Public/Lay Abstract

The majority of breast cancer (BC) fatalities are attributed to the spread of disease to other organs, causing metastasis. While many advances have been made in the successful treatment of localized BC, the treatment options for metastatic BC remain limited. BCs primarily metastasize to the bone, lung, liver and brain; and the most aggressive BC subtypes have higher levels of lung metastases. When tumors metastasize to the lung, long-term survival drops significantly. A gap in our ability to effectively treat BC patients with lung metastases lies in our lack of knowledge regarding how the lung changes during metastasis and how these changes may contribute to disease progression. My data suggest that metastases influence the behavior of adjacent lung cells and subsequently, lung cells begin to change what they secrete. This is important since one of the main roles of a particular lung cell called type II alveolar epithelial (AT2) cells is to secrete surfactant, which prevents the lung from collapsing during breathing. My data show that there are changes in the amount and composition of surfactant in mouse lungs with BC metastases. Interestingly, in other chronic lung conditions, AT2-derived surfactant has been shown to have an anti-inflammatory, and possibly anti-tumor, effect, and my preliminary studies indicate that lung surfactant inhibits BC cell growth. I theorize that lung surfactant also has an anti-metastatic function within the lung. I will investigate different aspects of this theory in three Specific Aims. In Specific Aim 1 I will examine how the composition of surfactant changes throughout metastatic progression in the lung using established mouse models of BC lung metastasis. Surfactant can also leak from the lung into blood, so I will examine how surfactant changes in blood from mice and BC patients to determine if circulating levels of surfactant can be used to detect lung metastases. I will further determine if these changes can be modeled in the laboratory using AT2 and BC cells to allow for more rapid analysis of potential lifesaving treatments. Specific Aim 2 will investigate how surfactant treatment affects BC cell growth and survival. I will alter the composition of surfactant to see which components are most effective at blocking BC cell survival in the laboratory. Finally, Specific Aim 3 will investigate whether treatment with surfactant can block lung metastatic growth in mice. Lung surfactant derivatives are currently FDA-approved for use in neonates to improve lung function when the lungs are underdeveloped. I will test whether these surfactant derivatives can be repurposed as treatments for patients with BC lung metastasis using a mouse lung metastasis model. The goal of this research is to improve the survival and quality of life of patients with metastatic BC. These studies will determine whether metastasis-induced changes in lung surfactant can be leveraged to diagnose and treat patients with BC lung metastases.