ADJUSTIBLE CURIE-TEMPERATURE NANOPARTICLES FOR IMAGING AND HIGHLY CONTROLLABLE HYPERTHERMIA CANCER THERAPY

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Introduction

Within the past decade a new method of localized hyperthermia has been developed which takes advantage of the noninvasive nature of electromagnetic heating, utilizing ferromagnetic nanoparticles introduced into the tumor to localize the heating. Modern clinical hyperthermia trials are based on the superparamagnetic ironoxide (SPIO) nanoparticles and focus mainly on the optimization of thermal homogeneity at moderate temperatures (41-43°C) in the target volume. Higher temperatures lead to wide-spread necrosis of normal tissue while temperature underdosage yields recurrent tumor growth. There is a compelling need for new physical concepts that may offer reliable temperature control in the targeted tumor volume.The unique nanomaterials recently synthesized in our group are lanthanum manganite particles with silver ions inserted into the perovskite lattice $La_{1-x}Ag_xMnO_3$. New nanoparicles have unusual, temperature-dependent magnetic properties. The unique feature of the doped manganites is the possibility to control their *Curie temperature* in the range of tumor hyperthermia interest. At its *Curie temperature*, a ferromagnetic particle loses its magnetic properties; this metal-insulator phase transition is tunable and reversible, so that when the particle cools down, it once again becomes ferromagnetic. Thus when these particles are placed into an alternating magnetic field, their temperature increases to desirable value and remains the same as long as the magnetic field is maintained. Due to the small size the ferromagnetic particles adopt the superparamagnetic behavior and are comparable to iron oxide as an MRI contrast agents. The goal of this presentation is to introduce newly synthesized nanomaterials and create a new platform for highly controllable hyperthermia cancer therapy and imaging. Systematic studies and optimization of new materials can open new horizons in cellular hyperthermia research for clinical applications.

Experimental

All samples were prepared using chemical homogenization method. The silver-containing pellets were sintered at 800 °C under the layer of the covering powder in alundum crucibles in air for 20 hours. Three series of silver-containing samples were prepared. Magnetic relaxation in nanoparticles is of substantial importance for the process of radio frequency (RF) heating. Up to the present, the relaxation rates in such systems were measured by means of non-resonant techniques. Recently, an original method of measuring extremely fast relaxation processes was elaborated in our group; method has been applied for studying new LaAgMnO nanoparticles. Magnetization was measured in the static magnetic field 230, 6250 Oe with the SQUID magnetometer. Magnetic resonance images were acquired on a Varian 600 MHz vertical microimaging scanner (Oxford Instruments, Abington, UK) equipped with a Unity/Inova console (Varian, Palo Alto, CA), operating at 14.1 T. A large heating power is desirable to reduce the amount of magnetic nanoparticles to be administrated to the subject. An advanced alternating-current (AC) magnetic field applicator was specially constructed for small animal experiments and was explored in the current studies.

Results and Discussion

Our experiments on the preparation of the composites of CMR manganites and metal silver have shown that in the case of $La_{1-x}MnO_{3+\delta}$ the vacancies in the A-sublattice of the perovskite structure can be filled by Ag^+ ions under the soft conditions of the synthesis. Neutron diffraction refinement of $La_{0.8}Ag_{0.2}MnO_{3.00}$ clearly proves the silver doping in the A-sublattice. Depending on $P(O_2)$–T synthesis conditions the solid solutions with the broad stoichiometry range $La_{1-x}Ag_yMnO_{3+\delta}$ ($0.3 \geq x \geq y$) were prepared. Note that the *Curie temperature* rises up and can exceed room temperature with the increase of silver content. A comparison analysis of heating characteristics between newly synthesized LaAgMnO materials and SPIO nanoparticles both exposed to alternating magnetic fields is shown in Fig. 1. An essential difference in heating behavior of regular SPIO and new silver doped nanoparticles clearly demonstrates the effect of adjustable *Curie temperature* in LaAgMnO samples. Data in Fig.1 are in excellent correlation with RF magnetic susceptibility (χ') results. *In vivo* imaging of manganite nanoparticles implanted into mouse brain (Figs. 1,2) demonstrated significant reduction in signal intensity thus suggesting strong MRI contrast effect below the *Curie temperature*. Biocompatibility testing of new nanomaterials shows negligible degradation of LaAgMnO compounds. In preliminary *in vivo* studies of the particles implanted into the brain of mice, no behavioral abnormalities were produced by the particles.

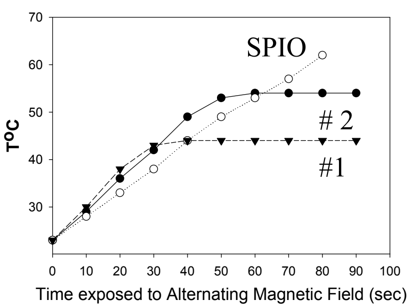

Fig.1. Comparison heating of SPIO and LaAgMnO nanoparticles (#1, 2) prepared at different conditions in aqueous suspensions when exposed to AC magnetic field.

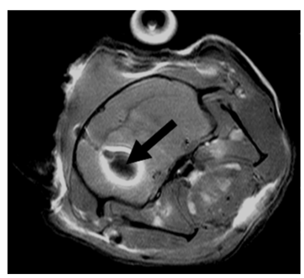

Fig.2. LaAgMnO particles (0.3μl) directly injected into the mouse brain shows a deep reduction in MRI signal intensity.

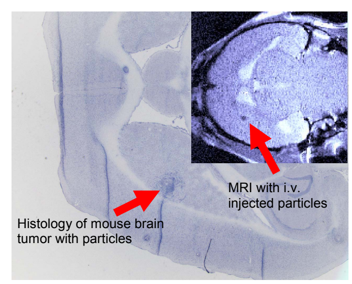

Fig 3. Correlation between MRI image and histology of nanoparticles location in mouse brain. Mouse was injected with LaAgMnO particles intravenously (i.v.)

Conclusion

The unique feature of newly synthesized doped manganites $La_{1-x}Ag_xMnO_3$ is the possibility to control their *Curie temperature* in the range of tumor cells hyperthermia interest ($41\text{-}44^0$ C) by proper adjusting the doping silver level (x). When these particles are placed into an external alternating magnetic field, their temperature increases to desirable value and remains the same as long as the magnetic field is maintained, thus producing therapeutic effect. The RF absorption/heating drops down sharply above the Curie temperature. As a result, constant temperature can be achieved, which is unaffected by an intensity of external electro-magnetic radiation thus preventing necrosis of normal tissue. The metal-insulator transition is reversible: when the temperature drops below the Curie point, then the LaAgMnO nanoparticles switch to superparamagnetic (and metallic) phase again. This alternative behavior makes the doped perovskite manganites ideal materials for cellular hyperthermia. Preliminary studies show that new nanoparticles are inert, stable and their properties are not affected by chemical or physical conditions in living tissue. In preliminary *in vivo* studies of the particles implanted into mice brain, no behavioral abnormalities were observed. Our studies of the magnetic relaxation properties of the particles indicate that they are comparable to SPIO as an MRI contrast agent, so we will be able to monitor the particle uptake and retention by MRI. The results indicate that newly synthesized nanomaterials may thus become clinically useful for highly controllable hyperthermia cancer therapy and imaging as an alternative to SPIO-based particles. This research was supported in part by the Human Frontier Society Program.