ESTROGENS-INDUCED CANCERS: A NEW MECHANISTIC PERSPECTIVE

Kamaleshwar P. Singh

Department of Environmental Toxicology, The Institute of Environmental and Human Health (TIEHH), Texas Tech University, Lubbock, TX 79409, USA

Abstract: Prolonged exposure to the elevated level of estrogens is a known risk factor for cancer. The target organs for estrogen-induced cancers are not only the estrogen-dependent organs, such as, breast, ovary, endometrial, and testis, but also estrogen-independent organs such as liver and kidney. The mechanism of estrogen-induced cancer is not fully understood. The classical estrogen-receptor dependent pathway does not account all the effects of estrogens. Therefore, the objective of this study was to evaluate estrogen receptor-independent pathways through which estrogen might lead to carcinogenic effects. In this study, the human kidney epithelial cells that do not express estrogen receptor alpha and beta as well as the other human cell lines that express estrogen receptors, were exposed to various doses of natural estrogen 17 beta-estradiol or synthetic estrogen diethylstilbestrol (DES). The effect of estrogen on cell proliferation, cell cycle, and genomic instability was determined. Previous studies have shown that estrogen also generates reactive oxygen species (ROS) and therefore the role of mitochondrial ROS in estrogen-induced cell proliferation and DNA damage was also evaluated. Finally, the role of epigenetic mechanism of DNA methylation in estrogen-induced genomic instability was also investigated. Findings of this study revealed that estrogen induces cell proliferation and DNA damage not only in estrogen receptor expressing cells but also in cells that do not express ER α and ER β. Our data also suggest that estrogen-induced ROS might be involved in cell proliferation and DNA damage. Additionally, the estrogens through epigenetic mechanism downregulates the expression of DNA repair genes that may lead to accumulation of mutations. In summary, this study provides a new mechanistic insight into the genotoxic and carcinogenic effects of estrogen through ER α and ER β -independent pathway.