Prenatal Exposure to TCDD Differentially Regulates SOD1, SOD2, and EGFR in the Rat Mammary Gland

Sarah Jenkins and Coral Lamartiniere, Department of Pharmacology and Toxicology, University of Alabama at Birmingham

In 2006, an estimated 212,920 women will be diagnosed with invasive breast cancer, and a projected 41,430 cases will result in mortality. Only 5-15% of breast cancer etiology can be attributed to hereditary causes. Other causative factors must exist in order to account for the high incidence of breast cancer. One hypothesis is that environmental chemicals that are hormone agonists or antagonists are contributing to increased susceptibility for breast cancer. Hence, endocrine disruptors, especially those with the ability to alter normal estrogen signaling, are being scrutinized for their potential role in the cause of breast cancer. One such compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been linked to reproductive abnormalities, decreased immune function, and carcinogenesis in animal models. Though the epidemiology data are conflicting, we have previously shown that prenatal exposure to TCDD resulted in an increased incidence of mammary tumor development in a dimethylbenz[a]anthracene (DMBA) model of rodent mammary cancer. Analysis of mammary gland maturation at 50 days postpartum (time of DMBA exposure) showed that prenatal exposure to TCDD altered the normal mammary gland morphology. This resulted in a poorly differentiated gland that was more susceptible to carcinogenic insult. To elucidate the molecular mechanisms responsible for these changes, we employed the use of discovery proteomics. Two-dimensional gel analysis and subsequent immunoblot confirmation validated the down-regulation of one protein, superoxide dismutase 1 (SOD1). SOD1 catalyzes the dismutation of superoxide anion radical to hydrogen peroxide, which is subsequently reduced to water by either glutathione peroxidase or catalase. A down-regulation of SOD1 in the mammary gland could provide an environment ill equipped to deal with subsequent free radical exposure. Further immunoblot analysis at days 21 (prepubertal) and 50 (time of DMBA exposure and sexual maturity) revealed a series of differentially regulated proteins. At d21, SOD1, SOD2, and EGF receptor (EGFR) were observed to be significantly down-regulated. This shows that the differential regulation of SOD1 was not a transient event and that further components of the superoxide anion radical pathway may be affected. However, at d50 both SOD2 and EGFR were observed to be significantly up-regulated. This stark contrast in differential regulation in the absence of the original effecter suggests that early exposure to TCDD has the ability to “imprint” a series of time-sensitive changes in the mammary gland that may contribute to an increased susceptibility for mammary cancer development later in life. Supported by NIEHS 1R21 ES012326-03, NIEHS 1U01 ES012771-02 and R25 CA47888.