Quantifying Syngeneic Breast Cancer Metastasis to the Lung and Response to Therapy Using Fluorescence Molecular Tomography (FMT)

Kristine Vasquez, Sylvie Kossodo, and Jeffrey D. Peterson, PerkinElmer

Abstract

Breast cancer is a prevalent clinical challenge today, with 10% of these patients showing cancer metastasis to distant organs in the body such as bone, liver, and lung, decreasing their 5-year relative survival rate to 20%. Thus, it is essential to develop robust in vivo methodologies that can help dissect the metastatic process and assist in the effective development of targeted therapeutic agents. To establish robust and non-invasive imaging measures of the metastatic disease process in a model resembling clinical disease, we used 4T1 mouse breast adenocarcinoma cells injected intravenously into normal, immunologically-competent BALB/c mice. Two near-infrared imaging agents, ProSense® (PerkinElmer), a cathepsin-activatable agent, and AngioSense® (PerkinElmer), a vascular agent, were used to image tumor growth and metastatic spread, respectively, in BALB/c mice with aggressive breast cancer growth. Fluorescence was imaged and quantified in living animals using optical Fluorescence Molecular Tomography (FMT 2500™, PerkinElmer) showing a consistent and significant increase in cathepsin signal as early as 7-10 days, with accompanying increases in lung weight (a current standard measure in lung metastasis models). A standard clinical treatment using 5-Fluorouracil (5-FU) significantly reduced lung cathepsin fluorescence with greater sensitivity than seen with decreases in lung weight. In addition, treatment with a small molecule integrin antagonist decreased both vascular and cathepsin signal more effectively than changes in lung weight. Quantification of protease activity and vascular leak provided important non-invasive measures of relevant tumor biology for comparison to standard measures of lung weight and histology. These data clearly demonstrate that deep tissue metastatic growth and response to treatment can be monitored in vivo in real time with a near-infrared imaging agents and quantitative FMT.

Results

2 weeks after inoculation with 4T1 cells, mice were injected with ProSense® (cathepsin activatable) and imaged by FMT quantitative tomography 24 hrs later. Liver, GI tract, and bladder regions were not imaged. Two-color representation of FMT 2500 tomography and FMT 2500 FRI imaging shows regions of biological co-localization.

Summary

Mouse models of cancer metastasis rely predominantly on ex vivo tissue weight, nodule counts, and/or histologic analysis of lung, liver, and bone. These techniques are cumbersome, quantitative in vivo imaging of deep tissue metastases, we will present a comprehensive description of a syngenic 4T1 Mouse Breast Adenocarcinoma Cells model that shows applicability to preclinical drug discovery and characterization of new probes for imaging lung cancer. Initial studies show that FMT (Fluorescence Molecular Tomography) is a powerful tool for monitoring metastatic burden in the lung region of an in vivo cancer model.

References

- Kristine Vasquez, Sylvie Kossodo, and Jeffrey D. Peterson, PerkinElmer