MRI Compatible Orthotopic Breast Cancer Window Chamber Model for Multi-Modality Imaging

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Introduction

Window chambers (WC) implanted in small animal models have been used extensively in vascular and cancer biology research [1]. They provide ready access to tissue, which can be visualized from the tissue to cellular level of spatial resolution via an optical microscope. For many types of studies WC models are superior to in vitro cell-culture because they reproduce the full complex microenvironment of living tissue. They are often superior to tumors implanted in animal models because they allow much finer grained imaging and analysis of the molecular and physical microenvironment of tumor growth, proliferation, metastasis, and therapeutic response. Orthotopic WC models are preferred because they observe disease processes in their native environment. Until recently [2], WC models have not been compatible with MRI due to the use of metal support structures. Here we report on an MRI compatible orthotopic breast cancer WC model that has been developed to provide a multi-modality imaging platform for breast cancer research and therapeutic development.

Materials and Methods

WC structures for insertion in a mouse mammary fat pad were designed using SolidWorks software and fabricated using an Objet Connex 350 rapid prototype printer. The WC (Fig. 1) consists of a 13mm dia. structure with a central hole that supports a 8mm removable coverslip. Implantation in the animal is accomplished by removing a small circular region of skin and nipple over one of the mammary glands. The skin is stretched and the WC inserted such that the skin retracts back into a groove on the outer diameter of the WC structure. A day or so after the initial implantation, super glue is used to secure the outer skin layer to the WC. For the studies reported here, 2 days after WC implantation MDA-MB-231 cancer cells (≈ 10^7) transfected to express GFP were injected into the mammary pad under the coverslip. Animals are housed in separate cages and kept in a high-humidity environment. For imaging experiments animals were anesthetized with isoflurane and secured to a mount structure that holds the WC so that it is accessible and stable (Fig. 2). To demonstrate multi-modality imaging, MRI was done on a Bruker Biospec 7T instrument with a 10mm dia. surface coil placed over the WC. Optical imaging was done with the same setup (RF coil removed) on a Nikon E600 C1 confocal fluorescence microscope. Nuclear imaging was done with a specialized instrument [3] that allows direct detection of positron emission by placing a scintillator over the tissue and detecting the optical emission with a low light level camera.

Fig. 1. WC structure with coverslip retaining ring.

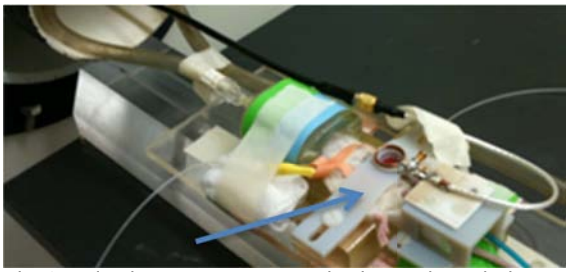

Fig. 2. Animal support structure. Plastic part (arrow) clamps the WC in place. Surface coil is mounted over the WC.

Multi-Modality Imaging Results

Fig. 3 shows example MR images with the mammary WC. The upper image is a small tumor in the fat pad just above the muscle layer of the peritoneal lining (12d post implant). The lower image is a larger tumor (13d post implant) imaged after Gd-DTPA injection. A central poorly perfused core is observed. The FOV shown is 1 cm with a pixel size of 75 μm and slice thickness of 2 mm (upper) and 0.3 mm (lower). Fig. 4 shows an optical confocal image at 400X. This is a MIP of a stack of confocal images. GFP expressing cells are observed (in green) and capillary vessels (in red) after injection of Albumin-Alexa 647 through the tail vein. Nuclear images (not shown) reveal high uptake of FDG into tumor showing increased glycolytic metabolism. Ongoing work is aimed at using the model to image pH, DCE perfusion, diffusion, hypoxia, and molecular pathways involved in tumor growth, proliferation, and response to therapy.

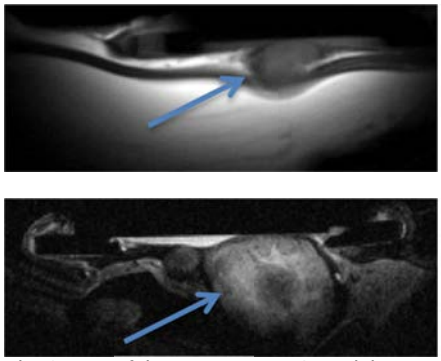

Fig. 3. MRI of the Mammary WC model. Sagittal spin echo image of small tumor (upper arrow) and larger tumor (lower arrow). Lower image after Gd injection.

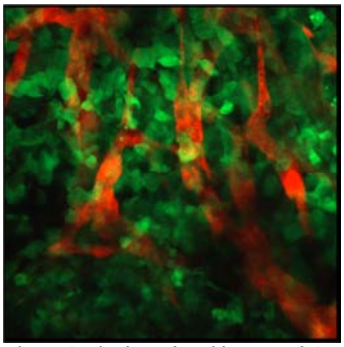

Fig. 4 Optical confocal image of GFP cells (green) and vascular capillary bed (red) at 200X magnification in mammary WC.

References:

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