Monitoring of Liver Tumor Response to Treatment by MRI

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Introduction

Non-invasive methods for detecting early response to therapy are critical for developing novel cancer therapy in preclinical experiments. Conventional ^{1}H MRI provides volumetric measurement of tumors (1) deep inside the body which are not accessible by caliper. ^{23}Na MRI is sensitive to changes in cellular metabolism and relative extracellular space and, thus providing additional information than that is available from ^{1}H MRI (2).In this study we applied ^{1}H and ^{23}Na MRI to investigate the effects of cancer therapy with a MEK pathway inhibitor in TGF- α transgenic mice that develop spontaneous hepatocellular carcinoma (HCC)(3). We believe that this report represents the first study of monitoring response to therapy in a spontaneous tumor model by ^{23}Na MRI.

Methods:

Male MT-42 (CD-1) TGF-α transgenic mice with spontaneous HCC were imaged every alternate week before and after treatment. After the tumors reached the desirable volume (> 500 µl), treated animals (n = 5) received the MEK inhibitor once daily through gavage. Control animals (n=4) received an equivalent dose of the carrier solution. MRI experiments were performed on a 9.4 T 31 cm horizontal magnet (Varian Inc, CA) equipped with a 12-cm gradient set capable of up to 38 gauss/cm. All images were obtained with a loop-gap volume resonator (30 mm ID coil and 25 mm in depth) dual tuned to 400 MHz for ^{1}H and 106 MHz for ^{23}Na. The mice were anaesthetized with 0.75% isoflurance delivered in medical air at 1 L/minute using a nose mask connected to a gas anesthesia machine. Warm air was blown through magnet bore to help maintaining the animal core temperature. Tumor growth was monitored by ^{1}H MRI. Proton density-weighted multi-slice 2D spin-echo images with fat suppression were acquired using following parameters: TR/TE 2000/13 ms, matrix size: 256 x 128, zero filled to 512 x 512, FOV 4 x 4 cm, slices 24, thickness =0.5 mm, gap =0.7 mm, 2 signal averaging, and 8 min 39 sec total scan time. The liver slices with only tumor were also acquired with respiratory gating to collect images without motion induced artifacts. Three-dimensional ^{23}Na MRI were obtained with a gradient-echo imaging sequence and the following imaging parameters: TR/TE 50/4 ms, matrix size 64 x 64 x 16, zero filled to 256 x 256 x 64, FOV 4 x 4 cm 64 signal averaging, and 16 min 21 sec total scan time. Processed data were analyzed with IVA a graphical user interface (INDYPET image processing software) for co-registering multi-slice 2D ^{1}H and 3D ^{23}Na MRI and for measuring tumor volume and sodium signal intensity (SI). Statistical analysis was performed using ANOVA.

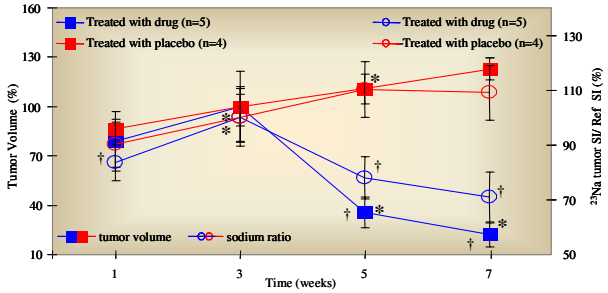

Fig 1. Tumor volume and sodium signal intensity ratio for control and treated groups (%). (* - significant w.r.t to previous, †- significant w.r.t to control)

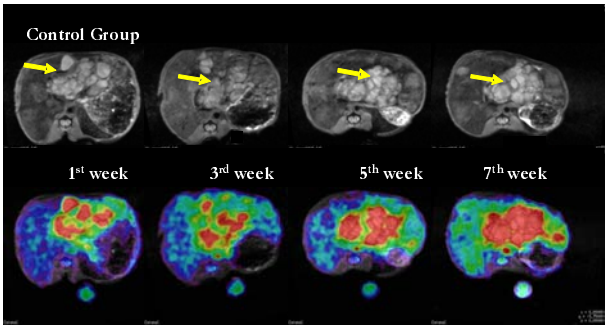

Fig 2(a): ^{1}H and ^{23}Na MRI of the control mouse with liver tumor

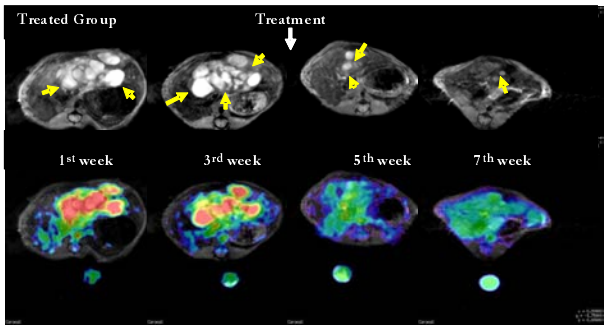

Fig 2(b): ^{1}H and ^{23}Na MRI of the treated mouse with liver tumor

Results and Discussion:

The time course of relative changes in tumor volume and average tumor ^{23}Na MRI SI relative to the reference for control and treated liver tumors are illustrated in figure 1. Because of inherent intra-tumor variability in the spontaneous tumor model, relative changes in tumor volume and ^{23}Na MRI SI, rather than absolute changes are shown. The control group showed a ~23% increase in tumor volume compared to baseline and increased necrosis over the two month study period. The treated animals showed a ~78 % decreases in tumor volume compared to baseline four weeks after initiating therapy with the targeted inhibitor. Tumor ^{23}Na MRI SI for the control group progressively increased (10-20 %) as the tumor volume increased over two months. On the other hand, the treated group showed a ~30% decrease in tumor ^{23}Na MRI SI after initiating the therapy (fig 2). The observed increase in tumor ^{23}Na MRI SI in control group may result from an increase in extracellular space or intracellular [Na^+]. Tumor extracellular space may increase with growth due to inefficient cell packing and leaky blood vessels in fast growing tissue. Intracellular [Na^+] may increase due to decreased Na^+/K^+-ATPase activity as a result of decreased perfusion and decreased cellular ATP levels. Increased activity of Na^+/H^+ anti-porter because of increased glycolysis and acid production may also contribute to increased intracellular [Na^+]. Tumor ^{23}Na MRI SI decreased in the treated group as the result of clearing of dead cells, better perfusion, and improved energetic status. These changes decrease both extracellular space and intracellular [Na^+] decreasing total tissue sodium.

Conclusion:

In summary, we demonstrated, for the first time, application of ^{1}H and ^{23}Na MRI for monitoring response to therapy in a spontaneous tumor model. The data presented show that a novel MEK inhibitor suppresses MEK activity in HCC evidenced by decrease in tumor volume by ~ 78 %. Tumors within the liver were readily identified and their development was monitored before and after therapy using MRI. ^{1}H and ^{23}Na MRI provide useful methods for preclinical evaluation of targeted therapy.

References:

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