

Title: Breast Cancer and the Environment: Which Genes Are Important?

Travis Salisbury, PhD, a molecular biologist, joined The Joan C. Edwards School of Medicine, Marshall University in August 2009. He is an associate professor in the Department of Pharmacology, Physiology and Toxicology. Prior to coming to Marshall University, Dr. Salisbury was a postdoctoral fellow at Washington State University (WSU). As a research fellow, he established that G protein coupled receptor (GPCR) signaling in pituitary gonadotropes signaled through the transcriptional coactivator β -catenin to regulate gene expression. This discovery was novel, considering that historically β -catenin had been shown to be important in Wnt signaling, which is a developmental pathway. Currently, Dr. Salisbury's laboratory is using genomics to identify new mechanisms by which environment factors may cause or promote breast cancer. We focus on the aryl hydrocarbon receptor (AHR), a transcription factor that drives environmentally-induced cancer. Such new insights will foster new methods to treat cancers and for cancer prevention.

ABSTRACT:

Environmental factors, such as exposures to pollutants, are believed to play a role in many cases of breast cancer; however it is not clear how this mediated. Dioxins are among the most stable and widespread pollutants in the environment, and they are produced as by-products of industry and municipal waste incineration. Dioxins have been implicated in breast cancer, but mechanisms by which this occurs is unclear. We hypothesize that dioxins link to breast cancer is mediated through changes in gene expression, and our primary objective is to identify dioxin-regulated cancer genes using genomics. RNA-Sequencing analysis revealed that dioxin regulated the expression of over 600 genes in MCF-7 breast cancer cells (BCCs).

Bioinformatics Pathway Analysis revealed that dioxin regulated genes (DRGs) were most highly associated with the cancer and cancer-associated pathways including cell growth and proliferation and molecular transport. Further analysis identified LAT1, an amino acid transporter that is overexpressed in breast cancer, as a primary gene target of dioxin. Short interfering RNA (siRNA)-directed knockdown of the dioxin receptor, AHR, confirmed dioxin-stimulated increases in LAT1 expression required AHR. Upregulation of LAT1 by TCDD coincided with increases in leucine uptake by MCF-7 cells. In MCF-7 and MDA-MB-231 breast cancer cells, LAT1 expression was reduced in response to knockdown of AHR expression.

Gene knockdown experiments demonstrated that proliferation of MCF-7 and MDA-MB-231 BCCs is dependent on both LAT1 and AHR. Collectively, these findings confirm the dependence of cancer cells on leucine uptake and establish a mechanism for regulation of LAT1 by dioxin.