

Title: Multimodality cellular and molecular imaging of concomitant tumor enhancement in a syngeneic mouse model of breast cancer metastasis

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Introduction: The mechanisms that influence metastasis, the cause of the majority of deaths from breast cancer, are poorly understood. One mechanism of interest called concomitant tumor resistance (CTR) describes the ability of the primary tumor to restrict the growth of distant metastases. Conversely, a primary tumor can likewise increase metastatic outgrowth, a phenomenon coined concomitant tumor enhancement (CTE). While imaging has been used to describe CTR/CTE effects in patients, the majority of studies evaluating CTR/CTE in preclinical models have relied on histological evaluation of tumor burden. Here we investigate the impact of a primary breast cancer tumor to influence experimental brain metastasis using cellular magnetic resonance imaging (MRI) and bioluminescence imaging (BLI). We hypothesized that the presence of a primary breast tumor will inhibit the growth of secondary metastases in the brain.

Methods: BALB/c mice (n=32) received an injection of vehicle (Control) or 3×10^5 parental 4T1 cells in the mammary fat pad (MFP) either 7 days (small MFP) or 14 days (large MFP) prior to intracardiac injection of 2×10^4 luciferase-expressing, iron-labeled brain-seeking 4T1BR5 cells. Cellular MRI and BLI were performed over the next 2 weeks to measure brain and whole-body cancer cell viability (BLI), whole-brain single cell arrest (iron-induced MR signal voids), and the number and volume of metastases at endpoint (MRI).

Results: Iron labeled cells were visualized in brain MR images as discrete signal voids on day 0 (arrested cells) which was not significantly different between Control and MFP mice. Brain BLI signal at day 0 was also not significantly different. At day 14, both small and large MFP mouse groups had significantly more brain metastases ($p < 0.05$) and brain tumor burden ($p < 0.05$) than Control mice. Whole-body and brain BLI signal at endpoint were not significantly different between small MFP mice and Control mice, but were significantly higher for the large MFP group compared to Control mice.

Discussion: The mechanisms of CTR and CTE remain unclear. These findings are in contrast to our previous study in immune compromised mice where we found the presence of a human MDA-MB-231 breast tumor significantly inhibited the growth of MDA-MB-231BR brain metastases. Other groups have suggested the immune system can play a crucial role in CTR/CTE effects. We found the presence of a primary tumor enhances the growth of brain and body metastases and secondly, this effect could be amplified by increasing the size of the primary tumor at the time of secondary injection. Using *in vivo* BLI/MRI we could determine this was not related to differences in initial arrest or clearance of viable cells in the brain, which suggests that the presence of a primary tumor can increase the proliferative growth of brain metastases in this syngeneic model.