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Magnetic Particle Spectrometry of 3D cancer cell spheroids

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Abstract

Superparamagnetic iron oxide nanoparticles (SPIONs) have a significant role in biomedical applications such as hyperthermia therapy or magnetic particle imaging. This study investigates the loading of 3D cell spheroids made from a pancreas cell line of rats with magnetic nanoparticles. Here, we show the uptake and a homogeneous distribution of nanoparticles in spheroids, while magnetic particle spectrometry (MPS) reveals a measurable difference in the magnetic behavior of nanoparticles in aqueous solution compared to those incorporated into spheroids.

I. Introduction

Due to the importance of superparamagnetic iron oxide nanoparticles (SPIONs) in biomedical applications such as targeted drug delivery, hyperthermia therapy and magnetic particle imaging, the uptake of SPIONs by cells and their penetration into cancerous tissue is of great interest [1]. In this study, 3D cell spheroids are used as they represent a more reliable in vitro model to study nanoparticle uptake by cancer cells compared to 2D cell cultures. To show that the nanoparticles were taken up by the spheroids, fluorescence microscopy of the spheroids was performed. Furthermore, magnetic particle spectrometry (MPS), a sensitive magnetic detection method [2], was used to investigate the difference between SPIONs in suspension and embedded nanoparticles.

II. Methods and materials

The following chapter describes the production of loaded spheroids and their preparation for fluorescent analysis and MPS measurement.

II.I. 3D Cell Culture

A mammalian cell culture from the pancreas of a rat (Rattus Norwegianus) designated Z29 (passage between 61 and 110) was used for all experiments. DMEM (Carl Roth GmbH & Co. KG, Karlsruhe, Germany) supplemented with 10% FCS (Gibco, Paisley, UK) and 2% Penicillin/Streptomycin (Gibco, NY, USA) was used for cultivation. The cells were incubated at 37°C with 5% CO_2 and passaged every 2-3 days.

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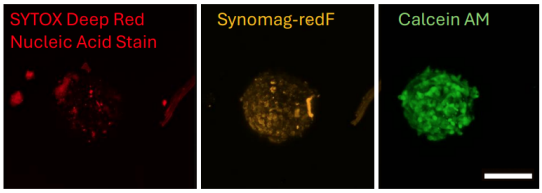

Figure 1: Maximum Intensity Projection of a Synomag-redF loaded spheroid labelled for dead cells (red), Synomag-redF (orange) and living cells (green). The scale bar corresponds to 50 µm.

Spheroids were fabricated from 1000 cells each and were incubated at 37°C with 5% CO_2. After two days, spheroids were loaded with fluorescently labeled SPIONs (Synomag-redF, 70 nm, 1.8 mg/mL, Micromod, Rostock, Germany) for the fluorescent analysis of spheroids or with plain SPIONs (Synomag-D, 70 nm, 4 mg/mL, Micromod, Rostock, Germany) for MPS measurement. 36 µl of SPION solution was added to the wells and filled up with DMEM to 100 µl. Afterwards spheroids were incubated for two days at 37°C and 5% CO_2.

II.II. Fluorescence Microscopy

15 spheroids, loaded with Synomag-redF, were stained with a live-dead kit (Invitrogen, Eugene, Oregon, USA) according to the protocol of the manufacturer. The stained spheroids were placed in a μ-dish (ibidi, Gräfeling, Germany) with 100 µl PBS (Carl Roth Gmbh & Co. KG, Karlsruhe, Germany). Images were captured using a laser scanning microscope (LSM 880, Carl Zeiss, Oberkochen, Germany).

II.III. MPS Measurement

For MPS measurement two different samples were used: 5 µl undiluted Synomag-D and 30 spheroids loaded with Synomag-D. A field strength of 20 mT and a frequency of 25 kHz with a measurement time of 40 ms were used.

III. Results and discussion

The fluorescent images of the live-dead staining of a loaded spheroid are shown in Figure 1. The Synomag-redF was taken up and was evenly distributed in the spheroid.

The MPS measurement shows a signal clearly distinguishable from the background for both samples. A different signal behavior was detected for SPIONs in aquaeous solution and inside spheroids and can therefore be separated from each other (see Figure 2). The magnetic properties change when the nanoparticles are integrated into the spheroids resulting in the change of the particle signal. This could be due to the particles being more immobilized which is most likely due to the degradation of the dextran coating in vitro compared to particles in solution.

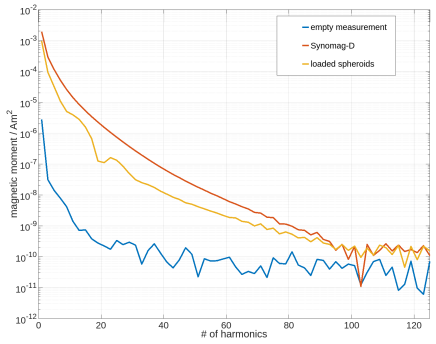

Figure 2: Magnetic particle spectrum (odd harmonics) of Synomag-D in solution (orange), spheroids loaded with Synomag-D (yellow) in comparison to an empty measurement (blue).

IV. Conclusion

Representative fluorescence images of SPION loaded cells demonstrate a homogeneous distribution of nanoparticles in the spheroid. Furthermore, the MPS measurements show a significant difference in the behavior of the nanoparticles in aqueous solution compared to those incorporated in spheroids. The parameters influencing the particle signal when incorporated into 3D cell spheroids will be investigated further.

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Author's statement

Conflict of interest: Authors state no conflict of interest.

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