

Current research on breast carcinogenesis

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ABSTRACT The majority of invasive breast carcinoma is thought to develop over long periods of time from certain pre-existing benign lesions. Subsequent tumor progression is driven by the accumulation of additional genetic changes combined with clonal expansion and selection. Epithelial- mesenchymal interactions are known to be an important factor for the normal development of the mammary gland and for the breast tumorigenesis. Insight into the mechanisms of the causation of cancer by estrogen will be identified determinants of susceptibility to breast cancer and new targets for prevention and therapeutic intervention.

KEY WORDS *Brest carcinogenesis; genetics; premalignant lesions*

Introduction

The natural history of breast cancer involves progression through defined pathological and clinical stages, starting with ductal hyperproliferation, with subsequent evolution into in situ and invasive carcinomas, and finally into metastatic disease. The majority of invasive breast cancer develop over long periods of time from certain pre-existing benign lesions. There are many types of benign lesions in human breast and only a few appear to have significant premalignant potential.

The best characterized premalignant lesions recognized today are referred to as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). All these lesions possess some malignant properties such as a relative loss of growth control, but they lack the ability to invade and metastasize and, in this sense, are premalignant (1). The pathologist described many years ago a histological continuum between normal epithelium in terminal duct lobular units (TDLUs) and invasive breast cancer (7).

Over the past twenty years , all of the studies has culminated in a histological model of human breast cancer evolution which proposes that stem cells in normal TDLUs give rise to atypical hyperplasias (ADH and ALH), which progress to in situ carcinomas (DCIS and LCIS), which eventually develop into invasive and metastatic disease (2).

There are many morphological differences between TDLUs and atypical hyperplasias and there are no unequivocal intermediate lesions between them. Wellings and co-workers proposed that a common alteration of TDLUs which they called "atypical lobules type A"(ALA) may be

involved in the transition from TDLUs to ADH and beyond (22). ALAs, which are referred to as unfolded lobules (ULs) resemble TDLUs in overall architecture but are much larger due to the proliferation and accumulation (i.e. hyperplasia) of the epithelial cells lining their acini. The structure of normal TDLUs themselves varies considerably as a function of hormonal status (e.g. menstruation, pregnancy)

This linear histological model of breast cancer evolution undoubtedly oversimplifies a very complex process. The histological appearances of premalignant lesions within specific categories are very similar (by definition), so there must be underlying biological abnormalities causing some to remain stable and others to progress.

The initiation of breast cancer is due to transforming events(genetic and epigenetic) in a single cell. Subsequent tumor progression is driven by the accumulation of additional genetic changes combined with clonal expansion and selection (19). However, many studies have focused mainly on the tumor epithelial cells, while the potential involvement of other epithelial and myoepithelial cells and the stroma in tumor progression have not been explored in sufficient depth.

Epithelial-mesenchymal interactions are known to be important for the normal development of the mammary gland and for the breast tumorigenesis (9). In vivo and in vitro studies have demonstrated that cells composing the microenvironment (myoepithelial and endothelial cells, fibroblasts, myofibroblats, leukocytes, and other cells types) and the ECM (extracellular matrix) molecules modulate tissue specificity of the normal breast as well as the

growth, survival, polarity, and invasive behavior of breast cancer cells (5, 6)

Among all leukocytes, macrophages have been the most extensively analyzed in breast tumor progression. Using various models systems, macrophages have been shown to play a role in promoting angiogenesis, invasion and metastatic spread (13).

A significant fraction of genes identified by Allien and colleagues (1) as abnormally expressed in tumor epithelial and stromal cells encode secreted proteins and receptors, implicating a role for abnormal autocrine/paracrine signaling in breast tumor progression. Correlating with this, several of the chemokines (e.g. CXC motif chemokine ligand 12 CXCL12 and CXCL14) overexpressed in tumor myoepithelial cells and myofibroblasts, respectively, enhance tumor cell proliferation, migration and invasion and promote angiogenesis and metastatic spread (1, 17). Because chemokine receptors are G protein-coupled receptors that are fairly good drug targets, efforts are ongoing to test whether the inhibition of chemokine receptors could potentially be exploited for the treatment of breast and other cancer types (4).

