Multi Parameter High-Resolution Magnetic Resonance Imaging and Spectroscopy of Tumors

P. Moerchel[1], G. Melkus[1], V. C. Behr[1], M. Kotas[2], P. Jakob[1], M. Flentje[2]

[1]Dept. of Experimental Physics 5, University of Würzburg, Würzburg, Germany, [2]Dept. of Radiation Oncology, University of Würzburg, Würzburg, Germany

Introduction: Over the past decade, MRI and MRS techniques have merged which allows for interrogation and functional characterisation of the tumor microenvironment non-invasively in living tissues with high resolution [1]. The chaotic vasculature evolution in tumor tissue results in an unbalanced blood supply and heterogeneities in perfusion and oxygenation. Tumor lactate level is an important marker for tumor aggressiveness, the potential for metastatic behaviour, and response to therapy [2].
An MRI and MRS protocol to measure these parameters in vivo on different tumor models was implemented on a high field 17.6 Tesla wide-bore spectrometer. In order to compare the MR-results with data from bioluminescence, these tumors were stained with specific markers and histologicaly processed.

Material and Methods: Experiments were carried out on 35 tumor-bearing nude mice for five different tumor models (FADU, HSC4, Cal-33, UT-SSC-45, UT-SSC-5). The mice were narcotized using isoflurane and the temperature was maintained at 35-37°C using the gradient cooling system. Data were obtained on a Bruker Avance 17.6 Tesla wide-bore spectrometer with a 200mT/m gradient system and a 38mm birdcage coil.
Perfusion in the tumors was measured using a MR-Spin-Labeling method [3] with a segmented inversion-recovery snapshot-flash sequence. With this method, perfusion maps with a spatial resolution of 200µm x 200µm and slice thickness of 1.2mm were obtained.
One relevant parameter in functional MRI is the BOLD-contrast [4]. BOLD maps were calculated from T_2^* maps acquired under normal air - and carbogen (95% O_2, 5% CO_2) breathing. A spatial resolution of 125µm x 125µm in-plane and slice thickness of 0.6mm was thereby achieved.
The lactate distribution of the tumor was measured with an acquisition-weighted spectroscopic imaging sequence [5]. To suppress effects from lipid infiltration of the tumor and the resonances of the lipids in the spectral range of lactate, a spectral editing filter was included. The selective multiple quantum filter (SelMQC) [6] provides a complete water and lipid suppression and refocuses only the lactate signal at 1.33ppm. For spectroscopic imaging, the number of experiments was 1200 with a k-space weighted accumulation scheme (Hanning), leading to an in-plane resolution of 1.33mm x 1.33mm (slice thickness 2mm).

Results: Data of one typical example of a CAL33 tumor are presented in Fig. 1a - 1d.
Fig. 1a shows a RARE image of the tumor and the mouse leg. The bright tumor is clearly silhouetted against the dark leg. Parameter maps and histology data of the tumor are superimposed on the corresponding RARE image.
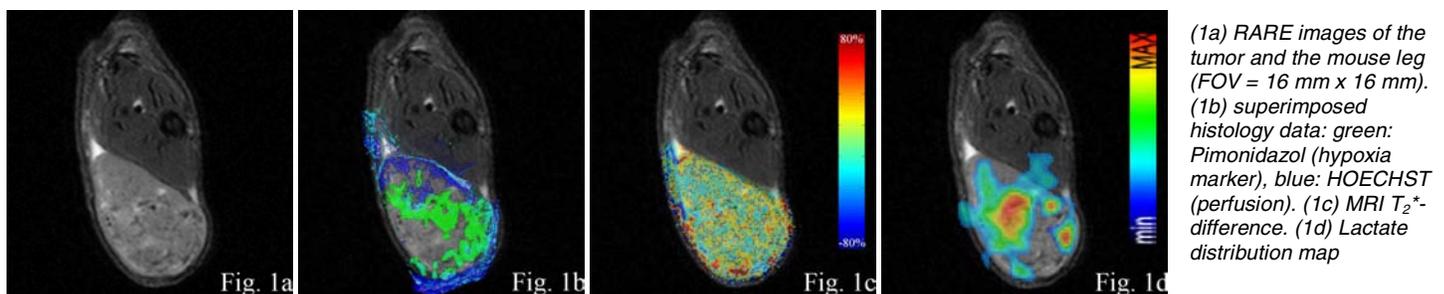Fig. 1b shows a section of the tumor stained with a hypoxia marker, Pimonidazol (green), and a perfusion marker, Hoechst (blue).
Fig. 1c presents results of the tumor T_2^* difference map. The scale in these pseudocolor images represents the relative change in T_2^* in percent while breathing carbogen compared and normalized to the T_2^* value while breathing room air. Comparison with the histology confirmed that hypoxic parts of the tumor (labelled green in 1b) show a T_2^* shortening in the BOLD-MRI map (1c). In areas where the Pimonidazol-marker cannot be found, the tumor is adequately supplied with oxygen. In these regions, the T_2^* parameter increases, which is an indication of the availability of more oxyhemoglobin during carbogen breathing.
The qualitative perfusion map of the tumor acquired with the spin-labeling technique (not shown) confirms that well-perfused regions correspond with positive values in the T_2^* difference maps, reflecting a better oxygenation of the tissue. As expected, no hypoxia marker could be found in these regions in the histology image.
The lactate distribution in the tumor (Fig. 1d) shows a correlation to the oxygenation state. In the areas where hypoxia is present, higher lactate levels exist (Fig. 1b, 1d). The green hypoxia pattern (Fig. 1b) correlates with low T_2^* changes in the difference maps (Fig. 1c). This is an indication of anaerobic glycolysis in the tumor where a poor supply of oxygen leads to lactate production.

Conclusion: MRI and MRS provide unique opportunities to characterize hypoxia and the metabolic microenvironment of tumors in vivo. As shown above, MR data correlates well with histology data. With such in vivo data, radiological therapies and treatment could be accomplished more efficiently.

(1a) RARE images of the tumor and the mouse leg (FOV = 16 mm x 16 mm). (1b) superimposed histology data: green: Pimonidazol (hypoxia marker), blue: HOECHST (perfusion). (1c) MRI T_2^*-difference. (1d) Lactate distribution map

References:
[1]   Gillies R J, Raghunand N R, Karczmar G S, Bhujwalla Z M. MRI of the Tumor Microenvironment. J Magn Reson Imag 2002;16:430-450.
[2]   Rofstad EK. Microenvironment-induced cancer metastasis. Int J Radiat Biol 2000;76:589–605.
[3]   Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med. 1992;23(1):37-45.
[4]   S. Ogawa et al. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Biophysics 1990;87:9868-9872.
[5]   Pohmann R, von Kienlin M. Accurate phosphorus metabolite images of the human heart by 3D acquisition-weighted CSI. Magn Reson Med 2001;45(5):817-26.
[6]   He Q, Shungu DC, van Zijl PCM, Bhujwalla ZM, Glickson JD. Singlescan in vivo lactate editing with complete lipid and water suppression by selective multiple-quantum-coherence transfer (Sel-MQC) with application to tumors. J Magn Reson B 1995;106:203–211.