Emily C Miller
Undergraduate
University of Oklahoma, Norman, Oklahoma

Dr. Judy Crabtree
Louisiana State University School of Medicine, Department of Genetics

"Therapy Resistant Breast Cancer Thrives: Notch 4 and Expression of Estrogen Responsive Genes"

Estrogen receptor positive breast cancer is the most common type of breast cancer. Women with ER+ breast cancer are given endocrine therapy to disrupt estrogen signaling in the body, but this treatment poses complications. A critical complication is the development of resistance to endocrine therapy, which may be caused by continued growth signaling and activation via crosstalk with other signaling pathways. One possible mechanism by which this signaling continues to occur is through activation of the Notch signaling pathway, which may allow resistant cells to survive. Further, an upregulation of Notch signaling is associated with poor prognosis and survival in ER+ breast cancer.

We hypothesize that Notch signaling, specifically Notch 4, is involved in crosstalk with the estrogen receptor, resulting in continued transcription of estrogen responsive genes in the absence of estrogen. The mechanism by which this crosstalk occurs in unknown. **Our experiments seek to understand the mechanism through which Notch 4 plays a role in the transcription of estrogen-responsive genes in the absence of estrogen.**

The cell line used for these studies was the ER+ breast cancer cell line MCF7, into which the Notch 4 intracellular domain (ICD) tagged with HA was cloned for overexpression. qRT-PCR was used to measure the expression of estrogen- and Notch- responsive genes that were previously found to be upregulated in the presence of Notch 1. These genes are *pS2, CD44, VEGFa, CCND1* and *C-MYC.* Next, DNA from previous ChIP (chromatin immunoprecipitation) studies under estrogen-free conditions was used to detect the presence of the estrogen receptor and Notch4ICD at the promoter region of these genes of interest by ChIP-PCR.

Future steps include further study of other possible upregulated target genes. Additionally, the results from this work may suggest the need for ChIP-Seq studies which would allow a global view of all the genes targeted by Notch 4 under estrogen-deprived conditions.

Understanding the mechanism through which Notch 4 has a role in estrogen responsive gene expression will allow further studies to begin to explore possible ways to interrupt Notch signaling. This will hopefully open the door for new treatments to address endocrine therapy resistance, leading to better prognosis for these patients.