Imaging Cancer Metabolism with Hyperpolarized Substances

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A better understanding of the molecular signature of cancer has allowed the development of a new generation of anti-cancer drugs that target specific molecular entities, such as receptors, genes, or signalling pathways. However, DNA sequencing and microarray-based disease profiling, together with the results of clinical trials using targeted therapies, have clearly demonstrated the intrinsic heterogeneity of human tumours, both genetically and phenotypically. Patients with similar tumour types frequently have markedly different responses to the same therapy. The development of these novel targeted cancer therapies could benefit significantly, therefore, from the introduction of imaging methods that allow an early assessment of treatment response in individual patients. These would allow an oncologist to rapidly assess the effectiveness of a new therapy. Ineffective treatments could be abandoned at an early stage and more effective treatments selected, with attendant welfare benefits for the patient and cost benefits for the health care system (1).

The aberrant metabolism displayed by tumor cells offers numerous opportunities for early detection of treatment response using metabolic imaging. The recent introduction of dissolution dynamic nuclear polarization (DNP), which can increase sensitivity in the MR experiment by more than 10,000x, has allowed a new approach to metabolic imaging using MRS (2). In this experiment a solution of the material to be polarized, typically a ^{13}C-labelled cell metabolite, is mixed with a stable radical and rapidly frozen to form a glass. The electron spin on the radical is polarized (to unity polarization) by cooling the sample to a very low temperature (~1.3 ˚K) in a magnetic field. The polarization is then transferred to the nuclear spin by exciting the electron spin resonance and currently nuclear spin polarizations, in favorable cases, of up to 50% are possible. The polarized compound is then brought rapidly to room temperature, without significant loss of this polarization, and injected into the biological system. The massive gain in sensitivity means that we can now image the location of the hyperpolarized ^{13}C-labeled molecule in the body and, more importantly, the rate of its metabolic interconversion with other metabolites, in the absence of any background signal.

Since the first publication of the method in 2003 there have been numerous studies *in vivo* using a variety of different hyperpolarized ^{13}C-labelled cell substrates (reviewed in (3)). For example, ^{13}C MRSI measurements of the conversion of hyperpolarized [1-^{13}C]pyruvate into lactate have been used to image tumor LDH activity and decreases in its activity due to chemotherapy-dependent decreases in NAD(H) concentration (4) and decreases in enzyme concentration due to inhibition of the PI3K-Akt pathway (5). Tissue pH has been imaged from the ratio of the signal intensities of hyperpolarized $H^{13}CO_3^-$ and $^{13}CO_2$ following intravenous injection of hyperpolarized $H^{13}CO_3$ (6). Tumour cell glutaminase activity, a potential measure of cell proliferation, has been determined using hyperpolarized [5-^{13}C]glutamine (7) and treatment-induced tumour cell necrosis has been imaged *in vivo* from measurements of the conversion of hyperpolarized [1,4-$^{13}C_2$]fumarate to malate (8-10). ^{13}C has been the most popular nucleus since the lifetime of the polarization for non-protonated carbons is relatively long, although other nuclei have been polarized using the technique (3).

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The main limitation is the very short lifetime of the hyperpolarization, which for the ^{13}C-labelled molecules that have been polarised to date is typically between 10 and 40 s *in vivo*. This limits the metabolites that will be useful to polarise to those that are rapidly transported into the cell and undergo fast metabolism, such that there is significant metabolism of the substrate within the lifetime of the polarization. In general, therefore, it seems likely that the technique will be useful for studying the metabolism of those substrates involved in catabolism rather than anabolism. Nevertheless, despite these limitations, the technique promises new insights into tissue metabolism *in vivo* and, since it uses endogenous molecules, should readily be translatable to the clinic. The initial results of a clinical trial with hyperpolarized [1-^{13}C]pyruvate have been reported recently (http://news.ucsf.edu/releases/new-prostate-cancer-imaging-shows-real-time-tumor-metabolism/).

References

1. Brindle K. New approaches for imaging tumour responses to treatment. Nature Rev Cancer 2008;8:1-14.
2. Ardenkjaer-Larsen JH, Fridlund B, Gram A, Hansson G, Hansson L, Lerche MH, Servin R, Thaning M, Golman K. Increase in signal-to-noise ratio of > 10,000 times in liquid-state NMR. Proc Natl Acad Sci U S A 2003;100(18):10158-10163.
3. Gallagher F, Kettunen M, Brindle K. Biomedical applications of hyperpolarized ^{13}C magnetic resonance imaging. Prog NMR Spectrosc 2009;55:285-295.
4. Day SE, Kettunen MI, Gallagher FA, Hu D-E, Lerche M, Wolber J, Golman K, Ardenkjaer-Larsen JH, Brindle KM. Detecting tumor response to treatment using hyperpolarized ^{13}C magnetic resonance imaging and spectroscopy. Nature Med 2007;13:1382-1387.
5. Ward CS, Venkatesh HS, Chaumeil MM, Brandes AH, Vancriekinge M, Dafni H, Sukumar S, Nelson SJ, Vigneron DB, Kurhanewicz J, James CD, Haas-Kogan DA, Ronen SM. Noninvasive detection of target modulation following phosphatidylinositol 3-kinase inhibition using hyperpolarized ^{13}C magnetic resonance spectroscopy. Cancer Res 2009;70(4):1296-1305.
6. Gallagher F, Kettunen M, Day S, Hu D-E, Ardenkjær-Larsen J, in 't Zandt R, Jensen P, Karlsson M, Golman K, Lerche M, Brindle K. Magnetic resonance imaging of pH *in vivo* using hyperpolarized ^{13}C-labeled bicarbonate. Nature 2008;453:940-943.
7. Gallagher FA, Kettunen MI, Day SE, Lerche M, Brindle KM. ^{13}C Magnetic resonance spectroscopy measurements of glutaminase activity in human hepatocellular carcinoma cells using hyperpolarized 13C-labeled glutamine. Magn Reson Med 2008;60(2):253-257.
8. Gallagher FA, Kettunen MI, Hu DE, Jensen PR, in't Zandt R, Karlsson M, Gisselsson A, Nelson SK, Witney TH, Bohndiek SE, Hansson G, Peitersen T, Lerche MH, Brindle KM. Production of hyperpolarized [1,4-^{13}C)]malate from [1,4-^{13}C)]fumarate is a marker of cell necrosis and treatment response in tumors. Proc Natl Acad Sci USA 2009;106:19801-19806.
9. Witney TH, Kettunen MI, Hu D-E, Gallagher FA, Bohndiek SE, Napolitano R, Brindle KM. Detecting treatment response in a model of human breast adenocarcinoma using hyperpolarised [1-^{13}C]pyruvate and [1,4-$^{13}C_2$]fumarate. . Brit J Cancer 2010;103:1400-1406.
10. Bohndiek SE, Kettunen MI, Hu D-E, Witney TH, Kennedy BWC, Gallagher FA, Brindle KM. Detecting tumor response to a vascular disrupting agent using ^{13}C magnetic resonance spectroscopy and hyperpolarized [1-^{13}C]pyruvate and [1,4-$^{13}C_2$]fumarate. Molec Cancer Ther 2010;9:3278-3288.