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Multistep model of the genetic alterations leading to breast cancer

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Breast cancer development is the result of the accumulation of genetic alterations in the epithelial cells of the breast. The main genetic alterations occurring in breast cancer are amplification of a number of oncogenes (approximately 10) and the inactivation of tumor suppressor genes. There are approximately five known tumor suppressor genes in breast cancer, but in view of the high frequency of loss of heterozygosity found for various chromosomal locations, many more tumor suppressor genes must play a role in breast cancer development. Translocations and activating mutations in oncogenes do not seem to play an important role in breast cancer development.

There are many reports in the literature on genetic alterations in invasive breast carcinomas; a limited number of reports describe the genetic alterations in carcinoma *in situ,* which is the only known precursor to invasive breast cancer. More recently, genetic abnormalities have also been described in normal epithelial cells adjacent to invasive breast cancer, as well as in benign epithelial proliferations.

From these data we can begin to construct a model of the development of breast cancer. It is not known in what cell in the normal breast carcinomas develop. The candidates for these precursors include ductal epithelial cells, myoepithelial cells and ductal "stem cells"; it has been hypothesized that the latter exist, but they have not been identified based on morphological or other characteristics. It is not known with certainty in what part of the ductal tree most carcinomas develop, but the most likely site is the terminal ductolobular unit.

It has been discovered that most genetic alterations found in invasive breast carcinoma are already present in carcinoma *in situ;* the genetic alterations involved in the progression from carcinoma *in situ* to invasive carcinoma remain to be elucidated. Very little is also known concerning the genetic alterations involved in the development of lymph node metastases and distant metastases.

It has become clear that, unlike the situation for colorectal cancer, there is not one linear route from a normal epithelial cell to invasive carcinoma, but that there are several distinct pathways leading to distinct histological types of carcinoma.

Based on the study of genetic alterations in relation to histological type, the following routes of invasive cancer development can be hypothesized to exist:

i) Normal epithelial cell → lobular carcinoma *in situ* (LOIS) → invasive lobular carcinoma (ILC). Inactivating mutations in the E-cadherin gene are almost always found in ILC and never in invasive ductal carcinoma (IDC). Inactivation of E-cadherin is already present in LCIS, indicating that this is an early step in the development of lobular cancer. Amplification and overexpression of cyclin D1 are also frequently found in ILC.
ii) Normal epithelial cell → well-differentiated ductal carcinoma *in situ* (DCIS) → IDC grade I. Loss of heterozygosity (LOH) on chromosome 16q is frequently found in well-differentiated DCIS; inactivation of a tumor suppressor gene located on 16q has not yet been identified in these tumors. LOH on 16q is less frequently found in poorly differentiated DCIS, indicating that inactivation of a tumor suppressor gene in this region is specific for the development of well-differentiated DCIS. Genetic alterations involved in the progression to invasion have not yet been identified.
ii) Normal epithelial cell → poorly differentiated DCIS → IDC grade III. Amplification of the *c-erbB-2/neu* gene and inactivating point mutations in the p53 gene are frequently found in poorly differentiated DCIS and these genetic alterations are absent in well-differentiated DCIS. There are no genetic alterations which have been shown to be involved in the progression to invasion. Amplification of the c-myc, fibroblast growth factor receptor I and II genes and of the cyclin D1 gene may be involved in the progression to invasion, not only in poorly differentiated breast cancer, but also in well-differentiated breast cancer.
iv) Based on morphological characteristics, an intermediately differentiated DCIS and IDC grade II are recognized. It is not known whether this represents a specific subgroup of breast carcinomas, characterized by specific genetic alterations.
v) A number of histological breast cancer types, which are all relatively rare, can be recognized. These types include mucinous carcinoma, metaplastic carcinoma and others. At present, only very little is known with regard to the genetic alterations in these tumor types.

In the coming years, more genetic alterations will be described and fully characterized in breast cancer. This will enable us to obtain a full genetic understanding of breast cancer development. Many of the genetic alterations identified are already present in DCIS; it will be particularly challenging to find the genetic alterations involved in the development of invasive and metastatic breast cancer.

Myoepithelial differentiation in breast carcinoma

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Myoepithelial cells have long been considered as a sort of residual component in breast parenchyma, devoid of specific function (be-