BOLD changes in the microenvironment are an early marker of micrometastatic breast cancer in the rat brain.

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Introduction

Blood oxygen level dependant (BOLD) MRI is related to tumor oxygenation and perfusion[1]. Tumors with low oxygenation (i.e., hypoxic) measured with BOLD are more aggressive, have a worse prognosis than those that are oxygenated, and have a poor response to therapy[2]. However, it is unknown whether BOLD can be used for diagnosis in addition to its prognostic potential. The purpose of this study was to determine the sensitivity of BOLD in detecting developing brain tumors in a rat model of breast cancer metastasis.

Materials and Methods

Five nude rats received an intracardiac injection of brain seeking $1x10^6$ MD-MBA-231BRL cells labeled with Feromoxides complexed with Protamine sulfate (FePro). MRI was performed on a 7T Bruker Biospec prior to injection and at days 1, 3, 8, 15, 22, 29, and 36 post-injection. Rats were delivered carbogen (95/5% O_2/CO_2) through a nosecone during MRI procedures. T2* weighted gradient echo images were acquired using a 2D multiple echo readout: TR=3500 ms, TE=3.5 ms (first-echo), 4.25 ms echo spacing, 12 echoes, 3x3 cm^2 FOV, 256x256 matrix, 0.5 mm slice thickness, 20 slices, 90° flip angle, 2 averages. Images from all echoes were averaged to create T2*-weighted images (BOLD contrast) with an effective TE of 27ms. T2-weighted images were collected with a 2D RARE sequence: TR/TE=5000/50ms, 8 averages. Rats underwent perfusion fixation at day 36. Excised brains underwent ex vivo MRI using a 3D gradient echo sequence, TR/TE = 500/10 ms, 3.0x1.5x1.25 cm^3 FOV, 512x256x128 matrix, 4 averages, 30° flip angle, and a 3D spin-echo sequence TR/TE = 2000/12 ms. Brains were sectioned and stained with H&E. Images were registered with AIR 5.0.

Results

The use of carbogen as an inhalation gas did not completely eliminate BOLD effects of large vessels (open arrow). At day 1 post injection of FePro breast cancer cells, numerous hypointense regions were detected on T2*w images throughout the rat brain consistent with clusters of tumor cells in the vasculature. A total of 34 cortical tumors were identified on the T2-weighted ex vivo MR images from 5 rats euthanized at day 36 post-injection. These regions were mapped to the in vivo images. Of these tumors, 26 had noticeable BOLD decreases in the corresponding region from the week prior (day 29) MRI, and 17 had BOLD decreases 2 weeks prior (day 22) MRI. As shown in Figure 1, a metastasis was detected with BOLD MRI prior to its development on T2w images. Importantly, the BOLD effects could be detected when the tumor was less than 500 µm.

Discussion and Conclusions

Although BOLD MRI is related to tumor oxygenation and perfusion, it is not a direct marker of pO_2. The contribution of flow effects must also be considered. In this study, carbogen inhalation gas did not eliminate the BOLD effects of large vessels[3]. Therefore, baseline scans and serial measurements were essential to specifically identify developing tumors. BOLD was an early marker of metastatic tumor development, and the changes are consistent with vascular abnormalities from undiagnosed micrometastasis disease. Despite the difficulties in attributing BOLD changes to oxygenation or perfusion, BOLD MRI may aid the detection of developing metastases.

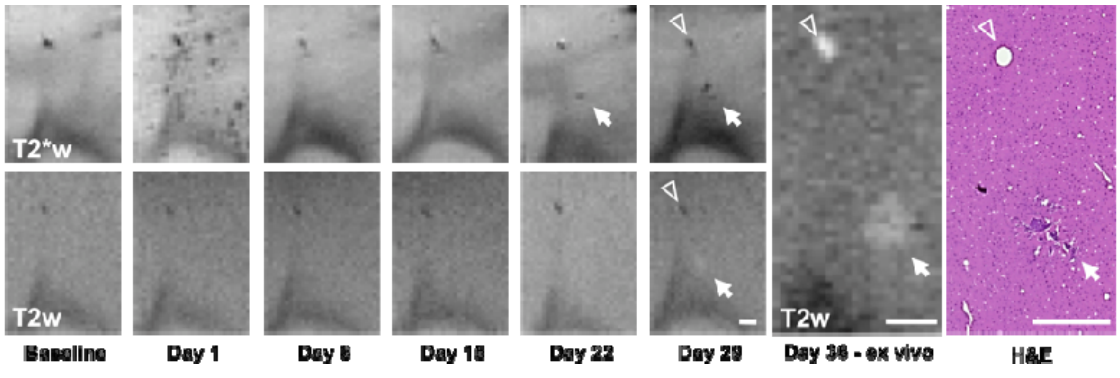

Figure 1. Serial T2*-weighted GE (top) and T2-weighted SE (bottom) images of the brain following injection of FePro labeled MD-MBA-231 cells. A developing tumor (arrows) is apparent on the T2*w image before detection on the T2w image. Baseline images are critical to differentiate tumors from large vessels (arrowheads). Scale bars indicate 0.5 mm.

References

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