In Vivo Detection of Radiation-Induced Metabolic Response in Rat Kidneys by 13C Hyperpolarized MRSI

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Introduction:

The safe delivery of an ionization radiation dose to a tumor is often limited by the irradiation of the adjacent normal tissues. In total body irradiation, for instance, unintended radiation dose to the kidneys can result in the loss of renal function and radiation-induced nephropathy[1]. Radiation injuries in radiosensitive late responding critical organs, such as the kidneys, can take months or years to become apparent as structural changes[2]. Early detection of radiation-induced tissue damage is beneficial to manage the risk of late complications and to better design radiation therapy. Changes of lactate dehydrogenase (LDH) and lactate levels have been observed in various *ex vivo* animal tissues within few days following x-ray irradiation[3, 4]. Therefore, it may be suggested that metabolic response may reflect early signs of radiation-induced tissue alterations when measured *in vivo*. ^{13}C hyperpolarized MRI/MR spectroscopic imaging (MRSI) is an emerging technique that can be utilized to measure *in vivo* metabolic response [5, 6]. The purpose of this study was to explore the potential of using currently available hyperpolarized ^{13}C MRSI techniques to detect radiation-induced metabolic alterations in rat kidneys at clinically relevant radiation doses.

Materials & Method:

Animal Model: The localized x-ray irradiation (200 kVp, 20 mA, HVL 1.0 mm Cu, and 1.5 mm Cu filtration) was delivered to the right kidney of 11 male Wistar rats (Charles River, Wilmington, MA) at a rate of 70 cGy/min. During irradiation, anesthetized animals were laid in the prone position on a jig which contained a couch and a ~9 mm thick lead shield with 3×1.5 cm^2 window to collimate the radiation beam to the right kidney. Surface radiation doses of 15, 18, and 26 Gy were administered targeting the right kidney in 3 – 4 fractions with ~5 min delay. The shielded (left) kidney was estimated to be receiving 5 – 6% of radiation dose predominantly from scattering according to thermoluminescence dosimeters (TLD). Irradiated animals were then housed for imaging at desired postirradiation times ranging from 2 – 28 days. Four rats, designated as normal, received no radiation.

Hyperpolarized ^{13}C MRSI: ^{1}H/^{13}C MRI/MRSI (3T Signa, GE Healthcare, Waukesha, WI) was performed on the irradiated rats at the desired postirradiation times. T_2 weighted ^{1}H MRI was used to visualize both kidneys in ~2 cm thick axial slab. The imaging probe was prepared by polarizing (Oxford Instruments Molecular Biotools, UK) 80 mM [1-^{13}C]pyruvate solution, containing 15 mM trityl radicals and Gd^{2+}, at 1.4 K and a 3.35 T magnetic field. The imaging agent was quickly dissolved in Tris/EDTA and NaOH at 37 °C before the injection. The polarized pyruvate solution was then injected into the rat via tail vain catheter during ~17 s followed by a saline flush to clear the tubing. A 3-shot spiral spectroscopic pulse sequence[7] was employed to obtain dynamic chemical shift spectra of ^{13}C metabolites at every 6th sec, starting 10 sec after the beginning of the injection, with an 8 cm axial FOV at 5×5 mm^2 resolution.

Data Analysis: MRSI data were reconstructed as described in [7] using custom-written Matlab (MathWorks Inc., Natick, MA) program. Metabolic maps of ^{13}C labeled pyruvate (Pyr), lactate (Lac), and alanine (Ala) were obtained from corresponding peak integrations. The average intensities (i.e. concentration) of metabolites were measured in the regions of interest (ROI) that were selected within each kidney following the same signal intensity guided by contours overlaid on the metabolic images.

