Hormones and Mouse Mammary Tumorigenesis

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Abstract

The hormonal milieu of the host influences viral and chemical carcinogen-induced mammary tumorigenesis in a variety of indirect ways. The effects of a high-fat diet on mouse mammary tumorigenesis are very limited and are convincing only for mice infected by the high-oncogenic mammary tumor virus. The relationship between fat content in the diet, the hormonal milieu of the host, and mammary tumor virus function is unexplored.

The hormonal influence on murine mammary tumorigenesis has been extensively studied and can be demonstrated in several different ways. However, there is little evidence that hormones (primarily ovarian steroids and prolactin) are primary carcinogens for the mammary gland. Hormones influence the neoplastic process in mammary glands by a permissive effect, i.e., they provide the morphological and physiological conditions upon which an oncogenic agent exerts its effects (2, 10, 17). Examples of the actions of hormones on the neoplastic process can be seen in Table 1.

1. Hormones are necessary for normal and preneoplastic development of the mammary gland in C3H mice, i.e., estrogen plus luteoid or corticoid plus prolactin or growth hormone. For tumor formation, the same hormone combinations are necessary, except that estrogen is facilitative rather than obligatory. Mammary carcinomas induced by MuMTV-S are hormone independent for growth, whereas those induced by MuMTV-plague or chemical carcinogens are frequently hormone dependent for growth.

2. Hormones synergize with MuMTV and chemical carcinogens in the induction of mammary tumors. For instance, in mice bearing the high (MuMTV-S) or low oncogenic variant of MuMTV, hormonal stimulation of the mammary gland through breeding or a pituitary isograft increases markedly the mammary tumor incidence (15). Similarly, pseudopregnancy or pituitary isografts facilitate mammary tumor induction by chemical carcinogens, such as 7,12-dimethylbenzanthracene and urethan (3, 5, 13). The mechanisms of this hormone synergism may be several. Hormones influence MuMTV infection of mammary tissues and replication in the target cells (11, 14, 18) and enhance the formation and transformation of MuMTV and chemical-carcinogen-induced lesions (4, 12). In carcinogen-treated mice, prolonged hormone stimulation by pituitary isografts does not act as a classical promoter (5, 13). This experiment is impossible to perform in MuMTV-infected mice since the initiating agent is always present.

3. The inductive effects of estrogens in mammary tumorigenesis have not been convincingly demonstrated. For instance, diethylstilbestrol induces mammary tumors in the presence of MuMTV-S (female C3H mice) but not in its absence (female C3Hf mice) (6).

4. Neonatal treatment of MuMTV-S-positive BALB/cfC3H mice with 17β-estradiol, testosterone, and progesterone enhances mammary tumorigenesis in the adult; however, in the absence of MuMTV-S, some mammary dysplasia, but no tumors, are induced by 18 months (8). Interestingly, in mice neonatally treated with testosterone, but not in diethylstilbestrol-, 17β-estradiol-, or prolactin-treated BALB/cfC3H and BALB/c mice, an increased level of circulating prolactin was seen in adult mice (16). The significance of enhanced levels of circulating prolactin is dubious since the levels reached are never as high as they are under conditions where prolactin is known to enhance mammary tumorigenesis. Additionally, Sinha et al. (21) have demonstrated that high levels are not a priori correlated with high mammary tumor incidences.

The data available so far suggest that hormones can modulate murine mammary tumorigenesis whether administered neonatally or to an adult, particularly when the oncogenic stimulus is strong and the hormonal alterations are drastic. The data available on the effects of high-fat diets on murine mammary tumorigenesis are limited and not very convincing. In the 3 experiments reported by Tannenbaum (20, 22), two strains of mice (C3H, DBA) were used, and the results support the hypothesis that an isocaloric high-fat diet enhances MuMTV-S-induced mammary tumorigenesis in female DBA mice but not in female C3H mice. However, the data are suggestive enough to warrant a series of experiments to determine whether a high-fat or a high-polyunsaturated-fat diet enhances mammary tumorigenesis in a variety of different tumor models, i.e., mice carrying the endogenous MuMTV (C3Hf, DBA/2f, BALB/c NIV, etc.) or mice exposed to chemical carcinogens (7,12-dimethylbenzanthracene). If a high-fat diet enhances murine mammary tumorigenesis, it would be interesting to determine the morphological stage of carcinogenesis which is sensitive to dietary influences. Since the growth of normal and neoplastic mammary cells has been shown in a limited number of recent experiments to be influenced by the fatty acid environment using both in vivo and in vitro methods (1, 7, 9, 19), it would also be informative to examine the regulation of DNA synthesis as a consequence of alterations in fat diet as well as examining possible changes in the hormonal milieu.

References


Table 1

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<td>Neonatal hormone treatment enhances mammary tumorigenesis</td>
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<td>Hormones act permissively, not inductively</td>
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1 Presented at the Workshop on Fat and Cancer, December 10 to 12, 1979, Bethesda, Md.
2 The abbreviations used are: MuMTV-S, murine mammary tumor virus-stand; MuMTV, murine mammary tumor virus.


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