Combined macromolecular DCE-MRI and hyperpolarized ^{13}C MRSI indicate an association between vascular and metabolic effects of imatinib in a prostate cancer bone metastasis model

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Introduction: Imatinib is a tyrosine kinase inhibitor of BCR-ABL c-KIT and platelet-derived growth factor receptor (PDGFR). Previously, an imatinib-induced switch from glycolysis to mitochondrial glucose metabolism was detected using ^{13}C MRS in BCR-ABL-positive leukemia cell extracts, whereas an anti-vascular effect of imatinib treatment was detected by immunohistochemistry in a PDGFR-expressing prostate cancer bone metastasis model [1, 2]. Recently we have demonstrated that macromolecular DCE-MRI can report the early vascular response to imatinib treatment as a decrease in vascular permeability and provide molecular mechanistic insight, implicating vascular endothelial growth factor (VEGF) in that response [3]. The purpose of this study is to investigate the metabolic changes that might accompany the vascular effects of imatinib by combining macromolecular DCE-MRI with hyperpolarized ^{13}C MRSI for the same tumor.

Methods: Tumors were initiated by intratibial injection of human prostate cancer cells (PC-3MM2) in male CD-1 nude mice [2] and studied (MRSI followed by DCE-MRI) when tumors reached ~7-10 mm in diameter, before (d0) and at the end of 2-days (d2) treatment with imatinib (provided by Novartis Pharma, Basel, Switzerland; 50 mg/kg; ip at d0, d1 and d2) and paclitaxel (Bristol-Myers Squibb, Princeton, NJ; 8 mg/kg; ip once at d0). In vivo studies were supplemented by immunohistochemistry of tissue sections. Dynamic 2D ^{13}C MRSI data was acquired using a dual-tuned ^{1}H-^{13}C mouse coil on a 3T GE scanner (GE Healthcare, Waukesha, WI) after iv injection of 350 μL (80 mM) ^{13}C$_1$-pyruvate hyperpolarized using a HyperSense (Oxford Instruments, Abingdon, UK) DNP polarizer. The sequence used a multiband excitation EPSI and 5x5x10 mm (0.25 cc) voxels. The 2D MRSI (TR/TE=250/160 ms, 20° lactate and 3.3° pyruvate flip angle) were dynamically acquired every 5 s following the start of injection [4, 5]. High-resolution macromolecular DCE-MRI was performed on the same scanner using a custom-built knee coil. A 3D-fSPGR sequence (TR/TE=24.7/3.4 ms, flip angle 35°, 2 NEX, slice thickness 600 μm, in-plane resolution 156x156 μm) was acquired pre and post injection of albumin-GdDTPA ([3]; ~85000 Da; 350 mg/kg iv).

Results: Both vascular permeability (DCE-MRI; Fig 1a) and lactate signal (MRSI; Fig 1b, c) were reduced at the end of two days treatment. Pyruvate signal was maintained, suggesting that tumor perfusion and substrate delivery remained high.

Immunohistochemistry of treated tumors indicated low expression of lactate dehydrogenase (LDH-A) and of hypoxia inducible factor (HIF-1α); apoptosis was detected in endothelial cells lining some of the tumor blood vessels.
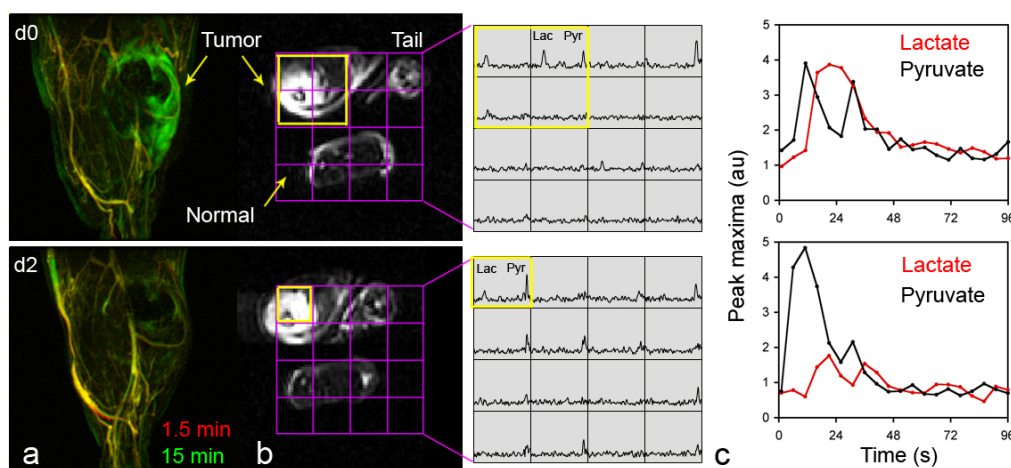

Figure 1: a. DCE-MRI presented as coronal maximal intensity projections (MIP) overlay of 1.5 (red) and 15 (green) minutes post contrast injection; b. 2D dynamic ^{13}C MRSI data including axial images (showing tail, tumor-bearing and normal limb) and corresponding spectral arrays (for pink voxels; 20 s post hyperpolarized pyruvate); and c. lactate and pyruvate dynamic curves in the tumor site (for yellow array indicated in b), at d0 (upper) and d2 (lower) of treatment.

Discussion: The transcription factor HIF-1 could be the connecting link between the vascular and metabolic effects observed here. HIF-1 controls both LDH (which catalyzes the pyruvate to lactate conversion) and VEGF (which involves in the vascular response to imatinib, as we showed before [3]) and in turn HIF-1 is regulated by signaling via the PI3K pathway downstream of receptor tyrosine kinase (i.e. PDGFR) which is being inhibited by imatinib. In addition, blockade of signaling of survival factors such as VEGF and PDGF could lead to apoptosis of tumor and stromal cells, resulting in depletion of the NAD and NADH cofactors that are required for the LDH activity and also resulting in a drop in hyperpolarized lactate levels [6]. In conclusion, our results demonstrate that combining DCE-MRI with hyperpolarized ^{13}C MRSI, together with and complementary data from immunohistochemistry, can help to reveal the mechanism of response to treatment and identify and validate new biomarkers of response.

References: [1] Gottschalk, S., et al. Clin Cancer Res, 10: 6661–8, 2004. [2] Kim, S.J., et al. Cancer Res, 64: 4201-8, 2004. [3] Dafni H., et al. Magn Reson Med, 60:822-833, 2008. [4] Cunningham C.H., et al. J Magn Reson 187: 357-362, 2007. [5] Larson P.E.Z., et al. J Magn Reson, 194:121-7, 2008. [6] Day, S.E., et al. Nat Med, 13:1382-7, 2007.