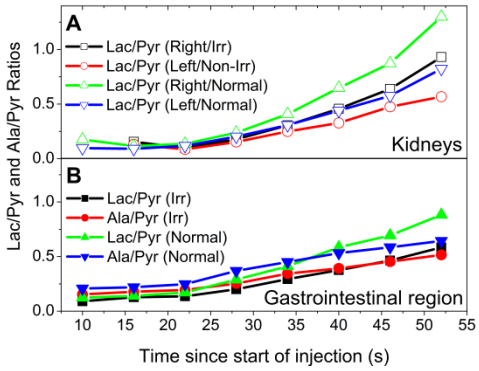

Figure 1: A and B are representative data of two rats (normal and irradiated – 18 Gy/28 days) showing dynamic MRCSI time points of Lac/Pyr and Ala/Pyr ratios in kidney ROIs (open symbols) and the gastronintestinel region ROIs ventral to the right kidney (closed symbols) following the tail vein injection of [1-^{13}C]pyruvate, respectively.

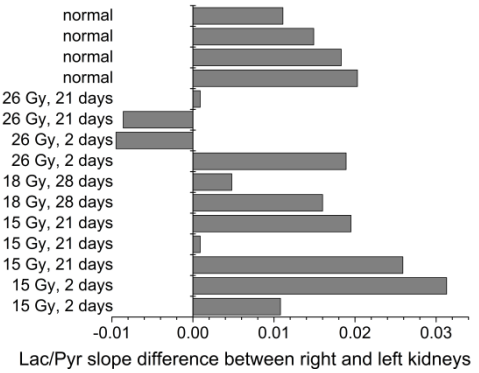

Figure 2: Difference of Lac/Pyr slopes between right and left kidneys versus radiation dose and postirradiation time of each rat.

Results:

Lac and Ala are downstream metabolic products of Pyr in the metabolic pathways in presence of NADH and are often characterized by Lac/Pyr and Ala/Pyr ratios. The slopes of the linear fit to Lac/Pyr ratios at times between 34 to 52 s were compared between the two kidneys since this ratio becomes more distinct between the two kidneys at later time-points (Fig 1-A). As illustrated in Fig 2, differences of slopes between right and left (i.e slope of the right minus that of the left) indicate that the Lac/Pyr ratio is higher in the right kidney ROI than that of the left with few exceptions (shown in negative and near-zero bars). The analysis represented in Fig 2 suggests that the slopes of Lac/Pyr ratios are unlikely to demonstrate a trend associated with both radiation dose and post irradiation time; these are two factors which affect the radiation damage of the kidneys. The intersubject variability of metabolic response may explain the variation (1.6±0.4%) in the difference of Lac/Pyr ratios among four normal rats (Fig 2). Furthermore, comparison of Lac/Pyr and Ala/Pyr ratios (Fig 1-B) in the more radiosensitive gastrointestinal region just ventral to the right kidney reveals that there is no significant metabolic difference in those tissues between irradiated and normal rats.

Discussion & Conclusions:

Our rationale to irradiate one kidney was to eliminate intersubject variability in response to the radiation treatment. Ala data, and hence total carbon, were not considered as a viable metric in the kidneys because the influence of high Ala levels observed in the tissues ventral to the irradiated kidney could be problematic at our resolution. In the analysis, we encountered two main issues: 1) the misalignment of kidneys in the coronal plane and 2) the proximity of Pyr signal from a blood vessel (vena cava and/or aorta, renal artery/vein) to the right kidneys in the axial plane. The first issue inevitably included partial volume from surrounding tissues, adversely contributing to metabolic measurements. The second issue was significantly reduced in the post processing by eliminating the blood vessel component. This was accomplished by taking advantage of the first dynamic image in which Pyr signal was largely limited to the blood vessel. Solving the partial volume problem needs further technological advancement in data acquisition that enables fast 3-D dynamic MRSI. Within our experimental errors and conditions, the metabolic response of radiation-induced tissue alterations in the late responding kidneys might not be strong enough to become visible in our metrics determined with ^{13}C hyperpolarized MRSI. Moreover, higher resolution and fast 3-D dynamic spectroscopic imaging capabilities are highly desired to increase the sensitivity and accuracy of measuring radiation-induced metabolic response in normal tissues.

Reference:

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