Susan G. Komen
Research Grants – Fiscal Year 2014

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The role of lncRNAs associated with neoadjuvant hormone therapy sensitivity

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Lead Organization: Washington University in St.Louis
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Public Abstract:

Currently, multiple clinical trials for estrogen receptor positive breast cancer patients have focused on using aromatase inhibitors, a form of hormone therapy that blocks the enzyme aromatase from synthesizing estrogen. However, despite the successes of using hormone therapy, only a subset of patients will respond to treatment. Therefore, this proposal focuses on understanding the mechanism of resistance to hormone therapy by studying patients enrolled in two aromatase inhibitor therapy clinical trials. To date breast cancer research has primarily focused on the deregulation of protein-coding genes, however due to recent technological advances our lab focuses on an emerging class of genes known as long intergenic non-coding RNAs (lncRNAs). LncRNAs genes are greater than 200 nucleotides in length and do not encode for a protein. While our understanding of lncRNA functional roles in cancer is still in its infancy, initial studies suggest that lncRNAs can function by binding with proteins, such as estrogen receptor alpha (ESR1), and guide them throughout the genome to activate genes necessary for tumor progression. Interestingly, despite the lack of estrogen following hormone therapy, patients with treatment resistant breast cancer still have active ER signaling. Therefore, we hypothesize that a subset of lncRNAs promotes hormone therapy resistance in breast cancer by binding directly to ESR1 and altering its function by enabling it to activate oncogenes. To accomplish this, Specific Aim 1 will use existing high-throughput sequencing data, generated by lead mentor Dr. Matthew Ellis, from patients enrolled in hormone therapy clinical trials to discover lncRNAs associated with aromatase inhibitor sensitivity. Specific Aim 2 will use cutting-edge genomics approaches to identify the subset of lncRNAs associated with treatment resistance that are capable of binding directly with ESR1. Specific Aim 3 will assess how lncRNAs promote treatment resistance by activating ESR1 signaling despite the presence of hormone therapy. We will also determine how a lncRNA guides ESR1 throughout the genome to activate specific gene targets necessary to promote resistance. In Specific Aim 4 we will generate models to validate that a lncRNA can promote treatment resistance and confirm that it activates downstream targets. Successful completion of these aims will significantly advance our understanding of treatment resistance in ER+ breast cancer. We will identify putative lncRNA biomarkers that can identify those ER+ breast cancer patients that may not respond to hormone therapy and therefore may benefit from alternative therapies. This research will also reveal novel therapeutic targets for treating hormone therapy resistant breast cancer patients, giving them another chance to fight their disease. In the longer-term we intend to focus on targeting specific lncRNAs to reduce the incidence of treatment resistance and ultimately to increase patient survival rates.