

Lay Abstract

Metastatic spread to the brain is a devastating and incurable stage of breast cancer. Indeed, most patients with brain metastases die within months because of a lack of effective treatments. Progress towards discovering and testing new treatments for brain metastasis is hindered by the limited understanding of how breast cancer cells spread to and seed in the brain, which in turn comes in part from having very few relevant preclinical mouse models available that accurately capture brain metastasis progression and biology. To address the need for instructive brain metastasis models, we developed new preclinical mouse models of brain metastases via tail-vein injection of E-cadherin-expressing, triple-negative and HER2+ inflammatory breast cancer cell lines. These mouse models have been validated and used for preclinical development and testing of new treatment strategies. We further established sublines from the HER2+ metastatic cell line that are still more likely to metastasize to the brain. With these sublines, we identified the soluble fragment of E-cadherin (soluble E-cadherin; sEcad) as a potential candidate protein associated with the aggressiveness of brain metastasis. Our preliminary investigations showed that high sEcad levels in serum from breast cancer patients correlate with an increased risk of brain metastases and death. We also found that human breast cancer cells that express high levels of sEcad are more aggressive; indeed, forcing breast cancer cells to overexpress sEcad enhances their ability to migrate, invade, avoid cell death, and colonize the brain in mice. In this project, we propose to determine exactly how sEcad-expressing breast cancer cells metastasize to the brain by using our unique mouse models. Since sEcad is not readily amenable to drug development, we reasoned that identifying the likely mechanism of action would allow us to identify targetable partners of sEcad. Using high throughput proteomic screening, we found protein disulfide isomerases (PDIs) as novel interacting partners of sEcad. We hypothesize that sEcad is critical to the spread of breast cancer cells to the brain, and acts by binding to and activating PDIs. We further postulate that blocking PDIs with existing inhibitors that can cross the blood-brain barrier will treat established brain metastases in mice. Our proposed study has high potential for clinical translation, in that positive results could lay the groundwork for clinical trials to reduce brain metastasis progression in women who are at high risk of this devastating disease. Our findings will also be useful for treating other types of cancer that spread to the brain, such as lung, skin, and kidney cancer.