Hyperpolarized ^{129}Xe Dissolved-Phase MR Spectroscopy in Mice Changes with Lung Cancer Progression

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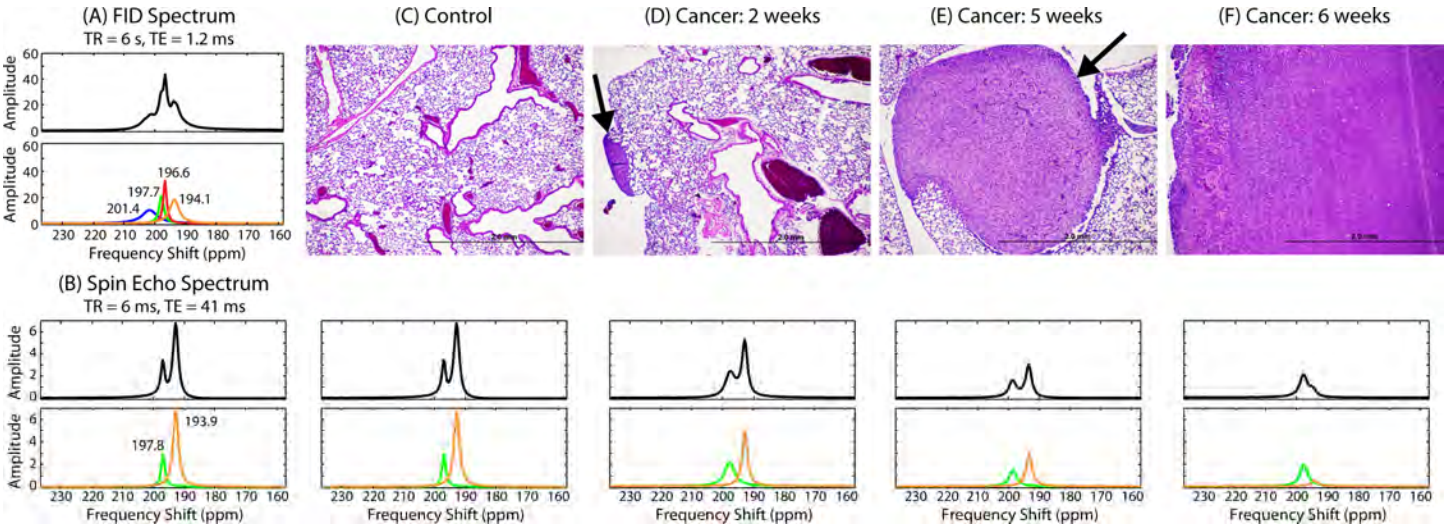
Target audience: Hyperpolarized ^{129}Xe MR Spectroscopy, Lung Cancer, Pre-clinical MRI

Purpose: Hyperpolarized (HP) ^{129}Xe has the powerful property that, upon inhalation, a modest fraction dissolves in the blood, which transports it to distal tissue compartments where it exhibits unique chemical shifts that are sensitive to the local tissue microenvironments. We hypothesized that these properties could make ^{129}Xe spectroscopy sensitive to pathology associated with tumor formation in the lung. We thus sought to detect and characterize unique ^{129}Xe resonances accompanying lung tumor formation in mice.

Methods: 6 week-old male BALB/c mice weighing ~18g were intravenously injected with ~50,000 4T1-GFP breast cancer cells known to create lung tumors over a period of 2-6 weeks. Prior to MRI, animals were anesthetized and intubated orally. They were then ventilated on an HP gas-compatible ventilator, and imaged in a quadrature ^{129}Xe coil at 2 T. All animals underwent respiratory-gated HP ^{129}Xe dissolved-phase spectroscopy (α = 90°, TR = 6 s). Spectra were acquired directly from the FID (TE = 1.2 ms), and after spin echo refocusing (TE = 41 ms) within a 2-cm slice encompassing the thoracic cavity, and then processed. Spectra were acquired every week from 2-6 weeks post injection of cancer cells. Following spectroscopy, the animals were euthanized and H&E histology was performed.

Results and Discussion: ^{129}Xe spectra acquired from the FID identified 4 closely-spaced resonances (Fig. A). The spin-echo spectra suppress the ^{129}Xe signal from fast-exchanging compartments within the alveolar septa while highlighting ^{129}Xe signal from distal, slowly exchanging compartments. While they exhibit ~10× lower signal than the FID spectra, they reveal two strong surviving peaks at 198 ppm (plasma and tissues) and 194 ppm (adipose tissue [1]), shown in Fig. B. Most striking was that the 194-ppm peak, associated with ^{129}Xe in adipose tissue, diminished dramatically with cancer progression. A modest reduction was seen as early as 2 weeks post-injection of cancer cells (Fig. D), which escalated to a 10-fold reduction by week 6 (Fig. F). Interestingly, reduction of the fat peak did not correlate with the weight of the animals, but closely matched the tumor burden as measured by H&E stained sections (Figs. D-F). Furthermore, the reduction in amplitude of the 194-ppm peak was accompanied with some broadening. This may be a signature of so-called white adipose tissue (WAT) browning, which is a hallmark of cachexia, a muscle and adipose tissue wasting syndrome accompanying cancer [2].



Conclusion: This pilot study has shown that ^{129}Xe spectroscopy is dramatically altered in progressively severe lung cancer. Particularly striking is the loss of the 194 ppm signal, which may be associated with WAT browning in cachexia. ^{129}Xe MRI could thus provide a novel ionizing radiation-free tool to study cachexia as it relates to tumor progression.

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References: [1] Swanson et al., Magn. Reson. Med. 42:1137–1145 (1999); [2] Petruzzelli et al., Cell Metabolism 20, 1–15, Sept 2014