Retraction Notice

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Nanoparticle-Assisted Ultrasound for Cancer Therapy

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Abstract

Herein, the concept and data for cancer treatment that combines ultrasound and nanoparticles is reported. Non-toxic gold and magnetic nanoparticles were used to enhance the ultrasound destruction of cancer cells in vitro. Separate monolayers of normal and cancer cells were treated by focused ultrasound with the result of more pronounced damage of cancer cells when biocompatible gold and magnetic nanoparticles were added in the culture media. The data obtained on different cell lines, indicate that nanoparticle-assisted ultrasound therapy can provide an effective new tool for cancer treatment and potentially can be combined with conventional methods of cancer diagnosis and therapy to further increase the overall cancer cure rate.

Keywords

Cancer, Nanoparticles, Ultrasound therapy

1. Introduction

Cancer is one of the top causes of death throughout the world. Many cancer patients die due to the serious side effects of chemotherapy or through a drug-resistance-related relapse after the treatment. It was established that a typical tumor has high degree of heterogeneity and can contain more than 100 different types of cells. If a specifically targeted drug is used, some types of cancer cells may survive, and become dominant in the tumor, making this drug eventually become useless for cancer therapy. If an adequate physical treatment is applied, it should reduce not only the side effects but also the growth of drug-resistant cancer cells. Radiation therapy is a standard physical method of cancer treatment. It includes gamma-rays, x-rays, electron beam, proton beam, and etc. Radiation therapy is intended to be directed only at the tumor. However, the

radiation is difficult to focus, so it also affects the normal tissues when it passes through the patient's body. Normal cells are affected by ionizing radiation, which causes undesirable side effects. [1] Moreover, radiation itself may cause DNA mutation in normal cells, causing them to become cancerous. Photodynamic therapy relies on the photosensitizing dyes to absorb light and convert the energy into cytotoxic molecules including singlet oxygen. [2] The main limitations of photodynamic method are solid tumor hypoxia [3] and relatively low light penetration depth. Other non-ionizing radiation therapies are mainly based on the hyperthermia of tumors due to larger sensitivity of tumor cells to heat than their normal counterparts. [4] [5] A new physical method, which does not cause DNA mutations or destruction of normal cells, is highly desired. In this work we applied nanoparticles with a medium-intensity ultrasound for the comparative treatment of human malignant and non-malignant cells.

2. Results

The basic concept of nanoparticle assisted ultrasound therapy is shown in **Figure 1**. We compare the results of normal and cancer cell under the treatment of nanoparticle assisted ultrasound irradiation technology. We observed selective killing of cancer cells by this approach.

The effect of ultrasound (US) and gold NPs on cancer (A549) and normal (BEAS-2B) lung cells were analyzed by counting of viable cells with flow cytometry. Results are shown in **Figure 2**. The obtained results show that cancer lung cells (A549) are more sensitive to damaging effect of US, than their normal counterparts (BEAS-2B cells). While adding of gold NPs into cells cultures leads to increase in cell death, showing the synergetic effect of US energy with nanoparticles. However, this synergetic effect is much more pronounced for malignant A549 cells than that for healthy BEAS-2B cells.

Presence of gold NPs in normal BEAS-2B cell culture comparatively to only

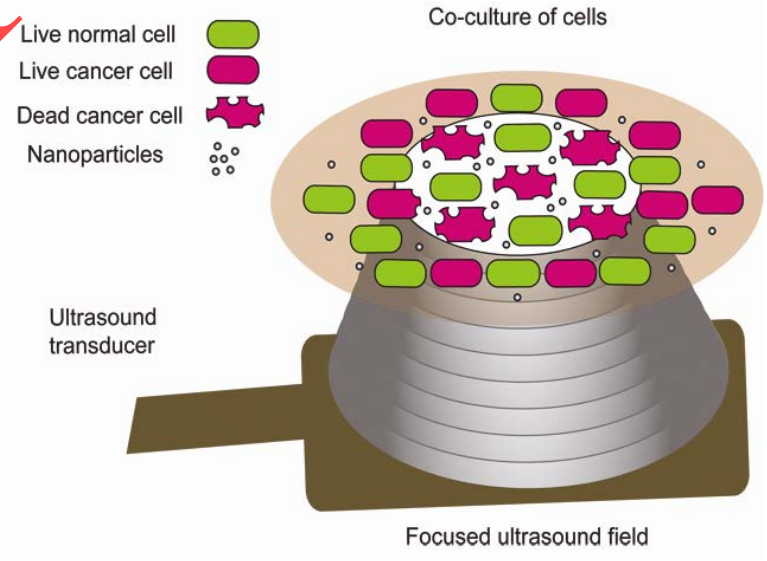

Figure 1. Conceptual scheme of nanoparticle-assisted ultrasound for cancer therapy.

