UC San Diego
MOORES CANCER CENTER

2023 MCC Cancer Biology and Signaling Pilot Project Award

Cancer Associated Fibroblast Response to Chemotherapy in Triple Negative Breast Cancer

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Scientific Abstract:

Almost 300,000 patients will be diagnosed this year with breast cancer in the US, with this number trending higher yearly. Ten to fifteen percent of these patients have triple negative breast cancer (TNBC), an aggressive subtype without targeted therapies. Tumor progression is promoted by fibroblast activation, involving expression of new markers, pro-tumorigenic signaling with tumor cells, and secretion of extracellular matrix and cytokines. CAFs also upregulate the autophagy cellular stress machinery to enhance tumor progression. Currently, the CAF or fibroblast responses at metastatic sites to chemotherapy are unknown. We hypothesize that chemotherapy activates CAFs and lung fibroblasts, and increases lung fibroblast and CAF autophagy to promote disease progression. To test this hypothesis, I propose the following specific aims: 1) Determine whether CAF marker expression increases in the primary tumor or lung fibroblasts after chemotherapy, 2) Test whether CAF and lung fibroblast autophagy is enhanced by chemotherapy, and 3) Evaluate whether chemotherapy enhances primary tumor relapse or lung metastasis. For SA1, EO771 TNBC cells will be injected into vehicle or chemotherapy treated mice, and CAF markers, i.e. aSMA, FAP, etc examined in the tumors and lungs, a metastatic site. For SA2, we will inject GFP-LC3 transgenic mice with EO771 cells, treat with vehicle/ chemotherapy, and evaluate autophagic flux by analyzing GFP and P62 signal. In SA3, we will quantify tumor relapse and lung metastasis by tail vein injection with chemotherapy. This study will identify biomarkers and clinical targets, and inform ongoing clinical trials evaluating autophagy inhibition as a targeted therapy.

Lay Abstract:

This proposal examines how non-tumor cells called fibroblasts change after chemotherapy. Fibroblasts are a critical cell in breast cancer progression. They are present but quiescent until wound healing or cancer elicits activation. Activated fibroblasts promote breast cancer growth, provide tumor cells with metabolites, alter immune recruitment, secrete pro-tumorigenic extracellular matrix, and express new proteins. While many studies examine fibroblast activation and growth of the initial breast tumor, there is a lack of data testing fibroblast response to chemotherapy locally and at sites that disease may spread to, such as the lungs. It is also unknown how chemotherapy and a cellular stress process called autophagy, central to fibroblast activation phenotypes, interact. Here, we test the hypothesis that chemotherapy contributes to fibroblast activation, promotes fibroblast autophagy, and promotes tumor relapse and metastasis. We will test this hypothesis using mammalian cells modeling the aggressive triple negative breast cancer subtype, together with mice. We will inject tumor cells into mice and treat with standard of care chemotherapy, and examine molecular changes associated with fibroblast activation both in the primary tumor and in the lungs, where these TNBC cells spread to. This work will

improve our understanding of the biology of disease recurrence/ spread after chemotherapy, the role of fibroblasts in this process, and how autophagy inhibitors, currently in clinical trial, may change fibroblasts to alter breast cancer progression after chemotherapy. This work may also uncover novel drug targets and/or biomarkers.