Abstract

Metastasis is the main cause of death in breast cancer patients; however, there are currently no treatments available to treat or prevent metastasis. This is in part because regulators of metastasis are not yet fully understood. Over the past century researchers began to study metastasis regulators by different hypotheses, such as the seed and soil hypothesis which focuses on studying the role of cancer cells, the seeds, and the tissue microenvironment, the soil, in regulating metastasis. Although lots of studies have focused on the microenvironment of metastatic sites and their roles in regulating metastasis, limited studies have focused on the role of the primary tumor microenvironment in regulating metastasis. Thus, investigating the role of the primary tumor microenvironment will provide more insight on metastatic regulators which may lead to the development of new therapeutic strategies to treat or prevent metastasis.

The aim of this study is to evaluate the role of primary tumor microenvironment in regulating metastasis using a triple negative breast cancer mouse model. Mammary glands contain two distinct microenvironments, soils: epithelium and stroma. Human breast cancer originates in the epithelial microenvironment of the mammary glands; however, researchers are using stromal microenvironment to generate mammary tumors and bypassing the epithelium. Therefore, we first tested if the epithelial microenvironment has an effect on tumor progression and/or metastasis when compared to stromal microenvironment. We chose the widely used 4T1 mouse model and delivered
the 4T1 cells intraductally into the epithelium. Our results show that the primary tumor’s epithelial microenvironment promotes more aggressive tumors compared to the stromal microenvironment.

Knowing that mammary glands exhibit left-right differences in epithelial and stromal gene expression, we next investigated the role of left versus right epithelial microenvironment in regulating metastasis. Here we show that the right epithelial microenvironment more effectively supports M2-like macrophage polarization which promotes more aggressive 4T1 cells and increased metastatic behavior. Furthermore, we tested if the left and right mammary tumor microenvironments have differences in therapeutic response against Emodin, a Chinese herb that targets M2-like macrophage polarization. Emodin treatment more effectively reduces metastasis in the right tumor group, while emodin treatment has no effect on the left tumor group. Taken together, our data indicates for the first time that the left and right mammary tumor microenvironments are different in metastatic support and therapeutic response.