Hormones, growth factors, and the regulation of tumor suppressor pathways involved in parity - induced protection of breast cancer

Lesley Anne Mathews, *University of Massachusetts - Amherst*

Abstract

Despite current advances in understanding breast cancer, in 2007 an estimated 178,480 new cases were diagnosed in female patients in the United States, and an estimated 40,640 deaths will occur due to this disease [1]. Numerous risk factors exist for breast cancer including current age, reproductive events, exposure to exogenous hormones or ionizing radiation, and genetic factors [2]. The research presented here is designed to answer questions specifically related to pregnancy and breast cancer risk (parity-induced protection against breast cancer), as well as the molecular pathways involved. ^ We first examined the relationship between p53, a known tumor suppressor gene of breast carcinoma in the mammary gland, and age at first parity in human breast tissue. Using explant cultures from reduction mammoplasty patients, we demonstrated an increase in radiation-induced accumulation of p53 in breast tissue from patients who have undergone an early parity compared to nulliparous patients, or late parous patients. We also demonstrated that p53 accumulation was positively correlated with an increasing number of pregnancies. These are the first studies using cultured human mammary tissue that demonstrate results consistent with experimental rodent models and observational human data.^ Next, a potential tumor suppressor gene within the breast, cellular retinol binding protein-1 (CRBP1), was found to be significantly up-regulated in response to parity in mice and humans, and that it utilizes transforming growth factor-beta (TGF-β) to confer its signals.^ Finally, we demonstrated that addition of insulin-like growth factor-I (IGF-I) to mouse mammary gland whole organ cultures (mWOCs) treated with estrogen and progesterone (E+P) could block the normal induction of apoptosis, p53, and its downstream target p21 in response to gamma radiation. In addition, while treatment with

E+P resulted in the up-regulation of insulin-like growth factor binding protein-3 (IGFPB3), TGF-β1, and CRBP1, this up-regulation was blocked upon co-treatment with IGF-I.^ Overall, the research presented here has furthered our knowledge of possible mechanisms by which an early parity can protect against breast cancer. These data suggest that numerous mechanisms can aberrantly alter signaling pathways involved in this protection such that the balance is shifted away from tumor suppression and growth arrest, and towards a phenotype that demonstrates an increased susceptibility toward cancer. ^

Subject Area

Biology, Molecular|Biology, Genetics|Health Sciences, Oncology

Recommended Citation

Lesley Anne Mathews, "Hormones, growth factors, and the regulation of tumor suppressor pathways involved in parity -induced protection of breast cancer" (January 1, 2008). *Doctoral Dissertations Available from Proquest*. Paper AAI3325147.
http://scholarworks.umass.edu/dissertations/AAI3325147