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Abstract

Extracellular Hyperthermia for the Treatment of Advanced Cutaneous Melanoma †

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Cancer remains a leading cause of death worldwide. Melanoma is an aggressive type of skin cancer, which originates from genetic mutations in melanocytes. Targeted therapy and immune checkpoint inhibitors are the current therapeutical approach to treat metastatic melanoma. However, the low response rate, melanoma's acquired therapy resistance and toxicity effects have limited the clinical outcomes of these therapies. Magnetic fluid hyperthermia is an emerging heat-based cancer therapy aiming to induce the apoptosis of malignant cells by locally increasing the temperature at the tumor site. This therapy uses superparamagnetic iron oxide nanoparticles (SPIONs) as agents, and have already been employed in clinical practice for brain tumors. SPIONs have biocompatibility properties and, due to their size, only become magnetic when an external magnetic field is applied. They have been extensively studied for biomedical applications. However, the internalization of SPIONs by cancer cells negatively affects their magnetic responsiveness, leading to lower levels of cell death by magnetic hyperthermia.

In this work, we studied the SPIONs internalization dynamics in the WM983b metastatic melanoma cell line and used small-molecular inhibitors of endocytosis to block the nanoparticles' internalization, with the aim of improving magnetic fluid hyperthermia through an extracellular performance. The SPIONs were synthesized by chemical co-precipitation and further stabilized with (3-aminopropyl)triethoxysilane (APTES).

The interaction between the SPIONs and melanoma cells in 2D and 3D models was assessed by optical microscopy at several timepoints of cell exposure to the stabilized SPIONs. The nanoparticles' intracellular location was assessed by confocal microscopy, functionalizing the APTES stabilized SPIONs with Rhodamine B fluorophore. The inhibition capacity of five small-molecular inhibitors was qualitatively and quantitatively evaluated by confocal microscopy, where it was determined that one of the chosen inhibited the functionalized SPIONs with a cellular uptake of lower than 20%. In vitro intra- and extracellular magnetic hyperthermia was performed to evaluate the effect of internalization on the SPIONs' heating capacity. Our results confirm the expected lower specific absorption rate (SAR) values of SPIONs for intracellular magnetic hyperthermia, which increase when SPIONs are in the extracellular environment due to cellular uptake blockade [1,2].

Here, we confirm the hypothesis that a pharmacological approach to blocking the SPIONs' cellular uptake improves magnetic fluid hyperthermia efficiency. This work could lead to great advancements in magnetic hyperthermia as a cancer treatment and opens a range of alternative combined therapies.

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