

Role of Endogenous and Environmental Agents on Mammary Gland Development and Cancer Susceptibility

Coral Lamartiniere, PhD, *University of Alabama at Birmingham.*

The four Breast Cancer and Environment Research Centers are committed to fundamental understanding of breast biology and how environmental agents alter development and susceptibility for breast cancer. Using multiple rodent models, we study how endogenous hormones regulate mammary cell differentiation and gland maturation and investigate gene and protein expressions at critical periods of development. Timing of exposure is carefully considered in determining the effects that environmental agents have on development and susceptibility for breast cancer. The Bay Area Breast Cancer and Environment Research Center (BABCERC) is focusing on how pubertal exposure to radiation can alter both mammary epithelial and stromal cell phenotypes to disrupt the regulation of growth and differentiation of cells. They have recently identified new molecular mediators activated during puberty and morphological signatures of putative mammary stem cells. Using rat and mouse models, Michigan State University Breast Cancer and the Environment Center (BCERC/MSU) investigates how increased lifetime exposure to the proliferative effects of progesterone is associated with the increased risk of breast cancer development. MSU has determined the cell type-specific pattern and regulation of estrogen receptor ($ER\alpha$), and progesterone receptor (PRA, and PRB) expression at puberty vs. sexual maturity and developed models for how these two hormones and certain genes that they regulate function in normal mammary gland development and can potentially affect susceptibility. The University of Cincinnati Breast Cancer and Environment Research Center (UCBCERC) looks into how fatty acids define not only mammary gland rates of maturation, but also the physiology of the animal in ways that impact the time frame of mammary gland susceptibility to initiation. UCBCERC preliminary data suggests that the type of fatty acid that the rat moms consume has a dramatic effect on the mammary gland morphology and that 'daughters' raised from mothers that consumed the high fat diets weighed more at weaning, and following induction with DMBA, formed more tumors. Fox Chase Breast Cancer and Environment Research Center (FCBCERC) has shown that the endocrine disruptors, bisphenol A (BPA), butyl benzyl phthalate (BBP) and TCDD given prenatally and neonatally/prepubertally alter mammary gland maturation, cell proliferation and gene and proteome expressions. Recent findings demonstrate that neonatal/prepubertal exposure to BPA results in an increased number of DMBA induced mammary tumors. The four BC&E Centers are now engaging in transdisciplinary research projects, including investigating ER and PR expressions in stem cells (BCERC/MSU and BABCERC), how stem cell populations react to endocrine disruptors (BABCERC and FCBCERC), genetic basis for differences in hormonal responsiveness and resistance and susceptibility to mammary tumorigenesis in mice (BCERC/MSU and BABCERC), how endocrine disruptors alter fat and obesity (FCBCERC and UCBCERC), and how sex steroid receptor expression is regulated in mammary tissue and tumors of rats exposed to endocrine disruptors (BCERC/MSU and FCBCERC). Linking of biology projects with human studies will be carried out *via* serum biomarkers.