Monitoring Cancer Response to Treatment with Hyperpolarized $^{13}$C MRS

Monitoring the cancer response to treatment, non-invasively, by medical imaging is a key element in the management of cancer. For patients undergoing treatment, it is crucial to determine responders from non-responders in order to guide treatment decisions. Currently, PET is the most widely used technique for imaging tumor function by measuring the uptake of the glucose analogue FDG. FDG-PET can visualize changes in metabolic activity and indicate if a patient will respond to a particular therapy, sometimes within hours of the first treatment. However, PET is not effective in all tumor types, and the patient is exposed to ionizing radiation. The introduction of hyperpolarized $^{13}$C MRS has opened completely new possibilities to study the biochemical changes in disease processes. Numerous $^{13}$C-labeled compounds were proposed to interrogate various aspects of cancer cell metabolism. The aim of this study is to investigate the relevance of [1-$^{13}$C]pyruvate and [1,4-$^{13}$C$_2$]fumarate in monitoring the changes in cellular metabolism and necrosis that may occur as a result of cancer therapy. This project also aims to improve existing $^{13}$C MRSI methods to efficiently utilize the signal from hyperpolarized 13C substrates. Firstly, we investigate the effectiveness of hyperpolarized [1-$^{13}$C]pyruvate in detecting the treatment response in two types of NSCLC xenografted in mice, in comparison with FDG- and FLT-PET. We show here a significant reduction in tumor lactate levels, obtained by MRS, in HCC-827 tumors, as well as lower FLT- and FDG-PET uptake with erlotinib treatment. These findings were validated ex vivo, where LDH activity level and Ki-67 IHC staining was significantly lower in treated HCC-827 tumors. Furthermore, the reduction in LDH activity levels correlated with the lactate levels found using $^{13}$C MRS. These findings indicate the hyperpolarized [1-$^{13}$C]pyruvate can be an alternative to FDG-PET.

In the second study, a polarization scheme for [1,4-$^{13}$C$_2$]fumarate in the SPINlab polarizer is presented. The feasibility of using [1,4-$^{13}$C$_2$]fumarate as marker for monitoring induced necrosis is demonstrated in vivo in two rat models; ischemia/reperfusion induced necrosis in kidneys and turpentine induced necrosis in muscle. High polarization was achieved for [1,4-$^{13}$C$_2$]fumarate in the SPIN lab and high [1,4-$^{13}$C$_2$]malate signal was observed from the necrotic tissue in both models. The elevated malate signal observed in the ischemia/reperfusion induced injury in kidney showed high correlation with well-known blood and urine bio-markers used to characterize acute kidney injuries. Moreover, simultaneous assessment of metabolism and necrosis was achieved using dual polarization of [1,4-$^{13}$C$_2$]fumarate and [1-$^{13}$C]pyruvate. Finally, a symmetric echo planar spectroscopic imaging sequence for hyperpolarized $^{13}$C spectroscopic acquisition in clinical scanners is presented with a reconstruction algorithm that separately reconstruct the data from odd and even echoes in order to reduce artifacts from gradient imbalances. The reconstruction algorithm employs re-gridding in the spatio-temporal frequency space to compensate for the chemical shift displacements. The sequence is compared with conventional phase-encoded chemical shift imaging on a clinical PET/MRI system in phantoms and a large animal model. The SNR per unit time of EPSI for $^{13}$C at thermal equilibrium was comparable to CSI. The reconstruction pipeline improved the localization compared to direct FFT, which resulted in spatial blurring. The encoding speed of EPSI allowed dynamic imaging of tumor metabolism with high spatial and temporal resolutions and reduced blurring due to T1 decay.

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