

Public/Lay Abstract

Breast cancer is the most commonly diagnosed cancer in women, with luminal (estrogen receptor [ER]+) breast cancer accounting for 75% of cases. Luminal breast cancers contain steroid hormone receptors (SR) such as ER and/or progesterone receptor (PR) and depend on these receptors to drive breast tumor growth. Endocrine therapy (e.g. tamoxifen [tam]) is used to treat ER+ patients and are initially effective. However, 40% of women eventually develop resistance to endocrine therapies and progress to metastatic disease. Chemotherapy can also be used to treat ER+ breast cancers, but patients often develop resistance to this approach as well.

Disease metastasis is the main cause of breast cancer mortality. ER+ tumors relapse late, which means that tumor cells can remain “quiet” for years to decades after remission before emerging again. Once the cancer spreads to other sites besides the breast, for example, to the bone or brain, it becomes difficult to control. One major challenge in treating metastatic breast cancer is therapy resistance. Progress in treatment of metastatic breast cancer is limited by strategies that primarily target fast growing tumor cells. Contributing factors to breast cancer progression to metastasis include breast cancer stem cells (CSC). CSCs are slow growing cells that exist as a minority population in breast tumors. Their ability to grow at a slower rate allows them to survive endocrine and chemotherapies that are aimed at targeting faster growing cells and enables them to become resistant to therapies. These resistant CSCs give rise to metastatic tumors, sometimes occurring many years after initial breast cancer diagnosis. Breast CSCs achieve their slower growth rates by adapting their metabolic needs and energy sources to tumor environments.

Breast cancer cell models used to study endocrine and chemotherapy resistance have increased levels of CSCs. It is important to understand how CSCs have adapted to survive breast cancer therapies in order to develop methods to specifically target them. Our lab has shown that PR is an important contributor to CSC populations in ER+ breast cancers. We show that blocking PR action reduces CSCs in both endocrine (TamR and *ESR1* mutant Y537S) and chemotherapy (paclitaxel [taxol]; TaxR) resistant breast cancer cells. Y537S ER is a mutated version of ER that has been shown to contribute to metastasis in ER+ breast cancer. Not enough is known about how PR drives CSC survival in metastatic ER+ breast cancer; thus, our studies aim to fill this knowledge gap.

The **objectives** of this proposal are to uncover what PR-controlled events promote CSC survival in the context of therapy resistance, and how this contributes to metastatic ER+ breast cancer. We propose that PR does this by reprogramming the metabolic needs of CSCs in order to allow them to survive harsh tumor environments that easily kill faster growing cancer cells. We and others have shown that breast cancer models of endocrine and chemotherapy resistance have altered metabolic needs. Our studies will identify how PR works with specific players known to be involved in cell metabolism, and how PR hijacks their normal metabolic processes to promote CSC survival. We will evaluate this in both endocrine and chemotherapy resistant models.

Impact. Despite advances in our understanding of breast cancer, this has not translated into better therapies. Standard of care options in ER+ breast cancer are ER-focused, and are limited because they primarily target fast growing tumor cells. Breast CSCs are slow growing and able to survive standard treatment, which allows them to contribute to metastatic tumor re-growth. These studies will define PR-driven players of CSCs and cancer cell metabolism to determine the therapeutic benefits of blocking their actions and in reducing metastatic burden of advanced ER+ breast cancer. Non-ER therapeutic targets, such as PR and others identified from our studies, can be developed in combination with current strategies to eliminate therapy resistant CSCs, and fundamentally redefine standard of care options for patients with stage IV metastatic breast cancer to extend lifespan.