Critical and poorly understood events in breast tumor progression that have dramatic effects on clinical management and outcome are the transition of DCIS to invasive carcinoma and the metastatic spread of primary tumors to distant organs. The diagnostic criterion that distinguishes invasive from in situ carcinomas is the disappearance of the myoepithelial cells as an organized entity.

Molecular studies revealed that myoepithelial cells associated with DCIS are not phenotypically normal; they have lost some of their differentiation markers and have upregulated genes promoting angiogenesis and invasion (1). While the physiological relevance of these molecular changes is unknown, these data lead to the hypothesis that the in situ to invasive carcinoma progression may be regulated by myoepithelial cells (3). Specifically, abnormal DCIS-associated myoepithelial cells together with various stromal cells may degrade the basement membrane, resulting in the progression of in situ carcinomas to invasive tumors. DCIS-associated myoepithelial cells have increased levels of EDM (extracellular matrix)-degrading enzymes, such as several MMPs (matrix metalloproteinases), compared with their normal counterparts (1). An alternative explanation of the histopathologic observations is that the differentiation of mammary epithelial stem cells to myoepithelial

cells may be progressively lost during tumorigenesis, resulting in the disappearance of the myoepithelial cell layer and progression to invasive cancer.

Estrogen Carcinogenesis in Breast Cancer

The exposure to estrogen is an important determinant of the risk of breast cancer. The mechanisms of carcinogenesis in the breast caused by estrogen include the metabolism of estrogen to genotoxic, mutagenic metabolites and the stimulation of tissue growth. Together, these processes cause initiation, promotion, and progression of carcinogenesis. Several endocrine-associated risk factors are regularly associated with an increased relative risk of breast cancer in postmenopausal women (10). One of these factors is obesity, which is probably related to an increased production of estrogen by aromatase activity in the adipose tissue.

Another factor is an elevated blood level of endogenous estrogen. An increased relative risk is also associated with higher-than-normal blood levels of androstenedione and testosterone, androgens that can be directly converted by aromatase to the estrogens estrone and estradiol, respectively (11). Elevated urinary levels of estrogens and androgens are also associated with an increased risk of breast cancer in postmenopausal women (18).

Compared with premenopausal patients, postmenopausal patients have quantitatively higher levels of cytosolic estrogen receptor and a greater proportion of their tumors are cytosolic estrogen receptor (CER) positive. Elderly patients with breast carcinoma when compared with younger patients were more often responsive to hormonal manipulation and had improved survival (15). Most investigators (8) have interpreted their data to suggest a significant correlation between CER levels and menopausal status. The analyses of the data from 1037 patients with primary breast carcinoma (in a study presented by K.S. Mc Karty in 1983) indicate that CER increases with age from the third through the tenth decade (15). Most previous studies (8, 14) have emphasized menopausal status, suggesting that premenopausal patients have a lower incidence of CER positive tumors as well as quantitatively lower tumor levels of estrogen receptor compared with postmenopausal patients.

The reason for the CER content increase with patient age may be related to a number of factors. Some studies have shown a negative correlation between serum estrogen levels and CER content

of the breast carcinoma. Since postmenopausal women have lower circulating estrogen levels, the higher CER levels observed in tumors from these patients have been suggested to be the result of an increase in unoccupied cytosolic receptor rather than an increase in total cytosol receptor (21). Saez et al. have postulated that the cyclic levels of serum progesterone in premenopausal patients limit CER synthesis (20). This later hypothesis is supported by the the menstrual cycle variations of CER observed in normal human endometrium and recently shown in normal human breast (12, 16).

In both the breast and endometrium, preleutal CER values were significantly higher than CER levels during the luteal phase when plasma progesterone is high. Thus, the higher CER levels observed in postmenopausal patients may be related to chronic unopposed estrogen stimulation, to a decrease in the progesterone down regulation of CER or a combination of these factors. The variation of CER by age may be an important clue to the biologic characteristics associated with malignant transformation but does not obviate the need for determination of CER in individual patients for purposes of treatment planning and prognostic assessment.

Conclusion

Breast carcinogenesis is a multi-step process that starts with hyperplasia, progressing through atypical hyperplasia to in situ carcinoma and a large number of biological characteristics must be evaluated during this evolution.

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