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Breast cancer protection: hormonal priming via p53?

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Keywords

Carcinogen-induced cancer, estrogen, p53, pregnancy, progesterone

Context

Epidemiological studies in women strongly correlate a reduced risk for developing breast cancer with early full-term pregnancy. While the molecular mechanisms that give rise to pregnancy-protective effects are not known, several hypotheses have been proposed. The paper presented here addresses the theory that the hormonal cues delivered during early pregnancy promote long-term biochemical changes in the mammary epithelia that influence the growth potential of cells when exposed to carcinogenic insult. Specifically, the authors are interested in the possibility that the tumor suppressor protein, p53, may function as such a biochemical mediator. Here, studies explore the spatial and temporal expression patterns of p53 *in vivo* using combinatorial hormone treatment to mimick early pregnancy in both rat and mouse models.

Significant findings

Rats treated with estrogen and prolactin (E/P) exhibit dramatically upregulated p53 expression only days after E/P treatment. Elevated p53 levels persist through involution and challenge with the carcinogen N-methyl-N-nitrosourea (MNU). p53 induction is concomitant with its accumulation in epithelial cell nuclei and increased transcriptional activation of two p53 targets, p21 and MDM2. Increased prolactin, which is sufficient to induce precocious mammary differentiation but is not protective against carcinogenic insult, does not induce p53 expression suggesting that p53 is not a differentiation marker. A parallel mouse model shows comparable p53 behavior in response to a pregnancy-like hormonal milieu. Proliferation studies in mice confirm earlier results in rats demonstrating that cells exposed to pregnancy hormones exhibit a proliferative block upon carcinogen challenge underscoring the possibility of a common p53-dependent molecular mechanism.

Comments

This study feeds into a larger body of work in support of the proposed 'cell-fate' hypothesis for protective effects of early pregnancy. While the data by no means provide definitive proof of the hypothesis, the authors make an intriguing case for p53 as a candidate molecular mediator of a sustained protective response. The novelty of this study lies with the demonstration that elevated p53 expression is sustained in response to transient estrogen and progesterone exposure during early pregnancy. Other data, while largely confirmatory in nature, essentially 'clean up' the rat and mouse pregnancy models and make them amenable to future studies of how p53 is stabilized to exert its protective effects.

Methods

Wistar-Furth Rats, Balb/c Mice, *in vivo* hormonal manipulations, estrogen and progesterone delivery via beeswax pellets, MNU and 7,12-dimethylbenz[a]anthracene carcinogen challenge, immunohistochemistry, bromodeoxyuridine cell proliferation assays

Additional information

References

1. Sivaraman L, Conneely OM, Medina D, O'Malley BW: p53 is a potential mediator of pregnancy and hormone-induced resistance to mammary carcinogenesis. Proc Natl Acad Sci USA. 2001, 98: 12379-12384.