the two different energy densities. Interestingly, NAC only suppresses cytotoxicity and ROS production when used with the lower energy density US treatment (US_n), while it seems to play a minor role in suppressing these effects at the higher energy density (US_t), which displayed a moderate hyperthermic condition.

Conclusions: The simultaneous exploitation of the targeting capacity of the gold nanoparticles and the sensitizing effect afforded by ultrasound, make FA-PEG-AuNPs promising nanosonosensitizers for the site-specific ultrasound-based treatment of cancer.

Key Words: Gold nanoparticles; folic acid; sonosensitizer; therapeutic ultrasound; sonodynamic treatment; cancer.

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