In vitro MR Thermometry on Magnetically Heated Iron Oxide Labeled Stem Cells

D. Haddad[1], J. Lorenscheit[2], M. Hildenbrand[1], M. Weber[3], R. Ebert[3], and P. M. Jakob[1,2]

[1]MRB Research Center Magnetic-Resonance-Bavaria, Würzburg, Germany, [2]Department of Physics, EP5, University of Würzburg, Germany,
[3]Orthopedic Institute König-Ludwig-Haus, University of Würzburg, Germany

Introduction: Iron oxide nanoparticles are commonly used as MR markers to label and track (stem) cells. They represent a strong magnetic perturbation and are therefore easily detected as hypointense spots in T_2* weighted MR images. Magnetic particle heating (magnetic field hyperthermia) can be used to heat the iron oxide particles and thus the iron labeled stem cells. Here we present a proof-of-principle *in vitro* study which shows that MR thermometry can be used to visualize the heat distribution in the vicinity of iron oxide labeled stem cells that were heated outside the MR spectrometer via magnetic particle heating.

Materials and Methods: Cells from the human mesenchymal stem cell line hTERT were labeled with five different iron oxide nanoparticles via electroporation. Intracellular iron content was determined with mass spectroscopy (ICP-MS). The cells were subsequently used as cell pellets (10^6 cells) or homogenously embedded in 250µl collagen type-I-hydrogels (10^6 and $3x10^5$ cells/250µl gel) and placed on agar beds in 5 mm MR tubes. The remaining volume was filled with standard cell culture medium. Magnetic particle heating was performed for 300 s at a frequency of 400 kHz with a 2kW IEW heating apparatus. Immediately after heating, the samples were transferred in a Bruker 11.7 T MR spectrometer, where the samples were monitored during the cooling process. To visualize the heat distribution and dissipation in the samples, MR thermometry measurements were performed repeatedly for 10 minutes with a 20 mm birdcage coil and the proton resonance frequency shift method using a FLASH experiment (TR= 50 ms, TE= 6 ms, spatial resolution = 156 x 156 µm², slice thickness = 0.5 mm). Spatially resolved temperature maps were calculated from the acquired phase images.

Results: The MR temperature maps show temperature differences of several °C between the vicinity of the labeled cells (cf. Fig.1-2) and the agar bed/cell culture medium. Depending on the specific iron oxide nanoparticle and intracellular iron content, temperature differences of 2 - 12 °C could be determined. The cells themselves could not be visualized due to the iron induced signal voids (cf. Fig.1+2). Intracellular iron contents ranging from 2 - 70 pgFe/cell could be measured for the different iron oxide nanoparticles. Samples with unlabeled control cells were also homogenously heated by 2 - 3 °C due to heat losses (radiation) from the heating apparatus (cf. Fig.4). The precision of the MR temperature measurements is better than 0.5 °C.

Discussion and Conclusion: Iron oxide labeled cells can be heated easily via magnetic particle heating. MR thermometry allows to visualize the spatial and temporal temperature distribution with high accuracy. Since the heating capacity depends on the composition and structure of the material of interest, different types of iron oxide particles yield different heating rates. The heating rates can also be controlled by varying the amount of iron oxide incorporated in the cells. Thus, the combination of MR thermometry and magnetic particle heating offers different possible applications: e.g. (1) MR guided and controlled thermal ablation for tumor therapy, (2) non-ambiguous identification and monitoring of iron oxide labeled (stem) cells in cell based therapies including the discrimination of the labeled cells from other "field perturbers" like air bubbles, blood clots etc., due to different heating rates. Even total signal loss induced by high amounts of iron oxide is no obstacle for MR identification and monitoring of the labeled and heated cells.

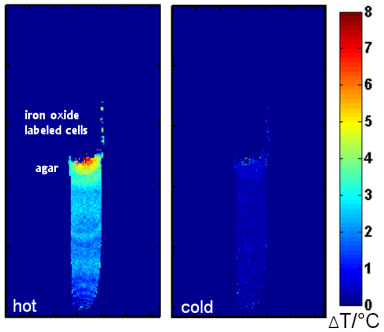

Fig.1: Temperature map: High temperature differences of more than 7 °C can be measured between the vicinity of the cells and the agar gel due to the high iron oxide concentration in the cells (10^6cells/250µl with 70pgFe/cell). Both images show the same 5 mm MR tube at different temperatures.

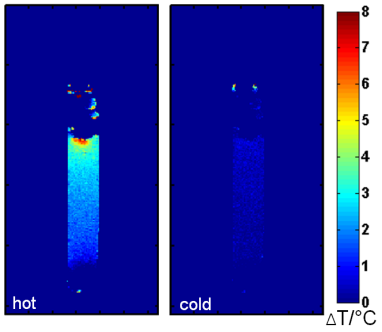

Fig.2: Temperature map: Intermediate temperature differences of about 5 - 7 °C can be measured between the vicinity of the cells and the agar gel due to the high iron oxide concentration in the cells (10^6cells/250µl with 22pgFe/cell).

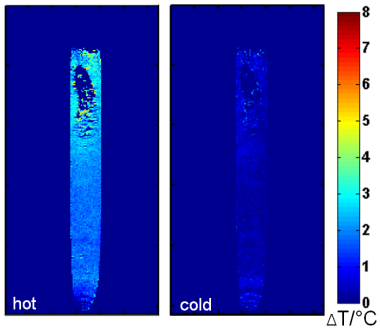

Fig.3: Temperature map: Only small temperature differences of 3 - 4 °C can be measured due to the low iron oxide concentration in this sample (10^6cells/250µl with 2pgFe/cell). The iron oxide induced signal void region is also much smaller.

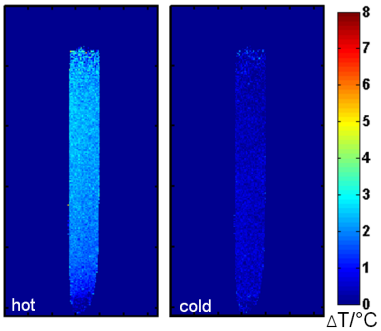

Fig.4: Temperature map: Temperature differences of 2 - 3 °C can be measured in the control sample because of direct heat losses (radiation) from the magnetic heating apparatus (10^6cells/250µl).