New Concepts and Approaches in the Analysis of Mammary Preneoplasia and Tumor Progression

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The main clinical problem concerning human breast cancer is its long latency before clinical detection. This is somewhat surprising when noting that the estimated length of the natural history of mammary neoplasia ranges between 15 and 25 years. The first step in the development of breast cancer is usually represented by preneoplastic, hyperplastic focal changes, which only rarely (5% of cases) clinically appear as benign tumors or dysplasias. Most often hyperplastic foci maintain subgross and subclinical sizes and require a long time (10–15 years) to undergo progression. Additionally, when malignant transformation occurs in the microenvironment of focal hyperplasias, a certain time (8–10 years) is required for the cancer to become detectable.

Therefore, knowledge of the early steps in human breast carcinogenesis is scanty. In contrast, much information is available concerning preneoplasia and early neoplasia in experimental models of mammary cancer. As far as we know, there does not seem to be any substantial difference in the biology of progression in experimental versus human breast cancer.

This paper is divided into two parts concerning the early steps of both experimental and human breast cancer. The aim is to provide new concepts that will be useful in the interpretation of morphologic findings. The rationale for this effort is twofold: (1) clinical progress may be hampered without adequate basic knowledge, and (2) potential progress lies in our ability to reevaluate, with an appropriate knowledge of the biology, what is already known and can readily be seen histologically.

INFORMATION ACQUIRED UTILIZING EXPERIMENTAL MODELS OF BREAST CARCINOGENESIS

There are several pathways in breast carcinogenesis and these pathways differ remarkably from each other in terms of the target structure involved, the hormones required for promotion, the type of preneoplastic change, if any, and tumor behavior. Four investigations providing a background for this review were supported by CNR contracts no. 84.00814.44 and no. 84.00458.44, Project "Oncology."
different extensively investigated models of breast carcinogenesis will be briefly analyzed.

Carcinogenesis by Dimethylbenzanthracene (DMBA) in Rats

Breast carcinogenesis by DMBA has been extensively investigated in rats.\textsuperscript{1,2} The model is peculiar to, although not exclusive to, DMBA since other carcinogens, such as adriamycin and daunomycin, have recently been shown to induce the same sequence of events.\textsuperscript{3} It is a model of acute chemical carcinogenesis in the sense that tumors develop in a short time period.\textsuperscript{1} It is also a “one-step” model of carcinogenesis, since tumors develop directly from the target structure, without intermediate preneoplastic steps.\textsuperscript{4} Target structures of DMBA carcinogenesis are the end and lateral buds, which represent sites of ductal development in immature mammary glands (Fig. 1). This model of breast carcinogenesis does not require lobuloalveolar differentiation. Accordingly, ovarian hormones and hormones of pregnancy, which usually stimulate breast carcinogenesis in rodents, have a preventive effect in this model of tumorigenesis since they reduce and delay the occurrence of mammary tumors.\textsuperscript{3,5} It may, therefore, be argued that differentiation of the mammary gland eliminates the target cells or makes the cells less susceptible to tumor transformation in this model.\textsuperscript{5}

Carcinogenesis by Methylcholanthrene (MC) in Mice

Carcinogenesis by MC has been extensively investigated in mice.\textsuperscript{6,7} It is a model of “chronic” chemical carcinogenesis in the sense that a long latency period is required for tumors to develop. In addition, it is a “two-step” model of carcinogenesis, since preneoplastic changes usually precede tumor formation. Thus, two steps are morphologically seen: one represents a transition from normal tissue to preneoplastic tissue, and the second represents the transition to mammary cancer.

Characteristics of the Glandular Tree

When MC is given by surface painting to virgin BALB/c female mice,\textsuperscript{8} several changes (diffuse or focal), become progressively apparent in the mammary glandular tree. The diffuse changes of the glandular tree can be categorized under the following five headings:

1. Disarrangement. The ducts become disarranged and follow a pattern of development that is clearly different from that seen in untreated controls. In particular, the characteristic 0.25-cm inter­ductal layer of fat seen in normal breasts is absent (Figs. 2–3).
2. Overcrowding. Because of the above features, the ducts appear overcrowded and closer to each other than normal.
3. Secretion. The ducts and alveoli are enlarged and filled with a milky secretion. This is probably related to the fact that MC favors prolactin release from the pituitary.\textsuperscript{9}
4. Poor lobuloalveolar differentiation. There are only a few alveoli and clusters of alveoli or lobules along the glandular tree in MC-treated virgin females.
5. Shortening of the glandular tree. Ductal ramification appears to be simplified because of the absence of the intermediate, small-sized ducts. The extralobular terminal ducts, which represent the lobular stalk are absent. Accordingly, lobules and alveoli often arise directly from large ducts (Fig. 4). In conclusion, MC-treated mice seem to have lost their morphogenetic memory governing the development of a normal glandular tree.\textsuperscript{8}