

Almost all breast cancer-related deaths are due to complications arising when the original primary tumor metastasizes, or spreads, to other organs. Therefore, attacking the mechanisms underlying metastatic progression and the resistance of metastatic lesions to cancer therapies is crucial for improving disease-free and overall survival of breast cancer patients. A major obstacle for cancer research and treatment, however, is the heterogeneity, or difference, of cancer cells within tumors: even within one tumor there are many different types of cancer cells with different properties including ability to survive, proliferate, metastasize, and respond to treatment. This heterogeneity is referred to as intratumor heterogeneity (ITH). Some of this heterogeneity is due to regional differences in the tumor microenvironment, such as differences in nutrient and oxygen availability, since different environments favor the survival of different types of cancer cells. This is especially evident in metastatic disease where tumors are growing in different organs each with its unique tissue architecture, metabolic states, and cell types. Increasing evidence also supports a role for diet-associated metabolic alterations influencing tumor progression and survival in part by their effects on the immune environment and cancer cell metabolism. Some of this heterogeneity is hereditary due to genetic and non-genetic (i.e., epigenetic) alterations in the tumor cells. Heterogeneity for heritable features, in combination with selection pressure by environmental forces, drives tumor evolution – disease progression and therapeutic resistance. If there are many types of cancer cells within a tumor, the chances are greater that some cancer cells will have the ability to survive when exposed to drugs, attacked by the immune system, or hidden in other parts of the body.

We have been investigating the clinical and functional relevance on intratumor heterogeneity in breast cancer using a combined approach of analyzing clinical samples and generating models that recapitulate the heterogeneity of the human disease. We have recently performed a comprehensive characterization of triple-negative breast cancer (TNBC) by analyzing gene expression, epigenetic, and metabolomic profiles and functional dependencies on certain pathways. We found that while gene expression patterns classify TNBC into three major subgroups, metabolomic and epigenetic profiles are much more heterogeneous and do not correlate with gene expression subtypes. We have also found associations between metabolic and epigenetic states.

Based on these observations, we hypothesize that the intratumor heterogeneity of cancer cells is significantly impacted by metabolic alterations in the microenvironment, in part modulated by diet (e.g., high fat vs. regular), and that this is particularly evident in metastatic disease where the unique metabolic environments of different organs enable the outgrowth of different subsets of breast cancer cells further increasing tumor heterogeneity. We also hypothesize that the metabolic environments of metastatic sites influence the activity of immune cells and make them less able to attack cancer cells, enhancing tumor growth. Lastly, we hypothesize that by characterizing mechanisms by which metabolic states regulate cancer cell heterogeneity and immune responses, we can develop more effective therapeutic strategies for metastatic TNBC. We propose three specific aims to achieve these goals: Aim 1 will focus on characterizing heterogeneity and metabolic states during metastatic progression in an experimental model of TNBC using a novel reporter system that enables the tracking of individual cancer cells and their immediate neighbors. In Aim 2 we will characterize the metabolomic and epigenetic profiles of metastatic TNBC from patients, with special emphasis on brain metastases, a particularly devastating form of metastatic disease. Lastly, in Aim 3 we will test combination treatment strategies designed based on results of Aims 1&2 in experimental models of metastatic TNBC.

While the proposal is largely a basic science study, we will also investigate fundamental clinical research questions including: How do diet and organ-specific metabolic states influence epigenetic heterogeneity of cancer cells and immune environments? Does this metabolic state-related cellular heterogeneity in breast tumors determine their ability to grow at metastatic sites and survive cancer therapies? Thus, the high clinical relevance of intratumor heterogeneity to therapeutic resistance and clinical outcome makes this proposal highly clinically relevant. Our interdisciplinary team of collaborators including medical oncologist with expertise in metastatic disease and patient advocate will greatly help focusing our study on clinical relevance and eventual clinical translation. Our past success with launching clinical trials in metastatic breast cancer patients gives us confidence that we will be able to achieve this goal. During the course of the study, we will identify interactions between metabolic and cancer-driving pathways that can be used as a basis for the design of combination therapies for the more effective elimination of tumors. Our focus will be on TNBC, which is currently the only major breast tumor subtype without effective rationally-designed targeted therapies and is characterized by high degree of heterogeneity and high risk of distant metastatic progression.