Study Offers Insight into Endocrine Disruption by Soy

By Eddy Ball
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First author Wan-Yee Tang of the University of Cincinnati (Photo courtesy of Shuk-mei Ho)

Newbold, above, has been a leader in endocrine disruption research at NIEHS. (Photo courtesy of Steve McCaw)
Along with her duties as department chair, Ho, above, is director of the Center for Environmental Genetics and co-leader of the Hormonal Malignancies Program in the Joint Cancer Center at the UC College of Medicine. (Photo courtesy of Shuk-mei Ho)

NIEHS Reproduction Group Biologist Wendy Jefferson (Photo courtesy of Steve McCaw)

NIEHS-supported researchers report compelling new evidence about the mechanisms linking genistein supplementation during development of mice to altered DNA methylation patterns that can lead to serious health complications later in life, according to a study published in the journal *Endocrinology*. The researchers identified novel uterine genes whose expression was altered by neonatal exposure to genistein (GEN) and diethylstilbestrol (DES) – an estrogenic chemical with well documented adverse transgenerational carcinogenic and reproductive effects.

Led by NIEHS grantee and Chair of the Department of Environmental Health at the University of Cincinnati (UC) Shuk-mei Ho, Ph.D. (http://www.eh.uc.edu/dir_individual_details.asp?qcontactid=702), and NIEHS Reproductive and Developmental Toxicologist Retha Newbold, the team also included UC Research Associate and NIEHS grantee Wan-Yee Tang, Ph.D. (http://tools.niehs.nih.gov/portfolio/sc/detail.cfm?appl_id=7514004), who was first author on the study, and NIEHS Reproduction Group Biologist Wendy Jefferson, Ph.D.

According to an editorial published in the same issue of *Endocrinology*, the study (http://www.ncbi.nlm.nih.gov/pubmed/18669593?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum) marks the first time specific molecular evidence has been identified that supports the
theory of a two-step process for epigenetic alterations triggered by endocrine disruption. Only one of the 14 uterine genes identified in the study had been previously characterized in the rodent uterus.

Animals in the study were housed according to NIEHS/NIH guidelines and fed NIH-31 laboratory mouse chow that tested negatively for estrogenic activity. By including a control group of mice that underwent ovary removal prior to puberty in their experiments, the investigators demonstrated that the process is dependent upon the presence of postpubertal ovarian steroids.

This finding adds important evidence for the argument that repressed epigenetic memories or "imprinting" of prenatal DES/GEN exposures during neonatal development may be triggered by a "second hit" of estrogen or estrogen-like compounds after puberty or as individuals age — setting up gene expression patterns favorable to tumor development and growth.

The study utilized unbiased methylation-sensitive restriction fingerprinting to determine differentially methylated gene sequences associated with neonatal exposure to DES/GEN. "These genes encode proteins involved in signal transduction, receptor activation, tumor angiogenesis, cell proliferation, apoptosis, intracellular trafficking, DNA repair and chromatin remodeling," the authors wrote. "A tight association between gene silencing and gene methylation, and the reverse, was observed."

Of the 14 genes influenced by exposure, the team chose one, nucleosomal binding protein 1 (Nsbp1) for further analysis because of its central role in chromatin remodeling and transcriptional activation. "The purported functions of Nsbp1," the investigators continued, "together with our current finding that the expression of Nsbp1 is under estrogen-mediated epigenetic regulation, have led us to speculate that Nsbp1 may participate in the tumorigenesis of the mouse uterus after neonatal exposure to DES/GEN."

The editorial in Endocrinology by University of Illinois at Chicago physiologist Gail Prins, Ph.D., noted that the findings could impact current practices regarding soy consumption by mothers and their infants. Depending on the timing of exposures to the phytoestrogen, the epigenetic alterations triggered by DES/GEN exposure during development could potentially offset the widely valorized chemoprotective and beneficial effects of soy consumption.

More completely understanding such timing, Prins concluded, is one of "many things that remain to be done." The study has set the direction for future studies to identify "secondary triggers for repressed epigenetic memories aside from just hormones," she continued, and to "formulate an 'epigenetic fingerprint' consisting of multiple genes that may be similar or unique for the separate estrogenic compounds, end organs or second hits." Such information could prove useful in early diagnosis or intervention, she concluded.

