Redox state imaging in a mouse model of aggressive prostate cancer

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Target Audience: Scientists interested in measuring tissue redox rates of prostate cancer *in vivo*.

Purpose: The use of stable free radical contrast agents (nitroxides) has been demonstrated in MRI and electron paramagnetic resonance imaging (EPRI)[1]. The agent 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPOL) is a superoxide dismutase mimetic that also shortens longitudinal relaxation time (T_1). After intravenous administration, the temporal rate of T_1-weighted signal normalization is increased in tissues that are more oxidizing. The redox status (balance of oxidizing and reducing species) is important in cancer progression[2], where cancer aggressiveness is related to increased tissue oxidation. The purpose of this work is to investigate the feasibility of measuring TEMPOL-enhanced signal dynamics in a mouse model of aggressive prostate cancer.

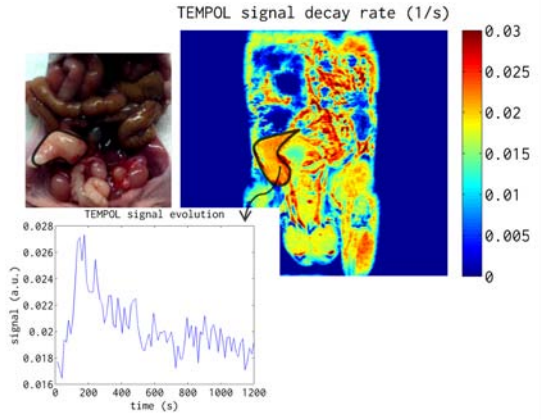

Figure 1. TEMPOL signal dynamics in a prostate tumor (outlined in black). The tumor border is defined by increased rate of decay of the TEMPOL signal.

Methods: 5 nude mice with an orthotopic xenograft prostate cancer model of PC3m-luciferase parental cells implanted into the anterior lobe of the prostate were imaged on a 4.7T Varian MR scanner. Animals were injected with 300 mM TEMPOL solution in PBS at 5uL/g body weight. TEMPOL was injected via tail vein during a dynamic 2D, T1-weighted GRE acquisition using the following parameters: TE/TR=min, FA=45 deg., resolution=~200x200x1000um, num. slices=10 slices, 100 volume repetitions, and a volume repetition time of approximately 12 seconds. Pixelwise exponential fitting was used to calculate the rate of signal normalization (and theoretical redox rate) after TEMPOL injection. Fitting was performed from time point of peak T1 signal and the following 35 image volumes (approximately 7 minutes). Histology and redox western blot was also collected in all animals.

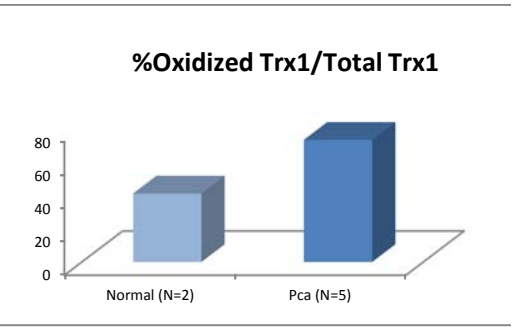

Figure 2. Analysis of Trx1 redox western blot, in prostate tissues demonstrated similar results; oxidized Trx1 was significantly increased in prostate of orthotopic xenograft mice (Fig. 3F) indicating a more oxidized state in prostate cancer.

Results and Discussion: An example of a prostate tumor with increased TEMPOL signal decay rate relative to other tissue is shown in Figure 1. PC3m is a model of aggressive cancer with high metastatic potential. Primary and metastatic lesions were generally identifiable by regions of increased TEMPOL signal decay rate. Figure 2 show results of redox blot, depicting a more oxidized tumor microenvironment in the PC3m mice, reinforcing the potential utility of TEMPOL-enhanced MRI.

Conclusion: TEMPOL-enhanced MRI may have potential to non-invasively measure prostate cancer redox status in orthotopic xenograft PC3M mice. Further work needs to be done to corroborate histological and whole tissue measures of redox state (western blot) to TEMPOL-enhanced MR. Such capabilities may allow differentiation between early, intermediate, and aggressive forms of metastatic prostate cancer.

References:

1. Davis RM et al. (2011). Anticancer Agents Med Chem. 11(4):347–58.
2. Dewhirst MW. (2009). Radiat Res. 172(6):653–65.