Monitoring Response of Tumors to Anti-Glycolytic Therapies Using Hyperpolarized Pyruvate

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Introduction: Many cancers preferentially metabolize glucose via fermentative glycolysis (conversion of pyruvate into lactate) rather than oxidative metabolism. Although tumor hypoxia is one common cause of enhanced glycolytic fermentation, many types of cancer exhibit enhanced rates of lactate formation even when there is sufficient oxygen available to support the TCA cycle. This feature of cancer metabolism, referred to as the Warburg phenomenon, may confer a survival advantage on tumor cells. Indeed, the reduced rate of oxidative metabolism reduces levels of potentially harmful reactive oxygen species and may also interfere with certain mechanisms of apoptosis. A major question is whether reversal of the Warburg phenomenon can be used as a method to selectively harm cancer cells. Recent studies have shown that administration of dichloroacetate (DCA), a drug that up-regulates the activity of pyruvate dehydrogenase and thus increases the rate of oxidative metabolism, can lead to reduced tumor growth in vitro and in vivo [1,2], including tumor regression in certain animal models. To date, however, there has been no methodology to non-invasively assess the response of tumors to DCA treatment. Here we report on studies of hyperpolarized pyruvate as a tool for monitoring the effects of DCA treatment.

Methods: A xenograft model of non-small lung cancer was prepared by subcutaneous injection of A549 cells in athymic nude mice. After allowing the tumors to grow for a period of four weeks, mice were divided into control and DCA treated groups. The treated group received DCA orally in drinking water at a concentration of 75 mg/liter for three days prior to imaging. Two hours prior to imaging, an intraperitoneal dose of 67 mg/kg was administered, followed by an intravenous dose of 16 mg/kg a few minutes before administration of hyperpolarized pyruvate. For imaging studies, mice were anesthetized by means of inhaled isoflurane and a narrow catheter was placed in the tail vein and connected to a long, thin tube. The anesthetized mice were placed in a 4.7T animal scanner (Bruker Biospin, Billerica MA) inside a linearly polarized proton birdcage coil, and an 8-10mm carbon-13 transmit/receive surface coil was placed over the tumor. The radius of the coil was sufficiently small to ensure that the signal from the coil was dominated by tumor. The location of the coil was verified by means of a water-filled fiducial marker attached to the coil that could be imaged prior to administration of pyruvate. This arrangement is illustrated in the rightmost panel of Fig. 1 (see below).

Results: In the left two panels of Fig. 1 we display representative data acquired in control and DCA treated tumors. For each data set the signals have been scaled such that the peak pyruvate signal is 1 and an arbitrary axis has been chosen such that the pyruvate maximum occurs at t=0. For clarity, only signals from pyruvate and lactate are shown. In the pair shown, the DCA treated tumor shows reduced levels of lactate relative to pyruvate, indicative of a response to treatment. A total of 3 control tumors and 5 DCA treated tumors were studied. Levels of lactate were quantified by the peak lactate signal divided by the peak pyruvate signal. For the three control tumors, this ratio was found to be 0.24±0.03, while for the 5 DCA treated tumors the ratio was 0.19±0.05. Of the DCA treated tumors, three showed ratios of less than 0.16, indicating an appreciable reduction in lactate, while two showed no reduction in lactate, with ratios of 0.25 and 0.23 respectively. Because the peak lactate signal is known to depend non-linearly on the pyruvate dosage, signal ratios of this type must be used with caution. However, because the pyruvate dose was carefully matched across the entire study group, this ratio provides a meaningful measure of lactate formation.

Conclusions: These data show that hyperpolarized pyruvate can be used to assess the response of tumors to DCA treatment. Although there is significant heterogeneity between tumors, a subset of the DCA treated tumors show an appreciable reduction in lactate signal. This reduction is likely a consequence of both reduced net formation of lactate and a reduction in the size of the endogenous lactate pool, which results in slower exchange of the carbon-13 label between pyruvate and lactate [4]. Studies to correlate the lactate signal with tumor growth rate are ongoing. Ultimately, these methods may provide a new tool for clinical cancer management by enabling rapid and non-invasive assessment of tumor response to therapy.