West Lafayette Sagamore Lions Club and Purdue University Center for Cancer Research

Breast Cancer Clinical Forum Key Note Speaker

November 14, 2013
PFEN 241
3:00 pm – 4:45 pm

Victoria Seewaldt, M.D.
Professor of Medicine, Duke University

“Loss of KCNK9 Imprinting during the initiation and progression of aggressive triple-negative breast cancers in African American women”
Abstract:
Imprinting is a normal regulatory process where one copy of the gene is inactivated resulting in monoallelic gene expression. Loss of normal imprinting results in a functional diploid state and overexpression of the target gene. There is evidence that abnormal imprinting links environmental exposures and diet to cancer initiation, progression, and phenotypic plasticity.

During imprinting either the maternal or paternal gene is inactivated, resulting in monoallelic expression. Loss of normal imprinting results in biallelic gene expression and overexpression of the gene product. Recently 126 human genes were identified by Randy Jirtle, Ph.D. that are predicted to be regulated by imprinting; 23 genes are associated with breast cancer including WT1, HOXA5, IGF2, H19, GATA3, and KCNK9. The KCNK9 gene product TASK3 is a pH sensitive potassium channel protein that can be targeted by potassium channel blockers. TASK3 is overexpressed in breast cancer but the mechanism that governs overexpression is not known.

Triple negative breast cancer (TNBC) frequently occurs in young women and carries a poor prognosis. While not all TNBC are lethal, 5 years after diagnosis, only 14% of pre-menopausal African American women with TNBC are alive. Since many TNBCs are chemotherapy-resistant at diagnosis, there is a need for new therapeutic and early detection strategies. Here we tested whether loss of KCNK9 imprinting may play a role in chemotherapy resistance of TNBC.

We identified the differentially methylated region (DMR) in the KCNK9 promoter and demonstrated that KCNK9 is regulated by methylation imprinting. In addition we identified and mapped the DMR-associated chromatin that is made accessible by loss of imprinting. We also show that there is preferential loss of normal KCNK9 imprinting in triple-negative breast cancer relative to other breast cancer subtypes. In high-risk premenopausal African American women, loss of KCNK9 imprinting is observed in non-cancerous mammary epithelial cells prior to the development of breast cancer. It is known that TASK3 (KCNK9 gene product) regulates the plasma membrane potential. We show that KCNK9 regulates mitochondrial membrane potential (ΔΨm) and overexpression of TASK3 increases ΔΨm and promotes apoptosis resistance.

This is the first identification of the KCNK9 DMR and DMR associated chromatin. We show that there is loss of KCNK9 imprinting in TNBC and that overexpression of KCNK9 results in apoptosis-resistance and increased metabolism. These studies provide a potential link between prenatal diet, environmental exposures, and development of apoptosis-resistant TNBC in adulthood.