Absolute Oxygen Images in SV40Tag Mouse Model Detect Local Hypoxia Two Weeks Before Ductal Carcinoma In Situ (DCIS) Detection with High Resolution T2 MRI

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The effect of cycling hypoxia has been shown to induce malignancy in cultured cells, promoting development of mutations of genes coding the p53 cell cycle checkpoint protein, defects in apoptosis. The effect of the ovarian cycle on the mammary gland is the natural mammalian analog of such cycling hypoxia. SV40Tag mice are a strain of mice genetically engineered to develop breast cancers (in females) and prostate cancers (in males) at nearly 100% of the time by the age of 16 weeks. Recent developments in absolute pO_2 imaging with inversion recovery (IR) electron paramagnetic resonance (EPR) with electron spin echo (IRESE) read out have produced absolute quantitative pO_2 image data from SV40Tag mice mammary glands that demonstrates

1) quantitative hypoxia—voxel pO_2 less than 10 torr-- in the very few image voxels (sub-volumes) of a DCIS

2) statistically significant hypoxia in the region of registered images *obtained two weeks prior* to the development of DCIS

This suggests that these early mammary cancers are responding not only to the transgenic predisposition provided by the SV40Tag genotype of the mice toward malignancy but to the estrus cycling hypoxic microenvironment to locate the development of the malignancy, as suggested by Graeber et al. This work is the first to validate the carcinogenic effect of normal local environment changes, as opposed to the local administration of toxin. This validates *in vivo* the conclusions of the experiments published by Graeber et al. positing the mutagenic and carcinogenetic effects of cycling hypoxia. It also suggests simple intervention to modulate the induction of breast cancers.