Regulation of the p53 tumor suppressor gene in the mammary gland and its role in tumorigenesis

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Abstract

Breast cancer is the most frequent tumor type among women. Heightened susceptibility of the breast to tumor development has been associated with early menarche, nulliparity, exposures to ionizing radiation, and family history, but the underlying molecular mechanisms are poorly understood. Unfortunately, the etiology of breast cancer is complex and is complicated by the fact that it is a heterogeneous disease. The *p53* tumor suppressor gene was altered in a large proportion of these spontaneous breast tumors implicating its involvement in the progression of breast cancer development. The aim of this dissertation was to determine the regulation of p53 in the normal mammary gland and whether it is involved in suppressing the development of mammary tumors. To evaluate the effect of *p53* on mammary tumor formation, the first component of this work involved the characterization of BALB/c- *p53*-deficient mice. BALB/c-$p53^{+/-}$ and $p53^{-/-}$ mice were examined for tumor spectrum and mammary abnormalities. Mammary transplants were performed to evaluate the role of p53 in tumor suppression in the mammary gland. This work demonstrated that p53 is critical in suppressing mammary tumorigenesis in the mammary gland as BALB/c mice deficient in *p53* readily develop mammary carcinomas. ^ The second element of this project examined the expression, localization and activity of p53 in normal mammary tissues. Since the mammary gland is a tissue that is sensitive and responsive to local and systemic hormones, the last chapter of this dissertation focused on the hormonal effects on p53 activity. Results from these experiments demonstrated that p53 was expressed at high levels localized to the cytoplasm of the ductal epithelium of the quiescent mammary gland. P53 was not responsive to radiation-induced DNA damage suggesting its function is compromised in the nulliparous mammary gland. Further experiments demonstrated that the functional state of wild type p53 in the mammary epithelium could be regulated by hormonal stimuli. ^

Subject Area

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