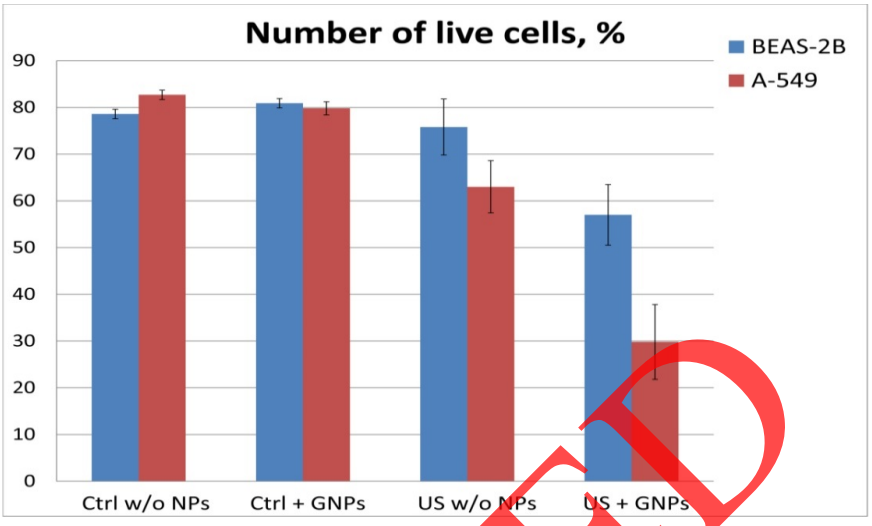

Figure 2. Flow cytometry data for BEAS-2B normal lung cells and A549 lung cancer cells with different treatments [6].

US treated cells, leads to decrease of the percentage of the number of live cells from 76% ± 6% to 57% ± 6%. Similarly, the percentage of live cancer A549 cells decreased from 63% ± 6% for US treated cells to 30% ±8 % for combination of US with NPs. These results clearly demonstrate that malignant lung cells exhibit a much greater influence of US with NPs than normal lung cells.

To compare the effect of ultrasound irradiation on normal and cancerous cells under the identical experimental conditions, the BEAS-2B and A549 cells were co-cultured and modified with fluorescent green and red proteins, respectively. Monolayers of the co-culture were then treated by US with and without adding of gold NPs. In order to estimate the cell damage, we analyzed the trypan blue-stained cells under optical microscope. The phase-contrast images of the trypan blue for BEAS-2B/A549 co-culture treated with the different combinations of US and NP under exposure of mercury lamp were obtained. This work aimed to eliminate the possible difference due to the small variation of US treatments and different culture conditions for cancer and normal cells. The combined treatment of cells with nanoparticle and ultrasound resulted in 7% ± 5% and 50% ± 15% for necrotic BEAS-2B and A549 cells, respectively. Thus, adding of gold NPs in the culture media right before the US exposure, enhances the damage of cells cultured both in separate and co-culture monolayers. However, the synergetic effect of US field and NPs was more pronounced for malignant lung A-549 cells and especially for the condition when A549 cells were co-cultured with their normal counterparts-BEAS-2B cells. The similar effect was discovered when separate monolayers of breast normal MCF-10A and cancer MDA- MB-231 cells were treated by combination of US with magnetic nanoparticles. Results also clearly demonstrated that malignant breast cells demonstrate larger damage, than their normal counterparts, especially for the combined US treatment.

To analyze a character of cell damage caused by US in combination with NPs, TEM images of breast healthy and carcinoma cells were obtained. Results show

the cancer cell membrane has more uneven structure after US, and especially after US with NPs than the membranes of the corresponding normal cells.

3. Discussion & Conclusion

Gold and super-paramagnetic iron oxide NPs possess a unique combination of physical and chemical properties, allowing them to act as highly multifunctional anti-cancer agents. Gold NPs have been tested as drug carriers, [6] and radio-sensitizers. [7] The gold NPs can simultaneously be used to visualize their location inside the body using photoacoustic imaging, [8] or optical coherence tomography, [9] in combination with X-ray imaging, [10] or electron microscopy. [11] The advantage of biocompatible gold and magnetic NPs is their low toxicity and ability to be used as contrast agents for various diagnostic methods of visualizing the tumor tissues.

In addition to thermal effects, [12] the ultrasound radiation is known to produce mechanical pressure that results in acoustic streaming and cavitation within cellular systems. [13] Free cavitation bubbles are formed in a liquid media when the local liquid pressure drops below the saturated vapor pressure at the rarefaction period of the propagated ultrasound wave. The inertial cavitation process leads to creation of shock waves, sonoluminescence and formation of free radicals, which can irreversibly damage cells. [14] It is known that the threshold of inertial cavitation can be decreased by adding nucleation agents and changing the host fluid parameters. [15] NPs may act as permanent source of nucleation sites for cavitating air bubbles, leading to enhancement of inertial cavitation in the culture media.

It is known that malignant and normal cells differ in their metabolism and morphology. Recently it was found, that cancer cells in general are softer than their benign counterparts. This fact is in line with our experimental results, and may explain why under tension/compression force of ultrasound, there was the preferred damage of membranes of cancer cells. TEM images made for the breast normal and cancer cells confirm that the structure of cell membrane is more irregular and "ragged" for malignant cells, especially after combined effect of US field with NPs.

This experiment shows that US exposure causes some cell damage for both normal and cancer types of cells, while the effect is somewhat greater for cancer cells. However, when NPs are added to the system, the resulting cell damage is much larger for cancer cells, than for the normal cells. The exact mechanism of this "nonlinear" selectivity is unknown and requires further investigation.

The synergetic effect of US field with NPs or nanoparticle-assisted ultrasound therapy can be potentially applied in therapy of tumors especially of hollow organs as well as in treatment of leukemia.Using the biocompatible gold and magnetic NPs expands the potential application of ultrasound therapy.

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