S17. Primary Prevention of Breast Cancer by Hormone-Induced Differentiation

I. Russo, D. Mailo, M. Liu, S. Fernandez, J. Russo

Fox Chase Cancer Center, Breast Cancer Research Laboratory, Philadelphia PA, United States of America

Breast cancer is a fatal disease whose incidence is gradually increasing in most industrialized countries. Primary prevention is the ultimate goal for the control of this disease. Although its accomplishment is hindered by the lack of identification of the agents or mechanisms that cause the disease, the knowledge that endocrine and reproductive factors significantly reduce cancer incidence has provided novel tools for designing cancer prevention strategies. Breast cancer risk is reduced by a full term pregnancy occurring before age 24, and additional pregnancies increase the rate of protection through induction of differentiation of the breast. We have reproduced in virgin rats the preventive effect of pregnancy by a 21-day treatment with the placental hormone human chorionic gonadotropin (hCG). This hormone prevents the initiation and inhibits the progression of chemically-induced mammary carcinomas; inhibits cell proliferation and increases apoptosis; induces the synthesis of inhibin, a tumor suppressor factor, downregulates the estrogen receptor alpha by methylation of CpG islands, and imprints a permanent genomic signature that characterizes the refractory condition of the mammary gland to undergo malignant transformation. The genomic signature induced by hCG is identical to that induced by pregnancy, as determined by comparing the mammary gland's genomic profile of virgin Sprague-Dawley rats that were treated with 100 IU/hCG for 21 days, or had implanted one pellet of 0.72 mg 17 beta-estradiol and one of 200 mg progesterone with that of pregnant and virgin control groups. RNA extracted from mammary gland tissues from the four groups of animals was studied employing an oligonucleotide microarray containing 1,300 known genes. In both hCG-treated and in pregnancy, but not in steroid treated groups, 194 genes were found to be significantly up modulated and commonly expressed. This genomic signature included activators or repressors of transcription genes, growth factors, cell division control, and DNA repair genes among others. Our data indicate that hCG, like pregnancy, induces permanent genomic changes that are not reproduced by steroid hormones, and in addition regulates gene expression through epigenetic mechanisms that are differentiation dependent processes. Our data lead us to conclude that hormonally-induced differentiation offers enormous promise for the primary prevention of breast cancer.