

Lay abstract:

Breast cancer is one of the most common cancers in the world, with over 70% of breast cancers harboring the oncogenic activation of the estrogen receptor α (ER α), a key oncogenic transcription factor that transcribes the DNA of specific genes into messenger RNA. Metastatic disease is responsible for the majority of breast cancer patient deaths and has remained a central, clinical challenge in treating breast cancer. There are emerging findings suggesting that ER α activity plays a role in metastasis. For example, several studies have detected the presence of ER α expression in metastatic tumors and a clinical correlation has also been reported between ER α -positive tumors and the development of bone metastasis. However how ER α helps breast cancer cells to colonize and adapt to survive in other organs such as bones, lymph nodes or lung is still poorly understood. Furthermore, even though the transcription activity of ER is the main target of the tamoxifen compound, unfortunately, many breast cancer patients develop resistance to tamoxifen therapy that in many cases is associated with metastatic ER+ breast cancer (ER+ mBC). The prognosis for ER+ mBC is a median five-year survival rate suggesting the need for new therapies that significantly impact progression-free and overall survival in this population.

Almost all research on the function of ER α in breast cancer has been predominantly centered on the role of ER α as a transcription factor. We have now, however, made a striking discovery that ER α can bind to specific messenger RNAs (mRNAs) and as an RNA-binding protein is involved in translating these mRNAs into proteins in the last step of gene expression, known as translation. This proposal aims to understand the mechanisms by which ER controls the translation of specific mRNAs into proteins that enable breast cancer cells to establish metastatic tumors. Specifically, our results are pointing to a role for ER α , as a novel RNA-binding protein, to establish a network of proteins that allow breast cancer cells to adapt and bypass many stress conditions that they encounter during tumor progression and when they need to grow in unrelated tissues. In addition, our preliminary data also show that these new features of ER α are important to desensitize ER+ breast cancer to the activity of clinical compounds that target ER α such as tamoxifen, inducing a drug resistance phenotype and metastasis formation.

The novelty and benefit of the research proposed is several fold. **1-**For over 30 years, a key driver of breast metastasis, ER α , has been studied through the lens of transcription (how genes become transcribed into RNA molecules). We have instead uncovered an entirely new mechanism for ER α in breast cancer metastasis as an RNA binding protein. **2-** Our research is characterizing a distinct step in gene regulation by ER α oncogene with previously unknown significance to breast cancer survival and response to therapies. **3-** Here we will harness this knowledge to develop new pre-clinical trials employing new inhibitors that target the function of ER in RNA metabolism underlying drug resistance and metastasis formation. The findings of this proposal will be instrumental in revealing a new "Achilles' Heel" of ER α oncogenic activity in metastatic breast cancer.