Identification of Candidate Target Genes for Metastasis and Cancer Cell Dormancy in a Novel Triple-Negative Breast Cancer Model

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It is an unfortunate situation that metastatic breast cancer will remain a leading cause of cancer death over the next decade. Nonetheless, there has been remarkable progress in the treatment and management of breast cancer that have substantially contributed to a prolonged disease-free lifespan and overall survival. In the US alone, we have more than 2.8 million breast cancer survivors, and many of them share concerns about therapy resistance, disease recurrence, and cancer metastasis. A major problem for the treatment of breast cancer is the fact that this malignancy is intrinsically heterogeneous, representing at least four or five diverse breast cancer subtypes that exhibit differences in their response to therapy and clinical outcome. Specifically, basaltype, triple-negative breast cancers (TNBCs) that occur more frequently in younger individuals, women of African American ancestry, or women who carry mutations in the *BRCA1/2* genes show a higher rate of metastasis. Since these aggressive cancers lack expression of certain hormone and growth factor receptors, they cannot be treated with approved targeted therapies, and standard chemotherapies are only effective in less than a third of the patients. In fact, the majority of TNBC patients have minimal residual disease in the form of dormant cancer cells in their breasts, lymph nodes, and distant organs. These cancer cells are responsible for a higher rate of metastatic recurrence. There is currently no consensus among scientists about the types of breast epithelial cells that give rise to this aggressive breast cancer subtype, and we do not fully understand which genes drive the metastatic dissemination of TNBC cells or the mechanisms that mediate the survival of a subset of dormant cancer cells following therapy. Many of these fundamental questions can be studied in biological systems such as genetically-engineered mouse models for breast cancer. Unfortunately, there are only a limited number of these models that develop sporadic tumors that are also capable of metastasizing to other organs, and none of these models develop *bona fide* basal-type mammary cancer. In this application for funding, we report for the first time the generation of a mouse model that develops metastatic basal-type mammary cancers that readily metastasize. As part of this project, we intend to more thoroughly characterize this model using molecular techniques. We plan to use genome-wide sequencing on primary and metastatic tumors from the same animals to identify genes that are differentially active and that may contribute the metastatic process (aim 1). Another distinct feature of our new breast cancer model is that we can turn-off the cancer-inducing oncogene, which then leads to cancer attrition with minimal residual disease. This uniquely positions us to identify the genes and molecular pathways that mediate the survival of dormant cancer cells (aim 2). Collectively, the genomic data that we will obtain from this exploratory-type project will help deciphering the molecular underpinnings that control the aggressive metastatic behavior of basal-type TNBC. Moreover, the rationale for the identification of genes that are responsible for cancer cell dormancy is to provide a scientific foundation for the development of targeted therapies to eradicate minimal residual disease in TNBC patients.