The role of ovarian hormones in p53-mediated resistance to mammary tumorigenesis

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Abstract

A full term pregnancy reduces breast cancer by up to 50%. In rodents, pregnancy or treatment with estrogen and progesterone to mimic pregnancy reduces mammary tumor incidence. The molecular mechanisms for parity-induced resistance to mammary tumorigenesis appear to involve a sustained increase in p53 responsiveness to cellular stresses. The following experiments tested whether pregnancy levels of ovarian hormones alter molecular pathways that prime p53 to be more responsive to DNA damage and if these pathways confer resistance to mammary tumors in a mouse model of Li-Fraumeni syndrome. Mice were treated with estrogen and progesterone (E+P) for 14 days, neonatally or at maturity. At 10 weeks of age, radiation-induced nuclear accumulation of p53 and apoptosis were increased similarly in the mammary epithelium from E+P-treated and parous mice compared to placebo. This effect was sustained for at least 7 weeks after E+P treatment and did not depend on the continued presence of ovarian hormones. Hormone-stimulation also enhanced apoptotic responses to ionizing radiation in BALB/c- *Trp53*+/- mice, a model of Li-Fraumeni syndrome. The appearance of spontaneous mammary tumors was delayed by parity in BALB/c-*Trp53*+/- mice. However, this protective mechanism was not preserved within epithelial progenitor cells because apoptotic responses to ionizing radiation and tumor incidence in epithelial transplants from E+P-treated donors was not different from nulliparous epithelial outgrowths. Therefore, E+P and parity confer a sustained increase in p53-mediated apoptosis within the mammary epithelium and suppresses mammary tumorigenesis, but this was not retained in epithelial outgrowths. Parity reduces the expression of estrogen receptor alpha (ERα). Activation of ERβ with an ERβ-specific agonist represses the expression of ERα. Parity-related alteration in the expression ratio of the two estrogen receptors in the mammary gland

could regulate p53 priming to enhance its responsiveness to genomic stress in the parous individual. ^

Subject Area

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