Regulation of p53 by Mdm4 and ovarian hormones in mouse mammary glands

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Abstract

p53 protein is considered a major player in maintaining the genomic integrity. It regulates cell cycle, recognizes damaged DNA, and promotes apoptosis of cells that are defective or developmentally programmed for removal. Most cancers, including breast cancer, lose genomic integrity and have impaired p53. Li-Fraumeni patients and BALB/c mice bearing germline mutations in one allele of the p53 tumor suppressor gene develop mammary tumors. The p53 pathway is also required for the protective effect of pregnancy on breast cancer. Therefore, identifying the cellular pathways that regulate p53 will provide improvements in assessing breast cancer risk in individuals as well as therapeutic targets. The function of p53 could be regulated directly by Mdm2 and Mdm4. While Mdm2 is clearly a negative regulator of p53, the roles of Mdm4 on p53 are still not fully defined. Transgenic mice which over-express Mdm4 specifically in mammary gland were used to investigate the effects of Mdm4 on p53 function. Ovarian hormones also regulate p53 activity, but through indirect mechanisms. Oligonucleotide-based transcriptional profiling was conducted to identify mechanisms, by which estrogen and progesterone enhance p53 activity in mammary epithelial cells. The results from these studies showed that Mdm4 is unlikely to be a primary regulator of p53 functions in mammary epithelium. In contrast, expression profiling revealed groups of genes that are associated with the sensitization of p53 by estrogen and progesterone as well as tamoxifen and progesterone. These results implicate a common pathway used to sensitize p53 which involves proteins in the extracellular matrix. ^

Subject Area

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