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MMTV-c-erbB-2 and MMTV-TGF alpha transgenic rats

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Introduction

Many transgenic models of neoplastic disease have been produced in mice, including models of breast cancer. In comparison, few transgenic rat models have been described. Nevertheless, the rat remains an interesting model since the origin, pathology and sensitivity to hormones of rat mammary tumours closely resembles those of the human.Both TGF alpha and c-erbB-2 are commonly expressed, dominantly acting oncogenes in human breast cancer. TGF alpha is a member of the EGF family of proteins that induce a mitogenic response by activating members of the EGF tyrosine kinase receptor family, which includes c-erbB-2. However, results from transgenic mouse models using these genes, or their activated products, are somewhat ambiguous in several respects.

Aims

To produce transgenic rats, carrying TGF alpha or c-erbB-2 under the control of the MMTV-LTR, as models of breast cancer. To study the pathology of the mammary gland in the generated rat lines and gain insight into the roles of the transgenes in mammary gland biology and pathology.

Comments

This work extends the generation of useful animal models of breast cancer to the transgenic rat. The recapitulation of important results from one model system (the transgenic mouse) in another is useful and informative. In addition, the knowledge gained previously from studies of spontaneous and carcinogen-induced rat mammary tumours can now be extended to include data from rats with predetermined genetic tendencies.

Methods

The generation of transgenic rats by microinjection of DNA into fertilised eggs is described, with particular reference to how this differs from techniques used in the mouse. Integrated transgenes were detected by Southern blot; transgene expression was confirmed by northern blot analysis of transgene RNA and by immunocytochemical detection of TGF-alpha and c-erbB-2. Rats were mated to stimulate expression of the transgenes and to produce F1 and F2 progeny. Whole-mount analysis of mammary glands was used to detect macroscopic hyperplasias, preneoplasias and tumours. Further histological and immunohistological analysis of these was performed.

Results

Production of transgenic rats was not as successful as that reported with mouse systems. Only 7% (7/105) and 14% (6/42) offspring from MMTV-c-erbB-2 and MMTV-TGF alpha microinjected eggs, respectively, carried transgenes. Copy number varied from less than 1 to 50 copies, with transmission to the F1 generation indicating that four founder rats were mosaic.No tumours appeared in the mammary glands of virgin females of either line. Various pathologies (see below) were however reported in multiparous rats, as has been reported previously for transgenes under control of the MMTV-LTR. Only a single ductal hyperplasia and a small area of fibroadenoma were seen in control non-transgenic rats of similar age and reproductive history.

MMTV-c-erbB-2 transgenics: 23 multiparous females were studied and all showed weak transgene staining in mid-pregnant mammary glands. Eighteen exhibited hyperplasia; four had cystic expansion; 15 had fibroadenoma; three had papillary adenoma; three had DCIS and two had carcinoma. All lesions exhibited staining for c-erbB-2 and this was particularly strong in the cystic expansions and the carcinomas.

MMTV-TGF-alpha transgenics: 29 multiparous females were studied and 11 developed large, solid, palpable lumps in the mammary gland after five or more pregnancies. The lumps grew up to 5 cm in diameter, always appeared on the 10th or 11th day of pregnancy and regressed the day before birth of offspring, the animals then lactated normally. Lumps reappeared more severely on subsequent pregnancies and other lesions were seen, including: fibroma (1), papillary ductal adenoma (3), lactating adenoma (2), ductal carcinoma in situ (4) and carcinoma (2).

Discussion

The techniques used to generate these rats differed from those used to generate transgenic mice, and a significant proportion of (mosaic) founder animals presumably resulted from integration of the transgene DNA following at least one cell division. Nevertheless, transgenic rats can be generated, and constructs using MMTV-LTR direct the expression to the same tissues as seen in mice, in a pregnancy dependent manner. All mammary lesions seen were stochastic in nature, suggesting that other genetic changes or a critical level of transgene expression were required. That these lesions were stimulated, at least in part,

by the transgenes is confirmed by the facts that they are multifocal, they express the relevant transgene and they were not present in non-transgenic littermate controls.

Over-expression of c-erbB-2 in the rat mammary gland leads to stochastic development of mammary carcinoma, as seen in mouse models, but at a lower frequency and without metastasis. However, in the rat a number of additional benign changes were seen, some of which may represent precursors of malignant lesions.MMTV-TGF-alpha rats were characterised by severe, pregnancy-dependent hyperplasia.The pregnancy-associated lesions may be due to hormonal influences on the MMTV promoter, and have been witnessed previously in a variety of mouse models.

Additional information

MMTV-c-erbB-2 transgenics: In four of the animals the fibroadenomas were macroscopically visible and in the other 11 they were initially identified as densely staining areas in whole-mounts. These lesions often occurred together with ductal hyperplasia of usual type or sclerosing adenosis. The carcinomas were classified as well differentiated, were locally invasive but exhibited no evidence of having metastasised to lungs, lymph nodes or other tissues examined.

MMTV-TGF-alpha transgenics: Histologically the lumps seen in these rats were made up of solid masses of tissue resembling normal lactating mammary gland and were considered to be severe hyperplasias (resembling lactating adenomas) rather than neoplasias. These hyperplasias stained moderately to strongly for TGF-alpha. Lobule number and size was increased and frequently the fat pads were filled with proliferating epithelium. These changes were also seen in earlier pregnancies by whole-mount analysis. Hyperplasia was seen in non-pregnant rats and there was evidence that lobules of hypeplastic, secretory epithelium were retained at least six weeks after weaning (following more than eight pregnancies).Hair loss seen in MMTV-TGF-alpha rats was consistent with sebaceous gland hyperplasia stimulated by the transgene.

References

1. Davies BR, Platt-Higgins AM, Schmidt G, Rudland PS: Development of hyperplasias, preneoplasias, and mammary tumors in MMTV-c-erbB-2 and MMTV-TGF alpha transgenic rats. Am J Pathol. 1999, 155: 303-314.